Abstract: Obesity is nowadays considered as a cause of cardiovascular disease, type 2 diabetes, osteoarthritis, malignancies but also contributed to reproductive disorders and fertility problems. There is an increase in relative risk of anovulatory infertility in women with pronounced obesity, and an increased time to conception. Obesity in related to the increased risk for hyperandrogenism and anovulation in reproductive aged women as it is a case in women with polycystic ovary syndrome (PCOS) as the most prevalent hyperandrogenic condition. It was confirmed a close relation of adipokines, obesity, metabolic syndrome and reproductive consequences. A reduction of weight for 5-10% leads to the improvement in clinical, metabolic and reproductive characteristics as it is a case in women with PCOS. The administration of insulin sensitizers is leading to the decrease of hyperinsulinemia, insulin resistance, establishment of normal menstrual cyclicity and ovulation in significant proportion of women with PCOS. Obesity may influence ovarian stimulation by its prolongation, increase in the dose of gonadotrophins used, incidence of follicular asynchrony and interruption of stimulation. Surgical treatment of obesity is an alternative therapeutic approach when the life style changes and pharmacotherapy is of no results. Till now, there are no enough evidence in favor for the bariatric surgery to be used in the treatment of obese women with PCOS.

Key words: obesity, reproduction, adipokines, polycystic ovary syndrome, therapy

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Obesity is nowadays considered as a multifactorial chronic disease that is mainly caused by an unbalanced energy intake through daily consumption of foods and other high energy substances, and energy expenditure. The imbalance in the energy turnover is further mediated by inadequate dietary habits, low frequency of exercise and genetic background [1]. The World Health Organization defined general weight and obesity into following categories of body mass index (BMI, kg/m²): underweight: <18, normal weight: 18.5-24.9, overweight: 25-29.9, obesity class 1: 30.0-34.9, obesity class 2: 35.0-39.9, obesity class 3: ≥ 40. Obesity is associated with cardiovascular disease (CVD), diabetes mellitus, osteoarthritis and malignancies such as colon and endometrial cancer. However, it is increasingly recognized that the obesity epidemic has also contributed to reproductive disorders and fertility problems [2].

Gonadal axis is controlling reproductive function via numerous endogenous and environmental factors that are influencing the axis. A few decades ago it was proposed that the metabolic condition and nutritional status influence activation of the reproductive axis in puberty and further reproductive capacity. On the other hand, it was previously recognized a relation between change in body composition and reproductive function of women. Occurrence of puberty is caused by the change in body weight and/or body weight [3]. Discovery of leptin was shown as possible explanation of this complex mechanism that consider coupling apetite regulation and energy turnover in the regulatuon of gonadan axis for the initiation of puberty [4, 5].

**Impact of obesity on fertility**

Obesity in women has been shown to increase time to conception [6]. The relative risk of anovulatory infertility is 2.7 in women with BMI≥ 32 kg/m² at age 18, while in ovulatory but subfertile woman the chance of spontaneous conception decreases by 5% for each unit increase in the BMI [7]. High BMI is associated with an increase in serum and follicular fluid leptin concentration and decrease in serum adiponectin levels. Lower adiponectin levels are associated with increased circulating insulin which can cause hyperandrogenaemia partly by inhibiting the hepatic SHBG (sex hormone binding globulin) production. Hyperandrogenaemia results in granulosa cell apoptosis, while peripheral conversion of androgens to estrogen in adipose tissue inhibits gonadotrophin secretion [8].

Besides the impact on ovarian function, obesity could influence neuroendocrine functions leading to the diminished possibility for ovulation and fertilization in otherwise healthy women. Obesity could influence reproductive function early in life, either during or after puberty. So far, obesity in connected to the increased risk for hyperandrogenism and anovulation in reproductive aged women that is the main characteristics of women with polycystic ovary syndrome (PCOS) as the most prevalent hyperandrogenic condition [9].
Increase in body weight and fat mass is associated with disturbed balance of sex steroids in fertile women. These changes include estrogens, androgens and SHBG. Concentrations of SHBG is regulated by estrogens, iodothyronins and growth hormone as stimulators, and androgens and insulin as inhibitors. Women with androgen type of obesity have lower concentrations of SHBG that is linked to the inhibitory capacity of insulin for the synthesis of SHBG in the liver. Due to the greater decrease of SHBG concentrations in women with central obesity, fraction of free testosterone pretend to be greater in relation to the women with peripheral type of obesity that lead to the condition of functional hyperandrogenism. On the other side, decreased concentration of SHBG could lead to the increased estrogenization in obese women and be important in the protection from the development of abdominal obesity phenotype in both fertile and postmenopausal women [10].

Advanced glycation end products (AGEs) have been considered to be among the main intermediaries in the development of several diseases and conditions such as type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome (MetS), CVD, aging, inflammation and neurodegenerative disorders and reproduction [11, 12]. The AGE-RAGE (receptor for AGE) system has been implicated in the pathogenesis of multiple metabolic diseases and more recently PCOS and infertility. This system has been targeted in PCOS animal models with promising results at the level of the hormonal imbalances and granulosa cell dysfunction observed in this disease. Clearly the application of AGEs (which are elevated in serum of women with PCOS) in vitro has a direct effect on granulosa cells by making these cells behave in a manner similar to those in women with PCOS [13].

**Adipokines in obesity, metabolic syndrome and reproduction**

Central type of obesity and insulin resistance are main factors for the development of MetS. Complex mechanism that linked adipose tissue excess with MetS are not fully elucidated although it is considered that adipokines have important role in the development of MetS [14]. It is considered that insulin resistance is caused by accumulation of free fatty acids in the liver released from the visceral adipose tissue of the obese subjects due to the constant hyperinsulinemia [15]. It is also considered that dysfunctional regulation of adipokines could have important role in the explanation of the existence of insulin resistance in obese subjects. Adipokines are mainly synthetized in the subcutaneous fat tissue and it believed that the increased concentrations of cytokines from the visceral adiposity could represent mechanism for the inhibition of subcutaneous adipokines production.

Some of the adipokines posses the key role in the development and evolution of MetS. Leptin has effect on the hypothalamic regulation of appetite, and have a role in the regulation energy expenditure and glucose metabolism. Selective leptin resi-
stance could present a mechanism that linked increase of fat tissue and development of MetS [16]. Adiponectin acts through the system of AMP kinase which leads to the formation cellular NO, increased fat oxidation and inhibition of inflammation. Decrease of adiponectin in obesity is caused by insulin resistance and hyperinsulinemia [17]. Prevalence of MetS is directly related to the prevalence of obesity and with high frequency is occuring in women with PCOS [18, 19]. Increased values of androgens in PCOS could influence adipokines production and consequently increase prevalence and cardiovascular effects of MetS. Adiponectin is inversely related to the testosterone values in women with PCOS. Androgens are in positive correlation with circulatory TNF–α and IL–18, and activate macrophages to secrete cytokines. Relation between androgens and inflammation is complex and could partially depend on the effects of androgens on fat tissue [20].

**Obesity and oocite quality**

Obesity increase the risk of infertility primarily due to ovulatory dysfunction and association with negative reproductive outcomes (Table 1).

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Effect on fertility</th>
<th>Metabolic syndrome</th>
<th>Mechanism</th>
<th>Potential therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>5–8 % of reproductive aged women</td>
<td>Anovulation</td>
<td>30-75 % obese, 30-40% IGT</td>
<td>1. hyperinsulinemia 2. hyperandrogenism leading to amenorrhoea/infertility</td>
</tr>
<tr>
<td>Obesity</td>
<td>25% of women in USA</td>
<td>Anovulation BMI&gt;30 kg/m² leads to 3 fold higher risk for fertility in comparison to BMI&gt;24 kg/m²</td>
<td>IR Riski factors for T2DM and CVD</td>
<td>1. IR / insulin excess 2. hyperandrogenism leading to amenorrhoea/infertility</td>
</tr>
</tbody>
</table>

* ART, assisted reproductive technique; CVD, cardiovascular disease; IR, insulin resistance; IGT, impaired glucose tolerance; T2DM, type 2 diabetes

Risk for anovulatory infertility increases with increase in BMI. Women with BMI > 30 kg/m² have three fold higher possibility for anovulatory infertility in comparison to omen with BMI < 24 kg/m² [21]. Also, overweight or obese women
have increased possibility for spontaneous abortion and stillbirth in comparison to
the women of normal weight and an increased risk of pregnancy complications and
congenital anomalies [40].

Obesity is linked to the decreased concentrations of anti-Mullerian hormone
(AMH) that is secreted from ovarian granulosa cells and that could result in decrease
of ovarian reserve or available secondary follicles in obese women AMH values are
in positive correlation with body weight in women with PCOS [23]. Women with
BMI > 25 kg/m² have lower levels of progesterone in the luteal phase that indicate
that obesity have negative effect on the corpus luteum function [24]. Recently, a re-
lationship between intrafollicular AMH and soluble RAGE (sRAGE) concentrations
further suggests that AGEs play a role in the inhibition of cellular proliferation or a
role in enhancing granulosa cell apoptosis [13].

Direct examination of oocyte quality showed that deranged metabolic environ-
ment of the mother is leading to the disturbed microenvironment in follicular
fluid, and consequently to the pure quality of the oocytes and embryos [25]. Increased level of
CRP in follicular fluid of obese women is of particular importance as it could indicate
on inflammation and increased oxidative stress that is related to the decreased potential
of oocytes to develop. Increased oxidative stress could be an additional mechanism
with which obesity influence oocyte quality [26].

**Interrelationship of obesity, infertility and therapeutic possibilities**

Treatment of obesity in women is improving their metabolic and reproductive
health with different degree. It was shown that in women with PCOS reduction of
weight for 5-10% leads to the improvement of the clinical characteristics of the syn-
drome. In obese women with PCOS followed during longer period, and that were
intially under dietary regiment and life style change, an improvement of metabolic and
reproductive characteristics were followed. It was shown that individual response on
the weight loss could vary significantly. From the total number of analysed women, in
48% of them a partial response occured while in the 37% of women with PCOS com-
plete remission of characteristic disturbances occured [27]. Dietary regimen is leading
to the decrease or normalization of androgens, establishing regular menstrual cycles
and ovulation, and correction of metabolic disorders. In the monitoring of the effects
of change in body mass, the assessment of steroid hormones could be helpful. High
androstenedione levels in omen with PCOS, that is present after the weight reduction,
could indicate on the increased production of androgens in ovarian theca cells and/or
adrenal glands independent from the weight increase or obesity [28].

It is known tht the administration of insulin sensitizers is leading to the decrease
of hyperinsulinemia, insulin resistance, establishment of normal menstrual cyclicity
and ovulation in 30-60% of women with PCOS [29].
Obesity negatively influence on the outcomes of assisted reproductive techniques. So in women that are treated from sterility, obesity may influence the ovarian stimulation by prolongation of length of stimulation, increase of the dose of gonadotrophines used, incidence of follicular asynchrony and the stimulation out rate. Obese women tend to respond poorly to ovulation induction using clomiphene citrate. Obesity and insulin resistance are predictors of suboptimal outcomes following ovulation induction using gonadotrophins. Women with high BMI need higher total doses of FSH to achieve ovulation. These women also face a higher risk of cycle cancellation and are less likely to ovulate [30]. However, other authors showed that in spite of increased doses of gonadotrophins and longer time till ovulation in obese women with anovulatory infertility, rates of ovulation and clinical pregnancy were comparable to those in normal BMI women [31]. Similarly in women with PCOS that were under the ovulation stimulation with clomiphene or gonadotrophins, increase of BMI is negatively influencing on the ovulation rate [32].

Targeting the AGE-RAGE system could be an area of potential therapy with its possible reversal of the ovarian dysfunction observed in PCOS. Additionally, there is an increased awareness that the accumulation of AGE products at the level of the ovarian follicle might trigger early ovarian aging, which might be significant in infertile women with diminished ovarian reserve. This is supported by the positive correlation between follicular fluid sRAGE levels and AMH protein concentration. The potential accumulation of AGEs in the ovary may account for compromised efficiency of vascularization and for activation of oxidative stress response through interaction with cellular RAGE [33].

Surgical treatment of obesity is an alternative therapeutic approach in the case when the life style changes and pharmacotherapy is of no results. There are no enough evidence in favor for the bariatric surgery to be used in the treatment of obese women with PCOS. It was shown that with bariatric surgery could be achieved complete cure in a certain number of women, improvement of hirsutism, normalization of androgens, establishment of normal menstrual cyclicity and ovulation, improvement in insulin sensitivity, and stabilization of diabetes and hypertension [34].

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References


[23] Piouka A, Farmakiotis D, Katsikis I, Macut D, Gerou S, Panidis D. Anti-Mullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. Am J Physiol Endocrinol Metab 2009;296:E238–243


