Obesity, Physical Activity and Female Fertility - A Review

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ABSTRACT

Obesity, a common public health issue amongst women of the reproductive age group is attributable to a combination of reduced exercise, changing dietary composition and increased energy intake. Gynaecologists and reproductive scientists have encountered the reproductive consequences of a society becoming obese with a higher frequency of women are diagnosed with disorders of menstruation, infertility and diabetes mellitus in pregnancy. Obesity impairs ovulation with its effect on implantation, oocyte development, oocyte quality, embryo and follicular development and is associated with irregular menses, an ovulation and miscarriage. Obese women suffer due to alterations in hypothalamic-pituitary axis as well. Weight loss through physical activity and lifestyle modification has been demonstrated to improve the chance of conception and restore ovulation. Many advances have been made recently on the effect of weight reduction in improving reproductive function in obese infertile women, and there is now a better understanding of how weight reduction through diet and exercise leads to improved reproductive performance. Therefore, it is essential to understand the impact of obesity on reproductive functions. This article highlights the complex relationship between obesity and reproduction and the role of physical activity in restoring fertility.

Keywords: obesity, infertility, reproduction, exercise, physical activity, weight loss.

INTRODUCTION

Rising rates of obesity represents a global public health challenge. It is increasingly being recognized that current obesity epidemic has also contributed to fertility problems. Infertility, a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse as defined by International Committee for Monitoring Assisted Reproductive Technology and World Health Organization has been recognized as a public health issue worldwide (Zegers-Hochschild et al., 2009). Infertility is acquiring a proportion of global epidemic affecting up to of 8-15% of couples during their reproductive lifetime (Vasant A, 2014). It has wide range of causes stemming from three general sources: physiological dysfunctions, unexplained issues and preventable causes. Out of all these obesity is the major preventable cause resulting in infertility.

1. The Effect of Overweight and obesity on fertility and conception

BMI and Infertility

Obesity is a state of excess adipose tissue and is one of the major causes contributing to several obesity related disorders such as dyslipidemia, cancers, hypertension, metabolic syndrome coronary heart disease and type II diabetes mellitus (Yang et al., 2009). It is a known risk factor for an ovulation and menstrual irregularities leading to Infertility (Sarwer et al, 2006).
Female obesity is associated with significant alterations in reproductive health and fertility as obese women are more likely to suffer infertility as compared to women with a normal body mass index (Matalliotakis et al. 2008). A number of factors contribute to conception delay in obese women which can be categorised as pathophysiological, psychosocial and sociobiological.

Obesity exerts its effect on embryo development, ovulation, endometrial development, pregnancy loss and implantation, thereby impairing fertility. It disturbs menstrual cyclicity by exerting its effect upon the hypothalamic-pituitary-ovarian (HPO) axis (Sarwer et al, 2006). Therefore Obesity, reproduction and fertility are considered complex systems affected by a number of variables.

Hassan & Killick 2004 in an observational study of 2112 consecutive pregnant women to investigate the effect of lifestyle factors that might impair fertility demonstrated, that a BMI of 25 kg/m² was significantly correlated with a increased time to pregnancy. The adverse effect of obesity on conception is also seen among women seeking assisted reproductive technology, with obese women manifesting higher miscarriage rates, lower implantation and pregnancy rates, and increased pregnancy complications (Pasquali et al, 2003). In a large systematic review and meta-analysis including 33 studies and 47,967 ART treatment cycles, Rittenberg et al, 2011 investigated the impact of BMI on pregnancy outcome and concluded that women with a BMI ≥25kg/m² had lower clinical pregnancy rates (relative risk (RR) 0.90 (95% confidence interval (CI) 0.85 to 0.94)), lower live birth rates (0.84 (0.77 to 0.92)), and were at increased risk of miscarriages (1.31 (1.18 to 1.45)) compared with women with a BMI < 25kg/m².

Maheshwari et al, 2007 in a systematic review concluded that women with BMI 20-25 kg/m² had a higher chance of achieving pregnancy in comparison with women of BMI >25, [combined odds ratio = 1.40 (95% CI: 1.22, 1.60)]. The combined odds of pregnancy were 1.47 (95% CI: 1.20, 1.80) for a woman with a BMI 20-30 kg/m² as compared to women with a BMI of >30 kg/m². This meta-analysis was unable to adjust for confounders such as duration of infertility, age and previous pregnancy. It was also unable to come to any firm conclusions about the impact of obesity on IVF live birth rates due to insufficient evidence. Some recent studies (Li et al, 2010, Zhang et al, 2010) have failed to confirm a direct association between high BMI and reduced live birth rates. Although there is evidence linking obesity with poor implantation and pregnancy rates, more robust studies are needed to substantiate this.

**Obesity risks- Pregnancy and live birth rates**

Maternal overweight and obesity are also established risk factors for stillbirth (Wattanakumtornkul et al, 2003), with a RR of 1.24 (95% CI 1.18 to 1.30) per 5-unit increase in maternal BMI (Zachariah et al, 2006). The impact of obesity on the risk of stillbirth is most pronounced at term. Adverse obstetrical conditions, placental abnormalities and foetal congenital anomalies are all considered to be involved in the underlying mechanism (Zachariah et al, 2006). During delivery, overweight and obese women experience more problems as compared to normal weight women. Increasing weight is associated with longer duration of labour, higher elective and emergency caesarean delivery rates (ORs up to 2.06 (1.84 to 2.30) in overweight women. There are higher risks of postpartum haemorrhage (obese women: 1.39 (1.32 to 1.46)), wound infections (obese women: 2.24 (1.91 to 2.64)), and urinary tract infections (Bellver et al, 2003). There is a vast evidence of the adverse impact of overweight and obesity on female reproductive health as both overweight and obesity in women is associated with increased risk of Infertility (Yilmaz et al, 2009). Obesity (Table: 1) is strongly associated with PCOS (one of the most
common causes of anovulation) and present in 30-75% of all women with PCOS (Pasquali et al, 2006; Pasquali et al, 2007). Although obesity is not the direct cause of PCOS, but it aggravates PCOS symptoms, e.g. hyperinsulinemia, impaired glucose tolerance, and dyslipidemia (Legro, 2012). Overweight and obese women with an ovulatory cycle also have decreased chances of spontaneous conception (Van der Steeg et al, 2008).

Table 1: Effect of obesity upon polycystic ovary syndrome (PCOS related to ovulation)

<table>
<thead>
<tr>
<th>Effect of Obesity</th>
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<tr>
<td>Increased peripheral aromatization to estrogen</td>
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<tr>
<td>Decreased sex hormone binding protein</td>
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<tr>
<td>Increased level of free estradiol and testosterone</td>
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<tr>
<td>Increased insulin stimulating androgen production from ovarian tissue</td>
</tr>
<tr>
<td>Reduced menstrual cyclicity</td>
</tr>
<tr>
<td>Increased prevalence of oligo/anovulation</td>
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Source: Majedah et al, 2004

2. Relationship between obesity and reproductive performance

a. Obesity and its effect on regulatory hormones

A complex hormonal mechanism works in balance to control the menstrual cycle, development of the endometrium and ovulation. Obesity has been shown to affect this balance via various direct and indirect mechanisms. Adipose tissue disturbs sex hormone secretion and bioavailability. Indirectly, obesity exerts its effect via leptin, insulin and the adipokines. Obesity is critical in controlling the regulation of sex hormone availability due to its ability to store lipid steroids such as androgens. Various measures of body fat are correlated with estrogen production and the concentration of sex hormone-binding globulin in the blood. There is also a strong association between obesity and insulin resistance, which is thought to reduce fertility (Sarwer et al, 2006). An increased LH to FSH ratio along with hyper secretion of LH has unfavourable effects on folliculogenesis; both conditions are observed in obese infertile patients (Butzow et al. 2000). In lean PCOS women, elevated LH is a major feature leading to hyperandrogenemia. In contrast, in obese PCOS women, it is elevated insulin resistance which is responsible for hyperandrogenism and its consequent effect upon ovulation and follicular development (Balen 2008, Balen et al. 2009). Leptin is a key protein, which delays the magnitude of the peripheral energy stores to the brain (hypothalamus), and has metabolic and reproductive functions (Pasquali et al 2006). PCOS women have been observed to have elevated serum leptin concentrations as compared to weight-matched controls (Brannian & Hansen 2002). It has been demonstrated that weight loss results in reduction in LH levels in PCOS patients without altering the pulsatility of LH secretion (Butzow et al. 2000).

b. Effect on oocyte and embryo

Being overweight or obese can have a detrimental effect on oocyte quality or maturity (Esinler et al. 2008). Due to a reduction in oocyte Quality, increased rates of miscarriage and very early pregnancy loss is seen in obese women. The developmental potential of the embryo is effected by impaired oocyte developmental competence which results in impaired implantation and abnormal implantation/trophoblastic invasion (Robker 2008). In a study by Esinler et al. 2008 to assess the impact of isolated obesity upon ICSI outcome suggested that obesity may be an independent risk factor for impaired oocyte maturation and concluded that obese women (BMI >30 kg/m2) required higher total doses of gonadotropin stimulation, despite of significantly fewer oocyte-cumulus complexes and metaphase II oocytes. Inconsistent findings have been reported with respect to the effect of obesity upon embryo quality (Dechaud et al. 2006). In a prospective study by Carrell et al, 2001 on 247 women undergoing IVF demonstrated that obese (BMI >30 kg/m2) women had significantly poorer quality embryos compared with women with BMI 20-30 kg/m2. Others were unable to demonstrate the relationship among the quality of the transferred embryos between the BMI strata (Dechaud et al. 2006).
effect of obesity upon implantation rate has been reported inconsistently. Some authors have identified a reduction in implantation rates among the obese women (Bellveret al.2010), whereas others have not demonstrated a weight related reduction (Dokras et al. 2006).

c. Oocyte quality

A good quality oocyte is a metaphase II oocyte with a clear zona pellucida, clear or moderately granular cytoplasm, and a small perivitelline space (Balaban and Urman, 2006). Furthermore, the maturity and quality of the oocyte is directly related to the quality of developing embryos with poorer quality embryos being associated with poorer fertilization rates and poorer subsequent embryo development (Moran et al., 2003). A large cohort study has shown that overweight women (BMI>25<30 kg/m$^2$) have significantly fewer oocytes retrieved (12.98± 6.91 vs. 14.49±7.96, P<0.001) (Zhang et al, 2010) as compared to women of normal weight. These findings were supported by a systematic review where the weighted mean difference (WMD) of the number of oocytes recovered in women with BMI >25 kg/m$^2$ was 0.58 (95% CI: 0.22, 0.94) in comparison with women with BMI <25 kg/m$^2$ (Maheshwari et al, 2007).

d. Oocyte fertilization and embryo quality

Oocyte fertilization rates have been shown to be lower in morbidly obese women (59% vs. 69%; P<0.03) (Jungheim et al, 2009). A large cohort study (Table: 2) has shown that in comparison with women of normal weight, overweight women (BMI>25<30 kg/m$^2$) have lower fertilization rates (60.8±23.3 vs. 61.1±23.0, P<0.001), fewer cleaved embryos (7.55±4.86 vs. 8.67 ±5.90, P<0.001), fewer high-grade embryos (4.65±3.96 vs. 5.59±4.81, P<0.001) and fewer cryo preserved embryos (4.44±4.55 vs. 5.49±5.55, P<0.001) (Zhang et al, 2010). Another study demonstrated that embryo quality (reflected by embryo grade, embryo utilization and cryopreservation) in women under 35 years of age was poorer in those who were obese (Metwally et al, 2007). A large retrospective study on 6500 IVF/ICSI cycles, however, concluded that the embryo quality was not impaired in overweight and obese women (Bellver et al, 2010). This can be explained by the fact that the average age of women in this study was between 34-35 years and does not appear to be in conflict with the previous findings.

Embryo quality is one of the most important factors predicting the success of the implantation process and subsequent pregnancy (Arceet al., 2006). Embryo grading is the only marker used to assess embryo quality (Dechaud et al., 2006). However, embryo grading is an inexact science with several methodological problems. Firstly, there are a number of different classification systems for embryo grading with no consensus regarding which of these is superior to the others (Arceet al., 2006). This makes it difficult to pool the results of various studies together in a meta-analysis (Desai et al., 2000). Secondly, the technique of embryo grading has been found to be highly subjective and subject to considerable intra-observer and inter-observer variability.

<table>
<thead>
<tr>
<th>Reproductive target</th>
<th>Effect</th>
<th>Study</th>
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<tr>
<td>Endometrium</td>
<td>Altered endometrial genetic profile resulting in Decreased uterine receptivity</td>
<td>Bellver et al 2010</td>
</tr>
<tr>
<td>The ovary and ovarian follicle</td>
<td>Increased ovarian rigidity resulting in Abnormal oocyte recruitment, abnormal ovulation, poor oocyte quality</td>
<td>Jungheim et al 2009</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>GnRH suppression</td>
<td>Tortoriciello et al 2004</td>
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<tr>
<td>Oocyte</td>
<td>Abnormal ovarian follicular environment, lipotoxic fat accumulation within the oocyte resulting in Poor oocyte quality</td>
<td>Yang et al 2009</td>
</tr>
<tr>
<td>Pre-implantation embryo</td>
<td>Insulin resistance, increased Apoptosis resulting in Poor embryo quality</td>
<td>Jungheim et al 2009</td>
</tr>
</tbody>
</table>

Table 2: Targets of obesity in relation to reproduction
Therefore, weight loss through physical activity and lifestyle modification has been demonstrated to improve the chance of conception and restore ovulation. Physical activity has been shown to confer a protective effect on fertility when coupled with weight loss in obese women (Clark et al, 1998).

3. Physical Activity and Fertility

The overall physical, emotional and increased general wellbeing benefits of being physically fit are well documented. Physical activity is one of the important factors for promoting health and decreasing the risk of lifestyle related diseases (Eriksson 2001; Kull, 2002). Regular exercise promotes an individual’s general health and wellbeing and provides protection from obesity, hypertension, cardiovascular disease, osteoporosis, diabetes, and psychological stress. Rich-Edwards et al. 2002 suggested that ovarian functioning may be protected by regular physical activity independent of BMI. In a study by Clark et al. (1995) of obese, infertile women found that losing weight, improving physical fitness and psychological well-being resulted in significant improvement in ovulation and pregnancy rates. The women in this study underwent a 6-month lifestyle modification programme that included a weekly group fitness component and at least two further exercise sessions per week. In addition to losing weight, each participant’s fitness level improved. Exercise improves ovarian function by increasing insulin sensitivity and the chance of conception. Exercise during pregnancy has also been reported to increase maternal well-being (Morris and Johnson, 2005).

The intensity and frequency of exercise has varying effects on female fertility. The complex relationship between exercise and reproductive potential is likely due to alterations in the hypothalamic-pituitary axis. In an Australian study by Clark et al., 1998 of 87 obese BMI 30 infertile women attending a weekly programme to promote lifestyle changes demonstrate that a relatively small amount of weight loss (average of 6.5 kg) was associated with resumption of ovulation. The relationship between obesity and reproductive problems is complicated. However, insulin resistance and estrogen production from fat cells can affect the ovaries and prevent ovulation. Weight loss improves insulin sensitivity and short-term reproductive fitness in overweight women and PCOS subjects and is additionally crucial for improving short- and long-term metabolic health. This can be accomplished through dietary control and exercise with the overall aim of energy expenditure exceeding energy intake over a short or medium period. (Norman et al, 2004). Studies of the effects of 12-24 week lifestyle interventions comprising diet, exercise and/or behavioural change in overweight infertile women with or without PCOS report improved ovulatory and menstrual regularity and reduced risk of miscarriage compared to pre-intervention (Miller et al, 2008).

Extreme exercise can negatively alter energy balance in the body and affect the reproductive system and may lead to an ovulation and infertility, whereas exercise may result in improved ovulation and fertility in anovulatory obese patients (Redman, 2006). When energy demand exceeds dietary energy intake, a negative energy balance may occur and may result in hypothalamic dysfunction and alterations in gonadotropin-releasing hormone (GnRH) pulsatility, leading to menstrual abnormalities, particularly among female athletes (Warren and Perlroth, 2001). A large Norwegian study found that women who were active daily were 3.2 times more likely to have fertility problems than inactive women (OR = 3.2, 95% CI 1.3-7.6). Additionally, in women who exercised a moderate amount (either 16-30 min or 30-60 min), the risk of infertility was decreased compared to women who exercised ≤ 15 min a day (OR = 0.3, 95% CI 0.2-0.5; OR =0.5, 95% CI 0.3-0.9 respectively). Exercising to exhaustion was associated with an increased
risk of infertility (OR = 2.3, 95% CI 1.2-4.5) (Gudmundsdottir et al, 2009). The Nurses’ Health Study found that vigorous exercise for a minimum of 30 minutes a day was also associated with decrease anovulatory disorder infertility (Chavarro et al, 2007). The frequency and amount of exercise also seems to impact outcomes in women pursuing IVF. A prospective study examined the exercise regimens of 2,232 women undergoing IVF. Women who reported regular exercise had a similar live birth rate compared to women who did not exercise (OR = 0.8, 95% CI 0.7-1.0). Women who exercised 4 or more hours per week for 1-9 years were 40% less likely to have a live birth (OR = 0.6, 95% CI 0.4-0.8), three times more likely to experience cycle cancellation (OR = 2.8, 95% CI 1.5-5.3), twice as likely to have an implantation failure (OR = 2.0, 95% CI 1.4-3.1) or pregnancy loss (OR = 2.0, 95% CI 1.2-3.4) compared to women who did not report exercise. In another study of 2,572 women, there were no differences in IVF outcomes between women who regularly exercised and those who did not. However, compared to women who did not exercise, women who exercised regularly for 1-5 years were at greater risk for failure for cycle stimulation (OR = 1.9, 95% CI 1.2-3.2), implantation failure (OR = 1.5, 95% CI 1.1-2.0), and failure to develop a live birth after a chemical pregnancy (OR = 1.9, 95% CI 1.3-2.8) (Morris et al, 2006).

Clark et al, 1995 suggested that as little as 5%-10% weight loss can improve fertility outcomes. Other studies have demonstrated that 5% weight loss results in improvement of endocrine parameters, such as lower fasting insulin levels, decrease in free testosterone, and increased frequency of ovulation. Additionally, weight loss causes a significant reduction in central fat deposits (11%) and serum luteinizing hormone levels (Huber-Buchholz et al, 1999) with return of normal menstrual cycles in four out of five women.

Reproductive function in overweight and obese women is improved by weight loss (Tang et al. 2006). It is, therefore suggested that overweight and obese women attending infertility clinics must be given the necessary advice and support to achieve the necessary weight loss. The first line of approach should be careful counselling on diet and exercise along with lifestyle modification; dietary education and guidance should ideally be given by a trained dietician.

CONCLUSION
Obesity impacts fertility and fertility treatment. Obesity is associated with poor oocyte quality, poor embryo and follicular development. Gradual and sustained weight loss improves the reproductive outcome in infertile women. Although the overall physical, emotional and increased general wellbeing benefits of being physically fit are well documented, however, there is a need for further research regarding the effects of different types and intensity of exercises on reproductive performance. It is reasonable to assume that the general health benefits associated with exercise and the consumption of a well-balanced diet would also apply to fertility. These lifestyle practices should therefore be recommended to couples attempting pregnancy. Further research is needed to clarify the effect that exercise may play on reproductive performance.

In the future, further research may be helpful in determining the optimal strategy for treating individual reproductive age women affected by obesity who would like to conceive.

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this paper.

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