Weighing the impact of obesity on female reproductive function and fertility

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Obesity in women is associated with serious reproductive sequelae. Given its prevalence among women of reproductive age, much recent attention has focused on the mechanisms by which obesity affects female reproductive function and fertility. This review summarizes the literature investigating the epidemiology and pathophysiology of obesity in women of reproductive age and proposes research strategies that may help inform approaches to improve reproductive function and outcomes among obese women.

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INTRODUCTION

Obesity is a common problem among women of reproductive age and is associated with numerous reproductive sequelae, including anovulation, irregular menses, subfertility, miscarriage, and adverse pregnancy outcomes, with lasting effects for children. These reproductive sequelae result from the effect of obesity on a number of different steps in the reproductive process, including ovarian follicular recruitment, oocyte development and quality, oocyte fertilization, and embryo development and implantation. Understanding obesity and its impact on female reproductive function is important because future generations, namely, the children of obese women, ultimately will be affected. In this review, recent work investigating obesity and its impact on various steps of the reproductive process is summarized, with a focus on reproductive events occurring prior to embryonic implantation. In addition, novel multidisciplinary strategies that may improve fertility and reproductive outcomes for obese women are outlined.

EPIDEMIOLOGIC STUDIES OF OBESITY AND REPRODUCTION

Using National Health and Nutrition Examination Survey (NHANES) data from 2009–2010, Flegal et al. estimated that the mean body mass index among women in the United States was 28.7 kg/m² and that 35.8% of adult women were obese. Epidemiologic investigation of obesity and time to pregnancy demonstrates that time to spontaneous pregnancy is increased among obese women (odds ratio [OR] 0.82, 95% confidence interval [95%CI] 0.72–0.95 in one study by Gesink Law et al.), including obese women who experience regular ovulation. Vahratian and Smith studied data from the 2002 National Survey of Family Growth and found that, among women seeking medical attention to become pregnant, obese women accounted for a larger percentage than normal-weight women. On the other hand, although more obese women may seek medical assistance to conceive, the National Survey of Family Growth data also demonstrated that obese women make up a smaller percentage of women who receive fertility-related services involving medical or surgical treatment. This suggests a possible disparity between the treatment provided to obese women who seek infertility care and that provided to normal-weight women. Whether this disparity is related to insurance coverage, race, policy, or other issues is unknown; however, it has been shown that health providers overwhelmingly believe weight-based restrictions for fertility treatment should exist.

With regard to miscarriage risk, there is a paucity of epidemiologic data on the association between obesity...
and miscarriage among women who conceive spontaneously. This is not surprising, as many obese women are anovulatory and require medical intervention to conceive. In addition, some obese women with irregular menses may not report or seek medical care for miscarriage, which could be mistaken for irregular bleeding. To address the knowledge gap, Boots and Stephenson recently published a systematic review and meta-analysis of studies on obesity and the risk of miscarriage. Among women who conceived spontaneously, they found an increased risk of miscarriage among obese women compared with normal-weight women (OR 1.31, 95%CI 1.18–1.46). The authors concluded that prospective studies investigating reproductive outcomes among obese women are needed to further investigate the relationship between obesity and the risk of miscarriage. Such prospective work would also be helpful in further informing associations between preconceptional obesity and adverse pregnancy outcomes, as much of the current work relies on weight and height measurements during pregnancy rather than prepregnancy.

**DATA FROM OBESE WOMEN TREATED WITH ASSISTED REPRODUCTIVE TECHNOLOGIES**

Women treated with assisted reproductive technologies (ARTs) represent a unique population in which to research associations between true preconceptional exposures (like obesity and/or impaired reproductive function) and reproductive outcomes. Numerous studies of women undergoing treatment with ART have demonstrated that obese women require significantly higher doses of gonadotropin than normal-weight women to produce a similar number of ovarian follicles during controlled ovarian hyperstimulation. Whether this is a result of decreased drug absorption, decreased sensitivity of the ovary, or both is unknown. Despite ultimately producing a similar number of visible ovarian follicles during controlled ovarian hyperstimulation, obese women have significantly lower serum estradiol levels than normal-weight women. This suggests there is something different about how the ovary in obese women responds to gonadotropin stimulation. Furthermore, mature oocytes from obese women are less likely to fertilize than oocytes from normal-weight women, suggesting that oocytes from obese women are of poorer quality. Compared with normal-weight women, obese women are less likely to achieve a clinical pregnancy after in vitro fertilization, are at higher risk of miscarriage after an ART conception, and are less likely to achieve a live birth after in vitro fertilization. These findings may be attributable to poor embryo quality among obese women, but they also may reflect abnormal endometrial development and implantation. Bellver et al. have published a number of studies supporting a role for the endometrium in the pathophysiology of reproduction in obese women, demonstrating that obese women have abnormal endometrial gene expression and that obese women receiving oocytes from healthy, normal-weight donors are less likely to conceive than normal-weight women.

Studies of obese women undergoing treatment with ART also offer a unique opportunity to investigate mechanisms by which obesity may adversely influence reproductive outcomes. Robker et al. have demonstrated that obesity is associated with an abnormal ovarian follicular milieu. In further translational work, they exposed mouse cumulus oocyte complexes to follicular fluid collected from obese women and showed that exposure to this fluid resulted in increased oocyte lipid content, increased endoplasmic reticulum stress, and impaired nuclear maturation. Their findings indicate that lipotoxic mechanisms may affect oocyte quality in obese women. These mechanisms are similar to those described in diabetic heart disease, in which exposure to excess fat leads to inappropriate storage of lipid in nonadipocyte cells (cardiomyocytes), resulting in impaired cellular function and, ultimately, cell death.

While ART studies offer a unique opportunity for studying mechanisms involved in the pathophysiology of reproduction in obese women, several important limitations must be considered before extrapolating findings to obese women seeking spontaneous conception. First, women undergoing treatment with ART are exposed to supraphysiologic levels of gonadotropin. As a result, their estradiol levels are much higher than those present during spontaneous conception. In addition, embryos from women undergoing treatment with ART are cultured in commercially produced culture media that could potentially wash out some abnormal effects of obesity on oocyte quality. Alternatively, this culture period could induce epigenetic changes in the embryos. Furthermore, numerous oocytes are often collected and fertilized, allowing for the selection of the best-quality embryos. Thus, obese women who conceive through ART may have different chances of conception and altered reproductive and pregnancy outcomes compared with obese women who attempt conception and conceive spontaneously, although these possibilities have not been thoroughly studied. Overall, when counseling obese women with infertility who require ART to conceive, it is important to keep in mind that pregnancy rates are still good, and age is always the overriding factor in predicting success with ART.

In addition to affording scientists the opportunity to directly measure associations between preconceptional exposures like obesity and individual steps of the early reproductive process, ART allows for direct associations to be made between these exposures and pregnancy

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outcomes. In studies of spontaneous conception and obesity-related pregnancy outcomes, maternal weight and height are typically available only at the time of the first prenatal visit. For many women, this visit does not take place until well into the first trimester, when weight has potentially changed enough to place them in a different category of body mass index. Registries from countries with national healthcare coverage offer some ability to capture true preconceptional exposures, but these data sets are limited by the information that was initially collected. Again, prospective studies of preconception exposures, conception, and pregnancy outcomes in the population of women undergoing treatment with ART are feasible because these women present prior to pregnancy. Luke et al. recently published a study of obesity using previously collected data from women undergoing treatment with ART. This study, which used the Society for Assisted Reproductive Technologies (SART) database, demonstrated a decreased chance of conception, an increased risk of miscarriage, and a decreased chance of live birth among obese women. The same study demonstrated that obese women using donor oocytes had the same chance of conceiving as normal-weight women using donor oocytes, but a lower chance of live birth, suggesting that the impact of obesity on oocyte quality may be more important than the impact on endometrial receptivity. When considering these findings, it is important to keep in mind that the investigators were limited by what was collected, and the SART database contains very little specific data on reproductive outcomes beyond chances of pregnancy and live births among obese women and whether conception was achieved with autologous or donor oocytes. Prospective studies investigating specific reproductive outcomes (neonatal congenital anomalies, fetal growth abnormalities, time in the neonatal intensive care unit, etc.) need to be performed in both the population of women conceiving spontaneously and women conceiving with ART or other fertility treatments. Additional prospective studies of immediate and long-term ART outcomes also should be performed among those conceiving with ART.

**ANIMAL MODELS OF REPRODUCTION IN OBESE SUBJECTS**

In addition to allowing precise control over exposures, animal models allow the collection of reproductive tissues that are not obtainable from women. Using murine models of obesity, it has been shown that hypothalamic hypogonadism may be important to the irregular menstrual pattern and anovulation that exists in the setting of obesity. In another murine model, increased apoptosis has been observed in the ovarian follicles in the setting of diet-induced obesity. In addition, oocytes from these mice were more likely to be immature than oocytes from mice on a regular diet. Resulting embryos demonstrated decreased insulin-like growth factor 1 receptor expression, suggesting decreased insulin signaling, and the resultant fetuses were growth restricted at midgestation. The offspring remained growth restricted at birth, but they caught up in size and – despite receiving the same postpartum diet – eventually surpassed offspring from mothers on the regular diet. Further investigation of the placentas collected from the mothers on the high-fat diet demonstrated increased levels of insulin-like growth factor 2 receptor mRNA, suggesting that fetal programming may have contributed to the lasting effects of the maternal diet on the offspring. To shed further light on whether this effect may have occurred at the preimplantation stage of development or in utero, further experiments exposing preimplantation embryos to high levels of saturated fat were performed. In these experiments, the embryos exposed to saturated fat were then transferred into normal animals and the fetal and offspring outcomes were compared with those of embryos cultured in control media and transferred into normal animals. Similar to the experiments in which the mothers were fed a high-fat or control diet, the offspring resulting from the embryos exposed to saturated fat were growth restricted at midgestation and at birth, but they demonstrated catch-up growth and eventually surpassed the offspring resulting from the control embryos. Altogether, this data suggests that brief preconceptional exposure to either obesity or a high-fat diet may lead to lasting effects on the offspring.

One obvious and important limitation of studies using animal models to inform women’s reproductive health is that the period of oocyte recruitment is much shorter in animals like mice than in women. Moreover, gestational periods are much shorter. Teasing out the importance of something like chronic exposure to obesity versus the normal aging process in women is difficult. Studies of women undergoing treatment with ART suggest that obesity is important prior to age 35, but after 35, age is the overriding factor in determining reproductive capacity in women. Given this, it may be reasonable that a woman who is 35 years or older quickly initiate fertility work-up and intervention if she has regular cycles and has failed to conceive after 6 months of unprotected intercourse rather than focus on weight loss.

**REPRODUCTIVE TISSUES AFFECTED BY OBESITY**

In light of the translational work investigating obesity and its impact on reproductive function, it is clear that obesity has the capacity to affect reproductive physiology at several levels. Reproductive organs and tissues affected by obesity include the hypothalamus, the ovary and
Overall, the existing epidemiologic, clinical, and laboratory studies of obesity demonstrate that obesity affects reproductive function. On the other hand, not all obese women experience poor reproductive health. Because of this, it is important to recognize that factors other than obesity may affect fertility and reproductive function in obese women. Two such likely factors are nutrition and physical activity.

Many have referred to obesity as a state of energy imbalance in which there is too much caloric intake and too little physical activity with the excess energy resulting in obesity. Teasing out the individual contribution of each element to reproductive function can be difficult. Fortunately, several studies investigating nutritional intake, lifestyle, and physical activity have been large enough to demonstrate that nutrition and physical activity are important to overall reproductive function, independent of obesity. Chavarro et al.28 have investigated lifestyle and reproductive function using data from the Nurses Health Study II, a long-term prospective study of lifestyle and chronic diseases in nurses. In this work, Chavarro focused on analyses for age, body mass index, smoking, physical activity, dietary energy intake, and history of oral contraceptive use. He found that women with a greater proportion of their daily food intake coming from carbohydrates had a higher risk of ovulatory infertility than women who limited their carbohydrate intake. Moreover, the dietary glycemic index was directly related to ovulatory function.

## IMPACT OF NUTRITION AND PHYSICAL ACTIVITY ON REPRODUCTIVE FUNCTION

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**Table 1:** Reproductive organs and tissues affected by obesity.

**Abbreviations:** GnRH, gonadotropin-releasing hormone.
infertility. Dietary glycemic index is a measurement of how much a particular food increases blood glucose levels. Chavarro also found that increased intake of saturated fat was related to an increased risk of ovulatory infertility, and that obtaining protein from vegetable sources rather than animal sources was related to a lower risk of ovulatory infertility. Interestingly, daily multivitamin use and iron supplementation were also associated with a lower risk of ovulatory infertility. Summarizing his work in *The Fertility Diet*, Chavarro offers the following nutritional guidance to improve ovulation and fertility: cut *trans*-fats out of the diet, choose unsaturated fats for cooking, choose vegetable-based proteins over animal proteins, choose whole grains over refined and simple carbohydrates, and supplement with a daily multivitamin and iron.

In addition to nutrition, physical activity is also important to overall energy balance. In a recent Internet-based survey of Danish women planning pregnancy, Wise et al. found a direct relationship between increasing vigorous physical activity and increased time to pregnancy in normal-weight women, but not in overweight and obese women. Furthermore, moderate physical activity was beneficial for all women trying to conceive. In other words, overweight and obese women who are trying to conceive would likely benefit from any form of physical activity.

**OBESITY AND REPRODUCTION AS COMPLEX SYSTEMS**

Some public health scientists studying the obesity epidemic 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. One such scientist outlined the characteristics of the obesity problem that make it a complex system, including a diverse range of personal and societal factors that may affect an individual’s energy balance (food intake and physical activity) along with a multiplicity of physiologic mechanisms that may be influenced by this energy balance. Given the complex nature of obesity, it is not surprising that some individuals are metabolically normal despite their obesity, whereas others suffer major sequelae.

Considering the definition of a complex system and how it applies to obesity, reproduction and fertility also may be considered complex systems because neither is dictated solely by an individual’s behavior and physiology but can be medically enhanced or avoided. Moreover, they are often influenced by social and economic pressures, among other things. Because of the complex nature of both reproduction and fertility, researchers and clinicians may wish to consider a multidisciplinary approach when investigating and treating obese women with reproductive sequelae.

**CONCLUSION**

Although obesity clearly affects reproductive function, there are likely many other factors that contribute to infertility and to the success of fertility treatment among obese women. In treating infertile obese women, it is important to weigh the risks and benefits of treating the woman immediately versus delaying treatment to allow for attempts at weight loss. As mentioned earlier, based on studies of women undergoing treatment with ART, it appears that the impact of obesity on fertility is greatest among women who are younger than 35 years of age. After age 35, age becomes a more important influence than obesity in determining the chances of conception. On the other hand, with regard to pregnancy outcomes, obese women would likely benefit from weight loss at any age, although limited pregnancy outcome data from obese women stratified by age are available. The most informative data supporting weight loss among obese women to improve pregnancy outcomes comes from gravid women who have undergone bariatric surgery and have had subsequent pregnancies. These data support weight loss to decrease complications during pregnancy, but the study was too small to demonstrate any differences in pregnancy or neonatal outcomes.

When considering treatment strategies for obese women who wish to conceive, it is important to keep in mind that weight loss will not guarantee pregnancy in those women who are experiencing infertility, nor will it guarantee a normal pregnancy outcome in those who do conceive. Assessing the risks and benefits of weight loss versus treatment for infertility is necessary. Ultimately, models of shared decision making may be helpful to those working with obese women who wish to conceive. In such models, healthcare providers and patients engage in a discussion about the competing risks and uncertainty of treatment outcomes. In the future, such discussions may be helpful in determining the optimal strategy for treating individual women of reproductive age who are affected by obesity and who would like to conceive.

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