OBESITY IMPACT ON REPRODUCTIVE FITNESS

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Abstract

Obesity has a worldwide high prevalence and it increases every year especially in developed countries. The ethiology is large including life style changed, reduced physical activity together with higher caloric intake and use of fast food. It became an epidemy with important and severe complication for reproductive system. It is difficult to treat the anovulatory infertility in obease womens because they have a low success chance after assisted reproductive treatment and they need higher doses of gonadothropin. This patient's category is characterized by low answer of ovarian stimulation and high risk of miscariege. The literature proved that weight loss improves the fertility. The patients should be informed about the impact of obeasity and overweight for pregnancy and the importance of weight lost before any infertility treatment.

Keywords: obeasity, infertility, assisted reproductive technology

Introduction

The obesity is a worldwide important health problem, that became more frequent among women of reproductive age. It consists in anormal and excessive accumulation of fat in the whole body, with severe impact for patients's health. According to World Health Organization (WHO), the overweight condition is defined as a body mass index (BMI) 25- 30 kg/ m2; to be framed as obease, a patient needs to have a BMI greater than 30 kg / m2. (1) Obesity is a complex, multifactorial disease affecting a third of worldwide population. (2) Is considered that, in 2023, about 38% of adults will be overweight and 20% obease. (3,4)

Obeasity involved also social, psychological and demographic problems. It's complications like, diabetes, arterial coronary artery disease, osteoarthritis and various malignancies (endometrial, breast or colon cancer) are lifethreting severe pathologies. Another obeasity impact is for reproductive system, especially in womens. It is associated with anovulation, menstrual disorders, infertility, difficulties in assisted reproduction or spontaneous abortion. (1)

Due to lower rates of implantation, increased risk of abortion and increased maternal and fetal complications during pregnancy, obese women have a lower chance of giving birth to a healthy newborn. (1)

This present paper aims to present the effects of obesity on fertility and the effective management of infertility in obese and overweight womens as well as the relationship between obesity and the occurrence of congenital malformations in newborns.

Epidemiology

The prevalence of obesity has significantly increased throughout the world, especially in developed countries due to a change in lifestyle including reduced physical activity, changes in nutritional style and increased caloric intake. (5) The etiology is multifactorial and involves several factors, such as endocrine disorders, hormonal disturbances, psychological disorders and the use of drugs (steroids and antidepressants). In the US and most European countries, 60% of women are overweight (≥ 25 kg / m2), and 30% are obese (≥30 kg / m2), 6% of whom have morbid obesity ≥35 kg / m2). (1,5,6)

Different European studies have shown that there are large differences in the prevalence of obesity among countries. A study from 2008 showed a low prevalence of obesity in French population (4- 6.2%), and at the opposite are the Czechs with an obesity rate of 30 to 32%.(7) It has been established that an increased prevalence of obesity exists in the southern regions of Italy and Spain and Eastern European countries, western and northern European countries have lower obesity rates. (7)

Obesity and reproduction

The relationship between obesity and reproductive function is known but further studies are still needed to elucidate pathogenic mechanisms. The negative effects of obesity for reproductive function are also well known. The first signs of reduced reproductive fitness in obese women are anovulatory cycles and /or subfertility. (8) It is difficult to explain how obesity affects the reproductive system..

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Obesity can affect reproductive function, by affecting the ovaries and the endometrium. Luteinising hormone (LH), estrone, androstenedione, triglycerides, insulin and low density lipoprotein levels are elevated, and high density lipoprotein levels are low in obese women. Due to these changes, the HPG axis deteriorates and various gynecological effects occur. (1)

Because of low pregnancy rates, increased rates of abortion and pregnancy complications, birth rates are low in obese women. (1) The methabolic profile of obese womens is characterized by hyperandrogenemia, insulin resistance and elevated leptin levels. Although adipose tissue is required for reproductive function and for normal development, excessive adipose tissue causes some reproductive disorders. It aggravates polycystic ovarian syndrome (PCOS) and anovulation and can cause hypothalamic hypogonadism.

Anovulation produces changes in the level of adiponectin and HPG axis as well as steroidogenesis in obese women. Adipokines are signaling molecules produced by adipose cells, correlated with inflammation and signaling disorders that can affect cellular metabolism. (8) Leptin, alpha tumor necrosis factor (TNFα), resistin, glargine, visfatin, interleukin 6 (IL-6), free fatty acids, adiponectin, chemerin are adipokins that can be correlated with the adverse effects induced by obesity (8)

Adipose tissue also affects follicular development by inhibiting gonadotropin secretion, by converting androgens to estrogen in adipose tissue. Therefore, almost all adipokines appear to have effects on reproduction by causing insulin resistance. Hyperinsulinemia and insulin resistance are causes of obesity, accompanied by hyperandrogenemia and alteration of steroidogenesis.

Leptin inhibits the production of estradiol in granular cells and insulin-induced ovarian steroidogenesis, acting on receptors in the teat cells. Another effect of leptin on reproductive functions is the regulation of early embryonic development. This may explain poor reproductive performance in obese women. (1,9)

Adiponectin-induced signaling is important for preimplantation embryonic development and process of implanting the zygote. (10)

Resistin and ghrelin are also involved in the pathophysiology of obesity and associated endocrine disorders, but the mechanism of action has not been fully elucidated. Resistin is a protein secreted by adipose tissue. It has been demonstrated that resistin induces insulin resistance and production of antibodies that are resistant to insulin sensitivity. (11)

Visfatin is secreted by several types of cells, including adipocytes, bone marrow, lymphocytes, muscles, liver, trophoblasts and fetal membranes. Visfatine exhibits insulin mimetic effects, increases glucose uptake in adipocytes and muscle cells and decreases the release of glucose from hepatocytes. The association between visfatin and obesity as well as the action of insulin are not fully understood. (12)

Chemerina is another adipokine that interferes with the adipocytes and glucose metabolism. Chemerin levels increase during metabolic syndrome and are also associated with obesity and type 2 diabetes. Chemerina interferes with follicular steroidogenesis stimulated by foliculostimulant hormone (FSH) and plays an important role in polycystic ovary pathogenesis. (13)

Lipotoxicity is another mechanism by which obesity can affect reproductive tissue. (8,14,15) In obesity, there is an excess of saturated long chain fatty acids due to increased secretion by adipocytes as well as by diet. When adipocytes can no longer store these fatty acids, other cells will store fat, which will induce an increase in the production of reactive oxygen species that causes mitochondrial dysfunctions, endoplasmic reticulum stress and apoptosis. At the reproductive tissue level, this mechanism will be used to treat granulosa cells and oocytes, resulting in oocyte maturation disorders as well as their quality abnormalities. (15, 16)

Another mechanism leading to hyperandrogenemia is hyperinsulinemia via IGF-1, secreted by human ovarian tissue and its receptors are located in the ovary. Insulin can bind IGF-1 receptors, as well as its own receptor. It causes decreased production of IGFBP-1 and SHBG in the liver and increased levels of serum androgen in obese women. Polycystic ovary is also a metabolic disorder characterized by hyperandrogenemia. Previously, the polycystic ovary was known only as a hyperandrogenic condition, possible etiologic factor for infertility. However, current data show that the polycystic ovary is associated with an increased risk of metabolic disturbances, insulin resistance (IR), hyperinsulinemia (HI), decreased glucose tolerance and obesity. In women with polycystic ovaries, weight loss decreases androgen levels and improves insulin resistance. (17,18)

The mechanism by which hyperandrogenemia and/or hyperinsulinaemia causes anovulation was not fully understood. Because of improving steroidogenesis due to insulin and its interaction with LH, it stops the follicular growth. Thus, premature luteinisation and follicular arrest develops and lead to obesity-induced menstrual cycle and oligoanalubital disorders.

In conclusion, the excess of estrogen and androgen plays a key role in the development of anovulatory cycles in obese patients.

Obesity, risk factor for infertility?

Infertility is defined as a lack of pregnancy, despite regular unprotected sexual intercourse after one year or therapeutic insemination in women under the age of 35 and after 6 months in women aged 35 years and over. (19) Although many overweight women are able to become pregnant, there is an increased prevalence of infertility in obese women.

Among the recognized causes of infertility are chromosomal abnormalities, inflammatory and autoimmune diseases, polymorphisms of thrombophilia related genes. In the Western Region of Romania, several studies have been conducted focusing on the incidence of chromosomal anomalies in infertility patients, the presence of cytogenetic abnormalities in spermatic fluid as well as the incidence of cytogenetic anomalies diagnosed in the fetal period. (20,21)

Studies have shown that the time required to achieve a spontaneous pregnancy in the general population is increased, but decreases in obese women, including those with normal ovulatory function. (22) The risk of infertility is three times higher in obese women than in normal weight women and their fertility appears to be affected both in natural and assisted. (23) The probability of pregnancy is reduced by 5% per unit of BMI exceeding 29 kg / m2. (24) Obesity causes infertility through various pathways, including by impairment of follicular development, qualitative and quantitative development of ovocytes, fertilization, embryo development and implantation.(25) Obstetricians have shown that anovulatory infertility and menstrual disorders are higher in overweight and obese women. (1)

Can obesity be correlated with un increased risk for miscarriage?

There was a correlation between obesity and significant increases in fetal as well as maternal death, preeclampsy, diabetes, fetal developmental anomalies, and other congenital anomalies during pregnancy. (26)

It is difficult to establish a correct link between abortion for women with spontaneous pregnancies, due to the fact that first trimester abortion may or may not be recognized, especially for women with non-fixed periods. In the event when assisted reproduction techniques are called upon, a much more accurate risk analysis of obesity, spontaneous abortion, pregnancy evolution and post-natal evolution is a possibility. Association between obesity and spontaneous abortion has been signaled in several studies, in general population, as well as in pregnancy assisted women.(27) A study involving 1644 women suffering from obesity with a control lot (3288 normoponderal women) has shown a higher risk of abortion of any kind. (28) Although there are some studies showing an increase of abortion risk in pregnant obese women, other studies have not found such correlation between the two pathologies. (28–30)

Embrionary chromosopathy, the most common form of spontaneous abortion during the first trimester of pregnancy does not apper to have an increased incidence for overweight women. Endocrine imbalances, such as polycystic ovary, hyperthyroidia, and insulin resistance are most common in overweight women. These conditions are known to cause spontaneous abortions.

In conclusion, endocrine anomalies, embrio quality and uterin receptivity could determin spontaneous abbortions in obese patients.

Does obesity influence embrionary development?

Maternal metabolic imbalances as well as ovocites quality have consequences on embryons. Weak embryons can develop due to ovocytes quality, as well as uterus quality. In-vitro experiments have shown that exposure at high concentration of palmitic acid of the pre-implant embryos leads to abnormal expression of IGF-1 in the embrio. The embrios exposed to palmitic acid had groth restriction and developed metabolic syndrome. (31) Furthermore, another study has shown that embrio's insulin resitance is associated with an increased risk for spontaneous abortion and that the use of metformin has been shown to reduce such risk. (32) Although a direct ethiopathogenic correlation between embryo resistance to insulin and spontaneous abortion in obese women has not been established, there are studies that support the idea of metformin use for improved quality of fetal development. (33)

Does obesity have consequences over the uterus receptiveness and zygot implantation?

One of the proposed mechanisms is endometrial influence induced by obesity which affects the implantation process, more so than fertility and early pregnancy development. Several reports over the potential endometer role in infertility occurrence during obesity have been done by taking ovocytes from healthy donours which have been administered to women with various BMI. (30) The results showed that the pregnancy success rate was significantly lower in obese women compared to women of normal weight.(30) There are different studies however, in which no such correlation could be established, namely obesity and zygot implantation. (34,35) Obese women have shown a significant difference in gene expression during zygot implantation window, especially for women with polichistic ovary. (36)

Could obesity influence the result of assisted reproduction?

Some studies have shown that overweight or obese women have poorer results after in vitro fertilization (IVF) compared with women of normal weight. A link between obesity and weak quality of embryos at women under 35 years old has been established, and young obese women have fewer chances of cryopreserved embryos. (37) Obese women with ovary stimulation need higher doses of gonadotropine administered during a longer period of treatment. (38)

Infertile obese women in need of assisted reproduction show some difficulties during treatment such as low ovarian response during ovarian stimulation, low ovocyte recovery, low ovocyte and embryo quality, low concentration of human chorionic gonadotrophine, low estradiol level, low number of mature ovocytes and embryo transfer. (1)

BMI is negatively associated with estradiol level of preovulatory follicle, which leads to reduced estradiol levels with increase in BMI. (39) Obesity is generally correlated with lack of follicular development as well as ovocyte number reduction and gonadothropine resistance. (40,41) Gonadothropine resistance can be induced by leptine, since an increase in leptine concentration in serum as well as in the follicular liquid in obese women determines a decrease in estradiol secretion at the granulous cells level which act as gonadothorine inhibitor when in high concentrations. (42) There is justification for high doses of gonadothropine administered to obese women which resides from differences of absorbtion, distribution and clearance rates in gonadothropine secreted by excess fat tissue. (39)

Recent meta-analyses investigated the influence of obesity over pregnancy rates after the fertility treatment. The results showed that overweight and obese women exhibit a significant reduction in pregnancy rate, and abortion rates were significantly higher compared to normal BMI women.((38,43) A different study with higher cohorts of patients wich received ovules from donors have shown a reduction of implantation chances, lower pregnancies onset, and a lower chance of healthy baby deliveries at obese women, but there was no significant difference regarding the abortion risk between normal weight and obese women. (30)

Obesity and infertility treatment characteristics.

Treatment of un-ovulatory condition in obese women is difficult, since obese women have a lower reproduction chance after assisted fertilization procedures and higher doses of gonadothropine are needed, there is a weak ovarian stimulation response and higher risk of spontaneous abortion.

Weight loss among the overweight and obese women proved to be beneficial for the reproduction rates, including fertility. (46) Therefore, it is important to determine which patients can benefit from weight loss as well as weight loss interval and ART program.

Weight loss of over 10-15% in obese patients have shown to lead to an increase in the pregnancy rate in the absence of fertilization treatment by 30%, and if there is an undergoing of drug therapy, chances increase by 50%. (47,48) In patients that have undergone surgical operations such as biliopancreatic diversion, 47% of the women with prior operation infertility have sustained pregnancy after the operation, which facilitated weight loss. Another important aspect to mention is the beneficial effect of weight loss for the pregnant woman as well as for the fetus. It was observed that weight loss is important for normalization of weight modification during gestation as well as for reducing the risk for macrosomia. (49)

The British Fertility Society recommends clinicians to counsel their patients with regards to their weight loss prior to commencement of any fertilization program, by indicating that no fertility stimulation treatment should be administered to women with BMI higher than 35kg/m2, and preferably up to BMI of 30kg/m2.(50)

The majority of overweight and obese women have an overweight and obese life partner, which represent an additional risk factor for achieving pregnancy. (51) Obese men have exhibited a lower sperm count, and there is a positive correlation between weight loss and sperm count as well as percentage of morphologically normal sperm. (52)

Nevertheless, in the event that weight loss will continue for an extended period of time, the patient may enter in a phase catabolic fertility, since advanced age is one of the determing conditons for deteriorating infertility factors.(1)

Conclusions

Overweight and obese patients should receive counselling with regards to the importance of weight loss prior to pregnancy and should be encouraged to enter weight loss programs before treatment for improving obstetrical results. The majority of fertility clinics have a protocol for the initiation of assisted fertility treatment, but there are no proof based indications on the fertility treatment for overweight or obese infertile women. Weight loss for obese women is considered essential as there are numerous scientifical reports ahowing that the chances of pregnancy rates significant increases if these women achieve weight reduction. There are several proposed mechanisms to explain the way obesity can lead to infertility. However, the exact physiopathology is not clearly understood.

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