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OBESITY AND REPRODUCTIVE FUNCTION IN WOMEN – PATHOGENETIC ORIGINS AND THERAPEUTIC IMPLICATIONS

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 ovultion 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. Surgcal 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/m^2): 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 associeted with disturbed bvalance of sex steroids in fertile women. These changes include estrogens, androgenes and SHBG. Concentrations of SHBG is regulated by estrogens, iodithyroins 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 adispose 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 citkines from the visceral adiposity could represent mechanuism 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 apetite, 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 inflamation. 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 adipoknes 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 citokines. 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 1. Metabolic and reproductive disorders in obesity and PCOS

	Prevalence	Effect on fertility	Metabolic syndrome	Mechanism	Potential therapy
PCOS	5–8 % of reproductive aged women	Anovulation	30-75 % obese, 30-40% IGT	1. hyperinsulinemia 2. hyperandrogenism leading to amenorrhoea/ infertility	1. Weight reduction/ physical activity 2. Insulin sensitizers 3. ART
Obesity	25% of women in USA	Anovulation BMI>30 kg/m^2 leads to 3 fold higher risk fior fertility in comparison to BMI>24 kg/m^2	IR Riski factors for T2DM and CVD	1. IR / insulin excess 2. hyperandrogenism leading to amenorrhoea /infertility	1. Weight reduction/ physical activity 2. Bariatric surgery

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

Risk for anovulatory infertility increases with increase in BMI. Women with BMI > 30 kg/m^2 have three fold higher possibility for anovulatory infertility in comparison to omen with BMI < 24 kg/m^2 [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 secreeted from ovarian granulosa cells and that could result in decrease of ovrian reserve or available secondary follicles in obese women AMH values are in possitive correlation with body weight in women with PCOS [23]. Women with BMI > 25 kg/m^2 have lower levels of progesterone in the luteal phase that indicate that obesity have negative effect on the corpus luteum function [24]. Rercently, a relationship 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 environment of the mother is leading to the disturbed microenvironment in follicular fluid, and consequently to the pure quality of the oocites 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 syndrome. 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 complete 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 sterioid 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 insuline sensitizers is leading to the decrease of hyperinsulinemia, insulin resistance, establishment of normal menstrual cyclicity and ovultion in 30-60% of women with PCOS [29].

Obesity negatively influence on the outcomes of assited 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 stimulaion 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].

Surgcal 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 acieved complete cure in a certain number of women, improvement of hirsutism, normaliyation of androgens, establishment of normall menstrual cyclicity and ovulation, improvement in insulin sensitivity, and stabilization of diabetes and hypertension [34].

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References

[1] Marti A, Martinez-Gonzalez MA, Martinez JA. Interaction between genes and lifestyle factors on obesity. Proc Nutr Soc 2008;67:1–8

[2] Metwally M, Li TC, Ledger WL. The impact of obesity on female reproductive function. Obesity Rev 2007;8:515-23.

[3] Frisch RE, McArthur JW. Menstrual cycle: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974;185:949-951

[4] Farooqi IS, Jebb SA, Langmack G et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med1999;341:879-884

[5] Macut D, Micić D, Pralong FP, Bischof P, Campana A. Is there a role for leptin in human reproduction? Gynecol Endocrinol 1998;12:321-326

[6] Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. Hum Reprod 2007;22:414-20

[7] Van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Burggraaff JM, *et al*. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod 2008;23:324-8).

[8] Metwally M, Li TC, Ledger WL. The impact of obesity on female reproductive function. Obesity Rev 2007;8:515-23].

[9] Franks S. Polycystic ovary syndrome: a changing perspective. Clin Endocrinol 1989;31:87-120

[10] Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 2000;21:697-738

[11] Yamagishi S, Nakamura K, Imaizumi T. Advanced glycation end products (AGEs) and diabetic vascular complications. Curr Diabetes Rev 2005; 1:93–106.

[12] Diamanti-Kandarakis E, Piperi C, Patsouris E, Korkolopoulou P, Panidis D, Pawelczyk L, Papavassiliou AG, Duleba AJ. Immunohistochemical localization of advanced glycation end-products (AGEs) and their receptor (RAGE) in polycystic and normal ovaries. Histochem Cell Biol 2007;127:581–589.

[13] Merhi Z. Advanced glycation end products and their relevance in female reproduction. Hum Reprod 2014;29:135-145.

[14] Halberg N, Wernstedt-Asterholm I, Scherer PE. The adipocyte as an endocrine cell. Endocrinol Metab Clin North Am 2008;37:753–768

[15] Carmina E, Orio F, Palomba S et al. Evidence for altered adipocyte function in polycystic ovary syndrome. Eur J Endocrinol 2005;152:389-394

[16] Gautron L, Elmquist JK. Sixteen years and counting: an update on leptin in energy balance. J Clin Invest 2011;121:2087-2093

[17] Matsuzawa Y. Adiponectin: a key player in obesity related disorders. Curr Pharm Des 2010;16:1896-1901

[18] Apridonidze T, Essah PA, Iuorno MJ et al. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:1929-1935

[19] Panidis D, Macut D, Tziomalos K, Papadakis E, Mikhailidis K, Kandaraki EA, Tsourdi EA, Tantanasis T, Mavromatidis G, Katsikis I. Prevalence of metabolic syndrome in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2013;78:586-592.

[20] Gonzales F. Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. Steroids 2012;77:300-305.

[21] Rich-Edwards JW, Goldman MB, Willett WC et al. Adolescent body mass index and infertility caused by ovulatory disorder. Am J Obstet Gynecol 1994;171:171–177

[22] Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 2009;301:636–650

[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

[24] Santoro N, Lasley B, McConnell D, et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. J Clin Endocrinol. Metab 2004;89:2622–2631

[25] Robker RL, Akison LK, Bennett BD, et al. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women. J Clin Endocrinol Metab 2009;94:1533–1540

[26] Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol 2005;3:28

[27] Pasquali R, Gambineri A, Cavazza C et al. Heterogeneity in the responsiveness to long-term lifestyleintervention and predictability in obese women with polycystic ovary syndrome. Eur J Endocrinol 2011;164:53–60

[28] Stener-Victorin E, Holm G, Nilsson L et al. Are there any sensitive and specific sex steroid markers for polycystic ovary syndrome? J Clin Endocrinol Metab 2009;95:810–819

[29] Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr Rev 2009;30:1–50

[30] Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology – a systematic review. Human Reproduction Update 2007;13:433–444

[31] Balen AH, Platteau P, Andersen AN, Devroey P, Sorensen P, Helmgaard L, *et al*. The influence of body weight on response to ovulation induction with gonadotrophins in 335 women with World Health Organization group II anovulatory infertility. BJOG 2006;113:1195-202

[32] Al-Azemi M, Omu FE, Omu AE. The effect of obesity on the outcome of infertility management in women with polycystic ovary syndrome. Arch Gynecol Obstet 2004;270:205–210

[33] Tatone C, Amicarelli F. The aging ovary-the poor granulosa cells. Fertil Steril 2013;99:12–17

[34] Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F et al. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 2005;90:6364–6369