The Overlooked Role of Obesity in Infertility

Safaa Al-Hasani, M.D.;[1] Khaled Zohni, M.D.;[2]

1 Department of Obstetrics and Gynecology, University of Schleswig-Holstein, Lübeck, Germany
2 Medical Sciences Division, Reproduction unit, National Research Center, Egypt

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Abstract

Being either underweight or overweight can affect a woman's fertility. Irregular menstrual cycles, reduced spontaneous and assisted fertility and an increased risk of miscarriage are risks associated with obesity that are often overlooked. Excessive weight and central distribution of body fat are both related to an increased risk of normogonadotrophic anovulation. Weight loss can re-establish ovulation in obese anovulatory patients or improve their response to ovulation induction. However, even a small amount of weight loss (5%) may improve fertility. Men who are overweight or obese have significantly lower sperm counts than men of normal weight.

Key words: Obesity, Overweight, Male and female infertility

Introduction

The non-fatal, but debilitating health problems associated with obesity include respiratory difficulties, chronic musculoskeletal problems, skin problems and infertility (1).

Prevalence

According to the WHO report issued in 2004, there are more than 1 billion overweight adults, and at least 300 million of them are obese. Current obesity levels range from below 5% in China, Japan and certain African nations, to over 75% in urban Samoa. But even in relatively low prevalence countries like China, rates are almost 20% in some cities. The rising epidemic reflects the profound changes in society and in behavioural patterns of communities over recent decades. While genes are important in determining a person's susceptibility to weight gain, energy balance is determined by calorie intake and physical activity. Thus societal changes and worldwide nutrition transition are driving the obesity epidemic. Economic growth, modernization, urbanization and globalization of food markets are just some of the forces thought to underlie the epidemic. In other words, as incomes rise and populations become more urban, diets high in complex carbohydrates give way to more varied diets with a higher proportion of fats, saturated fats and sugars. At the same time, large shifts towards less physically demanding work have been observed worldwide. Moves towards less physical activity are also found in the increasing use of automated transport, technology in the home, and more passive leisure pursuits (1).

As regards the future generations, childhood obesity is already epidemic in some areas and on the rise in others. An estimated 17.6 million children under five are estimated to be overweight worldwide. In the USA the number of overweight children has doubled and the number of overweight adolescents has trebled since 1980. The prevalence of obese children aged 6 to 11 years has more than doubled since the 1960s. Obesity prevalence in youths aged 12-17 has increased

Correspondence:
Safaa Al-Hasani, Department of Obstetrics and Gynecology, University of Schleswig-Holstein, Lübeck, Germany.
Email: sf_alhasani@hotmail.com

Table 1. WHO Classification of overweight in adults according to BMI [1]

Classification	BMI (kg/m^2)	Risk of associated illness
Underweight	< 18.5	Low (but greater risk of other clinical problems)
Normal range	18.5–24.9	
Overweight	> 25.0	Average
Pre-obese	25.0–29.9	Increased
Obese class I	30.0–34.9	Moderate
Obese class II	35.0–39.9	Severe
Obese class III	> 40.0	Very severe

dramatically from 5% to 13% in boys and from 5% to 9% in girls between 1966-70 and 1988-91 in the USA. The problem is global and increasingly extends into the developing world; for example, in Thailand the prevalence of obesity in 5 to 12 year olds girls rose from 12.2% to 15-6% in just two years (2). In England, about one quarter of men and women are obese. This is nearly double the number of people who were obese 10 years ago. Women are slightly more likely than men to be obese. More children are also overweight than they used to be. In 2003, 4 in 10 children under 11 were either overweight or obese. In 1995, the figure was 3 in 10. Boys are slightly more likely than girls to be obese (3,4).

Body Mass Index

The prevalence of overweight and obesity is commonly assessed by using body mass index (BMI), defined as ***the weight in kilograms divided by the square of the height in metres (kg/m^2)***.

The BMI values are age-independent and the same for both sexes. However BMI may not correspond to the same degree of fatness across different populations due, in part, to different body proportions. Therefore ideally, additional tools, such as waist circumference and waist-hip ratio, should also be used to assess obesity.

In the new graded classification system developed by the World Health Organization, a BMI of 30 kg/m2 or above denotes obesity (Table 1). It is highly likely that individuals with a BMI at or above this level have excessive body fat (1).

Waist circumference

Waist circumference is a convenient and simple measure which is unrelated to height, correlates closely with BMI and the ratio of waist-to-hip circumference, and is an approximate index of intra-abdominal fat mass and total body fat. Furthermore, changes in waist circumference reflect changes in risk factors for cardiovascular disease and other forms of chronic diseases, even though the risks seem to vary in different populations. There is an increased risk of metabolic complications for men with a waist circumference 102 cm, and women with a waist circumference 88 cm.

Recently, investigators reported that a patient's waist-to-hip ratio (WTHR) is a better predictor of obesity than their body-mass index (BMI).

To calculate the WTHR, the waist circumference at its narrowest and the hip circumference at the widest point in inches (or centimeters) are measured, and then the waist measurement is divided by the hip measurement. In women, the ratio should be 0.8 or less, and in men it should be 1.0 or less. Thus, in women the waist should be narrower than the hips, and in men the waist should be narrower or the same as the hips. It is a simple and useful measure of fat distribution.

Scientists have known for the past few years that, how fat is distributed in the body is at least as important as how much fat is in the body. Fat that is accumulated in the abdomen (leading to increased waist size, a pattern doctors refer to as "apple shape") causes more metabolic disruption than fat that is distributed in the hips or thighs (a pattern doctors refer to as "pear shape"). So, patients with metabolic syndrome and infertility have increased WTHR (5,6).

Apple Shape Pear Shape

Obesity and fertility, possible relation?

A negative effect of obesity on fertility was first noted 2500 years ago by Hippocrates, and obesity is now known to be associated with menstrual irregularities, chronic anovulation, PCOS and infertility (7,8). British researchers at the University of Hull in the United Kingdom found that males' high alcohol consumption, and females' smoking and high body weight

have significant negative impact on the time it takes a couple to achieve pregnancy (9).

A disproportionate number of women who seek treatment at infertility centers have a high BMI. For example, among more than 5000 infertile female patients seen at the Reproductive Medicine Unit at the University of Adelaide, Australia, 40% had a BMI exceeding 25 kg per m^2 (borderline or overweight), and 17% had a BMI exceeding 30 kg per m^2 (obese). Thus, excess weight appears to have a major impact on reproductive performance, and obesity can compromise reproductive performance in a variety of ways (Table 2). It should be noted that although many obese women are fertile and have children, the overall prevalence of reproductive disorders increases significantly once women reach the overweight and obese ranges. The large number of very overweight, fertile women should not lead practitioners to assume that weight disorders have little impact on reproduction (10-12).

Most of the time, obesity is associated with menstrual disorders and anovulation. As the impact of weight gain on the reproductive system is multifactorial, the respective roles of abnormalities such as hyperandrogenism, hyperinsulinism or estrogen production from adipose tissue are still a matter of debate. Furthermore, obesity itself may be a factor affecting ovarian response. Indeed, in women with no ultrasound evidence of PCOS, a higher dose of clomiphene citrate is needed to obtain ovulation *and* the response to gonadotropin induction of ovulation is inversely related to body mass index. Moreover, PCOS patients with moderate obesity have a blunted response to gonadotropin therapy compared with their nonobese counterparts and require a more prolonged stimulation and a higher dosage of FSH. It is likely that the pharmacokinetic profile of ART drugs is different in overweight compared to lean patients and may partly explain the need for higher doses. Weight reduction is beneficial in restoring ovulation or in reducing drug dosage. Weight reduction in obese patients reduces hyperandrogenism and hyperinsulinaemia, both factors influencing the ovarian response to FSH. Therefore, it is presumed that obesity is responsible for the relative ovarian insensitivity to infertility treatment (13-17).

How does obesity affect fertility?

The mechanism through which weight impairs fertility is not certain, but these patients have a lower concentration of sex hormone-binding globulin (SHBG) and increased androgens, insulin secretion and insulin resistance. It is of note that a positive significant correlation has been reported between ovarian volume and body mass index (BMI) in patients with polycystic ovary syndrome (PCOS) (18-20).

Table 2. Obesity: Impact on Reproduction

Menstruation: increased risk for amenorrhea, oligomenorrhea, and menorrhagia
Infertility: increased risk for infertility and anovulation; poor response to fertility drugs
Miscarriage: increased risk for miscarriage, both spontaneously and after infertility treatment
Glucose Intolerance: increased risk for diabetes mellitus
Pregnancy: increased prevalence of pregnancy-induced hypertension, gestational diabetes, cesarean section, and Down syndrome

5% to 10% of all women of reproductive age have polycystic ovary syndrome (PCOS). Clinical features of this disorder are listed in Table 3. Although some controversy exists regarding the definition of PCOS, the presence of menstrual abnormalities, hirsutism, obesity, and infertility makes the diagnosis unequivocal. Not all obese women have PCOS, nor are all women with PCOS obese, but the two conditions are closely related (21).

Initial investigations in patients with suspected PCOS should include a clinical examination and basic laboratory studies. The recommended work-up for these patients, as well as for any obese women with reproductive difficulties, appears in Table 4. It is particularly important to exclude glucose intolerance, through either a fasting blood glucose test or an oral glucose tolerance test. Some evidence has suggested

Table 3. Features of polycystic ovary syndrome

• Polycystic ovaries on ultrasonography (not always present)
• Menstrual disturbances (amenorrhea, oligomenorrhea)
• Dermatologic problems (acne, acanthosis nigricans, hirsutism)
• Weight disorders (obesity, central fat distribution)
• Infertility
• Pregnancy disorders (glucose intolerance and other glucose abnormalities, diabetes mellitus)
• Increased circulating androgen levels
• Increased insulin resistance and luteinizing hormone levels

Table 4. Recommended Work-Up

History
Menstrual history from puberty
Family history of cardiovascular, reproductive, and metabolic risk factors
Fertility issues
Current medications
Dermatologic problems
Dietary and eating habits
Physical Examination
Height, weight, BMI (kg/m^2)
Waist circumference
Hair, skin, pigmentation
Purple striae and signs of Cushing's syndrome
Laboratory Tests
Glucose tolerance
Lipid profile
Androgens (testosterone, free testosterone)
Prolactin and LH
FSH and thyroid hormones
Ovarian ultrasonography (optional)

BMI: body mass index; LH: luteinizing hormone; FSH: follicle-stimulating hormone.

that fasting glucose is not entirely reliable in patients with PCOS; instead, fasting and stimulated serum insulin values may be useful (11,22,23).

Moreover, weight loss in obese PCOS patients reduces circulating androgens and raises SHBG enhances insulin sensitivity regularly improves menstrual cyclicity and fertility rates. On clinical grounds, weight loss can re-establish ovulation in obese anovulatory patients or improve their response to ovulation induction (18,24-32).

How does obesity affect ART success?

Obesity and insulin resistance compromise the success of fertility treatment in PCOS. It is more prevalent among PCOS women who remain anovulatory after ovarian electrocautery and clomiphene citrate treatment. Ovulation induction with gonadotropins in obese PCOS women requires higher doses than in lean PCOS women, the rate of ovulatory cycles is lower, and the rate of multifollicular development and incidence of miscarriage is higher in obesity. Increased gonadotropin doses to compensate for relative gonadotrophin resistance induced by **obesity** might result in impaired oocyte or embryo quality, implantation failure and pregnancy complications, such as abnormal embryonic development and decreased invasional capacity of blastocysts *in vitro*, lower implantation rate, delayed implantation, increased length of gestation, lower birth weight and developmental retardation *in vivo*. Obesity may also jeopardize IVF results in PCOS, as high intrafollicular concentrations of leptin—a hormone produced by adipose tissue—are related to relative gonadotropin resistance during ovarian stimulation for IVF. Furthermore, android obesity—a common feature of PCOS—is associated with low pregnancy rate after IVF and obesity is also associated with an increased risk of miscarriage, partly due to the lower number of retrieved oocytes in obese women.

Insulin resistance in PCOS is also associated with an impaired progesterone synthesis by cultured granulosa—lutein cells *in vitro* Such a defect of progesterone release during the luteal phase may impair outcome of low-dose FSH stimulation in insulin-resistant PCOS women, since luteal phase support is usually not given with ovulation induction protocols. During long-term down-regulation and ovarian stimulation for IVF or ICSI, women receive luteal support (progesterone), which may hence overcome impaired corpus luteal function in hyperinsulinaemia. Thus, the effects that hyperinsulinaemia has on ovarian steroid synthesis *in vitro* or during low-dose FSH stimulation *in vivo* are minor when PCOS women receive long-term down-regulation and stimulation with recombinant FSH (33).

Exercise, low-calorie diet and insulin-lowering drugs such as metformin, troglitazone and acarbose decrease insulin levels, correct the endocrine abnormalities induced by obesity and insulin resistance, and thus may improve the results of infertility treatment, insulin resistance impairs the outcome of IVF in PCOS women, it would warrant co-treatment with insulin-lowering drugs or weight reduction before and during down-regulation and ovarian stimulation (33).

The mechanism through which body weight reduction modifies ovarian morphology can only be guessed: it might involve a more favourable endocrine environment after a rise in SHBG and a reduction in free androgens, and improved insulin sensitivity. The decrease in volume might be due to the reductions in microfollicles and ovarian stroma. The amount of ovarian stroma is correlated with overproduction of theca-derived steroids, particularly androstenedione (Kyei-Mensah *et al*., 1998), in PCOS patients: a reduction in ovarian volume and in the number of microfollicles could therefore be involved in lowering circulating androstenedione and improving the clinical picture of these patients during diet treatment (34).

Interestingly, Falsetti *et al.* (2000) reported a comparable improvement in ovarian morphology with long-term pharmacological inhibition of ovarian function in 140 PCOS patients under oral contraceptive treatment. While, Crosignani *et al* in 2003 showed comparable and quicker changes in the parameter after only moderate body weight reduction (35, 36).

At the same time, weight loss improves menstrual cyclicity, ovulation and fertility. Clark *et al*. (1998) found that weight loss re-established ovulation in obese anovulatory patients or improved their response to ovulation induction: in a series of 67 anovulatory women, 90% resumed ovulation after weight loss and 78% conceived. The same group confirmed these findings in a larger series (Clark *et al*., 2000), and similar results were obtained in preliminary observations by Crosignani *et al*., 1999, 2002. In another series, among the 27 out of 33 patients with irregular menstrual cycles who lost weight, 18 re-established regular cycles. A total of 60% had ovulatory levels of plasma progesterone after weight loss. In a year of observation, 10 spontaneous pregnancies occurred in the 25 patients who lost weight (40% pregnancy rate). Neither menstrual cycle improvement, ovulatory values of neither progesterone nor pregnancies occurred in the eight patients who did not lose weight. In contrast, it should be noted that resumption of ovulatory cycles and pregnancy was obtained even after a slight (5%) reduction of baseline body weight (31,32,37).

As with all weight-loss programs pursued for any purpose, compliance over the long term remains a major challenge. Research conducted by Clark *et al* has suggested that strict calorie counting is not necessary as long as patients exercise and heed dietary advice (10). In their studies, more than 90% of obese, oligomenorrheic women experienced a dramatic improvement in menstrual patterns, with a high spontaneous conception rate. Even women whose failure to conceive was unrelated to anovulation (e.g., male factor infertility, tubal blockage) had more success with assisted-reproduction pregnancies following weight loss. Surgically induced weight loss via gastric bypass or gastric restrictive procedures (vertical banding, gastroplasty, adjustable gastric banding) has also been shown to restore menstruation and pregnancy, but these operations have very high morbidity rates (10).

Life style modification

Several years ago, a group of clinicians at Queen Elizabeth Hospital (Woodville, South Australia) developed the Fertility Fitness program, which encouraged women to cease all medical treatment for infertility for 6 months while they attended special weekly meetings. At these meetings, the first hour was spent on exercise and the second on a seminar that provided relevant information regarding obesity and reproductive disorders. Exercise regimens were tailored to each woman's fitness level, and ranged from gentle walking to vigorous aerobic exercise. After patients participated in weekly meetings for 6 months, appropriate medical infertility treatments were instituted (e.g., ovulation induction with clomiphene citrate).

Participants lost an average of 10.2 kg. Ovulation was restored in 60 of 67 previously anovulatory women; among them, 52 achieved a pregnancy (18 spontaneously) and 45 had live births. The miscarriage rate dropped from 75% before the study to 18% during the study.

Based on these results, investigators concluded that most overweight women with infertility could expect to become pregnant after participating in an organized 6-month regimen of gentle weight loss (38,39).

Male factor

Danish researchers found men who are overweight or obese have significantly lower sperm counts than men of normal weight. In addition, men who were underweight also had lower sperm counts compared with normal-weight men.

The study showed that overweight men who had a body mass index (BMI, a measure of weight in relation to height used to measure obesity) over 25 had a nearly 22% lower sperm concentration and 24% lower total sperm count compared with healthy weight men. A BMI over 25 is considered overweight and a BMI over 30 is considered obese. Underweight men who had a BMI under 20 also suffered from similar reductions in sperm counts.The study also showed that as men's weight increased blood testosterone levels decreased (40).

How obesity can affect the male factor?

Aromatases and oestrogens play important roles in the function of the reproductive organs. In earlier work, Koloszar *et al* in 2002 found a correlation between weight and semen concentration.

It has been demonstrated that not only the BMI, but also the body fat distribution is a risk factor for several diseases. This suggests that it is not the type

Table 5. Correlation between weight, waist circumference, hip circumference and volume, total sperm count, total number of motile sperm and rapid progressive motile sperm count (41)

	Volume (ml)	Total sperm count (10^6)	Total motile sperm count (10^6)	Total rapid progressive motile sperm count (10^6)
Weight (kg)	- 0.01/0.906	- 0.24/0.031	- 0.22/0.048	- 0.22/0.053
Waist circumference (cm)	- 0.25/0.026	- 0.26/0.007	- 0.24/0.014	- 0.24/0.012
Hip circumference (cm)	- 0.012/0.27	- 0.22/0.009	- 0.21/0.035	- 0.21/0.028
Waist/hip ratio	- 0.3/0.007	- 0.2/0.08	- 0.2/0.081	- 0.18/0.101

Values are presented as r & p value.

of fat deposition that plays an important role in sperm production, but merely the amount of fat.

This could well be related to changes in the testosterone/ 17b-oestradiol ratio. The increased fat produces more oestrogen from testosterone, which suppresses the

hypothalamic and pituitary hormonal secretion and can affect the testis directly. Moreover, in obesity the SHBG levels are lower, which reflects on further testosterone deficiency. There are more precise methods for determination of the fat distribution in men, e.g. with the help of computed tomography or MRI, but these methods are not suitable in the daily routine because of the time and cost requirements. So, the simple measurement of waist and hip circumferences, and determination of their ratio could be more suitable.

Testosterone has marked effects on oestrogen production in males. Only 20% of the biologically active oestrogen is produced in the testis. The rest is aromatized from androstenedione produced by the adrenal gland. In males, the 17b-oestradiol level is correlated with the fat mass. The aromatization takes place predominantly in the subcutaneous abdominal fat tissue. Glucose homeostasis also changes under circumstances of abdominal obesity, and disturbances in the glucose metabolism lead to a deteriorated fertilizing capacity.

In 2002, Haidl, Raman & Schlegel, reported that oestrogen excretion can be decreased by the administration of aromatase inhibitors, which can exert an advantageous effect on the testosterone/17b-oestradiol ratio. Thus, there is a subsequent increase in sperm concentration (41-48).

Conclusion

Being either underweight or overweight can affect a woman's fertility. Women require approximately 17-21% of their body weight as fat in order to menstruate and ovulate normally. Women who are below their ideal weight or have low fat levels like female athletes can experience irregular menstruation and anovulation (failure to ovulate). Alternatively, women with fat levels that are too high may have a hormonal imbalance that reduces their fertility. However, even a small amount of weight loss (5%) may improve fertility. Therefore, maintaining a healthy weight may help restore menstrual and ovulatory cycles and consequently improve the chances of pregnancy (48).

In future, more attention should be paid to the weight of patients, especially the mass of abdominal subcutaneous fat, by measuring the waist/hip ratio not only in cases with oligozoospermia or asthenozoospermia, but also in those with normozoospermia, as an abnormal weight gain can result in deteriorated sperm motility characteristics (48).

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