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Reproductive disorders in obesity

Elia EM[1]*, Bazzano MV[1], Quintana R[2] and Paz DA[1,3]

[1]Laboratorio de Biología del Desarrollo, Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE-CONICET-UBA), Facultad de Ciencias Exactas y Naturales. Universidad de Buenos Aires, Buenos Aires, Argentina

[2]Procrearte, Red de Medicina Reproductiva y Molecular, Buenos Aires, Argentina

[3]Departamento de Biodiversidad y Biología Experimental, Facultad de Ciencias Exactas y Naturales,Universidad de Buenos Aires, Buenos Aires, Argentina

Abstract

Obesity is a major international problem related to many reproductive health problems. It is associated with multiple adverse reproductive outcomes such as infertility, ovulation dysfunction, miscarriage, preeclampsia, gestational diabetes mellitus, preterm delivery, operative delivery, and fetal growth disorders. Despite this, there is no absolute consensus about the effect of obesity on infertility treatment specially because it is unclear which mechanism contributes the most to subfecundity, and it is likely a cumulative process. Female obesity adversely affects reproductive function through alterations in the hypothalamic- pituitary-ovarian axis, oocyte quality, and endometrial receptivity. Once pregnant, the obese women have higher risk of adverse pregnancy outcomes. Weight loss improves reproductive potential in obese patients, however, changing eating behavior and maintenance of ideal weight is difficult and hard to achieve not only per se but also because many of the infertile patients who attend infertility clinics at an age >30 years may not have much time to wait until they can lose weight because age itself is the major factor of declining fertility. This makes it imperative to find a consensus for medical treatment of obese patients. Obstetrician gynecologists need to be aware of the negative impact of obesity on reproductive function so that they appropriately counsel their patients. Further work is needed to clarify the underlying physiopathology responsible for adverse effects of obesity on reproduction so that novel treatment approaches may be developed.

Abbreviations: BMI: body mass index; WHO: World Health Organization; IVF: in vitro fertilization, ICSI: intracytoplasmic sperm injection; PCOS: polycystic ovary syndrome; ART: assisted reproductive technique

Introduction

Overweight and obesity constitute health problems of increasing worldwide prevalence that present major public health concern. The worldwide prevalence of obesity has nearly doubled in the last three decades and according to the World Health Organization (WHO) [1], obese adults reached 300 million worldwide. Definitions of obesity can vary, but the most widely accepted definition adheres to the WHO body mass index (BMI) criteria. BMI is calculated as the body weight in kilogram divided by height in meters squared. A person is considered obese if his/her BMI is >30 kg/m^2. There are degrees of obesity: class 1 (30.0–34.9 kg/m^2), class 2 (35.0–39.9 kg/m^2) and class 3 (>40 kg/m^2). Obesity is a multifactorial chronic disease whose etiology is an imbalance between the energy ingested in food and the energy expended. This imbalance is promoted by complex interactions between inadequate dietary habits, diminished physical exercise and genetic background [2]. The pathological consequences of obesity include the development of other diseases, such as diabetes mellitus, heart disease, neurological disease and some forms of cancer [3]. Although the deleterious effect of female obesity on human reproduction was initially a subject of controversy [4], most recent studies have shown that obese women present an increased risk of subfecundity and infertility [5-8]. Even when they ovulate regularly, they have decreased conception rates (implantation and pregnancy rates) [4,9]. Miscarriage rates and pregnancy complications are also higher in this population [10-12]. Obese women have poor reproductive outcomes in all modes of conception: natural, ovulation induction, *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI) and even after ovum donation [13-18]. This is especially the case in women with higher BMIs, central distribution of fat or an association with polycystic ovary syndrome (PCOS) [19-21]. However, how female weight excess affects each component of the reproductive system (oocyte, embryo, and uterus) is not entirely clear, as information regarding this subject is often scarce [22-24]. That is why the molecular mechanisms that are involved in the association between obesity and reproductive disorders remain unclear. This article reviews the current scientific evidence regarding overweight and obesity on female reproduction.

Methods

The articles selected for this review were English-language, full-text articles and abstracts that were identified by a series of PubMed searches using keywords either alone or in combination and published before the 20 of December 2014. The data were extracted from the identified papers, and secondary data sources were identified within these papers. The keywords used included obesity, reproductive outcome,

Correspondence to: Evelin M Elia, Laboratorio de Biología del Desarrollo, Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE-CONICET-UBA), Facultad de Ciencias Exactas y Naturales. Universidad de Buenos Aires, Buenos Aires, Argentina, Tel: 0054-11-145763300; Fax: +54-11-45763384, **E-mail:** evelinmariel@gmail.com.ar

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reproduction, ovary, uterus, endometrium, ovulation, conception, uterine receptivity, implantation failure, pregnancy loss, miscarriage.

Reproductive function and obesity

The obesity effect is still debated in oocyte retrieval number, quality and maturity, fertilization, embryo quality and pregnancy rate, but the outcome tends to be worse in obese patients, especially those with morbid obesity [25-27]. PCOS which is included in some obesity studies may also affect the pregnancy rate as well [28]. Overall, the obese patient might have multiple dysfunctions affecting not only the oocyte but also the hormonal, metabolic and endometrial status. The degree of dysfunction needs to be identified to optimize their fertility however there are few studies examining the effect of body fat composition on outcomes in infertile patients. The classic clinical definition of infertility is the absence of conception after 12 months of regular, unprotected intercourse [29]. Currently, around 10–17% of the Western population is affected by infertility [30,31] with the negative impact that it has on the psyche and quality of life of the patients [32,33]. The fecundity of overweight or obese women is lower than normal weight women with the reduction in pregnancy rates of 8% in overweight and 18% in obese patients [34,35]. The effect of obesity on spontaneous pregnancy is clinically and epidemiologically obvious when the BMI is >29 kg/m. Moreover, regarding pregnancy in IVF, each unit increase of BMI decreases the probability of pregnancy by 2.2–4.3% [36].

It seems that obesity prolongs the time to pregnancy during ovulation induction, increases gonadotrophin dose, decreases the number of mature follicles and increases cycle cancellation rates [25]. The impairment of sex steroid hormone regulation may lead to longer periods of follicular stimulation, more follicular asynchrony, cycle cancellation and lesser live birth rates among obese patients who undergo IVF as their assisted reproductive technique (ART) when compared to normal weight infertile patients [37]. Since obesity decreases not only the chances of natural conception but also reduce the success rate of assisted reproductive techniques [30,37] obesity produce a "double" negative effect on the psyche and quality of life of the patients. This makes it imperative to find a consensus for medical treatment of obese patients, however there is no absolute consensus based on evidence regarding the effect of obesity on infertility treatment.

The ovary in obesity

Obesity is associated with oocyte abnormalities, however how changes in the ovarian follicle impact overall ovarian function is unknown [38]. In 2011, Shah *et al.* published a study of 1721 women undergoing a first IVF cycle with autologous embryos, finding that women with a BMI>35 had fewer normally fertilized oocytes than normal weight patients [39]. Additionally, the odds of clinical pregnancy and live birth were 50% lower in women with BMI>40 that normal-weight. Several studies demonstrate that obese women undergoing ART require longer durations of gonadotropin stimulation and increased amounts of gonadotropin than normal-weight women to produce a similar number of ovarian follicles [4,13,40,41]. This may be the result of altered absorption and/or metabolism of gonadotropins or steroidogenesis by the supporting cells of the ovarian follicle [39,41]. There is also evidence that follicular leptin levels correlate with BMI [42,43] and high intrafollicular levels of leptin have been associated with relative gonadotropin resistance during ovarian stimulation in PCOS patients [44].

Obesity, uterine receptivity and implantation

Several studies have attempted to define the effect of obesity on the endometrium. However, contradictory findings have been reported and studies varied in design [15,45-47]. It has been proposed that the oocyte donation model provides the best human model for discriminating between the effects of obesity upon the oocyte/embryo and the endometrium and uterine receptivity [15]. Using this model the first clinical studies provided conflicting results regarding implantation, pregnancy and miscarriage rates [45-47], which has lead to a scientific debate [48,49]. The validity of this model has been questioned by some authors, who have suggested that crucial differences may exist between non-obese and obese women who require oocyte donation and those who do not, thereby creating a bias in the results using this model [50]. The effect of obesity upon implantation rate has been inconsistently reported. It has been pointed relationship between recipient BMI and poor reproductive outcome that may be mediated by a reduction in uterine receptivity [15,51,52]. Some authors have identified a reduction in implantation rates among the obese women [17,53,54], whereas others have not demonstrated a weight related reduction [55-57]. Moreover, gene expression analysis during the window of implantation has revealed endometrial dysregulation in obese women versus normoweight controls, particularly when PCOS is associated [58]. A more recent meta-analysis from six centers totalling 4758 women investigating the impact of donor oocyte recipient obesity on pregnancy described no difference between obese versus nonobese women using donor oocytes in chance of pregnancy, embryo implantation, miscarriage or live birth [59]. Shortly after this meta-analysis was published, a larger study from a single center in Spain compiling data from 9587 women using donor oocytes found that obese patients showed decreased implantation, pregnancy and live birth rates without difference in miscarriage rates [60].

An unfavorable intrauterine milieu and impaired endometrial receptivity are plausible loci for the effect of obesity upon subfecundity; however, the evidence is inconsistent and obese women tend to suffer non-recurrent spontaneous pregnancy loss [4,61]. In the light of the above it is important to highlight that methodological problems in patient selection, inadequate description of cases or the retrospective nature of the scientific design have been frequently being blamed for the lack of consensus on this issue [62,63].

Pregnancy loss and obesity

Obese women are more likely to experience pregnancy loss once pregnant and elevated miscarriage rates are seen following natural conception, ovulation induction and assisted conception. A retrospective analysis of women with PCOS undergoing ovulation induction demonstrated an increased frequency of miscarriage among obese women (BMI>28 kg/m^2) when compared to normative controls [64]. A retrospective analysis of 5019 IVF/ICSI cycles in 2660 women in a Norwegian clinic observed a linear association between higher BMI and early pregnancy loss (<6 weeks) and miscarriage (6–12 weeks) [55]. Another meta-analysis demonstrated an increased risk of miscarriage among obese women (BMI>30 kg/m^2) undergoing assisted conception [13]. A further meta-analysis also found that patients with a BMI >25 kg/m^2 were found to have a significantly elevated odds of miscarriage regardless of the mode of conception.

Gestational problems in obesity

Many studies have already focused on maternal obesity and its outcome in pregnancy and correlating maternal BMI to higher

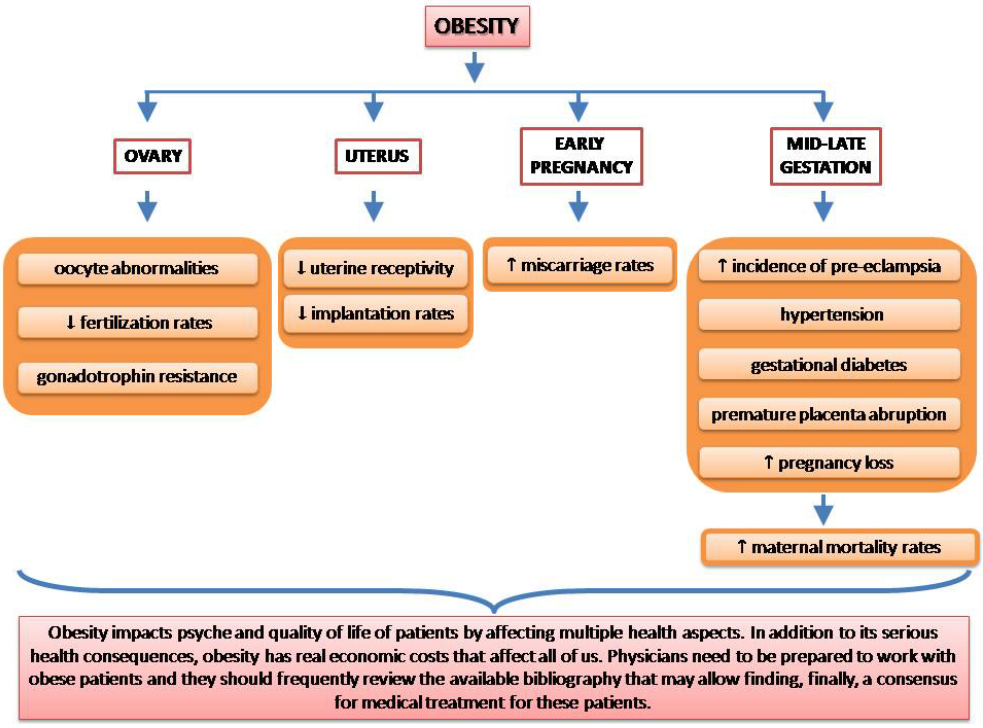
incidence of pre-eclampsia, hypertension, gestational diabetes, cesarean section and miscarriage [65]. Gravidity of an obese woman is integrated in high risk pregnancies due to higher frequency of specific complications either for the mother or neonate [66]. According to literature, it seems to be a positive linkage between incidence of caesarean delivery and overweight and obesity [66]; more precisely there is a dose- dependent effect regarding high maternal BMI and cesarean section [67,68]. Specifically, for one unit increase in maternal pre-pregnancy BMI, the odds for cesarean section were increased by 7% [69-71]. In a population based screening study including 5142 primiparae women, an increased caesarean delivery rate among obese and morbidly obese patients compared to the control group has been reported. In this study, the control group consisted of normal overweight women in order to describe in a more consistent way the typical USA obstetric population [72]. Roman *et al.* performed an aged and parity matched study between 2081 obese women and 2081 normal weight women. Cesarean section was performed in 25% obese patients while 15% in control group [73]. Additionally morbidly obese patients are even more probable to undergo a cesarean section compared to normal weight women [74]. In many studies, obese patients showed an increased incidence of cephalopelvic disproportion and premature placenta abruption situations that are "absolute" indications for cesarean section [66]. As a result the indirect incidence of cesarean section increases in obese patients with these pre-mentioned pregnancy complications [72,75-78].

Maternal mortality shows a decreasing tendency due to medical and pharmaceutical evolvement as well as to early diagnose and treatment of each pregnancy complication over the last decades in developed countries. There are few studies examining the relationship between maternal pre-pregnant obesity and mortality. It has been described that overweight and obese pre-pregnant patients showed increased rates of maternal mortality [79]. On the contrary, another study showed no correlation between maternal overweight/obesity and maternal mortality or adverse outcomes [68]. The issue of preterm delivery is controversial and it is not clear whether the onset of labor is due to obesity or other unremarkable reasons. Many studies has described an increased in the risk for preterm delivery in women with high BMI [67,72,80,81]. However, several works did not find significant statistical correlation between preterm delivery and maternal BMI [68,73,75,78,82,83]. Showed that pre-pregnancy obesity was correlated with increased the risks of preterm premature rupture of membranes (PPROM) and decreased risk of spontaneous pre-term delivery without PPROM [83].

Another investigators support a lower risk for preterm delivery in overweight and obese patients [77,84] as well as in morbid obese ones [74]. Finally, obesity and morbid obesity in African American women leads to decreasing incidence of preterm delivery [82], although Wise *et al.* suggested that obese. African American women are at greater risk for medically-indicated preterm delivery [85].

Reproductive function after weight loss

Weight loss programs reveal that 10–15% weight loss in overweight patients leads to 30% spontaneous pregnancy and up to 50% to drug induced pregnancy [86] as well as after the reduction in the waist circumference [87]. Regarding the role of weight loss in improvement of fertility, 47% of women who undertook a biliopancreatic diversion and were considered infertile preoperatively, achieved pregnancy after surgery [88]. Weight loss improves fertility, hormones, ovulation, live birth rate and psychometric measurement [89,90] providing many benefits for the obese patient. However, changing eating behavior and maintenance of ideal weight is difficult and hard to achieve [91,92]. The difficulty resides not only in the problem that represents changing eating behavior *per se* but also because many of the infertile patients who attend infertility clinics at an age >30 years may not have much time to wait until they can lose weight because age itself is the major factor of declining fertility [93,94] (Figure 1).



Conclusions

Obesity impairs reproductive outcome since it impair both natural and assisted conception. Notwithstanding its effect upon the probability of conceiving, it has important consequences upon the health and outcome of the gestation. Therefore it is important that obstetricians and gynecologists are aware of the physiopathology of obesity in reproduction as obesity is common and not going away [38]. In fact, the American College of Obstetricians and Gynecologists recently issued an opinion from the ethics committee stating that 'it is unethical for physicians to refuse to accept a patient or decline to continue care that is within their scope of practice solely because the patient is obese. However, if physicians lack the resources necessary for the safe and effective care of the obese patient, consultation or referral, or both are appropriate. The exact physiopathological mechanism through which obesity exerts its detrimental effect remains uncertain. It is likely that obesity exerts its effect upon conception and implantation through a cumulative impairment of several processes. Obesity affects ovulation, oocyte maturation, endometrial development, uterine receptivity, implantation and miscarriage. The British Fertility Society has issued policy and practice guidelines advising clinicians to advise patients to aim for a normal BMI prior to commencing fertility treatment. Indeed, these guidelines recommend deferring any treatment until a woman's BMI<35 kg/m^2, and recommending that BMI<30 kg/m^2 is preferable [30]. Weight loss is the first-line therapy for all obese women seeking fertility treatment and robust evidence supports this. Improvement in the reproductive function has been observed following weight loss surgery; however, conclusions drawn from the current literature must been interpreted with caution owing to the quality of the original data. As such, bariatric surgery cannot be recommended as a first-line fertility treatment for the obese women owing to operative morbidity and mortality and lack of clear supportive data [37]. Besides that, obese women that suffers subfertility have often tried losing weight without any success and they are working within a window of time in which obesity risks must be weighed against age-related decline in fertility [38].

When considering fertility issues in obese women, the obstetric and neonatal consequences of a pregnancy must be considered since pregnancy is a more risky endeavor in the obese women [66]. Pregnancy complications of maternal obesity include hypertension, pre-eclampsia, and eclampsia; and obese patients are more likely to undergo a cesarean section [66]. Maternal obesity has an unclear impact on maternal mortality. Although in developed countries maternal obesity is the most common cause of death among pregnant women [95], there is not enough evidence for this and further investigation is needed. The conception of a child is one of the most common desires experienced by people achieving adulthood. This longing is powered by personal, religious and social expectations; since in a patriarchal society reproduction is an obligation, a mission, a cultural mandate. Women become visible and obtained respect from motherhood and the inability to reach it generates significant psychological consequences such as feelings of failure and exclusion. In view of all the exposed information here described it is important to highlight that physicians need to be prepared to work with obese patients looking for conception, as well as the importance of frequently reviewing the available bibliography that may allow to find, finally, a consensus for medical treatment for these patients.

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