Fertility and Obesity

2

Ulrik Schiøler Kesmodel

Contents

U.S. Kesmodel, M.D., Ph.D.
Department of Obstetrics and Gynaecology, Aarhus University Hospital,
Brendstrupgaardsvej 100, Aarhus N, DK-8200, Denmark
e-mail: ulrikesm@rm.dk

P.G. Ovesen, D.M. Jensen (eds.), *Maternal Obesity and Pregnancy*,
DOI 10.1007/978-3-642-25023-1_2, © Springer-Verlag Berlin Heidelberg 2012

Abbreviations

ART	Assisted reproduction techniques
BMI	Body mass index
FSH	Follicle-stimulating hormone
ICSI	Intracytoplasmatic sperm injection
IUI	Intrauterine insemination
IVF	In vitro fertilization
LH	Luteinizing hormone
PCOS	Polycystic ovary syndrome
SHBG	Sex-hormone-binding globulin

2.1 Introduction

Factors that affect the chance of achieving a pregnancy are often beyond the control of the individual. Infertility of unknown origin alone account for approximately 20% of couples seeking fertility treatment with assisted reproduction techniques (ART), and even when infertility is attributed to a specific cause, it is often not modifiable without specific medical intervention. Examples include endometriosis, genetic disorders such as chromosomal translocations and poor sperm count (mostly of unknown origin).

Some factors such as damage to the fallopian tubes are theoretically preventable if all people adhered to lifelong monogamy, thus avoiding the risk of sexually transmitted diseases, but once the damage has occurred, it is not modifiable without medical intervention.

However, some factors often referred to as individual risk factors are potentially modifiable. Most of these are often referred to as lifestyle factors and include tobacco smoking, alcohol intake, coffee consumption and diet.

"Is there anything we can do?" is a frequent question among women and men having difficulty in achieving a spontaneous pregnancy. Therefore, modifiable factors are important, simply because they are modifiable. Each individual can choose to smoke or not smoke, drink alcohol in large daily amounts potentially affecting fertility, drink alcohol on rare occasions without affecting fertility in any measurable way, or not at all. At the same time, society may use structural measures such as tax and excise on alcohol and tobacco to regulate the use of these substances.

Obesity appears to fall somewhere in between these different factors that affect fertility. On the one hand, comparing with smoking and alcohol intake, obese is not something that one can directly choose to be or not to be. Still, for many women, it is modifiable through changes in, for example, diet and frequency of physical exercise. Even so, while many countries in the Western world have taken steps to ban tobacco smoking in many places accessible to the public, and while alcohol use is banned in many work places, no countries seem to have taken action towards prohibiting obesity.

The question is: How and to what extent does obesity actually affect fertility? And to what extent are the potential effects of obesity modifiable?

2.2 Measures of Fertility

From a demographic point of view, fertility refers to the number of live born children. This may be seen in relation to the size of the population (summary fertility rate), the number of women of fertile age (general fertility) or in relation to age-specific fertility rates (total fertility rate).[1]

In practice, population-based studies tend to describe fecundability rather than fertility. Fecundability is usually defined as a couple's probability of conceiving in a given menstrual cycle, assuming that they are actively trying to conceive and hence do not use any form of contraception. While this is not directly measurable for a specific couple, it may be indirectly calculated by using the mean fecundability of a population (Wilcox 2010).

Most of our knowledge of the effect of obesity on fecundability stems from population-based studies, usually cohort studies. Some few studies use samples, random or non-random, from the general population, but cohorts of pregnant women are often used, most likely because they are more easily accessible.

In these studies, women are often asked retrospectively how long they have attempted to achieve a spontaneous pregnancy. This information is subsequently used to calculate a measure of fecundability: time to pregnancy. Hence, when attempting to measure the chance of conception, the actual measure also involves measuring early survival of the fetus (Wilcox 2010).

In connection with fertility treatment, many measures are often used. A useful and straightforward measure is the proportion of women achieving an ongoing pregnancy per treatment cycle. This is an easily accessible outcome, but more to the point and of more interest to the couples undergoing treatment is the proportion of women achieving a live birth. This measure implies longer time for data collection and is therefore used less often. Other measures in relation to in vitro fertilization (IVF) treatment are number of oocytes retrieved per cycle or fertilization rates and implantation rates.

2.3 Hormonal Changes in the Obese Woman

Obesity is characterized by an increased number of adipose cells and excessive storage of triglycerides in the adipose cells. The hormonal interaction between the adipose tissue and other endocrine organs including the pituitary gland and the ovaries is complex and not fully understood, but some endocrine changes are well described and contribute to the current understanding of the potentially negative effects of obesity on reproductive function.

[1]The average number of children a hypothetical cohort of women would have at the end of their reproductive period if they were subject during their whole lives to the fertility rates of a given period and if they were not subject to mortality. Expressed as children per woman

2.3.1 Adipokines

In overweight and obese women, relative hypoxia among the adipocytes occurs as body mass index (BMI) increases, and this in turn leads to the release of a series of proteins named adipokines (Metwally et al. 2008).

Leptin is secreted by adipocytes and is the most well studied of these proteins. Leptin secretion is increased in the obese (Metwally et al. 2008; Sharpe and Franks 2002), and generally levels are higher in women than in men. BMI alone has been shown to account for >30% of the leptin variance in women. Leptin acts on the hypothalamus, the ovaries and the endometrium. At the hypothalamic level, leptin is involved in the regulation of energy intake and energy expenditure, essentially exercising a stimulatory role (Metwally et al. 2008). Leptin on the other hand inhibits ovarian function. At the initiation of puberty, leptin levels increase, and subsequently leptin levels vary across the menstrual cycle with highest levels in the luteal phase. In other species, leptin has been shown to inhibit the production of steroids in the granulosa and theca cells and may have a direct effect on the development of the follicles and on oocyte maturation.

Leptin levels are not consistently increased in women with polycystic ovary syndrome (PCOS).One explanation may be that mainly PCOS women with normal BMI do not seem to have higher levels of leptin, but given the effect of leptin on ovarian production of steroids, which is often affected in women with PCOS, this explanation is not entirely satisfactory.

Other adipokines include resistin, ghrelin and adiponectin, but the roles of these proteins in human reproduction (if any) are unclear. It has been described that resistin is associated with the amount of body fat and with occurrence of insulin resistance, but in women with PCOS resistin levels do not seem to be a risk factor for oocyte growth or maturation. Receptors for ghrelin have been identified in the female ovary, but otherwise its role in human reproduction is unknown. It is well described that adiponectin inhibits glucose production in hepatocytes and increases the turnover of fatty acids, but the role in reproduction is not clear.

2.3.2 Insulin Resistance

Insulin resistance and compensatory hyperinsulinaemia is seen in obese women, in general, but also among women with PCOS (Fig. 2.1) irrespective of BMI (Norman et al. 2004). One explanation may be that even normal-weight women with PCOS have increased intra-abdominal fat compared to other normal-weight women (Yildirim et al. 2003). The hyperinsulinaemia leads to changes in levels of sex-hormone-binding globulin (SHBG) and testosterone (see below) (Sharpe and Franks 2002), which essentially explains the increased occurrence of anovulation in obese women.

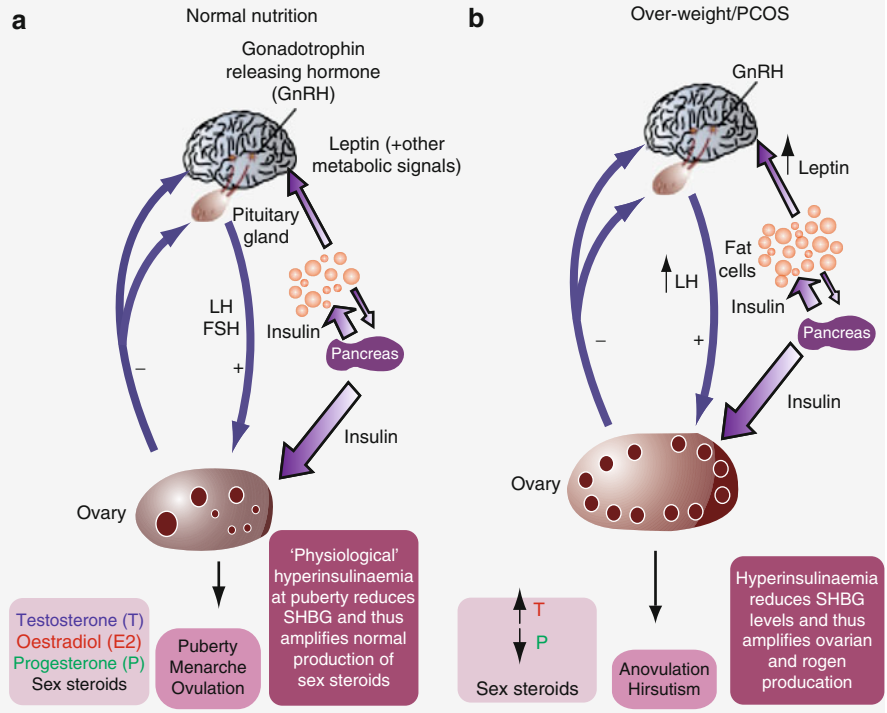

Fig. 2.1 Hormonal mechanisms that link nutrition/diet and female fertility. (**a**) Normal ovarian function – resulting in normal puberty and reproductive competence – is controlled primarily by the gonadotrophins *LH* (luteinizing hormone) and *FSH* (follicle-stimulating hormone) from the pituitary gland, the secretion of which is regulated by the brain hormone gonadotrophin-releasing hormone (*GnRH*). Nutrition is linked to the female reproductive system through the effects of a hormone emanating from fat cells (leptin) and by insulin from the pancreas, which alters the bioavailability of oestradiol (E_2) and testosterone (*T*) by affecting the production of SHBG (sex-hormone-binding globulin) from the liver. Insulin can also function directly on the ovary. (**b**) By contrast, in overweight women and/or those with polycystic ovary syndrome (*PCOS*), an increase in the number of fat cells results in a cascade of changes, involving increased leptin and insulin levels and a preferential increase in LH, but not FSH, levels. The net effect of these changes is to stimulate the partial development of follicles that secrete supranormal levels of T, but which rarely ovulate (hence low progesterone (*P*)). These changes are exacerbated by insulin-induced reduction in SHBG, which amplifies ovarian T production/action (Modified from Sharpe and Franks 2002)

Whether the insulin resistance and compensatory hyperinsulinaemia often observed in relation to PCOS is a primary symptom of PCOS that may be exacerbated by obesity or whether a primary effect of obesity is not clear.

Particularly in women with PCOS, beta-cell dysfunction in the pancreas, increased insulin secretion and deficiency in insulin action may contribute to the insulin resistance often observed in these women.

2.3.3 Sex Hormones

The hyperinsulinaemia directly affects the level of SHBG, which is reduced (Fig. 2.1). SHBG binds among other things testosterone, and a secondary effect is increased levels of free testosterone (Sharpe and Franks 2002). At the same time, hyperinsulinaemia per se directly affects the increase in production of testosterone in theca cells in the ovary.

Finally, a selective increase in LH secretion may be seen in obese women without affection of FSH production or secretion.

2.4 Obesity and the Menstrual Cycle

Obese women are well known to be at increased risk of menstrual disturbances (Hartz et al. 1979), including long cycle length (usually defined as >35 days) and anovulation. Even childhood obesity has been shown to be associated with menstrual difficulties in later life (Lake et al. 1997).

The menstrual disturbances may be further aggravated in the presence of PCOS as suggested in several studies (Norman et al. 2004).

2.5 Spontaneous Conception

Few studies have been conducted on the association between overweight and obesity and the chance of spontaneous conception in the general population (Koivunen et al. 2008). Most – but still few – studies have assessed the association in populations of pregnant women thus leaving out the most infertile women (Jensen et al. 1999; Gesink Law et al. 2007; Bolumar et al. 2000), while the association has not been much investigated among sub-fertile women (van der Steeg et al. 2008). Still, while the actual analyses performed differ slightly, the estimates found in the different populations are remarkably identical. Overall, there seems to be little or no association between overweight defined as a BMI of 25–29.9 (Table 2.1) irrespective of the measures used. With respect to obesity, estimates of the probability of conceiving per cycle compared with normal-weight women range between 0.77 and 0.82, and the chance of conceiving within 1 year has been estimated at 0.72 for obese women or 0.96 per unit increase in BMI beyond 29 (Table 2.1).

Studies assessing the potential influence of cycle irregularity have shown that while women with irregular cycles have a reduced chance of conception (Jensen et al. 1999), adjustment for cycle irregularity did not affect the association between obesity and fecundity (Jensen et al. 1999; Gesink Law et al. 2007).

One interesting finding is the effect modification by smoking described among pregnant women with planned pregnancies (Bolumar et al. 2000). While obese smokers had an 11.54 times increased risk of long waiting time to pregnancy compared with normal-weight smokers, no such association was apparent for

Table 2.1 Studies on the association between overweight and obesity (measured by body mass index) and fecundity. Only fully adjusted estimates are presented with 95% confidence intervals

Authors	*N*	Study period Country	Population	Data collection	BMI group	Results
Koivunen et al. (2008)	3,115	1997–1998	Population-based (birth cohort of 1966)	Retrospective	25–29.9	OR = 0.97 (0.84; 1.12)[a]
		Finland	PCOS women		≥30	OR = 0.72 (0.58; 0.90)[a]
Van der Steeg et al. (2008)	3,029	2002–2004	Population-based	At baseline and at follow-up at 12 months	Per unit ≥29	OR = 0.96 (0.91; 0.99)[a]
		The Netherlands	Subfertile, ovulatory women			
Gesink Law et al. (2007)	7,327	1959–1965	Pregnant women	16th week of gestation (retrospective TTP)	25–29.9	OR = 0.92 (0.84; 1.01)[b]
		United States	First planned pregnancy		≥30	OR = 0.82 (0.72; 0.95)[b]
Jensen et al. (1999)	28,629	1972–1987	Pregnant women	20th week of gestation (retrospective TTP)	26+	OR = 1.82 (1.50; 2.20)[c]
		Denmark	First recorded pregnancy only			OR = 0.77 (0.70; 0.84)[b]
Bolúmar et al. (2000)	2,887	1992	Pregnant women	After 20 weeks of gestation (retrospective TTP)	25–29.9	*Smokers*
		Denmark/France/ Germany/Italy/ Sweden	Planned pregnancies		≥30	OR = 0.80 (0.35; 1.81)[d]
					25–29.9	OR = 11.54 (3.68; 36.15)[d]
					≥30	*Non-smokers*
						OR = 0.80 (0.46; 1.40)[d]
						OR = 0.79 (0.25; 2.48)[d]

[a]Chance of conceiving within 1 year
[b]Probability of conception per cycle
[c]Risk of failure to conceive within 1 year
[d]Risk of time to pregnancy >9.5 months

non-smokers (Table 2.1). Effect modification by a third factor can be found only if one looks for such potential associations, and in most studies, other covariates are usually treated as potential confounders but not effect modifiers. The only other study where this specific association seems to have been assessed did not find smoking to be an effect modifier (Gesink Law et al. 2007).

Childhood obesity has been shown to be associated with reduced fecundity in married women later in life (Hartz et al. 1979), suggesting that the association between obesity and fecundity may not be limited to adult stature.

A recent Cochrane review suggests that the use of metformin in the treatment of women with PCOS may increase ovulation rates compared with placebo (OR = 2.12 (1.50–3.00)) and may increase clinical pregnancy rates compared with placebo (OR = 3.86 (2.18–6.84)) (Tang et al. 2010) by increasing insulin sensitivity. However, live birth rates were not affected (OR = 1.00 (0.16–6.39)) (Tang et al. 2010).

2.5.1 Selected Types of Bias in Studies of Fecundability

As in all observational studies, there are many types of bias. One particularly important type of selection bias is planning bias (Weinberg et al. 1994). Many pregnancies are unplanned. In at least some studies, obese women have been shown to be less likely to use contraception (Chuang et al. 2005), and if it is assumed that obese women may be less consistent in their use of contraception, then highly fertile obese women may conceive unintentionally, and hence they will never be eligible for a follow-up study of time to pregnancy. On the other hand, less fertile, obese women will be left for inclusion, and it will appear as if obesity increases time to pregnancy, even if this is not the case.

With respect to information bias, it is well known that obese women are more likely to underreport their weight compared to normal-weight women. If obesity is indeed associated with time to pregnancy but overweight is not, underreporting would result in some obese women appearing in the overweight group, suggesting an increased risk in this group. Hence, the weight limit would be set at too low a limit. This latter problem applies not only to studies on fecundability but also to studies on ART.

2.6 Assisted Reproduction

ART covers a number of fairly standardized treatments developed to help infertile couples or single women to achieve a pregnancy and, hopefully, a live birth. The three main types of treatments are ovulation induction in women with anovulation, intrauterine insemination (IUI) either with homologue sperm from the male partner or with donor sperm, or in vitro fertilization (IVF) with or without intracytoplasmatic sperm injection (ICSI).

2.6.1 Ovulation Induction

Ovulation induction is usually performed using either an ovulation inducing agent such as the anti-estrogen clomiphene citrate (CC) or mild ovarian stimulation with gonadotrophins (FSH or FSH + LH).

Ovulation induction with CC is generally performed with standard doses of 50–150 mg for 5 subsequent days per cycle.

In normogonadotropic women, with oligo- or amenorrhoea and a history of infertility, who ovulate after CC-treatment, BMI is not associated with chance of ovulation (Imani et al. 1999).

In normogonadotropic, anovulatory women with oligo- or amenorrhoea, with unknown response to CC, BMI predicts the chance of ovulation, with increasing BMI reducing the chance of ovulation (OR = 0.92 per unit increase in BMI) (Imani et al. 2002). However, BMI did not influence the chance of live birth (Imani et al. 2002). In line with these findings, BMI has been found to increase the risk of clomiphene-resistant anovulation (Imani et al. 1998).

In women with PCOS, CC may also improve clinical pregnancy rates (Tang et al. 2010).

A Cochrane review suggests that the additional use of metformin together with CC in the treatment of women with PCOS may increase ovulation rates compared with CC alone (OR = 3.46 (1.97–6.07)) and may increase clinical pregnancy rates compared with CC alone (OR = 1.48 (1.12–1.95)) (Tang et al. 2010) by increasing insulin sensitivity. However, live birth rates were not affected (OR = 1.05 (0.75–1.47)) (Tang et al. 2010). The latter finding may be due to the increased risk of miscarriage reported elsewhere.

In cases where stimulation with CC is not successful in inducing ovulation, mild ovarian stimulation with gonadotrophins may be used. A randomized controlled trial of anovulatory women with PCOS, resistant to CC, randomized to different subtypes of FSH (subsequently shown to yield comparable results) showed that overweight and obese women needed higher doses of FSH and more stimulation days (Balen et al. 2006). On average, overweight women needed an additional 268 IU of FSH, and obese women an additional 480 IU, yielding an increase in dose of 49 IU per unit increase in BMI (Balen et al. 2006). Treatment with FSH was prolonged approximately 1 day for each 3-unit increase in BMI (Balen et al. 2006). Also, there were fewer intermediate and large follicles in overweight and obese women. However, no differences in ovulation rates or clinical pregnancy rates were observed (Balen et al. 2006).

2.6.2 Intrauterine Insemination

While potential predictors of success in relation to intrauterine insemination are assessed in many studies, only very few have included a measure of weight or BMI in the analyses.

Two studies, apparently analyzing insemination cycles where both homologue sperm and donor sperm was used as appropriate, essentially the same results appeared.

A study of 2,040 women in Australia undergoing 5,089 IUI cycles with low-dose stimulation of the ovaries showed increasing fecundity with increasing BMI across all BMI categories, except for the very obese, who still had increased fecundity compared with normal-weight women (Wang et al. 2004). The adjusted chance of pregnancy was 1.52 (1.20–1.94) for overweight, 1.79 (1.27–2.52) for obese and 1.43 (0.91–2.26) for the very obese compared to normal-weight women. Cancellation rates were comparable between BMI groups.

A recent study of 477 women undergoing 1,189 IUI cycles with FSH stimulation showed a significant trend across BMI categories suggesting the need of increasingly higher doses of FSH with increasing BMI, lower oestradiol levels, thinner endometrial thickness and fewer follicles including fewer large follicles with increasing BMI (Souter et al. 2011). Even so, the chance of achieving a clinical pregnancy was 66–67% higher among both overweight and obese women compared to normal-weight women, and the chance of a live birth was respectively 1.91 (1.2–3.2) and 1.80 (0.96–3.5) times higher compared to normal-weight women (Souter et al. 2011).

Two studies assessing only cycles where donor sperm was used reached somewhat different results.

In a study of 489 women, most of them receiving insemination in unstimulated cycles, overweight was not associated with chance of pregnancy (Zaadstra et al. 1993). Obesity was negatively associated with chance of pregnancy (Hazard ratio (HR) of 0.431 (0.171–1.087)), albeit not significantly so because of small numbers. Interestingly, waist-hip ratio was significantly and negatively associated with fecundability (HR = 0.706 (0.562–0.887)).

In another study of 1,144 women stimulated with CC and FSH, only 21% of obese women and 33% of overweight women achieved a pregnancy compared to 42% among normal-weight women (Koloszar et al. 2002). While the time span is mentioned (1992–1998), the number of cycles is not clear.

There may be different explanations for the discrepancies reported. Firstly, the results of the two most recent studies would seem to suggest that while obese women need higher doses of FSH to produce a successful response in IUI treatments, once this is acknowledged, results are at least comparable or perhaps even better than those of normal-weight women. This may be due to the natural selection that occurs. Many for the obese women suffer from anovulation, but once this problem is solved by mild stimulation, the overweight and obese women are otherwise highly fertile. In contrast, the normal-weight women may have ovulation, and the reason they need treatment simply reduce their overall chance of conception.

In the Zaadstra study, most were inseminated in the natural cycle, and if overweight and obese women are more likely to have somewhat irregular cycles, the timing of insemination is likely to be poorer than that of normal-weight women.

Finally, donor sperm is usually used for healthy women with partners with poor sperm count, single women or women with a female partner, i.e. normal, healthy

women. When healthy women are inseminated with high-quality donor sperm, they are likely to perform better than women, who have difficulty in achieving a pregnancy with their partner, irrespective of the indication for treatment.

So, overall, the discrepancies may well be explained by actual differences between the groups of women treated even in the absence of selection or information bias or confounding.

2.6.3 IVF and ICSI

While it seems fairly consistent that obesity reduces fecundity in the spontaneous cycle, and while it appears that obesity does not much affect the chance of achieving a pregnancy once ovulation is induced in connection with, for example, ovulation induction treatment and IUI treatment, results on the effect of obesity in IVF and ICSI treatment is much less clear.

Firstly, one must acknowledge that while the effect of obesity on fertility and fecundity in the previous sections is generally estimated by assessing the direct effect on chance of pregnancy or live birth, studies on IVF tend to report all kinds of surrogate measures, including number of oocytes retrieved, number of mature oocytes, fertilization rates, implantation rates and embryo score apart from clinical pregnancy rate and occasionally live birth rate. While intermediate measures may be of some interest, they appear only interesting to the extent that they are directly linked to chance of pregnancy, or even better: live birth rate. This link is not entirely clear.

One remarkable finding in studies of general predictors of success in IVF treatment (irrespective of which of the above measures is assessed) is the fact that while the actual predictors found differ between studies, BMI does not appear to be a good predictor of success in IVF treatment (Ottosen et al. 2007; Kilic et al. 2010).

While many studies describe some significant association between obesity and one or more of the above outcomes, the findings are not consistent. Some report an association with live birth rate but not with fertilization or implantation rates (Fedorcsák et al. 2004), others describe an association with fertilization rate but not with pregnancy rate or live birth rate (Zhang et al. 2010), and others find no associations all together (Lashen et al. 1999).

One systematic review concluded that normalweight women (BMI 20–25) undergoing IVF treatment had a greater chance of pregnancy compared with overweight women (OR = 1.40 (1.22–1.60)), and normalweight/overweight women (BMI 20–30) had a greater chance of pregnancy compared with obese women with BMI >30 (OR = 1.47 (1.20–1.80)) (Maheshwari et al. 2007). Despite the fairly large number of studies on the association between BMI and IVF, the estimates were based on only three studies. Similarly, while it appears that overweight and obese women require higher doses of gonadotrophins compared to women with lower BMI (Maheshwari et al. 2007), these conclusion are based on only two studies. The review concluded that there is insufficient evidence on the effect of BMI on oocyte recovery, cycle cancellation, risk of ovarian hyperstimulation syndrome and not least live birth rate (Maheshwari et al. 2007).

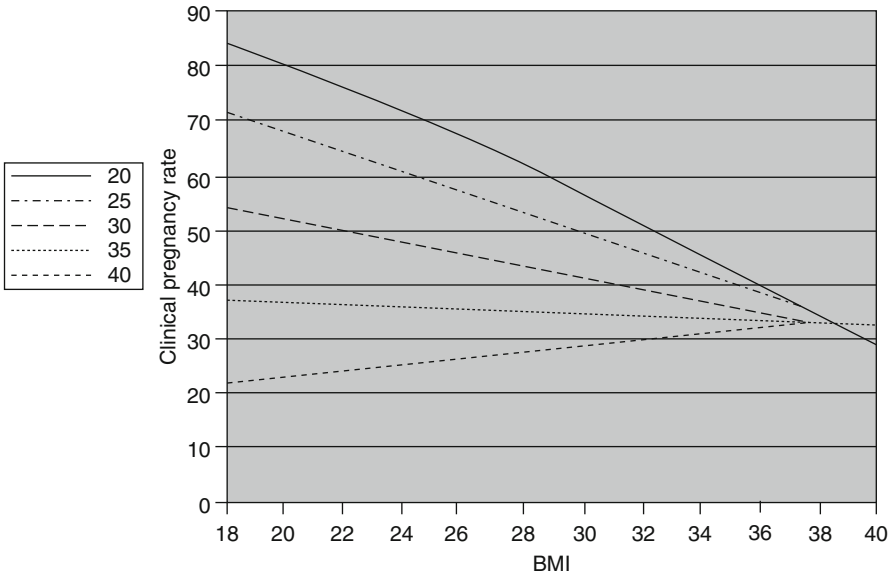

Fig. 2.2 The effect of age and BMI on clinical pregnancy rates. *Lines* illustrate the best-fit regression lines derived from multiple logistic regression for clinical pregnancy rates as a function of BMI and age at 5-year intervals: 20, 25, 30, 35 and 40 (From Sneed et al. 2008)

One study suggested that the effect of BMI on IVF success may be related to age (Sneed et al. 2008). While the chance of pregnancy in IVF treatment drops dramatically with increasing BMI among young women up to about 30 years of age, BMI seems largely to be of no consequence from age 35 onwards (Fig. 2.2). The interaction between BMI and age was also found for some of the above measures including number of oocytes retrieved, mature oocytes, fertilization rates and implantation rates. Such an interaction does not seem to have been assessed in other studies, even though it may seem biologically plausible: To the extent that obesity matters in IVF treatment, it probably matters most among the most fertile women. As fertility declines steadily with age, obesity no longer plays an important role in older women.

Another study assessing the effect of BMI and insulin resistance on oocyte quality suggested that insulin resistance (measured by oral glucose tolerance test) may interact with BMI to reduce oocyte and embryo quality (Cano et al. 1997).

The latter two findings are particularly interesting because of the inconsistent results with respect to the potential effect of obesity on IVF results. It may be that the inconsistencies are due to particular subgroups of overweight and/or obese women being at risk of adverse outcomes, for example young women and insulin-resistant women. Particular focus on identifying such subgroups seems to be warranted.

A Cochrane review suggests that the use of metformin before or during IVF treatment of women with PCOS does not affect clinical pregnancy rates (OR = 0.71 (0.39–1.28)) or live birth rates (OR = 0.77 (0.27–2.18)) (Tso et al. 2009).

2.7 Does Weight Loss Matter?

Weight loss is possible by for example comprehensive lifestyle intervention, whereas metformin, which is popular in the treatment of especially women with PCOS, does not appear to have much effect on weight in these women, although it has been shown useful in promoting weight loss among people at risk of diabetes in general. It has been shown that short-term and especially long-term weight management after initial weight loss is difficult in the obese. In a systematic review of dietary maintenance including studies spanning many decades, two alternative definitions of successful long-term (up to 14 years) weight management were used: (1) maintenance of the initial weight loss or further weight loss or (2) maintenance of at least 9–11 kg of the initial weight loss (Ayyad and Andersen 2000). Only about 15% of the women fulfilled the criteria, suggesting that dietary management alone may not be useful in the long run. It seems, perhaps not surprisingly, that weight gain is attenuated with supplemental physical activity and continued support (Ayyad and Andersen 2000).

What dietary interventions that may be the more useful is not clear. Some advocate low-energy and low-fat diet, others low-fat and high-carbohydrate intake.

Still, while weight loss may be difficult to maintain, even a small weight loss may have measurable short-term impact on measures of metabolism and fecundity (Norman et al. 2004).

A programme involving change in behaviour with respect to physical exercise and diet for a total of 6 months has been shown to be efficient in anovulatory women. In a small sample of 13 overweight, anovulatory women, an average weight loss of 6.3 kg was reached, 12 resumed spontaneous ovulation and 11 became pregnant (Clark et al. 1995). In a subsequent study of 67 anovulatory women, the average weight loss was 10.2 kg corresponding to a 10% reduction in BMI (Clark et al. 1998). Of the 67 women, 60 had spontaneous ovulation restored, 52 became pregnant and 45 carried the pregnancy to birth (Clark et al. 1998). Other studies have shown comparable results, suggesting that in obese women, weight loss of only about 10% of the initial weight may improve pregnancy rates (Norman et al. 2004; Clark et al. 1995, 1998).

At the same time, small reductions in weight of 5–10% of initial body weight may reduce the levels of insulin and androgens, thus contributing to the above effects (Norman et al. 2004; Clark et al. 1995, 1998).

For women with PCOS, a recent meta-analysis assessed the association between lifestyle intervention defined differently in different studies as physical activity, dietary intervention and/or behavioural advice and reproductive outcomes (Moran et al. 2011). Lifestyle intervention had an effect on a few metabolic factors, including a reduction in total testosterone (mean difference −0.27 nmol/L) and fasting insulin (mean difference −2.02 μU/mL), whereas no effect was seen for free androgen index or SHBG, glucose or cholesterol.

For anthropometric measures, an effect was observed for weight (mean difference −3.47 kg) and waist circumference (mean difference −1.95 cm) but not for BMI. For clinical measures, an effect was observed for hirsutism and excess hair growth (Moran et al. 2011).

Unfortunately, no data was available on direct measures of fecundability or fertility such as chance of achieving a pregnancy or live birth, or other clinically relevant measures including menstrual irregularity, anovulation or miscarriage (Moran et al. 2011). One very small study has suggested, however, that lifestyle – alone or in combination with metformin – may increase the chance of ovulation, at least if the woman manages to lose weight (Hoeger et al. 2004).

2.8 Male Obesity

2.8.1 Hormonal Changes in the Obese Man

It has consistently been shown that high BMI reduces both total testosterone and free testosterone levels, albeit free testosterone to a lesser degree (MacDonald et al. 2010). SHBG is also systematically lower in overweight and obese men compared to normal-weight men (MacDonald et al. 2010). FSH and LH do not seem to be affected by BMI in men. Levels of oestradiol generally appear unaffected by BMI (MacDonald et al. 2010), but a few studies have suggested slightly higher levels with increasing BMI (Jensen et al. 2004; Aggerholm et al. 2008) (Table 2.2).

2.8.2 Male Obesity and Sperm Quality

A meta-analysis of a selected amount of data suggests that male overweight and obesity do not materially affect sperm concentration, sperm count, volume or sperm motility (MacDonald et al. 2010).

Even so, some of the largest studies come to different conclusions. In the largest of the studies, no material differences were observed (Aggerholm et al. 2008). In another study, men with BMI >25 had lower sperm concentration, lower total sperm count and fewer normal forms (Jensen et al. 2004). The variation was, however, great, and the observed differences for sperm concentration and normal forms were small. Interestingly, a Chinese study showed increased sperm concentration and an increase in normal forms and motile sperm among overweight and obese men compared to normal-weight men (Qin et al. 2007). Again, while the findings are interesting, the actual differences were small (Table 2.3).

Sperm morphology is less well studied, but while results are mixed, the overall impression is that of no association.

It may seem surprising that systematic differences in levels of important reproductive hormones are observed while essentially no differences in sperm quality are observed across BMI categories. Here, it may be worth noting that spermatogenesis is mainly driven by free testosterone, which was only marginally reduced across BMI categories, and FSH, which was constant across BMI categories in most studies.

Table 2.2 Summary of results of studies investigating the association between male BMI and reproductive hormones (MacDonald et al. 2010)

Study	Size	Relationship between BMI and reproductive hormone						
		T	Free T	SHBG	E_2	Inhibin B	FSH	LH
Wu et al. (2008)	3,200	Negative	Negative	Negative				None
Aggerholm et al. (2008)	1,989	Negative		Negative	None	Inverse U-curve	None	None
Mohr et al. (2005)	1,677	Negative	Negative					
Jensen et al. (2004)	1,558	Negative	Positive (FAI)	Negative	Positive	Negative	None	None[a]
Svartberg et al. (2004)	1,548	Negative	Negative	Negative				
Qin et al. (2007)	990	Negative[a]			None		Positive[a]	None
Allen et al. (2002)	696	Negative	Negative	Negative				Negative
Schatzl et al. (2003)	561	Negative	Negative					
Muller et al. (2003)	400	Negative	Negative (Bio T)	Negative	Positive			
Meeker et al. (2007)	388	Negative[a]	Positive (FAI)[a]	Negative[a]		Negative[a]		
Ukkola et al. (2001)	324	Negative		Negative	None			
Meikle et al. (1989)	323	Negative	None	Negative			None	
Jankowska et al. (2000)	236	Positive[b]	None		None			
Andersson et al. (2004)	178					None	None	
Haffner et al. (2004)	178	Negative	Negative	Negative	None			
Hofstra et al. (2004)	160	Negative	Negative	None	Positive		None	None
Hautanen et al. (2004)	159	Negative		Negative				
Gomez et al. (2004)	134	None		Negative				
Jarow et al. (2004)	120	Negative[c]		Negative[c]	None			None
Kley and Krüskemper (1979)	116	Negative	Negative					
Giagulli et al. (2004)	110	Negative	Negative	Negative	Positive			Negative[d]

Full references for the studies cited in the table may be found in MacDonald et al. (2010)
Note: All relationships stated are statistically significant ($p \leq 0.05$) unless otherwise noted
Bio T bioavailable testosterone, *FAI* free androgen index
[a]No *P*-values or confidence intervals published, therefore statistical significance of these trends not reported
[b]Relationship was statistically significant in younger men (aged 22–39) but not older men (aged 40–67)
[c]These relationships found only in infertile groups of men (not fertile men)
[d]Levels of these hormones were only significantly reduced in severely obese men (BMI > 40)

Table 2.3 Meta-analysis of studies assessing the association between male BMI and sperm quality (MacDonald et al. 2010)

Semen parameter	Number of studies	Number of data entries used	Regression coefficient	95% confidence interval
Mean sperm concentration	4	14	−0.02	−8.24; 8.18
Median sperm concentration	2	7	1.57	−7.37; 10.53
Mean total sperm count	2	8	12.43	−164.95; 189.81
Median total sperm count	2	7	2.09	−35.79; 39.97
Semen volume	3	11	0.05	−0.05; 0.15
Average sperm motility	3	11	−1.07	−7.39; 5.25

Hence, while total testosterone levels and SHBG levels were systematically affected, the most important regulatory hormones seem to be only marginally affected, potentially creating a balance in sperm parameters between normal-weight men and overweight and obese men (MacDonald et al. 2010).

2.8.3 Male Obesity and Chance of Conception

Very few studies have investigated the role of male obesity in relation to chance of conception in the general population. In a study based on the Danish National Birth Cohort and hence based only on women who achieved a pregnancy, increased risk of long waiting time to pregnancy (>12 months) for overweight (25–29.9) and obese men (≥30) was observed. The overall risk of long time to pregnancy increased by 32% for each increment in BMI group. However, the risk depended on the BMI of the female partner: For example, an obese man with BMI ≥30 with a normal-weight partner had a 1.53 (1.32–1.77) times increased risk of long waiting time compared to a 2.74 (2.27–3.30) times increased risk if the female partner was also obese (Ramlau-Hansen et al. 2007). For comparison, an overweight man with BMI 25–29.9 with a normal-weight partner had a 1.18 times (1.10–1.27) increased risk of long waiting time compared to a 1.41 (1.28–1.56) times increased risk if the female partner was also overweight (Ramlau-Hansen et al. 2007).

No studies seem to have investigated the role of male weight or BMI in relation to IVF treatment.

2.9 Economic Consequences of Obesity in Relation to Fertility

It appears from the previous discussion that anovulation is the one problem that may unequivocally be attributed to overweight and obesity. Whether success rates of ovulation induction and IUI depend on the degree of overweight and obesity is debatable, and the extent to which overweight and obesity affect the results of IVF, treatment is unclear.

Table 2.4 Approximate costs of fertility treatment and pregnancy complications per pregnancy

ART treatment or pregnancy complication	Estimated cost per pregnancy achieved (Euro)
Ovulation induction	250
IUI	450
IVF	1,700
Miscarriage	683
Gestational diabetes mellitus	345
Hypertensive disorders in pregnancy	8,250
Caesarean section	3,350

Based on Koning et al. (2010)

Some studies have attempted to calculate the potential economic consequences of overweight and obesity in relation to fertility. As is clear from other parts of this book, obesity has an indisputably negative impact on many pregnancy and birth-related outcomes. If trying to estimate the cost of fertility treatment due to overweight and obesity, it may seem reasonable to include costs of pregnancy and birth complications, as has been done in some studies (Koning et al. 2010).

Based on the equivocal findings in the literature, cost-effectiveness analyses are based on assumptions of differences or lack of differences in effectiveness of different types of treatment. Such assumptions are always debatable (Koning et al. 2010).

The actual cost of achieving a pregnancy in anovulatory women also depends on the type of treatment chosen, and the actual cost of each type of treatment depends on many factors, including type of medical treatment, number of treatment days needed in case of ovarian stimulation and influence of factors that may affect the results of ART treatments other than overweight and obesity. Such factors could include smoking habits known to increase time to pregnancy and reduce the chance of clinical pregnancy and live birth in connection with ART (Waylen et al. 2009), and coffee consumption which appears to increase time to pregnancy and the risk of early miscarriage.

Whatever the assumptions, it appears evident that the cost of achieving a pregnancy or the cost of achieving a live birth is higher for overweight and obese, anovulatory women compared with normal-weight, anovulatory women. For overweight women, the costs may be approximately 50% higher and for obese women up to 100% higher (Koning et al. 2010).

Even so, it seems clear that the costs of fertility treatment per se are low compared to the subsequent costs related to pregnancy and birth complications, Table 2.4 (Koning et al. 2010; Goverde et al. 2000), which are likely to be unrelated to the mode of conception.

2.10 Is Limitation of Access to Fertility Treatment Based on BMI Fair?

Obesity is a growing problem worldwide, and in some countries more than half of all women are overweight or obese. A large proportion of overweight and obese women are of fertile age. At the same time, fertility rates are low in most countries

Table 2.5 Arguments for and against BMI-linked access to fertility treatment

Arguments for BMI-linked access	Arguments against BMI-linked access
Clinical pregnancy rates and live birth rates are lower for the obese following (some types of) fertility treatment	There is no clear evidence that weight loss may improve the outcome of fertility treatment
Higher drug doses are needed among the obese	Even if weight loss matters, lifestyle intervention and medical intervention with a view to weight reduction do not seem to have an effect of a clinically relevant magnitude
Treatment duration is longer for the obese	Limited access to fertility treatment may lead to stigmatization, low self-esteem and poor body image among the obese
The cost of fertility treatment is higher for the obese (because of longer treatment duration, higher drug doses, lower chance of success and higher risk of miscarriage)	In other areas of health care, risk of complications does not imply restrictions in access to treatment
Increased risk of complications in pregnancy among the obese (e.g. gestational diabetes and pre-eclampsia)	
Increased risk of complications during delivery among the obese (e.g. caesarean section, shoulder dystocia and stillbirth)	

Based on (Pandey et al. 2010) and others

in the Western hemisphere, with many countries having total fertility rates below two (United Nations 2006).

At the same time, it has been suggested that access to fertility treatment should be limited by BMI. In fact, in many countries, different cut-off values for BMI are already used to select women who may and may not receive fertility treatment. In the UK, the British Fertility Society advocates that "Women should aim for a normal BMI before starting any form of fertility treatment. Treatment should be deferred until the BMI is less than 35 kg/m^2, although in those with more time (e.g. less than 37 years; normal serum FSH concentration) a weight reduction to a BMI of less than 30 kg/m^2 is preferable" (Balen and Anderson 2007). In Denmark, most clinics have implemented cut-offs for BMI ranging between 30 and 40.

Arguments for and against BMI-linked access to fertility treatment have been presented (Pandey et al. 2010), and some are given in Table 2.5.

At present, arguments in favour of BMI-linked access to fertility treatment appear to dominate in public clinics, at least in some countries (Balen and Anderson 2007). Considering the evidence of the potential effects of overweight and obesity on fertility and fecundability presented in this chapter, it is interesting that the best of the arguments listed seems to be unrelated to the actual treatment, namely, risk of complications during pregnancy and delivery.

With respect to arguments against BMI-linked access to fertility treatment, as suggested in this chapter, there is no clear evidence that weight loss may improve

the outcome of fertility treatment, and even if weight loss matters, lifestyle intervention and medical intervention with a view to weight reduction do not seem to have an effect of a clinically relevant magnitude. This means that many obese women who are not very close to any given BMI cut-off limit will have serious difficulties in losing weight to an extent that make them eligible for treatment.

This may potentially lead to stigmatization, low self-esteem and poor body image, and it may even exacerbate obesity-related disease (Pandey et al. 2010).

In other areas of health care, risk of complications does not imply restrictions in access to treatment. Obesity increases the risk of peri- and post-operative complications, but this does not mean that obese women are generally denied access to operation, even for benign diseases.

Finally, but importantly, hardly any countries or clinics seem to impose restrictions based on other, comparable lifestyle factors. Although tobacco smoking has been shown to reduce the chance of achieving a clinical pregnancy and a live birth by 40–50% in connection with IVF (Waylen et al. 2009), no countries or fertility societies seem to have suggested that cigarette smokers should be denied fertility treatment on the ground that tobacco smoking lowers pregnancy rates and live birth rates and that tobacco smoking increases the risk of many complications during pregnancy and perinatally.

Given the fairly low cost associated with fertility treatment per se, the restrictions imposed in some countries are at least debatable.

Conclusion

A number of hormonal and clinical changes related to fertility and fecundity are observed in overweight and obese women: increased levels of leptin, which acts on the hypothalamus, the ovaries and the endometrium. Insulin resistance and compensatory hyperinsulinaemia is seen in obese women in general but also among women with polycystic ovary syndrome, and reduced levels of sex-hormone-binding globulin and increased levels of testosterone are observed. While it seems fairly consistent that obesity reduces fecundity in the spontaneous cycle, and while it appears that obesity does not much affect the chance of achieving a pregnancy once ovulation is induced in connection with, for example, ovulation induction treatment and IUI treatment, results on the effect of obesity in IVF and ICSI treatment are much less clear. While many studies describe significant associations between obesity and one or more outcomes in IVF, the findings are not consistent. It may be that the inconsistencies are due to particular subgroups of overweight and/or obese women being at risk of adverse outcomes, for example young women and insulin-resistant women. Particular focus on identifying such subgroups seems to be warranted. Small reductions in weight of 5–10% of initial body weight may reduce the levels of insulin and androgens and increase the chance of achieving a pregnancy.

For men, overweight and obesity reduce both total testosterone and free testosterone levels but do not materially affect sperm concentration, sperm count, volume or sperm motility. Pregnancy rates may also be affected by male obesity, although the evidence is insufficient.

It appears evident that the cost of achieving a pregnancy or the cost of achieving a live birth is higher for overweight and obese, anovulatory women compared with normal-weight, anovulatory women. For overweight women, the costs may be approximately 50% higher and for obese women up to 100% higher. Even so, it seems clear that the costs of fertility treatment per se are low compared to the subsequent costs related to pregnancy and birth complications.

Given the fairly low cost associated with fertility treatment per se, the restrictions on fertility treatment imposed in some countries on the basis of BMI are debatable.

References

Aggerholm AS, Thulstrup AM, Toft G, Ramlau-Hansen CH, Bonde JP (2008) Is overweight a risk factor for reduced semen quality and altered serum sex hormones profile? Fertil Steril 90:619–626

Ayyad C, Andersen T (2000) Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. Obes Rev 1:113–119

Balen AH, Anderson RA (2007) Impact of obesity on female reproductive health: British Fertility Society. Policy and practice guidelines. Hum Fertil 10(4):195–206

Balen AH, Platteau P, Andersen AN, Devroey P, Sørensen P, Helmgaard L, Arce JC (2006) The influence of body weight on response to ovulation induction with gonadotrophins in 335 women with World Health Organisation group II anovulatory infertility. BJOG 113:1195–1202

Bolumar F, Olsen J, Rebagliato M, Sáez-Lloret I, Bisanti L, European Study Group on Infertility and Subfecundity (2000) Body mass index and delayed conseption: a multicenter study on infertility and subfecundity. Hum Reprod 151(11):1072–1079

Cano F, Garcia-Velasco JA, Millet A, Remohi J, Simon C, Pellicer A (1997) Oocyte quality in polycystic ovaries revisited: indentification of a particular subgroup of women. J Assist Reprod Genet 14(5):254–261

Chuang CH, Chase GA, Bensyl DM, Weisman CS (2005) Contraceptive use by diabetic and obese women. Womens Health Issues 15(4):167–173

Clark AM, Ledger W, Galletley C, Tomlinson L, Blaney F, Wang X, Norman RJ (1995) Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod 10:2705–2712

Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ (1998) Weight loss in obese infertile women results in improvement in reproductive outcomes for all forms of fertility treatment. Hum Reprod 13(1502):1505

Fedorcsák P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, Omland AK, Åbyholm T, Tanbo T (2004) Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod 19(11):2523–2528

Gesink Law DC, Maclehose RF, Longnecker MP (2007) Obesity and time to pregnancy. Hum Reprod 22(2):414–420

Goverde AJ, McDonnell J, Vermeiden JPM, Schats R, Rutten FFH, Schoemaker J (2000) Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. Lancet 355:13–18

Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA (1979) The association of obesity with infertility and related menstural abnormalities in women. Int J Obes 3(1):57–73

Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS (2004) A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertil Steril 82(2):421–429

Imani B, Eijkemans MJC, te Velde ER, Habbema JDF, Fauser BCMJ (1998) Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligomenorrheic infertility. J Clin Endocrinol Metab 83(7):2361–2365

Imani B, Eijkemans MJC, te Velde ER, Habbema JDF, Fauser BCMJ (1999) Predictors of chances to conceive in ovulatory patients duirng clomiphene citrate induction of ovulation in normogonadotropic oligomenorrheic infertility. J Clin Endocrinol Metab 84(5):1617–1622

Imani B, Eijkemans MJC, te Velde ER, Habbema JDF, Fauser BCMJ (2002) A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligomenorrheic infertility. Fertil Steril 77(1):91–97

Jensen TK, Scheike T, Keiding N, Schaumburg I, Grandjean P (1999) Fecundability in relation to body mass and menstrual cycle patterns. Epidemiology 10(4):422–428

Jensen TK, Andersson AM, Jørgensen N, Andersen A-G, Carlsen E, Petersen JH, Skakkebæk NE (2004) Body mass index in relation to semen quality and reproductive hormones among 1,558 danish men. Fertil Steril 82(4):863–870

Kilic S, Yilmaz N, Zülfikaroglu E, Sarikaya E, Kose K, Topcu O, Batioglu S (2010) Obesity alters retrieved oocyte count and clinical pregnancy rates in high and poor responder women after in vitro fertilization. Arch Gynecol Obstet 282(1):89–96

Koivunen R, Pouta A, Franks S, Martikainen H, Sovio U, Hartikainen A-L, McCarthy MI, Ruokonen A, Bloigu A, Järvelin M-L, Morin-Papunen L (2008) Fecundability and spontaneous abortions in women with self-reported oligo-amenorrhea and/or hirsutism: Northern Finland Birth Cohort 1966 study. Hum Reprod 23(9):2134–2139

Koloszar S, Daru J, Kereszturi A, Zavaczki Z, Szollosi J, Pal A (2002) Effect of female body weight on efficiency of donor AI. Arch Androl 48(5):323–327

Koning AMH, Kuchenbecker WKH, Groen H, Hoek A, Land JA, Khan KS, Mol BWJ (2010) Economic consequences of overweight and obesity in infertility: a framework for evaluating the costs and outcomes of fertility care. Hum Reprod Update 16(3):246–254

Lake JK, Power C, Cole TJ (1997) Child to adult body mass index in the 1958 British birth cohort: associations with parental obesity. Arch Dis Child 77:376–381

Lashen H, Ledger W, Bernal AL, Barlow D (1999) Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization. Hum Reprod 14(3):712–715

MacDonald AA, Herbison GP, Showell M, Farquhar CM (2010) The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. Hum Reprod Update 16(3):293–311

Maheshwari A, Stofberg L, Bhattacharya S (2007) Effect of overweight and obesity on assisted reproductive technology - a systematic review. Hum Reprod 13(5):433–444

Metwally M, Ledger WL, Li TC (2008) Reproductive endocrinology and clinical aspects of obesity in women. Ann N Y Acad Sci 1127:140–146

Moran LJ, Huchison SK, Norman RJ, Teede HJ (2011) Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev (7) Art No:CD007506 DOI: 10 1002/14651858 CD007506 pub3 2011

Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX (2004) Improving reproductive performance in overweight/obese women with efective weight management. Hum Reprod Update 10(3):267–280

Ottosen LDM, Kesmodel U, Hindkjaer J, Ingerslev HJ (2007) Pregnancy prediction models and eSET criteria for IVF patients - do we need more information? J Assist Reprod Genet 24(1):29–36

Pandey S, Maheshwari A, Bhattacharya S (2010) Should access to fertility treatment be determined by female body mass index? Hum Reprod 25(4):815–820

Qin D-D, Yuan W, Zhou W-J, Cui Y-Q, Wu J-Q, Gao E-S (2007) Do reproductive hormones explain the association between body mass index and semen quality. Asian J Androl 9(6):827–834

Ramlau-Hansen CH, Thulstrup AM, Nøhr EA, Bonde JP, Sørensen TIA, Olsen J (2007) Subfecundity in overweight and obese couples. Hum Reprod 22(6):1634–1637

Sharpe RM, Franks S (2002) Envirinment, lifestyle and infertility – an inter-generational issue. Nat Cell Biol 4(suppl):33–40

Sneed ML, Uhler ML, Grotjan HE, Rapisarda JJ, Lederer KJ, Beltsos AN (2008) Body mass index: impact on IVF success appears age-related. Hum Reprod 23(8):1835–1839

Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC (2011) Women, weight, and fertility: the effect of body mass index onthe outcome of superovulation/intrauterine insemination cycles. Fertil Steril 95(3):1042–1047

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH (2010) Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo-amenorrhoea and subfertility. Cochrane Database Syst Revi (1) Art No:CD003053 DOI: 10 1002/14651858 CD003053 pub4 2010

Tso LO, Costello MF, Andriolo RB, Freitas V (2009) Metformin treatment before and during IVF or ICSI treatment in women with polycystic ovary syndrome. Cochrane Database Syst Rev (2) Art No:CD006105 DOI: 10 1002/14651858 CD006105 pub2 2009

United Nations DoEaSA (2006) World population prospects, the 2010 revision. http://esa.un.org/unpd/wpp/Sorting-Tables/tab-sorting_fertility.htm. Accessed 9 Sept 2011

van der Steeg JW, Steures P, Eijkemans MJC, Habbema JDF, Hompes PGA, Burggraaff JM, Oosterhuis GJE, Bossuyt PMM, van der Veen F, Mol BWJ (2008) Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod 23(2):324–328

Wang JX, Warnes GW, Davies MJ, Norman RJ (2004) Overweight infertile patients have a higher fecundity than normal-weight women undergoing controlled ovarian hyperstimulation with intrauterine insemination. Fertil Steril 81(6):1710–1712

Waylen AL, Metwally M, Jones GL, Wilkinson AJ, Ledger WL (2009) Effects of cigarette smoking upon clinical outcomes of assisted reproduction: a meta-analysis. Hum Reprod Update 15(1):31–44

Weinberg CR, Baird DD, Wilcox AJ (1994) Sources of bias in studies of time to pregnancy. Stat Med 13(5–7):671–681

Wilcox AJ (2010) Fertility and pregnancy: and epidemiologic perspective. Oxford University Press, New York

Yildirim B, Sabir N, Kaleli B (2003) Relation of intra-abdominal fat distribution to metabolic disorders in nonobese patients with polycystic ovary syndrome. Fertil Steril 79:1358–1364

Zaadstra BM, Seidell JC, van Noord PAH, te Velde ER, Habbema JDF, Vrieswijk B, Karbaat J (1993) Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ 306(6876):484–487

Zhang D, Zhu Y, Gao H, Zhou B, Zhang R, Wang T, Ding G, Qu F, Huang H, Lu X (2010) Overweight and obesity negatively affect the outcomes of ovarian stimulation and in vitro fertilisation: a cohort study of 2628 Chinese women. Gynecol Endocrinol 26(5):325–332

http://www.springer.com/978-3-642-25022-4

Maternal Obesity and Pregnancy
Ovesen, P.G.; Møller Jensen, D. (Eds.)
2012, VIII, 324 p., Hardcover
ISBN: 978-3-642-25022-4