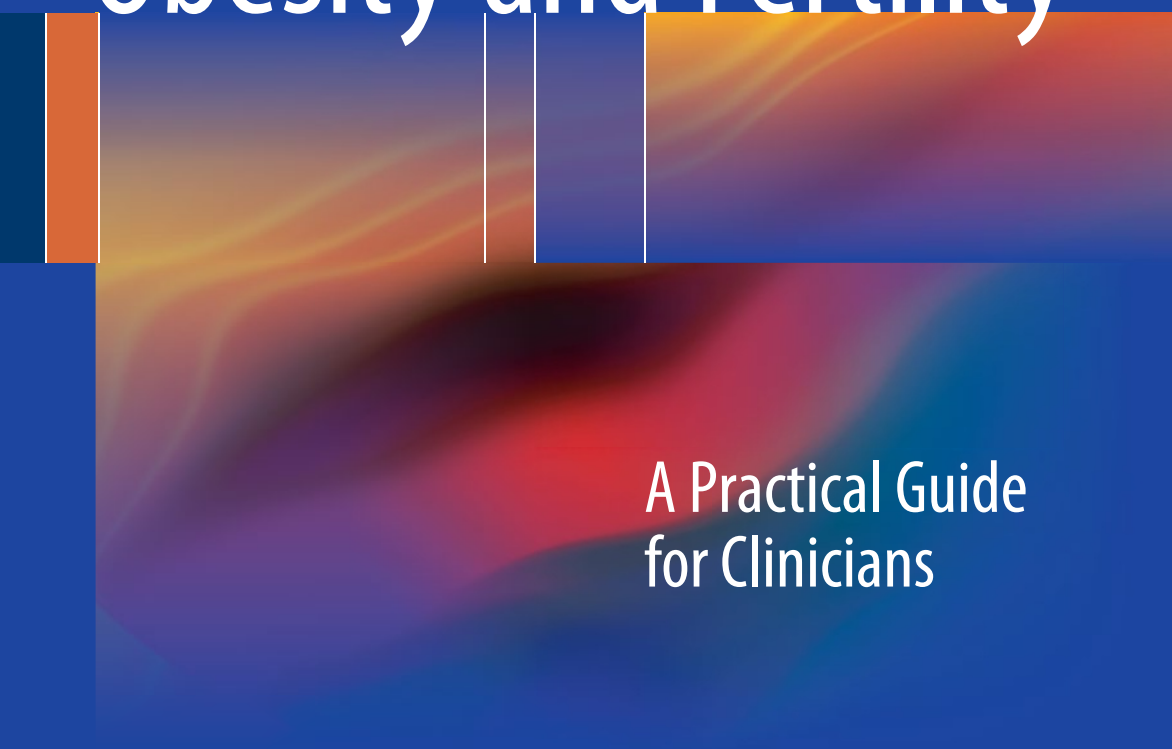
Emily S. Jungheim
Editor

Obesity and Fertility

A Practical Guide for Clinicians



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Preface

As the prevalence of obesity rises globally, it is imperative that we understand the impact of obesity on different physiologic processes and that we work to determine the mechanisms driving obesity's adverse effects on health. While we strive to improve health outcomes for everyone through application of knowledge gained in epidemiologic and basic science study, we must not lose sight of the fact that optimal outcomes for patients incorporate patient preferences. Nowhere in medicine is this more important than it is in the intersection between female fertility and obesity. For obese women, we must balance competing goals for fertility, family planning, pregnancy, minimization of long-term risks for the patient, and minimization of risks for her future children.

This book features chapters written by experts who have made the study of obesity and female fertility a focus in their daily work. It covers a gamut of topics relevant to reproductive age women from a number of different perspectives, including those from basic scientists who study the physiology of the menstrual cycle and early pregnancy, outcomes researchers who work to identify best practices in the delivery of contraceptive and prenatal care, and medical ethicists who advocate for policy that weighs the evidence in appropriate balance with principles that respect women's rights.

I am proud to have worked on this volume with the contributing authors. It is truly representative of the problems of obesity and fertility.

St. Louis, MO, USA — Emily S. Jungheim, MD, MSCI

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Chapter 1
Introduction to Obesity and Fertility

Violet Klenov and Emily S. Jungheim

The majority of Americans are overweight or obese [1]. This is problematic for clinicians and patients alike as obesity contributes to myriad of health problems including diabetes, coronary artery disease, and certain cancers [2–5]. While it is encouraging that obesity rates have begun to plateau, the epidemic of obesity will continue to challenge us for years to come. This book was compiled with reproductive scientists and women's health providers specifically in mind as it outlines our current understanding of how obesity affects female reproductive function across the lifespan.

A Note on Obesity and Male Reproductive Health

Although this book and most other work on obesity and reproductive health focuses on women, there is a growing body of literature demonstrating adverse effects of obesity on male reproductive function [6]. Obese men have decreased testosterone and gonadotropin levels, and increased circulating estrogen levels [6]. The increase in estrogen is likely secondary to peripheral aromatization of androgens. As estrogen negatively feedbacks onto the hypothalamus, a hypogonadotropic hypogonad state is created leading to lower sperm counts, poorer sperm quality, and increased rates of erectile dysfunction [6–9]. Increase in local heat secondary to obesity also impairs spermatogenesis [10]. Ultimately sperm from obese men can contribute to

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poor embryo quality [11]. Due to a paucity of data on the topic, we do not formally address male obesity and reproductive function in this book, but we look forward to seeing future research in this area.

Obesity and Female Reproductive Health

It is generally accepted that obesity adversely affects female reproductive function [12–14]. However, the mechanisms are not fully understood and are a popular area of research. Obesity likely affects reproductive health through a cumulative process starting with abnormalities in the hypothalamic–pituitary–ovarian (HPO) axis. Abnormal signalling through the hypothalamus and pituitary may affect follicular recruitment and influence subsequent oocyte quality thus contributing to overall subfertility in obese women. Studies of women undergoing assisted reproductive technologies (ART) provide a unique opportunity for direct visualization of reproductive tissues in obese women and have demonstrated that obesity also has direct effects on oocytes, embryos and on the endometrium. Several retrospective studies have associated obesity with increased risk for miscarriage in spontaneous conceptions [15], as well as in obese women receiving donor oocytes after IVF [16, 17]. The pathophysiology underlying this association is complex and likely multifactorial, involving the oocyte, embryonic development, and the endometrium.

Ultimately, obese women who conceive spontaneously or with ART are at increased risk for adverse pregnancy outcomes, including preeclampsia, gestational diabetes, fetal growth abnormalities, stillbirth, congenital abnormalities, and the need for cesarean delivery [10, 18]. Patients and their physicians must be aware of the additional risks obesity confers in pregnancy and outline a plan of care including counseling preconceptionally, antepartum, intrapartum and post-partum in order to decrease morbidity. Ensuring obese women are using the most effective methods of contraception until they are ready to conceive is also important to reduce unintended pregnancy and subsequently obesity-related morbidities.

Aside from fertility and pregnancy concerns, evidence demonstrates that obesity may influence the timing of puberty, the transition to menstrual cyclicity, and ovarian aging. The mechanisms by which obesity influences these transitions are not fully understood, but we have recruited experts in reproductive biology and reproductive specialists involved in the clinical care of obese women to summarize the current understanding of obesity's impact on female reproductive health.

Perhaps the most concerning information presented in the chapters that follow is that highlighting the fact that obesity's adverse effects are likely transgenerational (see Chap. 5). Children born to obese mothers are at increased risk for obesity, diabetes and cardiovascular disease later in life [19]. This is possibly secondary to epigenetic modifications of the embryonic genome in response to the alterations of the in utero environment caused by obesity.

Altogether, the impact of obesity on female reproductive health and the growing concern for a transgenerational impact of maternal obesity raise important questions regarding the policy and ethics of fertility care for obese women. These questions are also addressed in this collection by experts who have applied their clinical experience and research interests in women's health to develop thoughtful approaches to reproductive care for the obese woman.

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014;311(8):806–14.
2. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;345(11):790–7.
3. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007;298(17):2028–37.
4. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. J Obes. 2013;2013:291546.
5. Chescheir NC. Global obesity and the effect on women's health. Obstet Gynecol. 2011;117(5): 1213–22.
6. Hammoud AO, Gibson M, Peterson CM, Meikle AW, Carrell DT. Impact of male obesity on infertility: a critical review of the current literature. Fertil Steril. 2008;90(4):897–904.
7. Hammoud AO, Meikle AW, Reis LO, Gibson M, Peterson CM, Carrell DT. Obesity and male infertility: a practical approach. Semin Reprod Med. 2012;30(6):486–95.
8. Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med. 2000;30(4):328–38.
9. Sermondade N, Faure C, Fezeu L, Shayeb AG, Bonde JP, Jensen TK, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. Hum Reprod Update. 2013;19(3):221–31.
10. Practice Committee of American Society for Reproductive Medicine. Obesity and reproduction: an educational bulletin. Fertil Steril. 2008;90(5 Suppl):S21–9.
11. Jenkins TG, Carrell DT. The sperm epigenome and potential implications for the developing embryo. Reproduction. 2012;143(6):727–34.
12. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. Hum Reprod. 2007;22(2):414–20.
13. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI, Olsen J. Subfecundity in overweight and obese couples. Hum Reprod. 2007;22(6):1634–7.
14. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Burggraaff JM, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod. 2008;23(2):324–8.
15. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril. 2008;90(3):714–26.
16. Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod. 2004;19(11): 2523–8.
17. Bellver J. Obesity and the risk of spontaneous abortion after oocyte donation. Fertil Steril. 2003;79(5):1136–40.

18. Jungheim ES, Travieso JL, Carson KR, Moley KH. Obesity and reproductive function. Obstet Gynecol Clin North Am. 2012;39(4):479–93.
19. Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. Am J Obstet Gynecol. 2010;203(6):525–30.

Chapter 2
Obesity and the HPO Axis

Alex J. Polotsky and Manuel A. Doblado

Introduction

The obesity epidemic in the United States is accelerating. By 2015, approximately 41 % of US adults will have a body mass index (BMI) of greater than 30 kg/m^2 [1]. Female adiposity is associated with irregular menses, ovulatory dysfunction, decreased fertility, and a high risk of obstetrical complications. While adiposity–subfertility association is well documented, the underlying pathophysiology remains poorly understood. Abnormalities of reproductive hormones have been studied as potential causes for the aforementioned disorders but a unified mechanism has not yet been determined. Studying the female reproductive axis is difficult because many hormones are secreted intermittently in pulses that cannot be directly observed. This review will examine the current literature concerning the impact of obesity on the hypothalamic–pituitary–ovarian (HPO) axis and female fertility.

Definitions

Obesity, defined by a BMI greater than 30 kg/m^2, is becoming increasingly common with 35.7 % of all US adults being classified as obese based on the most recent National Health and Nutrition Examination Survey [2]. Traditionally, the

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reproductive effects of female obesity were attributed to anovulation and hyperandrogenism. These features, however, are characteristic of PCOS, which has an estimated prevalence of 2–8 % in reproductive age women [3]. Simple or nonsyndromic obesity is much more prevalent than PCOS and seems to have a different pathophysiology with respect to the obesity-related reproductive impairment. Most notably, PCOS is characterized by increased serum luteinizing hormone (LH) while obese women typically have overall lower serum LH. Obesity may modulate some aspects of pituitary physiology, such as the gonadotropin responsiveness to gonadotropin-releasing hormone (GnRH) [4]. While obesity can affect many aspects of PCOS, it is a cause of this syndrome and could certainly affect reproduction regardless of PCOS symptomatology [3]. In this review, we will focus on how obesity in the absence of PCOS affects the HPO axis.

Obesity and Fecundity

The relationship between female obesity and reproductive capacity of an individual, or fecundity, has been examined in several studies in a variety of populations in settings of assisted and unassisted conception. A prospective cohort study from the Netherlands studied the probability of conception among women presenting to a fertility clinic for artificial insemination. They found that women with higher waist–hip ratio as well as higher BMI were less likely to conceive than their counterparts with lower or normal metrics. There was no relationship between menstrual cycle length or regularity and obesity or body fat distribution, suggesting that a factor other than regular ovulation was responsible for this decreased probability of conception [5]. A retrospective cohort study from Norway also examined the effect of BMI on success of assisted reproductive technology (ART) treatment. Increased BMI was associated with a lower live birth rate, higher incidence of early pregnancy loss, increased FSH requirement, and fewer obtained oocytes [6]. Several other studies have examined fecundity in women not receiving any fertility treatment. A large, retrospective cohort study from the 7,327 US couples showed that women with higher BMI had a longer time to pregnancy than normal-weight subjects. This association remained when the analysis was restricted to women with regular menstrual cycles [7]. This implies that the lower fecundability seen in obese women is not simply related to increased probability of abnormal cycle length or anovulation. A Dutch study of ovulatory, subfertile women showed that obesity was associated with a lower probability of pregnancy compared to women with a BMI 20–29 kg/m^2. For every BMI unit above 29 there was a 5 % decrease in probability of pregnancy over 1 year [8]. Recent findings from the Study of Women's Health across the Nation indicate that obese adolescent girls are expected to have a threefold increased risk of lifetime nulliparity and a fourfold increased risk of lifetime nulligravidity [9].

Thus, most studies of obesity and fecundity suggest that obesity is associated with an increased time to pregnancy. The reasons behind this association are unclear. While obesity can be associated with an increased risk of abnormal menstrual cycle

length [10], the reduced fecundity persists even when women with abnormal cycle length, and thus the vast majority of anovulatory subjects, are removed from the analysis. This suggests that obesity affects several different aspects of the HPO axis above and beyond a yes-or-no effect on ovulation.

Obesity and Central Reproductive Hormones

Luteinizing Hormone

Several studies have shown a relationship between luteinizing hormone (LH) and BMI. Women with higher BMI have decreased LH pulse amplitude and overall decreased serum LH compared to normal-weight controls [11]. A study by Bohlke and colleagues suggested an inverse relationship between BMI and LH levels in premenopausal women without polycystic ovarian syndrome (PCOS) [12]. Another study found lower LH levels in women with higher BMI (>23.4) during the follicular phase compared to their counterparts with women with the BMI below this somewhat artificial cutoff [13]. Similarly, other researchers found significantly lower follicular LH levels in overweight and obese women compared to normal-weight women during the early follicular phase [14]. Finally, a large study of perimenopausal women showed obese and overweight women had significantly decreased daily urinary LH throughout the menstrual cycle as compared to normal-weight women [15]. Notably, whole cycle and peak LH increase significantly in women who have undergone bariatric surgery compared to preoperative women [16]. As these women lost a significant amount of weigh postoperatively, these results suggest that obesity or an obesity-related condition is directly responsible for this suppressed LH. Overall, most studies suggest that obesity may lead to a decreased LH, particularly starting from early follicular phase of the menstrual cycle. One proposed mechanism to explain the decreased LH seen in obese women is that the decreased SHBG also seen in obese women [17] leads to increased free estradiol. Thus, it could be hypothesized that this increased level of free estradiol may exert exaggerated negative feedback on the pituitary, leading to diminished gonadotropin output.

Follicle-Stimulating Hormone

Similar to LH, several studies have also shown decreased levels of follicle-stimulating hormone (FSH) in obese women. Women with higher BMI had significantly lower FSH levels compared to normal-weight women throughout the menstrual cycle [13]. Total cycle FSH level was also found to be negatively correlated with BMI in perimenopausal women [15]. As with LH, a possible explanation is the increased free estradiol present in obese women due to suppressed SHBG

production. Alternatively, reduced restraint from ovarian factors that normally exert negative feedback may also be at play as detailed below.

Obesity and Ovarian Hormones

Androgens

In perimenopausal women, BMI was positively correlated with total testosterone and free androgen index but negatively correlated with DHEAS and SHBG levels. Thus, obesity may be associated with an increase in ovarian androgen production but a decrease in adrenal androgen production as well as SHBG [17]. Another study found similar results among postmenopausal women with the metabolic syndrome [18]. Increased androgen effects in obese women could therefore be from two distinct but necessarily mutually exclusive mechanisms: increased ovarian production of androgens or increased free androgens present due to decreased SHBG. Both pathways remain plausible hypotheses and will need be carefully tested in light of recently developing data on the efficacy of androgen-increasing aromatase inhibition in treatment of female infertility.

Estradiol

Higher BMI may be associated with lower estradiol levels. Premenopausal obese women have lower serum estradiol than their normal-weight counterparts. However, postmenopausal obese women have significantly higher estradiol than normal-weight women [19]. This relationship in postmenopausal women was also noted in another study, which in addition found further increases in estradiol levels with the metabolic syndrome [18]. Not all studies have shown this trend towards lower estradiol levels in obese women. When estrone conjugates are measured in the urine throughout a menstrual cycle, there are no significant differences between different BMI categories [11, 15]. Notably, the latter two studies use urinary estradiol metabolites and the others used serum estradiol, which potentially may explain differences between the observed results.

Progesterone

Progesterone, similar to estradiol, seems to decrease with increasing BMI. Levels of pregnanediol glucuronide (Pdg), a metabolite of progesterone excreted in urine, are lower in obese perimenopausal women than in women with normal BMI [15].

A similar result was found in obese premenopausal women with normal cycles [11]. Postoperatively, women who underwent bariatric surgery and were ovulatory had significantly increased luteal Pdg secretion compared to preoperative women. Pdg levels in the postoperative group did not reach the level of normal controls, though it should be noted that the postoperative women still had significantly higher BMI than the normal-weight controls [16]. A larger recent study of 29 women has not demonstrated an improvement in luteal-phase quality after bariatric surgery [20]. However, the preponderance of evidence indicated that substantial weight loss after bariatric surgery is associated with improved ovulatory function, fertility, and pregnancy outcomes [19, 21].

Inhibins

Inhibins are a family of peptides produced by the ovary that are thought to regulate follicular development. Inhibin B, mainly produced by the granulosa cells of the preantral or small antral follicles, is decreased in overweight and obese women compared to normal-weight controls [14]. Similar results were found among perimenopausal women [19]. Notably, this relationship changes with the transition to menopause, with obese women having significantly higher inhibin B levels than normal-weight women [22]. The mechanism for decreased inhibin production in obesity is unclear, but implies that lower inhibin in obese women may reflect the harmful effect of obesity on folliculogenesis [23]. Further, obese women have a significant reduction in follicular inhibin B but NOT in the number of ovarian follicles. This suggests a functional rather than structural deficit [14]. This functional impairment suggests that the predominant impact of obesity is on granulosa cell function, rather than a large volume of distribution driving the reduced hormonal levels. Thus, obesity represents a paradox of reduced ovarian negative feedback restraint DESPITE decreased circulating FSH levels.

Anti-müllerian Hormone

Anti-müllerian hormone (AMH) is a member of the TGF-beta family and is produced by the granulosa cells of primary and preantral follicles. Serum AMH levels reflect the size of the primordial follicle pool [24]. Like inhibin, AMH levels are decreased with increased BMI in most studies. A study of late reproductive age women showed significantly decreased AMH in obese women compared to normal-weight women [25]. Another analysis showed this negative correlation between AMH and BMI was present among younger premenopausal women [22]. Like inhibin, the lower levels of AMH in obese women may reflect obesity-mediated impaired follicular function. While AMH has proven to be a reliable

marker of ovarian reserve, the decreased AMH seen in obese women is not thought to reflect decreased ovarian reserve. FSH, another marker of ovarian reserve, is often decreased in obesity as we have seen. This would suggest that ovarian reserve is likely normal in obese women and the atral follicle count is often unaffected [22].

Other Hormones as Potential Modulators of HPO function in Obesity

Ghrelin

Ghrelin is a peptide released by the gut that has a wide array of biological functions including modulation of GH secretion. Ghrelin levels correlate negatively with BMI in both obese patients and patients with anorexia nervosa [26]. In animal studies, ghrelin was found to stimulate the secretion of both FSH and LH at the pituitary gland [27]. In addition to the gut, other animal studies have shown that ghrelin is also produced by the ovary, specifically by the corpus luteum [28]. In vitro and animal studies suggest ghrelin is a potential target linking metabolism and fertility; however, more study will be needed to further characterize the relationship between ghrelin, obesity, and fertility in humans.

Leptin

Leptin is secreted primarily by adipocytes. Initially described as a satiety factor, it conveys a peripheral signal to the central nervous system about body fat stores [29]. Leptin secretion is proportional to body fat stores; levels are elevated in obesity and decreased in anorexia nervosa. Administration of exogenous leptin has been shown to lead to weight loss in leptin-deficient adults, but is not effective as a treatment for obesity when leptin expression is normal. This has led some to speculate that obesity may represent a state of "leptin resistance" [26]. Leptin seems to have an effect on both the ovary and the hypothalamus. In the ovary, the higher leptin level in obese women has been shown to decrease the production of estradiol in the granulosa cell in response to FSH [30]. Elevated leptin levels have been shown to directly suppress the gonads and decrease hormone steroidogenesis [31]. Leptin receptors are present in the hypothalamus and play a role in GnRH regulation. Leptin has been shown to stimulate GnRH secretion in a GnRH secreting cell line [32]. A study of the rat GnRH pulse generator showed leptin accelerates GnRH pulsatility [33]. The mechanism by which leptin regulates GnRH secretion is thought to be

complex, involving neuropeptides as well as nitric oxide [34]. As with ghrelin, more study is needed in humans to further understand the exact role leptin may play in reproduction.

Adiponectin

Adiponectin, another major adipokine, is the most abundant adipose gene transcript and is the natural peroxisome proliferator-activated receptor gamma (PPAR-gamma) ligand. It is an insulin sensitizer and is profoundly decreased in obesity and type II diabetes. Recent studies have also shown that adiponectin is produced by human theca cells [35] and is found in the ovarian follicular fluid [36]. Adiponectin levels are inversely correlated with BMI, especially in obese subjects [37] and weight loss ameliorates this trend [38]. While receptors for adiponectin are found mainly on skeletal muscle and hepatic tissues, adiponectin has been shown to influence ovarian function [39]. Recent studies have also shown that adiponectin may regulate GnRH receptor expression and inhibit basal and GnRH-stimulated LH secretion in animal models [35]. In human studies, adiponectin receptors were found on both granulosa and theca cells. In primary granulosa cell culture, adiponectin increased insulin-like growth factor 1 (IGF-1) potentiated secretion of progesterone and estradiol compared to IGF-1 alone [35]. This in vitro data from humans is consistent with the lower progesterone and estradiol levels seen in obese women in other studies.

Obesity as a State of Relative Hypogonadotropic Hypogonadism

Several recent studies have focused on what are classically thought to be nonreproductive hormones and their role in obesity-related infertility. One of these hormones is insulin. While insulin has been extensively studied in PCOS models of infertility, it has not been as thoroughly studied in obesity in the absence of PCOS. A recent study used a model of diet-induced obesity in a pituitary-specific insulin receptor knockout. Wild-type mice fed a high-fat diet became obese, had irregular estrous cyclicity and infertile compared to lean animals. The pituitary knockout animals, when fed a high-fat diet, also became obese and developed peripheral insulin resistance like the wild-type mice. However, their reproductive phenotype was very similar to the lean mice rather than the obese mice. Pituitary insulin knockout mice displayed normal estrous cyclicity and significantly more corpus lutea and higher fertility rates compared to the obese mice. Thus, insulin signaling at the level of the pituitary is implicated as a key player in regulating gonadotropin secretion [40]. It must be noted that the insulin receptor knockout mouse did not exhibit a completely normal reproductive phenotype, suggesting that there are factors other than insulin that are critical in obesity-related subfertility.

Conclusion

Female obesity exhibits pleiotropic influence on reproductive physiology and outcomes regardless of ovulation, as obesity is strongly linked with increased time to conception and reduced lifetime fertility even in regularly menstruating women. While the many changes to the hormonal milieu in obese women are still being detailed, the preponderance of studies demonstrate a harmful impact. Both LH and FSH are decreased in obesity and the mechanisms are only partially understood. Obesity is also associated with elevated SHBG levels, which may lead to increased levels of free estradiol or androgens. These elevated free estradiol and androgen levels may feedback on the pituitary leading to suppressed gonadotropin output. In addition to the central effects, obesity is also associated with decreased levels of ovarian inhibins, especially inhibin B. As inhibins are thought to play a role in the development of follicles, reduced inhibins may either lead to or be a result of disordered follicular development. This could potentially lead to the longer or irregular menstrual cycles commonly seen in obese women or underscore the relative gonadotropin deficits. However, antral follicle count in obesity is not reduced in most studies and neither is the age of menopause which both imply a qualitative rather than quantitative ovarian function decline. Levels of AMH are lower in obese women as well. While the function of AMH in this context is still not completely understood, it is an emerging marker of ovarian reserve. The decreased AMH levels seen in obesity may reflect an overall relative hypogonadal state induced by adiposity in women. The mechanism by which this relative hypogonadism comes about is still unclear and likely complex. Future directions should be concentrated on a better understanding of the mechanisms underlying the reproductive endocrinopathy of obesity. It would be critical to gain an insight on what component of the HPO (central vs. ovary) axis is primarily affected in obesity. This is especially important as the obesity epidemic is progressing unimpeded and the reproductive sequelae of obesity has been cited as one of the reasons for decreasing life expectancy in the twenty-first century [41, 42].

References

1. Wang Y, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. Epidemiol Rev. 2007;29:6–28.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009–2010. NCHS Data Brief No 82. Hyattsville: National Center for Health Statistics; 2012.
3. Legro RS. Obesity and PCOS: implications for diagnosis and treatment. Semin Reprod Med. 2012;30:496–506.
4. Pagán YL et al. Inverse relationship between luteinizing hormone and body mass index in polycystic ovarian syndrome: investigation of hypothalamic and pituitary contributions. J Clin Endocrinol Metab. 2006;91:1309–16.

5. Zaadstra BM et al. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ. 1993;306:484–7.
6. Fedorcsák P et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod. 2004;19:2523–8.
7. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. Hum Reprod. 2007;22:414–20.
8. Van der Steeg JW et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod. 2008;23:324–8.
9. Polotsky AJ et al. Association of adolescent obesity and lifetime nulliparity—the Study of Women's Health Across the Nation (SWAN). Fertil Steril. 2010;93:2004–11.
10. Jacobsen BK, Knutsen SF, Oda K, Fraser GE. Obesity at age 20 and the risk of miscarriages, irregular periods and reported problems of becoming pregnant: the Adventist Health Study-2. Eur J Epidemiol. 2012;27:923–31.
11. Jain A et al. Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. J Clin Endocrinol Metab. 2007;92:2468–73.
12. Bohlke K, Cramer DW, Barbieri RL. Relation of luteinizing hormone levels to body mass index in premenopausal women. Fertil Steril. 1998;69:500–4.
13. Ecochard R, Marret H, Barbato M, Boehringer H. Gonadotropin and body mass index: high FSH levels in lean, normally cycling women. Obstet Gynecol. 2000;96:8–12.
14. De Pergola G et al. Inhibitory effect of obesity on gonadotropin, estradiol, and inhibin B levels in fertile women. Obesity (Silver Spring). 2006;14:1954–60.
15. Santoro N et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. J Clin Endocrinol Metab. 2004;89:2622–31.
16. Rochester D et al. Partial recovery of luteal function after bariatric surgery in obese women. Fertil Steril. 2009;92:1410–5.
17. Santoro N et al. Correlates of circulating androgens in mid-life women: the study of women's health across the nation. J Clin Endocrinol Metab. 2005;90:4836–45.
18. Weinberg ME et al. Low sex hormone-binding globulin is associated with the metabolic syndrome in postmenopausal women. Metabolism. 2006;55:1473–80.
19. Freeman EW, Sammel MD, Lin H, Gracia CR. Obesity and reproductive hormone levels in the transition to menopause. Menopause. 2010;17:718–26.
20. Legro RS et al. Effects of gastric bypass surgery on female reproductive function. J Clin Endocrinol Metab. 2012;97:4540–8.
21. Teitelman M, Grotegut CA, Williams NN, Lewis JD. The impact of bariatric surgery on menstrual patterns. Obes Surg. 2006;16:1457–63.
22. Freeman EW et al. Association of anti-mullerian hormone levels with obesity in late reproductive-age women. Fertil Steril. 2007;87:101–6.
23. Gracia CR, Freeman EW, Sammel MD, Lin H, Nelson DB. The relationship between obesity and race on inhibin B during the menopause transition. Menopause. 2005;12:559–66.
24. Hansen KR, Hodnett GM, Knowlton N, Craig LB. Correlation of ovarian reserve tests with histologically determined primordial follicle number. Fertil Steril. 2011;95:170–5.
25. Su HI et al. Body size affects measures of ovarian reserve in late reproductive age women. Menopause. 2008;15:857–61.
26. Budak E et al. Interactions of the hormones leptin, ghrelin, adiponectin, resistin, and PYY3-36 with the reproductive system. Fertil Steril. 2006;85:1563–81.
27. Fernández-Fernández R, Tena-Sempere M, Aguilar E, Pinilla L. Ghrelin effects on gonadotropin secretion in male and female rats. Neurosci Lett. 2004;362:103–7.
28. Caminos JE et al. Expression of ghrelin in the cyclic and pregnant rat ovary. Endocrinology. 2003;144:1594–602.
29. Evans JJ, Anderson GM. Balancing ovulation and anovulation: integration of the reproductive and energy balance axes by neuropeptides. Hum Reprod Update. 2012;18:313–32.
30. Michalakis K, Mintziori G, Kaprara A, Tarlatzis BC, Goulis DG. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. Metabolism. 2013;62:457–78.

31. Baldelli R, Dieguez C, Casanueva FF. The role of leptin in reproduction: experimental and clinical aspects. Ann Med. 2002;34:5–18.
32. Magni P et al. Expression of a leptin receptor in immortalized gonadotropin-releasing hormone-secreting neurons. Endocrinology. 1999;140:1581–5.
33. Lebrethon MC, Vandersmissen E, Gérard A, Parent AS, Bourguignon JP. Cocaine and amphetamine-regulated-transcript peptide mediation of leptin stimulatory effect on the rat gonadotropin-releasing hormone pulse generator in vitro. J Neuroendocrinol. 2000;12:383–5.
34. Moschos S, Chan JL, Mantzoros CS. Leptin and reproduction: a review. Fertil Steril. 2002;77:433–44.
35. Chabrolle C et al. Adiponectin increases insulin-like growth factor I-induced progesterone and estradiol secretion in human granulosa cells. Fertil Steril. 2009;92:1988–96.
36. Gutman G et al. Recombinant luteinizing hormone induces increased production of ovarian follicular adiponectin in vivo: implications for enhanced insulin sensitivity. Fertil Steril. 2009;91:1837–41.
37. Brichard SM, Delporte ML, Lambert M. Adipocytokines in anorexia nervosa: a review focusing on leptin and adiponectin. Horm Metab Res. 2003;35:337–42.
38. Yang WS et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab. 2001;86:3815–9.
39. Tersigni C et al. Adipokines: new emerging roles in fertility and reproduction. Obstet Gynecol Surv. 2011;66:47–63.
40. Brothers KJ et al. Rescue of obesity-induced infertility in female mice due to a pituitary-specific knockout of the insulin receptor. Cell Metab. 2010;12:295–305.
41. Stewart ST, Cutler DM, Rosen AB. Forecasting the effects of obesity and smoking on U.S. life expectancy. N Engl J Med. 2009;361:2252–60.
42. Olshansky SJ et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med. 2005;352:1138–45.

Chapter 3
Childhood and Adolescent Obesity: Implications for Reproductive Health and Function

Matrika D. Johnson and Joseph S. Sanfilippo

Introduction

The problem of obesity is global and has incredible adverse potential for affected teens and young adult women. Despite multiple attempts at increasing public awareness, no advance in understanding the impact of the problem is apparent. The National Health and Nutrition Examination Survey (NHANES) 1999–2004 focused on the problem and the study has continued to try to reduce the national prevalence of overweight and obesity categories in the young aged female. The prevalence has been reported at 13.9–17.1 %, data reported between 1999 and 2004 [1, 2]. What happened to the "fear of fatness" among teens? [3].

Adequate education of adolescents requires understanding the problem as the long term. Reproductive consequences are numerous and include: polycystic ovary syndrome, decreased fertility, and endometrial cancer in addition to a number of other morbidities and increased mortality. We provide an overview of the epidemiology, potential etiologies, reproductive repercussions, as well as clinical diagnostic and management modus operandi for affected children and adolescents.

Definition

The body mass index (BMI) is the most commonly used and accepted measure of body weight composition in children aged 2 years old and greater [4]. The BMI is a measure of the weight in relation to height where body weight (in kilograms) is

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Table 3.1 Body mass index (BMI) classification by age [75, 94–98]

Category	Age 2–18	Age ≥18
Underweight	BMI < 5th percentile for age	BMI < 18.5
Normal weight	BMI > 5th to <85th percentile for age	BMI 18.5–24.9
Overweight	BMI > 85th to <95th percentile for age	BMI 25.0–29.9
Obese	BMI > 95th percentile for age	BMI ≥30 (Class I)[a]
Severe obesity	BMI ≥ 120 % of the 95th percentile for age or BMI ≥ 35 (whichever is lower)	BMI ≥35 (Class II)[a]
		BMI ≥ 40 (Class III)[a]

[a]Obesity classes defined by WHO

divided by height (in meters) squared. In the pediatric realm, other measures such waist circumference, waist-to-hip ratio, weight for height, and the World Health Organization (WHO) growth standards are available to evaluate childhood obesity but here we will focus on BMI.

In the adult population obesity is defined as a BMI ≥ 30 kg/m^2. In the pediatric population this definition varies by percentile for age and sex. Table 3.1 presents the growing consensus of BMI definitions in children between age 2 and 18 years of age in comparison to adults.

The distinction of the various BMI categories is important because medical sequelae of obesity increase as BMI increases. Thus, those girls that fall into the severe obesity subset need to be identified as they have a greater risk of obesity persistence into adulthood as well as medical and reproductive sequelae [1].

In this chapter overweight denotes girls with a BMI between the 85th and 95th percentile for their age while obesity denotes girls with a BMI greater than the 95th percentile for age, unless otherwise indicated.

Epidemiology

Today in the United States greater than one-third of children and adolescents are either overweight or obese [5]. The prevalence of obesity between 2009 and 2010 for all children (6–11 years) and adolescents (12–19 years) combined was 18.2 % with minimal difference between childhood obesity (18.0 %) and adolescent obesity (18.4 %) [5]. This is a dramatic increase given the overall prevalence for children and adolescents between 1976 and 1980 was 5.5 % (children 6.5 % and adolescents 5.0 %) [6].

The prevalence of obesity amongst female adolescents follows this increasing trend. In the time period from 1988 to 1994, the prevalence in female adolescents was 9.7 % and increased to 17.1 % between 2009 and 2010 (Fig. 3.1) [5, 7]. Additionally, there are racial and ethnic disparities in obesity prevalence amongst female adolescents. In 2009–2010 24.8 % of non-Hispanic black adolescent females were obese compared to 18.6 % of Mexican Americans, and 14.7 % non-Hispanic whites [5]. Socioeconomic level and education level of the head of the household

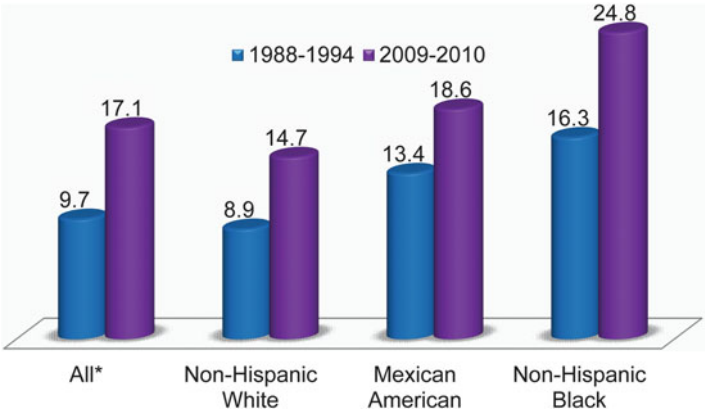

Fig. 3.1 Prevalence of obesity (in percentage) among adolescent females aged 12–19, by race/ethnicity from 1988 to 1994 and 2009 to 2010* [5, 7]. *All includes some races/ethnicities not represented in figure

play roles in the prevalence of adolescent obesity. In general, adolescents living at lower socioeconomic levels or in homes where the household head has less education are more likely to be obese, but these relationships are not consistent across all race and ethnicity groups [8].

Etiology

Obesity in children and adolescents is a multifactorial. It is the final product of an intricate relationship between environmental factors, genetics, and the emerging field of fetal programming, also known as the Barker hypothesis.

Environmental Factors

The environmental factors that have been implicated in childhood and adolescent obesity are myriad. Some of these issues include changes in family structure and meals, increased television and video games, and less physical activity. Medications, viruses, and environmental toxins have also been implicated. The best case can be made for those influences that increase caloric intake and decrease physical activity as those do directly contribute to obesity. More importantly, these are modifiable risk factors that can be adjusted to decrease rates of obesity.

Stimuli that are thought to increase caloric intake include increasing consumption of sugar-sweetened beverages, fast-food service, larger meal portions, school meals with poor nutritional content, and food with high glycemic indices as well as

along with fewer meals with the family [9–11]. Of these causes, most evidence available suggests sugar-sweetened beverages can be a significant contributor to obesity in some patient populations [12]. Conversely, those environmental elements thought to decrease physical activity include increasing use of television and video games with decreasing structured physical activity, side walk availability, and playgrounds [9, 11]. The best-established environmental factor that contributes to childhood obesity is television viewing. Several studies have shown a direct correlation between the prevalence of childhood and adolescent obesity and the amount of time spent watching television [13–19].

Genetic Factors

The precise mechanism of genetics in the development of obesity is difficult to elucidate as there is an intimate relationship between genetic and environmental factors. There are rare childhood genetic abnormalities that lead to obesity such as Prader–Willi which are beyond the scope of this chapter. Current literature suggests genetic factors account for approximately 30–50 % of the variation in fat distribution [20]. In the general population, genetic polymorphisms likely lead to an individual's susceptibility to the environmental factors that cause obesity; however, most genetic polymorphisms have yet to be isolated.

Fetal Programming

There is an emerging body of literature that conditions during the fetal and early postnatal period influence chronic disease through permanent effects on metabolic function. This concept is referred to as "fetal programming" [21–23]. Hales and Barker are directly linked to the concept of programming, or the Barker hypothesis whereby an insult or stimulus during a critical point in development has long-term consequences in the development of chronic disease [24, 25]. Fetal programming is thought to play a key role in the development of obesity as well as other metabolic disturbances such as type II diabetes, metabolic syndrome, and cardiovascular disease [26–32]. The proposed mechanism is that periods of undernutrition during fetal and early postnatal period result in changes in the metabolic milieu to slow down weight gain which permanently predisposes an infant to metabolic disturbances later in life [26, 29, 33–35]. This mechanism has been successfully validated in animal studies [27, 30, 31, 36–39].

Clinical Evaluation

A detailed history to include elements of: lifestyle, level of exercise, desktop-based activities such as computer games, laptop time, and other aspects of sedentary lifestyle remain important [40]. Genetic aspects and presumed predisposition must be explored.

The next major area is assessment by history, physical exam as well as laboratory testing, for those conditions outlined under clinical considerations. Briefly, these include focusing on disorders of glucose and insulin metabolism. Fasting plasma glucose remains an excellent screening tool. Metabolic syndrome must always be considered as this entity is a predictor of subsequent onset of type II diabetes mellitus and cardiovascular disease.

Menstrual history is of particular importance in the teen as oligomenorrhea while common, should be followed to see if the patient develops criteria that are met to establish the diagnosis of polycystic ovarian syndrome subsequently.

Cardiovascular history is an integral part of assessment of the obese teen and young adult female. It is important that the appropriate size cuff be used when measuring blood pressure. Unfortunately even teens can develop hypertension, left ventricular hypertrophy, and other cardiovascular disorders.

The lipid profile remains an integral part of assessment and must be focused on identifying hyperlipidemia. Other aspects of assessment include the gastrointestinal tract, orthopedic disorders that include: slipped capital femoral epiphysis, flat kneecap secondary to pressure, spondylolisthesis, scoliosis, and osteoarthritis [40].

Quality of life and assessment of the psychosocial aspects of a predisposed sedentary lifestyle merit consideration in this age group.

Other testing includes: chemical panel, complete blood count, and if warranted based upon clinical exam androgen levels.

Clinical Considerations

There are a plethora of comorbidities that occur secondary to childhood and adolescent obesity. These include abnormalities in the cardiovascular, dermatologic, endocrine, gastrointestinal, neurologic, psychosocial, and pulmonary systems. These comorbidities can have lifelong effects. For example, a study of over 850 girls demonstrated that girls, who were overweight during their childhood, had an increased risk of death secondary to all causes and specifically secondary to breast cancer compared to normal weight peers [41]. Here we will focus on abnormalities that effect reproductive function.

Growth and Puberty

Increased body weight in girls has been inconsistently associated with early onset of puberty [42–44]. Despite the inconsistency, it is definitively biologically plausible. Furthermore, obesity in childhood and adolescence has been associated with accelerated bone age and linear growth which may put obese girls at risk for short stature [45, 46]. It is not clear if early initiation of menses has a long-term effect on adult reproductive function.

Table 3.2 Diagnostic criteria for polycystic ovary syndrome[a] [52, 99, 100]

NIH 1990	Rotterdam[b] 2003	AES 2006
Anovulation or oligo-ovulation	Anovulation or oligo-ovulation	Ovarian dysfunction (either) Anovulation or oligo-ovulation Polycystic ovary by ultrasound
Clinical or biochemical hyperandrogenism (either) Clinical: Hirsutism, acne, male pattern balding Biochemical: High serum androgen concentration	Clinical or biochemical hyperandrogenism (either) Clinical: Hirsutism, acne, male pattern balding Biochemical: High serum androgen concentration Polycystic ovary by ultrasound	Clinical or biochemical hyperandrogenism (either) Clinical: Hirsutism, acne, male pattern balding Biochemical: High serum androgen concentration

NIH National Institute of Health, *AES* Androgen Excess and PCOS Society
[a]After exclusion of other causes of menstrual dysfunction and hyperandrogenism
[b]Criteria developed by European Society of Human Reproduction and Embryology and American Society of Reproductive Medicine. Two of three criteria required for diagnosis

Polycystic Ovary Syndrome

Obesity increases adolescent's risk of hyperandrogenism and polycystic ovary syndrome (PCOS). PCOS accounts for most cases of anovulation and hyperandrogenism in women and is the most common endocrine abnormality in obese females [47–49]. Given the possible long-term sequel, PCOS should be considered in adolescents with hirsutism, menstrual disturbances, acne which is resistant to treatment, or obesity. The long-term risks of PCOS include gynecological issues such as infertility and endometrial cancer as well as other endocrinopathies such as metabolic syndrome and type II diabetes mellitus.

Diagnosing PCOS during adolescence can be difficult as there are no formal diagnostic criteria for adolescents. Furthermore, given that it is a syndrome and not a disease, the clinical presentation can vary, especially in the adolescent population. Adolescent girls may present with menstrual disturbances, hirsutism, severe acne, hair loss, obesity, or acanthosis nigricans. The three sets of adult criteria are listed in Table 3.2. It is the current expert consensus that the diagnosis of PCOS can only be established 2 years after menarche in a female with hyperandrogenemia and menstrual irregularities [50].

PCOS has a great impact on reproductive function. This is primarily mediated by endocrine dysfunction. Girls with PCOS can experience abnormal pituitary function, abnormal steroidogenesis, and insulin-resistant hyperinsulinemia. All these factors culminate to create an endocrine milieu of hyperandrogenemia, elevated luteinizing hormone, and hyperinsulinemia with each factor acting independently and mutually to potentiate the others. Obesity exacerbates this endocrine dysfunction. Collectively these play a role in ovulatory dysfunction.

Most patients with PCOS, regardless of age, have symptoms of anovulation. Moreover, in adolescents regular menses does not ensure ovulation. During the first 2 years post menarche, roughly half of regular cycles are anovulatory [51]. Despite this, several girls with PCOS and regular menses do ovulate or have a minor ovulatory dysfunction that is revealed as unexplained infertility in adulthood [52, 53]. Ovulatory dysfunction in adolescence increases the risk of ovulatory dysfunction as an adult. The likelihood for prolonged dysfunction increases the longer these menstrual disturbances persist [54, 55].

Fertility

Ovulatory dysfunction in adolescence increases the risk of ovulatory dysfunction as an adult. The association between obesity and decreased fertility in women can be linked to the association of obesity and PCOS but PCOS is not the only cause of decreased fertility in obese females. In obese females with regular menses increasing BMI is associated with decreasing pregnancy rates and decreasing time to pregnancy [56–58]. It is possible the endocrine environment in obese females has an unfavorable influence on ovarian function, oocyte quality, endometrial receptivity, or any combination of these factors.

Endometrial Cancer

Obesity is a risk factor for endometrial hyperplasia and type I endometrioid carcinoma. In addition, chronic anovulation, such as that experienced in females with PCOS, is a risk factor as well. Both obesity and chronic anovulation increase endogenous estrogen exposure, the main risk factor for endometrial cancer [59]. In both conditions peripheral adipose tissue converts androgens to estrogens via aromatase which leads to continued proliferation of the endometrium and ultimately to endometrial hyperplasia or carcinoma. What's more is that obesity and PCOS commonly coexist but it is unclear if together they increase the risk of endometrial pathology. Regardless, endometrial hyperplasia and cancer are both presenting at younger ages in those girls with obesity and there is a clear association between BMI and early development of endometrial cancer [60]. A meta-analysis of 19 prospective studies in 2008 which included over three million women demonstrated that as BMI increased, the risk of developing endometrial carcinoma increased as well [61]. This is exacerbated by the fact that other associated factors of endometrial cancer such as nulliparity, infertility, type II diabetes mellitus, and hypertension are generally more prevalent in obese women.

Table 3.3 Diagnostic criteria for metabolic syndrome in adolescents [101–103]

Parameters	NHANES III 2002	Modified ATP III 2004	IDF 2007
Requirements	All five abnormalities	≥3 abnormalities	Waist circumference and ≥2 other abnormalities
Waist circumference	≥90th percentile	Not specified	≥90th percentile[a]
Blood pressure	≥90th percentile	Either	Either
Systolic		>95th percentile	>130 mmHg
Diastolic		>95th percentile	≥85 mmHg
High-density lipoprotein	<40 mg/dL	<5th percentile	<40 mg/dL
Triglyceride	≥110 mg/dL	>95th percentile	≥150 mg/dL
Glucose	Fasting ≥110 mg/dL	Impaired glucose tolerance	≥100 mg/dL

NHANES III National Health and Nutrition Examination Survey III, *ATP III* Adult Treatment Panel III, *IDF* International Diabetes Federation for ages 10–16
[a]Ethnic-specific waist circumference [103]

Metabolic Syndrome

Studies estimate that approximately 10 % of adolescents have metabolic syndrome [62–64]. The prevalence increases as the severity of obesity increases among adolescents. The adult criteria for metabolic syndrome were outlined previously in this chapter. Presently it is debated if adolescents should be diagnosed by the same adult criteria given that several physiologic pubertal changes mirror the changes in metabolic syndrome. Some suggested diagnostic criteria are listed in Table 3.3. As a consequence of this diagnostic quandary, it is difficult to compare pediatric studies of metabolic syndrome. Thus, the long-term consequence of metabolic syndrome in children and adolescents remains unclear.

Impaired Glucose Tolerance and Type II Diabetes Mellitus

Impaired glucose tolerance is a frequent sequelae of childhood and adolescent obesity. The prevalence ranges from 7 to 25 % in obese adolescents and children [65–67]. It can present independently or as a component of PCOS or metabolic syndrome. Moreover, impaired glucose can suggest an increased risk of developing type II diabetes mellitus.

Type II diabetes mellitus (T2DM) is an "adult disease" that is often seen in obese children and adolescents. The prevalence is approximately 4 % in obese adolescents and children [65]. The development of T2DM in childhood is not without added risk. Individuals who develop T2DM in childhood or adolescents are noted to have more rapid progression of diabetes-associated complications [68].

Hyperinsulinemia can be the initial defect prior to impaired glucose tolerance as well as type II diabetes mellitus. Obesity increases the risk of insulin resistance and thus hyperinsulinemia. Hyperinsulinemia can have multiple effects on the female reproductive system primarily by potentiating or initiating hyperandrogenemia [69]. Hyperinsulinemia is known to impact ovarian and adrenal function to increase androgens. It can also lower sex hormone binding globulin leading to increased amounts of free bioavailable testosterone. These factors can lead to PCOS or a PCOS-like phenotype.

Psychosocial

There are several psychosocial repercussions to childhood and adolescent obesity. The most punitive is discrimination from peers in the form of bias and bullying [70, 71]. Girls have more lasting effects from these experiences than boys. Adolescent girls exposed to such behaviors are more likely to have negative self-images during adulthood [70, 71]. Additionally, obese adolescent females are noted to complete fewer years of advanced education, decreased incomes, lower marriage rates, and higher poverty rates compared to nonobese counterparts in adulthood [72, 73].

Other Systemic Abnormalities

As previously mentioned, childhood and adolescent obesity is associated with abnormalities in a multitude of organ systems. Here we touch on other systems for completeness. Cardiovascular risks in obese children include hypertension and dyslipidemia, previously noted as components of metabolic syndrome, as well as abnormal cardiac structure and function and adult coronary artery disease. Hypertension is by far the most common comorbidity associated with obesity. Pulmonary issues include obstructive sleep apnea (OSA) and obesity hyperventilation syndrome. It should be noted that PCOS and obesity are independent risk factors for OSA, thus providers should prudently screen obese girls with PCOS for OSA. Gastrointestinal problems include nonalcoholic fatty liver disease (NAFLD), the most common cause of liver disease in children, and cholestasis [71, 74]. Orthopedic concerns consist of slipped capital femoral epiphysis, tibia vara, fractures, and musculoskeletal pain. Dermatologic comorbidities include hidradenitis suppurativa, intertrigo, and furunculosis. Lastly, neurologically obese children are at risk for idiopathic intracranial hypertension.

Management

Medical Management

Lifestyle changes, eating a healthy diet and regular exercise, are of the utmost importance when managing childhood and adolescent obesity. This category merits clinicians' well-spent time. The key principles are decreasing caloric intake, avoiding fad diet, and increasing the level of exercise. Ideally support and encouragement emanates from parent or guardian; this includes three meals a day that are well designed with regard to protein, carbohydrate, and fat content. Avoiding excessive amounts of sugars and fatty foods, limiting sugar-sweetened beverages, skim milk in place of whole milk are to be suggested. Excellent diets such as Weight Watchers® have proven to be successful long term.

Medications need to be carefully selected in teens and young adult females as the bottom line remains, "life style modification". Medications are listed in Table 3.4. Increased satiety and appetite suppression result from this medical treatment [75].

Surgical Management

Bariatric surgery is indicated in the teen and young adult when morbidity is of paramount importance and medical options have been unsuccessful. This is reserved for "life-threatening comorbidities" in this age group. Specifics include:

- Greater than 6 months of failed conservative, including medical approaches
- BMI > 40 kg/m^2 with major life-threatening comorbidities or BMI > 50 kg/m^2

Table 3.4 Weight loss medications

Medication	Approval for	Mechanism	Side effects
Metformin[a]	≥10 year of age	Protein kinase AMP activator. Lowers serum glucose and facilitates insulin utilization	GI: flatus and diarrhea
Orlistat[b]	≥12 years of age	Inhibits pancreatic lipase Alters lipid absorption	GI: intestinal cramps, flatus, and fecal incontinence
Sympathomimetic drugs[c]:		Stimulates norepinephrine or inhibit its reuptake Causes early satiety	May increase blood pressure
Benzphetamine	≥12 years of age		
Phentermine	>16 years of age		
Diethylpropion	>16 years of age		
Phendimetrazine	≥17 years of age		

GI gastrointestinal

[a]Metformin is not approved for weight loss and using it for weight loss is an off-label use

[b]Orlistat: Only long-term medication approved in United States for weight loss in adolescents

[c]Only approved for short-term use up to 12 weeks

Presurgical medical and psychological testing is recommended. Supportive family remains critical to success of surgical intervention.

Surgical options include roux-en-Y gastric bypass which has been among the surgical armamentarium since the 1960s. The procedure has been replaced by minimally invasive approaches such as adjustable gastric banding.

Persistence into Adulthood

Childhood and adolescent obesity is a major problem. It is a problem that affects multiple race and ethnicities in the United States as well as around the world. Current prediction models estimate that approximately 25 % of children less than 16-year-old will be obese by 2050 [76]. Childhood obesity leads to adult obesity with all its intrinsic problems. The Minneapolis Children's Blood Pressure Study reported that the highest risk for hyperinsulinemia, hypertension, and hyperlipidemia occurred when BMI over a period of 16 years was elevated [77]. With the current trend 50 % of women will be obese by 2050 [78].

There are numerous influences that contribute to which obese children and adolescents will become obese adults. Studies indicate that age of onset, severity, and parental obesity are major determinants [79–86].

Studies from the 1980s and 1990s indicated the obese adolescents are more likely to become obese adults compared to obese children. These studies indicate that approximately 80 % of obese adolescents aged 10- to 14-year olds, 50 % of obese 6-year-olds, and 25 % of obese preschool children will become obese adults [82, 87]. However, given the new environmental factors associated with obesity presented earlier in this chapter, primarily increased television viewing, these data may not be the same for today's youth. We may be seeing a generation where more obese children are becoming obese adults.

It is evident that severity of obesity in adolescents is a predictor of obesity in adulthood. In a study of over 8,000 adolescents 75 % of severely obese adolescents became severely obese adults while the same was true in only 8 % of obese adolescents [88].

It is not clear if gender is a determining factor as the available literature is mixed [89–93].

Prevention

Preventing childhood obesity should be a primary concern for all pediatric healthcare providers. Healthcare providers should routinely assess BMI and initiate a discussion of BMI with children and their families. Providers should assess and educate all children and their families on behaviors that put children at risk for obesity i.e., television viewing and sugar-sweetened beverages. Early intervention is crucial. When a

child is at risk, providers must address these concerns with the child and her family, provide obesity prevention education, thoroughly assess the child's dietary intake and physical activity, and suggest healthy nutritional and physical activity alternatives. In those children who continue to be at risk, providers should consider referral to a weight loss specialist. It is important that all providers who address childhood weight disturbances and their comorbidities do so in a supportive environment that focuses on the entire family rather than the child alone to yield the greatest benefit.

References

1. Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. J Pediatr. 2007;150(1):12–7. 1.
2. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA. 2006;295(13):1549–55.
3. Flynn MA. Fear of fatness and adolescent girls: implications for obesity prevention. Proc Nutr Soc. 1997;56(1B):305–17.
4. Deurenberg P, Weststrate JA, Seidell JC. Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. Br J Nutr. 1991;65(2):105–14.
5. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA. 2012;307(5):483–90.
6. Ogden CL, Carroll MD. Prevalence of obesity among children and adolescents: United States, trends 1963-1965 through 2007-2008: Centers for Disease Control and Prevention/ National Center for Health Statistics; 2014 [updated]. 2010. http://www.cdc.gov/nchs/data/hestat/obesity_child_07_08/obesity_child_07_08.htm.
7. Centers for Disease Control and Prevention. Update: prevalence of overweight among children, adolescents, and adults—United States, 1988-1994. MMWR Morb Mortal Wkly Rep. 1997;46(9):198–202.
8. Ogden CL, Lamb MM, Carroll MD, Flegal KM. Obesity and socioeconomic status in children and adolescents: United States, 2005-2008. NCHS Data Brief. 2005;2010(51):1–8.
9. Anderson SE, Whitaker RC. Household routines and obesity in US preschool-aged children. Pediatrics. 2010;125(3):420–8.
10. Plachta-Danielzik S, Kehden B, Landsberg B, Schaffrath Rosario A, Kurth BM, Arnold C, et al. Attributable risks for childhood overweight: evidence for limited effectiveness of prevention. Pediatrics. 2012;130(4):e865–71.
11. Taber DR, Chriqui JF, Powell L, Chaloupka FJ. Association between state laws governing school meal nutrition content and student weight status: implications for new USDA school meal standards. JAMA Pediatr. 2013;167(6):513–9.
12. Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. Am J Clin Nutr. 2013;98(4): 1084–102.
13. Berkey CS, Rockett HR, Gillman MW, Colditz GA. One-year changes in activity and in inactivity among 10- to 15-year-old boys and girls: relationship to change in body mass index. Pediatrics. 2003;111(4 Pt 1):836–43.
14. Blair NJ, Thompson JM, Black PN, Becroft DM, Clark PM, Han DY, et al. Risk factors for obesity in 7-year-old European children: the Auckland Birthweight Collaborative Study. Arch Dis Child. 2007;92(10):866–71.
15. Braithwaite I, Stewart AW, Hancox RJ, Beasley R, Murphy R, Mitchell EA, et al. The worldwide association between television viewing and obesity in children and adolescents: cross sectional study. PLoS One. 2013;8(9):e74263.

16. Dietz Jr WH, Gortmaker SL. Do we fatten our children at the television set? Obesity and television viewing in children and adolescents. Pediatrics. 1985;75(5):807–12.
17. Falbe J, Rosner B, Willett WC, Sonneville KR, Hu FB, Field AE. Adiposity and different types of screen time. Pediatrics. 2013;132(6):e1497–505.
18. Gortmaker SL, Must A, Sobol AM, Peterson K, Colditz GA, Dietz WH. Television viewing as a cause of increasing obesity among children in the United States, 1986-1990. Arch Pediatr Adolesc Med. 1996;150(4):356–62.
19. Kaur H, Choi WS, Mayo MS, Harris KJ. Duration of television watching is associated with increased body mass index. J Pediatr. 2003;143(4):506–11.
20. Bouchard C. Genetic determinants of regional fat distribution. Hum Reprod. 1997;12 Suppl 1:1–5.
21. Contreras C, Novelle MG, Leis R, Dieguez C, Skrede S, Lopez M. Effects of neonatal programming on hypothalamic mechanisms controlling energy balance. Horm Metab Res. 2013;45(13):935–44.
22. Fall CH. Fetal programming and the risk of noncommunicable disease. Indian J Pediatr. 2013;80 Suppl 1:S13–20.
23. Durnwald C, Landon M. Fetal links to chronic disease: the role of gestational diabetes mellitus. Am J Perinatol. 2013;30(5):343–6.
24. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992;35(7):595–601.
25. Hales CN, Barker DJ. The thrifty phenotype hypothesis. Br Med Bull. 2001;60:5–20.
26. Plagemann A. Perinatal nutrition and hormone-dependent programming of food intake. Horm Res. 2006;65 Suppl 3:83–9.
27. Plagemann A, Heidrich I, Gotz F, Rohde W, Dorner G. Obesity and enhanced diabetes and cardiovascular risk in adult rats due to early postnatal overfeeding. Exp Clin Endocrinol. 1992;99(3):154–8.
28. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev. 2005;85(2):571–633.
29. Ozanne SE, Hales CN. Lifespan: catch-up growth and obesity in male mice. Nature. 2004;427(6973):411–2.
30. Lopez M, Seoane LM, Tovar S, Garcia MC, Nogueiras R, Dieguez C, et al. A possible role of neuropeptide Y, agouti-related protein and leptin receptor isoforms in hypothalamic programming by perinatal feeding in the rat. Diabetologia. 2005;48(1):140–8.
31. Lopez M, Tovar S, Vazquez MJ, Nogueiras R, Seoane LM, Garcia M, et al. Perinatal overfeeding in rats results in increased levels of plasma leptin but unchanged cerebrospinal leptin in adulthood. Int J Obes (Lond). 2007;31(2):371–7.
32. Barker DJ. Fetal and infant origins of adult disease. London: BMJ; 1992.
33. Roseboom TJ, van der Meulen JH, Ravelli AC, Osmond C, Barker DJ, Bleker OP. Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. Mol Cell Endocrinol. 2001;185(1–2):93–8.
34. Barker DJ. Mothers, babies and health in later life. London: Churchill Livingstone; 1998.
35. Fall CH. Fetal and maternal nutrition. In: Stanner S, editor. Cardiovascular disease: diet, nutrition and emerging risk factors. The Report of the British Nutrition Foundation Task Force. Oxford: Blackwell; 2005. p. 177–95.
36. McCance RA. Food, growth, and time. Lancet. 1962;2(7258):671–6.
37. Gardner DS, Jackson AA, Langley-Evans SC. The effect of prenatal diet and glucocorticoids on growth and systolic blood pressure in the rat. Proc Nutr Soc. 1998;57(2):235–40.
38. Warner MJ, Ozanne SE. Mechanisms involved in the developmental programming of adulthood disease. Biochem J. 2010;427(3):333–47.
39. Vickers MH, Krechowec SO, Breier BH. Is later obesity programmed in utero? Curr Drug Targets. 2007;8(8):923–34.
40. De Silva NK, Helmrath MA, Klish WJ. Obesity in the adolescent female. J Pediatr Adolesc Gynecol. 2007;20(3):207–13.

41. Must A, Phillips SM, Naumova EN. Occurrence and timing of childhood overweight and mortality: findings from the Third Harvard Growth Study. J Pediatr. 2012;160(5):743–50.
42. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics. 2002;110(5):903–10.
43. Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics. 2001;108(2): 347–53.
44. Laron Z. Is obesity associated with early sexual maturation? Pediatrics. 2004;113(1 Pt 1):171–2; author reply 2.
45. Garn SM, Clark DC. Nutrition, growth, development, and maturation: findings from the ten-state nutrition survey of 1968–1970. Pediatrics. 1975;56(2):306–19.
46. Biro FM, Khoury P, Morrison JA. Influence of obesity on timing of puberty. Int J Androl. 2006;29(1):272–7; discussion 86-90.
47. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, et al. Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab. 2004;89(2):453–62.
48. Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab. 2006;91(1):2–6.
49. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. 2004;89(6):2745–9.
50. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010;203(3):201e1–5.
51. Apter D, Vihko R. Serum pregnenolone, progesterone, 17-hydroxyprogesterone, testosterone and 5 alpha-dihydrotestosterone during female puberty. J Clin Endocrinol Metab. 1977; 45(5):1039–48.
52. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The androgen excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456–88.
53. Suikkari AM, MacLachlan V, Montalto J, Calderon I, Healy DL, McLachlan RI. Ultrasonographic appearance of polycystic ovaries is associated with exaggerated ovarian androgen and oestradiol responses to gonadotrophin-releasing hormone agonist in women undergoing assisted reproduction treatment. Hum Reprod. 1995;10(3):513–9.
54. Southam AL, Richart RM. The prognosis for adolescents with menstrual abnormalities. Am J Obstet Gynecol. 1966;94(5):637–45.
55. van Hooff MH, Voorhorst FJ, Kaptein MB, Hirasing RA, Koppenaal C, Schoemaker J. Polycystic ovaries in adolescents and the relationship with menstrual cycle patterns, luteinizing hormone, androgens, and insulin. Fertil Steril. 2000;74(1):49–58.
56. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Burggraaff JM, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod. 2008;23(2):324–8.
57. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. Hum Reprod. 2007;22(2):414–20.
58. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI, Olsen J. Subfecundity in overweight and obese couples. Hum Reprod. 2007;22(6):1634–7.
59. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol. 1992;167(5):1317–25.
60. Pellerin GP, Finan MA. Endometrial cancer in women 45 years of age or younger: a clinicopathological analysis. Am J Obstet Gynecol. 2005;193(5):1640–4.
61. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569–78.

62. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350(23):2362–74.
63. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. Arch Pediatr Adolesc Med. 2003;157(8):821–7.
64. Lambert M, Paradis G, O'Loughlin J, Delvin EE, Hanley JA, Levy E. Insulin resistance syndrome in a representative sample of children and adolescents from Quebec, Canada. Int J Obes Relat Metab Disord. 2004;28(7):833–41.
65. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med. 2002;346(11):802–10.
66. Shalitin S, Abrahami M, Lilos P, Phillip M. Insulin resistance and impaired glucose tolerance in obese children and adolescents referred to a tertiary-care center in Israel. Int J Obes (Lond). 2005;29(6):571–8.
67. Maffeis C, Pinelli L, Brambilla P, Banzato C, Valzolgher L, Ulmi D, et al. Fasting plasma glucose (FPG) and the risk of impaired glucose tolerance in obese children and adolescents. Obesity. 2010;18(7):1437–42.
68. Copeland KC, Zeitler P, Geffner M, Guandalini C, Higgins J, Hirst K, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab. 2011;96(1):159–67.
69. Kase N. The polycystic ovary syndrome—challenges and opportunities in adolescent medicine. In: Altchek A, Deligdisch L, editors. Pediatric, adolescent, & young adult gynecology. Oxford: Blackwell; 2009. p. 316–39.
70. Stunkard A, Burt V. Obesity and the body image. II. Age at onset of disturbances in the body image. Am J Psychiatry. 1967;123(11):1443–7.
71. Huang JS, Barlow SE, Quiros-Tejeira RE, Scheimann A, Skelton J, Suskind D, et al. Childhood obesity for pediatric gastroenterologists. J Pediatr Gastroenterol Nutr. 2013; 56(1):99–109.
72. Sargent JD, Blanchflower DG. Obesity and stature in adolescence and earnings in young adulthood. Analysis of a British birth cohort. Arch Pediatr Adolesc Med. 1994;148(7): 681–7.
73. Gortmaker SL, Must A, Perrin JM, Sobol AM, Dietz WH. Social and economic consequences of overweight in adolescence and young adulthood. N Engl J Med. 1993;329(14):1008–12.
74. Lavine JE, Schwimmer JB. Nonalcoholic fatty liver disease in the pediatric population. Clin Liver Dis. 2004;8(3):549–58. 3.
75. Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013;128(15):1689–712.
76. Lanigan J, Barber S, Singhal A. Prevention of obesity in preschool children. Proc Nutr Soc. 2010;69(2):204–10.
77. Sinaiko AR, Donahue RP, Jacobs Jr DR, Prineas RJ. Relation of weight and rate of increase in weight during childhood and adolescence to body size, blood pressure, fasting insulin, and lipids in young adults. The Minneapolis Children's Blood Pressure Study. Circulation. 1999;99(11):1471–6.
78. Dent E. Obesity management. The fat of the land. Health Serv J. 2009;119(6149):18–20.
79. Guo SS, Roche AF, Chumlea WC, Gardner JD, Siervogel RM. The predictive value of childhood body mass index values for overweight at age 35 y. Am J Clin Nutr. 1994;59(4): 810–9.
80. Power C, Lake JK, Cole TJ. Body mass index and height from childhood to adulthood in the 1958 British born cohort. Am J Clin Nutr. 1997;66(5):1094–101.
81. Parsons TJ, Power C, Logan S, Summerbell CD. Childhood predictors of adult obesity: a systematic review. Int J Obes Relat Metab Disord. 1999;23 Suppl 8:S1–107.
82. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med. 1997;337(13):869–73.

83. Reilly JJ, Methven E, McDowell ZC, Hacking B, Alexander D, Stewart L, et al. Health consequences of obesity. Arch Dis Child. 2003;88(9):748–52.
84. Rudolf M. Predicting babies' risk of obesity. Arch Dis Child. 2011;96(11):995–7.
85. Whitlock EP, Williams SB, Gold R, Smith PR, Shipman SA. Screening and interventions for childhood overweight: a summary of evidence for the US Preventive Services Task Force. Pediatrics. 2005;116(1):e125–44.
86. Power C, Lake JK, Cole TJ. Measurement and long-term health risks of child and adolescent fatness. Int J Obes Relat Metab Disord. 1997;21(7):507–26.
87. Garn SM, LaVelle M. Two-decade follow-up of fatness in early childhood. Am J Dis Child. 1985;139(2):181–5.
88. The NS, Suchindran C, North KE, Popkin BM, Gordon-Larsen P. Association of adolescent obesity with risk of severe obesity in adulthood. JAMA. 2010;304(18):2042–7.
89. Garn SM, Cole PE. Do the obese remain obese and the lean remain lean? Am J Public Health. 1980;70(4):351–3.
90. Mellits ED, Cheek DB. The assessment of body water and fatness from infancy to adulthood. Monogr Soc Res Child Dev. 1970;35(7):12–26.
91. Deshmukh-Taskar P, Nicklas TA, Morales M, Yang SJ, Zakeri I, Berenson GS. Tracking of overweight status from childhood to young adulthood: the Bogalusa Heart Study. Eur J Clin Nutr. 2006;60(1):48–57.
92. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. Int J Pediatr Obes. 2009;4(4):281–8.
93. Patton GC, Coffey C, Carlin JB, Sawyer SM, Williams J, Olsson CA, et al. Overweight and obesity between adolescence and young adulthood: a 10-year prospective cohort study. J Adolesc Health. 2011;48(3):275–80.
94. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—The evidence report. National Institutes of Health. Obes Res. 1998;6(Suppl 2): 51–209S.
95. Barlow SE, Expert C. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120 Suppl 4:S164–92.
96. Wang Y. Cross-national comparison of childhood obesity: the epidemic and the relationship between obesity and socioeconomic status. Int J Epidemiol. 2001;30(5):1129–36.
97. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157–63.
98. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series. 2000;894:i-xii, 1–253.
99. Rotterdam EA-SPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19–25.
100. Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, editors. Polycystic ovary syndrome. Boston: Blackwell; 1992. p. 377–84.
101. Chi CH, Wang Y, Wilson DM, Robinson TN. Definition of metabolic syndrome in preadolescent girls. J Pediatr. 2006;148(6):788–92.
102. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents. Lancet. 2007;369(9579):2059–61.
103. Fernandez JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr. 2004;145(4):439–44.

Chapter 4
Nutrition in Human Fertility

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Identifying the extent to which modifiable lifestyle factors influence human fertility is of major clinical and public health significance. It is estimated that more than five million children have been born worldwide as a result of assisted reproduction [1]. In 2010 alone, there were nearly 150,000 assisted reproduction cycles resulting in more than 47,000 deliveries and the birth of 61,564 children in the United States [2]. These impressive figures notwithstanding, the number of subfertile couples benefiting from these therapies represents approximately one tenth of those estimated to meet the clinical definition of infertility and about 2 % of women estimated to be unable to get pregnant or carry a pregnancy to term nationwide [3]. This vast gap alone highlights the need to identify strategies to address infertility that do not rely solely on clinical interventions and can be implemented on a population-wide level.

On the other hand, there is a critical need to further improve success rates of infertility treatments. While the proportion of live births per initiated assisted reproduction cycle in the United States improved gradually through the 1990s, it has remained steady, at about 30 %, for almost a decade (Fig. 4.1). Unfortunately, very few predictors of successful infertility treatment are known and the strongest and best-characterized risk factor for unsuccessful infertility treatment, age [4, 5], is not modifiable. Moreover, the proportion of women delaying childbearing into their 30s and beyond 35 years has increased dramatically in the United States and other Western nations [6]. These facts highlight the need to identify potentially modifiable factors associated with fertility treatment outcomes.

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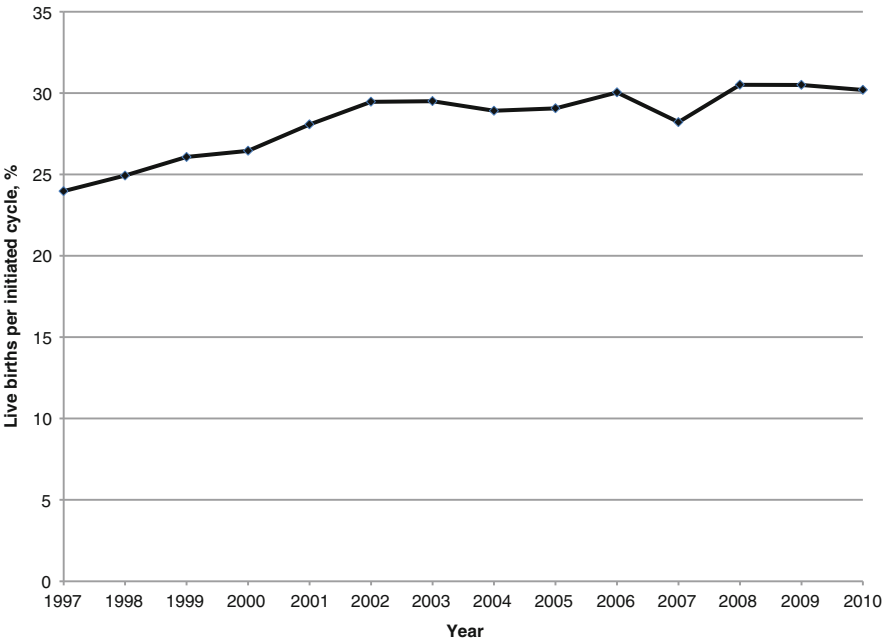

Fig. 4.1 Live birth rate per initiated assisted reproduction cycle, United States 1997–2010. Only data from fresh, nondonor cycles is included. Data obtained from the Centers for Disease Control and Prevention, Assisted Reproductive Technology Reports and Resources. Available at http://www.cdc.gov/art/artreports.htm (accessed August 6, 2013)

Emerging evidence further suggests that diet, a potentially modifiable factor, could have a major impact on human fertility independent of body weight. In this chapter we will review and summarize the current evidence linking diet to fertility in women and men, and to outcomes of infertility treatment.

Diet and Female Fertility

Interest in the role of diet on female fertility is longstanding. There are reports of animal models evaluating the effects of micronutrient deficiencies on ovulatory function as early as the 1960s [7] and prospective studies in humans evaluating the role of other dietary factors on fertility since the 1980s [8]. Most of the existing literature revolves around the potential role of two purported reproductive toxicants on fertility, caffeine, and alcohol, and is plagued with poor quality research. Recent findings, however, suggests that the role of diet on human fertility and on conditions associated with infertility may be much broader.

Diet as a Source of Purported Ovarian Toxicants: Caffeine, Alcohol, and Dairy

Most of the interest in evaluating the role of caffeine on reproductive performance in general and on fertility in particular can be traced back to a series of experiments in rodents which documented an increased frequency of fetal resorption and congenital malformations of the skeleton in rats receiving caffeine via oral intubation [9]. These experiments, however, have little relevance to human exposure given that the adverse effects of caffeine were only observed at doses equivalent to consuming 50–100 cups of coffee per day. In fact, experiments by the same and other research groups where caffeine was administered via drinking water and at exposure levels more relevant to humans failed to identify any reproductive hazards of caffeine [10, 11]. Physiologic mechanisms linking caffeine to female reproductive function are also unclear. Some evidence suggests that caffeine may inhibit ovulation or corpus luteum function [12–14] and caffeine has been associated with higher early follicular phase E2 levels [13, 15]. However, caffeine has not been associated with indicators of ovarian aging [16] and, on the other hand, it has been shown to improve insulin sensitivity [17, 18], which can result in improved ovulatory function in women with polycystic ovary syndrome [19] and possibly healthy women.

Nevertheless, the reputation of caffeine as a reproductive toxicant was reinforced by the findings of the first report on the relation between caffeine and fertility in humans. Wilcox and colleagues used data from a study aimed at identifying risk factors for early pregnancy loss to examine the relation between caffeine and time to pregnancy among pregnancy planners [8]. They found that consuming the equivalent of one cup of coffee per day resulted in a 50 % decrease in conception rate per cycle and that there was a dose response effect of caffeine consumption and fecundability. Although this study had major advantages, including its prospective design and its restriction to pregnancy planners, it was not originally aimed at assessing the effect of caffeine on fertility. Therefore, investigators did not assess caffeine intake in detail and failed to obtain data on potential confounding factors [8]. Furthermore, the study evaluated 104 women who did not conceive during their first 3 months of trying, but excluded 117 women who did conceive during that time period.

Since this report an additional 19 studies have evaluated the relation between caffeine and female fertility. While ten of these studies have found a relation between coffee or caffeine intake and decreased fertility [8, 12, 20–27], most of them are retrospective [12, 20–25, 27]. A problem with retrospective studies evaluating this relation is that, since caffeine is almost universally considered to be a risk factor for infertility in the general population and is endorsed as such in leading reproductive medicine textbooks [28], retrospectively assessing caffeine intake is all but guaranteed to result in differential recall of actual intake between fertile and subfertile women thus creating a spurious positive association between caffeine intake and fertility. In fact, detailed reviews of the literature regarding the reproductive effects of caffeine have shown that retrospective studies and studies of lower methodological quality are more likely to identify caffeine as a risk factor for

adverse reproductive outcomes, including infertility [29, 30]. When only the 8 prospective studies are considered, the majority [5] show no relation between caffeine and fertility [31–35] and one study even shows slightly higher fertility among caffeine consumers [36]. Only two prospective studies suggest a deleterious effect of caffeine on fertility [8, 37]. The largest and most recent of these prospective studies found no association between caffeine intake and risk of ovulatory infertility among 18,555 women followed over 8 years [34] and no relation with fecundability, the per-cycle probability of conception, among 3,628 women planning a pregnancy [33] (Fig. 4.2).

The relation between alcohol intake and fertility is equally cloudy. Alcohol has been found to induce a rise in estrogen resulting in decreased FSH secretion, impairing folliculogenesis and ovulation [13]. Animal studies indicate that alcohol may also have an acute effect at the level of the hypothalamus, inhibiting LH secretion and thus disturbing ovulation [38]. On the other hand, and like caffeine, alcohol intake has been linked to improved insulin sensitivity [39, 40] and is not linked to markers of ovarian aging [16]. As was the case in the caffeine literature, most of the 18 studies [27, 31, 34–37, 41–52] that have examined the association between alcohol intake and fertility in women have reported deleterious effects of alcohol. However, many of the methodological issues that plague the literature on caffeine and reproductive hazards also apply to the literature on alcohol, starting with study design issues; only seven of the studies conducted to date have been prospective [31, 34–37, 47, 48]. Among the prospective studies, three report decreased fertility with increasing alcohol intake [31, 37, 48], two report no association between alcohol and fertility [34, 36], one found decreased fertility with higher alcohol intake among women older than 30 years of age but a similarly strong association in the opposite direction among younger women [47], and one reported significantly decreased fertility among slow acetylators and no relation among rapid acetylators [35].

While a careful review of the existing literature on the relations of alcohol and caffeine with fertility does not provide compelling evidence that they significantly hamper fertility, the opposite belief is deeply ingrained in the general population and among healthcare providers. Despite much research, it is not possible to draw strong conclusions regarding the role of alcohol and caffeine on human fertility and further study is clearly needed. Because randomized trials of moderate caffeine or alcohol consumption in relation to fertility may be judged as unethical by many, large prospective observational studies of pregnancy planners, preferably in populations with different patterns of alcohol and caffeine use, are necessary to determine whether moderate consumption of these substances affects fertility.

Dairy foods are an additional dietary factor that has been considered as a potential reproductive toxicant. Lactose, the main carbohydrate in milk, is cleaved in the intestine into glucose and galactose. In animal experiments, rodents fed a high amounts of galactose have decreased ovulatory rates and develop premature ovarian failure (POF) [53, 54]. This observation led to the hypothesis that high intake of milk and dairy products may increase the risk of infertility due to ovulatory dysfunction

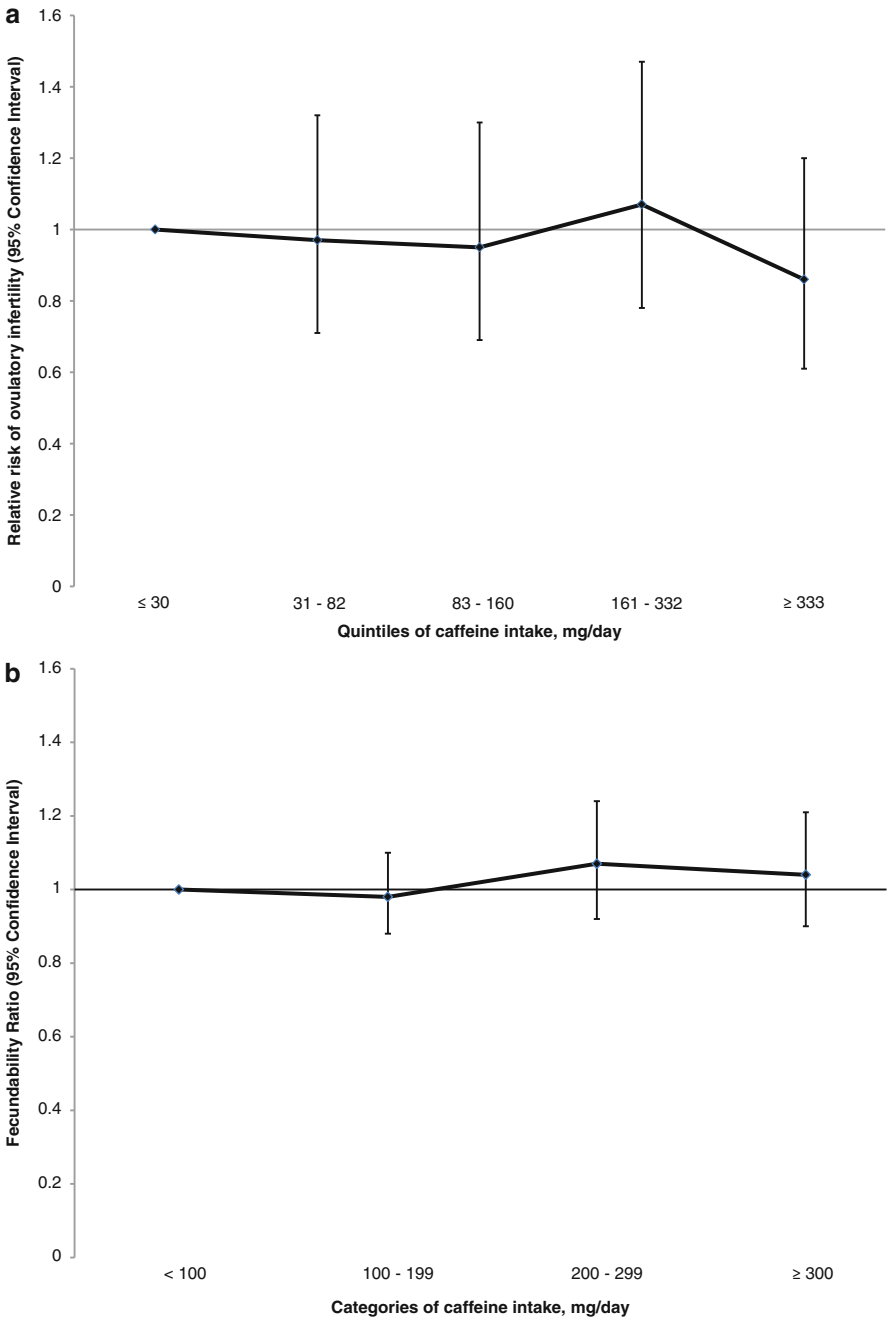

Fig. 4.2 Caffeine intake and fertility in women. (**a**) Caffeine and risk of ovulatory infertility among 18,555 participants in the Nurses' Health Study II [34]. Numbers greater than 1 indicate higher risk of infertility. (**b**) Caffeine intake and fecundability among 3,628 pregnancy planners in Denmark [33]. Numbers greater than 1 indicate greater probability of conceiving

in otherwise healthy women [55]. However, few studies have been conducted in humans [50, 55, 56] and their results are not consistent.

Cramer and colleagues found a positive correlation between per capita milk consumption and age-related decrease in fertility rates in 31 countries [55]. On the other hand, a case-control study following up on these findings [50] found that women who consumed three or more glasses of milk daily had a 70 % lower risk of infertility when compared to women who did not consume milk [50]. A subsequent prospective cohort study found no relation between total intake of dairy foods and risk of ovulatory infertility [56]. However, this study reported unexpected associations between intake of reduced fat dairy foods with higher risk of ovulatory infertility as well as an association between intake of full-fat dairy foods with lower risk of this condition [56]. A closer inspection of the animal models also suggests that diets with galactose contents that are closer to relevant intakes in humans do not result in POF or other signs of ovarian damage [57]. Collectively, these data suggest that galactose is unlikely to be an ovarian toxicant at the usual intake levels of humans. While the epidemiologic literature suggests that dairy foods may influence fertility, this literature is nascent and requires further replication.

Micronutrients and Female Fertility

Clues that micronutrients may influence human fertility have been hiding in plain sight for decades, as case reports and case series, in the literature [58–66]. Many, but not all [58, 59], of these reports are among women with celiac disease, a condition known to be associated with a higher frequency of infertility and micronutrient deficiencies, most commonly of iron, folic acid, vitamin B12, and vitamin D [66, 67]. A growing body of literature suggests these micronutrients may be important in female reproductive physiology and fertility.

The strongest evidence is for the role of folic acid and other nutrients involved in its metabolism. Folate-requiring reactions, collectively known as the one-carbon metabolism, encompass a series of related metabolic pathways where one-carbon moieties are transferred from donors to intermediate carriers and ultimately used in methylation reactions or as building blocks in the synthesis of DNA [68, 69]. This pathway has a greater relevance when folate requirements are heightened due to increased demand for DNA synthesis such as gametogenesis and early embryo development [70, 71]. As early as the 1960s, it was shown in the immature superovulated rat that either an excess or deficiency of folates partially inhibited ovulation [7]. In rhesus monkeys, folate restriction results in irregular menstrual cycles, progressive depletion of ovarian granulosa cells, and decreased preovulatory serum estradiol and mid-luteal progesterone [72]. In a prospective cohort study of healthy reproductive-age women who did not consume diet supplements, women in the highest tertile of folic acid intake (median intake 271 μg/day) had 16 % higher luteal progesterone levels and were nearly 70 % less likely to have anovulatory cycles than women in the lowest tertile of intake (median intake 101 μg/day) [73]. In a separate

prospective cohort study involving more than 18,000 participants, women in the top two quintiles of folic acid intake (median intakes 726 μg/day and 1,138 μg/day, respectively) were 40 % less likely to develop infertility due to anovulation than women in the lowest quintile of intake (median intake 243 μg/day) [74].

The effect of folic acid on ovulatory function may result from heightened ovarian responsiveness to FSH in high folate environments. In women undergoing controlled hyperstimulation with FSH, carriers of the T allele in position 677 of *MTHFR* (which leads to decreased enzyme activity and lower 5-methyltetrahydrofolate concentrations) have a decreased ovarian responsiveness to FSH, lower oocyte yield [75], and granulosa cells that produce less estradiol [76]. Similar effects have been found among carriers of the *MTHFR* A1298C variant [77]. In addition to its effect on ovulation, folic acid may further enhance fertility by improving embryo survival. In vitro studies of mouse preimplantation embryos show that endogenous folates are essential for embryo development due to its role in the synthesis of thymidine [71, 78]. Since thymidine does not accumulate in cells, accumulation of significant amounts of folates in the oocyte is required during gametogenesis to support the exponential increase in DNA synthesis that occurs during early embryo development [71, 78].

Iron status may also be important for ovulation and fertility as highlighted by studies regarding iron-transporting proteins in key ovarian cells. Transferrin (Tf) and its receptor (TfR) have been identified in granulosa cells and oocytes in several studies [79–81]. It has also been reported that granulosa cells can synthesize Tf which may be translocated to the oocytes [81]. Although it is possible that Tf and TfR are redundant in the ovary or do not play an important role in local iron metabolism, it has been suggested that these proteins are essential for ovum development and are required to support the increased iron demand of the developing follicle [80]. Additional evidence for a role of iron comes from studies documenting a higher risk of infertility among women with subclinical celiac disease. Undiagnosed celiac disease is more common among women with unexplained infertility than among fertile controls [66, 82]. Moreover, some of these infertile women have signs of iron deficiency including iron-deficiency anemia [66] and low ferritin levels without evidence of other nutrient deficiencies [82]. Intake of nonheme iron was more recently found to be related to lower risk of infertility due to anovulation in a large prospective cohort study [83]. Women in the highest quartile of nonheme iron intake (median intake 76 mg/day) had 40 % lower risk of infertility due to anovulation than women in the lowest quintile of intake (median intake 9.7 mg/day). Heme iron intake was unrelated to fertility [83].

The potential role of vitamin D on fertility has also received some recent attention. Physiologic and experimental data in animal models strongly suggest that vitamin D may play an important role in reproduction. Expression data shows that the vitamin D receptor (VDR) is present in the ovary [84, 85], the endometrium [84], and the placenta [86]. Vitamin D has also been found to stimulate the production of estradiol and progesterone in ovarian [85] and placental tissue [87], and to regulate the expression and secretion of hCG in human syncytiotrophoblasts [88] in vitro. Female rodents fed a vitamin D-deficient diet have reduced fertility [89, 90]. Knockouts for *VDR* and *1α-hydroxylase*, which catalyzes the hydroxylation of

25(OH)D into the biologically active $1,25(OH)_2D$, shed additional light into the role of vitamin D in reproduction. Female knockout mice have decreased fertility as a result of uterine hypoplasia, impaired follicular development, and anovulation [91–93]. Calcium supplementation partially reverses these reproductive effects in the knockout models [90, 94] and in the nutritional deficiency model [90], while vitamin D supplementation reverses them in the deficiency model [89], suggesting that there may be a combination of direct effects of vitamin D deficiency and effects mediated through secondary derangements in calcium and phosphorus homeostasis.

Human data on the role of vitamin D on fertility is less convincing. The three case-control studies that have evaluated vitamin D status in relation to PCOS provide mixed results. Li and colleagues found that vitamin D deficiency was nearly four times more common among 25 PCOS women than among 27 women with documented ovulation in Scotland [95]. This association was not adjusted for differences in BMI between these groups, however, and there were no statistically significant differences in PTH levels either [95]. Contrary to these results, Mahmoudi and colleagues found that 25(OH)D and PTH levels were significantly higher among 85 PCOS than among 115 ovulatory controls in Iran, independent of BMI [96]. A third study found no differences in the frequency of vitamin D deficiency between 93 PCOS and 71 controls in India [97]. Studies of vitamin D intake provide equally mixed results. Thys-Jacobs and colleagues supplemented 13 PCOS women with 50,000 IU of vitamin D weekly or biweekly plus 1,500 mg of Calcium daily for 6 months [98]. Regular menstrual cycles resumed in 7 of the 9 women with irregular menstrual cycles at baseline and two of them became pregnant [98]. Similarly, Wehr and colleagues supplemented 57 PCOS women with 20,000 IU of vitamin D weekly and found improvements in menstrual cyclicity in 30 % of women after 12 weeks of treatment and in 50 % of women after 24 weeks of treatment [99]. Nevertheless, a prospective study with more than 18,000 women found no evidence of a relation between vitamin D intake and risk of anovulatory infertility [56]. While vitamin D intake was strongly related to a lower risk of anovulatory infertility in age-adjusted analyses, this association disappeared upon adjustment for potential confounders, including BMI. A major limitation of this study, however, is that intake of vitamin D is a minor contributor to circulating levels of vitamin D [100]. In addition, vitamin D intake in the highest intake group (median intake = 783 IU/day) was substantially lower than in the single-arm trials suggesting a benefit of vitamin D supplementation. Therefore, lack of association with vitamin D intake in this study does not necessarily rule out an effect of vitamin D on anovulation-related infertility. Clearly, whether vitamin D plays a role on female fertility independent of its association with obesity remains an open question.

Diet as a Modifier of Insulin Sensitivity

Dietary factors may also influence fertility through their effects on insulin and glucose metabolism. Insulin resistance, hyperinsulinemia, and hyperglycemia may be critical in the development of PCOS as demonstrated by the effect of

insulin sensitizers and other antidiabetic medications on ovulatory function and fertility in these women [101–104]. These mechanisms may also influence ovulation and fertility among women with no clinical evidence of PCOS and those who do not meet all the diagnostic criteria [105–107]. For example, insulin resistance and postprandial hyperinsulinemia are more prevalent among oligomenorrheic non-PCOS infertile women than among eumenorrheic infertile women [105]. Likewise, diabetic women in the general population have lower fecundability than nondiabetic women [106]. Moreover, HbA1c levels within the nondiabetic range are inversely related to fecundability and positively related to characteristics of PCOS (free testosterone levels and cycle irregularity) among healthy pregnancy planners in the general population [107]. Since the quality and quantity of carbohydrates [108–111], the amount and sources of protein [112–115], and certain types of fat [116], are known to influence insulin sensitivity, it is possible that the macronutrient composition of diet could influence ovulatory function, and ultimately fertility.

The strongest evidence for this hypothesis to date comes from the Nurses' Health Study II, which used data from more than 18,000 women and nearly 27,000 pregnancies and failed pregnancy attempts. Analysis from this cohort of women revealed that a 2 % increase in energy intake from *trans*-fatty acids (approximately 4 g of *trans* fats) at the expense of carbohydrates was associated with a 73 % greater risk of ovulatory infertility after adjustment for potential confounders, and risk more than doubled when *trans* fats were consumed instead of monounsaturated fats [117]. The amount and source of protein were also related to ovulatory infertility in this study. Women in the highest fifth of total protein intake had 41 % higher risk of ovulatory infertility [118]. However, while protein from animal sources was associated to higher risk of infertility, protein from vegetable sources was associated with lower risk of infertility. Increasing protein intake by 5 % of calories (approximately 25 g of protein) was associated with a 19 % higher risk of ovulatory infertility when protein came from animal sources but a 43 % lower risk when protein came from vegetable sources [118]. Dietary glycemic load, a summary measure of the amount and quality of carbohydrates in the diet [119], was also positively related to a higher risk of ovulatory infertility. Women in the highest quintile of dietary glycemic load had 92 % higher risk of ovulatory infertility than women in the lowest quintile after adjustment for confounders [120].

This hypothesis is also consistent with findings from other studies among women with PCOS. Intake of high glycemic index foods was higher among 30 PCOS women than among 27 control women [121]. In addition, a small crossover feeding trial among 11 PCOS women [111] consuming a low carbohydrate diet (43 % vs. 56 % of energy) led to changes that would be expected to result in improved reproductive and metabolic outcomes including a reduction in free testosterone levels of borderline statistical significance [111]. The Nurses' Health Study II data appears to be at odds, however, with the findings of two small randomized trials comparing the reproductive effects of low protein (15 % of energy) vs. high protein (30 % of energy) weight loss diets among overweight PCOS women [122, 123]. The protein

content of diet had no effect on menstrual function or androgen levels in these studies, although there were some improvements in menstrual cyclicity [122] and reductions in circulating androgens [123] as a result of improved insulin sensitivity due to weight loss. However, since weight loss has such a dramatic effect on ovulatory function in PCOS women, it is not surprising that protein intake does not have a measurable effect on reproductive parameters within the context of significant weight loss.

Dietary Patterns and Fertility

Characterizing the global effect of multiple dietary factors as summarized by dietary patterns can provide a more realistic estimate of the effect that changing diet could have on fertility by taking into account the possible multiple interactions between individual foods and nutrients. The relation between dietary patterns and fertility has been examined in two prospective cohort studies to date (Fig. 4.3). In the Nurses' Health Study II, investigators generated a "fertility diet" score that ranked women according to their intake of eight dietary factors they had previously found to be independently associated to risk of ovulatory infertility [124]. The highest scores were assigned to women with high intakes of protein from vegetable sources, full-fat dairy foods, iron, the ratio of monounsaturated to *trans* fats and more frequent use of multivitamins; low intakes of protein from animal sources, dietary glycemic load, and low-fat dairy foods. This "fertility diet" score was strongly related to a lower risk of ovulatory infertility and infertility due to nonovulatory causes. Women in the highest quintile of the score had 66 % lower risk of ovulatory infertility and 27 % lower risk of infertility due to other causes than women in the lowest quintile of intake independently of age, parity, BMI, and other potential confounders [124]. Furthermore, the authors estimated that, assuming these relations were causal, 46 % of all infertility cases due to anovulation could be prevented by changes in diet composition alone [124].

Similar findings were reported among participants of the Seguimiento Universidad de Navarra (SUN) cohort, which follows university graduates in Spain. Higher adherence to a "Mediterranean pattern" diet, characterized by higher intakes of vegetables, fruit, fish, poultry, low-fat dairy, and olive oil, was associated with a lower risk of seeking medical help for difficulty getting pregnant [125]. Specifically, women in the highest quartile of intake of this dietary pattern had 44 % lower risk of difficulty getting pregnant than women in the lowest quartile. The findings of the two studies are generally consistent with each other, although full-fat and low-fat dairy foods were grouped into different risk profiles in the two studies. While these two studies strongly suggest that overall diet pattern have an impact on female fertility, further replication of these findings is warranted.

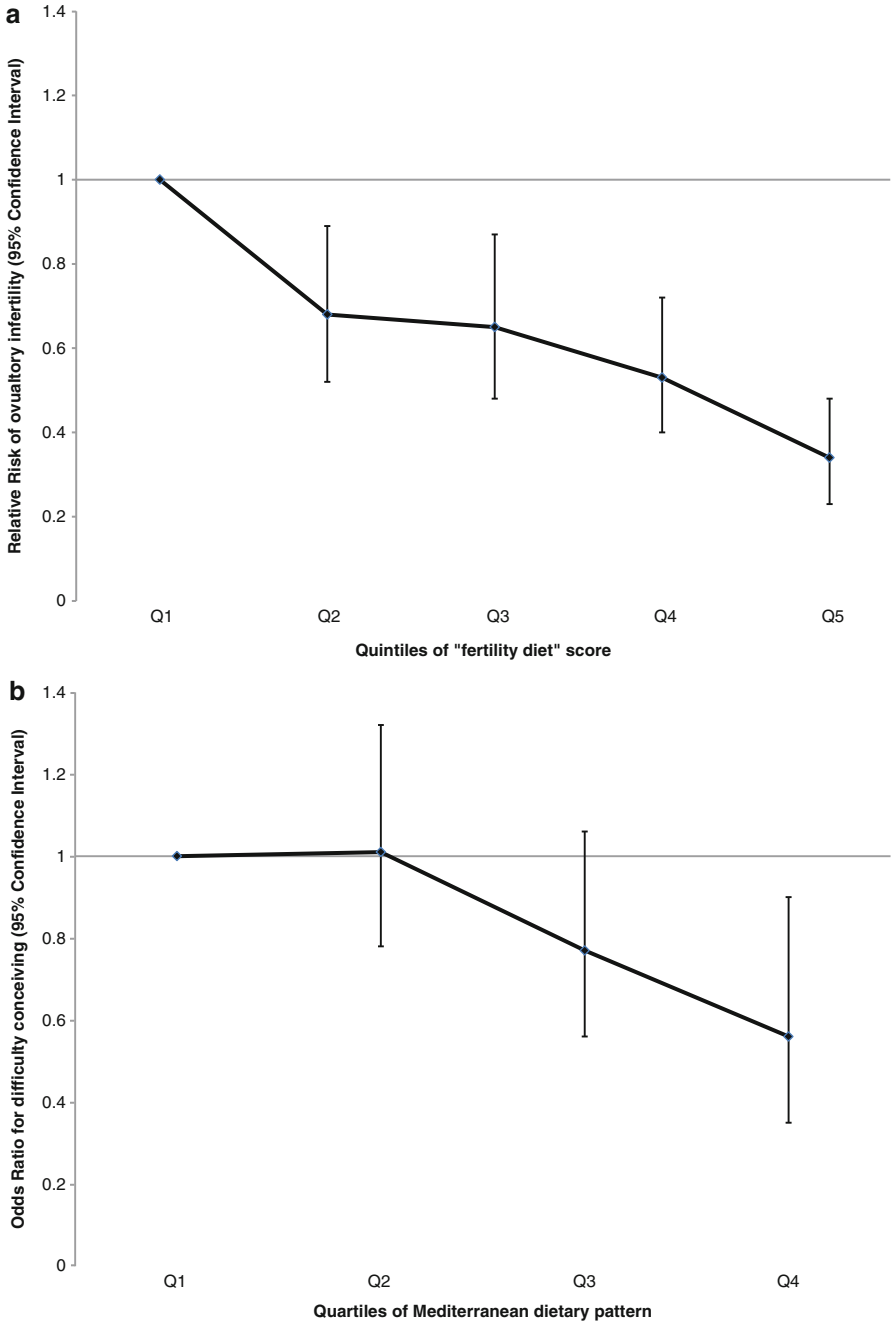

Fig. 4.3 Dietary patterns and fertility in women. (**a**) "Fertility diet" score and risk of ovulatory infertility [124] Numbers lower than 1 indicate lower risk of infertility. (**b**) Mediterranean dietary pattern and odds of difficulty conceiving [125]. Numbers lower than 1 indicate lower odds of self-reported difficulty conceiving

Diet, Semen Quality, and Male Fertility

Although reproductive abnormalities in the male partner can be identified as many as 58 % of the couples evaluated for infertility [126], infertility research has primarily focused on female factors. Mounting evidence, however, suggests that men's diets may have a nontrivial contribution to a couple's fertility. Most of the literature is based on studies examining the relation between diet and semen quality parameters which, although far from perfect proxies for fertility [127–130], shed light into the role nutrition has on male reproductive function. Most of the current evidence for a role of diet on fertility falls into one of four areas: dietary factors as purported reproductive toxicants, dietary factors that may protect sperm against oxidative damage, dietary factors as vehicles for environmental estrogens and dietary factors affecting the availability of substrates necessary for spermatogenesis. There is also some recent evidence suggesting that vitamin D may also be important in spermatogenesis.

Diet as a Purported Reproductive Toxicant: Caffeine and Alcohol

Just as in females, caffeine and alcohol have been some of the most extensively studied aspects of diet as potential determinants of semen quality. Although some studies suggest that caffeine intake may be related to higher sperm motility [131, 132], there is extensive evidence that caffeine intake is not related to semen quality parameters. A 2011 meta-analysis that combined data from 1,256 men across multiple studies found no relation between caffeine intake with sperm concentration, motility or morphology [133]. Moreover, studies not included in the meta-analysis also find little evidence of a relation between caffeine and semen quality [14, 133–136], including a single-center study of 2,554 young men in Denmark [136], larger than all other studies combined. Given the limited predictive value of semen parameters on fertility [127, 137–139], data on the three studies relating male caffeine intake to time to pregnancy among pregnancy planners is particularly important. Jensen and colleagues found that the male partner's caffeine intake was associated with a lower probability of conception when they were also nonsmokers [26], but two similar studies found association between caffeine and fecundability [26, 36, 43].

While chronic alcoholism can severely affect the reproductive hormone axis and spermatogenesis [140], there is not strong evidence to suggest that moderate alcohol consumption affects semen quality or fertility. The previously mentioned meta-analysis [133], which included data from 6,465 men for the evaluation of the relation between alcohol and semen parameters, found that alcohol consumption was related to lower ejaculate volume but was not related to sperm concentration, total count, motility, or morphology [133]. Also, the majority of the studies assessing alcohol consumption in the male partner in relation to a couple's time to pregnancy

have not found evidence of a deleterious effect of alcohol [36, 43, 44, 141]. Moreover, when a negative effect of male alcohol consumption has been documented, it has been among heavy drinkers. A retrospective time to pregnancy study among 2,112 pregnant women in the United Kingdom found that heavy alcohol consumption by male partners (defined as >20 unit/week) was associated with a significant reduction in fecundity (twofold longer time to pregnancy), but moderate consumption was not associated with decreased fecundability compared to those who did not consume alcohol [27].

Antioxidants and Male Fertility

There is also an extensive literature on the role of antioxidants on male fertility. Unlike the literature on alcohol and caffeine, however, most of the literature is based on randomized trials [142–176]. A description of the trials conducted to date can be found in Table 4.1. A meta-analysis published in 2011, evaluated the effects of antioxidant supplementation in subfertile men on semen quality parameters and, importantly, on clinical pregnancy and live birth rates [177]. Based on data from three trials [145, 146, 148] which collectively included 214 couples, the meta-analysis found evidence of a statistically significant increase in live births comparing in couples where men were randomized to antioxidants vs. control [177]. Similarly, based on data from 15 trials [142, 146, 148, 151, 157–161, 164, 166, 167, 169, 171, 174] which collectively included 964 couples, the meta-analysis found evidence of a statistically significant higher pregnancy rate in couples were men were randomized to antioxidants [177]. The meta-analysis also found evidence of significant benefit of antioxidant supplementation on sperm motility after 6 months of treatment (10 trials, 963 men) but not after 3 months (10 trials, 514 men) or 9 months (3 trials, 332 men) of treatment, as well as an increase in sperm concentration after 6 months (6 trials, 825 men) and 9 months (3 trials, 332 men) of treatment but not after 3 months of treatment (7 trials, 320 men) [177].

While this meta-analysis of randomized trials presents evidence that appears solid at face value, there are still many gaps in elucidating the role of antioxidants in the management of the couple seeking fertility treatment as clearly signaled by the authors by rating the quality of the evidence from this meta-analysis as “very low” and qualifying the results as inconclusive [177]. Some of the problems with individual trials are summarized in Table 4.1. There are additional problems with the meta-analysis that are worth considering. First, the definition of an antioxidant was extremely broad which led to the inclusion of trials of nutrients that are not antioxidants [178, 179] or that could influence male reproductive function through other mechanisms completely unrelated to preventing oxidative damage such as by influencing sperm DNA production [155], as discussed below. Second, very few trials examined a single antioxidant and the antioxidant doses varied greatly across studies. In fact, there were no two trials that compared the exact same intervention among all the trials included in the meta-analysis [177]. In other words, although

Table 4.1 Trials of antioxidant supplementation in men in relation to semen quality and fertility

Study	*N*, subject characteristics	Intervention	Control	Intervention Effect	Comments and concerns	Control
				Semen parameters	Clinical outcomes	
Wang 1983 [142]	46 idiopathic oligospermic men	Pentoxifylline (1,200 mg/day) for 6 months	Placebo	No effect	No effect	Blinding and randomization methods are not clear
Micic et al., 1988 [143]	90 idiopathic oligoasthenospermic men	1,200 mg Pentoxifylline for 3 months	No treatment	Increased sperm motility and morphology	Not reported	Blinding and randomization methods are not clear
Dawson et al., 1990 [144]	20 men with sperm agglutination >25 % and negative sperm antibodies	*Group 1*: 200 mg vitamin C *Group 2*: 1,000 mg vitamin C For 3 weeks	Placebo	Increased motility and morphology in treatment groups compared to baseline. Men in 1,000 mg group had higher increase in motility than 200 mg group	Not reported	Short intervention time
Kessopoulou et al., 1995 [145]	60 infertile men crossed over after 3 months of treatment and 1 washout per month	600 mg Vitamin E for 3 months	Placebo	Increased sperm concentration	Higher but not significant live birth rate	Pharmaceutical company-performed randomization
Suleiman et al., 1996 [146]	110 subfertile men	100 mg of Vitamin E, tid for 6 months	Placebo	Increased motility	21 % of spouses of men with improved motility became pregnant. No pregnancies in placebo arm	Only data on 52 men in the intervention arm and 35 men in the placebo arm were presented

Merino et al., 1997 [147]	47 idiopathic asthenozoospermic men	Pentoxifylline 1200 mg—400 mg/3 × day for 6 months	Placebo	Increased motility	Not evaluated	Blinding and randomization methods are not clear
Omu, et al., 1998 [148]	100 asthenozoospermic men	500 mg zinc sulfate for 3 months	Placebo	Increased sperm count, motility, sperm	Significant increase in pregnancy and live birth rates	Blinding methods are not clear
Scott et al., 1998 [149]	64 subfertile men	*Group 1*: Selenium 100 μg *Group 2*: Selenium 100 μg Vitamin A 1 mg, vitamin C 10 mg, vitamin E 15 mg QD for 3 months	Placebo	Increased sperm motility when data from groups 1 and 2 was considered together against placebo	5 pregnancies in intervention arms (11 %). No pregnancies on the placebo arm	Only data from men completing intervention is presented
Rolf, 1998 [150]	33 subfertile men with <50 % motile sperm and >7 × 10^6million sperm/mL	1,000 mg vitamin C 800 mg vitamin E QD for 8 weeks	Placebo	No effect	No effect	
Akiyama et al., 1999 [151]	10 infertile men	*Group 1*: 600 mg Ethylcysteine *Group 2*: 600 mg Vitamin E For 3 months	Crossover trial	No effect	Not evaluated	Intervention blinding not clearly described
Comhaire et al., 2000 [152]	33 infertile men	*Group 1*: 600 m Acetylcysteine g/day *Group 2*: 30 mg of βcarotene, 180 mg of alpha-tocopherol All patients received docosahexaenoic acid 1 g, 0.25 g of gammalinolenic acid, 0.10 g of arachidonic acid for 6 months	None	Increased sperm concentration among oligozoospermic men Decrease in sperm motility (grade A)	Overall pregnancy rate of 22.2 %. did not report pregnancy rate by treatment group	Outcomes are not presented by treatment group 82 % men completed the study

(continued)

Table 4.1 (continued)

Study	*N*, subject characteristics	Intervention	Control	Intervention Effect Semen parameters	Comments and concerns Clinical outcomes	Control
Nozha et al., 2001 [153]	22 oligoasthenoteratozoospermic men	*Group 1*: 400 mg Vitamin E, 200 µg selenium *Group 2*: 250 mg, vitamin B2, 250 mg vitamin B6, and 1 mg B12) For 3 months	No treatment	Increase in sperm motility in group 1	Not evaluated	Not clear how randomization or blinding was done
Wong et al., 2002 [154]	94 subfertile and 99 fertile men	*Group 1* (n=22): 5 mg folic acid *Group 2* (n=23): 66 mg zinc *Group 3* (n=24): 66 mg zinc and 5 mg folic acid for 26 weeks	Placebo	Zinc + folic acid increased concentration and morphology among subfertile men No effect among fertile men	Not evaluated	
Lombardo et al., 2002 [155]	100 oligoasthenospermic men	2 g L-carnitine	Placebo	Increased sperm concentration and motility	Not evaluated	Not clear why 14 men did not complete the trial. Funding source(s) not stated
Keskes-Ammar et al., 2003 [156]	54 subfertile men	225 µg Selenium 400 mg vitamin E BID 3 months	250 mg vitamin B1 250 mg vitamin B6 1 mg vitamin B12	Increased motility	Not evaluated	Treatment effects evaluated only among 20 men completing the trial

Zavaczki et al., 2003 [157]	20 subfertile men	3,000 mg Magnesium for 90 days	Placebo	No effect	One pregnancy reported in partner of treated men	Not clear how randomization was conducted
Lenzi et al., 2003 [158]	100 oligoasthenoteratozoospermic men	L-carnitine 2 g for 6 months	Placebo	Increased sperm concentration and motility	Increased pregnancy rate	Not clear how randomization was conducted
Lenzi et al., 2004 [159]	60 oligoasthenoteratozoospermic men	L-carnitine 2 g + L-acetyl-carnitine 1,000 mg for 6 months	Placebo	Increased sperm concentration, motility, and volume	Pregnancies in the treated but not control group	96 % of men completed the study (only men from placebo group withdrew)
Cavallini et al., 2004 [160]	325 infertile men	*Group 1*: L-carnitine 2 g, acetyl-L-carnitine 500×2 mg/day	Placebo	Increased sperm concentration, motility, and morphology	Increased pregnancy rate among both treated groups; higher among group 2	Only 40 % of men completed the study
		Group 2: L-carnitine 2 g, acetyl-L-carnitine 500×2 mg/day plus cinnoxicam suppository 1×30 mg (every 4 days) for 6 months		Greater increase in Group 2 than in group 1		Not clear how randomization was done
Balercia at al., 2005 [161]	60 idiopathic asthenozoospermic men	*Group 1*: L-carnitine 3 g	Placebo	Increased sperm motility among men treated with L-acetyl carnitine	Increased pregnancy rate	Not clear whether study was blinded to investigators
		Group 2: L-acetyl carnitine 3 g				
		Group 3: L-carnitine 2 g				
		1 g L-acetyl carnitine				
Greco et al., 2005 [162]	64 men with unexplained infertility with >15 % DNA fragmentation	1,000 mg Vitamin C	Placebo	No effect	*Not evaluated*	
		1,000 mg Vitamin E for 2 months				

(continued)

Table 4.1 (continued)

Study	*N*, subject characteristics	Intervention	Control	Intervention Effect Semen parameters	Comments and concerns Clinical outcomes	Control
Li et la., 2005 [163]	150 oligoasthenospermic men	L-carnitine 2 g, acetyl-L-carnitine 1 g for 3 months	100 mg vitamin E, 100 mg vitamin C for 3 months	Increased sperm motility and total motile sperm	Increased pregnancy rate	High dropout rate Methods of randomization not clear
Sigman et al., 2006 [164]	21 idiopathic asthenospermic men	2,000 mg L-carnitine 1,000 mg L-acetyl-carnitine	Placebo	No effect	No effect	
Tremellen et al., 2007 [165]	60 infertile men	6 mg Lycopene 400 IU Vitamin E 100 mg Vitamin C 25 mg Zinc 26 µgm Selenium 0.5 mg Folate	Placebo	Not reported	Increased pregnancy rate	Pregnancy only followed to 13 weeks
Omu et al., 2008 [166]	45 asthenozoospermic men with sperm concentration >20 million/mL	*Group 1* ($n=11$): 400 mg zinc sulfate *Group 2* ($n=12$): 400 mg zinc sulfate, 20 mg vitamin E *Group 3* ($n=14$): 400 mg zinc sulfate, 20 mg vitamin E, 10 mg vitamin C	No treatment	Increase in sperm motility No difference between treatment groups	Not evaluated	Not clear whether study was blinded to study participants or to investigators or whether there were dropouts

Menezo et al., 2007 [167]	58 men attending fertility clinics with either >15 % DNA fragmentation or >15 % sperm decondensation	400 mg vitamin C 400 mg vitamin E 500 µmol zinc 1 µmol selenium 18 mg β carotene for 3 months	No control	Decrease in sperm DNA fragmentation Conventional semen quality parameters not evaluated	Not evaluated	Study funding not stated
Galatioto et al., 2008 [168]	42 oligospermic men	Antioxidant combination[a]	No treatment	Increase in sperm count	No effect	Study funding not stated
Safarinejad et al., 2009a [169]	212 idiopathic oligoasthenoteratospermic men	300 mg coenzyme Q10 for 26 weeks	Placebo	Increased total sperm count, sperm concentration and motility	No effect	Study funding not stated
Safarinejad et al., 2009b [170]	468 idiopathic oligoasthenoteratospermic men	*Group 1*: 200 µg selenium *Group 2*: 600 mg *N*-acetyl-cysteine orally daily *Group 3*: 200 µg selenium, 600 mg *N*-acetyl-cysteine for 26 weeks	Placebo	Increased total sperm count, sperm motility, morphology, and volume in all three treated groups compared to baseline	Not evaluated	None
Balercia et al., 2009 [171]	60 infertile men	200 mg Coenzyme Q10	Placebo	Higher sperm motility	Increased pregnancy rate	
Cifti et al., 2009 [172]	120 men with idiopathic infertility	600 mg *N*-acetylcysteine	Placebo	Increased sperm volume and motility	Not evaluated	Not clear how randomization was done. No funding stated
Peivandi et al., 2010 [173]	30 infertile men crossed over after 8 weeks washout	2 g L-carnitine for 8 weeks	Placebo	Increased sperm concentration and motility	Increased pregnancy rate	Not clear how randomization was done

(continued)

Table 4.1 (continued)

Study	*N*, subject characteristics	Intervention	Control	Intervention Effect Semen parameters	Comments and concerns Clinical outcomes	Control
Moslemi et al., 2011 [174]	855 infertile men with idiopathic asthenoteratospermia	200 μg selenium 40 IU vitamin E for 100 days	None	21 % of men had ≥5 % improvement in motility and 3 % of men had ≥5 % improvement in morphology	11 % of spouses of men became pregnant	165 men dropped out
Safarinejad et al., 2012 [175]	228 men with unexplained infertility	200 mg ubiquinol for 26 weeks	Placebo	Increase in sperm concentration, motility, and morphology	Not evaluated	
Ghanem et al., 2012 [176]	228 men with idiopathic oligoasthenoteratozoospermia	25 mg clomiphene citrate and 400 mg vitamin E for 6 months	Placebo	Increase in sperm count and motility	Increased pregnancy rate	Study funding is not stated

[a]Antioxidant combination: NAC 10 mg/kg/die, Vit C 3 mg/kg/die, Vit E 0.2 mg/kg/die, Vit A 0.06 IU/kg/die, thiamine 0.4 mg/kg/die, riboXavin 0.1 mg/kg/die, piridoxin 0.2 mg/kg/die, nicotinamide 1 mg/kg/die, pantothenate 0.2 mg/kg/die, biotin 0.04 mg/kg/die, cyanocobalamin 0.1 mg/kg/die, ergocalciferol 8 IU/kg/die, calcium 1 mg/kg/die, magnesium 0.35 mg/kg/die, phosphate 0.45 mg/kg/die, iron 0.2 mg/kg/die, manganese 0.01 mg/kg/die, copper 0.02 mg/kg/die, zinc 0.01 mg/kg/die

pooled together in a single analysis, these were all trials of different interventions. Therefore it is very difficult to attribute the beneficial effects observed to any one nutrient or combination of nutrients and it is nearly impossible to identify the minimal doses of individual antioxidant nutrients that could be reasonably expected to have a clinical impact. Another major concern, particularly for trials reporting live birth or clinical pregnancy as the outcome, is that dropout rates were relatively high and tended to be higher in the control group raising concerns about differential reporting of hard clinical outcomes among controls.

Some of the gaps from the clinical trial literature can be filled by some observational studies addressing the role of antioxidants on semen quality. While few, they have documented dose–response relations between intakes of vitamins C, E, and carotenoids with higher sperm concentration and motility [180–182] or the risk of oligoasthenoteratospermia [183], suggesting that these nutrients may explain some of the beneficial effects observed in the trials. However, there is clearly much research needed to identify which antioxidants or combinations of antioxidants have positive effects on male fertility and at what doses.

Diet as a Vehicle for Environmental Estrogens

There is some concern that pro-estrogenic or anti-androgenic exposures, some of which may be delivered via diet, may affect spermatogenesis [184, 185]. Soy beans and soy-derived products are the main dietary source of isoflavones; plant-derived polyphenolic compounds with estrogenic activity. While generally considered to have a weak estrogenic activity [186–191], isoflavones can bind strongly to membrane estrogen receptors [192], exert nongenomic actions potentially deleterious to male fertility [193], and have been related to male reproductive disorders in mammals [194]. Human data on the relation between soy or isoflavones with male fertility is scarce and inconsistent. Mitchell and collaborators supplemented 14 young men with 40 mg/day of isoflavones for 2 months and found no appreciable changes in semen quality parameters or reproductive hormone levels compared to presupplementation levels [195]. Song and colleagues investigated the relation between isoflavone intake and semen quality in a group of 48 men with abnormal semen parameters and 10 men with normal semen parameters and found that isoflavone intake was positively related to sperm count and motility and inversely related to sperm DNA damage [196]. On the other hand, Chavarro and colleagues examined the relation between intake of soy and semen parameters among 99 male partners of couples seeking fertility treatment and found that higher intake of soy foods was associated with lower sperm concentration [197]. In agreement with these findings, a 2013 study of 609 idiopathic infertile men and 469 fertile controls in China by Xia and colleagues reported that urinary levels of isoflavones were related to lower sperm concentration, total count and motility, and higher odds of idiopathic male infertility [198]. This later study is important not only because it is larger than all the previous studies combined, but also

because it addresses one of the major arguments offered against a potentially deleterious role of soy on fertility: that Asian diets include high amounts of phytoestrogens from soy foods without any apparent deleterious effect on fertility. The data on this field is still developing and future work is needed, particularly focusing on the effects on fertility rather than semen quality, as well as further work among populations with high intake of soy.

Meat and dairy have also been hypothesized to be vehicles for environmental estrogens under modern dairy farming [199] and livestock production practices [200]. Specifically, because commercial milk is mostly obtained from pregnant cows [199, 201] there is concern that pregnancy hormones in milk [202, 203] could have reproductive effects in milk drinkers. Also, because anabolic sex steroids are administered to meat cattle for growth promotion in the United States and other countries [204] and residues are present in meat products [203], there is concern of reproductive consequences [200, 205] of meat consumption in places where this practice takes place.

Data on the relation between dairy and meat intake on semen quality is growing and suggests that these concerns may not be unfounded. Dairy food intake has been related to decreased secretion of LH, FSH, and testosterone [206]. In addition, intake of full-fat dairy foods has been related to lower sperm motility and morphology among healthy young men in the United States and to greater risk of oligoasthenoteratospermia among fertility patients in Spain [207, 208]. Also, a case-control study in Iran found a positive relation of borderline statistical significance between total dairy food intake and risk of asthenospermia [209]. A fourth study among fertility patients in the Netherlands, however, found no relation between dairy food intake and semen quality [210]. Data is equally split on the relation between meat intake and semen parameters. One study found meat intake to be related to lower semen quality among fertility patients in Spain [208], while another study among fertility patients in the Netherlands did not [210]. High beef consumption during pregnancy has been associated with lower sperm concentration among male offspring 30 years later [205]. It should be noted that the European Union banned the use of sex steroids for growth promotion in meat producing cattle in 1989 [204, 211] and therefore the association observed in the Spanish study cannot be attributed to sex steroid residues in beef. Further work, particularly in the United States and other countries where this practice still exists, is needed.

Diet and the Building Blocks for Spermatogenesis: DNA and Cell Membranes

As was the case for female fertility, there is also strong evidence that folic acid metabolism is important in spermatogenesis and male fertility. This metabolic pathway is involved in the synthesis of purines and thymidine which are ultimately used in DNA synthesis [68, 69], an essential step in spermatogenesis. One-carbon metabolism appears to be particularly active in the testes [212–214], and genetic [215] or pharmacologic [216–218] disruption of this metabolic pathway drastically affects

spermatogenesis in animal models. In humans, genetic variation in this pathway has been related to semen quality. A 2007 meta-analysis on the association between *MTHFR C677T* and male factor infertility reported pooled odds ratios (OR) (95 % confidence interval (CI)) for male factor infertility of 1.39 (1.15–1.69) for *TT* homozygotes and 1.23 (1.08–1.41) for *T* allele carriers [219]. Also, a large study conducted in Korea reported an association between homozygocity for the variant G allele in *MTR* A2756G and nonobstructive azoospermia (OR (95 % CI) = 4.63 (1.40–15.31)) as well as an association between being a carrier (OR (95%CI) = 1.75 (1.07–2.86)) or homozygote (OR (95%CI) = 2.96 (1.51–5.82)) for the variant G allele in *MTRR A66G* and oligoasthenoteratospermia [220].

Intake of folic acid also seems to impact sperm production. In two trials of folate supplementation, blood folate levels had increased fivefold and seminal plasma folate had increased threefold, but no changes were observed in sperm concentration or motility in one study [221], while a 53 % increase in sperm concentration and a doubling in the proportion of motile sperm were observed in another study [222]. Similarly, in a randomized trial of folate, zinc, folate + zinc or placebo, subfertile men assigned to the folate + zinc arm had a 74 % increase in total normal sperm count compared to preintervention values and a 41 % increase when compared to post-intervention values in the placebo arm which did not reach statistical significance [155]. Folates from dietary sources also appear to have an impact on semen quality. In a study among fertility patients in Spain, men in the highest tertile of folate intake had an 87 % lower risk of oligoteratospermia than men in the lowest tertile of intake [183]. Likewise, seminal plasma levels of vitamin B12 and folate are positively related to sperm concentration [223, 224] and, among men who have previously fathered a pregnancy and have sperm counts above 20×10^6/mL, seminal plasma folate is inversely related to sperm DNA fragmentation [225]. Furthermore, folate intake has been associated with a lower frequency of sperm aneuploidy [226]. Whether these effects on semen parameters have any impact on fertility is not known, however.

Diet could also influence male fertility by influencing the composition of cell membranes of sperm. Sperm dramatically increase the proportion of unsaturated fatty acids, particularly docosahexaenoic acid (DHA), in their membranes as they mature [227]. These changes appear to be the combined result of local metabolism and dietary input [228–232]. In humans, numerous studies have related sperm fatty acid composition with semen quality parameters suggesting a role of fatty acid metabolism on male fertility. For example, sperm membrane DHA content has been positively related to sperm motility [228, 233–237], sperm normal morphology [237] and sperm concentration [233, 236, 237], although some studies have found opposite relations [238]. Similarly, a lower content of saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) in sperm membranes has been associated with better semen quality parameters [233–237, 239]. Interestingly, sperm levels of *trans*-fatty acids, which cannot be endogenously synthesized and can therefore be considered biomarkers of intake, have been related to significantly lower sperm concentration among fertility patients [239] in agreement with rodent models showing decreased spermatogenesis and testicular degeneration when diets are supplemented with these fats [240–242].

The literature on fat intake and sperm quality is scarce. Two trials examined the effect of omega-3 on semen quality. DHA supplementation for 3 months failed to improve sperm motility in a group of 28 asthenospermic men [178], while omega-3 (DHA+EPA) fatty acid supplementation increased total sperm count, sperm concentration, and the percentages of motile and morphologically normal sperm [179]. A potential benefit of omega-3 polyunsaturated fatty acids (PUFAs) on sperm morphology has also been observed in observational studies among fertility patients [243]. Interestingly, two recent observational studies reported that saturated fat intake is inversely related to sperm concentration and total sperm counts among fertility patients [243] and among healthy young men [244]. Because saturated fat intake is not related to sperm or seminal plasma levels of saturated fats [243], it is unlikely that this relation is due to a relation between sperm fatty acid levels and sperm counts described above. Rather, it is possible that saturated fat intake has an indirect effect on spermatogenesis, perhaps by affecting circulating cholesterol levels as suggested by rodent models [245]. As is the case for other dietary factors, it is still to be determined whether any of the observed relations with semen parameters translates into relations with fertility; an important question that deserves further investigation.

Vitamin D and Male Reproductive Function

There has been increasing interest in the role of vitamin D role in reproduction [246]. The VDR is present in human testis and spermatozoa [247, 248] suggesting a role of vitamin D in human spermatogenesis. Vitamin D as $1,25(OH)_2D$ promotes intracellular calcium increase [249] through several channels present in the sperm tail such as CatSper and Voltage-dependent calcium channels [250, 251]. Calcium influx through these channels [252, 253], in turn, induces sperm motility [249, 254]. Furthermore, male *VDR* knockout mice have lower percentage of motile sperm and lower sperm counts [255], and female rats inseminated with semen from males fed a vitamin D-deficient diet have a smaller litter size [256].

However, the few epidemiologic studies investigating the relation between vitamin D and semen quality provide conflicting results. Two studies reported that circulating vitamin D levels are positively related to semen quality [254, 257], another found an inverse U-shaped association [258], and a third found no association [259]. In addition, no studies to date have evaluated whether male vitamin D status relates to fertility in couples trying to conceive naturally or to pregnancy and live birth rates among couples undergoing infertility treatment.

Dietary Patterns and Semen Quality

Two studies have also examined the relation of overall dietary patterns to semen quality parameters. Vujkovic and colleagues examined the relation between data-derived dietary patterns and semen quality among fertility patients in the Netherlands [210].

The investigators identified two diet patterns: a "health conscious" pattern characterized by high intakes of fruit, vegetables, fish and seafood, whole grains and legumes and low intakes of mayonnaise, meat products, refined grains and desserts; and a "traditional Dutch" pattern characterized by high intakes of potatoes, meat products, whole grains, margarine and mayonnaise, and low intakes of alcohol, non-alcoholic drinks, breakfast cereals, fruit, soup and desserts. The "health conscious" pattern was associated with lower sperm DNA fragmentation as measured with the DNA fragmentation index. In addition the "traditional Dutch" pattern was associated with higher sperm concentration. When individual foods in these dietary patterns were examined, higher intakes of fruits and vegetables were related to lower sperm DNA fragmentation and higher sperm motility [210].

Gaskins and colleagues used the same statistical technique to identify dietary patterns and related these to semen parameters among young, healthy men in the United States [260]. In this study, higher consumption of a "prudent pattern", characterized by high intakes of fish, chicken, fruit, vegetables, legumes, and whole grains, was positively associated with progressive sperm motility. When individual foods within this pattern were considered, only intake of cantaloupes was significantly related to progressive sperm motility [260]. While the patterns identified in the two studies are clearly different, there is some consistency in the relation of fruit-containing patterns, as well as intake of fruit or specific fruits with sperm motility. This relation should be investigated further as should the question of whether overall dietary patterns have an impact on a couple's fertility.

Diet and Fertility Treatment Outcomes

Although increasing evidence suggest that diet may be important for fertility, as discussed above, this does not necessarily imply that the same dietary factors related to fertility in the general population will also be related to treatment outcomes among couples undergoing fertility treatment. On one hand, some physiologic processes that may be affected by diet can be bypassed in the setting of infertility treatment and therefore dietary factors affecting natural fertility may have no influence on fertility treatment outcomes. On the other hand, fertility patients may be a population particularly susceptible to environmental factors, including diet, and therefore dietary factors that are not related to fertility in the general population could be important among couples seeking fertility care. While current evidence is limited, it is important to consider how diet relates to treatment outcomes in women seeking fertility treatment.

Studies on the relation between caffeine intake and fertility treatment outcomes are scarce. Although there is some concern of potential adverse effects of caffeine due to its documented presence in follicular fluid of women undergoing ART [261], data on the relation between caffeine intake and clinical outcomes is mixed. In a prospective study of 221 couples undergoing ART, female caffeine consumption was associated with a lower likelihood of achieving a live birth, whereas male

caffeine consumption was found to be a significant risk factor for multiple gestations in couples who achieved pregnancy through IVF or GIFT [14]. In a similar study among 664 couples participating in a randomized trial of IUI, women who had recently stopped drinking coffee had higher live birth rates than women who were current coffee drinkers or women who had never consumed it [262]. Interestingly, when analyses were restricted to women who were randomized to IUI, the relation with past coffee use persisted but live birth rates were also approximately two times higher among current coffee users than among never users. These findings do not suggest a true effect of caffeine but rather that women who decide to stop drinking coffee when undergoing fertility treatments may also be making other healthy lifestyle changes that improve pregnancy and live birth rates [262].

Evidence for a relation between alcohol intake and poor fertility treatment outcomes is equally scarce. The strongest evidence suggesting harm comes from a prospective cohort study of 2,545 couples undergoing their first IVF cycle which found that women who drink at least four drinks per week had a 16 % lower likelihood of a live birth compared with those who consume alcohol less often [263]. Although similar findings have been reported by others [264], an analysis of this association in the randomized trial of IUI mentioned above revealed a similar pattern to the findings for caffeine [262]. Discontinuing alcohol was associated with a higher likelihood of live birth, relative to women who never consumed alcohol. However, there were no differences in live birth rates between women who were current alcohol consumers and never consumers again suggesting that discontinuing alcohol may be a marker for other factors that predict successful treatment [262] and that this relation probably does not reflect a deleterious effect of alcohol on fertility treatment outcomes.

As was the case for natural fertility in women, the most compelling evidence for a dietary factor having an effect on fertility treatment outcomes is for folic acid and, more generally, the one-carbon metabolism. As discussed above, this metabolic pathway is related to response to controlled ovarian hyperstimulation [75]. In addition, higher follicular fluid homocysteine levels, a marker of low folate status, have been related to lower day 3 embryo quality [265], while blood levels of vitamin B12 were associated with higher day 3 embryo quality [266]. More importantly, this pathway also appears to be important for clinical outcomes. Among women undergoing infertility treatment in the Netherlands, a doubling in follicular fluid folate levels was associated with a 3-fold greater odds of becoming pregnant during an ART cycle [266]. A separate study in the United Kingdom [267] found no association between folate intake, plasma folate levels, or RBC folate levels and the likelihood of a live birth but reported a significantly higher rate of twin births in women with higher folate status, suggesting that folate may increase the likelihood of each potentially viable embryo to give rise to a live birth. In addition, women homozygous for the CC variant in *MTHFR* A1298C were less likely to achieve a clinical pregnancy or have a live birth after IVF than women with the AA wild-type genotype [267] suggesting a role of this metabolic pathway on ART outcomes. It should be noted that none of the countries where significant effects of this pathway

on fertility treatment outcomes have been observed (Germany, the Netherlands, and the United Kingdom) supplement their food supply with folic acid and thus the relevance of this findings to the United States and countries where foods are supplemented with this vitamin is uncertain.

While phytoestrogens may have a negative impact on spermatogenesis, as discussed above, recent data from randomized trials show that phytoestrogen supplementation during infertility treatment improves overall treatment success [268, 269]. A study randomizing 147 women with unexplained infertility undergoing clomiphene-stimulated cycles to phytoestrogen supplementation (120 mg/day) or placebo found that phytoestrogens increased the clinical pregnancy rate (37 % vs. 14 %) [268]. Similarly, a trial which randomized 213 women undergoing IVF to phytoestrogen supplementation (1,500 mg/day) or placebo found that phytoestrogen supplementation increased implantation rates (25 % vs. 20 %), clinical pregnancy rates (39 % vs. 21 %), and ongoing pregnancy rates (30 % vs. 16 %) [269].

As previously discussed, animal data strongly suggest a role of vitamin D on fertility but human data on its role on male and female fertility is conflicting. Data on a potential role of vitamin D on fertility treatment outcomes is equally conflicting. The first report in this topic found that follicular fluid levels of vitamin D were related to higher clinical pregnancy rates among 84 women undergoing IVF and that this association was independent of BMI and other potential confounders [270]. A subsequent report from a cohort of 101 women found that higher follicular fluid levels of vitamin D were associated with lower clinical pregnancy rate [271], shortly followed by a report where no association was found between follicular fluid or serum levels of vitamin D with clinical pregnancy rate among 82 women undergoing IVF [272]. Rudick and colleagues reported that serum vitamin D levels were unrelated to live birth rates in a cohort of 188 women undergoing IVF [273]. They noticed, however, that serum vitamin D levels were positively related to live birth rates among non-Hispanic whites, inversely related among Asians and unrelated among Hispanic whites [273]. Lastly, Firouzabadi found no relation of follicular fluid or serum vitamin D levels with clinical pregnancy rates in a cohort of 221 women undergoing IVF. Clearly, whether vitamin D plays any role on infertility treatment outcomes remains an open question.

Only one has so far examined the relation of preconception dietary patterns with ART outcomes [274]. Among 161 couples undergoing IVF, a data-derived "Mediterranean" pattern, characterized by high intakes of vegetable oils, vegetables, fruits, nuts, fish, and legumes, low dairy intake, and moderate intake of alcohol, was associated with 40 % higher odds of having a positive pregnancy test after embryo transfer. The relation with clinical pregnancy or live birth was not examined [274]. The authors suggested that these findings could partially result from higher intake of linoleic acid, a precursor to prostaglandins, resulting in improved endometrial receptivity and implantation [274]. This hypothesis is consistent with a report of higher implantation and pregnancy rates among women undergoing IVF with a higher ratio of serum linoleic to alpha-linolenic acid [275].

Summary

Accumulating evidence suggests that specific dietary factors and their related metabolism may be an important determinant of fertility in couples trying to become pregnant naturally as well as of treatment outcomes of couples undergoing fertility treatment. Very few systematic investigations of diet in relation to human fertility exist. However, collectively, the literature suggests that a few dietary factors may be important in natural and assisted reproduction. Specifically, folic acid and other nutrients involved in its metabolism may be important for ovulation, spermatogenesis, embryo development, and infertility treatment outcomes. While consistent, the clinical implications of this knowledge is limited due to the lack of randomized trials of folic acid supplementation among women and men aimed at examining fertility as an outcome. Therefore, while it is not unreasonable to recommend folic acid supplementation for the purpose of improving fertility, the extent of its effect on fertility is uncertain at this moment as is also uncertain whether supplementation in women beyond doses used for the prevention of neural tube defects can have additional benefits on fertility. Multiple randomized trials of the effect of antioxidants on semen parameters have been conducted suggesting a positive effect on semen quality. However, effects on live births or clinical pregnancies among couples seeking fertility care are inconclusive. Similarly, intake of some types of fats appears to be related to female and male factors influencing fertility. Data from animal studies strongly suggests a role of vitamin D on human fertility but human data has been highly inconsistent and equivocal and its clinical significance is unknown at this moment. Many studies have examined the roles of alcohol and caffeine on human fertility and suggested them to be harmful. However, the majority of studies suggesting harm tend to be retrospective and of low methodological quality whereas high quality prospective studies suggest that neither caffeine nor alcohol are important determinants of fecundity or semen quality. Their role on fertility treatment outcomes, however, has not been examined thoroughly and deserves further study. More generally, much more research is needed to understand how diet influences fertility. Specifically prospective studies with comprehensive dietary assessments and rigorous assessments of potential confounders, studies evaluating the role of men's diet on a couple's fertility, studies evaluating the interactions between male and female partner's diets on couple-based outcomes as well as studies among couples undergoing infertility treatment are sorely needed. In addition, randomized trials of specific factors where evidence has already accumulated are desirable.

References

1. ESHRE. The world's number of IVF and ICSI babies has now reached a calculated total of 5 million. Istanbul: European Society of Human Reproduction and Embryology; 2012 [cited 2012 October 16th]. http://www.eshre.eu/ESHRE/English/Press-Room/Press-Releases/Press-releases-2012/5-million-babies/page.aspx/1606

2. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2010 assisted reproductive technology success rates: national summary and fertility clinic reports. Atlanta: U.S. Department of Health and Human Services; 2012.
3. Chandra A, Martinez GM, Mosher WD, Abma JC, Jones J. Fertility, family planning, and reproductive health of US women: data from the 2002 National Survey of Family Growth. Vital Health Stat. 2005;23(25):1–160.
4. Malizia BA, Hacker MR, Penzias AS. Cumulative live-birth rates after in vitro fertilization. N Engl J Med. 2009;360(3):236–43. Epub 2009/01/16.
5. Choi B, Bosch E, Lannon BM, Leveille MC, Wong WH, Leader A, et al. Personalized prediction of first-cycle in vitro fertilization success. Fertil Steril. 2013;99(7):1905–11. Epub 2013/03/26.
6. Matthews TJ, Hammilton BE. Delayed childbearing: more women are having their first child later in life. NCHS Data Brief No. 21. Hyattsville: National Center for Health Statistics; 2009.
7. Willmott M, Bartosik DB, Romanoff EB. The effect of folic acid on superovulation in the immature rat. J Endocrinol. 1968;41:439–45.
8. Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. Lancet. 1988;332:1453–6.
9. Collins TF, Welsh JJ, Black TN, Collins EV. A study of the teratogenic potential of caffeine given by oral intubation to rats. Regul Toxic Pharmacol. 1981;1(3):355–78.
10. Collins TF, Welsh JJ, Black TN, Ruggles DI. A study of the teratogenic potential of caffeine ingested in drinking-water. Food Chem Toxicol. 1983;21(6):763–77. Epub 1983/12/01.
11. Thayer PS, Kensler CJ. Exposure of four generations of mice to caffeine in drinking water. Toxicol Appl Pharmacol. 1973;25(2):169–79. Epub 1973/06/01.
12. Bolumar F, Olsen J, Rebagliato M, Bisanti L. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. European Study Group on Infertility Subfecundity. Am J Epidemiol. 1997;145(4):324–34.
13. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Hum Reprod Update. 2007;13(3):209–23.
14. Klonoff-Cohen H, Bleha J, Lam-Kruglick P. A prospective study of the effects of female and male caffeine consumption on the reproductive endpoints of IVF and gamete intra-fallopian transfer. Hum Reprod. 2002;17(7):1746–54.
15. Lucero J, Harlow BL, Barbieri RL, Sluss P, Cramer DW. Early follicular phase hormone levels in relation to patterns of alcohol, tobacco, and coffee use. Fertil Steril. 2001; 76(4):723–9.
16. Kinney A, Kline J, Kelly A, Reuss ML, Levin B. Smoking, alcohol and caffeine in relation to ovarian age during the reproductive years. Hum Reprod. 2007;22(4):1175–85.
17. Agardh EE, Carlsson S, Ahlbom A, Efendic S, Grill V, Hammar N, et al. Coffee consumption, type 2 diabetes and impaired glucose tolerance in Swedish men and women. J Intern Med. 2004;255(6):645–52.
18. Salazar-Martinez E, Willett WC, Ascherio A, Manson JE, Leitzmann MF, Stampfer MJ, et al. Coffee consumption and risk for type 2 diabetes mellitus. Ann Intern Med. 2004; 140(1):1–8.
19. Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Hanley R, Fereshetian AG, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. J Clin Endocrinol Metab. 2001;86(4):1626–32.
20. Christianson R, Oechsli F, Van Den Berg B. Caffeinated beverages and decreased fertility. Lancet. 1989;333(8634):378.
21. Williams M, Monson R, Goldman M, Mittendorf R, Ryan K. Coffee and delayed conception. Lancet. 1990;335:1603.
22. Hatch EE, Bracken MB. Association of delayed conception with caffeine consumption. Am J Epidemiol. 1993;138(12):1082–92.

23. Stanton CK, Gray RH. Effects of caffeine consumption on delayed conception. Am J Epidemiol. 1995;142(12):1322–9.
24. Olsen J. Cigarette smoking, tea and coffee drinking, and subfecundity. Am J Epidemiol. 1991;133:734–9.
25. Grodstein F, Goldman MB, Ryan L, Cramer DW. Relation of female infertility to consumption of caffeinated beverages. Am J Epidemiol. 1993;137(12):1353–60.
26. Jensen TK, Henriksen TB, Hjollund NHI, Scheike T, Kolstad H, Giwercman A, et al. Caffeine intake and fecundability: a follow-up study among 430 Danish couples planning their first pregnancy. Reprod Toxicol. 1998;12(3):289–95.
27. Hassan MAM, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril. 2004;81:384–92.
28. Barbieri RL. Female Infertility. In: Straus III JF, Barbieri RL, editors. Yen and Jaffe's reproductive endocrinology. 5th ed. Philadelphia: Elsevier; 2004.
29. Leviton A, Cowan L. A review of the literature relating caffeine consumption by women to their risk of reproductive hazards. Food Chem Toxicol. 2002;40(9):1271–310.
30. Peck JD, Leviton A, Cowan LD. A review of the epidemiologic evidence concerning the reproductive health effects of caffeine consumption: a 2000-2009 update. Food Chem Toxicol. 2010;48(10):2549–76.
31. Hakim RB, Gray RH, Zacur H. Alcohol and caffeine consumption and decreased fertility. Fertil Steril. 1998;70(4):632–7.
32. Caan B, Quesenberry Jr CP, Coates AO. Differences in fertility associated with caffeinated beverage consumption. Am J Public Health. 1998;88(2):270–4.
33. Hatch EE, Wise LA, Mikkelsen EM, Christensen T, Riis AH, Sorensen HT, et al. Caffeinated beverage and soda consumption and time to pregnancy. Epidemiology. 2012;23(3):393–401. Epub 2012/03/13.
34. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Caffeinated and alcoholic beverage intake in relation to the risk of ovulatory disorder infertility. Epidemiology. 2009; 20(3):374–81.
35. Taylor KC, Small CM, Dominguez CE, Murray LE, Tang W, Wilson MM, et al. Alcohol, smoking, and caffeine in relation to fecundability, with effect modification by NAT2. Ann Epidemiol. 2011;21(11):864–72. Epub 2011/06/21.
36. Florack EIM, Zielhuis GA, Rolland R. Cigarette smoking, alcohol consumption, and caffeine intake and fecundability. Prev Med. 1994;23(2):175–80.
37. Jensen TK, Hjollund NHI, Henriksen TB, Scheike T, Kolstad H, Giwercman A, et al. Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. Br Med J. 1998;317:505–10.
38. Sadeu JC, Hughes CL, Agarwal S, Foster WG. Alcohol, drugs, caffeine, tobacco, and environmental contaminant exposure: reproductive health consequences and clinical implications. Crit Rev Toxicol. 2010;40(7):633–52.
39. Conigrave KM, Hu BF, Camargo Jr CA, Stampfer MJ, Willett WC, Rimm EB. A prospective study of drinking patterns in relation to risk of type 2 diabetes among men. Diabetes. 2001;50(10):2390–5.
40. Sierksma A, Patel H, Ouchi N, Kihara S, Funahashi T, Heine RJ, et al. Effect of moderate alcohol consumption on adiponectin, tumor necrosis factor-alpha, and insulin sensitivity. Diabetes Care. 2004;27(1):184–9.
41. Olsen J, Rachootin P, Schiodt AV, Damsbo N. Tobacco Use, alcohol consumption and infertility. Int J Epidemiol. 1983;12(2):179–84.
42. Grodstein F, Goldman MB, Cramer DW. Infertility in women and moderate alcohol consumption. Am J Public Health. 1994;85:1021–2.
43. Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. Am J Epidemiol. 1997;146(1):32–41.
44. Olsen J, Bolumar F, Boldsen J, Bisanti L. Does moderate alcohol intake reduce fecundability? A European multicenter study on infertility and subfecundity. Alcohol Clin Exp Res. 1997;21(2):206–12.

45. Parazzini F, Chatenoud L, Di Cintio E, La Vecchia C, Benzi G, Fedele L. Alcohol consumption is not related to fertility in Italian women. Br Med J. 1999;318:397.
46. Juhl M, Andersen AMN, Gronbaek M, Olsen J. Moderate alcohol consumption and waiting time to pregnancy. Hum Reprod. 2002;16:2705–9.
47. Tolstrup JS, Kjaeger SK, Holst C, Sharif H, Miunk C, Osler M, et al. Alcohol use as a predictor for infertility in a representative population of Danish women. Acta Obstet Gynecol Scand. 2003;82:744–9.
48. Eggert J, Theobald H, Engfeldt P. Effects of alcohol consumption on female fertility during and 18-year period. Fertil Steril. 2004;81:379–83.
49. Juhl M, Olsen J, Andersen AMN, Gronbaek M. Intake of wine, beer and spirits and waiting time to pregnancy. Hum Reprod. 2003;18:1967–71.
50. Greenlee AR, Arbuckle TE, Chyou PH. Risk factors for female infertility in an agricultural region. Epidemiology. 2003;14:429–36.
51. Idrovo AJ, Sanin LH, Cole D, Chavarro J, Caceres H, Narvaez J, et al. Time to first pregnancy among women working in agricultural production. Int Arch Occup Environ Health. 2005;78(6):493–500.
52. Spinelli A, Figa-Talamanca I, Osborn J. Time to pregnancy and occupation in a group of Italian women. Int J Epidemiol. 1997;26:601–7.
53. Bandyopadhyay S, Chakrabarti J, Banerjee S, Pal AK, Goswami SK, Chakravarty BN, et al. Galactose toxicity in the rat as a model for premature ovarian failure: an experimental approach readdressed. Hum Reprod. 2003;18(10):2031–8.
54. Swarts WJ, Mattison DR. Galactose inhibition of ovulation in mice. Fertil Steril. 1988;49:522–6.
55. Cramer DW, Xu H, Sahi T. Adult hypolactasia, milk consumption and age-specific fertility. Am J Epidemiol. 1994;139:282–9.
56. Chavarro JE, Rich-Edwards JW, Rosner B, Willett WC. A prospective study of dairy foods intake and anovulatory infertility. Hum Reprod. 2007;22(5):1340–7.
57. Lui G, Shi F, Blas-Machado U, Dong Q, Davis VL, Foster WG, et al. Ovarian effects of a high lactose diet in the female rat. Reprod Nutr Dev. 2005;45:185–92.
58. Rushton DH, Ramsay ID, Gilkes JJH, Norris MJ. Ferritin and fertility. Lancet. 1991;337:1554.
59. Hirson C. Coeliac infertility-folic-acid therapy. Lancet. 1970;1(7643):412. Epub 1970/02/21.
60. Sanfilippo JS, Liu YK. Vitamin B12 deficiency and infertility: report of a case. Int J Fertil. 1991;36(1):36–8. Epub 1991/01/01.
61. Gulden KD. Pernicious anemia, vitiligo, and infertility. J Am Board Fam Pract. 1990;3(3):217–20. Epub 1990/07/01.
62. Hoffbrand AV. Pathology of folate deficiency. Proc R Soc Med. 1977;70(2):82–4. Epub 1977/02/01.
63. Mackay G. Pregnancy following treatment for pernicious anaemia. Practitioner. 1972;208(246):509–10. Epub 1972/04/01.
64. Hall M, Davidson RJ. Prophylactic folic acid in women with pernicious anaemia pregnant after periods of infertility. J Clin Pathol. 1968;21(5):599–602. Epub 1968/09/01.
65. Jackson IM, Doig WB, McDonald G. Pernicious anaemia as a cause of infertility. Lancet. 1967;2(7527):1159–60. Epub 1967/12/02.
66. Collin P, Vilske S, Heinonen P, Hallstrom O, Pikkarainen P. Infertility and coeliac disease. Gut. 1996;39:382–4.
67. Collin P, Kaukinen K, Valimaki M, Salmi J. Endocrinological disorders and celiac disease. Endocr Rev. 2002;23(4):464–83.
68. Bailey LB, Gregory III JF. Folate. In: Bowman BA, Russell RM, editors. Present knowledge in nutrition. 9th ed. Washington DC: ILSI; 2006. p. 125–37.
69. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab. 2000;71(1–2):121–38.
70. Forges T, Monnier-Barbarino P, Alberto JM, Guéant-Rodriguez RM, Daval JL, Guéant JL. Impact of folate and homocysteine metabolism on human reproductive health. Hum Reprod Update. 2007;13(3):225–38.

71. Kwong WY, Adamiak SJ, Gwynn A, Singh R, Sinclair KD. Endogenous folates and single-carbon metabolism in the ovarian follicle, oocyte and pre-implantation embryo. Reproduction. 2010;139(4):705–15. Epub 2010/01/20.
72. Mohanty D, Das KC. Effect of folate deficiency on the reproductive organs of female rhesus monkeys: a cytomorphological and cytokinetic study. J Nutr. 1982;112(8):1565–76. Epub 1982/08/01.
73. Gaskins AJ, Mumford SL, Chavarro JE, Zhang C, Pollack AZ, Wactawski-Wende J, et al. The impact of dietary folate intake on reproductive function in premenopausal women: a prospective cohort study. PLoS One. 2012;7(9):e46276. Epub 2012/10/11.
74. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Use of multivitamins, intake of B vitamins and risk of ovulatory infertility. Fertil Steril. 2008;89:668–76.
75. Thaler CJ, Budiman H, Ruebsamen H, Nagel D, Lohse P. Effects of the common 677C→T mutation of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene on ovarian responsiveness to recombinant follicle-stimulating hormone. Am J Reprod Immunol. 2006;55(4):251–8. Epub 2006/03/15.
76. Hecht S, Pavlik R, Lohse P, Noss U, Friese K, Thaler CJ. Common 677C→T mutation of the 5,10-methylenetetrahydrofolate reductase gene affects follicular estradiol synthesis. Fertil Steril. 2009;91(1):56–61. Epub 2008/02/06.
77. Rosen MP, Shen S, McCulloch CE, Rinaudo PF, Cedars MI, Dobson AT. Methylenetetrahydrofolate reductase (MTHFR) is associated with ovarian follicular activity. Fertil Steril. 2007;88(3):632–8.
78. O'Neill C. Endogenous folic acid is essential for normal development of preimplantation embryos. Hum Reprod. 1998;13(5):1312–6. Epub 1998/07/01.
79. Balboni GC, Vannelli GB, Barni T, Orlando C, Serio M. Transferrin and somatomedin C receptors in the human ovarian follicle. Fertil Steril. 1987;48:796–801.
80. Aleshire SL, Osteen KG, Maxson WS, Entman SS, Bradley CA, Parl FF. Localization of transferrin and its receptor in ovarian follicular cells: morphologic studies in relation to follicular development. Fertil Steril. 1989;51:444–9.
81. Briggs DA, Sharp DJ, Miller D, Gosden RG. Transferrin in the developing ovarian follicle: evidence for de-novo expression by granulosa cells. Mol Hum Reprod. 1999;5:1107–14.
82. Meloni GF, Dessole S, Vargiu N, Tomasi PA, Musumeci S. The prevalence of coeliac disease in infertility. Hum Reprod. 1999;14(11):2759–61.
83. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Iron intake and risk of ovulatory infertility. Obstet Gynecol. 2006;108(5):1145–52.
84. Agic A, Xu H, Altgassen C, Noack F, Wolfler MM, Diedrich K, et al. Relative expression of 1,25-dihydroxyvitamin D3 receptor, vitamin D 1 alpha-hydroxylase, vitamin D 24-hydroxylase, and vitamin D 25-hydroxylase in endometriosis and gynecologic cancers. Reprod Sci. 2007;14(5):486–97. Epub 2007/10/05.
85. Parikh G, Varadinova M, Suwandhi P, Araki T, Rosenwaks Z, Poretsky L, et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. Horm Metab Res. 2010;42(10):754–7. Epub 2010/08/17.
86. Tanamura A, Nomura S, Kurauchi O, Furui T, Mizutani S, Tomoda Y. Purification and characterization of 1,25(OH)2D3 receptor from human placenta. J Obstet Gynaecol (Tokyo 1995). 1995;21(6):631–9. Epub 1995/12/01.
87. Barrera D, Avila E, Hernandez G, Halhali A, Biruete B, Larrea F, et al. Estradiol and progesterone synthesis in human placenta is stimulated by calcitriol. J Steroid Biochem Mol Biol. 2007;103(3–5):529–32. Epub 2007/01/30.
88. Barrera D, Avila E, Hernandez G, Mendez I, Gonzalez L, Halhali A, et al. Calcitriol affects hCG gene transcription in cultured human syncytiotrophoblasts. Reprod Biol Endocrinol. 2008;6:3. Epub 2008/01/24.
89. Kwiecinksi GG, Petrie GI, DeLuca HF. 1,25-Dihydroxyvitamin D3 restores fertility of vitamin D-deficient female rats. Am J Physiol. 1989;256(4 Pt 1):E483–7. Epub 1989/04/01.
90. Johnson LE, DeLuca HF. Vitamin D receptor null mutant mice fed high levels of calcium are fertile. J Nutr. 2001;131(6):1787–91.

91. Kovacs CS, Woodland ML, Fudge NJ, Friel JK. The vitamin D receptor is not required for fetal mineral homeostasis or for the regulation of placental calcium transfer in mice. Am J Physiol Endocrinol Metab. 2005;289(1):E133–44. Epub 2005/03/03.
92. Panda DK, Miao D, Tremblay ML, Sirois J, Farookhi R, Hendy GN, et al. Targeted ablation of the 25-hydroxyvitamin D 1alpha -hydroxylase enzyme: evidence for skeletal, reproductive, and immune dysfunction. Proc Natl Acad Sci U S A. 2001;98(13):7498–503. Epub 2001/06/21.
93. Yoshizawa T, Handa Y, Uematsu Y, Takeda S, Sekine K, Yoshihara Y, et al. Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. Nat Genet. 1997;16(4):391–6. Epub 1997/08/01.
94. Sun W, Xie H, Ji J, Zhou X, Goltzman D, Miao D. Defective female reproductive function in 1,25(OH)2D-deficient mice results from indirect effect mediated by extracellular calcium and/or phosphorus. Am J Physiol Endocrinol Metab. 2010;299(6):E928–35. Epub 2010/09/03.
95. Li HW, Brereton RE, Anderson RA, Wallace AM, Ho CK. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. Metabolism. 2011;60(10):1475–81. Epub 2011/05/10.
96. Mahmoudi T, Gourabi H, Ashrafi M, Yazdi RS, Ezabadi Z. Calciotropic hormones, insulin resistance, and the polycystic ovary syndrome. Fertil Steril. 2010;93(4):1208–14. Epub 2009/02/24.
97. Bhattacharya SM, Jha A. Association of vitamin D deficiency with clinical and biochemical parameters in Indian women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2013;123(1):74–5. Epub 2013/07/28.
98. Thys-Jacobs S, Donovan D, Papadopoulos A, Sarrel P, Bilezikian JP. Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. Steroids. 1999;64(6):430–5.
99. Wehr E, Pieber TR, Obermayer-Pietsch B. Effect of vitamin D3 treatment on glucose metabolism and menstrual frequency in polycystic ovary syndrome women: a pilot study. J Endocrinol Invest. 2011;34(10):757–63. Epub 2011/05/27.
100. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004;80(6):1678S–88.
101. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2010;1, CD003053. Epub 2010/01/22.
102. Galazis N, Galazi M, Atiomo W. d-Chiro-inositol and its significance in polycystic ovary syndrome: a systematic review. Gynecol Endocrinol. 2011;27(4):256–62. Epub 2010/12/15.
103. Sonmez AS, Yasar L, Savan K, Koc S, Ozcan J, Toklar A, et al. Comparison of the effects of acarbose and metformin use on ovulation rates in clomiphene citrate-resistant polycystic ovary syndrome. Hum Reprod. 2005;20(1):175–9. Epub 2004/10/30.
104. Penna IA, Canella PR, Reis RM, Silva de Sa MF, Ferriani RA. Acarbose in obese patients with polycystic ovarian syndrome: a double-blind, randomized, placebo-controlled study. Hum Reprod. 2005;20(9):2396–401. Epub 2005/07/12.
105. Ohgi S, Nakagawa K, Kojima R, Ito M, Horikawa T, Saito H. Insulin resistance in oligomenorrheic infertile women with non-polycystic ovary syndrome. Fertil Steril. 2008;90(2):373–7. Epub 2007/10/10.
106. Whitworth KW, Baird DD, Stene LC, Skjaerven R, Longnecker MP. Fecundability among women with type 1 and type 2 diabetes in the Norwegian mother and child cohort study. Diabetologia. 2011;54(3):516–22. Epub 2010/12/21.
107. Hjollund NHI, Jensen TK, Bonde JPE, Henriksen NE, Andersson AM, Skakkebaek NE. Is glycosilated haemoglobin a marker of fertility? A follow-up study of first-pregnancy planners. Hum Reprod. 1999;14:1478–82.
108. Murakami K, Sasaki S, Takahashi Y, Okubo H, Hosoi Y, Horiguchi H, et al. Dietary glycemic index and load in relation to metabolic risk factors in Japanese female farmers with traditional dietary habits. Am J Clin Nutr. 2006;83(5):1161–9.

109. Jeppesen J, Schaaf P, Jones C, Zhou M, Chen Y, Reaven G. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. Am J Clin Nutr. 1997;65(4):1027–33.
110. Garg A, Bantle JP, Henry RR, Coulston AM, Griver KA, Raatz SK, et al. Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus. JAMA. 1994;271:1421–8.
111. Douglas CC, Gower BA, Darnell BE, Ovalle F, Oster RA, Azziz R. Role of diet in the treatment of polycystic ovary syndrome. Fertil Steril. 2006;85(3):679–88.
112. Gannon MC, Nuttall FQ, Neil BJ, Westphal SA. The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. Metabolism. 1988;11:1081–8.
113. Gannon MC, Nuttall FQ, Saeed A, Jordan K, Hoover H. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. Am J Clin Nutr. 2003;78(4):734–41.
114. Rossetti L, Rothman DL, DeFronzo RA, Shulman GI. Effect of dietary protein on in vivo insulin action and liver glycogen repletion. Am J Physiol Endocrinol Metab. 1989; 257(2):E212–9.
115. Lavigne C, Marette A, Jacques H. Cod and soy proteins compared with casein improve glucose tolerance and insulin sensitivity in rats. Am J Physiol Endocrinol Metab. 2000; 278(3):E491–500.
116. Lefevre M, Lovejoy JC, Smith SR, DeLany JP, Champagne C, Most MM, et al. Comparison of the acute response to meals enriched with cis- or trans-fatty acids on glucose and lipids in overweight individuals with differing FABP2 genotypes. Metabolism. 2005;54(12):1652–8.
117. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Dietary fatty acid intakes and the risk of ovulatory infertility. Am J Clin Nutr. 2007;85(1):231–7.
118. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Protein intake and ovulatory infertility. Am J Obstet Gynecol. 2008;198(2):210e1–7. Epub 2008/01/30.
119. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA. 1997;277:472–7.
120. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. A prospective study of dietary carbohydrate quantity and quality in relation to risk of ovulatory infertility. Eur J Clin Nutr. 2009;63(1):78–86. Epub 2007 Sep 19.
121. Douglas CC, Norris LE, Oster RA, Darnell BE, Azziz R, Gower BA. Difference in dietary intake between women with polycystic ovary syndrome and healthy controls. Fertil Steril. 2006;86(2):411–7.
122. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88:812–9.
123. Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkamn CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. Fertil Steril. 2004;81:630–7.
124. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. Obstet Gynecol. 2007;110(5):1050–8. Epub 2007/11/06.
125. Toledo E, Lopez-del Burgo C, Ruiz-Zambrana A, Donazar M, Navarro-Blasco I, Martinez-Gonzalez MA, et al. Dietary patterns and difficulty conceiving: a nested case-control study. Fertil Steril. 2011;96(5):1149–53. Epub 2011/09/29.
126. Thonneau P, Marchand S, Tallec A, Ferial M-L, Ducot B, Lansac J, et al. Incidence and main causes of infertility in a resident population (1 850 000) of three French regions (1988-1989)*. Hum Reprod. 1991;6(6):811–6.
127. Sripada S, Townend J, Campbell D, Murdoch L, Mathers E, Bhattacharya S. Relationship between semen parameters and spontaneous pregnancy. Fertil Steril. 2010;94(2):624–30. Epub 2009/04/14.
128. Jedrzejczak P, Taszarek-Hauke G, Hauke J, Pawelczyk L, Duleba AJ. Prediction of spontaneous conception based on semen parameters. Int J Androl. 2008;31(5):499–507. Epub 2007/07/27.

129. Nallella KP, Sharma RK, Aziz N, Agarwal A. Significance of sperm characteristics in the evaluation of male infertility. Fertil Steril. 2006;85(3):629–34. Epub 2006/02/28.
130. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med. 2001;345(19):1388–93. Epub 2002/01/17.
131. Adelusi B, al-Twaijiri MH, al-Meshari A, Kangave D, al-Nuaim LA, Younnus B. Correlation of smoking and coffee drinking with sperm progressive motility in infertile males. Afr J Med Med Sci. 1998;27(1–2):47–50.
132. Sobreiro BP, Lucon AM, Pasqualotto FF, Hallak J, Athayde KS, Arap S. Semen analysis in fertile patients undergoing vasectomy: reference values and variations according to age, length of sexual abstinence, seasonality, smoking habits and caffeine intake. Sao Paulo Med J. 2005;123(4):161–6.
133. Li Y, Lin H, Li Y, Cao J. Association between socio-psycho-behavioral factors and male semen quality: systematic review and meta-analyses. Fertil Steril. 2011;95(1):116–23.
134. Oldereid NB, Rui H, Purvis K. Lifestyles of men in barren couples and their relationships to sperm quality. Eur J Obstet Gynecol Reprod Biol. 1992;43(1):51–7.
135. Ramlau-Hansen CH, Thulstrup AM, Bonde JP, Olsen J, Bech BH. Semen quality according to prenatal coffee and present caffeine exposure: two decades of follow-up of a pregnancy cohort. Hum Reprod. 2008;23(12):2799–805.
136. Jensen TK, Swan SH, Skakkebaek NE, Rasmussen S, Jorgensen N. Caffeine intake and semen quality in a population of 2,554 young Danish men. Am J Epidemiol. 2010;171(8):883–91. Epub 2010/03/27.
137. Lewis SE. Is sperm evaluation useful in predicting human fertility? Reproduction. 2007;134(1):31–40. Epub 2007/07/21.
138. Glazener CM, Coulson C, Lambert PA, Watt EM, Hinton RA, Kelly NJ, et al. The value of artificial insemination with husband's semen in infertility due to failure of postcoital sperm-mucus penetration—controlled trial of treatment. Br J Obstet Gynaecol. 1987;94(8):774–8. Epub 1987/08/01.
139. Polansky FF, Lamb EJ. Do the results of semen analysis predict future fertility? A survival analysis study. Fertil Steril. 1988;49(6):1059–65. Epub 1988/06/01.
140. Muthusami KR, Chinnaswamy P. Effect of chronic alcoholism on male fertility hormones and semen quality. Fertil Steril. 2005;84(4):919–24.
141. Jensen TK, Hjollund NH, Henriksen TB, Scheike T, Kolstad H, Giwercman A, et al. Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. BMJ. 1998;317(7157):505–10.
142. Wang C, Chan CW, Wong KK, Yeung KK. Comparison of the effectiveness of placebo, clomiphene citrate, mesterolone, pentoxifylline, and testosterone rebound therapy for the treatment of idiopathic oligospermia. Fertil Steril. 1983;40(3):358–65. Epub 1983/09/01.
143. Micic S, Hadzi-Djokic J, Dotlic R, Tulic C. Pentoxifyllin treatment of oligoasthenospermic men. Acta Eur Fertil. 1988;19(3):135–7. Epub 1988/05/01.
144. Dawson EB, Harris WA, Powell LC. Relationship between ascorbic acid and male fertility. World Rev Nutr Diet. 1990;62:1–26. Epub 1990/01/01.
145. Kessopoulou E, Powers HJ, Sharma KK, Pearson MJ, Russell JM, Cooke ID, et al. A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Steril. 1995;64(4):825–31. Epub 1995/10/01.
146. Suleiman SA, Ali ME, Zaki ZMS, El-Malik EMA, Nasr MA. Lipid peroxidation and human sperm motility: protective role of vitamin E. J Androl. 1996;17(5):530–7.
147. Merino G, Martinez Chequer JC, Barahona E, Bermudez JA, Moran C, Carranza-Lira S. Effects of pentoxifylline on sperm motility in normogonadotropic asthenozoospermic men. Arch Androl. 1997;39(1):65–9. Epub 1997/07/01.
148. Omu AE, Dashti H, Al-Othman S. Treatment of asthenozoospermia with zinc sulphate: andrological, immunological and obstetric outcome. Eur J Obstet Gynecol Reprod Biol. 1998;79(2):179–84.

149. Scott R, MacPherson A, Yates RW, Hussain B, Dixon J. The effect of oral selenium supplementation on human sperm motility. Br J Urol. 1998;82(1):76–80. Epub 1998/08/12.
150. Akiyama M. [In vivo scavenging effect of ethylcysteine on reactive oxygen species in human semen]. Nihon Hinyokika Gakkai Zasshi. 1999;90(3):421–8.
151. Rolf C, Cooper TG, Yeung CH, Nieschlag E. Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose vitamin C and vitamin E: a randomized, placebo-controlled, double-blind study. Hum Reprod. 1999;14(4):1028–33.
152. Comhaire FH, Christophe AB, Zalata AA, Dhooge WS, Mahmoud AMA, Depuydt CE. The effects of combined conventional treatment, oral antioxidants and essential fatty acids on sperm biology in subfertile men. Prostaglandins Leukot Essent Fatty Acids. 2000;63(3): 159–65.
153. Andrology (Abstracts P-001 to P-032). Human Reproduction. 2001;16(Suppl 1):103-15.
154. Lombardo F, Gandini L, Agarwal A, Sgro P, Dondero F, Lenzi A. A prospective double blind placebo controlled cross over trial of carnitine therapy in selected cases of male infertility. Fertil Steril. 2002;78 Suppl 1:68–9.
155. Wong WY, Merkus HMWM, Thomas CMG, Menkveld R, Zielhuis GA, Steegers-Theunissen RPM. Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial. Fertil Steril. 2002;77(3):491–8.
156. Keskes-Ammar L, Feki-Chakroun N, Rebai T, Sahnoun Z, Ghozzi H, Hammami S, et al. Sperm oxidative stress and the effect of an oral vitamin e and selenium supplement on semen quality in infertile men. Arch Androl. 2003;49(2):83.
157. Lenzi A, Lombardo F, Sgrò P, Salacone P, Caponecchia L, Dondero F, et al. Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. Fertil Steril. 2003;79(2):292–300.
158. Zavaczki Z, Szollosi J, Kiss SA, Koloszar S, Fejes I, Kovacs L, et al. Magnesium-orotate supplementation for idiopathic infertile male patients: a randomized, placebo-controlled clinical pilot study. Magnes Res. 2003;16(2):131–6. Epub 2003/08/02.
159. Cavallini G, Ferraretti AP, Gianaroli L, Biagiotti G, Vitali G. Cinnoxicam and l-carnitine/acetyl-l-carnitine treatment for idiopathic and varicocele-associated oligoasthenospermia. J Androl. 2004;25(5):761–70.
160. Lenzi A, Sgrò P, Salacone P, Paoli D, Gilio B, Lombardo F, et al. A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. Fertil Steril. 2004;81(6):1578–84.
161. Balercia G, Regoli F, Armeni T, Koverech A, Mantero F, Boscaro M. Placebo-controlled double-blind randomized trial on the use of l-carnitine, l-acetylcarnitine, or combined l-carnitine and l-acetylcarnitine in men with idiopathic asthenozoospermia. Fertil Steril. 2005;84(3):662–71.
162. Greco E, Iacobelli M, Rienzi L, Ubaldi F, Ferrero S, Tesarik J. Reduction of the incidence of sperm DNA fragmentation by oral antioxidant treatment. J Androl. 2005;26(3):349–53.
163. Li Z, Chen GW, Shang XJ, Bai WJ, Han YF, Chen B, et al. A controlled randomized trial of the use of combined L-carnitine and acetyl-L-carnitine treatment in men with oligoasthenozoospermia. Zhonghua Nan Ke Xue. 2005;11(10):761–4. Epub 2005/11/12.
164. Sigman M, Glass S, Campagnone J, Pryor JL. Carnitine for the treatment of idiopathic asthenospermia: a randomized, double-blind, placebo-controlled trial. Fertil Steril. 2006;85(5): 1409–14.
165. Ménézo YJR, Hazout A, Panteix G, Robert F, Rollet J, Cohen-Bacrie P, et al. Antioxidants to reduce sperm DNA fragmentation: an unexpected adverse effect. Reprod Biomed Online. 2007;14(4):418–21.
166. Tremellen K, Miari G, Froiland D, Thompson J. A randomised control trial examining the effect of an antioxidant (Menevit) on pregnancy outcome during IVF-ICSI treatment. Aust N Z J Obstet Gynaecol. 2007;47(3):216–21.
167. Galatioto PG, Gravina GL, Angelozzi G, Sacchetti A, Innominato PF, Pace G, et al. May antioxidant therapy improve sperm parameters of men with persistent oligospermia after retrograde embolization for varicocele? World J Urol. 2008;26(1):97–102. Epub 2007/11/06.

168. Omu AE, Al-Azemi MK, Kehinde EO, Anim JT, Oriowo MA, Mathew TC. Indications of the mechanisms involved in improved sperm parameters by zinc therapy. Med Princ Pract. 2008;17(2):108–16. Epub 2008/02/22.
169. Balercia G, Buldreghini E, Vignini A, Tiano L, Paggi F, Amoroso S, et al. Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. Fertil Steril. 2009;91(5):1785–92.
170. Ciftci H, Verit A, Savas M, Yeni E, Erel O. Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status. Urology. 2009;74(1):73–6.
171. Safarinejad MR. Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. J Urol. 2009;182(1):237–48.
172. Safarinejad MR, Safarinejad S. Efficacy of selenium and/or N-acetyl-cysteine for improving semen parameters in infertile men: a double-blind, placebo controlled, randomized study. J Urol. 2009;181(2):741–51.
173. Ghanem H, Shaeer O, El-Segini A. Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: a randomized controlled trial. Fertil Steril. 2010;93(7): 2232–5.
174. Peivandi S, Karimpour A, Moslemizadeh N. Effects of L-carnitine on infertile men's spermogram; a randomized clinical trial. J Reprod Infertil. 2010;10(4):245–52.
175. Moslemi MK, Tavanbakhsh S. Selenium-vitamin E supplementation in infertile men: effects on semen parameters and pregnancy rate. Int J Gen Med. 2011;4:99–104. Epub 2011/03/16.
176. Safarinejad MR, Safarinejad S, Shafiei N, Safarinejad S. Effects of the reduced form of coenzyme Q10 (ubiquinol) on semen parameters in men with idiopathic infertility: a double-blind, placebo controlled, randomized study. J Urol. 2012;188(2):526–31.
177. Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Antioxidants for male subfertility. Cochrane Database Syst Rev. 2011;1, CD007411. Epub 2011/01/21.
178. Conquer JA, Martin JB, Tummon I, Watson L, Tekpetey F. Effect of DHA supplementation on DHA status and sperm motility in asthenozoospermic males. Lipids. 2000;35:149–54.
179. Safarinejad MR. Effect of omega-3 polyunsaturated fatty acid supplementation on semen profile and enzymatic anti-oxidant capacity of seminal plasma in infertile men with idiopathic oligoasthenoteratospermia: a double-blind, placebo-controlled, randomised study. Andrologia. 2011;43(1):38–47. Epub 2011/01/12.
180. Eskenazi B, Kidd SA, Marks AR, Sloter E, Block G, Wyrobek AJ. Antioxidant intake is associated with semen quality in healthy men. Hum Reprod. 2005;20(4):1006–12.
181. Mínguez-Alarcón L, Mendiola J, López-Espín JJ, Sarabia-Cos L, Vivero-Salmerón G, Vioque J, et al. Dietary intake of antioxidant nutrients is associated with semen quality in young university students. Hum Reprod. 2012;27(9):2807–14.
182. Zareba P, Colaci DS, Afeiche M, Gaskins AJ, Jørgensen N, Mendiola J, et al. Semen quality in relation to antioxidant intake in a healthy male population. Fertil Steril. 2013; 100(6):1572–9.
183. Mendiola J, Torres-Cantero AM, Vioque J, Moreno-Grau JM, Ten J, Roca M, et al. A low intake of antioxidant nutrients is associated with poor semen quality in patients attending fertility clinics. Fertil Steril. 2010;93(4):1128–33.
184. Skakkebaek NE, Rajpert De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod. 2001; 16:972–8.
185. Sharpe RM. Hormones and testis development and the possible adverse effects of environmental chemicals. Toxicol Lett. 2001;120:221–32.
186. Kuiper GGJM, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β. Endocrinology. 1998;139(10):4252–63.
187. Branham WS, Dial SL, Moland CL, Hass BS, Blair RM, Fang H, et al. Phytoestrogens and mycoestrogens bind to the rat uterine estrogen receptor. J Nutr. 2002;132:658–64.
188. Miksicek RJ. Interaction of naturally occurring nonsteroidal estrogens with expressed recombinant human estrogen receptor. J Steroid Biochem Mol Biol. 1994;49:153–60.

189. Matthews J, Celius T, Halgren R, Zacharewski T. Differential estrogen receptor binding of estrogenic substances: a species comparison. J Steroid Biochem Mol Biol. 2000;74:223–34.
190. Harris HA, Bapat AR, Gonder DS, Frail DE. The ligand binding profiles of estrogen receptors α and β are species dependent. Steroids. 2002;67:379–84.
191. Song TT, Hendrich S, Murphy PA. Estrogenic activity of glycitein, a soy isoflavone. J Agric Food Chem. 1999;47:1607–10.
192. Thomas P, Dong J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disruption. J Steroid Biochem Mol Biol. 2006;102:175–9.
193. Fraser LR, Beyret E, Milligan SR, Adeoya-Osiguwa SA. Effects of estrogenic xenobiotics on human and mouse spermatozoa. Hum Reprod. 2006;21:1184–93.
194. Atanassova N, McKinnell C, Turner KJ, Walker M, Fisher JS, Morley M, et al. Comparative effects of neonatal exposure of male rats to potent and weak (environmental) estrogens on spermatogenesis at puberty and the relationship to adult testis size and fertility: evidence for stimulatory effects of low estrogen levels. Endocrinology. 2000;141:3898–907.
195. Mitchell JH, Cawood E, Kinniburgh D, Provan A, Collins AR, Irvine DS. Effect of a phytoestrogen food supplement on reproductive health in normal males. Clin Sci (Lond). 2001; 100:613–8.
196. Song G, Kochman L, Andolina E, Herko RC, Brewer KJ, Lewis V. Beneficial effects of dietary intake of plant phytoestrogens on semen parameters and sperm DNA integrity in infertile men [Abstract]. Fertil Steril. 2006;86:S49.
197. Chavarro JE, Toth TL, Sadio SM, Hauser R. Soy food and soy isoflavone intake in relation to semen quality parameters among men from an infertility clinic. Hum Reprod. 2008; 23(11):2584–90.
198. Xia Y, Chen M, Zhu P, Lu C, Fu G, Zhou X, et al. Urinary phytoestrogen levels related to idiopathic male infertility in Chinese men. Environ Int. 2013;59:161–7.
199. Davaasambuu G, Wang PY, Qin LQ, Hoshi K, Sato A. Is milk responsible for male reproductive disorders? Med Hypotheses. 2001;57(4):510–4.
200. Willingham EJ. Environmental review: trenbolone and other cattle growth promoters: need for a new risk-assessment framework. Environ Pract. 2006;8(01):58–65.
201. Davaasambuu G, Qin L-Q, Wang P-Y, Tezuka H, Teramoto S, Sato A. A two-generation reproduction study to assess the effects of cows' milk on reproductive development in male and female rats. Fertil Steril. 2004;82 Suppl 3:1106–14.
202. Pape-Zambito DA, Roberts RF, Kensinger RS. Estrone and 17β-estradiol concentrations in pasteurized-homogenized milk and commercial dairy products. J Dairy Sci. 2010;93(6): 2533–40.
203. Daxenberger A, Ibarreta D, Meyer HHD. Possible health impact of animal oestrogens in food. Hum Reprod Update. 2001;7(3):340–55.
204. Andersson A, Skakkebaek N. Exposure to exogenous estrogens in food: possible impact on human development and health. Eur J Endocrinol. 1999;140(6):477–85.
205. Swan SH, Liu F, Overstreet JW, Brazil C, Skakkebaek NE. Semen quality of fertile US males in relation to their mothers' beef consumption during pregnancy. Hum Reprod. 2007; 22(6):1497–502.
206. Maruyama K, Oshima T, Ohyama K. Exposure to exogenous estrogen through intake of commercial milk produced from pregnant cows. Pediatr Int. 2010;52(1):33–8.
207. Afeiche M, Williams PL, Mendiola J, Gaskins A, Jørgensen N, Swan S, et al. Dairy food intake in relation to semen quality and reproductive hormone levels among physically active young men. Hum Reprod. 2013;28(8):2265–75. Epub 2013 May 12.
208. Mendiola J, Torres-Cantero AM, Moreno-Grau JM, Ten J, Roca M, Moreno-Grau S, et al. Food intake and its relationship with semen quality: a case-control study. Fertil Steril. 2009;91(3):812–8.
209. Eslamian G, Amirjannati N, Rashidkhani B, Sadeghi M-R, Hekmatdoost A. Intake of food groups and idiopathic asthenozoospermia: a case-control study. Hum Reprod. 2012;27(11): 3328–36.

210. Vujkovic M, de Vries JH, Dohle GR, Bonsel GJ, Lindemans J, Macklon NS, et al. Associations between dietary patterns and semen quality in men undergoing IVF/ICSI treatment. Hum Reprod. 2009;24(6):1304–12.
211. European Commission. Opinion of the scientific commitee on veterinary measures relating to public health. Assessment of potential risks to human health from hormone residues in bovine meat and meat products. In: Directorate General XXIV Cpachp, editor. 1999.
212. Holm J, Hansen SI, Høier-Madsen M. A high-affinity folate binding protein in human semen. Biosci Rep. 1991;11(5):237–42.
213. Holm J, Hansen SI, Høier-Madsen M, Christensen TB, Nichols CW. Characterization of a high-affinity folate receptor in normal and malignant human testicular tissue. Biosci Rep. 1999;19(6):571–80.
214. Chen Z, Karaplis AC, Ackerman SL, Pogribny IP, Melnyk S, Lussier-Cacan S, et al. Mice deficient in methylenetetrahydrofolate reductase exhibit hyperhomocysteinemia and decreased methylation capacity, with neuropathology and aortic lipid deposition. Hum Mol Genet. 2001;10(5):433–43.
215. Kelly TLJ, Neaga OR, Schwahn BC, Rozen R, Trasler JM. Infertility in 5,10-methylenetetrahydrofolate reductase (MTHFR)-deficient male mice is partially alleviated by lifetime dietary betaine supplementation. Biol Reprod. 2005;72(3):667–77.
216. Cosentino MJ, Pakyz RE, Fried J. Pyrimethamine: an approach to the development of a male contraceptive. Proc Natl Acad Sci U S A. 1990;87(4):1431–5.
217. Kalla NR, Saggar SK, Puri R, Mehta U. Regulation of male fertility by pyrimethamine in adult mice. Res Exp Med (Berl). 1997;197(1):45–52.
218. Malik NS, Matlin SA, Fried J, Pakyz RE, Consentino MJ. The contraceptive effects of etoprine on male mice and rats. J Androl. 1995;16(2):169–74.
219. Tüttelmann F, Rajpert-De Meyts E, Nieschlag E, Simoni M. Gene polymorphisms and male infertility a meta-analysis and literature review. Reprod Biomed Online. 2007;15:643–58.
220. Lee H-C, Jeong Y-M, Lee SH, Cha KY, Song S-H, Kim NK, et al. Association study of four polymorphisms in three folate-related enzyme genes with non-obstructive male infertility. Hum Reprod. 2006;21(12):3162–70.
221. Landau B, Singer R, Klein T, Segenreich E. Folic acid levels in blood and seminal plasma of normo- and oligospermic patients prior and following folic acid treatment. Experientia. 1978;34(10):1301–2.
222. Bentivoglio G, Melica F, Cristoforoni P. Folinic acid in the treatment of human male infertility. Fertil Steril. 1993;60(4):698–701.
223. Wallock LM, Tamura T, Mayr CA, Johnston KE, Ames BN, Jacob RA. Low seminal plasma folate concentrations are associated with low sperm density and count in male smokers and nonsmokers. Fertil Steril. 2001;75(2):252–9.
224. Boxmeer JC, Smit M, Weber RF, Lindemans J, Romijn JC, Eijkemans MJC, et al. Seminal plasma cobalamin significantly correlates with sperm concentration in men undergoing IVF or ICSI procedures. J Androl. 2007;28:521–7.
225. Boxmeer JC, Smit M, Utomo E, Romijn JC, Eijkemans MJC, Lindemans J, et al. Low folate in seminal plasma is associated with increased sperm DNA damage. Fertil Steril. 2009;92(2):548–56.
226. Young SS, Eskenazi B, Marchetti FM, Block G, Wyrobek AJ. The association of folate, zinc and antioxidant intake with sperm aneuploidy in healthy non-smoking men. Hum Reprod. 2008;23(5):1014–22.
227. Lenzi A, Gandini L, Maresca V, Rago R, Sgro P, Dondero F, et al. Fatty acid composition of spermatozoa and immature germ cells. Mol Hum Reprod. 2000;6(3):226–31.
228. Conquer JA, Martin JB, Tummon I, Watson L, Tekpetey F. Fatty acid analysis of blood serum, seminal plasma and spermatozoa of normozoospermic vs. asthenozoospermic males. Lipids. 1999;34:793–9.
229. Jeong B-Y, Jeong W-G, Moon S-K, Ohshima T. Preferential accumulation of fatty acids in the testis and ovary of cultured and wild sweet smelt Plecoglossus altivelis. Comp Biochem Physiol B Biochem Mol Biol. 2002;131(2):251–9.

230. Sebokova E, Garg ML, Wierzbicki A, Thomson ABR. Alteration of the lipid composition of rat testicular plasma membranes by dietary (n-3) fatty acids changes the responsiveness of Leydig cells and testosterone synthesis. J Nutr. 1990;120:610–8.
231. Ayala S, Brenner RR. Effect of polyunsaturated fatty acids of the alpha-linolenic series in the lipid composition of rat testicles during development. Acta Physiol Lat Am. 1980;30(3): 147–52.
232. Ayala S, Brenner RR, Dumm C. Effect of polyunsaturated fatty acids of the α-linolenic series on the development of rat testicles. Lipids. 1977;12(12):1017–24.
233. Zalata A, Christophe A, Depuydt C, Schoonjans F, Comhaire F. The fatty acid composition of phospholipids of spermatozoa from infertile patients. Mol Hum Reprod. 1998;4(2): 111–8.
234. Gulaya NM, Margitich VM, Govseeva NM, Klimashevsky VM, Gorpynchenko II, Boyko MI. Phospholipid composition of human sperm and seminal plasma in relation to sperm fertility. Arch Androl. 2001;46(3):169–75.
235. Tavilani H, Doosti M, Abdi K, Vaisiraygani A, Joshaghani HR. Decreased polyunsaturated and increased saturated fatty acid concentration in spermatozoa from asthenozoospermic males as compared with normozoospermic males. Andrologia. 2006;38(5):173–8.
236. Aksoy Y, Aksoy H, Altinkaynak K, Aydin HR, Ozkan A. Sperm fatty acid composition in subfertile men. Prostaglandins Leukot Essent Fatty Acids. 2006;75(2):75–9.
237. Tavilani H, Doosti M, Nourmohammadi I, Mahjub H, Vaisiraygani A, Salimi S, et al. Lipid composition of spermatozoa in normozoospermic and asthenozoospermic males. Prostaglandins Leukot Essent Fatty Acids. 2007;77(1):45–50.
238. Khosrowbeygi A, Zarghami N. Fatty acid composition of human spermatozoa and seminal plasma levels of oxidative stress biomarkers in subfertile males. Prostaglandins Leukot Essent Fatty Acids. 2007;77(2):117–21.
239. Chavarro JE, Furtado J, Toth TL, Ford J, Keller M, Campos H, et al. Trans-fatty acid levels in sperm are associated with sperm concentration among men from an infertility clinic. Fertil Steril. 2011;95(5):1794–7. Epub 2010/11/13.
240. Jensen B. Rat testicular lipids and dietary isomeric fatty acids in essential fatty acid deficiency. Lipids. 1976;11(3):179–88.
241. Hanis T, Zidek V, Sachova J, Klir P, Deyl Z. Effects of dietary trans-fatty acids on reproductive performance of Wistar rats. Br J Nutr. 1989;61(03):519–29.
242. Veaute C, Andreoli MF, Racca A, Bailat A, Scalerandi MV, Bernal C, et al. Effects of isomeric fatty acids on reproductive parameters in mice. Am J Reprod Immunol. 2007; 58(6):487–96.
243. Attaman JA, Toth TL, Furtado J, Campos H, Hauser R, Chavarro JE. Dietary fat and semen quality among men attending a fertility clinic. Hum Reprod. 2012;27(5):1466–74.
244. Jensen TK, Heitmann BL, Jensen MB, Halldorsson TI, Andersson AM, Skakkebaek NE, et al. High dietary intake of saturated fat is associated with reduced semen quality among 701 young Danish men from the general population. Am J Clin Nutr. 2013;97(2):411–8. Epub 2012/12/28.
245. Saez Lancellotti TE, Boarelli PV, Monclus MA, Cabrillana ME, Clementi MA, Espinola LS, et al. Hypercholesterolemia impaired sperm functionality in rabbits. PLoS One. 2010; 5(10):e13457. Epub 2010/10/27.
246. Lerchbaum E, Obermayer-Pietsch BR. Vitamin D and fertility-a systematic review. Eur J Endocrinol. 2012;166(5):765–78.
247. Blomberg Jensen M, Nielsen JE, Jørgensen A, Rajpert-De Meyts E, Kristensen DM, Jørgensen N, et al. Vitamin D receptor and vitamin D metabolizing enzymes are expressed in the human male reproductive tract. Hum Reprod. 2010;25(5):1303–11.
248. Aquila S, Guido C, Perrotta I, Tripepi S, Nastro A, Andò S. Human sperm anatomy: ultrastructural localization of 1α,25-dihydroxyvitamin D3 receptor and its possible role in the human male gamete. J Anat. 2008;213(5):555–64.

249. Aquila S, Guido C, Middea E, Perrotta I, Bruno R, Pellegrino M, et al. Human male gamete endocrinology: 1alpha, 25-dihydroxyvitamin D3 (1,25(OH)2D3) regulates different aspects of human sperm biology and metabolism. Reprod Biol Endocrinol. 2009;7(1):140.
250. Bedu-Addo K, Costello S, Harper C, Machado-Oliveira G, Lefievre L, Ford C, et al. Mobilisation of stored calcium in the neck region of human sperm—a mechanism for regulation of flagellar activity. Int J Dev Biol. 2008;52(5–6):615–26. Epub 2008/07/24.
251. Zanatta L, Zamoner A, Zanatta AP, Bouraima-Lelong H, Delalande C, Bois C, et al. Nongenomic and genomic effects of 1alpha,25(OH)2 vitamin D3 in rat testis. Life Sci. 2011;89(15–16):515–23. Epub 2011/05/14.
252. Lishko PV, Kirichok Y, Ren D, Navarro B, Chung J-J, Clapham DE. The control of male fertility by spermatozoan Ion channels. Annu Rev Physiol. 2012;74(1):453–75.
253. Strünker T, Goodwin N, Brenker C, Kashikar ND, Weyand I, Seifert R, et al. The CatSper channel mediates progesterone-induced Ca^{2+} influx in human sperm. Nature. 2011; 471(7338):382–6.
254. Blomberg Jensen M, Bjerrum PJ, Jessen TE, Nielsen JE, Joensen UN, Olesen IA, et al. Vitamin D is positively associated with sperm motility and increases intracellular calcium in human spermatozoa. Hum Reprod. 2011;26(6):1307–17. Epub 2011/03/24.
255. Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y. Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. Endocrinology. 2000;141(4): 1317–24.
256. Kwiecinski GG, Petrie GI, DeLuca HF. Vitamin D is necessary for reproductive functions of the male rat. J Nutr. 1989;119(5):741–4.
257. Yang B, Sun H, Wan Y, Wang H, Qin W, Yang L, et al. Associations between testosterone, bone mineral density, vitamin D and semen quality in fertile and infertile Chinese men. Int J Androl. 2012;35(6):783–92.
258. Hammoud AO, Meikle AW, Peterson CM, Stanford J, Gibson M, Carrell DT. Association of 25-hydroxy-vitamin D levels with semen and hormonal parameters. Asian J Androl. 2012;14(6):855–9. Epub 2012/10/09.
259. Ramlau-Hansen CH, Moeller UK, Bonde JP, Olsen J, Thulstrup AM. Are serum levels of vitamin D associated with semen quality? Results from a cross-sectional study in young healthy men. Fertil Steril. 2011;95(3):1000–4. Epub 2010/12/03.
260. Gaskins AJ, Colaci DS, Mendiola J, Swan SH, Chavarro JE. Dietary patterns and semen quality in young men. Hum Reprod. 2012;27(10):2899–907. Epub 2012/08/14.
261. Al-Saleh I, El-Doush I, Grisellhi B, Coskun S. The effect of caffeine consumption on the success rate of pregnancy as well various performance parameters of in-vitro fertilization treatment. Med Sci Monit. 2010;16(12):CR598–605.
262. Huang H, Hansen KR, Factor-Litvak P, Carson SA, Guzick DS, Santoro N, et al. Predictors of pregnancy and live birth after insemination in couples with unexplained or male-factor infertility. Fertil Steril. 2012;97(4):959–67.
263. Rossi BV, Berry KF, Hornstein MD, Cramer DW, Ehrlich S, Missmer SA. Effect of alcohol consumption on in vitro fertilization. Obstet Gynecol. 2011;117(1):136–42. Epub 2010/12/22.
264. Klonoff-Cohen H, Lam-Kruglick P, Gonzalez C. Effects of maternal and paternal alcohol consumption on the success rates of in vitro fertilization and gamete intrafallopian transfer. Fertil Steril. 2003;79(2):330–9.
265. Ebisch IM, Peters WH, Thomas CM, Wetzels AM, Peer PG, Steegers-Theunissen RP. Homocysteine, glutathione and related thiols affect fertility parameters in the (sub)fertile couple. Hum Reprod. 2006;21(7):1725–33.
266. Boxmeer JC, Macklon NS, Lindemans J, Beckers NG, Eijkemans MJ, Laven JS, et al. IVF outcomes are associated with biomarkers of the homocysteine pathway in monofollicular fluid. Hum Reprod. 2009;24(5):1059–66.
267. Haggarty P, McCallum H, McBain H, Andrews K, Duthie S, McNeill G, et al. Effect of B vitamins and genetics on success of in-vitro fertilisation: prospective cohort study. Lancet. 2006;367(9521):1513–9. Epub 2006/05/09.

268. Shahin AY, Ismail AM, Zahran KM, Makhlouf AM. Adding phytoestrogens to clomiphene induction in unexplained infertility patients—a randomized trial. Reprod Biomed Online. 2008;16(4):580–8.
269. Unfer V, Casini ML, Gerli S, Costabile L, Mignosa M, Di Renzo GC. Phytoestrogens may improve the pregnancy rate in in vitro fertilization-embryo transfer cycles: a prospective, controlled, randomized trial. Fertil Steril. 2004;82(6):1509–13.
270. Ozkan S, Jindal S, Greenseid K, Shu J, Zeitlian G, Hickmon C, et al. Replete vitamin D stores predict reproductive success following in vitro fertilization. Fertil Steril. 2010;94(4):1314–9. Epub 2009/07/11.
271. Anifandis GM, Dafopoulos K, Messini CI, Chalvatzas N, Liakos N, Pournaras S, et al. Prognostic value of follicular fluid 25-OH vitamin D and glucose levels in the IVF outcome. Reprod Biol Endocrinol. 2010;8:91. Epub 2010/07/30.
272. Aleyasin A, Hosseini MA, Mahdavi A, Safdarian L, Fallahi P, Mohajeri MR, et al. Predictive value of the level of vitamin D in follicular fluid on the outcome of assisted reproductive technology. Eur J Obstet Gynecol Reprod Biol. 2011;159(1):132–7. Epub 2011/08/13.
273. Rudick B, Ingles S, Chung K, Stanczyk F, Paulson R, Bendikson K. Characterizing the influence of vitamin D levels on IVF outcomes. Hum Reprod. 2012;27(11):3321–7. Epub 2012/08/24.
274. Vujkovic M, de Vries JH, Lindemans J, Macklon NS, van der Spek PJ, Steegers EA, et al. The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. Fertil Steril. 2010;94(6):2096–101. Epub 2010/03/02.
275. Jungheim ES, Frolova AI, Jiang H, Riley JK. Relationship between serum polyunsaturated fatty acids and pregnancy in women undergoing in vitro fertilization. J Clin Endocrinol Metab. 2013;98(8):E1364–8. Epub 2013/06/20.

Chapter 5
Preconceptional Obesity and Fetal Outcomes: Transdisciplinary Evidence for Obesity's Effects on Fertility

Kelle H. Moley and Antonina Frolova

Introduction

The most recent National Health and Nutrition Examination Survey reported that the US age-adjusted prevalence of obesity in adults was 35.7 % in 2010 but has remained stable since 2003 [1], indicating a leveling off of the previously alarming rise. Despite this encouraging trend, several smaller studies showed that rates of prepregnancy obesity among reproductive-age women have continued to rise over this time period [2–4]. This is an important distinction because women of reproductive age are usually not yet burdened by the chronic conditions associated with obesity, such as heart disease, diabetes, and cancer. However, maternal obesity can also affect reproductive functions, contributing to infertility, multiple pregnancy complications, and adverse fetal outcomes [5–7]. The mechanisms by which obesity may hinder reproductive function remain largely unknown; thus, designing preconception counseling or interventions to prevent adverse pregnancy outcomes for obese patients remains a significant challenge.

This chapter will examine the current evidence that obesity affects reproduction at the preconception stages and causes abnormal development and function of oocytes, preimplantation embryos, or both. The chapter will first focus on the clinical evidence in human spontaneous conceptions and those using assisted reproductive technologies (ART) that suggest an early-stage reproductive dysfunction in

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obese women. Next, it will review the animal and in vitro models that demonstrate the effects of obesity on oocyte quality and subsequent early embryo development. Lastly, the chapter will discuss data suggesting that paternal obesity may also have detrimental effects on gamete and embryo quality.

Obesity and Oocyte/Embryo Quality in Human Reproduction

Compared to normal-weight women, obese women have a higher prevalence of infertility—defined as the inability to conceive within 12 months of having regular unprotected intercourse—and subfertility—requiring a longer time to pregnancy once a couple starts trying to conceive [8–13]. For example, analysis of data from 7,327 women enrolled in the Collaborative Perinatal Project revealed that fecundability, or the probability of conceiving in a given cycle, was reduced by 18 % in obese women; they required two months longer to conceive than women with a BMI in the normal range [14]. These findings indicate that obesity may affect female fertility at the earliest stages of pregnancy: pre- and peri-implantation.

Because obesity is a known risk factor for anovulation, subfertility in obese women has often been attributed to this disorder. However, several studies focused specifically on analyzing pregnancy in ovulatory women revealed that obesity negatively affects fertility even after adjusting for menstrual cycle length and regularity [12, 14, 15]. A follow-up prospective cohort study of 3,029 subfertile ovulatory women found that the chance of spontaneous pregnancy was reduced by about 5 % for every BMI unit above 29 kg/m^2 [16]. These data strongly argue that anovulation is not the only mechanism contributing to subfertility in obese women.

Studies directly investigating the effects of obesity on human oocyte and embryo quality are difficult to conduct. Therefore, the data are few and the results are inconsistent. One of the earliest such reports analyzed 398 in vitro fertilization (IVF) cycles and stratified the oocytes into "good quality"—those at metaphase I and II—and "bad quality"—those that were at germinal stages, were postmature, or had a fractured zona [17]. Oocytes retrieved from women with a BMI $\geq$ 25 were significantly less likely to be "good quality" than were those retrieved from women with a BMI of 20–25. Although other studies have found no differences in the quality of oocytes retrieved from obese women and those with a BMI in the normal range, they did report that maternal obesity is associated with lower mean embryo grade and lower numbers of embryos used in IVF cycles [18, 19]. These results suggest that even if an oocyte appears to develop properly and be competent for fertilization, underlying damage may adversely affect subsequent embryo quality. It must be noted, however, that other groups have reported no differences in the number or quality of embryos transferred or the implantation rates between obese and normal-weight women undergoing ART [20, 21].

Obese women who achieve pregnancy with ART are at increased risk for spontaneous abortion in the first trimester [21, 22] and very early pregnancy loss (before week 6 of gestation) [20]. Because embryo development this early in gestation is

most likely affected by gamete quality [23], these findings support a hypothesis that maternal obesity affects oocyte quality before fertilization, thus leading to defects in early embryo development or implantation, and subsequent early pregnancy loss.

It is possible that obesity affects the endometrium and creates an unfavorable environment for the implanting embryo. A way to differentiate between effects on the oocyte and the endometrium is to compare the outcomes of ART between obese women who use autologous oocytes and those who use donor oocytes. One study found that the rate of pregnancy loss persisted in obese women receiving donor oocytes, suggesting that altered endometrial receptivity was responsible [24]. A more recent, larger analysis, which used data from the Society for Assisted Reproductive Technology Clinic Online Reporting System on 45,163 ART embryo transfers, confirmed that obesity was associated with reduced rates of clinical intrauterine pregnancy in women who used autologous oocytes but not in women who used donor oocytes [25]. Although these studies were limited by the small number of women using donor oocytes, the data suggest that maternal obesity affects oocyte quality independent of any endometrial deficiencies.

Oocyte Quality and Function in Murine Models

Given the obvious difficulties with examining reproductive tissues in humans, researchers have turned to animal models to decipher the mechanisms responsible for subfertility in obese females. Several murine models of diet-induced obesity have now been reported. Although the studies differ in the fat content (22–36 %) of the diets, age at and duration of exposure, mouse strain, and other characteristics, they all report that female mice fed a high-fat diet (HFD) have significantly higher total body weight and adipose tissue weight than mice fed regular chow [26–28]. The HFD-fed mice also have elevated levels of fasting serum glucose and free fatty acids, suggesting altered energy metabolism similar to that which occurs in type 2 diabetes mellitus (T2DM). If mated naturally, the obese mice are more likely to be anovulatory than their chow-fed counterparts, but a significantly higher number of oocytes are recovered if they do ovulate [27]. However, if mice are superovulated with gonadotropin, ovarian follicles of the obese mice show evidence of increased apoptosis, and the subsequent oocytes are smaller than those from control mice and exhibit delayed maturation [26, 29]. These observations suggest that maternal obesity affects both follicles and oocytes.

Studies are now suggesting that oocytes from obese mice are impaired in their ability to sustain normal embryo growth. Fertilized oocytes isolated from obese mice demonstrate delayed progression starting from the four-to-eight-cell stage [27]. The resulting blastocysts also have aberrant cellular composition, with a greater number of cells constituting the trophectoderm than the inner cell mass. Another study found that two-cell embryos isolated from HFD-fed obese mice were more likely to be developmentally delayed (remained at or did not reach the two-cell stage) or to degrade than were embryos from control-fed mice [30]. Furthermore,

whereas more than 50 % of embryos isolated from control-diet-fed mice reached the blastocyst stage, less than 20 % of those from HFD-fed mice did so. Notably, when the morphologically normal blastocysts from obese and control females were transferred into uteri of control female mice, those from the obese group exhibited altered growth, characterized by smaller fetal and placental sizes at gestational day 14.5 [26, 30]. Additionally, 20 % of the fetuses from obese mothers had gross brain abnormalities; these were absent in the fetuses from control mice [30]. Together, these data suggest that maternal obesity begins to have detrimental effects as early as the oocyte stage and that some of the defects may be subtle, allowing the early embryo to appear morphologically normal, but lead to significant developmental abnormalities later in gestation. A number of possible mechanisms to explain the lasting effects of preconceptional maternal obesity on oocyte and embryo quality are being explored, such as aberrant glucose and insulin metabolism, mitochondrial dysfunction, cell division defects, and lipotoxicity.

Effects of Maternal Obesity on Oocyte and Embryo Quality: Possible Mechanisms

In an effort to understand the mechanisms by which obesity affects oocyte and embryo quality, it is useful to examine other disorders with similar metabolic consequences. For example, obesity is associated with both hyperglycemia and hyperinsulinemia, which also characterize T2DM. By contrast, type 1 diabetes mellitus (T1DM), which usually occurs as a result of an autoimmune disease that destroys the insulin-producing pancreatic beta cells, is characterized by severe hyperglycemia and low or absent serum insulin levels.

Hyperglycemia

Women with T1DM are known to be at a high risk for miscarriage and giving birth to infants with congenital malformations [31]. A murine genetic model of T1DM has significantly more apoptosis of granulosa and cumulus cells, both of which surround the maturing oocyte, than a non-diabetic control group [32]. Additionally, oocytes isolated from diabetic mice are smaller in size and have a delay in completion of meiosis I, a phenotype analogous to the murine diet-induced obesity model [26]. Although the hyperglycemia that characterizes obesity is less severe than that in T1DM, exposure to excess glucose could be responsible for aberrant follicular and oocyte development in both contexts.

The oocyte is not directly exposed to glucose; it instead receives nutrients, signaling molecules, and metabolic intermediates from the cumulus cells with which it is intimately coupled via gap junctions and paracrine signaling [33]. The cumulus cells in the cumulus–oocyte-complexes (COCs) are responsible for metabolizing

available glucose and supplying the oocyte with its major source of energy, pyruvate [34, 35]. In fact, oocytes denuded of their surrounding cumulus cells cannot metabolize glucose efficiently and require pyruvate supplementation for survival [36]. Therefore, hyperglycemia may indirectly impair oocyte development by altering cumulus cell function. One study showed that cumulus cells from mice with T1DM had increased apoptosis rates and significant mitochondrial dysfunction [37]. The apoptotic cumulus cells also demonstrated a diffuse cytochrome c staining pattern and decreased caspase-3 activation, suggesting activation of the apoptosis pathway. Although the exact initiating event for mitochondrial dysfunction is unclear, glucose deprivation through downregulation of glucose transporters is a strong possibility [33]. In support of this idea, hyperglycemia has been shown to result in downregulation of the glucose transporter GLUT1, decreased glucose uptake, and increased apoptosis in murine preimplantation embryos and cumulus cells [37–40]. Decreased glucose uptake in cumulus cells from mice with chemically induced T1DM also correlates with lower ATP levels in the COCs [41]. Whether or not these are the mechanisms by which maternal obesity affects oocyte quality needs to be determined, but the above models of T1DM and hyperglycemia provide a good starting point for future research.

Hyperinsulinemia

Unlike T1DM, obesity and T2DM are characterized by insulin resistance, which results in hyperinsulinemia in addition to hyperglycemia. Insulin signaling is mediated via the insulin receptor (IR) and insulin-like growth factor receptors (IGF1R and IGF2R), which are expressed in human, bovine, rat, and murine oocytes [42–46]. In vitro exposure of murine COCs to excess insulin produces morphologically normal oocytes but hinders subsequent embryo development from the two-cell to blastocyst stage [47]. However, this deleterious effect is only evident when follicle-stimulating hormone (FSH) is present in the culture media. Because insulin acts on granulosa cells in synergy with FSH to induce their differentiation and steroidogenesis [48], excess insulin may lead to aberrant differentiation of granulosa cells and an inability to support proper oocyte development [49, 50].

A recent study demonstrated that murine and human cumulus cells are capable of insulin-stimulated glucose uptake, whereas murine oocytes are not (human oocytes have not been assayed) [51]. This study also revealed that insulin activates the canonical phosphoinositide 3-kinase (PI3K) pathway, which is required for glucose transporter translocation to the cell surface, in cumulus cells. When mice were fed a HFD for four weeks, resulting in hyperinsulinemia without hyperglycemia, insulin-stimulated glucose uptake in the cumulus cells was significantly reduced. Impaired insulin sensitivity and subsequently decreased glucose uptake in cumulus cells is another potential mechanism for obesity's detrimental effects on oocyte and early embryo development.

Another group recently suggested that the peroxisome proliferator-activated receptor-gamma (PPARγ) pathway may mediate the adverse effects of maternal obesity on oocyte and early embryo development [27]. Activation of the PPARγ pathway in adipocytes stimulates transcription of genes involved in lipid and glucose metabolism, resulting in improved insulin and lipid homeostasis [52]. PPARγ is also expressed in murine, ruminant, and human ovarian tissues, particularly in the granulosa cells [53]. Treatment of mice with the PPARγ agonist and the insulin-sensitizing agent rosiglitazone for 4 days before ovulation reverses the delays in early embryo progression observed in fertilized oocytes harvested from mice fed a HFD prior to conception [27]. The treatment also shows a trend towards reversing the cellular composition abnormalities in resulting blastocysts. In addition, rosiglitazone alters the expression of several PPARγ target genes within the ovary, suggesting a direct effect in this tissue [27]. However, its administration leads to significant weight loss and lower levels of serum glucose, serum triglycerides, and insulin in HFD-fed mice. Thus, it is still unclear whether the observed effects on oocytes and early embryo development are a consequence of whole-body improvements in insulin sensitivity and subsequent reversal of hyperinsulinemia and hyperglycemia or reflect direct action of rosiglitazone on the ovary. Although further studies are required, we can glean some additional answers from rats with a conditional knockout of PPARγ in the ovary. The resulting females are either infertile or severely subfertile [54]. They have normal follicular development, ovulation, and corpus luteum size, but the majority of the resulting embryos fail to implant. Because PPARγ was specifically knocked down in the ovary but not the uterus in these experiments, it is reasonable to hypothesize that PPARγ plays a significant role in ovarian function, either through regulation of oocyte competence or steroidogenesis after ovulation. Together, the above studies suggest that insulin sensitizers that specifically affect the PPARγ pathway may reverse some of the adverse effects of hyperinsulinemia on oocyte developmental competence by altering glucose metabolism in granulosa and cumulus cells.

Mitochondrial Dysfunction

Mitochondrial abnormalities are another potential mechanism to explain poor oocyte quality and impaired embryo development in obese women. Like all other cells, oocytes rely on mitochondria for energy production in the form of adenosine triphosphate (ATP). As mentioned above, it is thought that the surrounding cumulus cells provide the oocyte with pyruvate [35], which is metabolized through the mitochondrial oxidative pathways to synthesize ATP. The importance of pyruvate metabolism was illustrated by a study examining the effects of conditional inactivation of one of the subunits of the pyruvate dehydrogenase complex, *Pdha1* [55]. The resulting oocytes appeared to progress through the growth phase but were unable to support embryo development after fertilization. As expected, the *Pdha1*-deficient oocytes also had decreased ATP levels. Interestingly, the developmental defect was

partially rescued in oocytes that were matured within intact COCs, suggesting that cumulus cells can provide the oocyte with ATP or other metabolites through gap junctions [55].

Mitochondrial distribution and morphology are altered in oocytes harvested from diet-induced obese mice [28]. Whereas mitochondria in control-derived oocytes are distributed diffusely throughout the ooplasm, mitochondria in obese-derived oocytes are perinuclear and in cortical clusters. Transmission electron microscopy of oocytes and the surrounding cumulus cells from obese mice reveal mitochondria that have fewer and disarrayed cristae, increased swelling, more vacuoles, and decreased electron density of the matrix [30]. Similar aberrations in mitochondrial morphology have been found in oocytes and cumulus cells from T1DM mouse models and in embryos undergoing cleavage arrest [37, 56, 57].

Maternal obesity also appears to alter the function of mitochondria in oocytes. Oxidative phosphorylation in mitochondria produces reactive oxygen species (ROS), which can damage the cell when present in excess. Mitochondria tightly regulate the redox status of cells by regenerating antioxidant systems and maintaining the NADPH:NADP+ ratio in the cytosol [58]. Using a low-toxicity potentiometric fluorescent dye, one group observed that oocytes from obese mice had a significantly higher inner mitochondrial membrane potential than those from control mice, and this difference persisted in the zygotes [28]. This was likely due to an increase in mitochondrial respiration because these oocytes and zygotes also had a shift of the redox status towards oxidation and increased rates of ROS production. One proposed mechanism for these findings is that the increased availability of energy substrates, such as carbohydrates and fatty acids, found in an obesogenic state causes mitochondrial hyperactivity and increased ROS production and ultimately leads to mitochondrial dysfunction and oocyte damage. A growing body of evidence suggests that abnormal energy balance in the oocyte due to mitochondrial abnormalities leads to abnormal spindle and chromosome alignments, oocyte maturation failure, and early embryo developmental defects [59].

Mitochondrial dysfunction induced by excess ROS is thought to cause compensatory upregulation of mitochondrial biogenesis in numerous cell types [60], and there is evidence that this may be the case in oocytes as well [57]. Oocytes derived from mice fed a HFD have significantly higher mitochondrial DNA copy number than those from control-fed mice [28, 30]. These oocytes also have increased expression of genes involved in mitochondrial biogenesis, including *PGC-1α*, *Drp-1*, *TFAM*, and *NRF1*. Interestingly, oocytes form obese mice have lower levels of citrate but unchanged levels of ATP, suggesting that although mitochondrial function is disturbed, overall oocyte metabolism is not, perhaps as a result of compensatory increases in mitochondrial number [30]. However, zygotes isolated from obese mice 24 h after mating show no evidence of increased mitochondrial biogenesis [28], nor do the number of zygotes recovered from the HFD and control groups differ. This is surprising given that signs of ROS-induced damage persist in obese-derived zygotes. This finding might be explained by the fact that a period of mitochondrial DNA turnover and maternal RNA destruction occurs shortly after fertilization [61]. These initial studies using the HFD-fed

murine model are still only correlative, with no proof that ROS-induced mitochondrial damage is responsible for the inability of the oocytes to support further embryo development. Further studies will also be needed to determine whether obesity's effects on ROS homeostasis contribute to the long-term developmental deficiencies observed in the offspring of obese mice, such as small fetal size and congenital abnormalities.

Spindle and Chromosomal Alignment Defects

Oocytes from mice on a HFD have a higher incidence of metaphase II chromosome misalignment, ectopic microtubule organizing centers, and malformed spindles than oocytes from mice fed a control diet [30]. Similar chromosomal abnormalities are found in oocytes from T1DM mouse models [41, 57]. It is thought that proper chromosome alignment and spindle formation relies on mitochondrial function and distribution within the cell [57, 62]. The *Pdha1*-deficient mice described above provide evidence for this; 98.4 % of the oocytes from these mice have gross abnormalities in meiotic spindle formation, chromosome alignment, and meiotic maturation [55]. Studies also link lower ATP levels in oocytes with abnormal spindle formation, suggesting that meiotic spindle formation requires adequate energy supplies [55, 63]. Alternatively, a biochemical study showed that microtubule assembly during spindle formation requires adequate NADPH, most likely for maintaining a proper redox state [64]. Although the pentose phosphate pathway was the provider of NADPH in this study, we know that in the oocyte, where glucose is poorly metabolized, mitochondrial metabolism of pyruvate regulates NADPH availability [58].

Oocytes with significant spindle or chromosomal alignment abnormalities are likely to fail to fertilize, generate embryos with aneuploidy, or produce embryos incapable of normal developmental progression. These abnormalities could contribute to the higher rates of infertility and spontaneous pregnancy loss observed in obese women. In support of this idea, a recent study reported that oocytes from obese women undergoing IVF often have gross morphological abnormalities, spindle anomalies, and non-aligned chromosomes [65, 66].

Lipotoxicity

Although the full function of adipose tissue is poorly understood, it is known that this tissue stores excess nutrients in the form of triglycerides and that it also plays an endocrine role as a source of adipokines [67, 68]. Accumulating evidence now suggests that both of these functions can become dysregulated in the context of obesity, thus damaging other tissues, including the reproductive tract [69]. As the storage capacity of adipose tissue becomes overwhelmed, triglycerides begin to

accumulate in non-adipose tissues. The resulting high levels of fatty acids cause a lipid-induced apoptotic cascade-termed lipotoxicity [70]. Although this process is not yet fully understood, the resulting increased oxidative stress is thought to induce endoplasmic reticulum (ER) stress, an unfolded-protein response, and apoptosis. Prime examples of lipotoxicity include lipid accumulation in the liver, skeletal muscle, heart, and pancreas; such accumulation contributes to the development of obesity, diabetes, and heart failure.

Mammalian oocytes contain lipid droplets, which are thought to be necessary for oocyte and preimplantation embryo development [71, 72]. For example, fatty acid oxidation is required for oocyte germinal vesicle breakdown and early embryo development through the blastocyst stage in mice [73, 74]. Mice fed a HFD for 4 weeks have higher levels of lipids within their oocytes and surrounding cumulus cells than mice fed a control diet [29]. These COCs also have increased expression of the ER stress marker genes *ATF4* and *GRP78* and decreased fertilization rates. Additionally, Wu et al. found that *ATF4* expression is elevated in granulosa cells from obese women, suggesting that ER stress contributes to lower conception rates in obese women [29]. The source of the excess lipid within oocytes and cumulus cells remains an unanswered question. Possibilities include de novo lipogenesis in the oocyte and cumulus cells or diffusion from the maternal serum or follicular fluid. Consistent with the latter possibility, increased triglyceride levels have been observed in the follicular fluid of obese women [75]. Another study also found that elevated follicular free fatty acid (FFA) levels are associated with poor COC morphology in women undergoing IVF [76]. Interestingly, this study found that serum FFA levels do not correlate with follicular FFA levels, suggesting that the follicular environment is the source for the excess lipids accumulating in the COCs and granulosa cells.

As adipose tissue accumulates to accommodate the excess energy, adipocytes grow in quantity and size and alter their secretory profiles [67]. One important secreted adipokine is leptin (the product of the *Obesity* [*Ob*] gene in mice), which primarily acts on the hypothalamus to regulate satiety. Levels of leptin in the serum and leptin mRNA in adipocytes both directly correlate with BMI in humans [77]. In addition to its stimulatory effects on the hypothalamic–pituitary–gonadal axis [78], leptin appears to directly regulate ovarian function. In fact, the leptin receptor is expressed in human and rodent oocytes, theca cells, and granulosa cells [79, 80]. Additionally, follicular fluid from women undergoing IVF contains leptin, the levels of leptin positively correlate with BMI [81], and increased follicular leptin levels are associated with poor ovarian response and decreased IVF success rates [82–84]. Numerous studies using human tissue and various animal models have shown that excess leptin has deleterious effects on oocyte and embryo development [83]. One such study reported that although there were no differences in number of oocytes retrieved, fertilized, or developed past the cleavage stage, the embryos generated from oocytes retrieved from women with high leptin:BMI ratios were of reduced quality at day three post-retrieval [84]. The subsequent implantation rates were also significantly lower in the high vs. low leptin:BMI groups (13.2 % vs. 26.7 %). These findings support a hypothesis that excess leptin has deleterious effects on the oocyte,

which in turn affect embryo quality and lead to increased pregnancy loss. It is also possible that developmental defects resulting from elevated leptin at the preconception stage persist in the surviving fetuses and contribute to some of the congenital defects reported in children of obese mothers.

Paternal Obesity and Implications for Fertility and Embryo Health

Although the majority of research has focused on maternal obesity and reproductive outcomes, recent data indicate that paternal obesity may also cause changes in the semen that alter embryo development and contribute to infertility [85, 86]. According to population studies, a high paternal BMI is associated with a longer time to conception and an increased risk of infertility among couples trying to conceive [8, 87]. This is in part due to lower sperm quality leading to decreased fertilization rates [88]. However, among couples undergoing IVF, paternal obesity is associated with decreased number of embryos progressing to blastocyst stage and lower pregnancy rates after embryo transfer [89, 90]. These findings suggest that paternal obesity compromises sperm function and the ability to generate a normal embryo.

Animal models of diet-induced paternal obesity support the observations in human pregnancies. Embryos originating from HFD-fed male mice have a reduced rate of progression to blastocyst stage, decreased implantation rates, and alterations in the cellular composition of the resulting blastocysts [85, 86]. To specifically analyze effects on sperm and eliminate confounders such as mating time, alterations in seminal fluid, and mating behavior, one group generated embryos by performing IVF with sperm from HFD- vs. control-fed mice [85]. Thus, they were able to demonstrate that the delay in early development, altered cell-lineage allocation, and lower implantation rates are due to defects in the sperm. This group also reported lasting effects of paternal obesity on the offspring, as evidenced by delayed fetal and placental development at gestation day 13.5.

Few mechanisms for how paternal obesity affects embryo development and survival have been proposed. Bakos et al. implicated increased oxidative stress and subsequent DNA damage in spermatozoa from obese mice [91]. DNA damage has also been observed in sperm from obese men [92], and this parameter has been associated with increased early pregnancy loss in spontaneous conceptions [93, 94]. Another group suggested that mitochondrial dysfunction observed in embryos sired by obese male mice may be responsible for the associated developmental delays [85]. Proteins encoded by paternal nuclear DNA are incorporated into the respiratory chain starting at the two-cell stage and, if the corresponding genes have obesity-induced DNA damage, could thus contribute to mitochondrial dysfunction. Lastly, epigenetic modifications in sperm from obese males have been proposed as a possible mechanism for altered embryo development [95]. For example, sperm from HFD-fed mice have increased levels of histone acetylation and DNA damage [96]. Similarly, obesity has been associated with hypomethylation of imprinted genes in

some tissues [97]; although this link has not been demonstrated in sperm, such hypomethylation has been observed in sperm from infertile men and has been linked with early pregnancy loss in rats [98, 99].

Conclusions and Future Directions

A link between parental obesity and subsequent oocyte quality and developmental competence has been established in both humans and mice. However, the mechanisms responsible for disruption of embryo development after exposure of gametes to an obesogenic environment are only beginning to be understood. Some of the proposed mechanisms in this chapter are based on correlative data and need extensive further experimental data for confirmation. Others are extrapolated from disease models, such as T1DM and T2DM, and will need to be confirmed in the context of obesity. Additionally, several studies highlight that further work is required to differentiate between direct effects of maternal obesity on the oocyte vs. the surrounding cumulus and granulosa cells. As the mechanisms by which obesity can alter early reproductive function are elucidated, specific interventions to decrease infertility rates and prevent adverse pregnancy outcomes in obese patients can be developed.

References

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012;307(5):491–7.
2. Fisher SC, Kim SY, Sharma AJ, Rochat R, Morrow B. Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003-2009. Prev Med. 2013;56(6): 372–8.
3. Kim SY, Dietz PM, England L, Morrow B, Callaghan WM. Trends in pre-pregnancy obesity in nine states, 1993-2003. Obesity (Silver Spring). 2007;15(4):986–93.
4. Hinkle SN, Sharma AJ, Kim SY, Park S, Dalenius K, Brindley PL, et al. Prepregnancy obesity trends among low-income women, United States, 1999-2008. Matern Child Health J. 2012; 16(7):1339–48.
5. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology. 2003;14(3):368–74.
6. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA. 2009;301(6):636–50.
7. Ovesen P, Rasmussen S, Kesmodel U. Effect of prepregnancy maternal overweight and obesity on pregnancy outcome. Obstet Gynecol. 2011;118(2 Pt 1):305–12.
8. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI, Olsen J. Subfecundity in overweight and obese couples. Hum Reprod. 2007;22(6):1634–7.
9. Green BB, Weiss NS, Daling JR. Risk of ovulatory infertility in relation to body weight. Fertil Steril. 1988;50(5):721–6.
10. Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JD, Vrieswijk B, et al. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ. 1993;306(6876):484–7.

11. Rich-Edwards JW, Goldman MB, Willett WC, Hunter DJ, Stampfer MJ, Colditz GA, et al. Adolescent body mass index and infertility caused by ovulatory disorder. Am J Obstet Gynecol. 1994;171(1):171–7.
12. Bolumar F, Olsen J, Rebagliato M, Saez-Lloret I, Bisanti L. Body mass index and delayed conception: a European Multicenter Study on Infertility and Subfecundity. Am J Epidemiol. 2000;151(11):1072–9.
13. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril. 2004;81(2):384–92.
14. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. Hum Reprod. 2007;22(2):414–20.
15. Jensen TK, Scheike T, Keiding N, Schaumburg I, Grandjean P. Fecundability in relation to body mass and menstrual cycle patterns. Epidemiology. 1999;10(4):422–8.
16. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Burggraaff JM, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod. 2008;23(2):324–8.
17. Wittemer C, Ohl J, Bailly M, Bettahar-Lebugle K, Nisand I. Does body mass index of infertile women have an impact on IVF procedure and outcome? J Assist Reprod Genet. 2000; 17(10):547–52.
18. Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod Biomed Online. 2007;15(5): 532–8.
19. Carrell DT, Jones KP, Peterson CM, Aoki V, Emery BR, Campbell BR. Body mass index is inversely related to intrafollicular HCG concentrations, embryo quality and IVF outcome. Reprod Biomed Online. 2001;3(2):109–11.
20. Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod. 2004;19(11): 2523–8.
21. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod. 2004;19(7):1644–6.
22. Wang JX, Davies MJ, Norman RJ. Obesity increases the risk of spontaneous abortion during infertility treatment. Obes Res. 2002;10(6):551–4.
23. Swain JE, Pool TB. ART failure: oocyte contributions to unsuccessful fertilization. Hum Reprod Update. 2008;14(5):431–46.
24. Bellver J, Rossal LP, Bosch E, Zuniga A, Corona JT, Melendez F, et al. Obesity and the risk of spontaneous abortion after oocyte donation. Fertil Steril. 2003;79(5):1136–40.
25. Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod. 2011;26(1):245–52.
26. Jungheim ES, Schoeller EL, Marquard KL, Louden ED, Schaffer JE, Moley KH. Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. Endocrinology. 2010;151(8):4039–46.
27. Minge CE, Bennett BD, Norman RJ, Robker RL. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. Endocrinology. 2008;149(5):2646–56.
28. Igosheva N, Abramov AY, Poston L, Eckert JJ, Fleming TP, Duchen MR, et al. Maternal diet-induced obesity alters mitochondrial activity and redox status in mouse oocytes and zygotes. PLoS One. 2010;5(4):e10074.
29. Wu LL, Dunning KR, Yang X, Russell DL, Lane M, Norman RJ, et al. High-fat diet causes lipotoxicity responses in cumulus-oocyte complexes and decreased fertilization rates. Endocrinology. 2010;151(11):5438–45.
30. Luzzo KM, Wang Q, Purcell SH, Chi M, Jimenez PT, Grindler N, et al. High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/ brain defects. PLoS One. 2012;7(11):e49217.

31. Greene MF. Spontaneous abortions and major malformations in women with diabetes mellitus. Semin Reprod Endocrinol. 1999;17(2):127–36.
32. Chang AS, Dale AN, Moley KH. Maternal diabetes adversely affects preovulatory oocyte maturation, development, and granulosa cell apoptosis. Endocrinology. 2005;146(5): 2445–53.
33. Purcell SH, Moley KH. The impact of obesity on egg quality. J Assist Reprod Genet. 2011;28(6):517–24.
34. Harris SE, Leese HJ, Gosden RG, Picton HM. Pyruvate and oxygen consumption throughout the growth and development of murine oocytes. Mol Reprod Dev. 2009;76(3):231–8.
35. Brinster RL. Oxidation of pyruvate and glucose by oocytes of the mouse and rhesus monkey. J Reprod Fertil. 1971;24(2):187–91.
36. Biggers JD, Whittingham DG, Donahue RP. The pattern of energy metabolism in the mouse oocyte and zygote. Proc Natl Acad Sci U S A. 1967;58(2):560–7.
37. Wang Q, Frolova AI, Purcell S, Adastra K, Schoeller E, Chi MM, et al. Mitochondrial dysfunction and apoptosis in cumulus cells of type I diabetic mice. PLoS One. 2010;5(12):e15901.
38. Moley KH, Chi MM, Knudson CM, Korsmeyer SJ, Mueckler MM. Hyperglycemia induces apoptosis in pre-implantation embryos through cell death effector pathways. Nat Med. 1998;4(12):1421–4.
39. Moley KH, Chi MM, Mueckler MM. Maternal hyperglycemia alters glucose transport and utilization in mouse preimplantation embryos. Am J Physiol. 1998;275(1 Pt 1):E38–47.
40. Moley KH, Mueckler MM. Glucose transport and apoptosis. Apoptosis. 2000;5(2):99–105.
41. Wang Q, Chi MM, Moley KH. Live imaging reveals the link between decreased glucose uptake in ovarian cumulus cells and impaired oocyte quality in female diabetic mice. Endocrinology. 2012;153(4):1984–9.
42. Lighten AD, Hardy K, Winston RM, Moore GE. Expression of mRNA for the insulin-like growth factors and their receptors in human preimplantation embryos. Mol Reprod Dev. 1997;47(2):134–9.
43. Samoto T, Maruo T, Ladines-Llave CA, Matsuo H, Deguchi J, Barnea ER, et al. Insulin receptor expression in follicular and stromal compartments of the human ovary over the course of follicular growth, regression and atresia. Endocr J. 1993;40(6):715–26.
44. Watson AJ, Hogan A, Hahnel A, Wiemer KE, Schultz GA. Expression of growth factor ligand and receptor genes in the preimplantation bovine embryo. Mol Reprod Dev. 1992;31(2): 87–95.
45. Zhang X, Kidder GM, Watson AJ, Schultz GA, Armstrong DT. Possible roles of insulin and insulin-like growth factors in rat preimplantation development: investigation of gene expression by reverse transcription-polymerase chain reaction. J Reprod Fertil. 1994;100(2): 375–80.
46. Acevedo N, Ding J, Smith GD. Insulin signaling in mouse oocytes. Biol Reprod. 2007; 77(5):872–9.
47. Eppig JJ, O'Brien MJ, Pendola FL, Watanabe S. Factors affecting the developmental competence of mouse oocytes grown in vitro: follicle-stimulating hormone and insulin. Biol Reprod. 1998;59(6):1445–53.
48. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocr Rev. 1987;8(2):132–41.
49. Latham KE, Bautista FD, Hirao Y, O'Brien MJ, Eppig JJ. Comparison of protein synthesis patterns in mouse cumulus cells and mural granulosa cells: effects of follicle-stimulating hormone and insulin on granulosa cell differentiation in vitro. Biol Reprod. 1999;61(2):482–92.
50. Eppig JJ, Hosoe M, O'Brien MJ, Pendola FM, Requena A, Watanabe S. Conditions that affect acquisition of developmental competence by mouse oocytes in vitro: FSH, insulin, glucose and ascorbic acid. Mol Cell Endocrinol. 2000;163(1–2):109–16.
51. Purcell SH, Chi MM, Lanzendorf S, Moley KH. Insulin-stimulated glucose uptake occurs in specialized cells within the cumulus oocyte complex. Endocrinology. 2012;153(5):2444–54.
52. Picard F, Auwerx J. PPAR(gamma) and glucose homeostasis. Annu Rev Nutr. 2002;22: 167–97.

53. Komar CM. Peroxisome proliferator-activated receptors (PPARs) and ovarian function—implications for regulating steroidogenesis, differentiation, and tissue remodeling. Reprod Biol Endocrinol. 2005;3:41.
54. Cui Y, Miyoshi K, Claudio E, Siebenlist UK, Gonzalez FJ, Flaws J, et al. Loss of the peroxisome proliferation-activated receptor gamma (PPARgamma) does not affect mammary development and propensity for tumor formation but leads to reduced fertility. J Biol Chem. 2002;277(20):17830–5.
55. Johnson MT, Freeman EA, Gardner DK, Hunt PA. Oxidative metabolism of pyruvate is required for meiotic maturation of murine oocytes in vivo. Biol Reprod. 2007;77(1):2–8.
56. Muggleton-Harris AL, Brown JJ. Cytoplasmic factors influence mitochondrial reorganization and resumption of cleavage during culture of early mouse embryos. Hum Reprod. 1988;3(8):1020–8.
57. Wang Q, Ratchford AM, Chi MM, Schoeller E, Frolova A, Schedl T, et al. Maternal diabetes causes mitochondrial dysfunction and meiotic defects in murine oocytes. Mol Endocrinol. 2009;23(10):1603–12.
58. Dumollard R, Ward Z, Carroll J, Duchen MR. Regulation of redox metabolism in the mouse oocyte and embryo. Development. 2007;134(3):455–65.
59. Van Blerkom J. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. Mitochondrion. 2011;11(5):797–813.
60. Lee HC, Wei YH. Mitochondrial biogenesis and mitochondrial DNA maintenance of mammalian cells under oxidative stress. Int J Biochem Cell Biol. 2005;37(4):822–34.
61. McConnell JM, Petrie L. Mitochondrial DNA turnover occurs during preimplantation development and can be modulated by environmental factors. Reprod Biomed Online. 2004;9(4):418–24.
62. Van Blerkom J. Mitochondria in human oogenesis and preimplantation embryogenesis: engines of metabolism, ionic regulation and developmental competence. Reproduction. 2004;128(3):269–80.
63. Zhang X, Wu XQ, Lu S, Guo YL, Ma X. Deficit of mitochondria-derived ATP during oxidative stress impairs mouse MII oocyte spindles. Cell Res. 2006;16(10):841–50.
64. Groen AC, Coughlin M, Mitchison TJ. Microtubule assembly in meiotic extract requires glycogen. Mol Biol Cell. 2011;22(17):3139–51.
65. Machtinger R, Combelles CM, Missmer SA, Correia KF, Fox JH, Racowsky C. The association between severe obesity and characteristics of failed fertilized oocytes. Hum Reprod. 2012;27(11):3198–207.
66. Depalo R, Garruti G, Totaro I, Panzarino M, Vacca MP, Giorgino F, et al. Oocyte morphological abnormalities in overweight women undergoing in vitro fertilization cycles. Gynecol Endocrinol. 2011;27(11):880–4.
67. Rajala MW, Scherer PE. Minireview: the adipocyte—at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology. 2003;144(9):3765–73.
68. Suganami T, Tanaka M, Ogawa Y. Adipose tissue inflammation and ectopic lipid accumulation. Endocr J. 2012;59(10):849–57.
69. Robker RL, Wu LL, Yang X. Inflammatory pathways linking obesity and ovarian dysfunction. J Reprod Immunol. 2011;88(2):142–8.
70. Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol. 2003;14(3):281–7.
71. Yang X, Dunning KR, Wu LL, Hickey TE, Norman RJ, Russell DL, et al. Identification of perilipin-2 as a lipid droplet protein regulated in oocytes during maturation. Reprod Fertil Dev. 2010;22(8):1262–71.
72. Sturmey RG, Reis A, Leese HJ, McEvoy TG. Role of fatty acids in energy provision during oocyte maturation and early embryo development. Reprod Domest Anim. 2009;44 Suppl 3:50–8.
73. Downs SM, Mosey JL, Klinger J. Fatty acid oxidation and meiotic resumption in mouse oocytes. Mol Reprod Dev. 2009;76(9):844–53.
74. Dunning KR, Cashman K, Russell DL, Thompson JG, Norman RJ, Robker RL. Beta-oxidation is essential for mouse oocyte developmental competence and early embryo development. Biol Reprod. 2010;83(6):909–18.

75. Robker RL, Akison LK, Bennett BD, Thrupp PN, Chura LR, Russell DL, et al. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women. J Clin Endocrinol Metab. 2009;94(5):1533–40.
76. Jungheim ES, Macones GA, Odem RR, Patterson BW, Lanzendorf SE, Ratts VS, et al. Associations between free fatty acids, cumulus oocyte complex morphology and ovarian function during in vitro fertilization. Fertil Steril. 2011;95(6):1970–4.
77. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334(5):292–5.
78. Moschos S, Chan JL, Mantzoros CS. Leptin and reproduction: a review. Fertil Steril. 2002;77(3):433–44.
79. Cioffi JA, Van Blerkom J, Antczak M, Shafer A, Wittmer S, Snodgrass HR. The expression of leptin and its receptors in pre-ovulatory human follicles. Mol Hum Reprod. 1997;3(6): 467–72.
80. Ryan NK, Woodhouse CM, Van der Hoek KH, Gilchrist RB, Armstrong DT, Norman RJ. Expression of leptin and its receptor in the murine ovary: possible role in the regulation of oocyte maturation. Biol Reprod. 2002;66(5):1548–54.
81. Hill MJ, Uyehara CF, Hashiro GM, Frattarelli JL. The utility of serum leptin and follicular fluid leptin, estradiol, and progesterone levels during an in vitro fertilization cycle. J Assist Reprod Genet. 2007;24(5):183–8.
82. Butzow TL, Moilanen JM, Lehtovirta M, Tuomi T, Hovatta O, Siegberg R, et al. Serum and follicular fluid leptin during in vitro fertilization: relationship among leptin increase, body fat mass, and reduced ovarian response. J Clin Endocrinol Metab. 1999;84(9):3135–9.
83. Brannian JD, Schmidt SM, Kreger DO, Hansen KA. Baseline non-fasting serum leptin concentration to body mass index ratio is predictive of IVF outcomes. Hum Reprod. 2001; 16(9):1819–26.
84. Mantzoros CS, Cramer DW, Liberman RF, Barbieri RL. Predictive value of serum and follicular fluid leptin concentrations during assisted reproductive cycles in normal women and in women with the polycystic ovarian syndrome. Hum Reprod. 2000;15(3):539–44.
85. Binder NK, Hannan NJ, Gardner DK. Paternal diet-induced obesity retards early mouse embryo development, mitochondrial activity and pregnancy health. PLoS One. 2012; 7(12):e52304.
86. Mitchell M, Bakos HW, Lane M. Paternal diet-induced obesity impairs embryo development and implantation in the mouse. Fertil Steril. 2011;95(4):1349–53.
87. Nguyen RH, Wilcox AJ, Skjaerven R, Baird DD. Men's body mass index and infertility. Hum Reprod. 2007;22(9):2488–93.
88. Du Plessis SS, Cabler S, McAlister DA, Sabanegh E, Agarwal A. The effect of obesity on sperm disorders and male infertility. Nat Rev Urol. 2010;7(3):153–61.
89. Bakos HW, Henshaw RC, Mitchell M, Lane M. Paternal body mass index is associated with decreased blastocyst development and reduced live birth rates following assisted reproductive technology. Fertil Steril. 2011;95(5):1700–4.
90. Keltz J, Zapantis A, Jindal SK, Lieman HJ, Santoro N, Polotsky AJ. Overweight men: clinical pregnancy after ART is decreased in IVF but not in ICSI cycles. J Assist Reprod Genet. 2010;27(9–10):539–44.
91. Bakos HW, Mitchell M, Setchell BP, Lane M. The effect of paternal diet-induced obesity on sperm function and fertilization in a mouse model. Int J Androl. 2011;34(5 Pt 1):402–10.
92. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. Fertil Steril. 2010;93(7):2222–31.
93. Kumar K, Deka D, Singh A, Mitra DK, Vanitha BR, Dada R. Predictive value of DNA integrity analysis in idiopathic recurrent pregnancy loss following spontaneous conception. J Assist Reprod Genet. 2012;29(9):861–7.
94. Brahem S, Mehdi M, Landolsi H, Mougou S, Elghezal H, Saad A. Semen parameters and sperm DNA fragmentation as causes of recurrent pregnancy loss. Urology. 2011;78(4): 792–6.

95. Palmer NO, Bakos HW, Fullston T, Lane M. Impact of obesity on male fertility, sperm function and molecular composition. Spermatogenesis. 2012;2(4):253–63.
96. Palmer NO, Fullston T, Mitchell M, Setchell BP, Lane M. SIRT6 in mouse spermatogenesis is modulated by diet-induced obesity. Reprod Fertil Dev. 2011;23(7):929–39.
97. Barres R, Zierath JR. DNA methylation in metabolic disorders. Am J Clin Nutr. 2011;93(4):897S–900.
98. Tunc O, Tremellen K. Oxidative DNA damage impairs global sperm DNA methylation in infertile men. J Assist Reprod Genet. 2009;26(9–10):537–44.
99. Pathak S, Kedia-Mokashi N, Saxena M, D'Souza R, Maitra A, Parte P, et al. Effect of tamoxifen treatment on global and insulin-like growth factor 2-H19 locus-specific DNA methylation in rat spermatozoa and its association with embryo loss. Fertil Steril. 2009;91(5 Suppl): 2253–63.

Chapter 6
Fertility Treatment Outcomes in Obese Women

Erika M. Munch and Divya Kelath Shah

Introduction

Despite a growing body of literature describing the relationship between body mass index (BMI) and fertility treatment outcome, transmission of this knowledge to patients remains inadequate. Though many women are aware of a general adverse impact of obesity on reproductive health, the scope of knowledge is often limited to late pregnancy complications such as higher rates of preeclampsia, gestational diabetes, stillbirth, and others as discussed in Chap. 10. By comparison, women often have little information about the effect of excess body weight on conception and early pregnancy.

This knowledge gap may reflect the challenge that clinicians face when attempting to interpret and apply the available data in a way that patients can understand. In a cursory view of the literature, it would be easy to see why this is difficult: heterogeneous definitions and clinical endpoints, inconsistencies in protocols among treatment centers, and a lack of prospective clinical trials make summarization of these published studies a formidable task.

Clinicians need a thorough but accessible review of the literature that allows them to convey pertinent information directly to patients and colleagues in order to improve educational efforts as well as clinical outcomes. To summarize the current literature of fertility treatment outcomes in obese women, we chose an approach that parallels the infertility evaluation and treatment process, highlighting the impact of obesity on each parameter in an accessible but comprehensive manner that facilitates patient counseling.

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Ovulation and Spontaneous Conception

Assessment of ovulatory status should be the first step in the infertility evaluation of obese women, as subsequent treatment is frequently based on the presence or absence of spontaneous ovulation.

Oligo- or anovulation is frequently associated with polycystic ovarian syndrome (PCOS). Over 50 % of women with PCOS and associated oligo-anovulation are overweight or obese [1, 2]. The ovulatory dysfunction in many PCOS patients is mediated by insulin resistance and hyperinsulinemia, which is augmented by the degree of obesity [3]. Insulin stimulates androgen production by ovarian theca cells and inhibits hepatic synthesis of sex hormone-binding globulin, resulting in an androgen-dominant environment that inhibits normal follicular maturation [4, 5]. With longer cycles and fewer ovulatory events, the chances of spontaneous conception for women with oligo-ovulation diminish dramatically; thus, interventions aimed to achieve regular ovulation are critical initial treatments for infertile obese women.

Spontaneous conception rates are compromised, however, even among ovulatory obese women [6–8]. A prospective Danish study assessed spontaneous pregnancy outcomes in more than 3,000 subfertile women. Regularly ovulating women with a BMI > 29 kg/m^2 had a significantly lower probability of pregnancy within the next year (HR 0.95 [95 % CI 0.91–0.99]), compared to women with a BMI of 21–29 kg/m^2. Additionally, the investigators noted a 5 % decrease in the probability of pregnancy for each unit of BMI > 29 kg/m^2, which was comparable to an age-related fertility decline of 1 year [9].

Weight Loss for Ovulation Induction

Sustained weight loss with the goal to resume ovulatory function is an effective but difficult—and therefore underutilized—treatment for obesity-related subfertility. Even small reductions in weight can result in a dramatic return of ovulation and pregnancy [10–12]. One novel small prospective study [11] examined 18 infertile, clomiphene-resistant obese women who participated in 6-month program of weekly sessions comprised of 1 h of exercise and low-impact aerobics, followed by a 1 h seminar on weight-related topics such as nutrition, eating habits, and obesity's effect on the endocrine system. The sessions were structured so that pursuit or discussion of infertility treatments was specifically excluded; the focus was to encourage positive changes in lifestyle and health independent of fertility concerns. Women were encouraged to participate in other extracurricular exercise activity and group support sessions outside of these mandatory sessions. Outcomes for women who completed the study (completion group) were compared to those who dropped out before completing the study (dropout group). Pregnancy outcomes for all women, including those who declined participation in the intervention (declination group), were followed for an additional year. Women who completed the full 6-month program lost an average of 6.3 kg. There were significant decreases in serum testosterone and insulin, and rises in sex hormone-binding globulin for

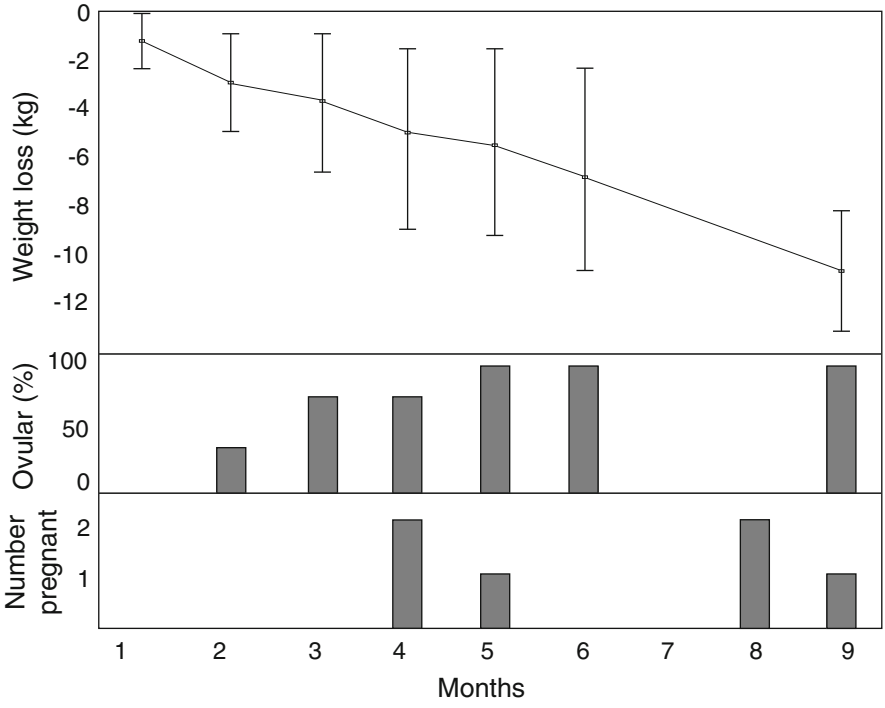

Fig. 6.1 Changes in weight and ovulation rates during the study period for those subjects who completed 6 months of trial. The number of spontaneous pregnancies is shown in the *bottom panel*. From Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Human Reproduction. 1995 Oct;10(10):2705–12. PubMed PMID: 8567797. With permission from Oxford University Press, UK

women in both the completion and dropout groups. Twelve of thirteen women in the completion group regained spontaneous ovulation after the 6-month intervention, compared to none of the dropout group. Eleven of the twelve women in the completion group who attempted pregnancy conceived within 1 year, as compared to 0/5 and 1/12 women in the dropout and declination groups, respectively (Fig. 6.1). Over 90 % of the participants resumed ovulation after a weight loss of only 4.3 kg; this amount is far less than the 5–10 % of total body weight that obese women are often recommended to lose to achieve ovulation. Obese women seeking to improve fertility with minimal pharmaceutical or procedural intervention should find these results encouraging.

Sustained weight loss is also among the more economical fertility treatments, as it is considerably less expensive than most other medical or surgical management strategies. The entire 6-month program in the aforementioned study cost considerably less than a single cycle of IVF at the same institution. While weight loss should be encouraged in all obese patients seeking fertility, it may be of particular interest to those with limited resources and/or a longstanding history of infertility.

Ovulation Induction and Superovulation

When ovulation is irregular or absent, women can undergo ovulation induction with oral or injectable medications; the response to these is generally attenuated in obese women compared to those of normal weight. Compared with women of normal weight, overweight and obese women often require higher doses of clomiphene, the first-line agent commonly used to induce ovulation. Previous work by Lobo and colleagues [13] has demonstrated a positive correlation between weight and ovulatory dose of clomiphene, with only 20 % of women over 200 lb ovulating in response to 50 mg clomiphene, and an additional 20 % ovulating at a dose of 100 mg. Elevated BMI, and more specifically central body fat distribution, can predict increased resistance to clomiphene; such women often require higher doses to achieve ovulation [14].

When clomiphene is ineffective at effecting ovulation, letrozole is a common second-line agent. This aromatase inhibitor has been found to induce ovulation in more than 25 % of patients with clomiphene resistance [15]. No published studies have examined the optimal dosing of letrozole for ovulation induction in obese women, possibly reflecting its off-label use for this indication. However, in a small study examining pregnancy outcomes in 90 obese and nonobese women undergoing treatment with letrozole and intrauterine insemination (IUI), there was no difference in pregnancy rates between obese and nonobese women [16].

If oral ovulation induction fails, the next treatment is typically gonadotropin injections, with or without the concurrent use of oral agents, in an attempt to stimulate multifollicular development. This treatment is often paired with intrauterine insemination (IUI) to maximize chances of conception. Obese women require greater quantities of medications to effect ovulation, not only with oral agents, but also with injectable gonadotropins. In a retrospective study of more than 300 women undergoing more than 800 cycles of superovulation and IUI, the mean total gonadotropin dosages per cycle were higher for obese women as compared to those of normal weight, even when analyzing only first cycles [17]. Peak estradiol levels during gonadotropin stimulation have been found to be inversely proportional to BMI, with lower estradiol levels per follicle in obese women [18]. However, once medication regimens have been optimized for peak estradiol and follicular development, obese women undergoing gonadotropin-IUI are generally able to achieve pregnancy rates comparable to those seen in normal weight women [18].

In Vitro Fertilization

When ovulation induction has failed to achieve pregnancy, many patients may proceed with the more intensive treatment of in vitro fertilization (IVF)—a process involving superovulation, oocyte retrieval, ex vivo fertilization and embryo culture, and embryo transfer. A common misconception among many patients is that any detrimental impact of obesity on fertility outcomes can be overcome using assisted reproductive technologies (ART), but obesity appears to impact each step of the IVF process, even at the microscopic level.

Ovarian Stimulation

Similar to superovulation with IUI, gonadotropin requirements are typically higher in obese as compared to nonobese women undergoing IVF. Obese women undergoing gonadotropin stimulation for IVF have lower peak [19–21] and per follicle estradiol levels [21]. Obese women require a greater total amount of gonadotropins to achieve a similar degree of follicular growth as compared to overweight or normal-weight women [22, 23], resulting in an increased length of gonadotropin stimulation prior to oocyte retrieval [20]. Given this gonadotropin "resistance," obese women are more likely to have a cycle cancellation, often related to poor ovarian response to follicular stimulation [24, 25].

The higher risks of cycle cancellation and increased gonadotropin requirement in obese women may lead to higher-than-average costs for IVF in obese women. In a retrospective analysis of more than 1,700 first IVF cycles, there were no differences in cost per IVF cycle across all ranges of BMI [26]. However, considering that multiple cycle starts might be required to ultimately lead to an oocyte retrieval, and the decreased chances of pregnancy in obese women undergoing ART (reviewed later in this chapter), the cumulative financial cost to achieve a "take-home baby" may be greater for obese women.

Special consideration should be given when considering ovulation induction outcomes in obese women with PCOS; this unique group is characterized by high antral follicle counts that should offer good chances for follicular recruitment in response to gonadotropin stimulation. However, obese women with PCOS also require higher doses of gonadotropins to achieve a comparable degree of follicular development to their nonobese counterparts. In one study of 72 patients with PCOS, women with a BMI ≥ 40 kg/m^2 required higher doses of gonadotropin to achieve the same number of mature follicles than those with a BMI < 40 kg/m^2 (2,606.8 IU versus 1924.6 IU, $p = 0.03$) [27]. This difference was noted even though there was no difference in the total number of follicles between the two groups (follicles >12 mm: $p = 0.5$, follicles >16 mm: $p = 0.87$).

Oocyte Retrieval, Maturity, and Fertilization

Oocyte retrieval for IVF can be particularly challenging in obese women. Visceral adipose and redundant inguinal tissue can make manipulation of a transvaginal ultrasound probe technically difficult, thereby compromising visualization of the ovaries. As discussed above, obesity is associated with lower peak estradiol levels and fewer follicles for a given level of estradiol. Thus, the total number of follicles available for oocyte retrieval may be lower than in nonobese women of a similar age. Jungheim and colleagues [27] described fewer oocytes retrieved in women with a BMI ≥ 40 kg/m^2 than those with a BMI < 40 kg/m^2 (8.9 versus 13.6, $p = 0.0006$), which is consistent with the findings of other studies [24, 28]. Several of the cases were noted to be technically difficult in the medical record, and when

these cases were removed from the analysis, there was no longer a difference in numbers of oocytes retrieved (10.42 versus 13.63, $p=0.06$).

Transabdominal oocyte retrieval is an alternative approach when patient obesity compromises transvaginal access to the ovaries. In a retrospective case-control study of 69 patients undergoing transabdominal oocyte retrieval owing to one or both ovaries being inaccessible through the vagina, comparable numbers of mature oocytes were retrieved transabdominally as compared to transvaginal (9.2 versus 7.3, $p=0.14$), though the total number of oocytes retrieved was less in the transabdominal group (11.9 versus 14.1, $p=0.008$) [29].

It is unclear whether obesity affects oocyte development, and some investigators have examined follicular fluid to identify correlations between serum and follicular metabolites that may be detrimental to the development of quality oocytes. Compared with nonobese women, obese women have higher serum concentrations of free fatty acids, and in a study of 102 women undergoing IVF, elevated follicular free fatty acids were associated with poor cumulus oocyte complex morphology [30]. Though this study did not find a strong correlation between follicular and serum free fatty acid concentrations ($r<0.31$ for each free fatty acid studied), another follicular fluid study found that elevated follicular total protein and lipoprotein A1 were correlated with serum values and were associated with poor chances for embryo development [28]. Clinical utility of these markers will depend on the ability of studies to depict a consistent correlation with BMI and treatment outcomes.

The total number of mature oocytes retrieved may also be lower in obese women. In a retrospective review of 1,293 patients undergoing their first IVF stimulation cycle, women with a BMI ≥ 40 kg/m^2 had significantly fewer mature oocytes retrieved compared to women with a BMI <40 kg/m^2 (11.69 ± 0.90 for a BMI ≥ 40, compared to 14.1 ± 0.32 for a BMI <25 kg/m^2, 14.16 ± 0.54 for a BMI 25–30 kg/m^2, 13.45 ± 0.49 for a BMI 30–40 kg/m^2, $p<0.02$) [20]. There are data to suggest, however, that changes in BMI might improve the mature oocyte yield. In a prospective cohort study, Chavarro and colleagues [31] noted that obese (BMI ≥ 30 kg/m^2) and overweight women (BMI 25–30 kg/m^2) had a higher yield of metaphase II oocytes after a short-term weight loss of >1 kg from initial baseline appointment to the time of retrieval as compared to similarly obese and overweight women whose weight did not change (10.1 [95 % CI 8.5–11.6] compared to 7.8 [95 % CI 6.9–8.8], $p=0.03$). This study hints at a biological plausibility for the observed association between BMI and oocyte maturity and quality. Unfortunately, the authors were not able to correlate this change in BMI with pregnancy or live birth rates; future studies might investigate this relationship further.

Some clinicians would suggest that insemination and fertilization rates, rather than subjective assessment performed by heterogeneously trained embryologists, provide a more objective assessment of oocyte maturity in obese women. Several published studies found no difference in fertilization rates between obese and nonobese women [20, 32, 33] but this is not a uniform finding [21].

Taken together, these data suggest that oocyte quality is impaired in obese women but is possibly reversible with a reduction in body weight.

Embryo Quality and Transfer

Data regarding the quality of embryos created from the oocytes of obese women are inconsistent. Several large retrospective studies show no correlation of embryo quality with obesity, specifically no differences in grade [24], number of cells [24, 33], or degree of fragmentation [33]. However, a smaller retrospective study of 426 cycles demonstrated that, compared to normal-weight women under 35 years old, obese women under 35 years old had lower embryo grades (2.3 ± 1.4 versus 2.0 ± 0.6, $p = 0.02$), fewer cryopreserved embryos (0.2 ± 1.2 versus 1.1 ± 2.2, $p = 0.04$), and higher numbers of discarded embryos (6.4 ± 0.7 versus 4.5 ± 0.3, $p = 0.007$) [32].

Transabdominal ultrasound, fast becoming a near universal tool in facilitating optimal placement of the transfer catheter during embryo transfer, is more difficult in obese women. It is plausible that the greater difficulty in optimal visualization during transabdominal ultrasound of obese women may lead to adverse IVF outcomes, but few researchers have investigated this hypothesis. A single retrospective review of 417 first IVF cycles revealed a nonsignificant increase in the inability to visualize the air bubbles during embryo transfer on women with a BMI > 25 kg/m^2 ($p = 0.06$); this was accompanied by a non-significant decrease in implantation rate, and no change in ongoing pregnancy rate [34]. Given the paucity of published studies examining embryo transfer protocol in obese patients, no summary statements can be made as to whether the known technical challenges in transfer in obese women result in adverse pregnancy outcomes.

Implantation and Clinical Pregnancy

Whether the endometria of obese women have poorer receptivity for implanting embryos is unclear. Assessment of the preconception endometrium, either by hysteroscopy or endometrial biopsy, is not compulsory in the infertility workup unless the patient has risk factors or symptoms suggesting abnormal pathology. However, in a retrospective study of over 200 women with infertility, asymptomatic obese women had a higher number of precycle endometrial polyps compared with nonobese women (52 % versus 15 %, $p = 0.04$); the authors suggest that hysteroscopy should be routinely performed in obese women prior to cycle start to optimize the endometrium prior to stimulation [35]. The effect of endometrial polyps on fertility is poorly understood and understudied; it is possible that obesity may be a common link between endometrial polyps and infertility.

In addition to macroscopic changes such as uterine polyps, obese women may have unidentified microscopic or biochemical alterations in the endometrium that alter uterine receptivity. Some studies have revealed lower implantation rates in obese women [33, 34, 36] but others have shown no difference [25, 37]. In a retrospective analysis of 4,609 patients undergoing their first IVF cycle, the odds of implantation were as low as 0.52 among obese women as compared to nonobese

women [38]. In a meta-analysis from 2007, Maheshwari summarized the findings of 21 studies and confirmed nearly a 30 % lower odds of pregnancy in overweight or obese women undergoing IVF [23]. The odds for implantation are also decreased in obese women with PCOS [34].

Many authors have tried to linearize implantation and clinical pregnancy rate data to mathematically predict patient outcomes with increasing BMI, with some limited success. A retrospective study of 171 women correlated a one unit increase in BMI with a 0.84 diminished odds of pregnancy; this was comparable to the diminishment in the odds of pregnancy with a one-unit elevation in baseline FSH. Conversely, a one-unit decrease in BMI increased the odds of pregnancy by 1.19 [36]. However, given the relatively low median BMI (20.5) of participants, with no patients above a BMI of 28, the applicability of this data to clinical practice is limited. In a larger retrospective study of over 6,000 women, nearly 25 % of overweight or obese women (BMI > 25 kg/m^2) had decreased odds of pregnancy; for each unit of BMI increase above 25 kg/m^2, there was a decrease in odds of pregnancy by 0.98. There was also a decrease in cumulative pregnancy rate with increasing BMI, from 93.7 % pregnancy within four cycles for women with a BMI < 20 kg/m^2, to 87.1 % for women with a BMI ≥ 30 kg/m^2 [33].

Obesity does not appear to impact the risk of multiple gestation after fertility treatment. In a retrospective cohort of 90 patients, there were no differences in rates of multiple gestations between obese and nonobese women undergoing letrozole/IUI cycles [16]. Similarly, there were no differences in multiple births in 4,609 fresh cycles of IVF across all ranges of BMI from <18.5 kg/m^2 to ≥40 kg/m^2 [38].

Endometrial Receptivity Versus Poor Embryo Quality: Which Is Responsible for the Decreased Pregnancy Rates in Obese Women?

While data suggest that the implantation rate for obese women is poorer than normal-weight women, the majority of studies are unable to differentiate the impact of embryo quality from that of endometrial receptivity. Are implantation rates low because of poor embryo quality or because of a hostile intrauterine environment? This is currently a heavily debated topic and there are data available to support both possibilities.

An ideal study would eliminate one of the variables in question—for example, examining implantation and pregnancy rates in obese women who undergo IVF using oocytes from nonobese donors. In a study of 10,000 first IVF cycles using oocytes from healthy normal-weight donors, rates of implantation were significantly lower when recipient BMI increased beyond 25 kg/m^2 (38.5 % in women with a BMI 25–29.9 kg/m^2 versus 39.9 % in recipients with a BMI 20–24.9 kg/m^2, $p < 0.001$), and dramatically so after recipient BMI increased beyond 30 kg/m^2 (30.5 % $p < 0.001$) [39]. Clinical pregnancy rates were similarly diminished with increasing BMI (55.9 % in recipients with a BMI 20–24.9 kg/m^2 compared to

54.3 % for a BMI 25–29.9 kg/m^2, and 45.4 for women with a BMI ≥ 30, $p < 0.001$). Clinical miscarriage rate and ectopic pregnancy rates were similar for all BMI groups. In the setting of unchanged laboratory and embryo parameters, these data suggest that uterine receptivity may be compromised in obese women.

Conflicting results have been reported, however, by a large analysis of 33,000 cycles from the Society for Assisted Reproductive Technologies (SART) database, which found a significant inverse association between obesity and pregnancy rate with the use of autologous oocytes, but no difference with the use of donor oocytes [40]. These data suggest an adverse impact of obesity on oocyte quality rather than endometrial receptivity. This concept was further supported by a recent meta-analysis comparing the chance of pregnancy in obese versus normal-weight donor oocyte recipients that did not include the aforementioned retrospective study of 10,000 cycles and found no difference in implantation (RR 0.93 [95 % CI 0.80–1.07]) or clinical pregnancy rates (RR 0.98 [95 % CI 0.83–1.15]) in obese as compared to normal-weight donor oocyte recipients [41].

Pregnancy Loss

Pregnancy loss is heterogeneously defined throughout the literature, with some studies focusing on first trimester loss and others looking at losses through the point of viability, thus complicating attempts to summarize the existing data on the topic. A meta-analysis of 21 retrospective and observational studies noted a 30 % increased odds of miscarriage (loosely aggregated as losses from conception through 20 weeks) among overweight or obese women following IVF [23]. A large study of 6500 IVF cycles did not demonstrate a significant change in the odds of miscarriage (OR 1.009 [95 % CI 0.989–1.028], $p = 0.643$) as defined as loss of an established pregnancy prior to 22 weeks [33]. The same study reported a significantly decreased odds of live birth in obese women (OR 0.981 [95 % CI 0.967–0.995], $p = 0.009$), however, suggesting an increased risk of pregnancy loss not captured by the primary analysis.

More recently, Metwally and colleagues [42] performed a meta-analysis of 16 studies, specifically examining miscarriage rates among obese and nonobese women, including both spontaneous pregnancies as well as those conceived via assisted reproduction. The authors demonstrated a significantly increased odds of miscarriage in women with a BMI > 25 kg/m^2 (OR 1.67 [95 % CI 1.25–2.25]), regardless of the mode of conception. A subanalyses of the data revealed no change in the odds of miscarriage among women conceiving with IVF but suggested that overweight and obese women may have significantly higher odds of miscarriage after oocyte donation (OR 1.52 [95 % CI 1.10–2.09]) and ovulation induction (OR 5.11 [95 % CI 1.76–14.83]). These data again raise the question of whether it is the endometrial receptivity or embryo quality that plays a dominant role in the achievement of an ongoing pregnancy. Based upon the presently available data, it appears that both processes may contribute to obesity's detrimental impact on clinical pregnancy.

Live Birth

The most relevant question to most infertile couples is the chances of live birth, or the "take-home baby" rate. As most infertility physicians do not provide obstetric care much beyond the first trimester, data collection on live birth often requires additional investigation. An early retrospective review of 2,660 couples reported that, after three cumulative cycles, the unadjusted cumulative live birth rate was 50.3 % of nonobese women, compared to 41.4 % of obese women ($p = 0.03$) [24], but this and other previously published data was insufficient for a 2007 meta-analysis to conclusively support a decreased live birth rate in obese women [23]. Height and weight were added to the SART Clinic Online Reporting System (SART CORS) database in 2007, facilitating a large study evaluating the impact of obesity on live birth rates using over 45,000 embryo transfers from this database. The authors reported that women with a BMI ≥ 30 kg/m^2 had a significantly decreased odds of pregnancy and live birth compared to nonobese women ($p < 0.0001$) [40]. Increasing obesity appears to further worsen the live birth rate, as illustrated (Fig. 6.2) by a 2012 retrospective analysis of 4700 first IVF cycles that demonstrated a reduced chance of live birth, up to 68 %, with increasing BMI (odds of live birth 0.63 [95 % CI 0.47–0.85] for women with a BMI 30–35, 0.39 [95 % CI 0.25–0.61] with a BMI 35–40 kg/m^2, and 0.32 [95 % CI 0.16–0.64] for a BMI ≥ 40 kg/m^2) [38]. Given the abundance of recently published studies on the topic [21, 33, 38, 39], it is likely that a meta-analysis of all currently available data may now demonstrate a clear reduction in live birth rates with maternal obesity.

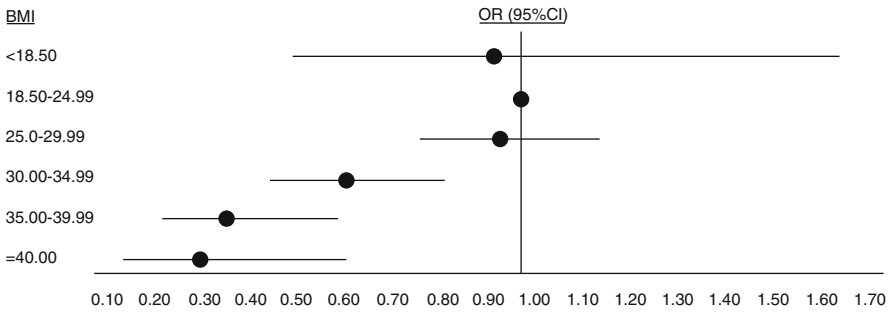

Fig. 6.2 Forest plot of adjusted live birth rate according to body mass index (BMI, kg/m^2) category (*circle* represents odds ratio [OR], *horizontal line* represents 95 % confidence interval [CI]). From Moragianni VA, Jones SM, Ryley DA. The effect of body mass index on the outcomes of first assisted reproductive technology cycles. Fertility and Sterility. 2012 Jul;98(1):102–8. PubMed PMID: 22584023. With permission from Elsevier Limited, UK

Conclusions

Several conclusions may be drawn from the available data:

- Obesity appears to exert a negative impact on most fertility treatment outcomes in women.
- Obese women are less likely to ovulate with standard doses of oral ovulation induction agents, and more likely to require higher doses of gonadotropins for ovarian stimulation.
- Despite maximal effort in obtaining a good stimulation, obese women have lower peak levels of estradiol, which may reflect a lower number of follicles available for retrieval. Poor stimulation may be partially overcome with a more aggressive dosing of gonadotropins.
- Whether lower implantation and pregnancy rates in obese women are the result of changes in endometrial receptivity or due to poor oocyte and embryo quality remains unclear.
- Regardless of the mechanism, ongoing pregnancy and live birth rates appear to be decreased in the obese population.

The challenges in summarizing the available data on fertility treatment outcomes in obese women are numerous given the heterogeneity of the published studies. As such, several limitations must be considered when evaluating the data presented in this chapter:

- The definitions of obesity used in studies are widely heterogeneous. Most authors abide by the WHO classification for obesity as a BMI $\geq$ 30 kg/m^2; however, others have variably defined obesity as a BMI $\geq$ 25 to $\geq$40 kg/m^2.
- The prevalence of PCOS in the obese population may confound the relationship between obesity and infertility treatment outcomes. Many studies fail to stratify obese women with and without PCOS, thus making attribution of outcomes related solely to BMI difficult.
- Clinical practice varies widely among providers of infertility care. Standard protocols may limit the ability of physicians to optimize gonadotropin stimulation for an obese patient. Assessment of oocyte and embryo quality is also subject to variation in the training and experience of an embryologist.
- There is no standard definition of clinical pregnancy or pregnancy loss. Depending on the study, clinical pregnancy is variably defined as positive beta HCG, presence of gestational sac and/or presence of a fetal pole with or without a heartbeat, or ongoing pregnancy at 8 weeks. Pregnancy loss may similarly be relegated to the first trimester or extend to the point of viability.

How do we put these data to practical use? Without overwhelming couples with the specifics of individual studies, healthcare providers should emphasize that the most straightforward way to improve fertility treatment outcomes in obese women is through weight loss. A modest reduction in BMI not only improves a woman's

chance of conceiving but also improves maternal and fetal outcomes during gestation. While medical treatment can improve pregnancy rates, it does not fully mitigate the negative impact of obesity on fertility treatment outcomes.

Finally, physicians and researchers should be motivated by the gaps in the current literature to coordinate and conduct multicenter prospective trials examining the impact of obesity on fertility treatment outcomes. A standard experimental approach will not only facilitate the consolidation of existing knowledge, but will also hopefully identify novel mechanisms by which to improve fertility outcomes in obese women.

References

1. Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R. Obesity and the polycystic ovary syndrome. Int J Obes Relat Metab Disord. 2002;26(7):883–96. PubMed PMID: 12080440.
2. Pasquali R, Gambineri A, Pagotto U. The impact of obesity on reproduction in women with polycystic ovary syndrome. BJOG. 2006;113(10):1148–59. PubMed PMID: 16827825.
3. Sharpe RM, Franks S. Environment, lifestyle and infertility—an inter-generational issue. Nat Cell Biol. 2002;4(Suppl):s33–40. PubMed PMID: 12479613.
4. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update. 2004;10(3):267–80. PubMed PMID: 15140873.
5. Nelson SM, Fleming R. Obesity and reproduction: impact and interventions. Curr Opin Obstet Gynecol. 2007;19(4):384–9. PubMed PMID: 17625423.
6. Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JD, Vrieswijk B, et al. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ. 1993;306(6876):484–7. PubMed PMID: 8448457. Pubmed Central PMCID: 1676805.
7. Rich-Edwards JW, Goldman MB, Willett WC, Hunter DJ, Stampfer MJ, Colditz GA, et al. Adolescent body mass index and infertility caused by ovulatory disorder. Am J Obstet Gynecol. 1994;171(1):171–7. PubMed PMID: 8030695.
8. Jensen TK, Scheike T, Keiding N, Schaumburg I, Grandjean P. Fecundability in relation to body mass and menstrual cycle patterns. Epidemiology. 1999;10(4):422–8. PubMed PMID: 10401878.
9. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Burggraaff JM, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod. 2008;23(2):324–8. PubMed PMID: 18077317.
10. Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. Fertil Steril. 1994;61(4):598–604. PubMed PMID: 8150098.
11. Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod. 1995;10(10):2705–12. PubMed PMID: 8567797.
12. Hollmann M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. Hum Reprod. 1996;11(9):1884–91. PubMed PMID: 8921059.
13. Lobo RA, Gysler M, March CM, Goebelsmann U, Mishell Jr DR. Clinical and laboratory predictors of clomiphene response. Fertil Steril. 1982;37(2):168–74. PubMed PMID: 7199484.
14. Douchi T, Oki T, Yamasaki H, Nakae M, Imabayashi A, Nagata Y. Body fat patterning in polycystic ovary syndrome women as a predictor of the response to clomiphene. Acta Obstet Gynecol Scand. 2004;83(9):838–41. PubMed PMID: 15315595.

15. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril. 2001;75(2):305–9. PubMed PMID: 11172831.
16. McKnight KK, Nodler JL, Cooper Jr JJ, Chapman VR, Cliver SP, Bates Jr GW. Body mass index-associated differences in response to ovulation induction with letrozole. Fertil Steril. 2011;96(5):1206–8. PubMed PMID: 21867999.
17. Dodson WC, Kunselman AR, Legro RS. Association of obesity with treatment outcomes in ovulatory infertile women undergoing superovulation and intrauterine insemination. Fertil Steril. 2006;86(3):642–6. PubMed PMID: 16782095.
18. Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC. Women, weight, and fertility: the effect of body mass index on the outcome of superovulation/intrauterine insemination cycles. Fertility and sterility. 2011;95(3):1042–7.
19. Lashen H, Ledger W, Bernal AL, Barlow D. Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization. Hum Reprod. 1999;14(3):712–5.
20. Dokras A, Baredziak L, Blaine J, Syrop C, VanVoorhis BJ, Sparks A. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstet Gynecol. 2006;108(1): 61–9.
21. Shah DK, Missmer SA, Berry KF, Racowsky C, Ginsburg ES. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. Obstet Gynecol. 2011;118(1): 63–70.
22. Dechaud H, Anahory T, Reyftmann L, Loup V, Hamamah S, Hedon B. Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer. Eur J Obstet Gynecol Reprod Biol. 2006;127(1):88–93.
23. Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology—a systematic review. Hum Reprod Update. 2007;13(5):433–44.
24. Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod. 2004;19(11): 2523–8.
25. Esinler I, Bozdag G, Yarali H. Impact of isolated obesity on ICSI outcome. Reprod Biomed Online. 2008;17(4):583–7.
26. Maheshwari A, Scotland G, Bell J, McTavish A, Hamilton M, Bhattacharya S. The direct health services costs of providing assisted reproduction services in overweight or obese women: a retrospective cross-sectional analysis. Hum Reprod. 2009;24(3):633–9.
27. Jungheim ES, Lanzendorf SE, Odem RR, Moley KH, Chang AS, Ratts VS. Morbid obesity is associated with lower clinical pregnancy rates after in vitro fertilization in women with polycystic ovary syndrome. Fertil Steril. 2009;92(1):256–61.
28. Valckx SD, De Pauw I, De Neubourg D, Inion I, Berth M, Fransen E, et al. BMI-related metabolic composition of the follicular fluid of women undergoing assisted reproductive treatment and the consequences for oocyte and embryo quality. Hum Reprod. 2012;27(12):3531–9.
29. Barton SE, Politch JA, Benson CB, Ginsburg ES, Gargiulo AR. Transabdominal follicular aspiration for oocyte retrieval in patients with ovaries inaccessible by transvaginal ultrasound. Fertil Steril. 2011;95(5):1773–6.
30. Jungheim ES, Macones GA, Odem RR, Patterson BW, Lanzendorf SE, Ratts VS, et al. Associations between free fatty acids, cumulus oocyte complex morphology and ovarian function during in vitro fertilization. Fertil Steril. 2011;95(6):1970–4. PubMed Pubmed Central PMCID: 3080431.
31. Chavarro JE, Ehrlich S, Colaci DS, Wright DL, Toth TL, Petrozza JC, et al. Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. Fertil Steril. 2012;98(1):109–16. PubMed Pubmed Central PMCID: 3389169.
32. Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod Biomed Online. 2007;15(5): 532–8.

33. Bellver J, Ayllon Y, Ferrando M, Melo M, Goyri E, Pellicer A, et al. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. Fertil Steril. 2010;93(2): 447–54.
34. Martinuzzi K, Ryan S, Luna M, Copperman AB. Elevated body mass index (BMI) does not adversely affect in vitro fertilization outcome in young women. J Assist Reprod Genet. 2008;25(5):169–75.
35. Onalan R, Onalan G, Tonguc E, Ozdener T, Dogan M, Mollamahmutoglu L. Body mass index is an independent risk factor for the development of endometrial polyps in patients undergoing in vitro fertilization. Fertil Steril. 2009;91(4):1056–60.
36. Ferlitsch K, Sator MO, Gruber DM, Rucklinger E, Gruber CJ, Huber JC. Body mass index, follicle-stimulating hormone and their predictive value in in vitro fertilization. J Assist Reprod Genet. 2004;21(12):431–6. PubMed Pubmed Central PMCID: 3455618.
37. Wattanakumtornkul S, Damario MA, Stevens Hall SA, Thornhill AR, Tummon IS. Body mass index and uterine receptivity in the oocyte donation model. Fertil Steril. 2003;80(2):336–40.
38. Moragianni VA, Jones SM, Ryley DA. The effect of body mass index on the outcomes of first assisted reproductive technology cycles. Fertil Steril. 2012;98(1):102–8.
39. Bellver J, Pellicer A, Garcia-Velasco JA, Ballesteros A, Remohi J, Meseguer M. Obesity reduces uterine receptivity: clinical experience from 9,587 first cycles of ovum donation with normal weight donors. Fertil Steril. 2013;3.
40. Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R, et al. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod. 2011;26(1):245–52.
41. Jungheim ES, Schon SB, Schulte MB, Deugarte DA, Fowler SA, Tuuli MG. IVF outcomes in obese donor oocyte recipients: a systematic review and meta-analysis. Hum Reprod. 2013;28(10):2720–7.
42. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril. 2008;90(3):714–26.

Chapter 7
Early Pregnancy in Obese Women

Christina E. Boots and Mary D. Stephenson

Introduction

As the obesity epidemic continues, more research is being done to elucidate the effects of increasing body mass index (BMI) on reproductive health. Increasingly, studies have shown that obesity increases the risk for anovulation, subfertility, infertility, poor IVF outcomes, as well as a multitude of pregnancy complications.

Specifically, obesity has been shown to have a negative impact on early pregnancy. In this chapter, we will focus on the association between obesity and early pregnancy loss, in spontaneous conception, in women with a history of recurrent pregnancy loss, as well as in the infertility population. How increasing BMI influences early pregnancy is still unclear but we will attempt to summarize what is known with respect to pathophysiology.

Early Pregnancy Loss

Miscarriage is broadly defined as the spontaneous loss of a pregnancy before reaching a viable gestation. The World Health Organization defines a miscarriage as the loss of a fetus less than 500 g [1]. However, in the research literature, miscarriage refers to the spontaneous loss of an intrauterine gestation, with other terms being used for nonvisualized or extra-uterine pregnancy loss. In 2011, Silver et al.

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proposed that the definition of early pregnancy loss include only those losses that spontaneously occurred at less than 10 weeks of gestation, and that fetal death includes all pregnancy losses between 10 and 20 weeks [2].

In the general population, 15–20 % of clinically recognized pregnancies end in miscarriage. The risk of pregnancy loss increases to 30–50 % when preclinical pregnancies are considered as well [3, 4]. Obese women are more likely to have irregular menses, and they are less likely to seek early medical care than normal-weight women [5, 6]. As a result, the rate of pregnancy loss may be underestimated in the obese population.

Mounting evidence suggests an association between obesity and the risk of miscarriage, especially in women undergoing assisted reproductive technology [7–9]. Although there is less published data from the general reproductive population and in women with recurrent pregnancy loss, recent publications suggest an association [10–13].

Spontaneous Conception

Limited data exists regarding the relationship between obesity and miscarriage in spontaneous conceptions. In 2004, Lashen et al. reported that obesity is significantly associated with an increased risk of first-trimester miscarriage, defined as 6–12 weeks of gestation (OR 1.2; 95 % CI 1.01–1.46; $P = 0.04$) [10].

In 2011, Boots and Stephenson published a systematic review and meta-analysis on obesity and miscarriage following spontaneous conception. Overall, six studies were included with a total of 3,800 obese women, 3,792 overweight women, and 17,146 normal BMI women. The percentages of women with one or more miscarriage were 16.6 % in the obese, 11.8 % overweight, and 10.7 % in the controls. The odds of having one or more miscarriage were increased for obese women (OR 1.31; 95 % CI 1.18–1.46) when compared to normal BMI women [12]. One of the limitations of this systematic review was the broad definition of "miscarriage" used in the studies. For example, two studies did not describe the gestational age at the time of the pregnancy loss, while another study included all pregnancy losses of less than 24 weeks, and another study included only pregnancy losses of less than 13 weeks. Additionally, five of the six studies were retrospective in design, and most of the studies used self-reported height and weight rather than an objective measurement, thereby limiting the reliability.

Recurrent Pregnancy Loss

Recurrent pregnancy loss (RPL) is a devastating disease that affects up to 5 % of couples [14]. Recently, the American Society of Reproductive Medicine (ASRM) redefined RPL as two or more failed pregnancies [15]. Previously, RPL was more strictly defined as three or more consecutive miscarriages, which the Royal College of Obstetricians and Gynecologists term "recurrent miscarriage" [16].

ASRM recommends initiating clinical evaluation after two ultrasounds or histopathologic documented pregnancy losses [15, 17]. Recently, Bernardi et al. and Foyouzi et al. concluded that chromosome testing of the second miscarriage should be performed, based on cost-effectiveness studies, to select which couples would benefit from a thorough RPL evaluation [18, 19].

Standard evaluation of RPL presently includes cytogenetic analysis of both partners, maternal thyroid stimulating hormone (TSH), prolactin, glucose, anticardiolipin IgG/IgM, beta-2 glycoprotein-1 IgG/IgM, lupus anticoagulant, and assessment of the uterine cavity [15, 17]. With a history of a fetal demise of at least 10 weeks size, evaluation also includes inherited thrombophilia testing, including Factor V Leiden, prothrombin gene mutation, protein C, protein S, antithrombin, and homocysteine [20]. Patients should be advised to avoid conception during the evaluation. Despite this extensive evaluation, almost half of the couples are left without an answer [14].

Recently, the association between obesity and pregnancy loss in the RPL population has been investigated in three studies. In 2004, as a subanalysis of a large case–control study, Lashen et al. evaluated the risk of recurrent early miscarriage, defined as three or more miscarriages of less than 12 weeks of gestation [10]. Despite a small sample size ($n = 10$), an association between obesity and recurrent early miscarriage was found to be significant (OR 3.5; 95 % CI 1.03–12.01; $P = 0.04$).

In 2010, Metwally et al. reported a retrospective analysis of 844 pregnancies in 491 women with a history of recurrent miscarriage, defined as three or more consecutive miscarriages. Sixty-nine obese women (BMI $\geq$ 30 kg/m^2) were found to have a significantly increased risk of miscarriage in the subsequent pregnancy as compared to normal-weight controls (OR 1.71; 95 % CI 1.05–2.8). Logistic regression analysis showed that an increased BMI was the second most important factor in predicting subsequent pregnancy outcome, after advanced maternal age [13].

Most recently, Lo et al. published a retrospective analysis of 696 women with unexplained recurrent miscarriage, of which 90 were obese (BMI $\geq$ 30 kg/m^2). The investigators found that obese women with a history of unexplained recurrent miscarriage had an increased risk of miscarriage in their subsequent pregnancy when compared to normal-weight women (OR 1.73; 95 % CI 1.06–2.83) [11].

Although only three studies have evaluated the association of obesity and miscarriage in women with a history of RPL all three studies have shown comparable results. BMI is a modifiable risk factor for women with RPL, and, therefore, we recommend measurement of height and weight at initial consultation, assistance with preconception weight loss, and measurement of weight at all subsequent pregnant and nonpregnant visits.

Advanced Reproductive Technology

The association between obesity and miscarriage has been extensively studied in women undergoing advanced reproductive technology (ART). Although many observational studies support this association [21–23], there are several studies that

did not find a relationship [24–26]. Between 2007 and 2011, three systematic reviews and meta-analyses were performed. Each included 12–33 observational studies and used either a BMI of 25 or 30 kg/m^2 as a cutoff [7–9]. Rittenberg et al. and Maheshwari et al. both concluded that obese women undergoing ART had a higher rate of miscarriage [8, 9]. Maheshwari et al. found moderate heterogeneity when comparing BMI < 25 to ≥25 kg/m^2 ($I2 = 46$ %), but no heterogeneity when comparing BMI < 30 to ≥30 kg/m^2 ($I2 = 0$ %) [9]. Conversely, Rittenburg et al. showed moderate heterogeneity when comparing both BMI < 25 to ≥25 kg/m^2 ($I2 = 48$ %) and BMI < 30 to ≥30 kg/m^2 ($I2 = 56$ %) [8].

However, Metwally et al. found conflicting results. In their primary analysis, which included all methods of conception (spontaneous conception, ovulation induction, and IVF/ICSI), there was a significant increase in miscarriage rates in women with a BMI ≥ 25 kg/m^2 compared to controls (OR 1.67; 95 % CI 1.25–2.25). In the subanalysis of only IVF/ICSI pregnancies, the association was not significant. The limitations of this meta-analysis are the inclusion of only one study with spontaneous conceptions and the absence of an assessment for heterogeneity [7].

Pathophysiology

Known risk factors for early pregnancy loss include age, diabetes, thyroid disease, and polycystic ovarian syndrome (PCOS) [27–30]. Many of these disease states are directly associated with obesity and may be confounding factors. The pathophysiology of obesity affecting early pregnancy remains elusive. Hypotheses and animal models suggest that the endocrine milieu associated with obesity affects the oocytes, the developing embryo, and the endometrium [31–36].

Oocytes and Embryos

Increasing evidence suggests that obesity affects oocyte quality, which subsequently impacts embryo quality [37]. The studies of Wang et al. and Luzo et al. showed that oocytes of high-fat-fed mice had increased mitochondrial dysfunction and abnormal morphology, as well as defects in spindle formation and chromosomal misalignment, when compared to lean controls. These abnormalities led to an increased frequency of oocyte aneuploidy [31, 38].

However, human studies have not associated obesity with an increased frequency of aneuploid miscarriages. In fact, two studies have shown that obese women are more likely to have euploid (46,XX or 46,XY) miscarriages compared to normal BMI women [32, 33]. In a retrospective case–control study from an infertility practice, consisting of 204 miscarriages, Landres et al. compared the frequency of euploid miscarriages in overweight or obese women (BMI ≥ 25 kg/m^2) to normal-weight women (BMI < 25 kg/m^2). There were 51 overweight or obese women with

a significantly increased frequency of euploid miscarriages (56.9 % vs. 36.6 %, $P = 0.04$) [32].

Recently, Boots et al. reported miscarriage chromosome results in women with a history of recurrent early pregnancy loss, defined as two or more losses of less than 10 weeks gestation [33]. The mean maternal age at miscarriage was similar between the obese and nonobese groups, 35.0 vs. 34.1 years. The frequency of euploid miscarriage among obese women was significantly increased compared to nonobese controls, 58 % vs. 37 % (RR = 1.63; 95 % CI 1.08– 2.47; $P = 0.02$) [33]. Since euploid miscarriage increases the risk of subsequent miscarriage, whereas an aneuploid miscarriage is considered a random event and does not increase the risk for subsequent miscarriage, these concordant studies suggest that obesity may be an independent risk factor for further miscarriage in women with RPL [39, 40]. To date, there are no studies that have reported on the impact of weight loss on the frequency of euploid miscarriage in women with RPL.

Although human studies suggest that obesity does not increase the frequency of aneuploid miscarriage, obesity maybe impacting the embryo's epigenetics [41, 42]. Studies show that metabolic insults from maternal dietary imbalance, increased fatty acids, and/or glucose intolerance during embryonic development can cause potentially stable epigenetic modifications, which could explain the lifelong effects seen in offspring [41–43].

Dabelea et al. compared siblings that were born before and after their mother was diagnosed with diabetes. The risk of developing diabetes was significantly higher in the siblings born after the mother developed diabetes, 73 % vs. 33 % (OR 3.7, 95 % CI 1.3–11.3, $P = 0.02$). BMI was also higher in siblings exposed to intrauterine diabetes with a mean increase of 2.6 kg/m^2 (0.9–4.3; $P = 0.003$) [44]. This work proposes that a hyperglycemic environment increases the risk of diabetes beyond the genetic risk alone.

The findings of Debalea et al. are supported by the study of Jungheim et al., who reported that pups from obese murine mothers have increased body fat and are at a higher risk of glucose intolerance and hypercholesterolemia [45]. Stothard et al. compared outcomes of embryos transferred from diabetic female mice to nondiabetic female mice to embryos transferred from nondiabetic to nondiabetic female mice [46]. The fetuses from diabetic female mice had significantly decreased implantation rates and higher rates of malformations. The effects of early, transient exposure to maternal obesity and/or the diabetic milieu appear to influence metabolic and morphologic consequences in offspring [46, 47].

Jungheim et al. reported that embryonic insulin resistance in a type II diabetic mouse model has been shown to increase the risk of miscarriage [48]. In addition, Eng et al. suggested that metformin, which increases insulin sensitivity, reverses this association in the mouse model [49]. In human studies, results are convergent. In 2009, Palomba et al. published a meta-analysis of 17 randomized controlled trials (RCT), which evaluated the pregnancy outcomes in 566 women with PCOS preconceptionally treated or not treated with metformin [50]. There was no difference in the miscarriage rate, 20.9 % vs. 21.2 % (OR 1.02, 95 % CI 0.65–1.21).

In 2012, Morin-Papunen et al. published a multicenter, double-blind, RCT of 320 women with PCOS, defined by Rotterdam criteria, who were randomized to

receive preconception metformin or placebo [51]. There was no difference in miscarriage rates between cohorts (15.2 % vs. 17.9 %, $P=0.8$). However, live birth rates were significantly increased in the metformin cohort (41.9 % vs. 28.8 %, $P=0.006$), and a nonsignificant trend was present in a subanalysis of obese (BMI ≥ 27 kg/m^2) women treated with metformin preconceptionally (35.7 % vs. 21.9 %, $P=0.07$). Although insulin resistance appears to contribute to the development and maintenance of early pregnancy, it remains unclear whether improvement in insulin sensitivity through the use of metformin alleviates this impact.

Endometrium

In addition to the oocytes and embryos, obesity and its hormonal and metabolic effects may negatively influence the endometrium. Obesity is associated with increased systemic estrogen, which has been shown to decrease endometrial receptivity [34]. Increased acute phase proteins and inflammatory cytokines, such as IL-6, PAI 1, and TNF, are elevated in obese women and have been shown to decrease implantation and impair maintenance of pregnancy [52–54].

Plasminogen activator inhibitor (PAI), produced by adipose tissue, is elevated in obesity and has been correlated with metabolic syndrome [52]. Glueck et al. has published two studies correlating an elevated plasminogen activator inhibitor activity (PAI-Fx) with PCOS and RPL [54, 55]. In 1999, Glueck et al. demonstrated that women with PCOS who have had prior miscarriages but no live births had a significantly higher PAI-Fx than women with PCOS who have had live births but no prior miscarriages, 67 % vs. 29 % ($P=0.05$) [54]. In 2003, Glueck et al. studied 33 women with PCOS and RPL and compared them to 16 women with RPL but without PCOS and to 116 normal controls (no PCOS or RPL). The patients with PCOS and RPL were statistically more likely to have higher PAI-Fx, 38 % vs. 8 % ($P=0.004$) [55]. These studies suggest that elevated PAI is associated with an increased risk of miscarriage.

Leptin is an adipose-produced hormone that regulates energy metabolism and interacts with nearly all reproductive organs, including the hypothalamus, the pituitary gland, and the ovaries. In addition, leptin and its receptor have been observed in secretory endometrium. Obesity has been associated with nearly universally elevated levels of leptin and subsequently, with a state of leptin resistance and relative deficiency [56]. Leptin production has been shown to have an important role in the early maintenance of pregnancy by stimulating the expression of matrix metalloproteinase by the cytotrophoblast [35] and modulating the function of local T lymphocytes and proto-oncogenes [57]. The importance of leptin's role in the endometrium has been speculated as the pathophysiology leading to miscarriage in obese women [56]. This hypothesis is supported by the study by Laird et al. which demonstrated that women with recurrent miscarriage ($n=53$) have lower serum leptin levels [58]. Women who subsequently miscarried had significantly decreased levels of plasma leptin at both 5–6 weeks and 7–8 weeks of gestation, as compared to women whose pregnancy resulted in a live birth. The investigators concluded that leptin may be protective of the early pregnancy [58].

Donor Oocyte Models

Human donor oocyte models provide a unique opportunity to differentiate the influence of obesity on the oocyte and the endometrium. Several retrospective cohort studies have investigated the pregnancy outcomes of obese and nonobese oocyte recipients using oocytes from normal BMI donors [59–61]. These studies have yielded conflicting results. Jungheim et al. published a systematic review and meta-analysis of 6 studies ($n = 4{,}758$) and concluded that the BMI of oocyte recipients did not impact IVF outcomes, including miscarriage rates [62].

In the largest and most recent retrospective analysis, Bellver et al. reported pregnancy outcomes in 9,587 oocyte recipients from normal BMI donors [36]. Although there was no difference in the clinical miscarriage rate between obese and nonobese recipients, the implantation rate, clinical pregnancy rate, and live birth rate decreased with increasing recipient BMI [36]. These conflicting results most likely represent a multifactorial etiology for poorer pregnancy outcomes in obese women.

Conclusions

Mounting evidence suggests that obesity negatively impacts early pregnancy by impairing implantation and maintenance of pregnancy. Although the pathophysiology has not been delineated, changes in oocyte quality, embryonic development, and the endometrium have been demonstrated in obese women. Future research is urgently needed to determine the pathophysiology.

Knowing how obesity impacts conception and the early maintenance of pregnancy is crucial to determine whether behavior modifications, such as weight loss, dietary alterations, or antioxidant supplementation, will reverse the effects. Preventing weight gain and obesity prior to conception is the only evidence-based recommendation at this time. Prospective trials and epidemiologic studies are needed to determine whether physicians should recommend preconception weight loss to reduce or perhaps prevent the devastating effects of obesity on pregnancy.

References

1. World Health Organization. Definitions and indicators in family planning, maternal and child health and reproductive health. WHO Regional Strategy on Sexual and Reproductive Health. Geneva: WHO; 2001.
2. Silver RM, Branch DW, Goldenberg R, Iams JD, Klebanoff MA. Nomenclature for pregnancy outcomes: time for a change. Obstet Gynecol. 2011;118:1402–8.
3. Wilcox AJ, Weiberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE. Incidence of early loss of pregnancy. N Engl J Med. 1988;319:189–94.
4. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertil Steril. 1996;65:503–9.

5. Olson CL, Schumaker HD, Yawn BP. Overweight women delay medical care. Arch Fam Med. 1994;3:8888–92.
6. Drury CA, Louis M. Exploring the association between body weight, stigma of obesity, and health care avoidance. J Am Acad Nurse Pract. 2002;14:554–61.
7. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril. 2008;90:714–26.
8. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online. 2011;23:421–39.
9. Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology: a systematic review. Hum Reprod Update. 2007;13:433–44.
10. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod. 2004;19:1644–6.
11. Lo W, Rai R, Hameed A, Brailsford SR, Al-Ghamdi AA, Regan L. The effect of body mass index on the outcome of pregnancy in women with recurrent miscarriage. J Family Community Med. 2012;19:167–71.
12. Boots C, Stephenson MD. Does obesity increase the rate of miscarriage in spontaneous conception? A systematic review. Semin Reprod Med. 2011;29:507–13.
13. Metwally M, Saravelos SH, Ledger WL, Li TC. Body mass index and risk of miscarriage in women with recurrent miscarriage. Fertil Steril. 2010;94:290–5.
14. Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. Fertil Steril. 1996;66:24–9.
15. Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril. 2013;99:63.
16. Royal College of Obstetricians and Gynaecologists. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage, Green-top guideline, vol. 17. London: RCOG; 2011.
17. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98:1103–11.
18. Bernardi LA, Plunkett BA, Stephenson MD. Is chromosome testing of the second miscarriage cost saving? A decision analysis of selective versus universal recurrent pregnancy loss evaluation. Fertil Steril. 2012;98:156–61.
19. Foyouzi N, Cedars MI, Huddleston HG. Cost-effectiveness of cytogenetic evaluation of products of conception in the patient with a second pregnancy loss. Fertil Steril. 2012;98:151–5.
20. Stephenson MD, Kutteh W. Evaluation and management of recurrent early pregnancy loss. Clin Obstet Gynecol. 2007;50:132–45.
21. Wang JX, Davies MJ, Norman RJ. Obesity Increases the Risk of Spontaneous Abortion during Infertility Treatment. Obes Res. 2002;10:551–4.
22. Rittenberg V, Sobaleva S, Ahmad A, Oteng-Ntim E, Bolton V, Khalaf Y, et al. Influence of BMI on risk of miscarriage after single blastocyst transfer. Hum Reprod. 2011;26:2642–50.
23. Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod. 2004;19:2523–8.
24. Dokras ABL, Blaine J, Syrop C, VanVoorhis BJ, Sparks A. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstet Gynecol. 2006;108:61–9.
25. Bellver J, Ayllon Y, Ferrando M, Melo M, Goyri E, Pellicer A, et al. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. Fertil Steril. 2010;93:447–54.
26. Winter E, Wang J, Davies MJ, Norman R. Early pregnancy loss following assisted reproductive technology treatment. Hum Reprod. 2002;17:3320–3.
27. Smith ML, Schust DJ. Endocrinology and recurrent early pregnancy loss. Semin Reprod Med. 2011;29:482–90.
28. Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. Eur J Endocrinol. 2009;160:985–91.

29. de La Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. Hum Reprod. 2002;17:1649–56.
30. Toulis KA, Goulis DG, Venetis CA, Kolibianakis EM, Negro R, Tarlatzis BC, et al. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis. Eur J Endocrinol. 2010;162:643–52.
31. Wang Q, Ratchford AM, Chi MM, Schoeller E, Frolova A, Schedl T, et al. Maternal diabetes causes mitochondrial dysfunction and meiotic defects in murine oocytes. Mol Endocrinol. 2009;23:1603–12.
32. Landres IV, Milki AA, Lathi RB. Karyotype of miscarriages in relation to maternal weight. Hum Reprod. 2010;25:1123–6.
33. Boots CE, Bernardi L, Stephenson MD. Does obesity increase the risk of euploid miscarriage in women with recurrent pregnancy loss? Fertil Steril. 2014;102(2):455–9. doi:10.1016/j.fertnstert.2014.05.005.
34. Simón C, Garcia Velasco JJ, Valbuena D, Peinado JA, Moreno C, Remohi J, et al. Increasing uterine receptivity by decreasing estradiol levels during the preimplantation period in high responders with the use of a follicle-stimulating hormone step-down regimen. Fertil Steril. 1998;70:234–9.
35. Sagawa N, Yura S, Itoh H, Kakui K, Takemura M, Nuamah MA. Possible role of placental leptin in pregnancy: a review. Endocrine. 2002;19:65–71.
36. Bellver J, Pellicer A, García-Velasco JA, Ballesteros A, Remohí J, Meseguer M. Obesity reduces uterine receptivity: clinical experience from 9,587 first cycles of ovum donation with normal weight donors. Fertil Steril. 2013;100:1050–8.
37. McConnell JM, Petrie L. Mitochondrial DNA turnover occurs during preimplantation development and can be modulated by environmental factors. Reprod Biomed Online. 2004;9:418–24.
38. Luzzo KM, Wang Q, Purcell SH, et al. High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/brain defects. PLoS One. 2012;7:e49217.
39. Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Hum Reprod. 2002;17:446–51.
40. Warburton D, Kiline J, Stein Z, Hutzler M, Chin A, Hassold T. Does the karyotype of a spontaneous abortion predict the karyotype of a subsequent abortion? Evidence from 273 women with two karyotyped spontaneous abortions. Am J Hum Genet. 1987;41:465–83.
41. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359:61–73.
42. Heerwagen MJR, Miller MR, Barbour LA, Friedman JE. Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. Am J Physiol Regul Integr Comp Physiol. 2010;299(3):R711–22.
43. Wakefield SL, Lane M, Schulz SJ, Hebart ML, Thompson JG, Mitchell M. Maternal supply of omega-3 polyunsaturated fatty acids alter mechanisms involved in oocyte and early embryo development in the mouse. Am J Physiol Endocrinol Metab. 2008;294:E425–34.
44. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes. 2000;49:2208–11.
45. Jungheim ES, Schoeller EL, Marquard KL, Louden ED, Schaffer JE, Moley KH. Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. Endocrinology. 2010;151:4039–46.
46. Wyman A, Pinto AB, Sheridan R, Moley KH. One-cell zygote transfer from diabetic to nondiabetic mouse results in congenital malformations and growth retardation in offspring. Endocrinology. 2008;149:466–9.
47. Stothard KJTP, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA. 2009;301:636–50.
48. Jungheim ES, Moley KH. The impact of type 1 and type 2 diabetes mellitus on the oocyte and the preimplantation embryo. Semin Reprod Med. 2008;26:186–95.

49. Eng GS, Sheridan RA, Wyman A, Chi MM, Bibee KP, Jungheim ES, et al. AMP kinase activation increases glucose uptake, decreases apoptosis, and improves pregnancy outcome in embryos exposed to high IGF-I concentrations. Diabetes. 2007;56:2228–34.
50. Palomba S, Falbo A, Orio FJ, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2009;92:1646–58.
51. Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippelainen M. Perheentupa, et al. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. J Clin Endocrinol Metab. 2012;97:1492–500.
52. Gosman GG, Katcher HI, Legro RS. Obesity and the role of gut and adipose hormones in female reproduction. Hum Reprod Update. 2006;12(5):585–601.
53. Levens ED, Skarulis MC. Assessing the role of endometrial alteration among obese patients undergoing assisted reproduction. Fertil Steril. 2008;89:1606–8.
54. Glueck CJ, Wang P, Fontaine RN, Sieve-Smith L, Tracy T, Moore SL. Plasminogen activator inhibitor activity: an independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. Metabolism. 1999;48:1589–95.
55. Glueck CJWP, Bornovali S, Goldenberg N, Sieve L. Polycystic ovary syndrome, G1691A factor V Leiden mutation, and plasminogen activator inhibitor activity: associations with recurrent pregnancy loss. Metabolism. 2003;52:1627–32.
56. Moschos S, Chan JL, Mantzoros CS. Leptin and reproduction: a review. Fertil Steril. 2002;77: 433–44.
57. Bajoria R, Sooranna SR, Ward BS, Chatterjee R. Prospective function of placental leptin at maternal-fetal interface. Placenta. 2002;23:103–15.
58. Laird SMQN, Anstie B, Li TC, Blakemore AI. Leptin and leptin-binding activity in women with recurrent miscarriage: correlation with pregnancy outcome. Hum Reprod. 2008;16: 2008–13.
59. Styne-Gross A, Elkind-Hirsch K, Scott RTJ. Obesity does not impact implantation rates or pregnancy outcome in women attempting conception through oocyte donation. Fertil Steril. 2005;83:1629–34.
60. Bellver J, Rossal LP, Bosch E, et al. Obesity and the risk of spontaneous abortion after oocyte donation. Fertil Steril. 2003;79:1136–40.
61. Bellver J, Melo MA, Bosch E, Serra V, Remohi J, Pellicer A. Obesity and poor reproductive outcome: the potential role of the endometrium. Fertil Steril. 2007;88:446–51.
62. Jungheim ES, Schon SB, Schulte MB, DeUgarte DA, Fowler SA, Tuuli MG. IVF outcomes in obese donor oocyte recipients: a systematic review and meta-analysis. Hum Reprod. 2013;28: 2720–7.

Chapter 8
Obesity in Pregnancy

Shayna N. Conner and Alison G. Cahill

Epidemiology of Maternal Obesity

The WHO defines obesity as a body mass index (BMI) ≥ 30 kg/m^2. Obesity is subdivided into Class I (BMI 30–34), Class II (BMI 35–39), and Class III (BMI ≥ 40) [1]. The prevalence of maternal obesity has increased markedly over the past two decades; currently, over one-third of reproductive-age women are obese, and 8 % are extremely obese (Class III). Obesity rates increase with parity and maternal age and differ along racial/ethnic lines. Among women of reproductive age, African Americans have the highest rates of obesity (59 %), followed by Hispanics (41 %) and non-Hispanic whites (33 %) [2–4].

Metabolism in Pregnancy

As maternal weight increases with pregnancy, so too does maternal fat deposition. In obese women, the accumulated fat tends to be visceral fat, which has been correlated with metabolic factors such as blood pressure, insulin sensitivity, and lipid distribution. Because of elevated progesterone, human placental lactogen, and estradiol, pregnancy induces hyperlipidemia, in which concentrations of very low-density lipoprotein and triglyceride are increased but high-density lipoprotein is increased only marginally. The hyperlipidemia of pregnancy is manifested to a higher degree in obese women [5].

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Another metabolic change in pregnancy is increase in protein synthesis in the second and third trimesters. Protein synthesis is highly active in the growing fetus and maternal tissues such as the liver, breasts, and uterus. Although the mechanisms are unclear, some data suggest that protein synthesis is impaired in obese women [6].

Pregnancy is associated with physiologic alterations in glucose metabolism. Fasting hypoglycemia, postprandial hyperglycemia, and hyperinsulinemia are observed in normal pregnancies. These physiologic effects are often different in obese women. For example, fasting hypoglycemia is less pronounced and can even be absent [7]. In addition, obese women often have enhanced insulin resistance, which exposes the fetus to hyperglycemia [8].

Weight Gain in Pregnancy

Recent evidence shows that excessive weight gain in pregnancy is associated with higher infant birth weight and postpartum weight retention. By contrast, poor maternal weight gain is associated with decreased infant birth weight [9, 10]. Therefore, careful attention should be paid in counseling patients regarding optimal weight gain in pregnancy. In 2009, the Institute of Medicine (IOM) published guidelines on gestational weight gain according to prepregnancy BMI [11]. However, the IOM did not differentiate women by age, race/ethnicity, or subclassifications of obesity. As a result, the weight-gain guidelines span a wide range (see Table 8.1), and individualization of care and counseling is required for the obese patient. For instance, previous studies have demonstrated that as obesity severity increases, the optimal weight gain to prevent outcomes such as preterm birth and fetal growth abnormalities decreases [12, 13]. Therefore, an overweight or obese pregnant woman whose fetus is appropriately grown (by clinical sizing or ultrasound) should not be required or encouraged to gain more weight in order to conform to the IOM guidelines.

Table 8.1 IOM weight gain guidelines for pregnancy based on prepregnancy BMI

Prepregnancy weight category	BMI (kg/m^2)	Recommended weight gain (pounds)	Mean (range) in pounds/week in second and third trimester[a]	Recommended weight gain for twin gestation (pounds)
Underweight	<18.5	28–40	1 (1–3)	No recommendations
Normal weight	18.5–24.9	25–35	1 (0.8–1)	37–54
Overweight	25–29.9	15–25	0.6 (0.5–0.7)	31–50
Obese	≥30	11–20	0.5 (0.4–0.6)	25–42

[a]Assuming a 1.1–4.4 lb weight gain in the first trimester

Comorbidities in Pregnancy

Although obesity by itself can be considered a comorbidity in pregnancy, many medical conditions that are common in obese women often complicate pregnancy. These include hypertension, diabetes, hyperlipidemia, obstructive sleep apnea (OSA), and history of bariatric surgery.

Chronic Hypertension

Chronic hypertension is present in up to 5 % of all pregnant women, and is much more common in obese women [14, 15]. Chronic hypertension can cause end-organ damage, thereby complicating pregnancy even further by causing cardiomegaly, ischemic heart disease, left ventricular hypertrophy, renal involvement, or retinopathy [16]. Additionally, chronic hypertension increases the maternal risks of overall mortality, preeclampsia, cesarean delivery, and placental abruption, and the fetal risks of growth restriction and fetal demise [17–19].

Pregestational Diabetes

Pregestational diabetes is present in 1 % of all pregnancies and is associated with significant morbidity in pregnancy [20]. As with chronic hypertension, women with pregestational diabetes may have significant involvement of the cardiac and renal systems. Risks that are increased by pregestational diabetes include preeclampsia, cesarean delivery, preterm delivery (PTD), spontaneous abortion (SAB), fetal demise, fetal growth abnormality, congenital anomalies, and neonatal complications [21–23].

Hyperlipidemia

Hyperlipidemia, which is common among obese women, is associated with an increased risk for preeclampsia [24, 25].

Obstructive Sleep Apnea

OSA, an underdiagnosed but common comorbidity of obesity in pregnancy, is also a known secondary cause of hypertension, cardiovascular disease, and mood disturbances [26, 27]. OSA has been associated with fetal growth restriction,

preeclampsia, and stillbirth [28]. However, one of the greatest considerations in obese women with sleep apnea is difficulty with anesthesia administration, especially when general anesthesia is required.

Bariatric Surgery

With the high rate of obesity, an increasing number of reproductive-age women are undergoing bariatric surgery [29]. Several studies have concluded that rates of many adverse maternal and neonatal outcomes are lower in women who become pregnant after bariatric surgery than in obese women who have not had bariatric surgery [30]. Nonetheless, there are some considerations for pregnant women with prior bariatric surgery. For instance, prior abdominal surgery can increase the risks incurred during a cesarean delivery, vitamin deficiencies can be a concern, especially in malabsorptive types of surgery, and testing for gestational diabetes may need to be altered because of rapid gastric emptying (or dumping syndrome) [31].

Maternal Complications and Risks

Pregnancy-associated maternal morbidities have consistently been shown to be higher among obese women than normal-weight women at all stages of pregnancy. Antepartum risks include gestational diabetes, gestational hypertension, and preeclampsia. Intrapartum complications include induction and cesarean delivery. Finally, postpartum complications such as venous thromboembolism and wound complication are increased in obese women.

Gestational Hypertension and Preeclampsia

Gestational hypertension complicates pregnancy in 4.8 % of normal-weight women and 10.2 % of obese women, thus putting obese women at increased risk of preeclampsia [32]. For example, a systematic review by Obrien et al. found that the risk of preeclampsia doubled for every 5–7 kg/m^2 increase in prepregnancy BMI [33]. Additionally, Bodnar et al. found that obese women were at threefold higher risk for preeclampsia than normal-weight women [34].

Gestational Diabetes

Prepregnancy BMI is a strong predictor in the development of gestational diabetes [35]. Torloni et al. reported that moderately obese (Class I and II) and morbidly obese (Class III) women have three- and over fivefold, respectively, higher risk of developing gestational diabetes than normal-weight women [36]. Furthermore, a recent meta-analysis reported that severely obese women (Class II and III) have an increased risk (OR 8.6) of gestational diabetes [37].

Induction of Labor and Cesarean Delivery

Obesity has been found to be an independent risk factor for induction of labor and cesarean delivery [38, 39]. For example, a retrospective cohort study by Kominiarek et al. reported that the risk for cesarean increased by 2–5 % for every 1 kg/m^2 rise in BMI [39], and several studies have demonstrated that obese women are at increased risk of cesarean regardless of parity or prior cesarean history [40]. Some studies have shown that obese women are at increased risk of cesarean during the first, but not the second stage of labor [41]. This may be due to differences in the labor curve in obese women, which will be discussed later in this chapter.

Venous Thromboembolism

The rate of hospitalization for pregnancy-associated venous thromboembolism has increased along with the rate of obesity. Ghaji et al. found that from 1994 to 2009, there was a 14 % increase in the total rate of venous thromboembolism; rates increased by 17 % and 47 % in the antepartum and postpartum periods, respectively. In the same time frame, the prevalence of obesity among pregnant women hospitalized for pregnancy-associated venous thromboembolism doubled [42].

Wound Complication

Obese women are at higher risk for wound complications after cesarean delivery, including separation and infection, than normal-weight women. Rates of such complications range from 3.5 to 30 % [43–47]. Additionally, a dose–response relationship exists between BMI and risk of post-cesarean wound complications [48] (Fig. 8.1).

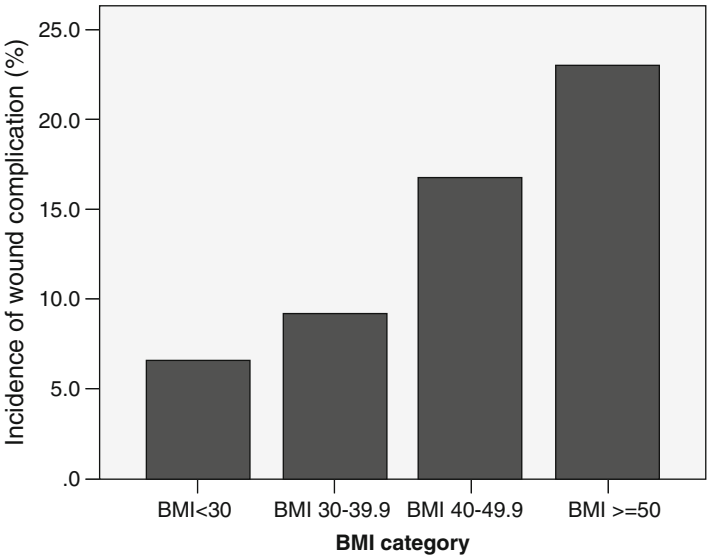

Fig. 8.1 Incidence of wound complication related to increasing BMI. Figure from: Conner SN, Verticchio JC, Tuuli MG, Odibo AO, Macones GA, Cahill AG. Maternal Obesity and Risk of Postcesarean Wound Complications. American Journal of Perinatology. 2013 Jun 13

Fetal and Obstetric Complications

Possible obstetric complications of maternal obesity include SAB and PTD. The fetal risks include macrosomia, stillbirth, and congenital anomalies.

Spontaneous Abortion

Several studies have observed an association between high BMI and risk of SAB. For example, a meta-analysis performed by Boots et al., which included a pooled cohort of over 28,000 women with spontaneous conception, found higher rates of SAB in obese women than normal-weight women (13.6 % vs. 10.7 %, OR 1.31, 95 % CI 1.18–1.46) [49]. Metwally et al. included overweight women in their meta-analysis and found that the OR for SAB in women with BMI>25 was 1.67 (95 % CI 1.25–2.25) [50]. Investigations into SAB rate in obese women after confirmed fetal heart activity reveal conflicting findings; some studies suggested an increased risk of SAB, whereas others showed no difference [51, 52]. Additionally, there is evidence that obese women undergoing infertility treatments have increased SAB rates [53, 54].

Preterm Delivery

The association between obesity and risk for PTD has not been well delineated. Rates of indicated PTD are clearly elevated among obese women because of comorbid conditions and increased rates of maternal, fetal, and obstetric complications, but the relationship between obesity and spontaneous PTD is not clear. Reviews have consistently shown that women in higher obesity classes (II and III) have increased risks for PTD, but risk estimates for women in obesity Class I are less consistent [55, 56]. A recent population-based retrospective cohort study of over 1.5 million deliveries found an overall increased risk for PTD in obese women and observed a dose response for higher BMI classes. However, when investigating the risk for spontaneous PTD, only extreme PTD (22–27 weeks' gestation) was found to be elevated in women with BMI $\geq$ 30 [57]. More data are needed to determine the risk of spontaneous PTD in obese women.

Macrosomia

Diabetes is a well-known risk factor for macrosomia (birth weight >4,500 g), but obesity alone has also been shown to be an independent risk factor for fetal macrosomia. A retrospective cohort study of over 12,000 deliveries found that, compared to subjects with normal BMI, obese women were at higher risk for birth weight in the 90th percentile or greater (16.8 % vs. 10.5 %) [58]. Furthermore, a recent meta-analysis found that obese women have over threefold higher risk for macrosomia than women with normal BMI (OR 3.23, 95 % CI 2.39–4.37) [59].

Stillbirth

Both large well-performed cohort studies and meta-analyses reveal maternal obesity, compared to normal BMI, is an independent risk factor for stillbirth (OR 1.63–2.8) [60–62] (see Table 8.2) [63].

Table 8.2 Obesity and risk of stillbirth

Study	Type of study	Stillbirth OR	95 % CI
Kristensen 2005 [60]	Retrospective cohort	2.8	1.5–5.3
Chu 2007 [61]	Meta-analysis	2.07	1.59–2.74
Flenady 2011 [62]	Meta-analysis	1.63	1.35–1.95

Table 8.3 Obesity and risk of specific congenital anomalies

Anomaly	Stothard et al. Meta-analysis	Watkins et al. Case control	Waller et al. Case control	Shaw et al. Case control
NTD/spina bifida	1.87 (1.62–2.15)	3.50 (1.20–10.30)	2.19 (1.69–2.85)	1.90 (1.30–2.90)
Hydrocephaly	1.68 (1.19–2.36)	–	1.27 (0.74–2.19)	–
Cardiac	1.30 (1.12–1.51)	2.00 (1.20–3.40)	1.33 (1.17–1.52)	–
Cleft lip and palate	1.20 (1.03–1.40)	–	1.07 (0.86–1.32)	–
Gastroschisis	0.17 (0.10–0.30)	–	0.19 (0.10–0.35)	–

Congenital Anomalies

Several investigations have shown an association between maternal obesity and increased risk of specific congenital anomalies. Obese women are at the highest risk for fetuses with neural tube defects, hydrocephaly, and cardiac defects [64–67] (see Table 8.3). Compounding this finding, limitations in ultrasound because of body habitus can make diagnosis of fetal anomalies difficult in women with high BMI.

Pregnancy Management Guidelines

Given the prevalence of obesity encountered in general obstetric practice, it is important to have an evidence-based approach to antepartum, intrapartum, and postpartum management to minimize morbidity in these patients. It is important to note, however, that patients are individuals with differing comorbidities, and their care should not be determined solely on the basis of BMI.

Initial Counseling

All initial prenatal visits for obese pregnant patients should include counseling regarding nutrition, weight gain, and anticipated risks to the pregnancy. Women should be informed of the recommendations about daily caloric intake, daily amounts of each food group for each trimester, and key vitamins and minerals required during pregnancy. This can be accomplished by providing patients with the education pamphlet from ACOG on nutrition during pregnancy or referring patients to a registered dietician for additional counseling. Obese pregnant patients should be counseled regarding optimal weight gain, as discussed previously in this chapter [11]. In addition, the initial counseling session should highlight maternal, fetal, and obstetric risks associated with obesity, and attention should be paid to portray accurate risk estimates.

Early Anatomy Scan

Most pregnant women undergo a routine anatomic survey to detect fetal anomalies during the second trimester, between 18 and 22 weeks' gestation [68]. Although obese women are at higher risk for fetal congenital anomalies, multiple large retrospective cohort studies have shown that the odds of detection of fetal anomalies are significantly decreased in obese women [69–71]. For example, Thornburg et al. found that whereas completion rates for a standard anatomic survey were 79 % for normal-weight women, they were 72 %, 61 %, and 49 % for women with Class I, Class II, and Class III obesity, respectively [71]. Another study reported that 66 % of fetal anomalies were detected with standard ultrasound examination in normal-weight women, but 25–48 % of such anomalies were detected in obese women [70]. Based on these findings, first-trimester ultrasound is emerging as an additional screening tool for detection of severe fetal anomalies in morbidly obese women. First-trimester evaluation of limited fetal anatomy can be performed transvaginally, thus avoiding the abdominal pannus. However, further research is needed to assess the benefit of first-trimester ultrasound for fetal anatomy screening in obese women.

Early Screening for Gestational Diabetes

Because maternal obesity increases the risks for gestational and pregestational diabetes, early screening can improve fetal outcomes. Performing a one-hour glucose challenge test as early as the first prenatal visit in women with BMI $\geq$ 30 can effectively identify women with undiagnosed type 2 diabetes [72, 73]. When early screening is negative, repeat screening should be implemented between 24 and 28 weeks' gestation.

Aneuploidy Screening

First and second trimester screening for aneuploidy should be routinely offered to all pregnant women [74]. Evidence suggests that high BMI is not associated with suboptimal visualization on first-trimester nuchal translucency measurement, but there is a higher likelihood that transvaginal views will be required to complete the assessment [75]. Additionally, there are no data to suggest that maternal serum screening accuracy is affected by maternal weight. Therefore, counseling on genetic screening options should be identical for obese and normal-weight women.

Monitoring Fetal Growth

Obese women are at increased risk for macrosomia and large-for-gestational-age infants [76, 77], but because of maternal habitus in obese patients, clinical sizing by Leopold maneuvers and fundal height measurements can often be misleading and overestimate fetal size. This problem is often obviated because many obese patients will have other comorbidities, such as diabetes or chronic hypertension, that act as indications for serial fetal growth assessment via ultrasound. For obese women with no indications for serial assessments of fetal growth, there is a paucity of evidence on the best method of screening for fetal growth abnormalities. It is reasonable to attempt clinical sizing based on maternal body habitus, and then obtain ultrasound measurements if fetal growth abnormality is suspected. Further research is required on this subject.

Antenatal Testing

Women with BMI $\geq$ 30 have increased rates of stillbirth independent from obesity-related comorbidities [61, 76, 78]. Antepartum fetal surveillance through the use of non-stress tests and biophysical profiles are currently implemented for a variety of other maternal and fetal indications in order to reduce the risk of stillbirth. In 2009, Signore recommended that the role of antenatal testing in obesity should be a focus of future research [79]. Currently, convincing data on the benefit of routine antenatal fetal surveillance solely for the indication of maternal obesity is lacking. Given the technical difficulties of performing fetal testing in obese pregnant women, the false-positive rate of non-reassuring testing must be investigated before fetal testing is routinely employed in obese women who lack additional comorbidities.

Delivery Planning

Anesthesia Management

The physiologic effects of pregnancy increase the difficulty of anesthesia administration, and increasing BMI can compound these technical challenges. For example, intubation for initiation of general anesthesia in emergent cesarean deliveries is more difficult in obese women than in normal-weight women and is of primary concern. Therefore, early placement of regional anesthesia has been advocated as a strategy to reduce the need for general anesthesia in emergent situations. Another concern was illustrated by a prospective cohort study by Bamgbade et al., which found that obesity was associated with increased difficulty in performing regional anesthesia. Although more than two attempts were required for successful placement, failure rates were not increased in obese women [80]. In addition to difficult

placement, obese women have been found to have more frequent persistent hypotension and fetal heart rate decelerations after epidural anesthesia [81]. Overall, in the anesthetic management of obese patients in labor, communication between obstetricians and anesthesiologists should be initiated early and often.

Induction of Labor

Because of higher rates of maternal and fetal complications in pregnancy, obese women are at increased risk for indicated induction of labor. Obese women are also more likely than normal-weight women to have a failed induction and undergo cesarean delivery. Wolfe et al. reported that the likelihood of a failed induction increased with increasing obesity class: 13 %, 20.2 %, 24.2 %, and 29 % for normal weight, obesity Class I, Class II, and Class III, respectively [82]. Furthermore, in a secondary analysis of a randomized controlled trial of women induced with prostaglandins, Pevzner et al. found that the duration of labor, oxytocin requirements, and cesarean delivery rates were significantly higher as the degree of obesity increased [83]. Therefore, it is prudent to weigh the risks and benefits of induction of labor in obese patients, especially in the case of elective induction.

Trial of Labor After Cesarean

Obesity has consistently been cited as a risk factor for failed trial of labor after cesarean, with failure rates increasing with increasing BMI [84, 85]. In a multicenter prospective cohort study of 14,529 women undergoing trial of labor after cesarean, the success rate for obese women was 68.4 %, whereas 79.6 % of nonobese women were successful [86]. Additionally, in a secondary analysis investigating maternal and neonatal morbidities from trial of labor, morbidly obese women were found to have a fivefold higher risk of uterine rupture or dehiscence than normal-weight women (2.1 % vs. 0.4 %) [87]. The etiology for decreased success rates in obese patients is unknown, but it is possible that physicians wish to avoid the morbidity associated with an emergent cesarean and thus have a lower threshold for advising a cesarean delivery. Another hypothesis is that obese women are more likely to fail trial of labor because their labor curve progression is different from their nonobese counterparts, thus leading to an increased likelihood of cesarean for labor arrest. Obese patients considering trial of labor after cesarean should be aware of the lower success rates but also consider their increased risk of morbidities incurred with cesarean delivery.

Labor Management: Changes to the Labor Curve

It is important to recognize that increasing BMI is associated with slower labor progression in both nulliparous and multiparous women [88]. A recent retrospective cohort study among 5,204 consecutive singleton term pregnancies who completed

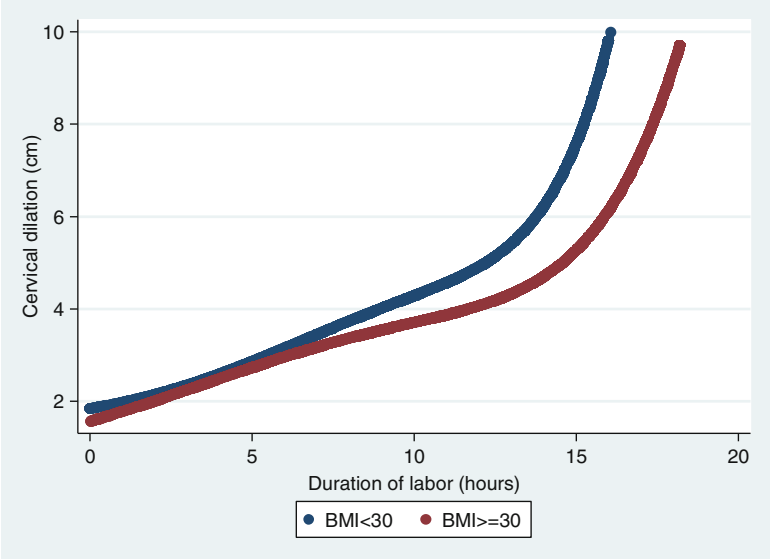

Fig. 8.2 Labor curve for obese versus nonobese women. Figure from: Norman SM, Tuuli MG, Odibo AO, Caughey AB, Roehl KA, Cahill AG. The effects of obesity on the first stage of labor. Obstet Gynecol. 2012 Jul;120 (1):130–5

the first stage of labor found that the overall duration of labor was longer, and progression of the early part of the first stage was slower, in obese women than in normal-weight women [89]. These findings should be considered before performing a cesarean for labor arrest in an obese patient (Fig. 8.2). However, there is no association between BMI and length of the second stage or risk for cesarean [90].

Cesarean Delivery

Compared to normal-weight women, obese women undergoing cesarean delivery face longer operative time, higher blood loss, increased rates of incisions other than Pfannensteil, and increased rates of wound complications [47, 48]. Additionally, postpartum venous thromboembolism risk is increased after cesarean and is compounded in obese women undergoing cesarean. Strategies to reduce surgical-related morbidity in obese women have been investigated and are described below.

1. Perioperative antibiotic prophylaxis
   For obese women, as for all obstetric patients, antimicrobial prophylaxis is recommended within 60 min before the start of a cesarean delivery [91, 92]. The recommended dose of 1 g of intravenous cefazolin should be increased to 2 g in patients with BMI > 30 or absolute weight more than 100 kg [93]. However, recent studies have suggested that even with a dose of 2 g of cefazolin, the tissue

concentration of the antibiotic in obese women at the time of skin incision is insufficient [94]. These studies suggest that further research is needed to determine the optimal dose to prevent infectious morbidity in obese patients.

2. Postpartum venous thromboembolism prophylaxis
   Because obesity, pregnancy, and cesarean delivery are all independent risk factors for venous thromboembolism, pneumatic compression devices should be placed prior to cesarean delivery for all women regardless of BMI. Evidence supporting a role of routine postpartum or post-cesarean chemoprophylaxis for venous thromboembolism is lacking. There are data regarding the use of low molecular weight heparin or unfractionated heparin in the postpartum period for women with history of thromboembolism or thrombophilia [95]. However, as confirmed by a recent Cochrane review [96], obesity alone as a risk factor for thromboembolism is not a current indication for administration of anticoagulation therapy in pregnancy and the early postnatal period. Additionally, prophylactic anticoagulation therapy is not without side effects and risks, such as bleeding and post-cesarean wound complications [97].
3. Wound management and incision guidelines
   Obese women with the same BMI can have vastly different body habitus and weight distributions; therefore, it is difficult to perform randomized trials on the best incision type for obese patients undergoing cesarean. Such information would be valuable, however, as increasing BMI has consistently been found to be associated with increasing risk for wound complications, including separation and infection [43–46]. Several cohort studies have demonstrated that vertical skin incisions place obese patients at increased risk for wound complications. For example, Thornburg et al. examined data from 623 women with BMI > 35 and found that the wound complication rates were 45.7 % with vertical skin incisions and 11.6 % with transverse incisions [44]. Similarly, in a study by Wall et al. involving 239 women with BMI > 35, vertical skin incisions were associated with an odds ratio of 12.4 for wound complication [98]. However, in clinical practice, vertical skin incision may be the best option for a safe fetal outcome in a morbidly obese patient with a large pannus. Clearly, the risks and benefits of a transverse versus a vertical skin incision must be weighed carefully, but the evidence points to a maternal benefit with transverse incisions in obese patients.

Prior to skin closure after cesarean, suture closure of the subcutaneous fat should be performed in patients with fat thickness greater than 2 cm. Evidence for this recommendation comes from a meta-analysis by Chelmow and colleagues, which found that suture closure of the subcutaneous dead space reduced wound complications after closure (RR 0.56, 95 % CI 0.36–0.86). The reduction was largely due to a decreased rate of wound seromas [99].

Recent evidence from randomized trials and meta-analyses reveals an overall lower wound complication risk in women with post-cesarean skin closure with sutures than with staples [100–102]. However, no study has shown sutures or staples to be superior in obese women. Figueroa et al. examined this question in a population in which the average BMI was >30 but found no difference in the rate of wound

complication for obese women who received staples versus suture [102]. Further research is needed to determine the optimal method of skin closure in obese patients undergoing cesarean.

Multiple randomized trials and meta-analyses have investigated the use of prophylactic subcutaneous drain placement in obese women undergoing cesarean and have consistently shown that this procedure does not decrease wound complication rate [103, 104]. Thus, subcutaneous drains should not be routinely placed at the time of cesarean delivery.

Summary

Understanding the evidence-based approach to caring for the obese pregnant patient cannot be understated. It is well established that obese women are at increased risk for maternal complications such as gestational diabetes, gestational hypertension and preeclampsia, induction of labor, cesarean delivery, venous thromboembolism, and wound complication in pregnancy. In addition, there is a higher rate of fetal complications including SAB, PTD, macrosomia, congenital anomalies, and stillbirth in obese women. The obese patient may have concomitant comorbidities that further complicate pregnancy. This chapter has described existing evidence and delineated pregnancy management guidelines for this patient population. However, it is important to recognize the current gaps in knowledge where further research is necessary. Specific areas that require further study include benefits of an early anatomy ultrasound in the first trimester, optimal method for screening for fetal growth abnormalities, the benefits of antenatal testing, dosage of perioperative antibiotics, the best strategy for venous thromboembolism prophylaxis, and the most efficacious wound closure method. The goal of future research should be to focus on strategies and interventions that will decrease maternal and fetal morbidity in obese women.

References

1. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series. 2000;894:i–xii, 1–253. PubMed PMID: 11234459.
2. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012;307(5):491–7. PubMed PMID: 22253363.
3. Ehrenberg HM, Dierker L, Milluzzi C, Mercer BM. Prevalence of maternal obesity in an urban center. Am J Obstet Gynecol. 2002;187(5):1189–93. PubMed PMID: 12439501.
4. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA. 2010;303(3):235–41. PubMed PMID: 20071471.
5. Nelson SM, Matthews P, Poston L. Maternal metabolism and obesity: modifiable determinants of pregnancy outcome. Hum Reprod Update. 2010;16(3):255–75. PubMed PMID: 19966268. Pubmed Central PMCID: 2849703.

6. Chevalier S, Burgess SC, Malloy CR, Gougeon R, Marliss EB, Morais JA. The greater contribution of gluconeogenesis to glucose production in obesity is related to increased whole-body protein catabolism. Diabetes. 2006;55(3):675–81. PubMed PMID: 16505230.
7. Mills JL, Jovanovic L, Knopp R, Aarons J, Conley M, Park E, et al. Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: the diabetes in early pregnancy study. Metabolism. 1998;47(9):1140–4. PubMed PMID: 9751245.
8. Sivan E, Chen X, Homko CJ, Reece EA, Boden G. Longitudinal study of carbohydrate metabolism in healthy obese pregnant women. Diabetes Care. 1997;20(9):1470–5. PubMed PMID: 9283800.
9. Siega-Riz AM, Viswanathan M, Moos MK, Deierlein A, Mumford S, Knaack J, et al. A systematic review of outcomes of maternal weight gain according to the Institute of Medicine recommendations: birthweight, fetal growth, and postpartum weight retention. Am J Obstet Gynecol. 2009;201(4):339e1–14. PubMed PMID: 19788965. Epub 2009/10/01. eng.
10. Nohr EA, Vaeth M, Baker JL, Sorensen T, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. Am J Clin Nutr. 2008;87(6):1750–9. PubMed PMID: 18541565.
11. Rasmussen KM, Yaktine AL (eds). Weight gain during pregnancy: reexamining the guidelines. The National Academies Collection: Reports funded by National Institutes of Health. National Academies Press: Washington DC; 2009.
12. Bodnar LM, Siega-Riz AM, Simhan HN, Himes KP, Abrams B. Severe obesity, gestational weight gain, and adverse birth outcomes. Am J Clin Nutr. 2010;91(6):1642–8. Pubmed Central PMCID: 2869513.
13. Beyerlein A, Schiessl B, Lack N, von Kries R. Optimal gestational weight gain ranges for the avoidance of adverse birth weight outcomes: a novel approach. Am J Clin Nutr. 2009;90(6):1552–8. PubMed PMID: 19812177.
14. Sibai BM. Chronic hypertension in pregnancy. Obstet Gynecol. 2002;100(2):369–77. PubMed PMID: 12151166.
15. Lawler J, Osman M, Shelton JA, Yeh J. Population-based analysis of hypertensive disorders in pregnancy. Hypertens Pregnancy. 2007;26(1):67–76. PubMed PMID: 17454219.
16. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. American journal of obstetrics and gynecology. 2000;183(1):S1-S22. PubMed PMID: 10920346.
17. Gilbert WM, Young AL, Danielsen B. Pregnancy outcomes in women with chronic hypertension: a population-based study. J Reprod Med. 2007;52(11):1046–51. PubMed PMID: 18161404.
18. Ferrer RL, Sibai BM, Mulrow CD, Chiquette E, Stevens KR, Cornell J. Management of mild chronic hypertension during pregnancy: a review. Obstet Gynecol. 2000;96(5 Pt 2):849–60. PubMed PMID: 11094241.
19. Zetterstrom K, Lindeberg SN, Haglund B, Hanson U. Maternal complications in women with chronic hypertension: a population-based cohort study. Acta Obstet Gynecol Scand. 2005;84(5):419–24. PubMed PMID: 15842204.
20. Lethbridge-Cejku M, Schiller JS, Bernadel L. Summary health statistics for U.S. adults: National Health Interview Survey, 2002. Vital Health Stat 10. 2004;222:1–151. PubMed PMID: 15791763.
21. Greene MF, Hare JW, Cloherty JP, Benacerraf BR, Soeldner JS. First-trimester hemoglobin A1 and risk for major malformation and spontaneous abortion in diabetic pregnancy. Teratology. 1989;39(3):225–31. PubMed PMID: 2727930.
22. Sheffield JS, Butler-Koster EL, Casey BM, McIntire DD, Leveno KJ. Maternal diabetes mellitus and infant malformations. Obstet Gynecol. 2002;100(5 Pt 1):925–30. PubMed PMID: 12423854. Epub 2002/11/09. eng.
23. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, et al. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. The National Institute of Child Health and Human Development—Diabetes in Early Pregnancy Study. Am J Obstet Gynecol. 1991;164(1):103–11. PubMed PMID: 1986596.

24. Demirci O, Tugrul AS, Dolgun N, Sozen H, Eren S. Serum lipids level assessed in early pregnancy and risk of pre-eclampsia. J Obstet Gynaecol Res. 2011;37(10):1427–32. PubMed PMID: 21676073.
25. Clausen T, Djurovic S, Henriksen T. Dyslipidemia in early second trimester is mainly a feature of women with early onset pre-eclampsia. BJOG. 2001;108(10):1081–7. PubMed PMID: 11702841.
26. Mannarino MR, Di Filippo F, Pirro M. Obstructive sleep apnea syndrome. Eur J Intern Med. 2012;23(7):586–93. PubMed PMID: 22939801.
27. Baguet JP, Barone-Rochette G, Tamisier R, Levy P, Pepin JL. Mechanisms of cardiac dysfunction in obstructive sleep apnea. Nat Rev Cardiol. 2012;9(12):679–88. PubMed PMID: 23007221.
28. Louis JM, Auckley D, Sokol RJ, Mercer BM. Maternal and neonatal morbidities associated with obstructive sleep apnea complicating pregnancy. Am J Obstet Gynecol. 2010;202(3): 261e1–5. PubMed PMID: 20005507.
29. Davis MM, Slish K, Chao C, Cabana MD. National trends in bariatric surgery, 1996-2002. Arch Surg. 2006;141(1):71–4; discussion 5. PubMed PMID: 16415414.
30. Maggard MA, Yermilov I, Li Z, Maglione M, Newberry S, Suttorp M, et al. Pregnancy and fertility following bariatric surgery: a systematic review. JAMA. 2008;300(19):2286–96. PubMed PMID: 19017915.
31. Poitou Bernert C, Ciangura C, Coupaye M, Czernichow S, Bouillot JL, Basdevant A. Nutritional deficiency after gastric bypass: diagnosis, prevention and treatment. Diabetes Metab. 2007;33(1):13–24. PubMed PMID: 17258928.
32. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. Am J Obstet Gynecol. 2004;190(4):1091–7. PubMed PMID: 15118648.
33. Kalhan SC, Gruca LL, Parimi PS, O'Brien A, Dierker L, Burkett E. Serine metabolism in human pregnancy. Am J Physiol Endocrinol Metab. 2003;284(4):E733–40. PubMed PMID: 12488240.
34. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. Ann Epidemiol. 2005;15(7):475–82. PubMed PMID: 16029839.
35. Ogonowski J, Miazgowski T, Kuczynska M, Krzyzanowska-Swiniarska B, Celewicz Z. Pregravid body mass index as a predictor of gestational diabetes mellitus. Diabet Med. 2009;26(4):334–8. PubMed PMID: 19388961.
36. Torloni MR, Betran AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, et al. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. Obes Rev. 2009;10(2):194–203. PubMed PMID: 19055539.
37. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007;30(8):2070–6. PubMed PMID: 17416786.
38. Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. Int J Obes Relat Metab Disord. 2001;25(8):1175–82. PubMed PMID: 11477502.
39. Kominiarek MA, Vanveldhuisen P, Hibbard J, Landy H, Haberman S, Learman L, et al. The maternal body mass index: a strong association with delivery route. Am J Obstet Gynecol. 2010;203(3):264e1–7. PubMed PMID: 20673867. Pubmed Central PMCID: 2933947.
40. Chu SY, Kim SY, Schmid CH, Dietz PM, Callaghan WM, Lau J, et al. Maternal obesity and risk of cesarean delivery: a meta-analysis. Obes Rev. 2007;8(5):385–94. PubMed PMID: 17716296.
41. Fyfe EM, Anderson NH, North RA, Chan EH, Taylor RS, Dekker GA, et al. Risk of first-stage and second-stage cesarean delivery by maternal body mass index among nulliparous women in labor at term. Obstet Gynecol. 2011;117(6):1315–22. PubMed PMID: 21606741.
42. Ghaji N, Boulet SL, Tepper N, Hooper WC. Trends in venous thromboembolism among pregnancy-related hospitalizations, United States, 1994–2009. Am J Obstet Gynecol. 2013; 209(5):433e1–8. PubMed PMID: 23810274.

43. Leth RA, Uldbjerg N, Norgaard M, Moller JK, Thomsen RW. Obesity, diabetes, and the risk of infections diagnosed in hospital and post-discharge infections after cesarean section: a prospective cohort study. Acta Obstet Gynecol Scand. 2011;90(5):501–9. PubMed PMID: 21306347.
44. Thornburg LL, Linder MA, Durie DE, Walker B, Pressman EK, Glantz JC. Risk factors for wound complications in morbidly obese women undergoing primary cesarean delivery. J Matern Fetal Neonatal Med. 2012;25(9):1544–8. PubMed PMID: 22233403.
45. Tran TS, Jamulitrat S, Chongsuvivatwong V, Geater A. Risk factors for postcesarean surgical site infection. Obstet Gynecol. 2000;95(3):367–71. PubMed PMID: 10711546.
46. Alanis MC, Villers MS, Law TL, Steadman EM, Robinson CJ. Complications of cesarean delivery in the massively obese parturient. Am J Obstet Gynecol. 2010;203(3):271e1–7. PubMed PMID: 20678746.
47. Myles TD, Gooch J, Santolaya J. Obesity as an independent risk factor for infectious morbidity in patients who undergo cesarean delivery. Obstet Gynecol. 2002;100(5 Pt 1):959–64. PubMed PMID: 12423861.
48. Conner SN, Verticchio JC, Tuuli MG, Odibo AO, Macones GA, Cahill AG. Maternal Obesity and Risk of Postcesarean Wound Complications. Am J Perinatol. 2014;31(4):299–304. PubMed PMID: 23765707.
49. Boots C, Stephenson MD. Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review. Semin Reprod Med. 2011;29(6):507–13. PubMed PMID: 22161463.
50. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril. 2008;90(3):714–26. PubMed PMID: 18068166.
51. Turner MJ, Fattah C, O'Connor N, Farah N, Kennelly M, Stuart B. Body mass index and spontaneous miscarriage. Eur J Obstet Gynecol Reprod Biol. 2010;151(2):168–70. PubMed PMID: 20488611.
52. O'Dwyer V, Monaghan B, Fattah C, Farah N, Kennelly MM, Turner MJ. Miscarriage after sonographic confirmation of an ongoing pregnancy in women with moderate and severe obesity. Obes Facts. 2012;5(3):393–8. PubMed PMID: 22797366.
53. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online. 2011;23(4):421–39. PubMed PMID: 21885344.
54. Wang JX, Davies MJ, Norman RJ. Obesity increases the risk of spontaneous abortion during infertility treatment. Obes Res. 2002;10(6):551–4. PubMed PMID: 12055331.
55. Torloni MR, Betran AP, Daher S, Widmer M, Dolan SM, Menon R, et al. Maternal BMI and preterm birth: a systematic review of the literature with meta-analysis. J Matern Fetal Neonatal Med. 2009;22(11):957–70. PubMed PMID: 19900068.
56. McDonald SD, Han Z, Mulla S, Beyene J, Knowledge SG. Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analyses. BMJ. 2010;341:c3428. Pubmed Central PMCID: 2907482.
57. Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikstrom AK, et al. Maternal obesity and risk of preterm delivery. JAMA. 2013;309(22):2362–70. PubMed PMID: 23757084.
58. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. Am J Obstet Gynecol. 2004;191(3):964–8. PubMed PMID: 15467573.
59. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PLoS One. 2013;8(4):e61627. Pubmed Central PMCID: 3628788.
60. Kristensen J, Vestergaard M, Wisborg K, Kesmodel U, Secher NJ. Pre-pregnancy weight and the risk of stillbirth and neonatal death. BJOG. 2005;112(4):403–8. PubMed PMID: 15777435.
61. Chu SY, Kim SY, Lau J, Schmid CH, Dietz PM, Callaghan WM, et al. Maternal obesity and risk of stillbirth: a metaanalysis. Am J Obstet Gynecol. 2007;197(3):223–8. PubMed PMID: 17826400. Epub 2007/09/11. eng.

62. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet. 2011;377(9774):1331–40. PubMed PMID: 21496916.
63. Nohr EA, Bech BH, Davies MJ, Frydenberg M, Henriksen TB, Olsen J. Prepregnancy obesity and fetal death: a study within the Danish National Birth Cohort. Obstet Gynecol. 2005;106(2):250–9. PubMed PMID: 16055572.
64. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA. 2009;301(6):636–50. PubMed PMID: 19211471. Epub 2009/02/13. eng.
65. Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. JAMA. 1996;275(14):1093–6. PubMed PMID: 8601928.
66. Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, et al. Prepregnancy obesity as a risk factor for structural birth defects. Arch Pediatr Adolesc Med. 2007;161(8):745–50. PubMed PMID: 17679655.
67. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. Pediatrics. 2003;111(5 Pt 2):1152–8. PubMed PMID: 12728129.
68. American College of Obstetrics and Gynecologists. ACOG Practice Bulletin No. 101: Ultrasonography in pregnancy. Obstet Gynecol. 2009;113(2 Pt 1):451–61. PubMed PMID: 19155920.
69. Best KE, Tennant PW, Bell R, Rankin J. Impact of maternal body mass index on the antenatal detection of congenital anomalies. BJOG. 2012;119(12):1503–11. PubMed PMID: 22900903.
70. Dashe JS, McIntire DD, Twickler DM. Effect of maternal obesity on the ultrasound detection of anomalous fetuses. Obstet Gynecol. 2009;113(5):1001–7. PubMed PMID: 19384114.
71. Thornburg LL, Miles K, Ho M, Pressman EK. Fetal anatomic evaluation in the overweight and obese gravida. Ultrasound Obstet Gynecol. 2009;33(6):670–5. PubMed PMID: 19479682.
72. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care. 2007;30 Suppl 2:S251–60. PubMed PMID: 17596481.
73. Committee on Practice Bulletins—Obstetrics. Practice bulletin no. 137: gestational diabetes mellitus. Obstet Gynecol. 2013;122(2 Pt 1):406–16. PubMed PMID: 23969827.
74. Bulletins ACoP. ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol. 2007;109(1):217–27. PubMed PMID: 17197615.
75. Gandhi M, Fox NS, Russo-Stieglitz K, Hanley ME, Matthews G, Rebarber A. Effect of increased body mass index on first-trimester ultrasound examination for aneuploidy risk assessment. Obstet Gynecol. 2009;114(4):856–9. PubMed PMID: 19888045.
76. Ovesen P, Rasmussen S, Kesmodel U. Effect of prepregnancy maternal overweight and obesity on pregnancy outcome. Obstet Gynecol. 2011;118(2 Pt 1):305–12. PubMed PMID: 21775846.
77. Lu GC, Rouse DJ, DuBard M, Cliver S, Kimberlin D, Hauth JC. The effect of the increasing prevalence of maternal obesity on perinatal morbidity. Am J Obstet Gynecol. 2001;185(4):845–9. PubMed PMID: 11641663.
78. Stillbirth Collaborative Research Network Writing G. Association between stillbirth and risk factors known at pregnancy confirmation. JAMA. 2011;306(22):2469–79. PubMed PMID: 22166606.
79. Signore C, Freeman RK, Spong CY. Antenatal testing-a reevaluation: executive summary of a Eunice Kennedy Shriver National Institute of Child Health and Human Development workshop. Obstet Gynecol. 2009;113(3):687–701. Pubmed Central PMCID: 2771454.
80. Bamgbade OA, Khalaf WM, Ajai O, Sharma R, Chidambaram V, Madhavan G. Obstetric anaesthesia outcome in obese and non-obese parturients undergoing caesarean delivery: an observational study. Int J Obstet Anesth. 2009;18(3):221–5. PubMed PMID: 19447599.
81. Vricella LK, Louis JM, Mercer BM, Bolden N. Impact of morbid obesity on epidural anesthesia complications in labor. Am J Obstet Gynecol. 2011;205(4):370e1–6. PubMed PMID: 21864821.

82. Wolfe KB, Rossi RA, Warshak CR. The effect of maternal obesity on the rate of failed induction of labor. Am J Obstet Gynecol. 2011;205(2):128e1–7. PubMed PMID: 21621187.
83. Pevzner L, Powers BL, Rayburn WF, Rumney P, Wing DA. Effects of maternal obesity on duration and outcomes of prostaglandin cervical ripening and labor induction. Obstet Gynecol. 2009;114(6):1315–21. PubMed PMID: 19935035.
84. Gunatilake RP, Smrtka MP, Harris B, Kraus DM, Small MJ, Grotegut CA, et al. Predictors of failed trial of labor among women with an extremely obese body mass index. Am J Obstet Gynecol. 2013;209(6):562e1–5. PubMed PMID: 23891628.
85. Goodall PT, Ahn JT, Chapa JB, Hibbard JU. Obesity as a risk factor for failed trial of labor in patients with previous cesarean delivery. Am J Obstet Gynecol. 2005;192(5):1423–6. PubMed PMID: 15902126.
86. Landon MB, Leindecker S, Spong CY, Hauth JC, Bloom S, Varner MW, et al. The MFMU Cesarean Registry: factors affecting the success of trial of labor after previous cesarean delivery. Am J Obstet Gynecol. 2005;193(3 Pt 2):1016–23. PubMed PMID: 16157104.
87. Hibbard JU, Gilbert S, Landon MB, Hauth JC, Leveno KJ, Spong CY, et al. Trial of labor or repeat cesarean delivery in women with morbid obesity and previous cesarean delivery. Obstet Gynecol. 2006;108(1):125–33. PubMed PMID: 16816066.
88. Kominiarek MA, Zhang J, Vanveldhuisen P, Troendle J, Beaver J, Hibbard JU. Contemporary labor patterns: the impact of maternal body mass index. Am J Obstet Gynecol. 2011;205(3):244e1–8. PubMed PMID: 21798510. Pubmed Central PMCID: 3212654.
89. Norman SM, Tuuli MG, Odibo AO, Caughey AB, Roehl KA, Cahill AG. The effects of obesity on the first stage of labor. Obstet Gynecol. 2012;120(1):130–5. PubMed PMID: 22914401. Epub 2012/08/24. eng.
90. Robinson BK, Mapp DC, Bloom SL, Rouse DJ, Spong CY, Varner MW, et al. Increasing maternal body mass index and characteristics of the second stage of labor. Obstet Gynecol. 2011;118(6):1309–13. Pubmed Central PMCID: 3760498.
91. American College of Obstetrics and Gynecology. ACOG Practice Bulletin No. 120: Use of prophylactic antibiotics in labor and delivery. Obstet Gynecol. 2011;117(6):1472–83. PubMed PMID: 21606770.
92. Smaill FM, Gyte GM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev. 2010;1, CD007482. PubMed PMID: 20091635.
93. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy. 2007;27(8):1081–91. PubMed PMID: 17655508.
94. Pevzner L, Swank M, Krepel C, Wing DA, Chan K, Edmiston Jr CE. Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean delivery. Obstet Gynecol. 2011;117(4):877–82. PubMed PMID: 21422859.
95. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J, American College of Chest Physicians. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):844S–86. PubMed PMID: 18574280.
96. Tooher R, Gates S, Dowswell T, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. The Cochrane database of systematic reviews. 2010;5, CD001689. PubMed PMID: 20464719.
97. Limmer JS, Grotegut CA, Thames E, Dotters-Katz SK, Brancazio LR, James AH. Postpartum wound and bleeding complications in women who received peripartum anticoagulation. Thromb Res. 2013;132(1):e19–23. PubMed PMID: 23735589.
98. Wall PD, Deucy EE, Glantz JC, Pressman EK. Vertical skin incisions and wound complications in the obese parturient. Obstet Gynecol. 2003;102(5 Pt 1):952–6. PubMed PMID: 14672469.
99. Chelmow D, Rodriguez EJ, Sabatini MM. Suture closure of subcutaneous fat and wound disruption after cesarean delivery: a meta-analysis. Obstet Gynecol. 2004;103(5 Pt 1):974–80. PubMed PMID: 15121573.

100. Basha SL, Rochon ML, Quinones JN, Coassolo KM, Rust OA, Smulian JC. Randomized controlled trial of wound complication rates of subcuticular suture vs staples for skin closure at cesarean delivery. Am J Obstet Gynecol. 2010;203(3):285e1–8. PubMed PMID: 20816153.
101. Tuuli MG, Rampersad RM, Carbone JF, Stamilio D, Macones GA, Odibo AO. Staples compared with subcuticular suture for skin closure after cesarean delivery: a systematic review and meta-analysis. Obstet Gynecol. 2011;117(3):682–90. PubMed PMID: 21343772.
102. Figueroa D, Jauk VC, Szychowski JM, Garner R, Biggio JR, Andrews WW, et al. Surgical staples compared with subcuticular suture for skin closure after cesarean delivery: a randomized controlled trial. Obstet Gynecol. 2013;121(1):33–8. PubMed PMID: 23262925.
103. Hellums EK, Lin MG, Ramsey PS. Prophylactic subcutaneous drainage for prevention of wound complications after cesarean delivery—a metaanalysis. Am J Obstet Gynecol. 2007;197(3):229–35. PubMed PMID: 17826401.
104. Ramsey PS, White AM, Guinn DA, Lu GC, Ramin SM, Davies JK, et al. Subcutaneous tissue reapproximation, alone or in combination with drain, in obese women undergoing cesarean delivery. Obstet Gynecol. 2005;105(5 Pt 1):967–73. PubMed PMID: 15863532.

Chapter 9
Contraceptive Counseling in Obese Women

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The concurrent epidemics of unintended pregnancy and obesity intersect in the field of family planning. Obesity in reproductive-age women has translated into increased rates of adverse neonatal and maternal outcomes [1–5]. Effective and appropriate contraceptive counseling in this population can help ensure that pregnancies are planned and medical comorbidities are optimally managed.

There are significant gaps in the current scientific literature regarding the best and most effective contraceptive options for overweight and obese women. The majority of contraceptive research is limited to women within 130 % of ideal body weight. Additionally, the lack of robust data coupled with the increased risk of medical comorbidities makes contraceptive recommendations challenging for clinicians.

This chapter will discuss common concerns about contraceptive use in overweight and obese women, describe available reversible and permanent contraceptive methods starting with long-acting reversible contraceptives (LARC), and review the available literature for each contraceptive method addressing both pharmacokinetic and clinical outcomes data. Throughout this chapter we will refer to two documents developed by the Centers for Disease Control and Prevention (CDC) designed to helped clinicians navigate their patient's specific clinical characteristics in determining the appropriateness of a method; the United States Medical Eligibility Criteria (MEC) [6] and Selected Practices Recommendations (SPR) [7]. The MEC provides recommendations for contraceptive methods on a scale of 1–4 for any given medical condition (Table 9.1). A **category 1** means the methods is recommended without restriction. A **category 2** method is one where the theoretical

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Table 9.1 United States medical eligibility criteria

Category 1	Method can be used without restriction
Category 2	Benefit outweighs the theoretical or proven risk
Category 3	Theoretical or proven risk outweighs the benefit
Category 4	Unacceptable health risk

or proven risk of the medical condition is generally outweighed by the benefit of the method. If the theoretical or proven risk of the medical condition usually outweighs the benefit of the method, it is labeled as **category 3**. Finally, if there is sufficient evidence that a method poses an unacceptable health risk, it is **category 4**.

Common Contraceptive Concerns in Obese Women

Effectiveness is one of the most important characteristics for women when choosing a contraceptive method [8]. Effectiveness of hormonal contraception may be impacted by metabolic differences in women of differing weights [9, 10]. Until recently, the majority of pharmacokinetic data excluded overweight and obese women. Recent studies indicate there may be differences in the metabolism between normal and overweight women [11–14], but data from clinical research studies has not shown increased method failure rates [15, 16].

A second common concern in this population is increased risk of venous thromboembolism (VTE) with estrogen-containing contraceptives given the increased incidence of VTE in obese populations [17]. Given VTE is a rare event in the reproductive-age population, there is limited data investigating whether obese patients have an increased risk when using combined hormonal methods. Current expert opinion allows the use of estrogen-containing methods in obese women if no other contraindications exist (e.g., personal history of VTE, hypertension, or cardiovascular disease).

Lastly, many obese women have medical comorbidities such as diabetes or hypertension and clinicians are faced with navigating complex medical histories to counsel women on safe and effective contraceptive methods. Most medical comorbidities affect eligibility for estrogen-containing contraception. Nonhormonal and progestin-only methods remain safe for women with most medical comorbidities. We encourage healthcare providers to use the US MEC to maneuver these individual patient characteristics.

Long-Acting Reversible Contraceptives

There are currently four LARC methods available in the United States, three intrauterine devices (IUDs) and one subdermal implant. LARC methods are the most effective reversible methods with failure rates less than 1 % [18]. They have very

few contraindications and are particularly well-suited for the overweight and obese population as none of these methods contain estrogen (MEC 1). LARC methods do require a clinician visit for insertion and removal, which may be interpreted as an access barrier. However, it also provides clinicians with an opportunity to provide counseling related to the woman's obesity-related health risks.

Intrauterine Devices

There are currently two well-studied IUDs available in the United States: the 52 mg levonorgestrel intrauterine system (LNG-IUS) and the copper T380 intrauterine device (Cu-IUD) (Fig. 9.1). The LNG-IUS is currently FDA-approved for up to 5 years of use. The T-shaped frame contains 52 mg of the progestin levonorgestrel. There are several mechanisms by which pregnancy is prevented; cervical mucus thickening, inhibition of sperm motility and capacitation, and thinning of the endometrial lining [18]. The LNG-IUS also has several non-contraceptive benefits. Average monthly blood loss decreases significantly and up to 20–40 % of women will become amenorrheic after 1 year of use [19–21]. This may be of particular benefit to women who experience difficulty with menstrual hygiene as a result of severe obesity. The rate of amenorrhea may be influenced by BMI; one study found that women with higher BMI had a delay to amenorrhea, but 25–72 % achieved amenorrhea between the fourth and fifth year of use [22]. Regardless of whether amenorrhea is achieved, the LNG-IUS offers protection against endometrial hyperplasia and adenocarcinoma, an important benefit in this population who are exposed to excess circulating estrogens. The LNG-IUS has been investigated as a nonsurgical treatment for endometrial hyperplasia and malignancy [23–25] and is frequently considered in obese women who have comorbidities that make them poor surgical candidates or where future fertility is desired [26, 27].

The Cu-IUD is a nonhormonal method in which the T-shaped frame is wrapped in copper wire. This method is currently FDA-approved for up to 10 years of use making it one of the most cost-effective reversible methods available [28]. Pregnancy is prevented mainly through the spermicidal action of the copper ions [29]. Because the Cu-IUD does not deliver any hormone to the endometrium, it does not improve the bleeding profile of users. Despite the lack of hormone, it has been shown to also provide protection against endometrial hyperplasia and adenocarcinoma, likely as a result of the endometrial inflammatory process [24].

A third IUD, the 13.5 mg LNG-IUS, has recently been approved by the FDA for up to 3 years of use. There is limited data about the use of this method in overweight and obese women. Due to a lower dose of levonorgestrel, the rate of amenorrhea was dramatically lower (12 % vs. 40 %) in the studied population (<130 % ideal body weight). Given that the rate of amenorrhea may be lower in obese women with the 52 mg LNG-IUS, the 13.5 mg is even less likely to result in amenorrhea. Similarly, there is currently no data evaluating the extent to which this device provides endometrial protection against hyperplasia and adenocarcinoma.

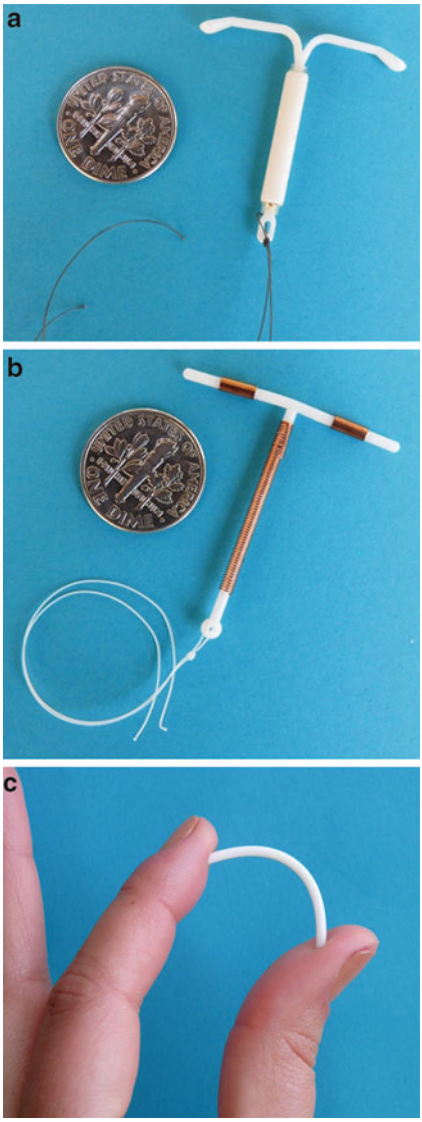

Fig. 9.1 Long-acting reversible contraceptive methods. (**a**) 52 mg LNG-IUS (**b**) Cu-IUD (**c**) ENG implant

Like all contraceptive methods, there are risks to IUD use. Spontaneous expulsion occurs in 2–10 % of users [30, 31]. There is no data to suggest that this rate is higher in obese women. Obese women who expel their IUD should be managed in the same manner as normal-weight women. Uterine perforation at the time of insertion is low, estimated at less than 1/1,000 insertions [32]. The risk of perforation is correlated to clinician experience and is lower in more experienced clinicians [32]. There is no data that indicates perforation rates are related to body weight, although clinicians may perceive insertions to be more difficult in obese women. If perforation is recognized at the time of insertion, the device can be easily removed.

However, if perforation is unrecognized at the time of insertion and the IUD is found to be intra-abdominal, removal of the IUD may be challenging in the obese patient. The standard recommendation for an extrauterine IUD is laparoscopic removal. In an obese or morbidly obese woman, laparoscopic removal may be technically difficult. In such an instance, some clinicians have chosen to leave the LNG-IUS in situ [33, 34]. Because the Cu-IUD acts primarily through an inflammatory response, careful consideration of surgical risk should be completed before deciding to leave the IUD in the abdomen. One small study compared intraoperative laparoscopic findings in women who were undergoing removal of intra-abdominal IUDs and found no difference in adhesion formation between the two devices [35]. However, these results should be interpreted with caution as the time since insertion was relatively short ranging from days to 7 months. Given that perforation is rare, there is no evidence regarding the contraceptive efficacy of intra-abdominal LNG-IUS, therefore another form of effective contraception should be initiated.

Subdermal Implant

The subdermal etonogestrel implant is a single ethylene vinyl acetate rod measuring 4 cm in length that continuously releases the progestin etonogestrel (ENG) (Fig. 9.1). The continuous release of ENG suppresses ovulation, inhibits endometrial proliferation, and thickens cervical mucus [18, 36]. Results of pharmacokinetic studies of the implant in overweight and obese women suggest that this population has a lower serum concentration of ENG [11, 37]. However, the levels remain well above the level required for ovulation suppression. The significance of this finding is unknown given the small sample size. A large observational study revealed no increase in the rate of unintended pregnancy in overweight and obese implant users [16]. Furthermore, a study evaluating serum ENG levels in overweight and obese women at the end of three and four years of implant use found that ENG levels were similar in obese and normal-weight women, and that those levels remained above the threshold for ovulation supression [38].

Unlike IUDs, initiation of the implant does not require a pelvic exam. The device is placed superficially under the skin of the arm after administration of local anesthesia. The major disadvantage of the implant is unpredictable irregular bleeding. Bleeding patterns can range from amenorrhea to daily spotting. Obese women may be less bothered by the irregular bleedings as obese women have a higher incidence of irregular bleeding than normal-weight women. Several potential interventions have been suggested to address the irregular bleeding patterns [39], but there is limited evidence to suggest that any of these interventions are effective.

User-Dependent Methods

Methods that require continued action from the user are termed *user-dependent methods*. These include injectables, the vaginal ring, the contraceptive patch, and oral contraceptive pills.

Depot Medroxyprogesterone Acetate

DMPA is an injectable progestin that is administered every 11–13 weeks. It prevents pregnancy primarily by ovulation suppression [40], and secondarily through thickening of the cervical mucus and endometrial alterations [41–43]. Typical-use failure rates range between 2 and 6 % [18, 44]. While one study found lower levels of medroxyprogesterone acetate in obese women, these levels were still considered sufficient and there is no evidence to suggest there is an increased risk of failure in obese DMPA users [13, 45].

The absence of estrogen is one advantage of DMPA for obese women The American College of Obstetrics and Gynecology released a bulletin stating that DMPA is a safe method for women with known risk factors for cardiovascular disease, thromboembolism, congestive heart failure, and cerebrovascular disease [46]. Similar to the LNG-IUS, DMPA users can expect significant reduction in menstrual blood loss or complete menstrual suppression, which occurs in up to 50 % of users at 12 months [47, 48]. Like other progestin-only methods, DMPA also provides endometrial protection and has been shown to reduce the risk of endometrial cancer by as much as 80 % [49, 50].

DMPA does have several disadvantages. DMPA has been associated with weight gain, which may be a particular disadvantage for already obese women. Some studies suggest that overweight and obese women, particularly adolescents, may experience more weight gain than normal-weight users [51–53] with DMPA use. Long-term DMPA use has been associated with a temporary and usually reversible decrease in bone density [54–57]. The combined evidence on weight gain and bone loss support the current MEC category 2 for women with BMI >30 and less than 18 years old. For women greater than 18 years, the recommendation remains category 1.

Combined Hormonal Contraceptives

Combined hormonal contraceptives (CHC), which contain both estrogen and progestin, are among the most commonly-used reversible methods in the United States [58]. CHC include the vaginal ring, transdermal patch, and combined oral contraceptive pills (COCs). All of these methods work primarily by ovulation suppression and secondarily by cervical mucus thickening. The type and amount of progestin does vary between different formulations. Concerns about effectiveness in the obese women are not unfounded. Several pharmacokinetic studies in COC users have found that hormonal half-life, time to steady state, drug clearance, and peak hormone levels may be different in obese women compared to normal-weight women [59, 60]. Despite potential differences, obese women in these studies were not found to be at any increased risk of ovulation [59, 61]. Studies of transdermal patch users found serum hormone levels to be correlated with body weight and limited evidence

suggests that women weighing more than 90 kg are at increased risk of failure and pregnancy [62]. Although these studies were limited by small samples of obese women, 5 of the 15 documented pregnancies were in women over 90 kg. These women accounted for only 3 % of the study population, but represented 33 % of the pregnancies, suggesting that if these women are unwilling to consider a different method they should be counseled on a potential increase in the risk of failure. Lastly, as with COCs and the patch, the vaginal ring has been shown to have with lower serum hormone levels in obese women [14]. However, these lower levels were sufficient to reliably suppress ovulation. Obese ring users were also evaluated for prolonged use and were found to have therapeutic hormone levels even when a single ring was used for six continuous weeks [63]. Clinical outcomes data from a large observational study found that obese users of COCs, the patch, and the ring did not have an increased risk of an unintended pregnancy [15]. In summary, current data suggests that there may be pharmacokinetic differences in obese women using COCs and the ring, but that these differences do not translate into higher failure rates or increased risk of unintended pregnancy. The available data on the patch suggests that obesity is associated with a higher risk of failure and pregnancy.

Nearly all of the risks associated with CHC are related to the estrogen component, despite the fact that most of the contraceptive effect is due to the progestin. Clinicians' concerns about using these methods in the obese women stem from the known associated comorbid conditions (e.g., hypertension, thromboembolism) that are relative or absolute contraindications to estrogen-containing methods. Nearly all CHC in the United States contain ethinyl estradiol (EE) in doses ranging from 10 to 50 mcg [18]. CHC are contraindicated in women with a personal history of thromboembolism (MEC category 4); however, use in women who are at higher risk for thromboembolism because of obesity is not contraindicated. The current MEC category for CHC use in obese women without a personal history of VTE or other contraindicated comorbid condition is 2. This categorization recognizes the elevated relative risk in obese women, which may be as high as threefold [64], but also takes into account the fact that the absolute risk is still quite small. The risk of VTE may differ by the CHC preparation. Studies comparing the transdermal patch to equivalent COCs are conflicting but suggest that there may be as much as a twofold increase in VTE among patch users [59, 65–67]. Risk of VTE in ring users has been estimated at 149 per 100,000 women, compared to 53 per 100,000 patch users [68]. Despite this elevated absolute risk, it is important to remember that the risk of thromboembolism in pregnancy and postpartum is four to five times higher than in a woman using any estrogen-containing contraceptive [69]. Therefore, the increase in VTE risk with CHC is less than the risk of VTE if she should become pregnant.

The presence of comorbid conditions in the obese population is common with hypertension and diabetes mellitus (DM) topping the list. Multiple medical problems can make contraceptive counseling difficult, but also makes pregnancy complicated and occasionally dangerous. Hypertension, even if well controlled, is category 3 for CHCs and becomes a category 4 if uncontrolled or vascular disease has been documented. CHC becomes less appropriate as the number of comorbid conditions increases. For example, insulin-dependent DM alone is category 2, however in the

presence of end organ sequelae (e.g., retinopathy, neuropathy, and nephropathy) it becomes category 3 for continuing a previously initiated method and category 4 for initiating a new method. Similarly, the CDC has created a category for women "with multiple risk factors for cardiovascular disease." Although "multiple" is not clearly defined, the category includes age, obesity, smoking, hypertension, and diabetes, many of which describe obese women. If a clinician interprets "multiple" to means 2 comorbid conditions, then any CHC method for these women would be considered category 3 for continuing a previously initiated method, and category 4 for initiating a new CHC method.

Progestin-Only Oral Contraceptives

Progestin-only pills (POP) are a safe method for obese women. Formulations of POPs in the United States are limited to norethindrone, although there are POPs containing a variety of progestins available in other countries. POPs prevent pregnancy through a combination of mechanisms including ovulation inhibition, cervical mucus thickening, and endometrial alteration, although they do not reliably suppress ovulation [18]. Typical-use failure rates in the general population mirror that of COCs, although unlike COCs, serum progestin levels are nearly undetectable 24 h following administration [70]. This finding results in the current emphasis on strict compliance of dosing at the same time every day. There are no studies specifically addressing effectiveness in the obese population, but POPs are currently categorized as category 1.

Special Populations

Increasing numbers of morbidly obese women are opting for surgical treatment of their obesity [71]. There is currently several options for bariatric procedures ranging from restrictive (gastric banding) to the traditional malabsorptive procedures (Roux-en-Y, sleeve gastrectomy, biliopancreatic diversion) [72]. Because obesity is associated with anovulation and subsequently infertility [73], many of these women may not be using effective contraception prior to their surgery as they do not consider themselves at risk for pregnancy. With rapid weight loss following surgery, these women will likely become ovulatory again; without effective contraception, they will be at risk of unintended pregnancy. The American College of Obstetricians and Gynecologist currently recommends that women delay pregnancy for 12–18 months following bariatric surgery as rapid weight loss can pose additional maternal and neonatal risk [74]. For women who have undergone a malabsorptive procedure, use of oral contraception is not generally recommended as the absorption of the steroid is likely impaired. This recommendation is based on few studies with small sample sizes [75, 76]. If women prefer oral contraceptives, consideration of nonoral routes

is encouraged, for example vaginal administration [77–79]. There have been few if any studies evaluating other methods in this population. The effectiveness of the ENG implant in women who had undergone a Roux-en-Y gastric bypass was evaluated in one small study. Findings indicate that ENG levels decrease at 3 and 6 months after surgery with increasing weight loss, but remain well above the serum levels required for effectiveness [37]. There has also been one study evaluating the LNG-IUS in an adolescent bariatric surgical population and found the LNG-IUS was an acceptable and effective option in this setting [80]. Studies have shown that few women are referred for contraceptive counseling prior to their surgical intervention [81] indicating that obstetrician-gynecologists should be proactive about assessing obese patient's desires and plans for surgical weight loss.

Permanent Sterilization

Female sterilization, also known as tubal ligation or tubal occlusion, is one of the most common methods of contraception among women in the United States with approximately 27 % relying on this method between 2006 and 2010 [82]. In overweight and obese women, surgical contraception, which includes tubal ligation, is the type of contraception most often used [83]. Tubal ligation is often a choice for women who have completed childbearing, do not wish to have user-dependent contraception, or have contraindications to hormonal forms of contraception. In addition, it is highly effective, with a cumulative 5-year failure rate of 13 per 1,000 [84]. Several options exist for sterilization and preference is influenced by timing, surgical or anesthesia risk, and technical ease.

Postpartum Tubal Ligation

Postpartum tubal ligation includes those procedures performed at the time of cesarean or immediately following vaginal delivery. The most popular techniques include the Pomeroy and Parkland methods due to their ease and effectiveness [84]. Both methods involve a complete transection of the mid-isthmic portion of the fallopian tube. The 5-year failure rate is 6 per 1,000, making postpartum tubal ligation the most effective form of sterilization [85]. Pathologic confirmation of complete tubal transection ensures immediate protection, regardless of BMI [86].

Disadvantages of postpartum tubal ligation in obese women are often related to mode of delivery. When performed at the time of cesarean delivery, the fallopian tubes are generally easily visible and accessed in the surgical field. When performed after a vaginal delivery, a separate procedure is required. Normally, this procedure is easily performed through a small infraumbilical incision where the fallopian tubes can be accessed. Some clinicians consider obese women as poor candidates for immediate postpartum sterilization after a vaginal delivery as this procedure can

be technically challenging due to the increasing depth of subcutaneous tissue and difficulty accessing the tubes. In addition, even if the tubes are accessible, it may be difficult to minimize tension on the tissue, thus possibly causing laceration of the fallopian tubes, tearing of the mesosalpinx, and subsequent bleeding [84]. Due to the possibility of the latter complications, studies have been performed researching the use of titanium (Filshie®) clips for postpartum tubal ligation for easier access, but these studies have shown the titanium clip to be less effective, possibly secondary to the edema and engorgement of the tubes during pregnancy [87–89].

Interval Tubal Ligation

Interval tubal ligation includes those procedures performed before a pregnancy occurs or at any point after the postpartum period. These procedures can be performed hysteroscopically or laparoscopically.

Hysteroscopic Tubal Occlusion

Hysteroscopic tubal occlusion is performed transcervically avoiding any surgical incisions. The only hysteroscopic occlusion method currently available in the United States is Essure® which consists of stainless steel and nickel-based coils that contain polyethylene terephthalate fibers. These coils cause an inflammatory reaction and subsequent scar formation within the tubes, resulting in occlusion. Sterilization is not immediate and must be confirmed with hysterosalpingogram at 3 months. Therefore, an interval form of contraception must be used until tubal occlusion has been verified. Clinical trials of women with successful Essure placement show only 3.5 % tubal patency at 3 months and 0 % patency at 6 months [88]. Hysteroscopic occlusion has a failure rate of 1.6 per 1,000 and there is no evidence to suggest BMI affects this rate [90].

In addition to the effectiveness, the hysteroscopic occlusion has multiple advantages for obese women. This procedure can be performed under local anesthetic with a paracervical block, thus removing the increased risk of general anesthesia. It is a minimally invasive procedure that does not involve abdominal incisions or entry into the peritoneal cavity. Therefore, unlike postpartum or laparoscopic forms of tubal ligation, it virtually avoids the need for a larger surgery such as laparotomy which carries additional morbidity in obese women [91].

Laparoscopic Tubal Ligation

Laparoscopic tubal ligation is performed through two or more subcentimeter incisions in the abdomen. Sterilization can be accomplished by various techniques including titanium clips (Filshie®), silicone rings (FalopeRing®), and bipolar coagulation. Other forms not often used are unipolar coagulation and spring-loaded clips.

The titanium clips provide immediate occlusion of the fallopian tube as well as cause necrosis of the tubal section over time. Ten-year failure rates for this method are estimated between 2 and 10 per 1,000 [92]. The mechanism of occlusion for the silicone ring is similar to that of the titanium clips and 5-year failure rates have been estimated at 10 per 1,000 [85]. Bipolar coagulation results in sterilization through fulguration of three adjacent tubal segments. A 5-year failure rate of 16.5 per 1,000 has been reported [85].

The main advantage of laparoscopic tubal ligation over hysteroscopic occlusion is immediate effectiveness. Like hysteroscopy, laparoscopy is considered a minimally invasive technique as it avoids a laparotomy incision. Yet, despite being minimally invasive, many studies show that complications with surgery and anesthesia can arise secondary to obesity, including difficulties with access and maintenance of the airway and adequate intraoperative ventilation. The technical component of laparoscopy may also be more difficult. Safe entry into the peritoneal cavity and maintenance of sufficient pneumoperitoneum may be a challenge. In patients where pneumoperitoneum could not be achieved for tubal ligation, over 70 % of the patients were obese. This same review found that obesity was an independent risk factor for one or more complications occurring during laparoscopic tubal ligation including unintended major surgery (i.e., conversion to laparotomy), transfusion, febrile morbidity, life-threatening events, or rehospitalization [93]. Other studies have shown complications including longer operating times and longer hospital stays [94].

Conclusion

The most effective contraceptive method is one chosen by a woman who has participated in the decision-making process [95]. Many of these women will present with complicated histories and will take time to appropriately evaluate. Additionally, helping patients understand the relative and absolute risks associated with reversible methods is complicated at best. Use of the MEC and actively involving your patient in the decision process increases the likelihood that the patient will choose an appropriate contraceptive method. Lastly, remember that the risk of contraception in this population must be kept within the context of risk with pregnancy; pregnancy carries a much greater risk of morbidity and mortality than any contraceptive method. Ensuring that pregnancy when it does occur is planned will ultimately improve the overall health of these women and their families.

References

1. Crane JM, Murphy P, Burrage L, Hutchens D. Maternal and perinatal outcomes of extreme obesity in pregnancy. J Obstet Gynaecol Can. 2013;35(7):606–11. PubMed PMID: 23876637.
2. Scott-Pillai R, Spence D, Cardwell CR, Hunter A, Holmes VA. The impact of body mass index on maternal and neonatal outcomes: a retrospective study in a UK obstetric population, 2004-2011. BJOG. 2013;120(8):932–9. PubMed PMID: 23530609.

3. Minsart AF, Buekens P, De Spiegelaere M, Englert Y. Neonatal outcomes in obese mothers: a population-based analysis. BMC Pregnancy Childbirth. 2013;13. PubMed PMID: 23398843. Pubmed Central PMCID: 3575268.
4. Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikstrom AK, et al. Maternal obesity and risk of preterm delivery. JAMA. 2013;309(22):2362–70. PubMed PMID: 23757084.
5. American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 549: obesity in pregnancy. Obstet Gynecol. 2013;121(1):213–7. PubMed PMID: 23262963.
6. Curtis KM, Tepper NK, Marchbanks PA. Putting risk into perspective: the US medical eligibility criteria for contraceptive use. Rev Endocr Metab Disord. 2011;12(2):119–25. PubMed PMID: 21541854.
7. Division of Reproductive Health NCfCDP, Health Promotion CfDC, Prevention. U.S. Selected Practice Recommendations for Contraceptive Use, 2013: adapted from the World Health Organization selected practice recommendations for contraceptive use, 2nd edition. MMWR Recomm Rep. 2013;62(RR-05):1–60. PubMed PMID: 23784109.
8. Lessard LN, Karasek D, Ma S, Darney P, Deardorff J, Lahiff M, et al. Contraceptive features preferred by women at high risk of unintended pregnancy. Perspect Sex Reprod Health. 2012;44(3):194–200. PubMed PMID: 22958664.
9. Grimes DA, Shields WC. Family planning for obese women: challenges and opportunities. Contraception. 2005;72(1):1–4. PubMed PMID: 15964284.
10. Trussell J, Schwarz EB, Guthrie K. Obesity and oral contraceptive pill failure. Contraception. 2009;79(5):334–8. PubMed PMID: 19341843. Pubmed Central PMCID: 3638205.
11. Mornar S, Chan LN, Mistretta S, Neustadt A, Martins S, Gilliam M. Pharmacokinetics of the etonogestrel contraceptive implant in obese women. Am J Obstet Gynecol. 2012;207(2):110 e1–6. PubMed PMID: 22717269.
12. Society of Family Planning, Higginbotham S. Contraceptive considerations in obese women: release date 1 September 2009, SFP Guideline 20091. Contraception. 2009;80(6):583–90. PubMed PMID: 19913155.
13. Segall-Gutierrez P, Taylor D, Liu X, Stanzcyk F, Azen S, Mishell Jr DR. Follicular development and ovulation in extremely obese women receiving depo-medroxyprogesterone acetate subcutaneously. Contraception. 2010;81(6):487–95. PubMed PMID: 20472115.
14. Westhoff CL, Torgal AH, Mayeda ER, Petrie K, Thomas T, Dragoman M, et al. Pharmacokinetics and ovarian suppression during use of a contraceptive vaginal ring in normal-weight and obese women. Am J Obstet Gynecol. 2012;207:39.e1–6. PubMed PMID: 22727346. Pubmed Central PMCID: 3403702.
15. McNicholas C, Zhao Q, Secura G, Allsworth JE, Madden T, Peipert JF. Contraceptive failures in overweight and obese combined hormonal contraceptive users. Obstet Gynecol. 2013;121(3):585–92. PubMed PMID: 23635622.
16. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. Obstet Gynecol. 2012;120(1):21–6. PubMed PMID: 22678035.
17. Blokhin IO, Lentz SR. Mechanisms of thrombosis in obesity. Curr Opin Hematol. 2013;20(5):437–44. PubMed PMID: 23817170.
18. Hatcher R, Trussel J, Nelson A, Cates W, Kowal D, Policar M. Contraceptive technology. 20th ed. New York: Ardent Media; 2011.
19. Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol. 1990;97(8):690–4. PubMed PMID: 2119218.
20. Baldaszti E, Wimmer-Puchinger B, Loschke K. Acceptability of the long-term contraceptive levonorgestrel-releasing intrauterine system (Mirena): a 3-year follow-up study. Contraception. 2003;67(2):87–91. PubMed PMID: 12586318.
21. Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro C, Petta C. Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. Contraception. 2002;65(2):129–32. PubMed PMID: 11927115.

22. Stoegerer-Hecher E, Kirchengast S, Huber JC, Hartmann B. Amenorrhea and BMI as independent determinants of patient satisfaction in LNG-IUD users: cross-sectional study in a Central European district. Gynecol Endocrinol. 2012;28(2):119–24. PubMed PMID: 21848413.
23. Wildemeersch D, Anderson E, Lambein K, Pauwels P, Dhont M. Successful treatment of early endometrial carcinoma by local delivery of levonorgestrel: a case report. Obstet Gynecol Int. 2010;2010:431950. PubMed PMID: 20981240. Pubmed Central PMCID: 2963141.
24. Benshushan A, Paltiel O, Rojansky N, Brzezinski A, Laufer N. IUD use and the risk of endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2002;105(2):166–9. PubMed PMID: 12381481.
25. Orbo A, Arnes M, Hancke C, Vereide AB, Pettersen I, Larsen K. Treatment results of endometrial hyperplasia after prospective D-score classification: a follow-up study comparing effect of LNG-IUD and oral progestins versus observation only. Gynecol Oncol. 2008;111(1):68–73. PubMed PMID: 18684496.
26. Minig L, Franchi D, Boveri S, Casadio C, Bocciolone L, Sideri M. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Ann Oncol. 2011;22(3):643–9. PubMed PMID: 20876910.
27. Brown AJ, Westin SN, Broaddus RR, Schmeler K. Progestin intrauterine device in an adolescent with grade 2 endometrial cancer. Obstet Gynecol. 2012;119(2 Pt 2):423–6. PubMed PMID: 22270425. Pubmed Central PMCID: 3266511.
28. Trussell J, Lalla AM, Doan QV, Reyes E, Pinto L, Gricar J. Cost effectiveness of contraceptives in the United States. Contraception. 2009;79(1):5–14. PubMed PMID: 19041435. Pubmed Central PMCID: 3638200.
29. Alvarez F, Brache V, Fernandez E, Guerrero B, Guiloff E, Hess R, et al. New insights on the mode of action of intrauterine contraceptive devices in women. Fertil Steril. 1988;49(5):768–73. PubMed PMID: 3360166.
30. Veldhuis HM, Vos AG, Lagro-Janssen AL. Complications of the intrauterine device in nulliparous and parous women. Eur J Gen Pract. 2004;10(3):82–7. PubMed PMID: 15534571.
31. Group ECW. Intrauterine devices and intrauterine systems. Hum Reprod Update. 2008;14(3):197–208. PubMed PMID: 18400840.
32. Mechanism of action, safety and efficacy of intrauterine devices. Report of a WHO Scientific Group. World Health Organization technical report series. 1987;753:1–91. PubMed PMID: 3118580.
33. Sezer SD, Odabasi AR, Kucuk M, Yuksel H. Lost intrauterine contraceptive device inserted 42 years before: a case report. Clin Exp Obstet Gynecol. 2011;38(1):90–3. PubMed PMID: 21485737.
34. Markovitch O, Klein Z, Gidoni Y, Holzinger M, Beyth Y. Extrauterine mislocated IUD: is surgical removal mandatory? Contraception. 2002;66(2):105–8. PubMed PMID: 12204783.
35. Haimov-Kochman R, Doviner V, Amsalem H, Prus D, Adoni A, Lavy Y. Intraperitoneal levonorgestrel-releasing intrauterine device following uterine perforation: the role of progestins in adhesion formation. Hum Reprod. 2003;18(5):990–3. PubMed PMID: 12721174.
36. Van den Bosch T, Donders GG, Riphagen I, Debois P, Ameye L, De Brabanter J, et al. Ultrasonographic features of the endometrium and the ovaries in women on etonogestrel implant. Ultrasound Obstet Gynecol. 2002;20(4):377–80. PubMed PMID: 12383321.
37. Ciangura C, Corigliano N, Basdevant A, Mouly S, Decleves X, Touraine P, et al. Etonorgestrel concentrations in morbidly obese women following Roux-en-Y gastric bypass surgery: three case reports. Contraception. 2011;84(6):649–51. PubMed PMID: 22078197.
38. McNicholas C, Maddipati R, Swor E, Zhao Q, Peipert JF. Use of the Etonogestrel Implant and Levonorgestrel Intrauterine Device Beyond the U.S. Food and Drug Administration-Approved Duration. Obstet Gynecol. 2015;125(3):599–604.
39. Weisberg E, Hickey M, Palmer D, O'Connor V, Salamonsen LA, Findlay JK, et al. A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. Hum Reprod. 2009;24(8):1852–61. PubMed PMID: 19369294. Pubmed Central PMCID: 2710284.

40. Petta CA, Faundes A, Dunson TR, Ramos M, DeLucio M, Faundes D, et al. Timing of onset of contraceptive effectiveness in Depo-Provera users. II Effects on ovarian function. Fertil Steril. 1998;70(5):817–20. PubMed PMID: 9806559.
41. Petta CA, Faundes A, Dunson TR, Ramos M, DeLucio M, Faundes D, et al. Timing of onset of contraceptive effectiveness in Depo-Provera users: part I. Changes in cervical mucus. Fertil Steril. 1998;69(2):252–7. PubMed PMID: 9496338.
42. Croxatto HB. Mechanisms that explain the contraceptive action of progestin implants for women. Contraception. 2002;65(1):21–7. PubMed PMID: 11861052.
43. Mishell Jr DR. Pharmacokinetics of depot medroxyprogesterone acetate contraception. J Reprod Med. 1996;41(5 Suppl):381–90. PubMed PMID: 8725700.
44. Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. N Engl J Med. 2012;366(21):1998–2007. PubMed PMID: 22621627.
45. Jain J, Dutton C, Nicosia A, Wajszczuk C, Bode FR, Mishell Jr DR. Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera. Contraception. 2004;70(1):11–8. PubMed PMID: 15208047.
46. Bulletins-Gynecology ACoP. ACOG practice bulletin. No. 73: use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol. 2006;107(6):1453–72. PubMed PMID: 16738183.
47. Schwallie PC, Assenzo JR. Contraceptive use—efficacy study utilizing medroxyprogesterone acetate administered as an intramuscular injection once every 90 days. Fertil Steril. 1973;24(5):331–9. PubMed PMID: 4698589.
48. Belsey EM. Vaginal bleeding patterns among women using one natural and eight hormonal methods of contraception. Contraception. 1988;38(2):181–206. PubMed PMID: 2971505.
49. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer. 1991;49(2): 191–5.
50. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer. 1991;49(2): 186–90.
51. Bonny AE, Ziegler J, Harvey R, Debanne SM, Secic M, Cromer BA. Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. Arch Pediatr Adolesc Med. 2006;160(1):40–5. PubMed PMID: 16389209.
52. Curtis KM, Ravi A, Gaffield ML. Progestogen-only contraceptive use in obese women. Contraception. 2009;80(4):346–54. PubMed PMID: 19751857.
53. Mangan SA, Larsen PG, Hudson S. Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. J Pediatr Adolesc Gynecol. 2002;15(2):79–82. PubMed PMID: 12057528.
54. Cundy T, Cornish J, Roberts H, Elder H, Reid IR. Spinal bone density in women using depot medroxyprogesterone contraception. Obstet Gynecol. 1998;92(4 Pt 1):569–73. PubMed PMID: 9764630.
55. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Injectable hormone contraception and bone density: results from a prospective study. Epidemiology. 2002;13(5):581–7. PubMed PMID: 12192229.
56. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. Arch Pediatr Adolesc Med. 2005;159(2):139–44. PubMed PMID: 15699307.
57. Clark MK, Sowers MR, Nichols S, Levy B. Bone mineral density changes over two years in first-time users of depot medroxyprogesterone acetate. Fertil Steril. 2004;82(6):1580–6. PubMed PMID: 15589863.
58. Mosher WD, Jones J. Use of contraception in the United States: 1982-2008. Vital Health Stat. 2010;23(29):1–44. PubMed PMID: 20939159.

59. Edelman AB, Carlson NE, Cherala G, Munar MY, Stouffer RL, Cameron JL, et al. Impact of obesity on oral contraceptive pharmacokinetics and hypothalamic-pituitary-ovarian activity. Contraception. 2009;80(2):119–27. PubMed PMID: 19631786. Pubmed Central PMCID: 2736633.
60. Westhoff CL, Torgal AH, Mayeda ER, Pike MC, Stanczyk FZ. Pharmacokinetics of a combined oral contraceptive in obese and normal-weight women. Contraception. 2010;81(6):474–80. PubMed PMID: 20472113. Pubmed Central PMCID: 3522459.
61. Westhoff CL, Torgal AH, Mayeda ER, Stanczyk FZ, Lerner JP, Benn EK, et al. Ovarian suppression in normal-weight and obese women during oral contraceptive use: a randomized controlled trial. Obstet Gynecol. 2010;116(2 Pt 1):275–83. PubMed PMID: 20664386.
62. Zieman M, Guillebaud J, Weisberg E, Shangold GA, Fisher AC, Creasy GW. Contraceptive efficacy and cycle control with the Ortho Evra/Evra transdermal system: the analysis of pooled data. Fertil Steril. 2002;77(2 Suppl 2):S13–8. PubMed PMID: 11849631.
63. Dragoman M, Petrie K, Torgal A, Thomas T, Cremers S, Westhoff CL. Contraceptive vaginal ring effectiveness is maintained during 6 weeks of use: a prospective study of normal BMI and obese women. Contraception. 2013;87(4):432–6. PubMed PMID: 23312933. Pubmed Central PMCID: 3606661.
64. Dinger JC, Cronin M, Mohner S, Schellschmidt I, Minh TD, Westhoff C. Oral contraceptive effectiveness according to body mass index, weight, age, and other factors. Am J Obstet Gynecol. 2009;201(3):263.e1–9. PubMed PMID: 19481720.
65. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. Obstet Gynecol. 2002;99(5 Pt 1):820–7. PubMed PMID: 11978293.
66. Holt VL, Scholes D, Wicklund KG, Cushing-Haugen KL, Daling JR. Body mass index, weight, and oral contraceptive failure risk. Obstet Gynecol. 2005;105(1):46–52. PubMed PMID: 15625141.
67. Brunner LR, Hogue CJ. The role of body weight in oral contraceptive failure: results from the 1995 national survey of family growth. Ann Epidemiol. 2005;15(7):492–9. PubMed PMID: 16029841.
68. Lopez LM, Grimes DA, Gallo MF, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2008;(1):CD003552. PubMed PMID: 18254023.
69. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton 3rd LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005;143(10):697–706. PubMed PMID: 16287790.
70. McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. Contraception. 1994;50(6 Suppl 1):S1–195. PubMed PMID: 10226677.
71. Santry HP, Gillen DL, Lauderdale DS. Trends in bariatric surgical procedures. JAMA. 2005;294:1909–17. PubMed PMID: 16234497.
72. Elder KA, Wolfe BM. Bariatric surgery: a review of procedures and outcomes. Gastroenterology. 2007;132(6):2253–71. PubMed PMID: 17498516.
73. Practice Committee of American Society for Reproductive Medicine. Obesity and reproduction: an educational bulletin. Fertil Steril. 2008;90(5 Suppl):S21–9. PubMed PMID: 19007633.
74. Practice ACoG. ACOG committee opinion. Number 319, October 2005. The role of obstetrician-gynecologist in the assessment and management of obesity. Obstet Gynecol. 2005;106(4):895–9. PubMed PMID: 16199657.
75. Gerrits EG, Ceulemans R, van Hee R, Hendrickx L, Totte E. Contraceptive treatment after biliopancreatic diversion needs consensus. Obes Surg. 2003;13(3):378–82. PubMed PMID: 12841897.
76. Victor A, Odlind V, Kral JG. Oral contraceptive absorption and sex hormone binding globulins in obese women: effects of jejunoileal bypass. Gastroenterol Clin North Am. 1987;16(3):483–91. PubMed PMID: 2449395.
77. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 105: bariatric surgery and pregnancy. Obstet Gynecol. 2009;113(6):1405–13. PubMed PMID: 19461456.

78. Merhi ZO. Weight loss by bariatric surgery and subsequent fertility. Fertil Steril. 2007; 87(2):430–2. PubMed PMID: 17113090.
79. Merhi ZO. Bariatric surgery and subsequent sexual function. Fertil Steril. 2007;87(3):710–1. PubMed PMID: 17123521.
80. Hillman JB, Miller RJ, Inge TH. Menstrual concerns and intrauterine contraception among adolescent bariatric surgery patients. J Womens Health. 2011;20(4):533–8. PubMed PMID: 21413894. Pubmed Central PMCID: 3075047.
81. Mody SK, Hacker MR, Dodge LE, Thornton K, Schneider B, Haider S. Contraceptive counseling for women who undergo bariatric surgery. J Womens Health. 2011;20(12):1785–8. PubMed PMID: 21988600.
82. Jones J, Mosher WD, Daniels K. Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995, National Health Statistics Reports, 2012, No. 60.
83. Schraudenbach A, McFall S. Contraceptive use and contraception type in women by body mass index category. Womens Health Issues. 2009;19(6):381–9. PubMed PMID: 19879452.
84. Peterson HB. Sterilization. Obstet Gynecol. 2008;111(1):189–203. PubMed PMID: 18165410.
85. Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. Am J Obstet Gynecol. 1996;174(4):1161–8. discussion 8–70. PubMed PMID: 8623843.
86. American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 133: benefits and risks of sterilization. Obstet Gynecol. 2013;121(2 Pt 1):392–404. PubMed PMID: 23344305.
87. Rodriguez MI, Edelman AB, Kapp N. Postpartum sterilization with the titanium clip: a systematic review. Obstet Gynecol. 2011;118(1):143–7. PubMed PMID: 21691172.
88. Kerin JF, Cooper JM, Price T, Herendael BJ, Cayuela-Font E, Cher D, et al. Hysteroscopic sterilization using a micro-insert device: results of a multicentre Phase II study. Hum Reprod. 2003;18(6):1223–30. PubMed PMID: 12773450.
89. Rodriguez MI, Seuc A, Sokal DC. Comparative efficacy of postpartum sterilisation with the titanium clip versus partial salpingectomy: a randomised controlled trial. BJOG. 2013; 120(1):108–12. PubMed PMID: 22925277.
90. Bradley LD, Price TM, Van Herendael BJ, Cayuela E. Long-term follow-up of hysteroscopic sterilization with the Essure micro-insert. J Minim Invasive Gynecol. 2009;16(6 suppl):S14–5.
91. Povedano B, Arjona JE, Velasco E, Monserrat JA, Lorente J, Castelo-Branco C. Complications of hysteroscopic Essure((R)) sterilisation: report on 4306 procedures performed in a single centre. BJOG. 2012;119(7):795–9. PubMed PMID: 22360159.
92. Kovacs GT, Krins AJ. Female sterilisations with Filshie clips: what is the risk failure? A retrospective survey of 30,000 applications. J Fam Plann Reprod Health Care. 2002;28(1):34–5. PubMed PMID: 16259814.
93. Jamieson DJ, Hillis SD, Duerr A, Marchbanks PA, Costello C, Peterson HB. Complications of interval laparoscopic tubal sterilization: findings from the United States collaborative review of sterilization. Obstet Gynecol. 2000;96(6):997–1002. PubMed PMID: 11084192.
94. Chi IC, Wilkens L. Interval tubal sterilization in obese women—an assessment of risks. Am J Obstet Gynecol. 1985;152(3):292–7. PubMed PMID: 4003474.
95. Dehlendorf C, Levy K, Kelley A, Grumbach K, Steinauer J. Women's preferences for contraceptive counseling and decision making. Contraception. 2013;88(2):250–6. PubMed PMID: 23177265.

Chapter 10
Obesity and Ovarian Aging (Diminished Ovarian Reserve and Menopause)

Melanie Meister and Amber R. Cooper

Natural Ovarian Aging

Cessation of ovarian function is generally thought to be driven by oocyte depletion through atresia and ovulation and occurs earlier than the aging of other organ systems in otherwise healthy females [1, 2]. While more recently controversial, the dogma of ovarian aging is that females are born with a finite number of oocytes, which remain arrested at Prophase I of meiosis, and the depletion of this predetermined oocyte population results in reproductive senescence [3]. The average age of reproductive senescence, i.e., menopause, in the United States is 51.4 [4] but ranges from 42 to 58 [1] suggesting that variation exists among females in the number of oocytes, rate of follicular depletion, or both. In general, however, the overall rate of follicular depletion appears to accelerate with age [2, 3]. Emerging evidence suggests that mitotically active germline stem cells may persist in the oocytes of postnatal women and contribute to the pool of available follicles [5, 6].

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The Stages of Menopause

The Stages of Reproductive Aging Workshop (STRAW) was held in 2001 with the goal of clarifying nomenclature and developing a system to define stages of female reproductive aging [1]. The workshop generated a seven-stage system determined by variations in cyclic regularity and hormone levels among women from puberty to death. Most women will progress chronologically through these stages but some will bounce back and forth [1]. The duration of each stage is variable and the natural menopausal transition occurs more as a continuum. These stages provide a basis for understanding the menopausal transition from the clinical perspective of changes in menstrual cycle and the biological perspective of hormonal changes.

The STRAW criteria were revised in 2011 at the "STRAW+10" workshop to improve generalizability and applicability to several groups that were excluded during the initial consensus conference. This follow-up conference, therefore, broadened the applicability of these stages to include smokers, women with BMI >30, women who had previously undergone hysterectomy, those with chronic menstrual cycle irregularities, uterine or ovarian anomalies, heavy exercisers, and those with significant illness including cancer [7].

The stages begin at menarche and are numbered with the Final Menstrual Period as zero, those stages preceding the FMP designated as negatives and those following the FMP as positives. During the Early Reproductive Period (−5) cycles are initially variable but progressively become more regular. Reproductive potential increases as cycles become more regular, and FSH levels are normal. Once cycles are regular, women are within The Peak Reproductive Period (−4). Eventually, subclinical changes begin with a slight decline in the reproductive potential and mild elevation in FSH, these subtle changes mark the onset of The Late Reproductive Period (−3). This stage was further subdivided during STRAW+10. (−3b) is characterized by essentially regular cycles, normal FSH, but low AMH, AFC, and Inhibin B. The transition to (−3a) results in subtle menstrual cycle changes (shorter cycles), increased FSH, and decreased AMH, AFC, and Inhibin B. This subdivision highlights the importance of the subtle change in hormonal milieu that is not initially reflected in menstrual cycle changes. Once cycles are more variable, the woman has reached The Early Menopausal Transition (−2). At this stage cycles change by seven or more days from previous length, but no cycles are skipped. Hormonal changes include increased FSH, low AMH, and low AFC. The Late Menopausal Transition (−1) is defined by variable cycle length with two or more missed cycles and a period of amenorrhea for 60 days or more. It is during this stage that vasomotor symptoms predominate and FSH is notably elevated.

The Final Menstrual Period (0) is retrospectively defined after 12 months of amenorrhea. The Early Postmenopausal Period (+1) includes the retrospectively defined first year of amenorrhea and the following 4 years. This is a period of increased vasomotor symptoms and elevated FSH. It, too, was subdivided for further clarification into: (+1a), the end of the 12-month period of amenorrhea where FSH and estradiol levels are variable; (+1b), the remainder of the 4-year period

characterized by rapid changes in FSH and estradiol; and (+1c), with ultimate stabilization of high FSH and low estradiol. Finally, The Late Postmenopausal Period (+2) begins 5 years after the final menstrual period and lasts for the remainder of the woman's life with persistently elevated FSH.

The characteristics of the menopausal transition are noted to differ among races, smokers, and by body habitus. African American women and Hispanic women of Mexican descent begin the transition at an earlier age than women of other races [4, 8]. Obese women, on average, enter the menopausal transition sooner, but ultimately progress through the stages at a slower rate [8]. The etiology for this finding is unclear and is unlikely attributable solely to elevated BMI. Smokers, on the other hand, typically progress through the stages of menopause faster than nonsmokers and, on average, are younger at the time of their final menstrual period [8].

The Endocrinology of Menopause

The menopausal transition is characterized by hormonal shifts that occur as a result of feedback on the hypothalamic-pituitary-ovarian axis [9]. As the follicular pool is depleted, and the number of small antral follicles declines, the production of Inhibin B decreases [10]. Inhibin B is produced by the granulosa cells of the growing follicles and is the primary regulator of FSH secretion during the follicular phase. The decrease in Inhibin B levels lifts the inhibitory tone over the hypothalamic-pituitary-ovarian axis allowing FSH levels to increase [11]. This ultimately leads to attenuation of the follicular phase and resultant shortening of cycles [12, 13]. Initially, the elevated FSH maintains secretion of estradiol from the granulosa cells of the growing follicles, but this elevation is transient.

Cycles during the Early (−2) and Late (−1) Menopausal Transition stages are often anovulatory, although ovulatory cycles still occur. Dominant follicle selection and corpus luteum formation during these ovulatory cycles is preserved early on with associated normal or occasionally supratherapeutic estrogen and progesterone levels during the luteal phase [8, 10, 12]. Anovulatory cycles classically consist of low Inhibin B, elevated FSH, and low estradiol [13].

Primary Ovarian Insufficiency and Diminished Ovarian Reserve

Although the reproductive system appears to age at a faster rate than the other organ systems, ovarian aging and reproductive senescence that occurs younger than age 40 is pathologic. Primary Ovarian Insufficiency (POI), formerly Premature Ovarian Failure (POF), is defined by at least 4 months of amenorrhea and two serum FSH levels in the menopausal range, separated by at least 1 month, occurring in women

younger than 40, and is seen in about 1 % of the population [7, 14]. Despite their high levels of gonadotropins, one-third of these women demonstrate ovarian follicles on pelvic ultrasound, half intermittently produce estrogen-suggesting preservation of some ovarian function [14], and nearly 20 % spontaneously ovulate even after the diagnosis [15]. In fact, 5–10 % achieve pregnancy [14] suggesting the physiology of primary ovarian insufficiency is complex and does not merely represent premature menopause.

The etiology of POI is vast and, in many cases, poorly understood [16]. It is broadly classified as either depletion of ovarian follicles or follicular dysfunction [15]. Causes of ovarian follicle depletion include genetic disorders (autosomal translocations, trisomies, and X-chromosome abnormalities like Turner Syndrome and FMR1 premutations); somatic disorders (galactosemia); autoimmune disorders; and direct ovarian damage (ovarian surgery, oophorectomy, exposure to viral/environmental toxins, chemotherapy, or radiation therapy) [17, 18]. Follicle dysfunction includes signal defects (FSH-receptor mutation, LH-receptor mutation, and G-protein mutation), enzyme deficiencies (isolated 17,20-lyase deficiency, aromatase deficiency), autoimmunity, and insufficient follicle number (luteinized graafian follicles) [14]. Although specific etiologies have been described, 65–90 % of cases remain idiopathic, occurring in karyotypically normal females [15, 19].

Eighty-five to Ninety percent of cases of POI are sporadic [14]. The remaining 10–15 % of cases have an affected first-degree relative and history may elicit other autoimmune disorders consistent with autoimmune polyglandular syndrome, rheumatoid arthritis, or systemic lupus erythematosus; intellectual disorders, Parkinsonian symptoms, or history of fragile X syndrome is suggestive of an FMR1 premutation [14]. Despite an association with autoimmune disorders, there is no role for testing for ovarian autoantibodies as these are nonspecific [14].

The term *ovarian reserve* was one coined through advances in assisted reproductive technologies. It generally describes the pool of primordial follicles available for recruitment and ultimately determines an individual's reproductive potential [18]. Typically, tests of ovarian reserve are utilized during the infertility workup to predict a patient's response to controlled ovarian stimulation with in vitro fertilization (IVF) [18]. The purpose of predicting ovarian reserve is to enable clinicians to better counsel patients who desire IVF on their potential for success and, in some cases, to help determine the stimulation protocol. POI is considered the most severe phenotype of a depleted or dysfunctional ovarian reserve. The term diminished ovarian reserve (DOR) has also evolved over the last several decades, though a general consensus of criteria for diagnosis are generally lacking. DOR can be a function of advanced chronological age or a pathologic condition that results in fewer follicles available for activation than would be expected based on a female's age alone. As the quantity and quality of the available oocytes decrease, so too does the efficacy of the granulosa cells, contributing to both the altered hormonal milieu and degree of impaired reproductive potential [20].

When followed for an entire menstrual cycle and compared with healthy controls, young women with diminished ovarian reserve were noted to have significantly higher early follicular phase FSH, prolonged duration of FSH and LH surge,

and subsequently significantly lower concentrations of estrogen metabolites during the luteal phase [20]. Physiologic ovarian aging, however, is a time of relative hyperestrogenism without the protracted FSH/LH surge seen in young women with diminished ovarian reserve [20]. Furthermore, when young women with diminished ovarian reserve do ovulate, their hormone levels during those cycles more closely resemble those seen in normal reproductive-age women, not perimenopausal women [12].

Assessment of Ovarian Reserve

Numerous tests and assays have been developed to predict ovarian reserve. Currently available tests include FSH, Inhibin B, estradiol, AMH, and transvaginal ultrasound to determine antral follicle count. Of these, the most sensitive and specific are anti-müllerian hormone (AMH) and antral follicle count (AFC) [18].

Classically, early follicular FSH and estradiol was the test of choice, and, when elevated on cycle day 3 >10 mIU/mL and >80 pg/mL respectively, suggested an overall diminished ovarian reserve [10, 21]. As elevated estrogen will cause feedback inhibition on FSH, both hormones are checked to avoid false negative results. However, high threshold levels of FSH are needed to achieve specificity in predicting poor response to stimulation or nonpregnancy, limiting its usefulness [22].

Inhibin B is a heterodimeric glycoprotein secreted from growing follicles, and secretion decreases as follicles are depleted [23]. Early follicular phase Inhibin B, therefore, has been used as a marker ovarian reserve. The magnitude of the change in Inhibin B is more predictive of progression through the stages of menopause than a predetermined value, which makes interpreting the results difficult [8]. Finally, Inhibin B secretion continues even after a dominant follicle has been selected, thus it does not consistently reflect true ovarian reserve [24, 25].

At present, the most accurate and reliable tests are anti-müllerian hormone (AMH) and antral follicle count (AFC).

The antral follicle count is measured as the number of follicles visible on transvaginal ultrasound, typically obtained during the early follicular phase [26], and is used as a surrogate measure of the primordial follicle pool [24]. Two perpendicular measurements are made of each identified follicle, and those with an area of 2–10 mm are counted as antral follicles [27]. AFC is considered normal when 5–10 antral follicles are identified on each ovary [10]. This has been demonstrated to be a good marker of ovarian reserve with higher precision than age or basal FSH, ease of obtaining, low intercycle variability, and low-to-moderate interobserver variability [28].

Anti-Müllerian hormone (aka Mullerian-inhibiting substance) is a homodimeric glycoprotein member of the TGF-beta superfamily initially identified by its role in male sex differentiation during embryogenesis [29]. In females, AMH is undetectable at birth but increases gradually and finally reaches a stable level at puberty [29]. It is produced by the granulosa cells of primary, secondary, and early antral follicles,

and is responsible for regulating steroidogenesis and folliculogenesis within the ovary [30]. A decline in serum AMH represents one of the first clinically detectable signs of diminished ovarian reserve [29, 31, 32].

While not without limitations, AMH is increasingly used as a marker of ovarian reserve. In addition to its early decline, it is relatively stable throughout the menstrual cycle, is minimally influenced by hormonal contraceptives, has less intercycle and intracycle variability, and is comparable among women of various races [29, 32]. Further, AMH secretion ceases once the dominant follicle is selected, so AMH levels more accurately reflect the pool of growing follicles without significant influence by the dominant follicle [25]. The AMH assay is more sensitive than FSH, Inhibin B, or estradiol for detecting diminished ovarian reserve [29, 30], and serum AMH correlates better with IVF outcomes than AFC, FSH, Inhibin B, or estradiol [30].

Additional tests for ovarian reserve include the clomiphene citrate challenge test (CCCT), ovarian volume assessment (OVVOL), ovarian vascular flow, ovarian biopsy, exogenous FSH ORT (EFORT), and Gonadotropin releasing hormone agonist stimulation test (GAST) [22]. These are functional assays and are less often used clinically.

Obesity and Ovarian Aging

Both natural and pathologic ovarian aging are complex processes in need of significantly more research. The influence of obesity on ovarian aging and ovarian screens is predominantly unknown with relatively little data. However, there is suggestion that obesity has an association with the aging process and/or the interpretation of ovarian reserve screens.

The WHO classifies weight in terms of BMI, and considers those with BMI of 25 kg/m^2 or greater overweight and 30 kg/m^2 or greater obese. Obesity causes detrimental effects to most organ systems, including the reproductive system. Adipose tissue secretes peptides, called adipokines, which act systemically, interacting with the hypothalamic-pituitary-ovarian axis, cardiovascular, immune system, and metabolic system [19].

The four primary adipokines include leptin, adiponectin, ghrelin, and resistin [33]. Leptin is involved in neuronal control of body fat and levels increase in obesity. It exerts a direct inhibitory effect on growing follicles via inhibition of steroidogenesis in theca and granulosa cells [33]. This is one proposed reason for poor response to controlled ovarian stimulation in obese women, and explains their altered levels of reproductive hormones as compared to women of normal weight.

Adiponectin enhances fatty acid utilization, inhibits atherosclerosis, and inhibits glucose production by the liver [34]. Studies in porcine ovaries demonstrate adiponectin receptors on granulosa cells and activation of these receptors stimulates vascular endothelial growth factor synthesis and modifies the enzymes of the steroid synthesis pathway [33]. Analogous changes occur in the preovulatory process, thus alterations in adiponectin may lead to abnormalities with ovulation [33]. Resistin and ghrelin are the other primary adipokines, and although resistin levels

are increased in obesity, neither has a significant impact on oocyte maturation or ovarian function [33].

Overweight and obese women demonstrate menstrual cycle dysfunction. Cycles are more often anovulatory, and ovulatory cycles are longer with longer follicular phases in particular [13, 31]. At menopause there is a decrease in the ratio of estrogens to androgens [19, 35]. Overall fat mass increases with redistribution of fat leading to increased central adiposity and waist circumference [19, 35]. As a result, postmenopausal women are predisposed to increased BMI, insulin resistance, metabolic syndrome, and cardiovascular disease [8, 19, 35]. The redistribution of adiposity postmenopausally generates a decline in Leptin levels but no appreciable change in the other adipokines [33, 36].

The interpretation of studies examining a relationship between BMI and ovarian aging must be done cautiously with particular attention to the etiology of the ovarian dysfunction. For example, obese women with PCOS may have a significantly altered process of follicular depletion or pool size compared with obese women without PCOS or normal-weight women, which could be more influenced by PCOS than the BMI The same holds true for POI. POI in the setting of Turner Syndrome will often be associated with elevated BMI secondary to the metabolic consequences inherent in the disease itself. In contrast, karyotypically normal women with POI, in general, manifest a *lower* BMI than normally menstruating women [19, 21, 35]. Again, the relationship between BMI and ovarian aging/oocyte depletion in such examples may be a byproduct of the underlying conditions rather than adiposity, though quality of the embryos remains unknown.

Interestingly, despite a lower BMI, POI appears to be an independent risk factor for the development of metabolic disease [35]. Insulin sensitivity in these patients is significantly decreased from normal [35], and the lipid profiles and blood pressure trends for women suffering from POI more closely resemble chronologically older women with increased LDL, decreased HDL, higher triglycerides, and mildly elevated blood pressures [19]. These women are at increased risk for cardiovascular, skeletal, neuropsychiatric complications, and all cause mortality over their age-matched counterparts secondary to long-term estrogen depletion [17, 20].

Obesity and Reproductive Hormones

While obesity itself may not have a primary role in oocyte pool depletion, it can contribute to the clinical manifestation of the menopausal process. Women undergoing natural menopause with a BMI of 30 kg/m^2 or greater have significant differences in their reproductive hormone milieu as compared to normal-weight women [37]. This can lead to confusion in interpreting tests of ovarian reserve, especially in patients pursuing ART.

Estradiol levels in obese women are significantly lower through the Early Menopausal Transition (−2), normalize during the Late Menopausal Transition (−1), and then are significantly higher during the Postmenopausal Period [13, 35, 38, 39].

The higher estradiol levels measured in postmenopausal obese women result from the peripheral conversion of androgens to estrogens by aromatase within adipose tissue. The inverse relationship between adiposity and estrogen levels in premenopausal women is less intuitive. Sex hormone-binding globulin levels are positively correlated with estrogen levels in premenopausal women, and negatively correlated with BMI in all women [40]. Thus, as BMI increases, SHBG decreases with a subsequent decrease in estrogen. Further, insulin resistance is a known complication of obesity. Elevated serum insulin results in low levels of sex hormone-binding globulin and hyperandrogenism, which can induce granulosa cell apoptosis and impaired ovarian function [41].

Inhibin B levels are also affected by BMI. Overweight and obese premenopausal women consistently demonstrate lower serum Inhibin B levels than women of normal weight [23, 24, 37, 39, 41].

FSH levels in postmenopausal obese women are also significantly lower than their normal-weight counterparts, but the divergence in FSH levels between obese and normal-weight women is typically not evident until the time of the Final Menstrual Period or the Early Postmenopausal Period [13, 37]. The association between FSH and BMI is weaker in premenopausal and perimenopausal women [24, 41], but some studies report a negative association [38, 39] as demonstrated in postmenopausal women.

Several authors have investigated AFC in obese women, but there does not appear to be a clear relationship, independent of other factors. Obese women demonstrate comparable AFCs with normal-weight women [24, 37, 39, 41].

Studies evaluating a relationship between AMH and BMI are conflicting, but most suggest an inverse correlation [24, 31, 35, 37, 41]. The temporal relationship of AMH and ovarian aging, however, does not appear to be affected. The decline in AMH throughout the stages of menopause proceeds at the same rate regardless of the starting AMH level or BMI [31]. Multiple mechanisms have been proposed to explain the apparent relationship between AMH and BMI including increased catabolism of AMH in the setting of excess adiposity, a negative impact on ovarian function, or diminished ovarian reserve [29, 31]. Interestingly, when women with diminished ovarian reserve are examined independently, an association between BMI and AMH has been reported, while the same study demonstrated no association between BMI and AMH in women with normal ovarian reserve [21, 42].

Conclusions

Increased adiposity negatively impacts fertility, but the mechanism has not yet been fully elucidated.

The relative leanness of women suffering from POI and the normal AFC in obese women suggest that obesity does not directly deplete ovarian reserve. Obesity may, however, impair ovarian function as demonstrated by the disruption of normal ovulation and altered hormonal balance in these women. Extrapolating information from the proven effects of adipokines on ovarian function supports this notion.

The lower levels of AMH identified in obese women may suggest an impact of obesity on ovarian aging that is still undefined. Alternatively, this may simply be a result of sequestration or increased clearance of the hormone independent of ovarian function.

While there does not appear to be a direct cause-and-effect relationship between obesity and POI, there may be metabolic derangements in these women, potentially related to increased insulin resistance, that contributes to their pathologic ovarian aging.

Finally, as more obese women seek treatment for infertility, clinicians are faced with the difficult task of interpreting tests of ovarian reserve despite conflicting evidence for the effects of obesity on the accuracy of the assays. Given the prevalence of obesity in numerous countries there remains a significant need for continued research pursuits related to the complex and bidirectional relationship between obesity and ovarian aging.

References

1. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N. Stages of reproductive aging workshop (STRAW). J Womens Health Gend Based Med. 2001;10(9):843–8.
2. Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, Klein NA. A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause. Hum Reprod. 2008;23(3):699–708.
3. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-lie: implications for forecasting menopause. Hum Reprod. 1992; 7(10):1342–6.
4. Gold EB, Bronberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, Skurnick J. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol. 2000;153(9):865–74.
5. Johnson J, Canning J, Kaneko T, Pru JK, Tilly JL. Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature. 2004;428:145–50.
6. White YAR, Woods DC, Takai Y, Ishihara O, Seki H, Tilly JL. Oocyte formation by mitotically active germ cells purified from ovaries of reproductive-age women. Nat Med. 2012;18(3): 413–22.
7. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. Menopause. 2012;19(4):387–95.
8. Sammel MD, Freeman EW, Liu Z, Lin H, Guo W. Factors that influence entry into stages of the menopausal transition. Menopause. 2009;16(6):1218–27.
9. Burger HG, Hale GE, Dennerstein L, Robertson DM. Cycle and hormone changes during perimenopause: the key role of ovarian function. Menopause. 2008;15(4):603–12.
10. Gurtcheff SE, Klein NA. Diminished ovarian reserve and infertility. Clin Obstet Gynecol. 2011;54(4):666–74.
11. Welt CK, McNicholl DJ, Taylor AE, Hall JE. Female reproductive aging is marked by decreased secretion of dimeric inhibin. J Clin Endocrinol Metabol. 1999;84(1):105–11.
12. Santoro N, Rosenberg Brown J, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metabol. 1996;81(4):1495–501.
13. Santoro N, Lasley B, McConnell D, Allsworth J, Crawford S, Gold EB, Finkelstein JS, Greendale GA, Kelsey J, Korenman S, Luborsky JL, Matthews K, Midgley R, Powell L, Sabatine J, Mchocken M, Sowers MF, Weiss G. Body size and ethnicity are associated with

menstrual cycle alterations in women in the early menopausal transition: the Study of Women's Health Across the Nation (SWAN) daily hormone study. J Clin Endocrinol Metab. 2004; 89(6):2622–31.
14. Nelson LN. Primary ovarian insufficiency. N Engl J Med. 2009;360:606–14.
15. Kalantaridou SN, Davis SR, Nelson LM. Premature ovarian failure. Endocrinol Metab Clin. 1998;27(4):989–1006.
16. Cooper AR, Baker VL, Sterling EW, Ryan ME, Woodruff TK, Nelson LM. The time is now for a new approach to primary ovarian insufficiency. Fertil Steril. 2011;95(6):1890–7.
17. DeVos M, Devroey P, Fauser BCJM. Primary ovarian insufficiency. Lancet. 2010;376: 911–21.
18. Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011;26(7):1616–24.
19. Michalakis C, Coppack SW. Primary ovarian insufficiency: relation to changes in body composition and adiposity. Maturitas. 2012;71:320–5.
20. Pal L, Zhang K, Zeitlian G, Santoro N. Characterizing the reproductive hormone milieu in infertile women with diminished ovarian reserve. Fertil Steril. 2010;93:1074–9.
21. Buyuk E, Seifer DB, Illions E, Grazi RV, Lieman H. Elevated body mass index is associated with lower serum anti-mullerian hormone levels in infertile women with diminished ovarian reserve but not with normal ovarian reserve. Fertil Steril. 2011;95:2364–8.
22. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests of predicting ovarian reserve and IVF outcome. Hum Reprod Update. 2006;12(6):685–718.
23. Gracia CR, Freeman EW, Sammel MD, Lin H, Nelson DB. The relationship between obesity and race on inhibin B during the menopause transition. Menopause. 2005;12(5):559–66.
24. Su HI, Sammel MD, Freeman EW, Lin H, DeBlasis T, Gracia CR. Body size affects measures of ovarian reserve in late reproductive age women. Menopause. 2008;15(5):857–61.
25. ESHRE Capri Workshop Group. Fertility and aging. Hum Reprod Update. 2005;11(3):261–76.
26. LaMarca A, Spada E, Sighinolfi G, Argento C, Tirelli A, Guilini S, Milai S, Volpe A. Age-specific nomogram for the decline in antral follicle count throughout the reproductive period. Fertil Steril. 2011;95(20):684–8.
27. Broekmans FJM, de Ziegler D, Howles CM, Guogeon A, Trew G, Olivennes F. The antral follicle count: practical recommendations for better standardization. Fertil Steril. 2010;94(3):1044–51.
28. Hsu A, Arny M, Knee AB, Bell C, Cook E, Novak A, Grow DR. Antral follicle count in clinical practice: analyzing clinical relevance. Fertil Steril. 2010;95(2):474–9.
29. Karkanaki A, Vosnakis C, Panidis D. The clinical significance of anti-Mullerian hormone evaluation in gynecological endocrinology. Hormones (Athens). 2011;10(2):95–103.
30. Hazout A, Bouchard P, Seifer DB, Aussage P, Junca AM, Cohen-Bacrie P. Serum antimullerian hormone/mullerian-inhibiting substance appears to be a more discriminatory marker of assisted reproductive technology outcome than follicle-stimulating hormone, inhibin B, or estradiol. Fertil Steril. 2004;82(5):1323–9.
31. Freeman EW, Gracia CR, Sammel MD, Lin H, Chong-Leong Lim L, Strauss III JF. Association of anti-mullerian hormone levels with obesity in late reproductive-age women. Fertil Steril. 2007;87:101–6.
32. LaMarca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Carducci Artenisio A, Stabile G, Volpe A. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update. 2010;16(2):113–30.
33. Mostafa M, Ledger WL, Li TC. Reproductive endocrinology and clinical aspects of obesity in women. Ann N Y Acad Sci. 2008;1127:140–6.
34. Benetti-Pinto CL, Castro N, Grassiotto OR, Garmes HM. Leptin and adiponectin blood levels in women with premature ovarian failure and age- and weight-matched women with normal menstrual cycles. Menopause. 2010;17(1):174–7.
35. Corrigan EC, Nelson LM, Bakalov VK, Yanovski JA, Vanderhoof VH, Yanoff LB, Bondy CA. Effects of ovarian failure and X-chromosome deletion on body composition and insulin sensitivity in young women. Menopause. 2006;13(6):911–6.

36. Hong SC, Yoo SW, Cho GJ, Kim T, Hur JY, Park YK, Lee KW, Kim SH. Correlation between estrogens and serum adipocytokines in premenopausal and postmenopausal women. Menopause. 2007;14(5):835–40.
37. Freeman EW, Sammel MD, Lin H, Gracia CR. Obesity and reproductive hormone levels in the transition to menopause. Menopause. 2010;17(4):718–26.
38. Randolph JF, Sowers M, Gold EB, Mohr BA, Luborsky J, Santoro N, McConnell DS, Finkelstein JS, Korenman SG, Matthews KA, Sternfeld B, Lasley B. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J Clin Endocrinol Metab. 2003;88(4):1516–22.
39. DePergola G, Maldera S, Tartagni M, Pannacciulli N, Loverro G, Giorgino R. Inhibitory effect of obesity on gonadotropin, estradiol, and inhibin B levels in fertile women. Obesity. 2006;14(11):1954–60.
40. Pasquali R, Vicennati V, Bertazzo D, Casimirri F, Pascal G, Tortelli O, Morselli Labate AM. Determinants of sex hormone-binding globulin blood concentrations in premenopausal and postmenopausal women with different estrogen status. Metabolism. 1997;46(1):5–9.
41. Malhotra N, Bahadur A, Singh N, Kalaivani M, Mittal S. Does obesity compromise ovarian reserve markers? A clinician's perspective. Arch Gynecol Obstet. 2013;287:161–6.
42. Sahmay S, Usta T, Erel CT, Imamoglu M, Kucuk M, Atakul N, Seyisoglu H. Is there any correlation between AMH and obesity in premenopausal women? Arch Gynecol Obstet. 2012;286:661–5.

Chapter 11
Obesity, Reproductive Outcomes, and Access to Infertility Treatments: A Clinical and Ethical Debate

Samantha Schon and Samantha Butts

Introduction

The obesity epidemic has significantly impacted risks in obstetrics and gynecology. Pregnancy-related complications in obese pregnant women include increased risk of fetal anomalies, gestational diabetes mellitus, stillbirth, fetal macrosomia, and Cesarean delivery. Obese women also have unique challenges to fertility and fecundity such as increased risk of early miscarriage compared to normal-weight women [1]. Obesity is associated with disordered ovulation and menstrual cycle irregularity, most notably in women with polycystic ovary syndrome (PCOS) which affects 5–10 % of reproductive-age women [2, 3]. While overweight or obese status is not a requisite for the diagnosis of PCOS, 50–75 % of affected individuals are overweight or obese [2, 4] Anovulation is the primary defect leading to infertility in obese women with PCOS.

As with normal-weight women, the treatment of infertility in overweight and obese women must be individualized to maternal factors, paternal factors, and risks and benefits of various treatments. Numerous clinical reports have demonstrated that infertility treatments (regardless of the underlying cause) in overweight and obese women result in lower odds of live birth than in normal-weight women. A major finding of the Cooperative Multicenter Reproductive Medicine Network Trial of Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome was that subjects with a body mass index (BMI) greater than 30 kg/m^2 had a significantly lower rate of live birth than those with BMI less than 30 kg/m^2 independent

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of assigned treatment (clomiphene citrate, metformin, or the treatments combined) [5]. The risk of early pregnancy loss has also been shown to be greater in obese women who conceive with fertility treatments compared to nonobese women [2]. Modest weight loss—between 5 and 10 % of total body weight—restores ovulatory cycles in many oligoovulatory women with PCOS [6]. In addition, significant weight loss as occurs with bariatric surgery, drastically reduces perinatal complications that often occur in the pregnancies of obese women [2]. Despite concerns about risks to fetal growth and development following surgical weight loss, pregnancies conceived at least 12 months following bariatric procedures have not been associated with significant perinatal morbidity [7, 8].

Assisted reproductive technologies (ART) such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are often recommended to women with specific infertility diagnoses (i.e., tubal factor, severe oligospermia) or to those who have not achieved a pregnancy with treatments such as ovulation induction or artificial insemination. Obesity has been noted to negatively impact multiple facets of ART such as response to gonadotropins, cycle cancellation rates, clinical pregnancy rates, and live birth rates [9, 10]. Obesity may also diminish live birth rates in IVF when donor oocytes are used and the recipient is obese [11], however, the literature has not consistently supported this association [12].

These data support the fact that obesity challenges fecundity in both natural and assisted attempts at conception. In light of the diminished efficacy of ART in obese women using autologous oocytes, the specific risks of treatment (i.e., ovarian hyperstimulation syndrome, egg retrieval procedure, and conception of multiples) and the known benefits of weight loss to reproductive outcomes, a debate has emerged around the implementation of body mass index (BMI) cutoffs that would restrict obese women from infertility treatments. While formal guidelines that directly address this debate do not exist in the United States, many fertility practices both domestically and abroad currently limit access to infertility treatments for obese women. The goal of this chapter is to summarize the current literature addressing the use of BMI as a criterion for access to infertility treatment and ART. The principles of respect for autonomy, justice beneficence/nonmaleficence will be introduced to develop a bioethical framework within which to consider this debate.

Arguments Supporting a BMI Cut Off

In the United States there are currently no official guidelines advocating a specific BMI above which infertility treatment should be discouraged or refused. Globally, however, the recommendation and enforcement of BMI thresholds is prevalent and growing. Examples of these policies and arguments for their use are discussed below.

The New Zealand System

In New Zealand, a clinical ranking system known as clinical priority access criteria (CPAC) was first introduced in the 1990s with a stated goal of ranking patients for elective, publicly funded procedures. In 2000, this was extended to patients seeking treatment for infertility [13]. Given that obesity is considered to decrease the likelihood of successful infertility treatment, the CPAC ranking system was only applied to women within the BMI range of 18–32 [14, 15]. One retrospective study examined the effect of these criteria on women outside of the BMI range, and reported that while similar proportions of women in different BMI categories would have been eligible for publicly funded ART, the number actually receiving treatment was lower in the higher BMI group [14]. They also found that women with a BMI >32 were less likely to receive private ART [14]. The authors argued that women with BMIs between 32 and 35 were able to modify their lifestyle and achieve a weight loss that then enabled them to receive treatment. Those in support of CPAC claim that this system has allowed for more equitable care and greater access to ART in New Zealand and that most evidence supports the need for weight improvement measurements [14]. Evidence cited includes increased rates of infertility, increased maternal and neonatal complications, and increased costs of treatment in overweight and obese women. Also noted, are the benefits of weight loss in improving fertility outcomes in this population [16].

The United Kingdom

While the United Kingdom does not have an enforced BMI threshold for ART, their reproductive societies have recommended BMI ranges for those undergoing ART. The most recent National Institute for Health and Care Excellence (NICE) guidelines suggest that BMI should be in the range of 19–30 kg/m^2 before commencing with assisted reproduction, and that a woman with a BMI outside this range is likely to have a lower chance of successful assisted reproduction [17]. The British Fertility Society (BFS) states that infertility treatment should be deferred if BMI is in excess of 35 and that obese infertile women under the age of 37 should be encouraged to reduce their BMI to less than 30 [18]. The basis for these recommendations include diminished odds of natural conception and successful fertility treatment in obese women, as well as the increased risk of miscarriage, pregnancy complications, and congenital anomalies. The BFS also addresses the decreased safety of fertility treatment in obese women and the potential negative long-term health effects on both mother and child [18]. In accord with these recommendations, it has been reported that two-thirds of clinics in the United Kingdom apply a BMI cutoff to patients being evaluated for infertility treatments [19].

Additional Arguments for BMI Cutoffs

Other reports have proposed that women with a BMI >35 should lose weight prior to conception and not prior to receiving infertility treatment [20]. In this case it is argued that given the significant risks of obesity to both the mother and fetus, the woman should actually be protected against pregnancy during the time of weight loss and that the combination of weight loss, contraception, and folic acid should become the standard in the preconceptual care of obese women [20].

Proponents of using BMI cutoffs to determine access to infertility treatments have focused on the importance of weight loss in specific patient populations. Balen et al. have suggested that weight loss should be a prerequisite to the treatment of obese women with PCOS. In this case, the authors argue that weight loss should first be achieved to improve the endocrine profile, frequency of ovulation, and likelihood of a healthy pregnancy [21], and that all treatment aimed at ovulation induction should be deferred (including metformin), until these patients reach a BMI cutoff of 35 kg/m^2 [21].

The likelihood that both ART and pregnancy are more expensive in obese patients is used as an argument supporting BMI cutoffs in populations where fertility treatment is publicly funded. In one study by Koning et al., a theoretical model was developed to evaluate costs of treating different populations of infertile women (i.e., ovulatory and anovulatory normal weight and obese women). In both ovulatory and anovulatory subfertile women, overweight and obesity resulted in decreased fecundity and an increase in the number of pregnancy complications and costs per live birth [22]. While this argument has been put forth by proponents of BMI cutoffs [16], the authors of the study conclude that their data does not demonstrate a reason to withhold treatment, especially as there has been no evidence that weight loss impacts live birth rates and pregnancy-related complications [22].

The US Perspective

In the United States there are no official guidelines regarding infertility treatment for obese women. In a recent survey examining physician practice patterns and beliefs, 42.9 % of surveyed infertility centers used a BMI cutoff to determine access to any treatment and 73.9 % of medical directors of infertility practices believed that a cutoff should exist. Furthermore, 54.8 % of centers had a cutoff for access to IVF and 82.9 % of IVF medical directors believed that a cutoff should exist [23]. In contrast to the BMI threshold of 30 kg/m^2 in Europe and New Zealand, the recommended cutoffs reported by clinics in the United States ranged from 30 to 55, with the most common recommendation being 40 kg/m^2 [23]. The most provocative finding of this study is that a majority of IVF medical directors believe that a BMI cutoff should be implemented. While there are currently no official statements from US reproductive societies, it seems apparent that a widespread interest exists in the development of formal guidelines for BMI thresholds defining access to infertility treatment in the United States.

Even in the absence of formal guidelines limiting access to infertility treatments according to BMI, national data suggests that overweight and obese women with infertility are less likely to receive treatment than normal-weight women. A secondary analysis of the 2002 National Survey of Family Growth, demonstrated that compared to nonobese women, those with class II/III obesity (30.0–34.9/≥35 kg/m^2) were most likely to seek medical attention to become pregnant, but least likely to receive medical or surgical fertility-related services [24]. In addition, obese women had the lowest percentage of private insurance, the highest percentage of uninsured status, and the lowest household income [24].

Arguments Against a BMI Cut Off

Opponents of BMI thresholds argue that a policy of restriction is difficult to define, defend, and implement [25]. These same opponents note that many studies describing diminished success rates of fertility treatment are evaluating outcomes such as increased drug dose or ovulation and are not in fact looking at outcomes such as clinical pregnancy or live birth. Furthermore, not all studies demonstrate decreased live birth rates with increasing BMI [25].

Another central tenet of the argument against BMI cutoffs is the treatment delay inherent to weight loss efforts. Preventing older obese women from attempting pregnancy until they have lost weight may cost valuable time, further decreasing chances of conception [25]. It has been argued that while ART success rates decrease with increasing BMI, the same relationship is observed with increasing age, especially in patients older than 40 [22]. Although fertility societies in the United Kingdom recommend a BMI cutoff for access to ART, a recent European Society of Human Reproduction and Embryology (ESHRE) task force concluded that obese women approaching the end of their fertile period should not be forced to achieve weight loss before treatment is considered [26].

Opponents of BMI cutoffs also argue that asking obese women to defer treatment for weight loss adds to a sense of stigmatization for these patients. It has been pointed out that women are entitled to choose a less-than-ideal treatment if they have received appropriate information on risks, benefits, and effectiveness [27].

Finally, the notion that offering ART to obese infertile women is not cost effect remains a current matter of debate. In a study using patient level data, Maheshwari et al., found no significant difference in cost per live birth resulting from ART in women who are overweight and obese compared with women with a normal BMI [28].

Bioethical Framework

The core principles of ethics—autonomy, beneficence/nonmaleficence, and justice—can be applied to further interpret the debate about the use of BMI cutoffs to determine access to infertility treatments [29]. Respecting the autonomy of patients acknowledges their right to freely make medical choices after informed of the risks,

benefits, and alternatives to such choices. Considering patient autonomy would also lend support to the argument to treat an obese woman with infertility and against BMI cutoffs to restrict access to care. The principles of beneficence and nonmaleficence obligate providers to prioritize the well being of patients and to avoid treatments that expose them to excessive risk. When considering these specific principles, an argument can be made that supports the implementation of BMI cutoffs for access to care when the risk to benefit ratio of treatment is unacceptably high. In certain clinical scenarios, beneficence/nonmaleficence may conflict with the principle of respect for patient autonomy. As pertains to the current debate, this could transpire if a provider believes that the risk of ART in an obese patient is high and the benefit is low but the patient wishes to move forward despite extensive counseling. This conflict highlights the concept that no single principle is absolute in the process of ethical decision-making.

The principle of justice applies to the delivery of care to individuals and to consideration of the societal impact of medical decision-making [29]. Justice asserts that individuals should be treated equally and is the principle invoked in determining allocation of limited healthcare resources such as organ transplants. Examining the debate of obesity and access to infertility treatments through the lens of justice introduces an additional level of complexity to this argument. If a just approach to the allocation of infertility treatments is that all women with infertility should receive care, then obesity should not be used to limit access. When considering justice from the perspective of society at large, treating infertility in overweight and obese women who develop treatment complications and/or perinatal morbidity could strain healthcare resources. Ultimately, continued ethical appraisal of this debate will be valuable in finding the best approach to care for obese women with infertility.

Conclusion

While there is ongoing controversy regarding the implementation of BMI cutoffs for access to infertility treatments in general and to ART specifically, it is evident that obesity constitutes a significant obstacle to receiving infertility treatment. As the rate of overweight and obesity continues to grow, especially among reproductive-age females, physicians will have to best integrate the current available evidence when counseling and treating their patients. Furthermore, given the increasing consensus that BMI restrictions should be applied, reproductive societies will need to formally address this important issue.

References

1. The Committee on Obstetric Practice. Obesity in pregnancy, ACOG Committee opinion, no. 315; 2005.
2. Practice Committee of the American Society for Reproductive Medicine. Obesity and reproduction: an educational bulletin. Fertil Steril. 2008;90(5 Suppl):S21–9.

3. Guzick D. Polycystic ovary syndrome. Obstet Gynecol. 2004;103:181–93.
4. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med. 2005;352:1223–36.
5. Legro RS, Barnhart HX, Schlaff WD, et al. Cooperative multicenter reproductive medicine network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007;356:551–66.
6. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88:812–9.
7. Sheiner E, Balaban E, Dreiher J, Levi I, Levy A. Pregnancy outcome in patients following different types of bariatric surgeries. Obes Surg. 2009;19:1286–92.
8. Sheiner E, Levy A, Silverberg D, Menes TS, Levy I, Katz M, et al. Pregnancy after bariatric surgery is not associated with adverse perinatal outcome. Am J Obstet Gynecol. 2004;190:1335–40.
9. Luke B, Brown M, Stern JE, Missmer SA, Fujimoto V, Leach R. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod. 2011;26:245–52.
10. Dokras A, Baredziak L, Blaine J, Syrop C, VanVoorhis BJ, Sparks A. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstet Gynecol. 2006;108:61–8.
11. Bellver J, Rossal LP, Bosch E, Zuniga A, Corona J, Melendez F, Gomez E, Simon C, Remohi J, Pellicer A. Obesity and the risk of spontaneous abortion after oocyte donation. Fertil Steril. 2003;79:1136–40.
12. Styne-Gross A, Elkind-Hirsch K, Scott R. Obesity does not impact implantation rates or pregnancy outcome in women attempting conception through oocyte donation. Fertil Steril. 2005;83:1629–34.
13. Hadorn DC, Holmes AC. The New Zealand priority criteria project. Part 1: overview. BMJ. 1997;314:131–4.
14. Gillett WR, Putt T, Farquhar CM. Prioritising for fertility treatments—the effect of excluding women with a high body mass index. BJOG. 2006;113:1218–21.
15. Gillett WR, Peek JC, Herbison GP. Development of clinical priority access criteria for assisted reproduction and its evaluation on 1386 infertile couples in New Zealand. Hum Reprod. 2012;27:131–41.
16. Farquar CM, Gillett WR. Prioritising for fertility treatments—should a high BMI exclude treatment? BJOG. 2006;113:1107–9.
17. National Institute for Clinical Excellence. Fertility: assessment and treatment for people with fertility problems. 2013. http://publications.nice.org.uk/fertility-cg156.
18. British Fertility Society. British fertility society issues new guidelines on the effect of obesity on female reproductive health. 2007. http://www.fertility.org.uk/news/pressrelease/07_11-ObesityFemaleHealth.html.
19. Zachariah M, Fleming R, Acharya U. Management of obese women in assisted conception units: a UK survey. Hum Fertil. 2006;9:101–5.
20. Nelson SM, Fleming RF. The preconceptual contraception paradigm: obesity and infertility. Hum Reprod. 2006;22:912–5.
21. Balen AH, Dresner M, Scott EM, Drife JO. Should obese women with polcystic ovary syndrome receive treatment for infertility? BMJ. 2006;25(332):434–5.
22. Koning AMH, Kuchenbecker WKH, Groen H, Hoek A, Land JA, Khan KS, Mol BWJ. Economic consequences of overweight and obesity in infertility: a framework for evaluating the costs and outcomes of fertility care. Hum Reprod Update. 2010;16:246–54.
23. Haris ID, Python J, Roth L, Alvero R, Murray S, Schlaff WD. Physicians' perspectives and practices regarding the fertility management of obese patients. Fertil Steril. 2011;96:991–2.
24. Vahratian A, Smith YR. Should access to fertility-related services be conditional on body mass index? Hum Reprod. 2009;7:1532–7.
25. Pandey S, Maheshwari A, Bhattacharya S. Should access to fertility treatment be determined by female body mass index? Hum Reprod. 2010;25:815–20.
26. Dondorp W, de Wert G, Pennings G, Shenfield F, Devroey P, Tarlatzis B, Barri P. Lifestyle-related factors and access to medically assisted reproduction. Hum Reprod. 2010;25:578–83.

27. Laredo SE. Obesity, polycystic ovary syndrome, infertility treatment: asking obese women to lose weight before treatment increases stigmatization. BMJ. 2006;332:609.
28. Maheshwari A, Scotland G, Bell J, McTavish A, Hamilton M, Bhattacharya S. The direct health services costs of providing assisted reproduction services in overweight or obese women: a retrospective cross-sectional analysis. Hum Reprod. 2009;24:633–9.
29. The Committee on Ethics. Ethical decision making in obstetrics and gynecology, ACOG Committee opinion no. 390; 2007.

Chapter 12
Surgical Interventions and Reproductive Function in Obese Women

Julie S. Rhee and Jason Y. Rhee

Introduction

The growing epidemic of obesity weighs heavily on societies around the world. According to the World Health Organization (WHO) 65 % of the world's population lives in countries where overweight and obesity kills more people than underweight [1]. "Globesity" as it has been termed, has spurred a tremendous amount of research, encompassing both long-term health outcomes of obesity and potential treatment options. Of the treatment options, surgical intervention is exceedingly common and effective [2, 3]. A 2014 meta-analysis of 37 randomized controlled trials investigating modern bariatric practices, found a 92 % resolution of diabetes, 75 % resolution of hypertension, 76 % resolution of dyslipidemia, and 96 % resolution of obstructive sleep apnea [4, 5].

Although obesity affects both men and women, women are not only more likely to be obese but they also comprise the majority patients undergoing bariatric surgery. Women account for over 80 % of all patients undergoing bariatric surgery between ages 18 and 45 [6]. In one observational study, 30 % of women undergoing bariatric surgery stated that future pregnancy was important and 32 % intended on becoming pregnant within 2 years [7]. Although published data on this topic is sparse, it is of paramount importance that clinicians are aware of the existing literature regarding the impact of bariatric surgery on fertility so patients may be counseled appropriately prior to undergoing a procedure.

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Bariatric Surgical Options

In general, weight loss with bariatric surgery can be accomplished through two different mechanisms: restriction of the stomach capacity versus reduction of the absorptive capacity of the gastrointestinal tract (Table 12.1). Laparoscopic adjustable gastric banding (LAGB) and laparoscopic vertical gastroplasty (sleeve gastrectomy) fall into this category of restrictive procedures, while laparoscopic Roux-en-Y gastric bypass (LRYGB) incorporates both restricting the volume of the gastric pouch and bypassing 50–150 cm of small intestinal tract, thus creating a malabsorptive state. Laparoscopic adjustable banding and Roux-en-Y bypass are the two most common bariatric procedures performed today. Solely malabsorptive procedures include jejunoileal bypass, biliopancreatic diversion and biliopancreatic diversion with duodenal switch. These malabsorptive procedures are not commonly performed. It is important to distinguish the type of bariatric procedure as the term "bariatric surgery" is often used to encompass all types of surgeries with the intent of weight loss; however, the techniques and the physiologic impact of each type of surgery vary dramatically. As research continues, a deeper understanding of the differences is becoming more appreciated. As technology improves and techniques change, it is clear the type of surgical intervention must be taken into consideration when interpreting the literature.

Overall, extensive research has outlined the benefits of bariatric surgery, namely improvement or complete resolution of various medical comorbidities [8]. However, the research of bariatric surgery and its overall impact on fertility and pregnancy outcomes is still evolving as the practice of bariatric surgery develops. For example,

Table 12.1 Bariatric procedures and their mechanism

Mechanism	Bariatric procedure	Concerns specific to reproductive age women
Restrictive	Laparoscopic adjustable gastric band (LAGB)	• Can be adjusted during pregnancy if issues with nausea or inadequate weight gain
		• Risk of gastric ulceration during pregnancy
		• Risk of nutritional deficiencies
	Vertical banded gastroplasty	• Risk of nutritional deficiencies
	Sleeve gastrectomy	
Malabsorptive	Jejunoileal bypass	• These procedures are rarely performed due to long-term associated morbidity
	Biliopancreatic diversion	
	Biliopancreatic diversion with duodenal switch	
Restrictive and malabsorptive components	Roux-en-Y	• May interfere with absorption of oral contraceptives
		• Risk of internal hernia and bowel obstruction during pregnancy
		• Risk of nutritional deficiencies (more common than with solely restrictive procedures)

several cases of increased fertility after bariatric surgery were reported after biliopancreatic diversion (BPD) [9, 10], a procedure in which the majority of the stomach pouch is removed to reduce food intake while the remaining portion of the stomach is connected to the lower portion of the small intestine. Weight loss with BPD has been reported to improve fertility; however, BPD has fallen out of favor and is rarely performed in the United States due to concerns of malnutrition, hepatic, and renal failure [11]. Despite this, bariatric surgery shows promise to improve fertility for obese women wanting to achieve pregnancy.

Obesity, Reproductive Physiology, and Polycystic Ovary Syndrome

Obesity's impact on adverse reproductive sequelae and altered hormonal milieu has been described [12–15] and different mechanisms have been proposed as discussed elsewhere in this book. In general, obesity increases the risk of anovulation and menstrual cycle abnormalities. In ovulatory women menstrual cycle length is altered with obesity manifesting as a longer follicular phase and a shorter luteal phase. Associated mechanisms are discussed elsewhere in this book, but briefly, it has been demonstrated that as BMI increases, follicular phase is lengthened and the luteal phase is shorter [12]. These changes are associated with decreased urinary luteinizing hormone (LH) and follicle stimulating hormone in the follicular phase, and decreased luteal phase pregnanediol-3-glucuronide (Pdg), a progesterone metabolite. Overall this suggests corpus luteum dysfunction with decreased capacity for implantation and maintenance of a healthy pregnancy. Consistent with this, a separate study also demonstrated reduced LH pulse amplitude and lower levels of urinary Pdg in ovulatory morbidly obese women, again indicating altered function of the corpus luteum [13].

Adipokines are hormones produced by adipose tissue, and a number of adipokines have been implicated as having effects on reproductive physiology including adiponectin, resistin, and leptin. Of these leptin is perhaps the best studied. Leptin secretion correlates directly with total body adiposity. Obese women have excess serum leptin concentrations with subsequent inhibition of ovarian steroidogenesis and follicular growth [16]. A study examining the contrary scenario, found that leptin administration in women with hypothalamic amenorrhea due to strenuous activity or low weight resulted in a resumption of gonadotropin secretion, follicular development, and ovulation, demonstrating the important physiologic role that leptin plays in female reproductive function [17].

Polycystic Ovarian Syndrome (PCOS) is associated with obesity, anovulation, and insulin resistance and other metabolic derangements. About 30–70 % of patients with PCOS are obese [18]. Insulin resistance and a hyperinsulinemic state in PCOS patients lead to stimulation of excess androgen production that inhibits normal follicular growth and maturation [19]. This then leads to oligo- and anovulation in many women with PCOS, with subsequent subfertility. The ovulatory dysfunction

associated with PCOS has been attributed primarily to the hyperandrogenic environment, but is augmented by factors associated with obesity, i.e., hyperinsulinemia and increased levels of leptin [14, 15].

Impact of Bariatric Surgery on Reproductive Physiology

Bariatric surgery restricts caloric intake and nutrient absorption, thereby promoting weight loss and decreasing overall total body adiposity. Leptin concentrations decrease with weight loss after bariatric surgery and research in murine models have shown improved fertility after reduction of leptin levels after decreased caloric intake and dietary modification [20, 21]. A recent study investigating leptin levels after bariatric surgery demonstrated that, regardless of the type of surgical procedure, levels of leptin and insulin resistance significantly decreased following bariatric surgery, further suggesting that weight loss alters the endocrinologic balance [22]. Also, cytokines such as interleukin-6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1) are higher in obese women and can contribute to ovulatory dysfunction and implantation failure. Levels of these cytokines are lower after bariatric surgery, which help improve ovulatory function and implantation [23].

A 2006 survey of 98 anovulatory women found that 70 of these women regained ovulatory function after bariatric surgery, and that average weight loss was higher among those who regained ovulatory function compared to those who did not (61.4 vs. 49.9 kg respectively) [24]. This is consistent with a 1998 survey of 56 anovulatory overweight women showing that 90 % of women regained ovulatory menstrual cycles after bariatric surgery. In this study, women who regained ovulatory function also had an overall greater average weight loss compared to women who did not regain function [25]. In a recent study of 20 obese women with PCOS who underwent LRYGB, with a mean follow-up time of nearly 4 years, 82 % experienced normalization of their menstrual cycles and of those patients who had not conceived prior to surgery (50 %), all patients who further desired pregnancy became pregnant within 3 years [26]. In another study of 24 obese women with PCOS who underwent LRYGB, all women resumed normal menstrual cycles after a mean of 3.4 months postoperatively. Eighteen of 23 subjects had moderate to complete resolution of hirsutism. The study also notes that of the five subjects who were infertile prior to surgery, all women were able to conceive without ovulation induction using clomiphene postoperatively [27]. However, given that most of these studies are retrospective with small sample sizes, the current lack of well-designed studies does not allow for definite conclusions or formal recommendations to be made regarding the reproductive benefit of bariatric surgery in women with PCOS.

In regards to ovulatory women undergoing bariatric surgery, a recent study by Legro et al. demonstrated improved, shorter follicular phase length from 22 days preoperatively to approximately 14 days after bariatric surgery [28]. The study also noted improved hyperandrogenemia and sexual function after bariatric surgery. In a follow-up study, investigators measured urinary excretion of LH and Pdg during the luteal phase before and after bariatric surgery in obese women. Levels of both

hormones increased post-surgery, but still remained below levels seen in controls [28]. Taken together these data suggest that while bariatric surgery may help improve ovulatory function in obese women, there may be a certain amount of weight loss required to completely restore function, or perhaps there are lingering effects of obesity on the hypothalamic–pituitary–ovarian axis after weight loss surgery.

Bariatric Surgery and Fertility

Based on available literature, it is difficult to conclude whether bariatric surgery improves fertility per se, as most studies that have reported on fertility following bariatric surgery demonstrate that not all patients prior to surgery struggled with infertility or even attempted pregnancy. On the other hand, it is well established that weight loss with bariatric surgery improves ovulatory function and menstrual regularity as discussed above.

In a 2008 systematic review by Maggard et al., authors identified a number of studies demonstrating improved menstrual regularity, ovulation, and improvements in androgen levels after bariatric surgery, but only six studies specifically addressing female fertility after bariatric surgery [6]. One of the identified studies compared preoperative and postoperative reproductive histories of women who underwent bariatric surgery and had lost greater than 50 % of excess weight. 29/115 women (25 %) had reported infertility prior to bariatric surgery and there was data on nine women who conceived after surgery. Of these women 8 were in the group that had reported infertility prior to surgery. While this data is helpful, it is difficult to deduce any causal effects given that the follow-up time was not mentioned in this study and the number of patients who tried to conceive prior to surgery was unknown. The difficulty of determining how many patients actually desired pregnancy preoperatively or postoperatively is a common theme seen in studies.

In regards to fertility after specific types of bariatric procedures, there is one recent study. This study conducted in Italy and published in 2012, investigated 110 women who had undergone bariatric surgery (intragastric balloon placement, LAGB, sleeve gastrectomy, and LRYGB) who were identified with subfertility prior to surgery [29]. After surgery, 69 % of those patients became pregnant, with greater weight loss and lower BMI being positively associated with pregnancy. The endocrinologic changes that take place with significant weight loss were not investigated in the study. The authors did not find a difference in pregnancy rates across the different types of bariatric surgical methods.

Although the data looking specifically at female fertility is limited, since the main premise of bariatric surgery is weight loss and any improvement of fertility may be an “unintended” outcome, at minimum, physicians can counsel patients by stating that research indicates that surgical intervention via bariatric surgery may have a benefit on future fertility. One can infer that although there is limited evidence of improved fertility as gauged by increased pregnancy rates, there is ample evidence that hormone levels and menstrual cycles do seem to normalize in women post-surgery via the multiple physiologic mechanisms previously described in this chapter.

Bariatric Surgery and In Vitro Fertilization

Despite the fact that bariatric surgery may improve ovulatory function and fertility in obese women, some women who undergo bariatric surgery may still require aggressive fertility treatment like in vitro fertilization (IVF). Despite this, few data exist regarding IVF in women who have undergone bariatric surgery. In a case series by Doblado et al., the authors show evidence that IVF is safe and effective in women who have undergone bariatric procedures [30]. On the other hand, the authors raise the point that special considerations need to be made for women who have undergone bariatric surgery in the setting of IVF. First, the authors state that ovarian hyperstimulation syndrome could lead to serious complications including ascites and increased intraabdominal pressure which could in turn increase the risk of intestinal obstruction and internal hernia, two late complications of bariatric surgery. Internal hernia presents clinically with nausea and abdominal pain which could mimic OHSS.

Overall, there seems to be sufficient evidence to suggest that obesity adversely impacts IVF outcomes, however, it is difficult to deduce based on existing literature if weight loss actually improves clinical pregnancy rate and live birth outcome in women undergoing IVF. Given that little has been published on the impact of surgical intervention on IVF outcomes, it would be difficult to counsel patients that undergoing bariatric surgery prior to undergoing IVF would be beneficial. Furthermore, patients and physicians must weigh the risks and benefits of surgical weight loss and the delay in time to conceive that one must account for following surgery. More work is needed to investigate the true impact of weight loss via surgical intervention on the outcome of IVF.

Time to Wait for Conception After Surgery

The optimal timing of conception after bariatric surgery has not been determined, as the trajectory of weight loss and recovery for each patient is different. However, rapid weight loss generally plateaus after 18 months post-surgery, after which, the concerns for nutritional deficiencies are somewhat diminished. Constrained by the limited nature of research on this topic, the American College of Obstetricians and Gynecologists (ACOG) published a practice bulletin in 2009 that does not make any recommendations regarding the timing of conception, but ACOG recommends closer surveillance of maternal weight and nutritional status, in addition to regular ultrasounds for serial monitoring of fetal growth, for those women who conceive <12 to 24 months after bariatric surgery [31].

In attempts to address the question of optimal timing for conception, a 2011 study compared pregnancy outcomes in 104 women who conceived during the first year following bariatric surgery to outcomes from 385 women who conceived after the first year following bariatric surgery [32]. The study found no differences in

Table 12.2 Preconception counseling for women who have undergone bariatric surgery

• Recommend waiting 12–24 months prior to conceiving to maximize benefit of weight loss surgery and to avoid exposing the fetus to rapid changes in maternal weight
• Evaluate for micronutrient deficiency and supplement as necessary
• For women who have a history of infertility, complete an infertility work up of referring them to the appropriate specialist for evaluation if they fail to conceive within a reasonable amount of time

risks of hypertensive disorders, diabetes, adverse perinatal outcomes, or bariatric complications between the groups. Cautions regarding this study were raised however as the majority of the women studied had undergone restrictive procedures (88 %) vs. procedures incorporating malabsorption components like Roux-en-Y which carry a higher risk of nutritional deficiencies.

In a retrospective study spanning 3 years, pregnancies before 1 year (early group, 21 subjects) and after 1 year (late group, 13 subjects) following LRYGB were not statistically different in terms of fetal weight, term pregnancy, and obstetric complications [33]. However, the limitations of this study make it difficult to draw any strong conclusions. Namely, the two cohorts were statistically different in age at pregnancy, average BMI at pregnancy and average weight gain during pregnancy. Though no statistically significant differences were observed in the outcome measures, with larger cohorts, the trend observed in major complications may have resulted in a statistically significant difference between the groups.

Nutrition is an important issue post bariatric surgery, particularly in women who undergo malabsorptive procedures as they may experience deficiencies in iron, folate, vitamin B12, calcium, and vitamin D. All women should be screened for nutritional deficiencies prior to proceeding with pregnancy, and special supplementation is advised during pregnancy (Table 12.2).

Bariatric Surgery and Maternal/Neonatal Outcomes

Until recently, the data regarding maternal and neonatal outcomes was based on studies comparing outcomes from women who delivered post bariatric surgery to control populations. These data were summarized in a 2008 systematic review and meta-analysis published in the Journal of the American Medical Association demonstrating lower maternal complication rates including lower rates of gestational diabetes, and lower rates of preeclampsia after bariatric surgery compared to obese women without surgery. In regards to neonatal outcomes, this same paper found no differences between neonatal outcomes for children born to women who had undergone bariatric surgery and outcomes for children born to nonobese controls. The outcomes they looked at included premature delivery, low birth weight, and macrosomia.

Since 2008, several studies have been published suggesting that there may be an increased risk of preterm birth and small for gestational age in children born to mothers who have undergone bariatric surgery; however, none of these studies compare pregnancies in the same women pre- and post-surgery [34, 35]. More recently, in 2012, a group in Israel published a paired analysis investigating pregnancies in 144 women who had a child before bariatric surgery and one after between 1998 and 2008. This work demonstrated a reduction in maternal hypertensive disorders (31.9 % vs. 16.6 %, $p=0.004$), gestational diabetes (20.8 % vs. 7.6 %, $p=0.001$), and cesarean due to labor dystocia (5.6 % vs. 2.1 %) despite older age at second pregnancy (26.4 vs. 32.2 years, $p<0.001$) [36]. Importantly, eight of the women in the study were admitted to the hospital during their pregnancies for complications related to their bariatric procedures. These complications included anemia, vomiting or dysphagia, and gastric band slippage. Following pregnancies occurring between 2006 and 2012, this same group found similar outcomes for second deliveries after bariatric surgery suggesting sustainable benefits for maternal outcomes after bariatric surgery [37]. Neither of these studies found any benefit for the neonates born after bariatric surgery.

Since the surgical and physiologic fundamentals of bariatric surgery differ depending on type of surgery, it is important to consider difference in maternal and fetal outcomes when comparing one type of surgery to another. In a recent study published in 2012, authors investigated outcomes for 42 pregnancies in 36 women who had undergone bariatric procedures [38]. Twenty-two of the pregnancies were in women who had undergone LAGB, and 20 of the pregnancies in women who had undergone LRYGB. The authors found no difference in gestational age at delivery, fetal weight, maternal complications, or fetal outcomes for pregnancies in women who had LAGB versus LRYGB. Future comprehensive meta-analyses of pregnancy outcomes in women undergoing different surgical techniques would be helpful given the small size of many of these studies [34].

Conclusion

Bariatric surgery as a weight loss intervention has dramatically increased in the past 10 years for women of reproductive age. It has been shown to be an effective weight loss tool for many overweight and obese patients. The effect of surgical weight loss on future fertility is unknown and remains to be further investigated. Given there is sufficient data to show decreased pregnancy rates in obese women desiring to conceive, weight loss overall is beneficial to restoring normal reproductive function. However, whether bariatric surgery improves pregnancy rates and live birth rates remains to be elucidated, as similar cohorts of patients have not been adequately compared in the literature. Given there is evidence demonstrating altered reproductive hormone profile in obesity which reverts after weight loss surgery, bariatric surgery remains a sound option for women who desire relatively rapid weight loss and wish to maintain future fertility.

References

1. WHO. http://who.int/mediacentre/factsheets/fs311/en/
2. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med. 2005;142:532–46.
3. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. Ann Intern Med. 2005;142:547–59.
4. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg. 2014;149:275–87.
5. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart. 2012;98:1763–77.
6. Maggard MA, Yermilov I, Li Z, et al. Pregnancy and fertility following bariatric surgery: a systematic review. JAMA. 2008;300:2286–96.
7. Gosman GG, King WC, Schrope B, et al. Reproductive health of women electing bariatric surgery. Fertil Steril. 2010;94:1426–31.
8. O'Brien PE, Dixon JB, Laurie C, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. Ann Intern Med. 2006;144:625–33.
9. Friedman D, Cuneo S, Valenzano M, et al. Pregnancies in an 18-year follow-up after biliopancreatic diversion. Obes Surg. 1995;5:308–13.
10. Marceau P, Kaufman D, Biron S, et al. Outcome of pregnancies after biliopancreatic diversion. Obes Surg. 2004;14:318–24.
11. Livingston EH. Obesity and its surgical management. Am J Surg. 2002;184:103–13.
12. Santoro N, Lasley B, McConnell D, et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: the Study of Women's Health across the Nation (SWAN) Daily Hormone Study. J Clin Endocrinol Metab. 2004;89:2622–31.
13. Jain A, Polotsky AJ, Rochester D, et al. Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. J Clin Endocrinol Metab. 2007; 92:2468–73.
14. Gosman GG, Katcher HI, Legro RS. Obesity and the role of gut and adipose hormones in female reproduction. Hum Reprod Update. 2006;12:585–601.
15. Michalakis KG, Segars JH. The role of adiponectin in reproduction: from polycystic ovary syndrome to assisted reproduction. Fertil Steril. 2010;94:1949–57.
16. Brannian JD, Zhao Y, McElroy M. Leptin inhibits gonadotrophin-stimulated granulosa cell progesterone production by antagonizing insulin action. Hum Reprod. 1999;14:1445–8.
17. Welt CK, Chan JL, Bullen J, et al. Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med. 2004;351:987–97.
18. Panidis D, Farmakiotis D, Rousso D, Kourtis A, Katsikis I, Krassas G. Obesity, weight loss, and the polycystic ovary syndrome: effect of treatment with diet and orlistat for 24 weeks on insulin resistance and androgen levels. Fertil Steril. 2008;89:899–906.
19. Shah DK, Ginsburg ES. Bariatric surgery and fertility. Curr Opin Obstet Gynecol. 2010; 22:248–54.
20. Tortoriello DV, McMinn J, Chua SC. Dietary-induced obesity and hypothalamic infertility in female DBA/2J mice. Endocrinology. 2004;145:1238–47.
21. Tortoriello DV, McMinn JE, Chua SC. Increased expression of hypothalamic leptin receptor and adiponectin accompany resistance to dietary-induced obesity and infertility in female C57BL/6J mice. Int J Obes (Lond). 2007;31:395–402.
22. Terra X, Auguet T, Guiu-Jurado E, et al. Long-term changes in leptin, chemerin and ghrelin levels following different bariatric surgery procedures: Roux-en-Y gastric bypass and sleeve gastrectomy. Obes Surg. 2013;23:1790–8.

23. Uzun H, Zengin K, Taskin M, Aydin S, Simsek G, Dariyerli N. Changes in leptin, plasminogen activator factor and oxidative stress in morbidly obese patients following open and laparoscopic Swedish adjustable gastric banding. Obes Surg. 2004;14:659–65.
24. Teitelman M, Grotegut CA, Williams NN, Lewis JD. The impact of bariatric surgery on menstrual patterns. Obes Surg. 2006;16:1457–63.
25. Sharpe RM, Franks S. Environment, lifestyle and infertility—an inter-generational issue. Nat Cell Biol. 2002;4(Suppl):s33–40.
26. Jamal M, Gunay Y, Capper A, Eid A, Heitshusen D, Samuel I. Roux-en-Y gastric bypass ameliorates polycystic ovary syndrome and dramatically improves conception rates: a 9-year analysis. Surg Obes Relat Dis. 2012;8:440–4.
27. Eid GM, Cottam DR, Velcu LM, et al. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2005;1:77–80.
28. Legro RS, Dodson WC, Gnatuk CL, et al. Effects of gastric bypass surgery on female reproductive function. J Clin Endocrinol Metab. 2012;97:4540–8.
29. Musella M, Milone M, Bellini M, Sosa Fernandez LM, Leongito M, Milone F. Effect of bariatric surgery on obesity-related infertility. Surg Obes Relat Dis. 2012;8(4):445–9.
30. Doblado MA, Lewkowksi BM, Odem RR, Jungheim ES. In vitro fertilization after bariatric surgery. Fertil Steril. 2010;94:2812–4.
31. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 105: bariatric surgery and pregnancy. Obstet Gynecol. 2009;113:1405–13.
32. Sheiner E, Edri A, Balaban E, Levi I, Aricha-Tamir B. Pregnancy outcome of patients who conceive during or after the first year following bariatric surgery. Am J Obstet Gynecol. 2011;204:50.e1–6.
33. Dao T, Kuhn J, Ehmer D, Fisher T, McCarty T. Pregnancy outcomes after gastric-bypass surgery. Am J Surg. 2006;192:762–6.
34. Roos N, Neovius M, Cnattingius S, et al. Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study. BMJ. 2013;347:f6460.
35. Kjaer MM, Lauenborg J, Breum BM, Nilas L. The risk of adverse pregnancy outcome after bariatric surgery: a nationwide register-based matched cohort study. Am J Obstet Gynecol. 2013;208:464.e1–5.
36. Aricha-Tamir B, Weintraub AY, Levi I, Sheiner E. Downsizing pregnancy complications: a study of paired pregnancy outcomes before and after bariatric surgery. Surg Obes Relat Dis. 2012;8:434–9.
37. Amsalem D, Aricha-Tamir B, Levi I, Shai D, Sheiner E. Obstetric outcomes after restrictive bariatric surgery: what happens after 2 consecutive pregnancies? Surg Obes Relat Dis. 2014;10:445–9.
38. Facchiano E, Iannelli A, Santulli P, Mandelbrot L, Msika S. Pregnancy after laparoscopic bariatric surgery: comparative study of adjustable gastric banding and Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2012;8:429–33.

Chapter 13
Conclusions: Establishing an Ethically and Medically Sound Framework for Integrating BMI Limits into Infertility Care for Obese Women

Lisa M. Cookingham, Elizabeth M. Graf, and Ginny L. Ryan

Introduction

Obesity is an increasingly common comorbidity for women seeking infertility care in the United States (US) and other countries, and infertility care providers share the concerns of all women's healthcare providers regarding risks and costs of obesity-related complications of surgery, pregnancy, and delivery for these women. As this book has highlighted, maternal obesity also has a significant impact on the health of offspring in the first and even subsequent generations. This reality puts both the obese infertile population, who suffer deeply with infertility and with the challenge of losing weight, and their care providers, whose goal is to optimize reproductive outcomes, in a very difficult position.

In non-emergent medical interventions and surgical procedures, the standard of care is to proceed only when benefits outweigh the risks for the individual patient. Some surgeons and surgical groups in the United States have generalized this practice by implementing policies restricting certain procedures (such as joint replacements) to those under a particular body weight or body mass index (BMI), assuming that this will decrease procedural and postoperative risks and improve outcomes for these patients [1, 2]. No doubt these restrictions are also driven by a desire to decrease providers' liability and institutional costs. Cost has also been the major driver of BMI limits for infertility care in countries which subsidize this care, such as in Europe and Australia, with the understanding that these countries have an ethical obligation to control medical costs in the interest of population health [3, 4].

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In the United States, however, infertility care has been limited more by an individual's ability to pay for this care and by age limits than by federal or state regulations, medical comorbidity or sociodemographic category. In our Western, liberal democratic society, reproduction is considered a fundamental and compelling evolutionary, sociocultural, and personal interest for individuals and the community, though not so important as to compel adequate insurance coverage. Thus there must be a significant level of evidence that pregnancy is life-threatening or patients are unable to provide "minimally adequate or safe care for offspring" before practices can withhold assisted reproductive care. For example, disability, sexual orientation, and marital status alone are not considered valid reasons to withhold infertility care [5]. Nor has it been the general practice for individual clinics or federal regulators to restrict infertility care due to obesity-related costs, since this care is paid for through personal means or private insurance.

With the rise of extreme obesity in the United States, however, and the increasing rates of obesity-related complications for mothers and babies, there is a greater understanding that these complication costs are shared by all of society. There is also emerging evidence that obesity impacts the success of infertility care. All of this has resulted in a growing conversation about limiting infertility treatment, and especially assisted reproductive technologies (ART), in the United States based on BMI. In a recent online survey study of public opinion in this country, for example, 55 % of respondents supported BMI limits to access to ART [6]. The challenges for care providers motivated by compassion and guided by evidence is to weigh the ethical and medical issues involved in these policies, implement them fairly and appropriately, and focus on medical rather than social outcomes. Obesity must be understood by both patient and provider to be a medical risk factor for experiencing infertility and for treatment failure, as well as for suboptimal pregnancy outcome. In this way, BMI limits may be appropriately framed as medical goals rather than social judgments.

Background for Our Policy: "One Healthy Baby at a Time"

In our center's infertility practice, we are guided by the goal, "One Healthy Baby at a Time." From this goal has arisen a successful mandatory single-embryo transfer policy for in vitro fertilization (IVF) patients who have very good prognosis for success. This policy, instituted in 2004, is applicable clinic-wide and for all practitioners, and this consistency has been vital to the policy's just application and the ability to track outcomes. Patients have demonstrated understanding that this policy is motivated not by desire to restrict their autonomy but to optimize safe outcomes for their families, and the rate of risky multiple gestations in our program has decreased by 50 % [7]. An important component of this policy has been early notification of patients through preappointment informational materials and counseling at their initial intake appointment.

Our practice also has previous experience with limiting treatment based on BMI for those patients who desire to use our shared risk (commonly known as "war-

ranty") program for IVF payment. This program was developed for those who have no insurance coverage for IVF, and it offers significant reimbursement to qualified patients who do not achieve an ongoing pregnancy. Because this program involves shared financial risk between our IVF practice and the patient, it has been considered ethically and medically appropriate for the practice to limit enrollment to those patients with the best chance of pregnancy success. Identifying that extreme obesity is associated with a lower chance of conception and ongoing pregnancy, we have limited our shared risk program to those patients with a BMI under 40. Again, this policy is practice-wide and fairly applied, and experience has shown that patients often have good success with losing weight to meet qualifications when motivated by this economic incentive.

Individual infertility providers in our practice had been intermittently setting BMI limits for all infertility treatments (including oral ovulation induction and intrauterine insemination) for a number of years, especially for those patients who have other medical comorbidities such as uncontrolled diabetes or hypertension. This was sometimes unjust and frustrating, however, due to inconsistent application between different patients seeing the same provider and between different providers seeing the same patient. As a result, there was a call from within our practice for a consistent, specific, and medically supported protocol for limiting treatment based on BMI while incorporating other medical comorbidities and age.

At our academic hospital, we have experienced multiple cases of obesity-related complications in our fertility clinic and labor and delivery unit. From infertility treatment failures to technically difficult oocyte retrievals that challenge anesthesiologists or cause excessive blood loss, these complications were undeniably related to the body habitus of the patients involved. Even more alarming were two separate cases of maternal deaths resulting from obesity-related complications of pregnancy and delivery. It was these latter 2 cases that put a tragic face on this issue and provided the final impetus to begin to develop our policy on obesity and infertility care in late 2012.

At the outset of establishing this policy, we were acutely aware that this practice could be viewed as discriminatory, offensive, or unethical. We wanted to ensure that our policy was not a manifestation of subconscious bias but instead a practical tool to focus our conscientious practice of reproductive care resulting in healthy outcomes for moms and babies. Thus prior to devising any specific guidelines, we investigated the pertinent medical literature, including guidance from our professional organizations, and other sources of ethical guidance that could best direct our efforts.

Professional Guidelines

The American Congress of Obstetricians and Gynecologists (ACOG) currently provides no specific guidance regarding the propriety of restricting infertility care or discouraging pregnancy based on BMI criteria. ACOG has clearly acknowledged obesity-related problems in reproductive-age women, however, with multiple publications citing specific recommendations for obese women who are pregnant or

seeking preconception care. In a recent *Committee Opinion* from January 2013, recommendations include preconception assessment and counseling for obese women, including "provision of specific information concerning the maternal and fetal risks of obesity in pregnancy" as well as "encouragement to undertake a weight-reduction program" [8]. ACOG also recommends that all overweight and obese women be offered a consultation with a nutrition specialist and encouraged to partake in an exercise program; additionally, ACOG recommends that counseling should continue in the postpartum period and prior to attempting pregnancy again [8]. Furthermore, ACOG has supported initiatives to tackle obesity, such as the "OBesity Project," which aims to educate providers and patients about the consequences of obesity in an obstetric population [9].

Like ACOG, the American Society for Reproductive Medicine (ASRM) provides no specific guidance regarding restricting fertility care based on BMI criteria. In 2008, an *Educational Bulletin* published by ASRM acknowledged that obesity has an adverse effect on assisted reproductive technologies (ART) success, including decreased rates of fecundity and increased rates of miscarriage [10]. Specific recommendations for preconceptual counseling of obese women were outlined, advising providers to discuss the medical, obstetric, and neonatal consequences, as well as the long-term implications, of obesity on the patient and potential offspring [10]. No explicit recommendations are detailed regarding alterations of, or restrictions on, fertility treatment in obese women; however, ASRM does emphasize diet and exercise as the first-line treatment for obesity-related infertility [10].

Despite the lack of specific guidance from ACOG and ASRM regarding restrictions, one group's publication describes what is actually occurring in fertility clinics across the country. Harris et al. found in 2011 that 42.9 % and 54.8 % of these clinics actually have a BMI cutoff for controlled ovarian hyperstimulation and IVF, respectively, and a full 73.2 % and 82.9 % of survey respondents thought a BMI cutoff should exist for these 2 treatment types, respectively [11]. The study reported that clinics use a variety of cutoffs for BMIs ranging from 30 to 55 kg/m^2, with a mode and median of 40 kg/m^2. The authors suggest there is already a practical consensus among providers of fertility care that guidelines should exist and that a national recommendation would be advantageous in developing policies that are acceptable, both medically and ethically.

Principle-Based Ethics: Beneficence

According to ACOG, beneficence "means doing or producing good," and "expresses the obligation to promote the well-being of others" [12]. This principle obliges providers to act in a manner most likely to benefit the patient. As evidenced in our Introduction, beneficence was the primary reason for developing this policy and the guiding principle throughout the development process. The shared physician and patient goal of a favorable outcome from any fertility treatment applies to all patients, whether obese or not. With this in mind, restricting treatment to patients

that are not in optimal health, based on BMI and/or laboratory abnormalities, was incorporated to optimize the chance of a favorable outcome for both the patient and the potential offspring. Encouraging safe weight loss and therapeutic lifestyle changes not only increases the opportunity to achieve this shared goal, but also has a beneficial impact on the patient's overall health status. Additionally, we strongly encourage partners to participate in these changes with our patients in an effort to promote the well-being of the couple and family.

Principle-Based Ethics: Non-maleficence

The principle of non-maleficence goes hand-in-hand with the principle of beneficence. Non-maleficence is most commonly recognized by the Latin phrase *primum non nocere*, which means "first, do no harm." It requires that providers not intentionally cause harm or injury to their patients and do their best to avoid foreseeable harms. When considered with beneficence, the principles together direct that providers on balance strive to do more good than harm. This supports our concern regarding the potential risk for complications resulting from fertility treatment, including the harm that could result from difficult fertility procedures, such as oocyte retrievals, and the potential complications of pregnancy and delivery that may have never occurred if we had not assisted with the pregnancy's conception. If we as physicians are aware of the increased rate of medical complications that can arise from an obese woman carrying a pregnancy (i.e., gestational diabetes, gestational hypertension, preeclampsia) and the increased rate of operative and postoperative complications that can arise from an obese woman delivering a baby (i.e., excessive blood loss, wound breakdown and infection, endometritis), is it ethically sound to assist in achieving pregnancy?

Principle-Based Ethics: Justice

The principle of justice is often separated into "commutative" justice, implying an obligation to treat all people equally according to their particular need, and "distributive" justice, implying an obligation to equitably allocate goods in a society [12]. Distributive justice is an important consideration in healthcare systems where infertility care is publicly funded and resources are limited. In New Zealand, for example, a system was developed to prioritize access for patients seeking publicly funded fertility treatments and patients were excluded if their BMI was >32 kg/m^2. Commentators suggested that the system encouraged a healthy lifestyle and reinforced the public health message of obesity as a major health problem, and that weight loss achieved by patients in order to partake in publicly-funded treatments was "good medicine" as demonstrated by decreased obstetric complications and improved neonatal health, with concurrent reduction in the cost of ART overall [13]. While infertility care is not publicly funded in the United States, it would be naïve

to ignore the impact that complicated pregnancies and deliveries, unhealthy children, and multigenerational obesity has on societal costs. Furthermore, better controlling these costs related to obesity and pregnancy may help facilitate improved insurance coverage for infertility care.

Commutative justice is more difficult to apply to infertility care policies related to obesity. If obesity were solely a societal categorization without substantive health impacts, such as marital status or sexual orientation, it would be unjust to treat anyone differently in provision of medical care based on their BMI or body weight. As previous chapters have evidenced, however, significant obesity more often carries with it important health risks for moms, babies, and future generations and thus weight categorizations are more than simply societal groupings. In developing our obesity and infertility policy, however, we wanted to be inclusive of our entire population and not just those whose BMI and other medical comorbidities put them out of the range of immediate infertility treatment. Thus our goal is to share the policy, and each patient's BMI, with all of our patients through distribution of the "Obesity and Infertility" information and policy description sheet. In this way, all patients can see that we have identified obesity as an important medical morbidity for reproductive-age women, can situate their own weight (and their partner's weight) in comparison to the normal range, and can ask about resources to assist in their own efforts to maintain a healthy weight.

Principle-Based Ethics: Respect for Autonomy

The principle of autonomy "acknowledges an individual's right to hold views, to make choices, and to take actions based on her own personal values and beliefs" [12]. With regard to reproduction, patients have the right to place their own values on childbearing and to make choices regarding their health and healthcare based on those views. Providers are obligated to inform patients of the risks, benefits, and alternatives to their medically indicated options for infertility care. After providing complete information, respect for autonomy suggests that providers respect the decision-making capacity of the patient herself. This does not mean, however, that the patient can demand any treatment "carte blanche," regardless of medical propriety. Respect for autonomy must be balanced by a physician's right to practice medicine in accordance with his or her conscientious practice.

Conscientious Practice

A controversial topic in the field of obstetrics and gynecology at times, conscientious practice is most commonly invoked when a healthcare provider refuses to provide a legal medical intervention such as abortion or emergency contraception based on her own religious or moral views. As noted above, however, conscientious practice may also be used to describe a physician's day-to-day practice of weighing an

individual's risks and benefits related to a particular procedure or medical option and deciding that this particular option is not medically appropriate for that patient in those circumstances. While the provider should be allowed to make this determination on the basis of conscientious practice in the case of clear medical evidence, great care must be taken to avoid the practice, or even appearance, of paternalistic and prejudicial judgment.

Our Obesity and Infertility Care Policy: Development and Implementation

We spent several months reviewing the above resources and the medical literature, as well as holding formal and informal meetings to discuss parameters of the policy with all team members (physicians, embryologists, nurses) in our Reproductive Endocrinology and Infertility division as well as our Obstetrics and Gynecology department. We also sought feedback from our Hospital Advisory Committee's Ethical Issues Subcommittee. In general, we met with less resistance in these meetings than we anticipated, as there was a shared understanding of the significant reproductive risks of obesity. Colleagues provided guidance on similar policies in place in their particular subspecialties, and most discussion involved the clinical evidence for particular BMI cutoffs and the propriety of mandatory referrals and laboratory assessment.

The Ethical Issues Subcommittee "considered both medical and ethical issues involved in the policy, with focus on a variety of interrelated questions, including: reproductive freedom, the difference between positive and negative rights, the best interests of the potential mother, the best interests of the potential child, distributive justice and resource allocation, the conscientious practice of professionals, and analogies to other clinical contexts that involve obesity or behavioral constraints." (Minutes of the Meeting of the Ethical Issues Subcommittee, November 13, 2012, The University of Iowa Hospitals and Clinics). A key point that arose in this discussion was the fact that reproduction is currently considered a negative right rather than a positive right; in other words, women and families should be free from interference in pursuing their reproductive goals but care providers should not feel compelled to assist in attaining these goals to the detriment of their patient's well-being and against their own medical judgment.

Early in the process we recognized the need to provide medically appropriate and readily available weight loss assistance to obese patients, and especially those patients whose BMI and/or other medical comorbidities would not immediately allow them to proceed with infertility treatment. We consulted with providers specializing in weight management, exercise physiology, nutrition, and perinatology, and partnerships were solidified. Our goal was to have these referral services readily available for our obese patients in order to optimize the complete and multidisciplinary management of their infertility and obesity.

In addition to developing resources for our patients, we also wanted to ensure that our staff and referral sources were equipped for the implementation of our policy.

We created talking points for our schedulers so they could inform new and existing patients of the change in our practice. Within our electronic medical record system, we created premade phrases that could be utilized in clinic notes and in letters to new and returning infertility patients. Additionally, we attempted to contact all known referrers by letter (including the 2-page information sheet and policy description, see Box 13.1) so they were aware of the policy prior to transferring patient care

Box 13.1 Obesity and infertility information sheet and policy description

UNIVERSITY of IOWA HOSPITALS & CLINICS
University of Iowa Health Care

Department of Obstetrics & Gynecology

Division of Reproductive Endocrinology & Infertility
200 Hawkins Drive
Iowa City, IA 52242-1080
319-356-1767 REI Scheduling
319-356-8483 IVF Scheduling

Obesity and Infertility

This section to be completed by provider:

Your current weight _____ Your BMI _____
Your target weight_____ Your target BMI _____
Your partner's current weight _____ Your partner's BMI _____

Primary Care Provider _____

BMI	Weight Status
18.5-24.9	Normal
25-29.9	Overweight
30 and Above	Obese
40 and Above	Morbidly Obese

What is BMI and how is it used?
BMI is a number calculated from a person's weight and height, and is a fairly reliable indicator of body fatness for most people. It is used widely as a screening tool to identify possible weight problems in adults. It is often used along with other tests, such as evaluations of diet, physical activity, family history of disease, blood pressure measurements, and laboratory tests of blood sugar and cholesterol, to estimate risks of disease in a person.

What are the effects of obesity on getting pregnant?
There is strong evidence that getting pregnant is easier with a normal body weight, which is generally found with a BMI between 20 and 25 (see above). When a person has a BMI above 25, there is a lower natural pregnancy rate and a lower chance of responding to fertility treatment. This gets worse as the BMI gets further away from the normal range.

One reason for reduced fertility rates with increasing weight is a higher chance of anovulation, meaning an egg is not released each month. Numerous studies have shown that weight loss of 5 to 10% can result in return of ovulation and improved fertility. Even with our most advanced treatments such as in vitro fertilization (IVF), pregnancy rates are reduced in a person who is obese. Obesity makes the IVF procedures of egg retrieval and embryo transfer more difficult. Even when these procedures go well, there is increasing evidence of a lower IVF pregnancy rate in obese patients.

What are the effects of obesity on pregnancy?
There are a number of increased risks for obese women who are pregnant. These include a higher rate of blood clot formation, high blood pressure during pregnancy, miscarriage, and stillbirth. It is also more common for obese women to deliver a premature baby. There is an increased risk of gestational diabetes, which can be difficult to manage and can lead to larger babies, more difficulty with delivery (often requiring a C-section), and some early blood sugar problems with the baby. If an obese woman has a C-section, she is more likely to have

Box 13.1 (continued)

problems with healing than a woman with a normal weight. There is also some evidence to suggest that birth defects are more common in babies born from obese women.

What are the effects of obesity on my partner?
It is also important to consider the influence that partners have on dietary and exercise habits of others in the household. Also, overweight and obese men are more likely to have lower sperm counts with lower motility (normal sperm movement), and this may impact the chance of getting pregnant naturally or having a successful fertility treatment.

For all these reasons, we think it is very important that women attempt to lose weight prior to achieving a pregnancy through infertility treatment. It would be ideal if this weight loss effort was shared by your partner, especially if your partner's BMI is also in the overweight or obese category.

This is why we have established the following policy within our program:

Obesity and Infertility Care Policy

If BMI <30:
- Begin / continue treatment with standard preventive care measures.

If BMI 30 – 39.9:
- Begin / continue treatment with standard preventive care measures and encouragement of safe weight loss through therapeutic lifestyle change.

If BMI 40 – 49.9 and age ≥35 or ovarian reserve testing abnormal:
- Check that patient has been screened for glucose, lipid, endometrial and blood pressure abnormalities.
- Proceed with treatment while encouraging safe weight loss.

If BMI 40 – 49.9 and age <35 with normal ovarian reserve testing (or donor egg recipient):
- Check that patient has been screened for glucose, lipid, endometrial and blood pressure abnormalities.
- Primary care provider or similar consultant may recommend bariatric surgery.
- If Hgb A1c ≥6.5% and/or there are significant medical problems that could be improved with weight loss, patient must undergo an effort at therapeutic lifestyle change and medical management for at least 6 months, and may consider bariatric surgery if appropriate. HgbA1c must be below 6.5% before initiating treatment.
- If Hgb A1c <6.5% and no significant medical problems, encourage safe weight loss and proceed with treatment.

If BMI ≥ 50
- Infertility evaluation may continue. Treatment will be initiated only when BMI falls below 50 (see details in above category for BMI 40 – 49.9). Glucose, lipid, endometrial and blood pressure abnormalities should be screened for, preferably through co-management with the patient's primary care provider or other Internist or Family Practitioner. Active therapeutic lifestyle change should be encouraged and co-managed, and bariatric surgery consultation considered.

NOTE: There is no policy related to a partner's BMI, however we strongly encourage partners to share therapeutic lifestyle change and work towards safe weight loss, especially for obese men.

to our team. As with the single-embryo transfer policy described above, we felt strongly that patients should be made aware of this policy early in their relationship with our clinic. Thus, we included our 2-page information sheet and policy description with our scheduling letters and information packets for all new infertility patients. Following these measures, a date was set to implement the policy.

Challenges in Development: Medically Appropriate Limits

As mentioned above, this issue was the most common source of discussion during development of our policy. While many measures of well-being worsen even with mild and moderate obesity, it is also true that many obese women have very healthy pregnancies and long and active lives. Comorbidities that tend to track with obesity, such as hypertension and glucose intolerance, are more risky to certain pregnancy and delivery outcomes than the obesity itself, yet it is hard to predict whether a particular woman will manifest these comorbidities during a future pregnancy. It is also difficult to decide upon a level of increased risk, or decreased efficacy, which is compelling enough to warrant delay in a much desired treatment for infertility. Furthermore, there is little evidence in the literature looking at reproductive outcomes for women in the very highest BMI categories or reproductive outcomes specifically for obese women treated for infertility.

Our experience with a BMI limit of 40 kg/m^2 in our shared risk IVF program has generally been positive, with interested couples demonstrating motivation and success in meeting this criterion. The survey of infertility clinics in the United States noted above also suggests physicians feel that 40 kg/m^2 may be a reasonable limit for provision of IVF treatment [11]. Other countries with subsidized infertility care set limits that are significantly lower, such as 30 kg/m^2 in England (http://www.hfea.gov.uk/fertility-treatment-cost-nhs.html#1). For a woman who is 5 ft 4 in. tall, a BMI limit of 40 kg/m^2 or 30 kg/m^2 means she could weigh up to 230 lb or 175 lb, respectively, and still receive care. By way of comparison, the average adult woman in the United States is 5 ft 4 in. tall and weighs 166 lb [14]. Since we were very motivated by medical indications in development of this policy, we decided that the evidence was less equivocal regarding the reproductive risks of very severe obesity, and thus we chose 50 kg/m^2 as our limit to start. This means that a woman of average height can weigh up to 290 lb and still receive infertility care in our clinic, assuming that other medical untreated comorbidities do not exist. While this is our upper limit for now, we are certainly open to lowering this BMI limit as medical knowledge and policy efficacy dictate.

Challenges in Development: Time-Sensitivity

Since acute weight loss may be just as detrimental to a woman's health and the efficacy of their infertility treatment, we encourage steady but moderate weight loss supervised by a primary care physician. Unfortunately, for women in their late 30s and early 40s and those with diminished ovarian reserve, time is of the essence in proceeding with infertility treatment. As described in our policy, we understand that not all patients have the time needed to make effective lifestyle changes leading to weight loss and improved glucose control, and thus there are exceptions to our BMI policy for situations such as these when BMI is between 40 and 49. Similarly, if oocyte freezing is sought for fertility preservation prior to cancer

treatment, for example, exceptions to the policy can be made. As a practice, we reserve the right to discuss particular medical situations as a group and make rare exceptions to our policy, always keeping in mind the primacy of the health of our patients and their offspring.

The issue of time also arose in considering how improved obesity counseling and support from our physicians, nurses, and schedulers would likely increase the length of clinic visits and amount of clinical work. Efforts were made to have resources readily available to faculty and support staff to facilitate these efforts (see Box 13.1), but there is no question that effective obesity care takes additional time in clinic, and more clinic visits. Our expectation is that making obesity care a routine part of the whole team's practice will result in improved efficiency and efficacy over time.

Challenges in Development: Readability and Utility of Policy

We initially considered developing a larger number of policy-related resources that would meet the needs of patients, support staff, nursing, and physicians. This quickly became confusing, however, and we decided instead to simplify our 2-page information sheet and policy description. This 2-page document became an informational resource for previsit patients, a worksheet for patient-provider interactions, and a reference for practice physicians and nurses and referring providers. In order to effectively meet all of these needs, the document had to be thorough but concise and relatively simple to read. We recognize that the final result may not be fully understandable by patients of every reading level; however, we plan to overcome this issue by working through the document in person with each patient so that the message is personalized.

Challenges in Development: Prepayment for Infertility Care

One of our main reasons to inform patients and referring providers of this obesity and infertility care policy prior to their first visit is to avoid the situation where a patient prepays for her visit upon arrival and then is informed that she is not a candidate for immediate infertility intervention due to her BMI and/or medical comorbidities. All patients will still receive a full evaluation and comprehensive treatment plan, including plans for weight management. While we hope that this is well worth the cost of a visit, we understand that patients do not expect to face further delays to their conception plans when they present to an infertility clinic. This frustration can be exacerbated by the long distances that some of our patients travel from within and outside of the state to seek care. Advance information and careful clinical counseling will be vital to avoiding this unfortunate situation.

Response and Evaluation

Despite the fairly recent introduction of our Obesity and Infertility Care policy, we have already received an overwhelmingly positive response from both our internal women's healthcare providers and from referring providers. Some have commented that the policy was overdue, and we have had suggestions to lower the BMI limit further. We have also heard that referring providers use this information to counsel and encourage their patients to work towards a healthier BMI as part of their infertility management.

In general, patients who have been thoroughly counseled regarding the rationale behind such a policy have responded positively as well. We have had a few patients who have disapproved of the restrictions, and it is difficult to know how many patients have gone elsewhere for care after learning of our policy. This would be a regrettable outcome of policy introduction, since we are in a stronger position than ever to effectively and safely provide high-quality infertility care to our patients after mobilizing available resources for obesity treatment.

While we recognize that the policy is not without flaw, we will continue to refine and reevaluate our guidelines based on evolving medical evidence, our clinical outcomes, and changes in local healthcare resources. We look forward to conducting formal research into the acceptance and impact of the policy on our patients and providers, and we are dedicated to providing full evaluation and treatment planning for any patient that seeks our assistance, regardless of BMI status. We hope to set an example for other practices and offer guidance for other infertility care providers in an effort to improve the health of women nationwide. Even though infertility care providers often interact with women for a limited time during their reproductive lives, and most do not provide obstetrical care for the pregnancies whose conception they assist with, as obstetrician/gynecologists we cannot ignore the fact that we have a vital role in the health and well-being of our patients, their offspring, and their families. It is very clearly our responsibility to identify obesity in our patients and facilitate treatment in a medically and ethically appropriate manner.

References

1. Hayashi A. Pearls and pitfalls: orthopaedics and obesity. http://www.aaos.org/news/aaosnow/jun09/clinical1.asp. Accessed 11 May 2013.
2. Preoperative Body Mass Index (BMI) evaluation for total joint replacement patients. http://www.flagstaffboneandjoint.com/pdf/preoperative-body-mass-index.pdf. Accessed 11 May 2013.
3. Assessment and treatment for people with fertility problems. NICE Clinical Guidelines CG156, Recommendation 1.2.6.3 and 1.5.2.1. National Institute for Health and Care Excellence. 2013. http://publications.nice.org.uk/fertility-cg156/recommendations. Accessed 11 Dec 2013.
4. Balen AH, Anderson RA. Policy and Practice Committee of the BFS. Impact of obesity on female reproductive health: British Fertility Society, Policy and Practice Guidelines. Hum Fertil (Camb). 2007;10(4):195–206.
5. The Ethics Committee of the American Society for Reproductive Medicine. Access to fertility treatment by gays, lesbians and unmarried persons. Fertil Steril. 2009;92:1190–3.

6. Shah DK, Ginsburg ES, Correia KF, Barton SE, Missmer SA. Public opinion regarding utilization of Assisted Reproductive Technology (ART) in obese women. J Womens Health (Larchmt). 2013;22(11):978–82.
7. Kresowik JD, Stegmann BJ, Sparks AE, Ryan GL, van Voorhis BJ. Five-years of a mandatory single-embryo transfer (mSET) policy dramatically reduces twinning rate without lowering pregnancy rates. Fertil Steril. 2011;96(6):1367–9.
8. American College of Obstetricians and Gynecologists. Obesity in pregnancy. Committee opinion No. 549. Obstet Gynecol. 2013;121:213–7.
9. Barmat LA, Barnhart K, Baxter J, Blumenthal SL, Edelson M, Ekbladh L. et al. The obesity project—the obesity epidemic in OB/GYN. http://mail.ny.acog.org/website/Obesity/OBesity_Project_Final_102012.html. Accessed 11 Dec 2013.
10. Practice Committee of American Society for Reproductive Medicine. Obesity and reproduction: an educational bulletin. Fertil Steril. 2008;90 Suppl 3:S21–9.
11. Harris ID, Python J, Roth L, Alvero R, Murray S, Schlaff WD. Physicians' perspectives and practices regarding the fertility management of obese patients. Fertil Steril. 2011;96(4):991–2.
12. American College of Obstetricians and Gynecologists. Ethical decision making in obstetrics and gynecology. ACOG Committee opinion no. 390. Obstet Gynecol. 2007;110:1479–87.
13. Farquhar C, Gillett W. Prioritising for fertility treatments—should a high BMI exclude treatment? BJOG. 2006;113:1107–9.
14. Body Measurements. Measured average height, weight, and waist circumference for adults ages 20 years and over. http://www.cdc.gov/nchs/fastats/bodymeas.htm Source: Fryar CD, Gu Q, Ogden CL. Anthropometric Reference Data for Children and Adults: United States, 2007-2010 (Tables 4, 6, 10, 12, 19, 20). National Center for Health Statistics. Vital Health Stat 2012;11(252).

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