Obesity corresponds to excess body fat and is defined by a body mass index of above 30 kg/m². Its prevalence has strikingly increased during the past 2 decades, constituting one of the fastest-growing health problems worldwide.\(^1\) At the turn of the millennium, obesity affected 300 million adults throughout the world, and this increasing prevalence is a major public health hazard.\(^2\) This current epidemic of obesity is related to the changing pattern of nutrition.\(^3\) Further, there is a genetic susceptibility for some individuals to obesity.\(^4,5\)

Body mass index (BMI) is used widely in epidemiological studies as a good indicator of adiposity.\(^6,7\) In the west, 24% of women in England are obese,\(^8\) and 61% of women in the US are either overweight or obese. Recent studies demonstrate an escalating incidence in developing countries.\(^9-14\) The majority of those are women of reproductive age, and many of the risk factors that are linked to obesity may also predispose them to infertility.\(^15,16\) The prevalence of obesity in Saudi Arabia, however, is 35.5%, approaching the western community and it is expected to increase particularly in women.\(^17\) Furthermore, many ethnic groups who either migrate to western societies or adopt a western life style are prone to obesity in their changed environment. This is a result of a chronic imbalance between energy intake and energy expenditure where the energy supply is stored as fat.\(^18\) The energy intake has become more calorie dense, coexisting with a decline in the level of physical activity.\(^3\) This probably explains the cause as well as the consequence of the obesity epidemic.\(^19\) A low level of physical activity is certainly a strong predictor of mortality.\(^20-22\) The deleterious effects of obesity on general health are enormous, including social, psychological, and demographic problems.\(^23,24\) There is a greater increase in the prevalence of chronic medical disorders, particularly related to cardiovascular and type II diabetes mellitus.\(^10,12,25\) Furthermore, there is an increase in the incidence of sleep apnea, arthritis and cancer, leading to an increase in mortality and morbidity.\(^1,10,20\) In the field of obstetrics and gynecology, however, obesity is considered a risk factor for a whole host of conditions related to reproduction.\(^26,27\)
addition, there is an increase rate of complications during pregnancy such as, an increased risk of miscarriage and raised blood pressure, pre-eclampsia, diabetes mellitus, and subsequently an increase in the rate of operative delivery.\textsuperscript{28-30} Further, wound infection and thrombo-embolic phenomena are not uncommon. The prevalence of hormone dependent gynecological tumors, endometrial, and breast cancer are also on the increase.\textsuperscript{31}

With regard to obesity and reproduction however, it produces a variety of endocrine alterations in the reproductive system, thus, creating difficulty in managing infertility.\textsuperscript{32} It had been reported in 2 Saudi studies that a third of women needing assisted reproductive techniques (ART) are obese.\textsuperscript{33,34} Weight and body mass are known to be of importance to the maintenance of regular reproductive cycles. In some women, obesity is associated with menstrual irregularities, hirsutism, infertility, and decrease in the success of fertility treatment.\textsuperscript{15,16,35} Because weight loss in obese women can correct ovulatory dysfunction, it is not uncommon for infertility specialists to recommend loss of some amount of weight before proceeding with fertility treatment.\textsuperscript{36-41}

Obesity continues to increase rapidly in the Kingdom of Saudi Arabia. However, attempts to lose weight are not common in the Kingdom. Such an increase in obesity will tremendously affect public health, as obesity is strongly associated with several health hazards such as cardiovascular complications and diabetes mellitus. This review article is timely because of the increasing epidemiological trends in obesity that we are facing in the reproductive endocrinology clinics. Moreover, there is increasing evidence that intervention with fertility treatment is not yielding, which can be frustrating, and devastating to both couples and physicians. Whereas, when women do things to help themselves with regard to weight loss, they can conceive naturally or achieve good response with fertility treatment and have a good outcome. The aim of this article is to focus attention on the impact of obesity on menstrual cycles and reproduction, but not across the life time of the woman. It will then describe the implications of obesity on the outcome of fertility treatment. This review will also include effects of obesity on pregnancy and delivery, but the implication on fetal morbidity and mortality will not be tackled.

This article will be structured to reflect on the role of body weight on reproduction. Specific paragraphs will discuss; (i) the epidemiological and clinical evidence of the association between obesity and reproductive disorders (ii) the pathophysiological aspects by which obesity may impair fertility, with particular emphasis on androgen disorders; (iii) major factors explaining the strong association between obesity, including polycystic ovarian syndrome (PCOS) and the potential pathophysiological mechanisms of obesity on PCOS. This article will therefore, focus on relevant reviews of and analysis of current evidence published in the last 5 decades.

This article was based on a comprehensive literature search that has been conducted across all sources relevant to reproductive endocrinology in the clinical context. The aim was to perform thorough literature search of journal publications. The English literature search has covered the period between 1950 and 2011; using Medline, Embase, ERIC, and the PsycholINFO database, and using the search terms; obesity, BMI, women impact, reproduction, insulin resistance (IR), infertility, and in vitro fertilization (IVF). These references were supplemented with: a traditional hand search of medical journals and potential relevant abstracts from relevant international meetings, and secondary sources, such as textbooks.

**Assessment of body composition.** Body weight and its constituent components of fat mass and lean tissue, play an important role in modulating reproductive development and function.\textsuperscript{35} Body weight is often expressed simply as mass, which is useful at the population level for describing the ecological relationships, such as that between the prevalence of low birth weight and perinatal mortality. Body weight is also useful when considering a time series within a population, or an individual, as it then reflects relative change that itself carries information of value. In addition to absolute weight, are measures of relative weight, expressed either, for example, as z-scores against a reference population or, most commonly, relative to height. This later construct is often expressed as BMI (kg/m\textsuperscript{2}).\textsuperscript{35} The BMI is a simply measured proxy for body composition and is based on the early work of Lambert Quetelet.\textsuperscript{42} The BMI, is the weight (wt) in kilogram (kg) divided by the height in meters squared (m\textsuperscript{2}); BMI: Wt (kg)/height (m\textsuperscript{2}). The ideal BMI is between, 19-25 A BMI of 26-29 is considered overweight while a BMI above 30 is defined as obesity.

According to the World Health Organization (WHO, 2000), lean is defined as a BMI < 18.5 kg/m\textsuperscript{2}, normal weight as BMI between 18.5 and 24.8 kg/m\textsuperscript{2}, overweight as BMI between 25.0 and 29.9 km/m\textsuperscript{2} and obese as BMI ≥ 30 kg/m\textsuperscript{2}. Variations on BMI include Ponderal index (kg/m\textsuperscript{3}), which is commonly used when assessing body composition in babies.\textsuperscript{43}

Body weight can also be broken down into constituent components and relative distribution around the body. For example, models of body composition include versions of 2 components (fat and fat-free mass); 3 components (fat, water, and protein); and 4 components
(fat, water, protein, and osseous mineral). Percentage of body fat is best determined by displacement, however, clinically, this is impractical, but BMI corresponds closely to densitometry measurements and is a good indicator of adiposity. Although not commonly used, parameters for the assessment of obesity include; waist circumference and waist: hip ratio. A waist circumference of >80 cm in women is an accepted indicator of visceral fat accumulation. In addition to the rudimentary measurement of BMI, techniques of body composition assessment are shown in Table 1.

The distribution of fat, central compared with peripheral, or visceral compared with subcutaneous, is important because of the regional variation in adipocyte metabolism. Most methods estimate total adiposity; skin folds, DEXA, CT, MRI, or ultrasound can distinguish central from peripheral fat. However, CT, MRI, or ultrasound can further subdivide central fat into visceral and subcutaneous. Each of these methods constitutes a different balance of precision, participant burden, cost, and relevance to the causal pathway and outcome of interest.

**Body weight and the onset of puberty.** Fifty years ago, Tanner observed from the Harvard Growth Study that early maturation, based on age at peak height velocity, was positively associated with a higher weight/height ratio. It has since been argued that menarche (the onset of menstruation) occurs at a critical level of 'fatness' and it appears that hypothalamic events leading to pubertal development and the achievement of reproductive competence may be triggered by metabolic/endocrinological changes due to an increase in fat. This has been confirmed in a study demonstrating that percent body fat (FAT%) using bioelectrical impedance was related to age at menarche, and duration of menstrual cycles in ballet dancers. There is a related body of research indicating that obesity in females as assessed by BMI is associated with an early onset of puberty and long cycles.

Furthermore, recent data suggest that excess adiposity during childhood may influence pubertal development as well. In particular, excess adiposity during childhood may advance puberty in girls. Obesity in peripubertal girls may also be associated with hyperandrogenemia and a high risk of adolescent polycystic ovary syndrome (PCOS). Insulin resistance and compensatory hyperinsulinemia may represent a common thread contributing to many of the pubertal changes reported to occur with childhood obesity. Weight and body mass are known to be of some importance to the maintenance of regular reproductive cycles. Certainly, either excess weight or marked weight loss can be associated with cycle disturbances; anovulation and delayed conception. In a larger scale retrospective study, Rich-Edward et al. found that women with a BMI > 24 kg m² at the age of 18 years were at a significantly higher risk of primary anovulatory infertility.

**Metabolic effects of obesity on estrogen.** A BMI greater than 30 is associated with abnormalities in estrogen metabolism. Fat acts as a steroid reservoir and a precursor for the synthesis of androgens to oestron and oestradiol and hence to oestriol by enhancement of the 16-hydroxylase pathway. Oestron, while not a potent steroid, upon sustained exposure, has a significant estrogenic activity particularly on the endometrium (lining of the womb). Fishman et al. examined the influence of body weight on oestradiol (E2) metabolism. They demonstrated that weight influences the direction of E2 metabolism. Also, body weight may play a significant role in anovulation, since obesity is associated with hormonal aberrations, decreased sex hormone binding globulin (SHBG), elevated serum E2, and elevated levels of androgens.

**Obesity and PCOS: Pathophysiological aspects.** The PCOS is one of the most common endocrine disturbances in women. It accounts for 90% of women with anovulation who attend infertility clinics. It is a heterogeneous disorder, the definition of which has been refined through the years. The syndrome's cardinal features are; characteristic ovarian morphology on ultrasound, menstrual irregularity, hyperestrogenism, decreased SHBG, hyperandrogenism, and IR. The latter 2 disturbances have significant reproductive and metabolic consequences. Abdominal/ truncal (increased waist-to-hip ratio) obesity is another important feature of PCOS, which worsens the clinical, endocrine and metabolic features of the syndrome.

This type of obesity is associated with more pronounced hyperandrogenism and IR. These 2 lead to chronic anovulation, through mechanisms primarily involving the insulin-mediated overstimulation of ovarian steroidogenesis and decrease in SHBG concentration.

The prevalence of obesity in PCOS has been estimated to be around 40%. However, marked

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**Table 1 - Techniques of body composition assessment.**

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<td>Skin fold thicknesses and waist-hip ratio</td>
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<td>Total body water using isotopically labeled water</td>
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<td>3</td>
<td>Hydro-densitometry based on underwater weighting</td>
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<td>Bio-impedance analysis</td>
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<td>Total body potassium</td>
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<td>7</td>
<td>Dual-energy X-ray absorptiometry</td>
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<td>Computed tomography</td>
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<td>Magnetic resonance imaging</td>
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<td>10</td>
<td>Ultrasound</td>
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Source: [Al-Nuaim](www.smj.org.sa)
Obesity on reproduction ...

Al-Nuaim


Figure 1 - Diagram illustrating the complex nature of the relationship between obesity and reproductive abnormalities in simple obesity and obesity-related PCOS. The diagram illustrates how factors related to obesity may participate in the complex interaction between androgens, neuroendocrine centers, insulin and insulin resistance, leptin and other factors and gonadal and extragonadal mechanisms leading to reproductive disorders in simple obesity (the abdominal phenotype) (box A), and particularly when it is associated with PCOS (box B). PCOS - polycystic ovarian syndrome, SHBG - sex hormone-binding globulin, THF α - tumor necrosis factor, IGF - insulin-like growth factor. Adapted with permission from: Pasquali R, Gambineri A. Metabolic effects of obesity on reproduction. Reprod BioMedicine Online 2006: 12: 542-551.24

Further, there is a confirmed link between nutrition and reproduction.77 Whereby, extremes of weights impact on fecundity, by increasing the probability of anovulation.78-80 Fecundity is used to define the monthly probability of conception for a couple that is sexually active, not using contraception and capable of getting pregnant. It is the biological capacity of reproduction, whereas fertility is the actual production of a live offspring.81 The mechanism by which underweight impacts on ovarian function is by disturbing the hypothalamic control of gonadotrophins (Gns) secretion. While the ovarian dysfunction in obese women is as a result of different endocrine and metabolic alterations, such as effects on steroids metabolism and altered secretion of and action of insulin and other adipokines, such as leptin resistance and adiponectin.82-85 These are emerging as potential agents in the pathogenesis of hyperandrogenism and anovulation in obese women. Leptin is considered the main peripheral signal that affects food intake and energy balance. Obesity is a classic condition of circulating leptin excess. Leptin is found to have an inhibitory effect on ovarian functions leading to anovulation.85-87 Leptin is the main product of body fat, it regulates the Gn surge that initiates the development of prepubertal stage (Figure 1).85,88

The association between abnormal weight and infertility has also been well documented.15,63,79,80,89 Support for this association is provided by studies documenting resumption of ovulation and improved

variation has been noted in this frequency, which also varies according to ethnicity and geographic location.66 The pathogenesis of obesity in PCOS is unclear however. Obesity could be the consequence of genetic factors,9 or alternatively due to life style factors such as diet and a sedentary existence.67 More specifically, the role of diet in the genesis of obesity and lipid abnormalities in women with PCOS has not been established. In the general population and in certain ethnic groups, it is well-known that high fat/carbohydrate diet markedly influences the prevalence of obesity and metabolic abnormalities. Obese women with PCOS are more likely to have menstrual irregularities and anovulation than lean women with PCOS.68,69 Furthermore, IR in women with PCOS appears more common than in the general population.70,71

Insulin resistance and, thus, secondary hyperinsulinemia may contribute to the hyperandrogenism, anovulation, dyslipidemia, and glucose intolerance in women with PCOS. The gonadotrophic effects of insulin on ovarian steroid hormone synthesis were shown in vivo and in vitro.72-75 The exaggerated insulin action on the ovarian tissue may present the pathogenic mechanism leading to the disturbances of the endocrine profile and menstrual cycles and hence to infertility in some obese women.72-74

**Obesity and fertility.** Worldwide, several authors have shown that the risk of anovulatory infertility increased in women with increasing BMI values.1,39,63,76
Obesity on reproduction ... Al-Nuaim

Excess body weight is known to impair the response to CC and it has been suggested that obesity per se is associated with an altered pituitary response to endogenous luteinizing releasing hormone from the hypothalamus. Conversely, women who are underweight, commonly show a disturbance in the hypothalamic-pituitary-gonadal axis and a loss of CC responsiveness. Shepard et al. in a retrospective study, analyzed several factors relating to the induction of ovulation with CC. They identified that body weight is significantly different in responders and non-responders and found a positive linear relationship between body weight and the dose of CC required to induce ovulation. Lobo et al. in a prospective study, found that weight and obesity were correlated positively with the dosage of CC required to achieve ovulation. Although once ovulation occurred, obesity did not influence the ability to conceive. Obese women with PCOS are less likely to respond to CC than lean women with PCOS. They are therefore more likely to be referred for Gn therapy. However, moderately obese women with PCOS respond more poorly to Gn therapy than their lean counterparts. These women are again less likely to ovulate and, if they do respond, they would require a larger daily dose of Gn and a longer duration to affect an optimal response.

A number of articles in the literature revealed a relationship between weight, induction of ovulation, and the dosage of CC. However, there are no data concerning the influence of weight, and the optimal dose of Gn therapy needed in order to achieve successful induction of ovulation while minimizing adverse affects of ovarian hyper-stimulation and multiple pregnancies. A direct influence of body weight on ovarian response to exogenous Gns has been shown for women requiring larger dose of Gn therapy to affect an optimal response. Hamilton-Fairly et al. suggested that even moderate obesity adversely affects the response of women with PCOS to low dose Gn therapy. The association of obesity with a poor pregnancy outcome is reinforced by a similar finding in the general population.

However, the factors that affect the dosage of Gns and the duration of treatment necessary to stimulate ovarian response leading to ovulation and pregnancy remains obscure. Obesity is associated with abnormalities in estrogen metabolism, and the distribution of drugs in the body is dependent on the amount of adipose tissue. Exactly why women with greater body mass require higher Gn dosage is unclear. However, it may be related to the larger amount of body surface, inadequate E<sub>2</sub> metabolism, and decreased SHBG, which may alter adequate induction of estrogen receptors. Possibly, the intramuscular absorption of the drug is slower or incomplete in obese women due to fat infiltration of muscle, or decreased muscle vascularity and increased subcutaneous fat.

In normally cycling women, Halme et al. demonstrated an increased response to Gn injection in women with lower body fat. Others have found a positive relationship between body weight, and both the number of days and dose of Gns required to induce superovulation in ART in women with normal cycles. Lewis et al. showed that body weight did not markedly influence the response to ovarian hyper stimulation in normal cycling women.

**Obesity and ART outcomes.** High BMI has been shown to adversely affect the outcomes of ART treatment. However, the effect of body weight on the outcome of IVF has not been well established. The apparent absence of an adverse effect of excess BMI on IVF outcome has been described by Lashen et al. Some studies however, have shown lower IVF success rates in obese women while others could not find a negative effect. Obesity has adverse effect on the outcomes of ART, impairing fecundity and reducing pregnancy rates. This appears to be impaired by several factors including androgens, insulin, and leptin. Salha et al. indicated that high BMI is detrimental to the success of IVF and has an important influence on the distribution and metabolism of human chorionic gonadotrophin, the trigger of ovulation. A systematic review of IVF outcomes among overweight and obese
women demonstrated that the does of Gns required are higher in women with BMI of ≥ 25 kg/m² in comparison with BMI of ≤ 25 kg/m². Further, Gns requirements were higher in obese women BMI ≥ 30 kg/m² when compared with none obese women. Li et al showed in a large cohort study that overweight women required more ampoules of Gns, and faced an increased risk of cycle cancellation due to poor follicular development. A recent study showed that overweight women have significantly lower oocytes retrieval in comparison with normal weight women. Whereas Metwally et al had demonstrated that oocyte quality is unaffected by BMI. Although there is evidence linking obesity with poor implantation and pregnancy rates, more robust studies are needed to substantiate these findings.

**Obesity and pregnancy.** Weight in pregnancy is composed of both weight gains during pregnancy and pre-pregnancy weight. Pre-pregnancy obesity was associated with poor pregnancy outcome. Maternal obesity in pregnancy carries significant risks for both mother and fetus such as; an increased rate of miscarriage, gestational diabetes, macrosomia, pre-eclampsia, cesarean section and still birth. There is an increase in congenital malformation, especially neural tube defects. It has also been suggested that central compared with peripheral fat is more closely related to birth weight, gestational carbohydrate intolerance, and hypertension. Further, it has been demonstrated that maternal pre-pregnant BMI predicts infant’s birth weight, and childhood obesity. This would eventually, establishes a risk profile for the development of subsequent metabolic disease in children.

**Positive energy balance and reproduction.** A sedentary lifestyle leading to obesity, is associated with significant health hazards, including increased risk of cardiovascular, metabolic diseases and cancer. These diseases are associated with higher rates of mortality and morbidity. These individuals are also susceptible to the development of several reproductive complaints and the ultimate fate is reduced reproductive outcomes and infertility. Nevertheless, in many cases of positive energy balance, reproductive function can be restored with simple changes in lifestyle habits that lead to reduction in body weight and body fat and improvements in insulin sensitivity. This again strongly suggests that weight reduction presents cause-related and the cheapest treatment of hormonal imbalance in obese women.

**The implication of weight loss on fertility.** Overweight and obesity have been observed to impair both natural and assisted conception, and so, the benefits of weight loss have been discussed in various contexts in this article. However, to emphasize it further, Clark et al recommended that as little as 10-15% of weight loss can improve fertility outcomes. This success is achieved through improvement of endocrine profile, such as; decrease in free testosterone, luteinizing hormone, and lower fasting insulin levels, which would then lead to regularizing menstrual cycles and thus an increase in the frequency of ovulation and spontaneous conception, and further can enhance success with fertility treatment if the need arise.

For someone who is eagerly wishing to conceive, weight loss can be difficult. However, giving an insight on the implications of central fat deposition on the hormonal milieu that is pertinent to ovulation and conception would increase the women’s motivation and compliance to losing weight. Weight loss can be achieved through various means. However, simple life style modification can be very rewarding. Also, weight loss can be achieved through diet restriction, physical activity both individually or in a group. Furthermore, pharmacological measures such as Metformin (insulin sensitizing agent), or Orlistat (a lipase inhibitor that reduces gastrointestinal fat absorption) can be helpful in this regard. In rare instances however, bariatric surgery is a last resort. It is therefore, recommended that the overweight and obese couple attending fertility clinics should be advised and supported to lose weight, to raise their awareness on adopting a sustainable healthy lifestyle. The couple should be reassured that, in the process of losing weight, the couple have the likelihood of conceiving naturally or do so on the first trial of intervention. Weight loss can have short term and long-term benefits on the individual, offspring and society. However, advice against rapid weight loss and excess energy should be stressed, as this may have a negative impact on the individual and treatment outcomes. The British Fertility Society has issued policy and practice guidelines advising specialists to encourage women to aim for a normal BMI prior to commencing fertility treatment.

**Physical activity and its effect on reproduction.** The reproductive system is tightly coupled with energy balance, and changes in the status of energy balance through changes in physical activity can impact on the reproductive system. According to the Centre of Disease Control, physical activity is defined as, “any bodily movement produced by skeletal muscle that result in expenditure of energy.” In an effort to combat the increasing secular trend of overweight and obesity, several organizations including the WHO and the American College of Sports Medicine, have announced recommendations to the public for physical activity. They advocated that to reduce the risk of chronic diseases and improve overall health status, people of all ages should perform a minimum of 30 minutes of moderate-intensity physical activity on most days of the week, but also emphasize that greater health benefits can be derived from physical activity that is more vigorous and longer in duration.
In conclusion, the rising epidemic of obesity reflects the tremendous changes in society and the behavioral pattern of the society. The deleterious effect of obesity on general health is now obvious, this include greater prevalence of chronic medical conditions as well as increased morbidity and mortality secondary to these problems. Obesity represents an important risk factor on fertility, which can exacerbate many of the symptoms of PCOS and increase the cardiac risk profile of the syndrome. Women who are overweight should therefore be advised to lose weight before conception in order to improve their chances of successful outcome. This is because obese women do not respond easily to infertility treatment. Further, these medications have a number of side effects, and spontaneous conception might occur during the process of weight reduction. Women coming for IVF treatment cycles are also advised to try to normalize their weight before commencing a cycle of IVF. Financial, emotional, and time expenditures for both women and physicians alike warrant a clearer understanding of the factors affecting the dosage and duration of treatment with Gn's.

Why heavier women may need more hormones to induce ovulation is yet to be clarified. Further studies for drug absorption and metabolic clearance rate in normal and obese women would address the questions posed. Obesity continues to increase rapidly in the Kingdom of Saudi Arabia. However, attempts to lose weight are not common in the Kingdom. Such increase in obesity will tremendously affect public health. Reduction in overweight and obesity is therefore, of considerable importance to a healthy nation. There is a great need for strategies and programs for weight reduction as well as weight maintenance that must be of a higher public health priority.

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