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Weighing the impact of obesity on female reproductive function and fertility

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Abstract

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

Keywords

Female obesity; reproduction; assisted reproductive technology

I.Introduction

Obesity is a common problem among reproductive age women, and it is associated with numerous reproductive sequelae including anovulation, irregular menses, subfertility, miscarriage, and adverse pregnancy outcomes with lasting effects for children born to obese mothers. These reproductive sequelae result from obesity's effects 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 as ultimately the weight of the impact will be carried by future generations—namely the children of obese women. In the following pages, we review recent work investigating obesity and its impact on various steps of the reproductive process. We focus our review on reproductive events occurring prior to implantation. In concluding our review we outline novel multidisciplinary strategies that may improve fertility and reproductive outcomes for obese women.

II. Epidemiologic studies of obesity and reproduction

Using National Health and Nutrition Examination Survey (NHANES) data from 2009–2010, Flegal and colleagues estimated that the mean body mass index (BMI) among women in the United States was 28.7 kg/m^2 and that 35.8 percent of adult women were obese.[1] Epidemiologic investigation of obesity and time to pregnancy demonstrates that time to spontaneous pregnancy is increased among obese women (OR=0.82, 95% CI: 0.72–0.95 in one study by Gesnick Law and colleagues) ,[2,3] and that this is true for obese women who

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experience regular ovulation[2]. Varatian and colleagues studied data from the 2002 National Survey of Family Growth (NSFG) and found that obese women account for a larger percentage of women seeking medical attention to become pregnant compared to normal weight women.[4] On the other hand, more obese women may seek medical assistance to conceive, the NSFG data also demonstrated that obese women make up a smaller percentage of those women who receive fertility-related services involving medical or surgical treatment. This suggests that there may be a disparity in the treatment provided to obese women who seek infertility care compared to normal weight women.[4] Whether this disparity is related to insurance coverage, race, policy, or other issues is unknown; however, it has been shown that overwhelmingly health providers believe weight-based restrictions for fertility treatment should exist.[5]

In regards to miscarriage risk, there is a paucity of epidemiologic data investigating the association between obesity and miscarriage among women who conceived spontaneously. This is not surprising as many obese women are anovulatory and require medical intervention to conceive. Also, 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 colleagues recently published a systematic review and meta-analysis investigating obesity and miscarriage risk and found an increased risk of miscarriage among obese women compared to normal weight women who conceived spontaneously (OR 1.31, 95% CI 1.18–1.46) .[6] The authors concluded that prospective studies investigating reproductive outcomes among obese women are needed to further investigate the relationship between obesity and miscarriage risk. 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 pregnant weight and height measurement rather than pre-pregnant.

III. Garnering knowledge of obese reproduction from women undergoing assisted reproductive technologies

Women undergoing assisted reproductive technologies (ART) offer a unique opportunity to research associations between true preconceptional exposures (like obesity and reproductive function) and reproductive outcomes. Numerous studies of women undergoing ART have demonstrated that obese women require significantly higher doses of gonadotropin to achieve a similar number of ovarian follicles during controlled ovarian hyperstimulation (COH) .[7] Whether this is a result of decreased drug absorption, decreased sensitivity of the ovary, or both is unknown. Despite ultimately achieving a similar number of visible ovarian follicles during COH, obese women have significantly lower serum estradiol levels than normal weight women. This suggests there is something different about how the obese ovary responds to gonadotropin stimulation.[8,9] Also, 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.[8] Obese women are less likely to achieve a clinical pregnancy after IVF compared to normal weight women,[9] they have a higher risk of miscarriage after an ART conception,[10,11] and they are less likely to achieve a live birth after IVF compared to normal weight women.[7,12] These latter risks may be a result of poor embryo quality among obese women,[13] but they also may be a result of abnormal endometrial development and implantation.[7] Bellver and colleagues have published a number of studies supporting a role for the endometrium in the pathophysiology of obese reproduction demonstrating that obese women have abnormal endometrial gene expression,[14] and that obese women receiving oocytes from healthy, normal weight donors are less likely to conceive than normal weight women.[15]

Studies of obese women undergoing ART also offer a unique opportunity to investigate mechanisms by which obesity may adversely influence reproductive outcomes. Robker and colleagues have demonstrated that obesity is associated with an abnormal ovarian follicular milleu.[16] 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.[17] Their findings indicate that lipotoxic mechanisms may affect oocyte quality among obese women. These mechanisms are similar to those described in diabetic heart disease—where exposure to excess fat leads to inappropriate storage of lipid in non-adipocyte cells (cardiomyocytes), resulting in impaired cellular function and ultimately cell death.[18]

While ART studies offer a unique opportunity for studying mechanisms involved in the pathophysiology of obese reproduction, several important limitations must be considered before extrapolating findings to obese women seeking spontaneous conception. First, women undergoing ART are exposed to supraphysiologic levels of gonadotropin. As a result, their estradiol levels are much higher than those of spontaneous conception. Also, embryos from women undergoing 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.[19] 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 to obese women who attempted 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 outcomes. In studies of spontaneous conception and obesity-related pregnancy outcomes, maternal weight and height are typically only available at the time of the first prenatal visit. For many women, this visit is not until well into the first trimester when weight has potentially changed enough to place them in a different BMI category. Registries from countries with national health care 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 ART are feasible as these women present prior to pregnancy. A recent study of obesity using previously collected data from women undergoing ART was published using the Society for Assisted Reproductive Technologies (SART) database by Luke et al. This study demonstrated a decreased chance of conception among obese women, increased risk of miscarriage, and a decreased chance of live birth.[12] 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 obesity's impact on oocyte quality may be more important than the impact on endometrial receptivity.[12] When considering this data, it is important to keep in mind that the investigators were limited by what was collected, and there is very little specific data on reproductive outcomes beyond chances of pregnancy and live birth among obese women as well as whether they conceived with autologous or donor oocytes.[12] 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.

Additional prospective studies of immediate and long term ART outcomes must be performed among those conceiving with ART.

Animal models of obese reproduction

In addition to allowing precise control over exposures, animal models allow for collection of reproductive tissues that are not possible in 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.[20] In another murine model, increased apoptosis has been observed in the ovarian follicles in the setting of diet-induced obesity.[21] 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 signalling, and resultant fetuses were growth-restricted at mid-gestation. The offspring remained growth-restricted at birth, but they caught up in size and eventually surpassed offspring from mothers on the regular diet despite being on the same post-partum 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 pre-implantation stage of development or in utero, further experiments exposing pre-implantation 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 to those of embryos cultured in control media and transferred into normal animals.[22] 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 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 compared to women. Also, 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 ART would suggest that obesity is important prior to age 35, but after 35, age is the overriding factor in determining reproductive capacity in women.[12,23] 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 six months of unprotected intercourse rather than focusing on weight loss.

V. Reproductive targets of obesity

Given the translational work investigating obesity and its impact on reproductive function, it is clear that obesity has the capacity to affect one's reproductive physiology at several levels. Reproductive targets of obesity include the hypothalamus,[20,24] the ovary and ovarian follicle,[21,25, 26] the oocyte,[16,17] the embryo,[21] and the uterine endometrium.[14] Table I lists these targets along with some of the supporting studies that have shed light on the mechanisms by which obesity affects these targets. This table also lists the sources of specimens used in the supporting work. What is clear from this list is that it is difficult to infer the effects of obesity on reproductive specimens that originate from women as the majority of our information has been generated from specimens collected in animal models. Moving forward, it may be helpful to invest in storage of biologic specimens collected from women participating in reproductive studies to further inform reproductive care. Ultimately

women may be willing to donate unused oocytes and embryos to research once they have achieved their family building goals. Establishing tissue banks where these types of specimens are stored along with serum specimens, genetic information and endometrial biopsy specimens may allow for quick, meaningful, and novel study in reproductive medicine.[27]

IV. Impact of nutrition and physical activity on reproductive function

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 include nutrition and physical activity.

Many have referred to obesity as a state of energy imbalance where 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 in fact important to overall reproductive function independent of obesity.

Chavarro and colleagues have investigated lifestyle and reproductive function using data from the Nurses Health Study II (NHS II), a long-term prospective study of lifestyle and chronic diseases in nurses. In his work, Dr. Chavarro focused on women with ovulatory infertility and controlled his analyses for age, body size, parity, smoking, physical activity, total 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, and that the dietary glycemic index was directly related to ovulatory 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 a book The Fertility Diet, Dr. 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, 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 and colleagues found a direct relationship between increasing vigorous physical activity and increased time to pregnancy in normal weight women, but not for overweight and obese women, and that moderate physical activity was beneficial for all women trying to conceive[28]. In other words, overweight and obese women who are trying to conceive would likely benefit from any form of physical activity.

IV. Obesity and reproduction as complex systems

Some public health scientists studying this epidemic and its effects on health outcomes have referred to obesity as a “complex system”, defined as a system of heterogeneous parts interacting in non-linear ways to influence the behavior of the parts as a whole.[29,30] One such scientist outlined 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.[30] Given the complex nature of obesity, it is not surprising that some individuals are metabolically normal despite their obesity, whereas others suffer major sequelae.[31]

Considering the definition of a complex system and how this definition applies to obesity, reproduction and fertility may also be considered complex systems as they are not only dictated by an individual's behavior and physiology, but they can be medically enhanced or avoided, and they are often influenced by social and economic pressures among other things. Because of the complex nature of each of these health issues taken individually, researchers and clinicians may wish to consider a multidisciplinary approach when investigating and treating obese women with reproductive sequelae.

V. Conclusions

Obesity clearly affects reproductive function, however, there are likely many other factors that contribute to infertility and success of fertility treatment among obese women. In treating obese women with infertility, it is important to weigh the risks and benefits of treating the woman immediately versus delaying treatment for attempts at weight loss. As mentioned earlier in this review, based on studies of women undergoing ART, it appears that obesity's impact on fertility is greatest among women who are younger than 35 years of age.[12,23] After age 35, age becomes more important than obesity in regards to chance of conception. On the other hand, in regards 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.[32] These data support weight loss to decrease complications during pregnancy, but the study was too small to demonstrate a difference 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. Weighing the risks and benefits of weight loss versus treatment for infertility is necessary. Ultimately, models of shared-decision making may be helpful in working with obese women who wish to conceive. In such models, health care providers and patients engage in a discussion of the competing risks and uncertainty of treatment outcomes[33]. In the future such discussions may be helpful in determining the optimal strategy for treating individual reproductive age women affected by obesity who would like to conceive.

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Table 1

Reproductive targets of obesity

Reproductive target	Proposed mechanisms	Outcome	Supporting studies and source of specimens
Hypothalamus	Neuropeptide Y upregulation, GnRH suppression	Abnormal GnRH pulsatility with subsequent oligo/anovulation	Tortoriello et al (murine)[2], Jain et al (human)[24]
The ovary and ovarian follicle	Increased ovarian rigidity, granulosa cell apoptosis	Abnormal oocyte recruitment, abnormal ovulation, poor oocyte quality	Hirshfield-Cytron et al (murine)[25], Woodruff et al (murine)[26]; Jungheim et al (murine)[21]
Oocyte	Abnormal ovarian follicular environment, lipotoxic fat accumulation within the oocyte	Poor oocyte quality	Robker et al (human)[16], Yang et al (murine)[17]
Pre-implantation embryo	Insulin resistance, increased apoptosis	Poor embryo quality	Jungheim et al (murine)[21]
Uterine endometrium	Altered endometrial genetic profile, suboptimal decidualization	Decreased uterine receptivity	Bellver et al (human)[15]