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# Obesity and Reproductive Function

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## SYNOPSIS

Obesity is associated with multiple adverse reproductive outcomes, but the mechanisms involved are largely unknown. Public health scientists studying obesity and its effects on health outcomes have referred to obesity as a “complex system”, defined as a system of heterogeneous parts interacting in nonlinear ways to influence the behavior of the parts as a whole[1,22]. By this definition, human reproduction is also a complex system which may explain some of the difficulty in identifying the mechanisms linking obesity and adverse reproductive function. Despite the difficulties, research on obesity and reproduction is important as there is an epidemic of obesity among reproductive age women with associated consequences for future generations. In this review we discuss the adverse reproductive outcomes associated with obesity and data from translational studies of the mechanisms involved. We conclude with a brief discussion of public health policy as it relates to the treatment of infertility in obese women.

### Keywords

fertility; obesity; reproduction; public health

## MEASURING OBESITY AND REPRODUCTIVE RISK

Disentangling the individual components of obesity associated with poor health outcomes is difficult. Body mass index (BMI) or overall body size adjusted for height, is obviously, the most accessible measure of obesity as the tools for measuring BMI are readily available. On the other hand, adiposity (regional or total body fat), adipokine production, and lifestyle components may also contribute individually or together to overall obesity-related health risk. The bulk of the work relating obesity to health risks has focused on chronic diseases, however, we are learning more about components of obesity that relate to reproductive risk.

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## Body mass index

In general, the risk of obesity-related reproductive morbidity is associated with increasing BMI. BMI categories are as follows:

- Overweight 25–29.9 kg/m$^2$: increased disease risk
- Class I obesity 30–34.9 kg/m$^2$: high disease risk
- Class II obesity 30–34.9 kg/m$^2$: very high disease risk
- Class III obesity ≥ 40 kg/m$^2$: extremely high disease risk[3]

These standard BMI categories are born out of associations made between obesity and risks of developing chronic conditions like diabetes and cardiovascular disease. While these conditions may exist in some obese women of reproductive age, many of these young women have not had long enough exposure time to manifest these diseases. Instead, signs of poor reproductive function like anovulation and/or subfertility may be the first obesity-related morbidity younger women experience. Standard BMI categories were not developed to relate the risk young women face of poor reproductive function. Despite this, BMI is the measure used most often in counseling obese women regarding the reproductive and pregnancy risks. In fact, some providers and practice organizations advocate for restricting fertility treatment to women based on BMI[4].

There may be more specific measures associated with reproductive risk in obese women as BMI represents a measure of total body energy balance. Recent translational work has demonstrated that better predictors of metabolic risk and disease may exist such as quantity of visceral adipose tissue, and intrahepatic triglyceride content[5]. Also, epidemiologic work has shown strong associations between lifestyle factors such as diet and physical activity and risk of cardiovascular disease, both of which influence energy balance and BMI, but are independent factors[6,7]. Whether or not there are better markers than BMI of obesity-related reproductive risk is yet to be determined. Further study of relationships existing among adipokines, various measures of adiposity, and lifestyle factors such as diet and physical activity and reproductive outcomes may prove useful. In the meantime studies of reproductive risk and obesity that categorize risk by BMI represent the majority of the data that can be used clinically in counseling obese women.

## Adipokines

Adipokines are signalling molecules produced by adipose cells and their production varies with adipose mass. Adipokines that may be important to obesity-related morbidity include leptin, tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), free fatty acids, and adiponectin[8–10]. Abnormalities in adipokines may cause inflammation and abnormal cell signalling which in turn lead to impaired cellular metabolism and function.

Emerging evidence links abnormalities in adipokines to abnormal reproductive function[8]. For example, leptin may affect reproductive function at the level of the hypothalamus, providing both the signal to initiate reproductive maturation and to maintain normal signalling of the hypothalamic-pituitary-ovarian axis[8,11, 4]. This has been demonstrated in a mouse model of diet-induced obesity in which hyperleptinemia causes central leptin resistance and hypogonadism[11]. Such a mechanism could explain findings of altered pulsatile luteinizing hormone amplitude in obese women[12]. Also, leptin and TNFα levels vary between follicular and luteal phases of the menstrual cycle[8]. Although the significance of these variations in adipokines between the stages of the menstrual cycle is unknown, it is possible they may affect signalling within the hypothalamic-pituitary-ovarian axis required for normal oocyte recruitment and ovulation. Other work has demonstrated that adiponectin signalling may be important to pre-implantation embryonic development and implantation[13].

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We have recently shown that elevated free fatty acid levels are associated with impaired oocyte maturation and decreased chances of pregnancy[14,15]. The specific role of various adipokines in reproductive function is largely unknown, but the aforementioned examples suggest they may provide an important link between obesity and pathologic reproductive function.

## Lifestyle: Dietary factors

Dietary choices that contribute to obesity may also play a role in the adverse reproductive outcomes associated with obesity. The potential role of diet in reproductive function has been elegantly demonstrated through work with the Nurses Health Study II (NHSII), a prospective epidemiologic cohort study in which the lifestyle patterns of nurses are tracked and long term health outcomes are followed. In a series of publications, dietary choices such as vegetable sources of protein over animal proteins, and limiting intake of trans-fats and refined carbohydrates have been shown to be associated with decreased risks of ovulatory infertility independent of BMI and total caloric intake[16–18]. Work demonstrating that dietary changes improve ovulatory function in anovulatory obese women has yet to be done but certainly the prospective research that has come from NHSII on lifestyle and ovulatory infertility is intriguing and offers clinicians and their patients a place to institute lifestyle changes that may help with weight loss which does improve ovulatory function in obese women[19].

*Lipotoxicity* is one mechanism by which fat intake may influence reproductive tissues[20–24]. This process is characterized by excess circulating long-chain saturated fatty acids which are produced by adipocytes themselves and also obtained through the diet. When the adipocytes can no longer store these fatty acids other non-adipose cell types begin to store fat. This leads to an increase in the production of reactive oxygen species with subsequent mitochondrial dysfunction, endoplasmic reticulum stress and ultimately cell death[25]. Reproductive tissues affected include granulosa cells and oocytes leading to impaired oocyte maturation and poor oocyte quality[24,26]. In a murine model, we have recently shown that brief pre-implantation embryonic exposure to excess palmitic acid, a long chain saturated fatty acid obtained through the diet and produced by adipocytes, can result in fetal growth restriction with subsequent post-delivery catch up growth and a metabolic-like syndrome in adulthood[21]. Whether or not this work is representative of what happens in the human condition is unknown, however, it does suggest pre and peri-conceptional diet and obesity have long-term, lasting impact on the offspring.

## Lifestyle: Physical activity

Lack of physical activity decreases energy expenditure and contributes to developing and continuing obesity. Whether or not lack of activity and exercise directly contribute to the pathophysiologic mechanisms linking obesity to disease is unclear.[27] On the other hand, in another analysis using NHSII data that controlled for BMI, women with the highest levels of physical activity were less likely to suffer from ovulatory infertility than women who had low levels of physical activity.[19] In another recent study of physical activity and time to pregnancy, increased physical activity levels were associated with decreased time-to-pregnancy.[28] Altogether, poor dietary choices and decreased levels of physical activity contribute to the development and sustenance of obesity[27], and therefore physical activity may be an important component to improve reproductive function in the setting of obesity.

## A culmination of risk factors: Adverse reproductive outcomes in obesity

**Anovulation—**Increasing BMI and obesity are associated with increased reproductive risks including menstrual irregularities, typically a result of anovulation[29]. Metabolic abnormalities induced by obesity, like insulin resistance, may promote the development of

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polycystic ovary syndrome (PCOS), a condition diagnosed by the presence of oligomenorrhea and hyperandrogenism, however, not all anovulatory obese women meet these diagnostic criteria. As discussed, adipokines may have effects on hypothalamic-pituitary signalling and communication that inhibit ovulation, and pose another mechanism by which obesity may increase the risk of irregular menses and anovulation[11,12]. Different women may have a different threshold for anovulation at various different body weights and overall adiposity as hypothalamic-pituitary signalling depending on other environmental exposures and genetic factors[30].

**Subfertility—**While anovulation certainly contributes to subfertility among obese women, even in obese women with regular cycles, time to pregnancy is increased compared to women of normal weight[31]. It has been argued this is due to decreased frequency of sexual intercourse among obese women, however, in work done through the NIH-sponsored Reproductive Medicine Network's Pregnancy in Polycystic Ovary Syndrome Trial, obesity was not associated with decreased frequency of sexual intercourse in couples trying to conceive[32]. Whether or not subfertility in ovulatory obese women is secondary to poorer oocyte or embryo quality, impairments in embryo implantation, or a combination of all of these factors is unknown.

**Miscarriage—**It is difficult to get a true measure of the risk of miscarriage among obese women who conceive spontaneously as many women with early pregnancy loss may not realize they are pregnant and therefore may never present to their physicians. This may be especially true for obese women with irregular menses. On the other hand, studies of women undergoing fertility treatments offer a unique opportunity to capture preconceptional exposures like obesity and relate these preconceptional exposures to reproductive outcomes like miscarriage and others including ovulation, time to pregnancy, pregnancy risks, and neonatal outcomes[33]. Despite the opportunity for preconceptional exposures that infertile women and women undergoing assisted reproductive technology offer for such measures, data from a recent meta-analysis of obesity and miscarriage risk demonstrate that in general obesity is associated with an increased risk of miscarriage, however, the evidence linking obesity to increased risk of miscarriage in women undergoing assisted reproductive technologies is insufficient.[34] It is possible that ART may counter the increased risks of miscarriage in the setting of obesity by allowing for selection of better embryos and therefore lower risk of miscarriage, improved endometrial conditions through administration of supraphysiologic doses of gonadotropin or alternatively by allowing for correction of abnormal oocyte metabolism through in vitro culture out of the abnormal environment obesity poses. Data supporting these hypotheses are lacking.

**Adverse pregnancy outcomes—**In pregnancy, obesity is associated with significant increased risk of maternal and fetal morbidity including increased risk of preeclampsia, gestational diabetes, fetal growth abnormalities, stillbirth, congenital abnormalities, and the need for cesarean section[35]. This is true for obese women who conceive with in vitro fertilization as well[36].

The reproductive phenotype of obesity varies in its severity, as some women conceive without difficulty and proceed through pregnancy without complication, while others may suffer from some or a combination of the reproductive outcomes discussed. Currently beyond measurements of BMI and history of pre-existing diabetes, there are few reliable risk factors to predict which obese women are going to have adverse reproductive and pregnancy outcomes. Regardless of how minor the reproductive phenotype an obese woman expresses, emerging evidence that children born from obese mothers are at increased risk of obesity-related morbidity later in life is concerning as we may be propagating the obesity-related health problems that are already common today in this so-called "Fifth Phase of the

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Epidemiologic Transition: The Age of Obesity and Inactivity"[37–40]. The mechanisms leading to this increased risk of obesity in the offspring are unknown, but laboratory data from animal models suggest maternal obesity imposes epigenetic changes that lead to obesity in the offspring[20,41]. Anticipated findings from the National Children's Study, an ongoing prospective cohort study of 100,000 children that includes collection of data regarding pregnancy exposures and development of chronic disease, may shed more light on these concerns[42].

## OBESITY'S REPRODUCTIVE TARGETS

### The central nervous system (CNS)

As mentioned previously, obese women exhibit decreased LH pulse amplitude and decreased excretion of progesterone metabolites[12]. In addition to causing anovulation, abnormal LH pulsatility may affect ovarian follicular steroidogenesis leading to abnormal oocyte recruitment and poor oocyte quality and/or altered endometrial development, and it could affect function of the corpus luteum in the luteal phase. How decreased LH pulse amplitude specifically affects subsequent reproductive function has yet to be discerned, but in any case it does highlight the fact that mechanisms leading to anovulation in obese women may be different than those leading to anovulation in thin women with PCOS[30]. We have demonstrated that ART outcomes in morbidly obese women with PCOS are worse than those in women with PCOS who are not morbidly obese, suggesting that it is not chronic anovulation alone or abnormal CNS signalling that affects the ovarian follicle and subsequent reproductive function, but perhaps some other component of obesity that is also important[43].

### The ovary, ovarian follicle & oocytes

We recently investigated the effects of diet-induced obesity in a reproductive mouse model[20]. We isolated ovaries from obese mice and non-obese controls and stained them for apoptosis. The ovaries taken from the obese mice demonstrated increased apoptosis in the cells of the ovarian follicles. Oocytes isolated from the obese mice were smaller and fewer oocytes were mature compared to those from the control mice. In another study using a diet-induced obesity model, Igosheva et al found that preconceptional obesity is associated with altered mitochondria in mouse oocytes and zygotes, possibly the result of oxidative stress. Obese mice were less likely to support blastocyst development compared to lean mice. The authors concluded that abnormal oocyte and early embryonic mitochondrial metabolism contributes to poor reproductive outcomes in obese women[44].

It could be that abnormal signalling from the CNS alone results in abnormal ovarian follicular recruitment and development with poor quality oocytes in obese women, work from Robker et al suggests otherwise. Dr. Robker has demonstrated that insulin levels are increased in ovarian follicular fluid isolated from obese women undergoing in vitro fertilization (IVF) compared with moderate-weight women[45]. In further work using a diet-induced obesity model, Dr. Robker has shown that a high-fat diet is associated with lipid accumulation in oocytes along with markers of a lipotoxic response[22]. Similarly, in specimens isolated from women undergoing IVF, we demonstrated that increased ovarian follicular fluid free fatty acid concentrations are associated with poor oocyte quality.[14] Supporting the theory that dietary factors, adipokines, or some other circulating factors directly affect the ovarian follicle, granulosa cells exposed to increasing concentrations of palmitic acid, a long-chain saturated fatty acid obtained through the diet and made by adipocytes, undergo apoptosis with decreased hormone steroidogenesis[46].

In addition to abnormal endocrine and paracrine cues along with circulating adipokines, inflammatory factors, and metabolites, other factors may play a role in ovarian follicular

health. Citing evidence from in vitro models of ovarian follicular development and unpublished work demonstrating increased rigidity in ovaries from obese versus non-obese mice, Woodruff, et.al. hypothesize that the physical environment of the ovary may also contribute to the pathologic features of polycystic ovaries[47].

### The embryo

Abnormal metabolism and other oocyte quality issues may carry over into abnormal embryonic metabolism and competence. This has been demonstrated in animal models of type 1 diabetes, and is suspected to be important in the setting of obesity based on maternal models of diet-induced obesity[20,4820]. Poor embryo quality may originate with the oocyte, but an abnormal tubal or uterine environment may also influence embryo quality. In an in vitro model of obesity, we exposed pre-implantation embryos to excess amounts of palmitic acid—a fatty acid that has been detected in uterine and tubal fluid[21]. This exposure resulted in abnormal embryonic expression of the IGF-1 receptor, which is responsible for insulin signalling in the embryo. When transferred back into normal recipient mice, the palmitic acid-exposed embryos resulted in growth-restricted fetuses and offspring demonstrated a metabolic-like syndrome.[21] Data from a similar model of type II diabetes demonstrate that embryonic insulin resistance is associated with increased risk of miscarriage, and that metformin, an insulin sensitizer, reverses this risk[49]. Obesity also induces insulin resistance and could potentially cause similar issues of insulin resistance in pre-implantation embryos[20]. Whether or not embryonic insulin resistance underlies the increased risk of miscarriage seen among obese women is unknown, but there is evidence to suggest that treating women with recurrent miscarriages with metformin improves chances of a live birth[50]. Randomized controlled trials supporting the routine use of metformin in obese women with recurrent pregnancy loss are lacking.

### The endometrium

The endometrium is yet another potential target of the abnormal milieu created by obesity. One model that has been used to address the endometrium specifically is the donor oocyte model. In this model, oocytes from healthy donors are transferred into women who are typically unable to conceive with their own oocytes. Researchers have evaluated the impact of increasing donor oocyte recipient BMI on embryonic implantation rate, clinical pregnancy rate, miscarriage rate, and chances of live birth. These studies have yielded conflicting results with several studies demonstrating a BMI-related impact on measures of reproductive success[51,52] and others demonstrating no effect[53,54]. In any case, however, alterations in endometrial gene expression in the peri-implantation period have been noted to be different in obese versus non-obese women[55].

## IMPROVING REPRODUCTIVE FUNCTION IN OBESE WOMEN WITH SUBFERTILITY

### An opportunity for intervention

Obesity-related anovulation and subfertility may provide an important opportunity for preconceptional intervention and improvements in reproductive function and outcomes. These opportunities go beyond interventions for obesity as they include opportunities to screen for pregestational diabetes mellitus and optimization of glucose control in women who are diabetic, opportunities to screen for preconceptional rubella and varicella vaccination, counseling regarding healthy diet and lifestyle preconceptionally and during pregnancy including use of prenatal vitamins, and screening for any other previously undiagnosed medical issues important to healthy pregnancy outcome such as thyroid disease.



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Pregnancy has been referred to as a “teachable moment” for weight control and obesity prevention, as pregnancy may motivate women to adopt improved lifestyle habits that may lead to better weight control[56]. We agree that efforts should be made to educate and counsel pregnant women about weight gain and a healthy lifestyle during pregnancy, however, for obese women preconception interventions may offer more potential for an impact on subsequent reproductive and pregnancy outcomes than intra-gestational interventions.

## Weight loss through lifestyle changes

There is little data regarding lifestyle changes in subfertile obese women and improvements in spontaneous conception and other reproductive outcomes. The majority of data that exists examines lifestyle changes in women with PCOS, and even that data is limited. In a recent Cochrane review on lifestyle intervention and PCOS, authors investigated the effectiveness of lifestyle intervention in improving reproductive outcomes in women with PCOS[57]. The authors limited their search to randomized controlled trials comparing lifestyle intervention to minimal or no treatment in women with PCOS and concluded that there was no existing data demonstrating an effect of lifestyle on clinical reproductive outcomes. We performed a systematic review of the literature to include observational studies eliminated by the Cochrane review and to include studies of obese women without PCOS. We searched Medline to June, 2012 using the keywords “weight loss” and “reproduction”. We limited our search to studies in women published in English within the past five years. With this search we identified eight studies. Six of the studies investigated reproductive function after treatment with medical therapies including metformin, orlistat, sibutramine, and myo-inositol[58–63]. One study outlined the strategy of an ongoing trial evaluating the costs and effects of a structured lifestyle program in overweight and obese subfertile women in Norway, but no results were available[64]. Only one study reported specifically on the effects of a lifestyle intervention on reproductive function in obese women, and this was in obese women preparing to undergo IVF[65]. This study by Moran et al randomized 38 overweight and obese women to active dietary modification and exercise or standard treatment prior to IVF. The authors found a significant effect of the intervention on BMI and weight, but no difference in pregnancy or live births between the intervention versus the control group. The sample size was small which limited the outcomes investigated.

Clearly, further work investigating preconceptional weight loss and reproductive function is needed, particularly translational work investigating specific steps in the reproductive process so that improved treatments and evidence-based management can be developed for obese women hoping to conceive.

## Weight loss through bariatric surgery

Clinically meaningful weight loss through lifestyle changes may be difficult for some women. Bariatric surgery may offer greater and more sustainable weight loss. In 2008, JAMA published a systematic review of pregnancy and fertility following bariatric surgery by Maggard et al[66]. They found that reproductive age women accounted for 49% of all patients undergoing bariatric surgery. Overall they concluded the data support improved pregnancy outcomes in women who have undergone bariatric surgery compared to obese women without bariatric surgery. These outcomes included decreased risk of gestational diabetes and preeclampsia, and improved neonatal outcomes. In their search, studies regarding fertility were limited. They identified six observational studies published between 1988 and 2004. All six studies demonstrated improvement of menstrual cycles in women who underwent bariatric surgery, but none of the studies investigated fertility as a primary outcome.



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To determine if additional studies had been published since the JAMA review regarding the subject of bariatric procedures and fertility, we performed a review of Medline to June, 2012 limiting studies to those performed in women and published in English within the past five years. Keywords searched were: “bariatric surgery and reproduction”. Forty articles were identified, but fifteen articles were reviews[67–82], sixteen articles were on pregnancy outcomes after bariatric surgery[83–98], three were commentaries or author replies[99–101], two investigated contraceptive use post-bariatric surgery[102,103], one was a cross-sectional assessment of reproductive health in women undergoing bariatric surgery[104], one was a case report of empty follicle syndrome in a woman post-bariatric surgery undergoing IVF[105], and one article was a case series of IVF in women who had previously undergone bariatric surgery[106]. In these last two articles, special considerations were outlined for IVF in women with previous bariatric surgery[106]. Only one of the articles identified investigated reproductive function after bariatric surgery. In this article, Rochester et all discuss improvements in LH and progesterone metabolite excretion after weight loss in obese women who have undergone bariatric surgery[107].

## Competing risks in the setting of infertility: obesity versus age

As discussed, for obese women with infertility, weight loss may offer improved fertility. On the other hand, after age 35 there may be less of an effect of obesity on fertility rates with IVF[108,109, 102], although the obstetrical risks obesity poses remain. Furthermore, after age 35 there is a decrease in success of IVF in all women undergoing IVF, regardless of infertility diagnosis or BMI[109]. These issues make for a difficult clinical scenario as age and obesity become competing risks in treating women with infertility. Also, preconceptional weight loss does not guarantee pregnancy nor does it guarantee a pregnancy and delivery free of complication. For these reasons, some women with infertility may choose to accept obesity-related risks and proceed with fertility treatment instead.

## Fertility treatment for obese women

Numerous studies have demonstrated decreased efficacy of fertility treatments in obese women[33,43]. As a result, some centers offering fertility treatments have put BMI limits on who they will treat and what types of treatment they will offer. In fact, in New Zealand where fertility treatments are covered under the national health care plan, there is a BMI cutoff of 32 $kg/m^2$ that limits access to in vitro fertilization. In the United States some fertility treatment centers have BMI restrictions, however, these restrictions vary from center to center and they are not universally enforced[110]. Furthermore, despite decreased efficacy of fertility treatments, the success of various fertility treatment strategies still offer a reasonable chance of success in obese women[43,111]. Subsequently members of the Ethics Committee of the American Society for Reproductive Medicine recently proposed that restricting access to fertility treatment based on BMI is discriminatory[112].

## The need for transdisciplinary research and novel approaches

We propose that obesity research as it relates to reproduction requires a transdisciplinary approach as both obesity and reproduction are complex systems affected by social, environmental, biological, economic, and genetic influences to name a few. Tackling the problem of obese reproduction will require cooperative efforts among experts in all of these fields of study. Ultimately this type of research may help inform models of shared decision-making in which physicians and patients mutually decide how to proceed with strategies for fertility. These models may be especially helpful as there is a significant degree of uncertainty that exists in treating obese women with infertility[113]. Such models would likely include consideration of the potential risks and benefits an individual (at a given age and weight) would gain from fertility treatment with or without a strategy for weight loss prior to or during treatment.

## CONCLUSIONS

There are many components of obesity that may affect the different steps of the reproductive process leading to adverse reproductive outcomes. Clearly there is good data demonstrating that weight loss improves ovulatory function in obese women and improves pregnancy outcomes. On the other hand, female fertility is limited by time, the reproductive phenotype of obesity is variable, and current measures of obesity are not reliable predictors of these phenotypes. Because of the complex nature of obesity and of reproduction, when an obese woman with subfertility presents for fertility treatment, an individualized yet systematic approach is needed.

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## KEY POINTS

- There is an epidemic of obesity among reproductive age women and men.
- Numerous epidemiologic and translational studies demonstrate adverse effects of obesity on various stages of the reproductive process, although the underlying mechanisms are largely unknown.
- Of all the evidence linking obesity to adverse reproductive function and outcomes, the most concerning is that demonstrating links between preconceptional maternal obesity and long-term disease in the offspring.
- Weight loss through lifestyle interventions or surgical therapy may improve reproductive function and outcomes, but data is limited.
- Given the epidemic of obesity in reproductive age women and men, efforts to understand the impact of obesity on reproductive function and outcomes are an important component of future public health policy.