Obesity as a disruptor of the female fertility

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Obesity as a disruptor of the female fertility

GRADUATE THESIS



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Abbreviations

AMH	Anti-Müllerian hormone
AMPK	Adenosine monophosphate-activated protein kinase
ART	Assisted reproductive technology
BFD	Body fat distribution
BMI	Body mass index
CC	Clomiphene citrate
FSH	Follicle-stimulating hormone
GABA	gamma-Aminobutyric acid
GnRH	Gonadotropin-releasing hormone
HMG	Human menopausal gonadotropin
ICSI	Intracytoplasmic sperm injection
IGFBP	Insulin-like growth factor binding proteins
IGF-I	Insulin-growth factor-I
IGF-IR	Insulin-like growth factor-I receptors
IRS	Insulin receptor substrate
IVF	In vitro fertilization
IWL	Intensive weight loss
JAK/STAT	Janus Kinase/Signal Transducer and Activator of Transcription
LGI	Low glycemic index
LH	Luteinizing hormone
LOD	Laparoscopic ovarian drilling
NICE	National Institute for Health and Care Excellence
PCOS	Polycystic ovary disease
PPAR-γ	Proliferator-activated receptor gamma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SET	Structured exercise training
SHBG	Sex hormone binding globulin
WC	Waist circumference
WHO	World Health Organization

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Summary

Obesity as a disruptor of the female fertility

Author: Zrinka Šakić

Obesity is increasing worldwide and has a detrimental influence on female reproductive health. Particularly in obese women the hypothalamic-pituitary-ovarian axis is disrupted and they frequently suffer from menstrual dysfunction which eventually leads to anovulation and infertility. Majority of women with an ovulatory disorder contributing to their infertility have polycystic ovary syndrome (PCOS) and a significant proportion of women with PCOS are obese. The development of obesity in women with PCOS, in turn, amplifies and may even unmask the biochemical and clinical abnormalities characteristic of this condition. In obesity, the adipocytes act as an endocrine organ through secretion of adipokines that are commonly involved in metabolic regulation and inflammatory process. Additionally, hormonal imbalance such as insulin resistance and hyperandrogenism further contribute to fertility dysfunction. Overweight and obese women have lower outcomes following fertility treatments than the normal population. They poorly respond to induction of ovulation, require higher doses of gonadotropins and longer treatment courses for follicular development and ovulatory cycles. Weight loss is essential for the improvement of reproductive outcomes in obese women with and without PCOS. Women should be provided with assistance to lose weight, including psychological support, dietary advice, exercise classes and where appropriate, weight reducing agents or bariatric surgery.

Keywords: obesity; female fertility; PCOS

Sažetak

Pretilost kao narušitelj reprodukcijske sposobnosti žena

Autor: Zrinka Šakić

Učestalost pretilosti raste širom svijeta te ima štetan utjecaj na reproduktivno zdravlje žena. Osobito kod pretilih žena dolazi do poremećaja hipotalamičko-hipofizno-ovarijske osi te zbog toga često pate od menstrualne disfunkcije koja naposlijetku dovodi do anovulacije i neplodnosti. Većina žena s ovulacijskim poremećajem koji doprinosi njihovoj neplodnosti imaju sindrom policističnih jajnika (PCOS), a značajan udio žena s PCOS-om je pretilo. Razvoj gojaznosti kod žena s PCOS-om zauzvrat pojačava i može čak razotkriti biokemijske i kliničke abnormalnosti karakteristične za ovo stanje. Kod pretilosti adipociti djeluju kao endokrini organ putem izlučivanja adipokina koji su obično uključeni u regulaciji metabolizma i upalnom procesu. Osim toga, hormonalni disbalans, kao što su inzulinska rezistencija i hiperandrogenizam, dodatno doprinosi disfunkciji plodnosti. Žene s prekomjernom tjelesnom težinom i pretilošću imaju smanjene ishode nakon tretmana plodnosti u usporedbi s normalnom populacijom. One pokazuju slabiji odgovor na indukciju ovulacije, iziskuju veće doze gonadotropina te dulje liječenje za folikularni razvoj i ovulacijske cikluse. Gubitak težine je neophodan za poboljšanje reproduktivnih ishoda kod pretilih žena sa i bez PCOS-a. Ženama bi trebalo pružiti pomoć pri mršavljenju, uključujući psihološku podršku, savjete o prehrani, tečajeve vježbanja i, prema potrebi, sredstva za smanjenje tjelesne težine ili barijatrijsku kirurgiju.

Ključne riječi: pretilost; plodnost; PCOS

1. Introduction

Obesity is a globally increasing health problem and has an impact on many aspects of reproductive health. It is a common problem among women of reproductive age. Obesity and overweight involve abnormal and excessive fat accumulation that negatively affects health status. The World Health Organization (WHO) defines overweight and obesity in terms of body mass index (BMI). An individual with a BMI of 25–29 is classed as overweight and one with BMI above 30 as obese. As of 2014, over 600 million adults and 15% of women worldwide were known to be obese, which was more than double the numbers reported in 1980 (1). Female obesity has a great impact on reproductive function and the hormonal milieu. In relation to fertility, it is most frequently associated with polycystic ovary syndrome (PCOS) which is the commonest endocrinopathy in women of reproductive age. Most women with PCOS are overweight, with estimates of the prevalence of obesity in PCOS ranging between 38 and 88% (2). Infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (3). The link between obesity and infertility is complex. The available knowledge supports the concept that androgen alterations and their balance with estrogen represent the most important mechanism responsible for the development of subfertility or infertility in obese women (4). This focuses on the potential influence of the altered metabolic state on the reproductive health of women, the effects of obesity on fertility, and the management of infertility in obese and overweight women.

2. Obesity and infertility

Obesity represents a significant cause of infertility and its negative effect has been recognized since the days of Hippocrates: “The girls get amazingly flabby and podgy … People of such constitution cannot be prolific … fatness and flabbiness are to blame. The womb is unable to receive the semen and they menstruate infrequently and little. As good proof of the sort of physical characteristics that are favorable to conception, consider the case of serving wenches. No sooner do they have intercourse with a man than they become pregnant, on account of their sturdy physique and their leanness of flesh (5).”

Obesity is known to contribute to ovulatory dysfunction and to compromise ovarian response to ovulation induction agents such as clomiphene (6). Approximately 15% of women undergoing assisted reproductive technology (ART) are overweight or obese and their success in treatment is significantly reduced (7). In addition, obese women who achieve pregnancy have higher risks of miscarriage and maternal complications associated with pregnancy such as gestational diabetes, hypertensive disorders, preterm birth, and cesarean section (6,8). Simple obesity has many deleterious consequences on general health and is associated with myriad medical conditions including type 2 diabetes mellitus, cardiovascular diseases, osteoarthritis, sleep apnea, breast cancer, uterine cancer, polycystic ovary disease (PCOS) and metabolic syndrome. Pivotal role in infertility of obese women is played by insulin resistance and hyperinsulinemia. Insulin stimulates steroidogenesis in the ovary resulting in an increase of serum androgens and also fall in sex hormone binding globulin (SHBG) which is synthesized by the liver. SHBG is the carrier protein for sex steroid hormones. Moreover, adipose tissue stores excess sex steroids which are readily available and raise plasma androgens. These mechanisms have a detrimental effect on the ovulatory capacity of the ovary (5). Guidelines from the National Institute for Health and Care Excellence (NICE) recommend that women with a BMI $\geq$ 30 kg/m² should be informed about the health benefits of weight loss before conceiving for both themselves and the baby. Moreover, health professionals should advise, encourage and help women to reduce weight before becoming pregnant using evidence-based behavior change techniques and specific dietary advice, and offer weight-loss programs involving diet and physical activity to their obese patients (9).

Moreover, The British Fertility Society advises to abstain from fertility treatment in women with BMI over 35 kg/m² (10) and to start lifestyle intervention aimed at weight reduction, although there is not enough convincing evidence that weight reduction eventually leads to more spontaneous achieved uncomplicated pregnancies. It is debatable whether the restriction of access to fertility treatment on the ground of female BMI is in accordance with the ethical standards of the medical profession. Moreover, the decision to postpone the fertility treatment to allow weight loss often results in a further increase in maternal age in women who are not very young. Time lost and poor success of conventional weight loss strategies would jeopardize the chances of conception for many women.

2.1 Reproductive endocrinology in the obese woman

Until recently, the precise mechanism of communication between adipose tissue and the female reproductive system was considered largely a mystery. In addition to its role in lipid storage, white adipose tissue is the source of critical endocrine signals in the control of body weight and a range of diverse protein factors, termed adipokines, which are considered the essential link in the communication between the central nervous system and peripheral tissues. As body mass increases, a state of relative hypoxia occurs within the clusters of adipocytes, evoking an inflammatory response that results in the release of adipokines. The adipokines such as leptin, adiponectin, resistin, visfatin, and ghrelin are among the most investigated factors that may have an impact on the reproductive performance of obese women (11).

Leptin

Leptin is a polypeptide hormone which name is derived from the Greek word *leptos* meaning ‘thin’. Correspondingly, the ultimate aim of leptin is to prevent obesity. This is achieved by inhibition of feeding at the hypothalamic level and increased energy expenditure. Once bound to specific receptors, it induces the expression of several hypothalamic neuropeptides that regulate neuroendocrine function as well as energy intake and expenditure. Its effect on the hypothalamic-pituitary axis is stimulatory. Levels of leptin have been shown to display circadian and ultradian variations, and these variations have been associated with minute-to-minute variations in luteinizing hormone (LH) and estradiol levels. Therefore, leptin may be responsible for providing the brain

with information on the crucial amount of fat stores necessary for LH-releasing hormone secretion and activation of the hypothalamic-pituitary-gonadal axis. The amount of leptin delivered to the brain is greater in women than in men due to higher concentrations of leptin in the cerebrospinal fluid in women. This suggests that women may be more resistant to the action of leptin and consequently need a higher level to achieve an adequate response (11). Leptin affects GnRH pulse neurons indirectly through GABA or kisspeptin. Knockout models for the leptin receptor that is found on GABA-specific neurons display delayed puberty and decreased fecundability in animal models. Correspondingly, a loss-of-function gene mutation in the kisspeptin gene results in delayed or absent puberty. Hypothalamic kisspeptin levels often correlate with leptin levels in line with low energy states, making this an alternate pathway for leptin signaling. Both low serum leptin levels and low hypothalamic kisspeptin levels decrease LH secretion by the pituitary, ultimately affecting ovulation (12). At the ovarian level, supraphysiologic levels of leptin inhibit androstenedione and progesterone production. Additionally, human granulosa and cumulus cells exposed to leptin in vitro lead to a downregulation in anti-Müllerian hormone (AMH) gene expression via the JAK/STAT pathway potentially leading to ovulatory dysfunction (12). Serum leptin levels vary over the course of the menstrual cycle, increasing during the late follicular and luteal phases. The reason for this increase is not clear, however, it may result from an increase in leptin production from adipocytes in response to increased caloric intake, hypothalamic release of neuropeptide Y, or the release of leptin from the mature follicle. Furthermore, leptin's influence on follicular development and oocyte maturation may have important implications for ovulation induction and assisted reproductive technologies. Elevated leptin concentrations in obesity can then lead to inhibition of steroidogenesis in the granulosa and theca cells, which may partly explain poor fertility in obese patients (11).

To summarize, normal leptin homeostasis is required for normal physiologic functions at the level of the hypothalamus and the ovaries. While low levels of leptin could disrupt the pulsatile release of GnRH, supraphysiologic levels of leptin could disrupt ovarian folliculogenesis.

Adiponectin

Adiponectin is a protein hormone similar to the TNF superfamily. It is produced by adipocytes in white adipose tissue, and binds to 3 receptors, AdipoR1, AdipoR2, and T-cadherin, to affect the cell function of the enzyme adenosine monophosphate-activated protein kinase (AMPK). AdipoR1 and AdipoR2 receptors are ubiquitously expressed and largely on female reproductive tissues, including ovary, placenta, endometrium, and oviduct. It has been shown that adiponectin inhibits LH and GnRH release, indicating its possible role in modulating the central reproductive endocrine axis. Circulating adiponectin levels decrease with obesity and increase with weight loss. Its major effects are devoted to increasing the insulin sensitivity by stimulating glucose uptake in liver and muscles while decreasing hepatic gluconeogenesis and promoting the fatty acid β-oxidation in the skeletal muscle. Consequently, adiponectin reduces triglyceride accumulation and enhances insulin sensitivity. Reduced expression of AdipoR1 and AdipoR2 has been also observed in endometria of women with recurrent implantation failure compared with fertile women, suggesting an important role of adiponectin signaling in uterine receptivity and its possible contribution to implantation failures and pregnancy loss in women with maternal metabolic conditions such as obesity and PCOS (13). Adiponectin serum levels drop down in obesity and in insulin resistance while increasing with weight loss (14).

Resistin

Resistin is protein adipokine that positively correlates with body fat and is inhibited by thiazolidinediones. It is strongly related to the insulin resistance found in obese individuals and therefore may act as a link between obesity and the occurrence of type 2 diabetes (11). The resistin gene polymorphism is associated with BMI in women with PCOS, suggesting that it might be related to adiposity in PCOS (13). A randomized placebo-controlled study recently showed that treatment with the insulin sensitizer rosiglitazone significantly reduces the serum resistin levels in overweight women with PCOS, thus implying the contribution of this adipokine to the insulin sensitivity improvement during treatment (15).

Visfatin

Visfatin is an endocrine, autocrine as well as a paracrine peptide with many functions and it is expressed by a variety of tissues and cell types, including adipocytes, lymphocytes, bone marrow, liver, muscle, trophoblast, and fetal membranes. In vitro studies have demonstrated that visfatin stimulates glucose uptake in both adipocytes and muscle cells while suppressing the release of glucose by hepatocytes. A recent meta-analysis revealed that plasma visfatin is significantly increased in both overweight and obese subjects, or in patients with type 2 diabetes mellitus and metabolic syndrome (16,17). It has been also reported that the gene expression and circulating levels of visfatin are increased in women with PCOS as compared with their age and BMI matched controls (18).

Ghrelin

Ghrelin is a peptide identified as the endogenous ligand for the growth hormone secretagogue receptor. It is produced in the stomach and is involved in the short-term regulation of feeding (11). Gastric expression (and consequent plasma concentrations) of ghrelin typically increase on fasting and decrease following food intake. There is now extensive data supporting the role of ghrelin not only as an established orexigenic hormone in metabolism but also in reproduction. Studies suggest stimulatory (pituitary in vitro) and predominantly inhibitory (hypothalamus via kisspeptin, and gonads) actions of ghrelin on the reproductive axis. The exact action of ghrelin may, therefore, vary between reproductive tissues and hormonal ambiance. In terms of ghrelin's overall role, multiple lines of evidence suggest that ghrelin serves as an important link between metabolism and reproduction by informing higher brain centers of changes in peripheral energy balance. This role of ghrelin appears to be key in the regulation of puberty as well as menstrual cyclicity depending on energy balance (19).

3. Obesity and PCOS

Polycystic ovary syndrome is a major cause of female infertility and is characterized by clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries, and chronic oligo- and/or anovulation. It is a heterogeneous condition also associated with features of the metabolic syndrome. Based on the Rotterdam consensus workshop the prevalence of

PCOS rates up to 15% (20). It was estimated that between 38 and 88% of women with PCOS are overweight or obese (21,22). Obesity in women with PCOS not only involves the peripheral tissue but also a significant increase occurs in the intra-abdominal fat, which is independent of obesity (23). Studies have shown that even modest weight loss of 5% body weight in obese women has resulted in the increase of insulin sensitivity, SHBG and trends toward normalization of reproductive hormonal profiles favoring restoration of menstrual cyclicity in women with and without PCOS (6,24). From that, it can be concluded that adiposity plays a crucial role in the development and maintenance of PCOS and strongly influences the severity of both its clinical and endocrine features in many women with the condition. Although not all women with PCOS are obese, PCOS is associated with a disorder of energy balance, which predisposes to obesity (5). To the contrary, a likely explanation for the mechanisms underlying the development of obesity in women with PCOS is the combined effect of a genetic predisposition to obesity in the context of an obesogenic environment such as poor diet and reduced exercise. The development of obesity in women with PCOS, in turn, amplifies and may even unmask the biochemical and clinical abnormalities characteristic of this condition. One implication of this is that many obese women with PCOS may have remained asymptomatic because they have not become obese (2). Obesity in PCOS affects reproduction via various mechanisms among which hyperandrogenism, increased luteinizing hormone (LH) and insulin resistance play a pivotal role (25).

3.1 Impact of obesity on reproduction in women with PCOS

Women with PCOS, notably those with regular menstruation, are not necessarily infertile. However, women with menstrual irregularities may have difficulties to conceive. The main cause of infertility in PCOS is anovulation. Obesity seems to be an additional factor which contributes to the reduced fecundity (26). There are several mechanisms via which obese women with PCOS may have fertility problems.

The consequences of insulin resistance

Burghen et al. initially established in 1980 the presence of insulin resistance in women with PCOS (27). Currently, it is known that weight gain in both normal women and those with PCOS is associated with the development of insulin resistance. Furthermore, ever since the evidence that the use of insulin-sensitizing drugs in women with PCOS (without

any associated weight loss) significantly improved the characteristic metabolic and endocrine features, ovulatory function, menstrual cyclicity, and fertility rates, it was led to a hypothesis that insulin resistance and the associated hyperinsulinemia play an important role in the etiology of PCOS (2,24). In addition, it was ascertained that genes most commonly associated with the mutated PCOS phenotype are those that control the insulin receptor, the insulin receptor substrate (IRS-1 and 2), calpain 10, peroxisome proliferator-activated receptor gamma (PPARγ) polymorphisms, and genes for expression of androgen-producing enzymes. Mutations of the insulin receptor gene lead to autophosphorylation and extreme insulin resistance (28).

Insulin is an important hormone for glucose metabolism, adipocyte function, and energy homeostasis. It has a role in central anorexigenic control and in the signaling of GnRH neurosecretion. It is involved in the hypothalamic-pituitary-ovarian axis as a co-gonadotropin and substantially affects the function of theca and granulosa follicle cells.

Insulin interacts synergistically with LH within the theca cells of polycystic ovaries and causes activation of the enzyme P450c17α which is the crucial enzyme in the biosynthesis of ovarian androgens such as testosterone (24,29,30). A further adverse effect of hyperinsulinemia on the polycystic ovaries includes the arrest of ovarian follicle development at 5-10 mm thereby contributing towards anovulation (31,32). In women with PCOS, hyperinsulinemia may also lead to adverse effects at some non-ovarian sites. These include the pituitary gland via enhancement of pituitary LH pulse amplitude, the liver through suppression of hepatic synthesis of sex hormone-binding globulin (SHBG) and the adrenal glands through stimulation of P450c17α activity thereby increasing androgen production (2).

Understanding why many (particularly obese) women with PCOS are significantly more insulin resistant than their age- and BMI-matched female counterparts is essential. Women with PCOS have an abnormal distribution of adipose tissue mainly in visceral and abdominal subcutaneous depots which is called an android body fat distribution (BFD). It can contribute to hyperandrogenemia through its adverse effects on insulin sensitivity and consequent co-gonadotropic effects of hyperinsulinemia on the ovaries. There is a vicious circle in which android fat endorses more android fat generation further exacerbating the predisposition towards weight gain in women with PCOS. The cycle can, fortunately, be interrupted by dietary intervention and/or use of insulin-sensitizing

drugs. Apart from BFD, there are suggestions that adipose tissue behaves differently in women with PCOS and their BMI-matched female counterparts. This behavior includes abnormalities of lipolysis, steroid hormone metabolism (both sex steroids and cortisol) and appetite regulation by circulating adipocyte-derived factors (2).

Another proposed mechanism of hyperandrogenism induced by hyperinsulinemia occurs through the insulin-like growth factor-I (IGF-I) which is secreted by human ovarian tissue while its receptors are also located in ovaries. Insulin can bind IGF-I receptors (IGF-IR) as well as its own receptors and activate the tyrosine kinase of the β- subunit resulting in triggering the intracellular events that potentiate those normally mediated by IGF-I. Therefore, the insulin-like growth factor binding proteins (IGFBP) include a group of secreted proteins which bind to IGF-I and IGF-II with high affinity and modulate the biological actions of IGF (33). When the IGFBPs bind and activate the IGF-IR, the hepatic synthesis of IGFBP-I is decreased thus making IGF-I more biologically available with the final effect of enhancing the androgen production by theca interstitial and stromal cells.

In addition, one study showed that insulin reinforces the activity of the LH on granulosa cells by exerting two distinct effects on the preovulatory follicle, namely the steroidogenesis activation and the inhibition of mitosis thus restraining the terminal differentiation of those cells (34). As a result of the enhanced steroidogenesis due to insulin and its interaction with LH, the unfavorable environment produces the blockage of the follicle growth. Hence, the premature luteinization and the consequent follicular arrest result in menstrual cycle disorders and oligo-anovulation which appear strictly related to obesity (35). The increased estrogen production, due to peripheral conversion, impairs the function of the hypothalamic-pituitary-gonadal axis and portrays both estrogen excess and hyperandrogenism as major causes of anovulation in these patients (13).

Hyperandrogenism

Ovarian hyperandrogenism is a key feature of PCOS. The intrinsic amplified steroidogenic capacity of theca cells results in increased ovarian androgen secretion. Endocrine mechanisms may contribute to hyperandrogenism and these include pituitary luteinizing hormone (LH) hypersecretion, relative follicle-stimulating hormone (FSH)

insufficiency and high levels of insulin and anti-Müllerian hormone (AMH) inhibiting aromatase activity. Ovarian hyperandrogenism in PCOS may arrest folliculogenesis through inhibition of granulosa cell proliferation and maturation, estrogen and progesterone secretion, aromatase action and increase of 5α-reductase activity. Obesity amplifies hyperandrogenism in PCOS resulting in increased total testosterone, free androgen index and decreased sex hormone-binding globulin (SHBG). Obese women with PCOS exhibit a higher degree of insulin resistance and compensatory hyperinsulinemia which contributes to androgen excess. It is obvious that obesity may deteriorate hyperandrogenism in women with PCOS, which is involved in anovulatory infertility (25).

Hypersecretion of LH

In women with PCOS, LH levels are frequently elevated due to anovulation and lack of progesterone and hyperandrogenemia, which attenuates the progesterone negative feedback effect. However, obese PCOS women demonstrate a blunted LH secretion, through mechanisms acting at the pituitary and not the hypothalamic level. These mechanisms may involve the aforementioned insulin and leptin. It was hypothesized that high LH levels in circulation may cause premature luteinization and anovulation (34). It seems that in lean but not obese women with PCOS, elevated LH is a significant mechanism of anovulation (25).

4. AMH in obese patients

Anti-Müllerian hormone (AMH) is a product of the granulosa cells of small antral and pre-antral follicles, and clinically, it may be reflective of the prediction of ovarian reserve in women undergoing fertility evaluation and treatment (36).

For this reason, it is important to evaluate the change in the levels of AMH, as a fertility parameter in obese women with or without PCOS, submitted to aerobic exercise with the aim of losing weight. The slimming via exercise or diet is considered one of the most important targets in lifestyle modification programs capable to induce an improvement in reproductive function among obese women with PCOS (37). In addition, a recent large retrospective study established a positive association between BMI and serum AMH

levels in infertile patients. One of the possible explanations for the positive association of BMI and AMH serum levels observed in the observed patients is a hormonally mediated relationship. It is known that circulating androgens, insulinemia and insulin resistance increase along with BMI. The same parameters were shown to be positively associated with serum AMH levels. Consequently, increasing insulin in parallel with BMI can indirectly stimulate, through increased intraovarian androgen synthesis, the AMH production by granulosa cells. However, the findings also suggested that a low AMH level in a patient with moderate body weight excess (BMI < 40 kg/m^2) cannot be explained by increased adiposity. Therefore, these patients should be advised to start the treatment for infertility as soon as possible instead of postponing treatment until body weight is optimized (38).

5. Influence of obesity on infertility treatment

Overweight and obese women have lower outcomes following fertility treatments than the normal population. They poorly respond to induction of ovulation, require higher doses of gonadotropins and longer treatment courses for follicular development and ovulatory cycles. In addition, the oocyte yield is lower in obese women resulting in a higher rate of cycle cancellation (39). Two studies performed in large cohorts of Danish women planning pregnancies showed an inverse relation of fecundity with respect to the BMI increase (40). Therefore, in these women weight loss is strongly recommended in order to improve the fertility functions. However, body weight reduction during the periconceptual period might have an impact on the conceptus, therefore, it is advisable that an attempt to lose weight via various methods to be completed before the achievement of pregnancy (41).

However, the majority of women find dieting and lifestyle changes time consuming and they do not comply with these measures. Correspondingly, several pharmaceutical compounds are used for ovulation induction. The extent to which excess body fat can affect the treatment outcome during ovulation induction has not been fully addressed.

Clomiphene citrate

Clomiphene citrate is considered the first-line treatment for ovulation induction in anovulatory infertile women with PCOS. In properly selected PCOS patients, the cumulative pregnancy rate after six cycles of treatment exceeds 60% and after 10 cycles 90% (25). The inability of the ovaries to respond to this drug during 6 months of treatment, known as clomiphene resistance, has been associated with various hormonal and clinical characteristics of women, including BMI (42). It has been recently shown that structured exercise training combined with a hypocaloric diet for 6 weeks was adequate to increase the response to clomiphene and the ovulation rate in overweight and obese PCOS patients (43).

Low-dose FSH

Low-dose protocols of human menopausal gonadotropin (HMG) or FSH protocols are used as a second-line treatment for ovulation induction in PCOS in case of clomiphene resistance or failure (44). The effectiveness of treatment with gonadotropins in PCOS is affected by various parameters including BMI. In a retrospective analysis of data, women with BMI >28 kg/m² undergoing ovulation induction showed a lower ovulation rate and an increased miscarriage rate than normal controls, although the proportion of women who became pregnant was similar with that of women with normal BMI (45). It has been found that obese as compared to lean women require higher doses of gonadotropins possibly due to the higher number of immature follicles and the higher insulin resistance and free androgen index (46). Although BMI plays a critical role in the prediction of the outcome of treatment with ovulation induction in PCOS, a quantitative approach to the real effect has not been investigated.

Laparoscopic ovarian drilling

Laparoscopic ovarian drilling (LOD) is a surgical treatment where electrocautery or laser is used to destroy parts of ovaries in order to possibly restore regular ovulation cycles. It is considered a second-line treatment option in women with PCOS, and it competes with FSH for cases of clomiphene resistance. An extremely low multiple pregnancy rate has been shown with LOD. Obesity seems to affect the effectiveness of LOD, as it has been shown in a retrospective study of 200 PCOS patients, pre-treated with clomiphene

unsuccessfully (47). According to that study, in women with a BMI ≥ 35 kg/m² ovulation and pregnancy rates were significantly lower as compared to moderately overweight and normal-weight women. However, it was shown that BMI did not have any influence on the conception once ovulation was achieved.

Insulin sensitizers

Insulin-sensitizing agents reduce insulin resistance and hyperinsulinemia, to a large extent reverse the endocrinopathy and effectively and safely ameliorate the reproductive, metabolic and cardiovascular morbidity in PCOS. Improved pregnancy outcomes in women with PCOS receiving metformin, a representative of this drug category, may be attributed to its ability to reduce insulin resistance as well as hyperinsulinemia and the inhibition of the hypofibrinolytic plasminogen activator resulting in improvement of oocyte quality and folliculogenesis for the amelioration of PCOS (48). The action of metformin is widely discussed in the literature, which is considered as the first-line medication for the treatment of type 2 diabetes. The major effects of metformin include its property to decrease liver glucose production by suppressing hepatic gluconeogenesis as well as the increase of insulin sensitivity and peripheral glucose uptake (49). The molecular mechanism of metformin is not entirely understood. Multiple potential mechanisms of action have been proposed and are thought to contribute to improve the oocyte maturation in PCOS and may exert a definitive favorable effect on infertility associated with inefficient oocyte differentiation and maturation. However, it has been recommended, due to the non-significant improvement in outcomes, to use metformin only in cases with an impaired glucose tolerance (25).

In vitro fertilization

In vitro fertilization (IVF) is a third-line treatment for PCOS unless other infertility factors are present. In IVF/intracytoplasmic sperm injection (ICSI) cycles, obesity and PCOS were found to independently decrease oocyte size (50). An increased miscarriage rate was found in a mixed population of obese women undergoing IVF/ICSI as compared to women with normal weight, while a tendency for a higher miscarriage rate was found in women with a BMI >25 kg/m² regardless of the mode of conception. Although obese women with PCOS require higher amounts of gonadotropins for ovarian stimulation, the ideal protocol has not been identified.

6. Systematic review

The prevalence of obesity along with ovulatory dysfunction and female infertility is increasing. The majority of women with an ovulatory disorder contributing to their infertility have PCOS and a significant proportion of those women are obese. In contemporary literature, obesity, PCOS and infertility are intertwined, and it is difficult to create a clear distinction between them. This "gray area" stems from the correlated pathophysiology of these disorders, as well as the frequent coexistence of the pathologies. Furthermore, obesity has a significantly hazardous effect on fertility in women, on the outcome of the fertility treatment interventions, and leads to major maternal and fetal complications. Thus, when infertility is associated with obesity, one of the essential goals of the restoring reproductive function is the reduction of the insulin resistance mostly by weight loss and reduction of visceral fat. The objective of this systematic review was to assess the studies performed on this topic and to investigate whether a body weight loss improves fertility in all women independent of PCOS and/or other aforementioned pathologies.

6.1 Methods

Inclusion criteria

Only randomized controlled trials (RCT) published from May 2004 to May 2019 which enrolled female patients above 18 years of age were included.

Search strategy and selection criteria

This review was performed by searching PubMed using the following search terms: 'obesity, female infertility'. The titles and abstracts were independently screened to determine if they met the inclusion criteria. Full texts of the chosen articles were assessed to confirm this. Reference lists of relevant articles were screened for additional studies.

Data collection

From the included articles the following data was extracted: the number of patients in the study, study length, outcome studied, presence of PCOS, and the mean weight loss.

Data analysis

A systematic analysis was performed comparing fertility rates in weight loss vs. non-weight loss cohorts with and without PCOS. Data was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

6.2 Results

The initial literature search yielded 34 articles, 23 were excluded after the title and abstract review. Seven articles were included in the systematic analysis after full-text review of 11 articles (**Figure 1**). The major characteristics of the included studies are displayed in **Table 1**. Comparison of studied population characteristics is shown in **Table 2**.

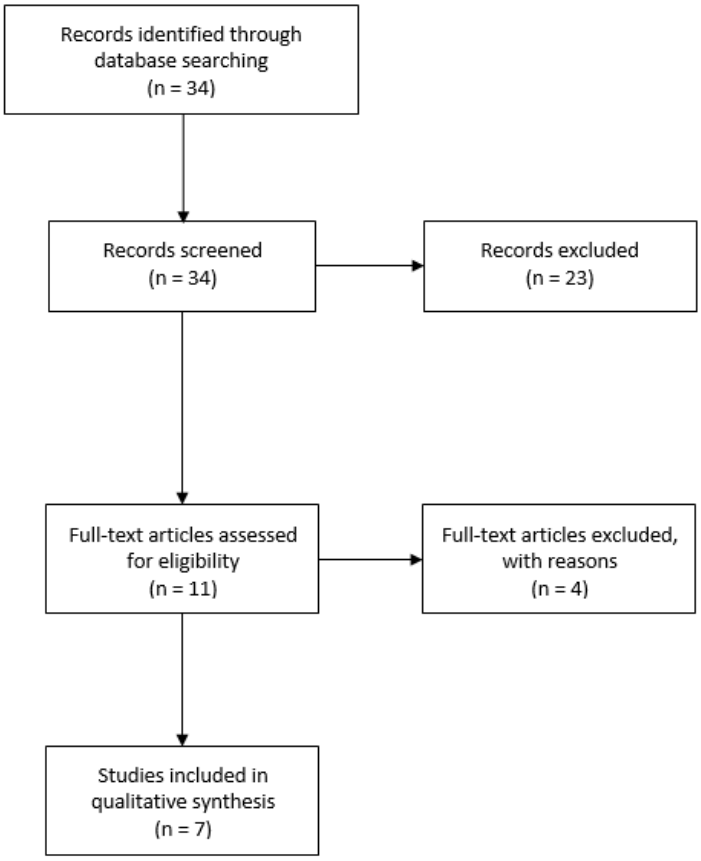


Figure 1 PRISMA flow chart showing literature search

Table 1 Selected studies

Study	Study length (years)	Patient number	PCOS patients, non-PCOS patients or no subdivision	Outcome studied	Result for weight loss intervention group
Becker et al.	2	26	PCOS[¶] and non-PCOS with no subdivision	Pregnancy rate; oocyte retrieval	**Pregnancy rate[¶¶]:** 21,4%
Einarsson et al.	6,3	295	PCOS and non-PCOS, **subdivided results**	Live birth rate; pregnancy rate	**Live birth rate:** 29,6% **Pregnancy rate:** 34,9%
Legro et al.	5,3	118	PCOS	Ovulation rate; pregnancy rate; live birth rate	**Ovulation rate:** 60% **Pregnancy rate:** 26% **Live birth rate:** 26%
Mutsaerts et al.	5	564	PCOS and non-PCOS with no subdivision	Vaginal birth of healthy singleton at term; live birth rate; pregnancy rate	**Vaginal birth of healthy singleton at term:** 27,1% **Live birth rate:** 43,9% **Pregnancy rate:** 62,5%
Palomba et al.	1,6	96	PCOS	Ovulation rate	**Ovulation rate:** 37,5%[ɣ]; 12,5%[ɣɣ] **Pregnancy rate:** 3,1%
Rothberg et al.	1,5	11	PCOS and non-PCOS with no subdivision	Pregnancy rate; live birth rate	**Pregnancy rate:** 50%[*] **Live birth rate:** 50%[*]
Sim et al.	4	47	PCOS and non-PCOS with no subdivision	Pregnancy rate; live birth rate	**Pregnancy rate:** 48,1% **Live birth rate:** 44,4%

¶ Fifteen percent of patients evaluated had PCOS

¶¶ This was not a primary outcome studied. These patients (3/14) in the intervention group experienced a spontaneous pregnancy during the follow-up

* Neither ovulation nor conception reached statistical significance (3/6 women ovulated and conceived in the IWL group vs 0/5 in the SCN group)

ɣ Group allocated to SET plus hypocaloric diet for 6 weeks plus one-cycle of CC added after the first 2 weeks

ɣɣ Group allocated to SET plus hypocaloric diet for 6 weeks

Table 2 Comparison of studied population characteristics

Study	Palomba et al.	Legro et al.	Sim et al.	Rothberg et al.	Becker et al.	Mutsaerts et al.	Einarsson et al.
Number of patients in intervention group	32	50	22	11	11	289	152
PCOS patients, non-PCOS patients, Mixed	PCOS	PCOS	Mixed	Mixed	Mixed	Mixed	Mixed
Type of intervention	Diet + Exercise	Diet + Medication	Diet + Exercise	Diet	Diet	Diet + Exercise	Diet
Duration of intervention (weeks)	6	16	12	16	12	26	16
Age (years) (mean [SD])	28,4 ± 8,3	28,6 ± 3,4	32,9 ± 3,3	32 ± 4	31,4 ± 0,9	29,7 ± 4,5	33,1 ± 1,3
Weight (kg) (mean [SD])	86,2 ± 7,0	96 ± 15,8	95,8 ± 12,7	107,5 ± 12	77,0 ± 2,1	-	92,4 ± 8,0
BMI (mean [SD])	31,1 ± 3,0	35,1 ± 4,6	35,1 ± 3,8	41 ± 3	28,67 ± 0,6	36 ± 3,6	33,1 ± 1,3
Weight loss (kg) (mean [SD])	4,4 ± 1,0	6,2	6,6 ± 4,6	14 ± 6; 5 ± 5*	4,51 ± 0,83	5,3 ± 6,1	9,4 ± 6,6

*First results are for intensive weight loss group, second for the standard-of-care nutrition (SCN) group

6.3 Discussion

Obesity is associated with a decrease in fertility and contributes to many couples seeking assisted reproductive methods to achieve pregnancy. Studies included in the review generally show a positive effect on fertility, despite observing for different primary outcomes and using different styles and duration of intervention. Participants in the studies were either exclusively patients with PCOS or a mixed group, and only one study provided a sub-analysis between PCOS and non-PCOS obese females. No study has examined exclusively obese non-PCOS patients. Average weight loss in all studies was 6,93 kg, however, this is to be interpreted with great care, as the studies had different designs, including different interventions, goals, and duration.

Most interventions were based on a caloric restriction and some form of physical exercise and lasted from 6 weeks up to 6 months. Three studies combined dietary intervention with physical activity, one study used weight loss medication in combination with caloric restriction and three studies used exclusively dietary modification.

PCOS – only patients

Women with PCOS are frequently obese and insulin resistant which is associated with resistance to ovulation induction, lower pregnancy rates and a higher risk of pregnancy complications (51). Two of the included studies exclusively focused on the effect of lifestyle modification on fertility. The primary outcome studied was different, however, both demonstrated positive reproductive effects. Interventions differed in intervention length (6wk vs 16wk) and intensity, and additionally, the lifestyle group in the study by Legro et al (51) involved the use of weight loss medication. Otherwise, patient baseline characteristics were similar (weighted mean age (SD) 28,5 ± 5,4; BMI 33,5 ± 4; BW 92,2 ± 12,4 kg). Results of both studies are in synchrony with current recommendations of weight loss prior to fertility treatment in obese PCOS patients. Additionally, Legro et al. provided proof that use of preconception oral contraception alone may worsen the metabolic profile with no benefit to ovulation, and possibly impair fertility. Palomba et al. (31) primarily focused on the intervention effect on the probability of ovulation under clomiphene citrate treatment. Clomiphene citrate (CC) is the first-line therapy for the induction of ovulation in the infertile women with PCOS, however, ~20% of patients are unresponsive, although a maximum dosage is used. These patients are defined generally

as CC-resistant. The administration of metformin in conjunction with CC is perhaps the most common second-line treatment for PCOS-related anovulation. When it is administered in pretreatment protocols, metformin seems to sensitize the ovary to CC via mechanisms that are related to its insulin-sensitizing action (52). Most importantly, it was suggested that the reduction in waist circumference and its correlation with ovulation enhancement is pivotal in increasing ovulatory response after CC treatment. Visceral fat could change acutely in response to lifestyle modification and reduce androgens and insulin resistance independently of body weight.

Mixed patient groups

Five studies have involved patients with and without PCOS and have mixed reported outcomes. Weighted mean parameters were age 32,5 ± 4,8 and BMI 37,0 ± 3,0. Three smaller RCTs have demonstrated higher pregnancy rates and live birth rates. Two studies (6,53) involved only dietary regimes for 12 and 16 weeks, one (54) diet and exercise for 12 weeks. These short-term weight loss regimens support clinical recommendations for weight loss prior to ART. Sim et al. have shown that a loss of only 6.9% of initial body weight is sufficient to enhance pregnancy rates despite the fact that the amount of weight loss required for the restoration of fertility is unclear. Added to the same level of relevance is the change in body fat distribution, evident by the decrease in waist circumference (WC) measurements. Only one of the studies compared short term intensive and standard weight loss measures and achieved significantly better results with intensive weight loss. This study, however, investigated a small sample (n=11). A study done by Becker et al established that a low glycemic index (LGI) diet promoted a decrease in BMI, percentage of body fat, and leptin concentrations, which overall improved oocyte development and pregnancy rate. However, although the LGI diet-induced many positive metabolic changes, the study has failed to show reductions in insulin concentrations and possibly the effect may be visible if the duration of intervention was longer than 12 weeks.

These studies could help elucidate possible benefits from specific diets during weight loss, as insulin sensitization and adjustment of the hormonal balance may be quicker achieved with specific diets.

Conversely, two large RCTs conveyed in the Netherlands (8) and countries of Northern Europe (55) did not find an effect of weight loss reduction on live birth rates. These were

large studies (n=564; n=295, respectively), with patients' baseline characteristics similar to the abovementioned studies. Interestingly, both of these studies have shown increased rates of natural conception and live births after spontaneous pregnancy in weight loss groups. Einarsson et al. (55) postulated that these higher rates could simply be explained by the fact that intervention group had approximately 4 months more prior to IVF to achieve spontaneous pregnancy which resulted in the intervention group being older than the control group at the time of IVF. This is important to take into consideration since age is the most prominent predictor of success after IVF. In the Dutch LIFEstyle study, only 38% of patients have decreased their weight by the desired 5% - 10% of baseline. These patients were sub-analyzed and they did have better results than the rest of patients in the intervention arm but had the same outcomes as controls. Studies also stress the importance of weight loss due to the association of obstetric complications in obese women, and patients from the same study were re-analyzed and it was shown that weight loss has decreased hypertensive pregnancy complications and preterm birth.

Comparison of PCOS and non-PCOS obese patients

Considering the shared mechanisms affecting fertility in PCOS and obesity, certain overlap and benefit for weight loss could be expected for both groups of patients. All studies included PCOS patients, but only one performed a sub-analysis comparing the two patient groups. The only study that analyzed separately PCOS and non-PCOS patients was done by Einarsson et al, which, surprisingly, failed to demonstrate benefit from weight loss in PCOS patients. This study contraries other studies mentioned, as they have demonstrated significant differences after the intervention. Pointing towards similarities between obese PCOS and non-PCOS females are the same results from this study, and if any confounder affected the results then both groups would have been equally affected. A possible explanation for improved outcomes in some of these studies may be of psychological origin. Infertility can result in a complex life crisis with psychological distress including grief, depression and marital-sexual disharmony (56). Moreover, successful weight loss may have reestablished a sense of achievement as obese infertile women have a perceived sense of failure at both weight maintenance and fecundity (57). Losing weight and its associated achievement might be transferable to fertility. While recognizing the substantial risks associated with obesity in pregnancy,

healthcare providers may be hesitant to recommend weight loss because of concerns about the safety of weight loss in the periconception period. Likewise, patients are often reluctant to delay fertility treatments to attempt weight loss because of concerns about the limited success, the lengthy time necessary to achieve weight loss and the belief that the risks of pregnancy associated with obesity are small and manageable (58). Weight reduction strategies investigated in a preconception population include diet, surgical interventions (59) and medical procedures (60). A multidisciplinary approach appears to be of predominant importance. In conclusion, weight loss has been shown to improve reproductive outcomes by alleviating fertility, as well as by regularizing menstrual cycles and increasing the chance of spontaneous ovulation and conception in anovulatory overweight and obese women. Despite some controversies, beneficial effects are multi-level and beside fertility improvement include alleviation of pregnancy-related and obstetric complications.

7. Improving reproductive performance in obese women

Weight loss is vital for the improvement of reproductive outcomes in obese women with and without PCOS. It can be achieved through lifestyle changes, dieting, and anti-obesity drugs. For those with severe forms of obesity, bariatric surgery is one of the last resorts.

7.1 Diet

The first-line treatment of obese infertile women with or without PCOS is lifestyle intervention including a hypo-caloric diet. Exercise-only methods seem to be insufficient and a combination with dietary modifications, caloric restrictions, and behavioral interventions is required. Weight loss results in a reversal of the obesity-associated adverse biochemical profile with decreased insulin resistance and restoration of menstrual regularity and ovulatory function (61). Dietary treatment of obesity aims to increase calorie expenditure over calorie intake. This is best achieved by combining exercise with a reduction in calorie intake of approximately 500 calories per day with only 30% of daily calories coming from fat (62). There is no doubt that lifestyle modification is very important but it should involve properly trained personnel and women prepared to bear the psychological stress.

7.2 Anti-obesity drugs

These pharmacological agents are mainly indicated when patients fail to lose at least 10 percent of body weight, despite lifestyle changes and a low-calorie diet. However, they are not a substitute for diet and lifestyle changes. The majority of these drugs, such as sibutramine, have been removed from the market due to adverse effects particularly related to the cardiovascular system. A drug which is still in use for the treatment of obesity and has been also tested in PCOS is orlistat. This drug inhibits intestinal lipase activity, thus reducing fat absorption, but may result in steatorrhea. Various data suggest that orlistat leads to a significant reduction in weight/BMI in overweight/obese PCOS women. Most studies also reported that orlistat significantly reduces testosterone and IR markers and improves lipid profile (63). Randomized open-label trials comparing metformin and orlistat therapy in PCOS women have indicated that orlistat therapy alone reduces androgen levels, restores ovulation and lowers BMI (11,64) as effectively as metformin.

7.3 Bariatric surgery

Bariatric surgery remains an option for those who have failed to lose weight by other means. Laparoscopic adjustable gastric banding is one of the most popular procedures, and preliminary studies on pregnancies occurring after the surgery have shown the procedure to be safe, well tolerated, and associated with a lower incidence of gestational diabetes and maternal hypertension (65).

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Biography

Zrinka Šakić was born in Zagreb, Croatia in 1994, where she graduated from elementary school and gymnasium. After graduating gymnasium with excellent marks, she enrolled at the University of Zagreb Medical School in English in 2013. Throughout her studies, she was actively involved in teaching as a student assistant in History taking and physical examination. She was awarded the Dean's commendation for the academic year 2016/2017. She has actively participated with her colleagues in DiaTransplant 2018 Congress of Nephrology with a paper titled "Community acquired Legionnaire's disease in a renal transplant recipient" which was later published in Prilozi journal (doi: 10.2478/prilozi-2018-0041). She was a coauthor of a poster presentation titled "From minimal swelling of the right knee to septic arthritis" which was a part of 5th Congress for Preventive Pediatrics of Serbia. Moreover, she is an active member of a students' section for dermatovenerology. Recently, she has attended a Mayo clinic workshop on Checklist for Early Recognition of Critical Illness in Injury (CERTAIN) which was a part of international collaboration to improve critical care practice. Besides her native language and English, she speaks German with intermediate proficiency (B1).