

## Obesity and infertility

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**ABSTRACT** Obesity has reached epidemic proportions and is widely known to be associated with a number of wide-ranging health complications, including heart disease and cancer; but to what extent does obesity cause infertility and cause complications in pregnancy? This paper reviews the evidence.

### KEYWORDS

**LIST OF ABBREVIATIONS** Body mass index (BMI), follicle-stimulating hormone (FSH), intra-cytoplasmic sperm injection (ICSI), luteinising hormone (LH), polycystic ovary syndrome (PCOS), sex hormone binding globulin (SHBG), World Health Organisation (WHO)

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It is half a century since obesity was introduced into the international classification of diseases. In the twenty-first century, it has become an epidemic. The prevalence of obesity is rising to epidemic proportions at an alarming rate in developed 'westernised' countries and also in less developed countries around the world. The health, economic and psychosocial consequences of the increasing incidence of obesity are substantial. It is widely recognised that increasing BMI (weight in kilograms divided by the square of the height in metres) (see Table 1) is associated with numerous health complications, which range from non-fatal debilitating conditions such as osteoarthritis, to life-threatening chronic diseases such as coronary heart disease, diabetes, and certain cancers.

Obesity results from a chronic imbalance between energy intake and energy expenditure. Environmental factors, such as the increased availability of high caloric/energy-dense food, or the decreased need for physical activity, contribute to its development, and their influence is amplified by genetic predisposition.

### OBESITY AND REPRODUCTIVE PATHOPHYSIOLOGY

It is well known that an increase in body weight and fat tissue is associated with several abnormalities of sex steroid balance. Obesity alters important homeostatic factors such as the pancreatic secretion of insulin. Hyperinsulinemia and insulin resistance are widely accepted to be involved in the underlying mechanisms linking obesity to multiple metabolic abnormalities and to alteration in steroidogenesis. Such alterations involve both androgens and oestrogens and overall, their carrier protein, SHBG.<sup>1</sup>

In fact, body fat distribution has been shown to substantially affect SHBG concentrations. Fat accumulation in the abdominal viscera (visceral fat) has been described as a possible cause of insulin resistance and the resulting metabolic syndrome. Female subjects with central obesity, and with a higher proportion of visceral fat usually have high insulin resistance leading to lower SHBG concentrations in comparison with matched subjects with peripheral obesity.

The net decrease in SHBG concentration observed in obesity leads to alterations in the availability of free-circulating androgens and oestrogens, for delivery to target tissues. Due to the greater reduction of SHBG concentration, the percentage of free testosterone tends to be higher in women with central obesity than in those with peripheral obesity leading to a state of 'functional hyperandrogenism'. The pattern of body fat distribution can regulate androgen production and metabolism to a significant extent. In fact, women with central obesity have higher testosterone production rates than those with peripheral obesity.

It is thought that obesity is a condition of insulin resistance and compensatory hyperinsulinemia. In insulin resistance syndrome, excess insulin is capable of stimulating steroidogenesis, excessive androgen production from the theca cells and excessive oestrogen production from the granulosa cells of the ovaries. In addition, by directly inhibiting SHBG synthesis, excess insulin may further increase the delivery of free androgens to target tissues. The excess in local ovarian steroidogenesis induced by excess circulating insulin may cause premature follicular atresia and then favour anovulation.

Classification	BMI (kg/m <sup>2</sup> )	Risk of co-morbidities
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5–24.9	Average
Overweight	25.0–29.9	Mildly increased
<b>Obese</b>	<b>&gt;30.0</b>	
Class I	30.0–34.9	Moderate
Class II	35.0–39.9	Severe
Class III	>40.0	Very severe

**TABLE 1.** WHO classification of obesity.

Accumulating data conclude that insulin resistance and hyperinsulinemia resulting in hyperandrogenemia are the hormonal abnormalities which disturb ovarian function in women with excess adipose tissue. However these abnormalities seem not to be associated with total fat mass *per se* but more so with visceral fat accumulation. Thus, excess weight appears to have a major impact on reproductive performance, and obesity can compromise reproductive outcome in a variety of ways (see Table 2).

### FERTILITY ISSUES

Fertility processes involve a complex of factors and mechanisms of both ovarian and extra ovarian origin. Obesity may interfere with many neuroendocrine and ovarian functions, thereby reducing both ovulatory and fertility rates in otherwise healthy women. Oligo-ovulation, anovulation and subfertility are present in obese females with a relative risk of anovulatory infertility of 3.1 for women with a BMI >27 compared with women of BMI 20–25. Many obese women have normal ovulatory menstrual cycles, remain fertile and have no apparent hyperandrogenism. However, currently there is substantial evidence to support the relationship between obesity and anovulatory infertility.<sup>2</sup> Obesity during puberty and early adolescence has a strong association with infertility in the future. The mechanisms via which obesity is linked to anovulation remain unclear, and most likely several hormonal changes are involved. As discussed in the previous section, hyperinsulinemia and hyperandrogenism are believed to cause alterations in steroidogenesis and thus the endocrine milieu leading to anovulation.

### POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome is a heterogeneous clinical entity characterised by signs and symptoms of

hyperandrogenism and anovulatory disorders often associated with infertility and obesity. The association of the clinical features of truncal obesity, oligo- or amenorrhoea, and hirsutism with biochemical evidence of hyperandrogenaemia, elevated luteinising hormone and suppressed SHBG and characteristic ovarian morphology on ultrasound, have formed the basis of the diagnosis of PCOS for some years. However, biochemical abnormalities are seen in women with regular menstrual cycles and normal ovaries on ultrasound but who present with hirsutism or acne; and women of normal body mass who present with oligomenorrhoea will frequently exhibit biochemical and ultrasound signs of PCOS. The key underlying abnormality that leads to anovulation, infertility and long-term health risk appears to be insulin resistance – hyperinsulinaemia. Excess insulin leads to disruption of the ordered FSH LH production as well as their function leading to ovulatory problems and cycle irregularity. The current consensus opinion regarding the diagnostic criteria for PCOS is shown in Table 3.

An additional factor involved in the dysregulation of the complex endocrine circuit may be an increased tone of the opioid system, which has been demonstrated in the presence of obesity, as well as in women with PCOS.

Several peptides are emerging as potential candidates involved in the pathogenesis of hyperandrogenism and related infertility in women with PCOS. Leptin is considered to be one of the main peripheral signals that affect food intake and energy balance, and obesity is a classic condition of circulating leptin excess. Leptin is found to have an inhibitory effect on ovarian function leading to anovulation.

Approximately half of all women with PCOS are overweight or obese. Polycystic ovarian syndrome is the

<b>Menstruation:</b>	increased risk for amenorrhea, oligomenorrhea, and menorrhagia due to ovulatory dysfunction.
<b>Infertility:</b>	increased risk for infertility and anovulation; poor response to fertility drugs.
<b>Miscarriage:</b>	increased risk for miscarriage, both spontaneously and after infertility treatment.
<b>Pregnancy and labour:</b>	increased prevalence of pregnancy-induced hypertension, gestational diabetes, thromboembolism, urinary tract infections, induction of labour, instrumental delivery, caesarean section, anaesthetic and postoperative complications including uterine infections.
<b>Neonatal morbidity/mortality:</b>	increased risk to the fetus of macrosomia, potentially leading to birth trauma; increased risk of neonatal admission to the intensive care unit; increased risk of neonatal death.
<b>Congenital anomalies:</b>	increased risk for the fetus of neural tube defects and heart defects.

**TABLE 2** Obesity: impact on reproductive performance.

most common cause of anovulatory infertility in young women and the history of weight gain frequently precedes the onset of clinical manifestations of the syndrome, suggesting a pathogenetic role of obesity in the development of PCOS and the related infertility. Even though the total BMI in non-obese women with PCOS is normal, the intra-abdominal preperitoneal and visceral fat accumulation may contribute to the hormonal dysregulation leading to anovulation. There is increasing evidence that intra-abdominal or visceral fat is either causative or a very early effect of PCOS.<sup>3</sup>

### OBESITY AND RESPONSE TO FERTILITY TREATMENT

Obesity and insulin resistance are unfavourable conditions to ovarian response during induction of ovulation. Most studies show conclusive evidence that increasing BMI negatively influences the responsiveness to ovulation induction agents like clomiphene citrate and gonadotrophins and obese women require multiple courses and high doses of these drugs to achieve ovulation. Pre-treatment with metformin on the responsiveness to these agents in obese anovulatory women has shown conflicting results.

*In vitro* fertilisation and ICSI are choices in the treatment ladder for anovulation, once ovulation induction has failed. Here again, obesity appears to adversely affect the treatment outcome, impairing fecundity and reducing the pregnancy rate.

### EFFECT OF WEIGHT LOSS ON FERTILITY

Therapies aimed at favouring weight loss should represent the primary interventional strategy in obese women with anovulation or PCOS. There is long-standing clinical

evidence concerning the efficacy of weight reduction upon both clinical and endocrinological features of obese infertile women. Available studies indicate that weight loss is associated with significant improvement in reproductive function, with a reduction in hyperandrogenism, hyperinsulinaemia, and altered gonadotrophin pulsatile secretion.<sup>5</sup> Weight loss results in increases in SHBG, reductions in testosterone, and androgenicity, improved menstrual function, improved conception rates, and reduction in miscarriage rates. This does not appear to be related to the amount of weight loss, since it can be achieved after only mild to moderate weight loss, as has been shown in several studies. Even a 5% reduction in body weight has been shown to restore ovulation. Not only the excessive amount, but also the distribution of fat is clearly related to loss of fertility. Redistribution of fat with the loss of a small volume of critical intra-abdominal fat, which may be only a small percentage of the total body fat, may explain the improvement in clinical, metabolic and endocrine factors.

Lifestyle modification programmes which involve exercise and sensible eating patterns can lead to improved reproductive function in the form of ovulatory cycles and fertility.<sup>2</sup> However, the most effective method for achieving and maintaining weight loss is unclear. Gradual weight loss is best achieved through a sensible eating plan that can be maintained over long periods of time. The likelihood of maintaining weight loss is increased when diet is combined with regular exercise, cognitive behaviour therapy, and a supportive group environment. Group programmes which includes regular exercise, and group discussion of topics such as coping with the psychological impact of infertility, developing healthy eating patterns, and the effects of obesity on infertility may produce considerable improvement in the outcome of treatment for infertility.

**Diagnostic criteria of PCOS**

The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group – 2003<sup>4</sup>

**1999 criteria (both 1 and 2)**

1 Chronic anovulation  
2 Clinical and/or biochemical signs of hyperandrogenism, and exclusion of other aetiologies

**Revised 2003 criteria (2 out of 3)**

1 Oligo- and/or anovulation  
2 Clinical and/or biochemical signs of hyperandrogenism  
3 Polycystic ovaries and exclusion of other aetiologies (congenital adrenal hyperplasias, androgen-secreting tumours, Cushing's syndrome)

**TABLE 3.** Diagnostic criteria of PCOS.**CONCLUSION**

The rising epidemic of obesity reflects the profound changes in society and in behavioural patterns of communities over recent decades. Even though genes are important in determining a person's susceptibility to weight gain, the actual energy balance is determined by calorie intake and physical activity. Obesity causes abnormalities of sex hormones in women of reproductive age leading to oligo-ovulation, anovulation and subfertility. Furthermore, obesity is associated with increased risk of miscarriage, pregnancy and labour complications, neonatal morbidity and mortality, and congenital malformations. Therapies aimed at favouring weight loss should represent the primary interventional strategy in obese women with anovulation and infertility. There is long-standing clinical evidence concerning the efficacy of weight reduction upon both clinical and endocrinological features of obese, infertile women. Lifestyle modification programmes which involve

exercise and sensible eating patterns can lead to improved reproductive function in the form of ovulatory cycles and fertility. Weight reduction is associated with better success rates in infertility treatment programmes, including ovulation induction and various assisted reproductive techniques. Thus, weight reduction is the appropriate treatment for women with obesity-related endocrine derangement, menstrual irregularities and infertility.

**KEYPOINTS**

- Obesity in women is associated with abnormalities of sex steroids, hyperinsulinaemia and increased androgen production.
- Obesity may cause anovulatory infertility.
- When pregnancy does occur in obese women, it may result in increased rates of miscarriage, neonatal morbidity and congenital abnormalities.
- Polycystic ovary syndrome is frequently associated with obesity, insulin resistance and infertility.
- Treatment strategies include ovulation induction, IVF and ICSI, but weight reduction of 5% may restore ovulation.

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