

Vücut Kitle İndeksinin Doğurganlık, Gebelik ve Doğum Üzerine Etkileri**The Effects of Body Mass Index on Fertility, Pregnancy and Delivery**Ayla ESER¹, İkbâl KAYGUSUZ¹, Müberra NAMLI KALEM¹, Metin CANBAL²¹ Turgut Özal University School of Medicine Department of Obstetrics and Gynecology, Ankara, Türkiye² Turgut Özal University School of Medicine Department of Family Medicine, Ankara, Türkiye**ÖZ**

Obezite, beraberindeki birçok kronik sağlık sorunuyla birlikte tüm dünyada halk sağlığı sorunu olmuştur. Doğurganlık, gebelik ve doğum üzerinde etkileri olan aşırı kilo (Vücut Kitle İndeksi-VKİ=25.0-29.9 kg/m²) ve obezitenin (VKİ ≥30.0 kg/m²) genç kadınlar arasındaki yaygınlığında artış görülmektedir. Obezite ve aşırı kilo aynı zamanda erkek fekunditesinin düşmesine de sebep olmaktadır. Obezite ve aşırı kiloluluğun başarılı in vitro fertilizasyon üzerindeki etkilerine dair tam anlamıyla net sonuçlar bulunmamaktadır. Düşük VKİ'ye sahip ve/veya gebelikte önerilenden daha az kilo alan kadınların düşük doğum ağırlığına sahip bebek sahibi olma riski daha yüksektir. Diğer yandan, yüksek VKİ, artmış gestasyonel hipertansiyon, pre-eklampsi, doğum induksiyonu, makrozomi ve sezaryenle doğum insidansı ile doğrudan ilişkilidir. Bu makalede VKİ'nin doğurganlık, gebelik ve doğum üzerine etkilerini güncel literatür bilgileri ışığında değerlendirmek amaçlanmıştır

Anahtar Kelimeler: VKİ, fertilité, gebelik, doğum.**ABSTRACT**

Obesity is a worldwide public health issue, associated with many chronic health issues. There is increasing prevalence of overweight (body mass index –BMI= 25.0-29.9 kg/m²) and obesity (BMI ≥30.0 kg/m²) in young women, which impacts on fertility, pregnancy and delivery outcomes. Obesity and overweight also contribute to reduced male fecundity. Effects of obesity and overweight on successful in vitro fertilisation outcomes are less clear. Women with low BMI and/or less-than-recommended gestational weight gain are at higher risk of delivering low birth weight babies. On the other hand, high BMI is linked with increased incidence of gestational hypertension, preeclampsia, induction of labour, macrosomia and caesarean delivery. This article aims to present a review of the recent scientific literature about the effects of BMI on fertility, pregnancy and delivery.

Keywords: BMI, fertility, pregnancy, delivery**Introduction**

Obesity and overweight has reached epidemic levels in developed countries, and its prevalence is increasing alarmingly in developing countries (1,2). According to World Health Organisation (WHO) estimates, in 2014 more than 1.9 billion or 39% of adults worldwide were overweight, with over 600 million of these defined as obese (3). The WHO estimates show that most of the global population now live in countries where overweight and obesity, both preventable conditions, kill more people than underweight. Obesity and overweight contribute to increased risk of metabolic syndrome, cardiovascular disease (CVD) and diabetes mellitus (4-7), as well as cancer, stroke, depression and arthritis (8-12). Along with these associations, overweight and obesity also appear to be often overlooked key causes of infertility. Overweight and obesity are usually defined according to body mass index (BMI).

BMI is defined as a person's weight in kilograms divided by the square of their height in meters (kg/m²) and is used to determine whether a person is normal weight, underweight, overweight or obese. WHO have defined BMI cut-off points for classification of individuals as underweight (<18.5 kg/m²), healthy weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²) and obese (≥30.0

kg/m²) (13). The National Institutes of Health (NIH) in the United States define extreme or morbid obesity as ≥40.0 kg/m² or a BMI greater than 35 kg/m² with comorbidities (14,15). BMI is a useful measure of total obesity and overweight or underweight, being strongly associated with population level health effects. It is correlated with CVD, and metabolic syndrome risk markers, for example, increased inflammatory markers (16) and adipocyte fatty acid binding protein (17). However, it can only be taken as a measure of relative weight status and is not informative about body-fat distribution or adiposity. This would require additional measurements such as waist circumference (WC), which acts as a surrogate measure of abdominal adiposity.

Additional quantity and distribution of body fat is connected to fertility loss in women (18). The reduction in fecundity that obese women encounter may have several contributing causes, for example, endocrine aberrations that result in metabolic dysfunctions, adversely affecting follicular growth, implantation and clinical pregnancy development (19). In the general population, obesity is often linked not only with reduced fertility, but also with lower success rates of IVF.

Impact of overweight and obesity on fertility is not limited to women. High

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BMI in men is associated with reduced fertility along with hormone alterations and decreased semen quality (20). Overweight and obesity in men have been associated with low ejaculate volume, sperm concentration and total sperm count, although studies from Denmark and the United States suggest there is little effect on some semen parameters, including concentration and motility (21,22). Men with high BMI also suffer a higher risk of erectile dysfunction (23), which further could reduce fertility. Consumption of a high-energy diet, which contributes to obesity and overweight, has in itself been implicated in negative effects on testicular metabolism and sperm parameters, with consequences for male fertility (24).

Beyond fertility itself, there is a higher rate of spontaneous miscarriages in obese versus normal BMI women and an increased danger of birth defects (25,26). Complications in pregnancy in relation to overweight were recognised as far back as 1945 (27). Several studies have reported a clear connection between maternal overweight and adverse obstetric and perinatal issues (28-30). Obesity is a factor in several reproductive problems including increased maternal, foetal and neonatal complications (31,32). Preterm delivery is one of the main causes of infant death in the USA and weight gain during pregnancy has long been associated with preterm delivery (27). Perinatal problems that have been identified with maternal obesity and pregnancy also include an increased risk of neural tube defects, birth asphyxia, birth injury, and neonatal hypoglycaemia (28,33). Two large surveys from the Swedish Medical Birth Registry have linked a pre-pregnancy diagnosis of obesity and morbid obesity with late foetal death and adverse pregnancy outcomes (34). Maternal obesity has also long been correlated with increased danger of diabetes and chronic hypertension before pregnancy and difficult pregnancy outcomes which include gestational diabetes, hypertensive disorders, thromboembolism, preeclampsia, caesarean deliveries, prolonged deliveries, foetal macrosomia, postpartum endometritis and a prolonged postpartum hospital stay (35). Weight loss may reverse the adverse effects associated (36). High maternal BMI has also been recently associated with preimplantation phenotypic changes in embryos (37).

BMI has been accepted as an accurate measure for over or underweight and its relationship with pregnancy complications. In the UK, for example, the Health Survey for England 2013 suggested that 33% of women are classified as overweight and 24% as obese; 28% of pregnant women are also considered overweight (38). According to the 2014 MBRRACE-UK confidential enquiry into maternal mortality and morbidity, 22.4% of women who died as a direct or indirect result of pregnancy from 2009 to 2012 were overweight, while 27.1% of them were obese (39). This was consistent with the overall figures on prevalence of obesity among women of reproductive age according to the Health Survey of England (38), but was higher than previously estimated figures of obesity prevalence in pregnancy (40). Recent studies revealed that the occurrence of obesity in women in the USA has become a major concern with 61%, 33% and 6.9% of women being overweight, obese and morbidly obese while 18.5-38.3% of pregnant women are estimated to be obese (1).

The focus of this review is on studies examining the association of BMI with fertility, pregnancy and delivery.

BMI in Fertility

BMI has a negative impact on fertility in both women and men. Subfertility is defined as the inability to conceive even after twelve months of unprotec-

ted intercourse; prevalence is increasing worldwide, including in developing countries, alongside the rise in obesity and overweight. Delay in conception leads to several issues, including disappointment of the concerned couple and the health service costs. Fecundity and time to pregnancy is reduced in both overweight and obese women (41,42). Moreover, this reduced fecundity may have its roots in foetal life, as high or low maternal birth-weight has been associated with waiting time to pregnancy > 1 year in a study of 21 786, suggesting that subfecundity may be partly programmed by factors that cause or correlate with foetal growth (43). Obesity has a social as well as a biological effect on reproductive behavior, which also increases the risk of lower fertility (28). Underweight, overweight and obesity in among females in adolescence is a predictor of having fewer children in adulthood than those with normal range (27,44). A BMI below 20 kg/m² also reduces the chance of conception in many women (45).

Ovulatory infertility has been reported to be two to three times higher in women with BMI >27 kg/m². Meanwhile BMI >32 kg/m² has been suggested to have an adverse effect on the outcome of fertility treatment using ovulation induction (46,47). Other recent studies, however, have not found a link between BMI of either males or females in fertilisation rate during in vitro fertilisation (48,49). This suggests that, as the research findings on BMI and pregnancy success among IVF couples are limited and conflicting, further research should focus on other adiposity measures. Few studies have examined any link between central adiposity or altered body-fat distribution in fertility, despite the adverse impact of central adiposity on factors such as estrogen metabolism and oligomenorrhea (50,51). Results of one study suggested that body-fat distribution was a significant factor in ovulatory infertility in women, with waist to hip ratio (WHR) being inversely related to probability of conception in any given cycle (52). Another study showed that WHR of greater than 0.8 impaired the rate of pregnancy resulting from IVF embryo transfer (18). Nevertheless, high BMI has been associated with reduced fecundity and time to pregnancy (41,42). In one study of 1651 Danish women participating in an internet-based prospective cohort study of pregnancy planners, impact of WC or WHR on time to pregnancy was dependent on adjustment for female BMI (42).

Obesity has been associated with ovulatory dysfunction. For example, obesity results in elevations of tissue levels of the pro-inflammatory advanced glycation end-products (AGEs) and their receptors (RAGE), which can in turn disrupt the ovarian microenvironment and compromise oocyte competence and fertility (53). Obesity is also connected with metabolic disturbances, which disrupts the oocyte and follicular cell function (54). Weight control improves the fertility of women by improving ovulation. Modest loss of weight of about 10 % to 1-2 months effectively maintains a proper hormonal and menstrual balance, ovulation and pregnancy (55). Proper weight management prior to pregnancy, reduces obstetric complications and health problems of the newborn and reduces the need for assisted reproduction technique treatment as well (46,47).

Male obesity has also been associated with reduced fecundity (56-58). and obesity in both partners increases the risk of subfecundity for a couple (19). Obesity and reduced semen quality have been associated in several studies. For example, overweight and obesity have been associated with increased prevalence of azoospermia or oligozoospermia (57) and loss of weight may associated with improvement in semen quality (59). However, studies from

both Denmark and the United States suggest that some semen parameters, for example, concentration and motility, are less affected by obesity (21,22).

BMI in Pregnancy

Beyond the impact on fertility, being over weight and obesity and obese have also been shown to have negative impact on pregnancy. Higher BMI in women is associated with the incidence of preeclampsia/pregnancy-induced hypertension, gestational diabetes, induction of labour and caesarean delivery as compared to those having a lower BMI with better pregnancy outcomes (60). A number of investigations have reported a clear relation between maternal overweight and adverse obstetric and perinatal outcomes (28). Since pregnancy is associated with weight gain, and reports suggest that weight gain is positively correlated with BMI before pregnancy, it is highly recommended that overweight women should gain less than normal weight during pregnancy (61). Most studies show a mean weight gain of 0.4 to 3.8 kg, as a result of pregnancy, but these reports examine follow-up periods ranging from 6 weeks to 156 months (with some variation) (62). The relation between BMI and weight gain during the gestational period is shown in Table 1.

Table 1: Rate of change of BMI during pregnancy (NICE. 2010)⁷⁹

Pre-pregnancy BMI	BMI	Total weight gain	Rates of weight gain 2nd and 3rd trimester (average range/week)
Underweight	Less than 18.5	13kg to 18kg	0.5kg to 0.6kg
Normal weight	18.5 to 24.9	11.5kg to 16kg	0.4kg to 0.5kg
Overweight	25 to 29.9	7kg to 11.5kg	0.2kg to 0.3kg
Obese	30 or more	5kg to 9kg	0.2kg to 0.3kg

For the super-obese, with BMI of 50 kg/m² or higher, a recent retrospective cohort study of 1,034 women suggested that weight gain within Institute of Medicine (IOM) guidelines was not associated with a statistically increased odds of preterm birth or low birth weight (63). However, excessive weight gain significantly increased the risk of pregnancy-induced hypertension and cesarean delivery without guarding against a delivery of low-birth-weight neonates. Weight gain below guidelines in the super-obese cohort was not associated with increased maternal or neonatal risk. The results of this study suggest that super-obese women may need separate gestational weight gain recommendations. Maternal obesity is associated with risks to the fetus including fetal macrosomia and malformation (64). A recent study has also linked high maternal BMI with pre-implantation phenotypic changes in embryos(37).

In terms of preeclampsia risk, one survey showed that the possibility of preeclampsia doubled in every 5 to 7 kg/m² rises in pre-pregnancy BMI (60). The hazard of preeclampsia in obese women, having BMI 30 to 39.9 Kg/m² and morbidly obese women, with BMI > 40 kg/m², increases sharply in women in their first pregnancy. A significantly lower risk of preeclampsia has been observed in underweight women (BMI <19.9) (60). Obesity has been identified as the leading cause of preeclampsia in the United States and other developed countries (65); asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthase has been proposed as one potential convergence point for obesity and increased preeclampsia risk. Risk of preeclampsia and pregnancy-induced hypertension in overweight and obese women may be associated with insulin resistance. Along with obesity, many features of insulin resistance syndrome have been associated with preeclampsia and pregnancy-induced hypertension, such as hypertension, hyperinsulinemia, glucose

intolerance and lipid abnormalities, as well as increases in leptin, TNF- α , tissue plasminogen activator, plasminogen activator inhibitor-1, and testosterone (66). In a recent prospective observational study on 72 nulliparous pregnant women with BMI \geq 24 kg/m², levels of the insulin-sensitivity regulator adipocyte fatty acid-binding protein 4 (FABP4) at 24 weeks was associated with subsequent development of pregnancy-induced hypertension (67).

As might be expected given the link between maternal BMI and insulin resistance (55), gestational Diabetes (GDM) is also directly related to maternal BMI and body size. Women with a high BMI (> 30 kg/m²) are 3.6 times more likely to develop GDM compared with women with normal BMI (29). Therefore, pre-pregnancy weight control and maintenance are of immense importance for these women. The combination of high maternal weight and GDM, as well as either condition separately, also increases the risk of developing chronic diabetes and/or CVD (68). Furthermore, in a recent prospective cohort study of 163 children aged 9-10 years, maternal GDM was associated with child insulin resistance, as was maternal pre-pregnancy BMI up to 30 kg/m² (69). These studies highlight the need to effectively manage maternal weight and GDM in order to protect the health of both the mother and the child on a long-term basis.

Women with high BMI are susceptible to polycystic ovarian syndrome (PCOS) (19). Obese women with PCOS also have worse pregnancy outcomes than normal-weight women with PCOS. In a recent retrospective comparative cohort study of 93 overweight (BMI \geq 25 kg/m²) and 107 normal weight (BMI < 25 kg/m²) women with PCOS, the overweight women were shown to have worse perinatal outcomes from singleton pregnancies than normal-weight women (70). The overweight women had significantly more preterm births and mean birth-weight of new-borns was significantly higher. In terms of IVF outcomes, in a recent retrospective cohort study which included 101 cycles from 79 women younger than 40 years old with PCOS, obese women (\geq 30 kg/m²), had substantially less chance of clinical pregnancy per cycle start and of clinical pregnancy per embryo transfer than lean women (18.7-24.9 kg/m²) (71). There was a trend toward decreased ovarian hyperstimulation syndrome incidence with increasing BMI among women with PCOS. This type of study is important in making treatment decisions in an IVF context. Overweight, infertile patients undergoing assisted reproductive technology (ART) therapy typically require larger gonadotropin dosages, make fewer mature oocytes, comprise inferior embryo quality and have a greater risk of miscarriages (72-75).

Other complications of pregnancy for women with a high BMI include pelvic joint pain and higher risk of thromboembolism (9) and blood clots as compared to those with normal BMI. There is also a relationship between BMI and hyperemesis gravidarum (HG), also known as persistent nausea and vomiting of pregnancy (NVP) (76). There are indications in the literature that being either underweight or obese pre-pregnancy can contribute to development of HG (77,78).

BMI in delivery

The evidence for an impact of undue weight gain in pregnancy on preterm delivery is equivocal. The studies indicating such an association have tended to define excessive weight gain differently, measured weight gain at different periods during pregnancy, inconsistently assessed interaction with BMI, and were confined to low income women (27,28,79). However, there is some evidence to support a link of high maternal BMI with increased risk of preterm

delivery as well as other delivery complications. For example, in a retrospective cohort study of 24241 nulliparous women with a singleton pregnancy, it was observed that obese women were at higher risk of preterm delivery (before 33 weeks), while morbidly obese women were at increased risk of induced labour or emergency caesarean section (46). Weight gain pregnancy gain may have a direct relation to preterm delivery, which could be explained by several factors such as physical activity, energy and nutrient uptake and maternal diabetes and hypertension (80). Besides high BMI, low BMI (<19.8 kg/m²) and weight at conception or delivery, and poor maternal weight gain (<0.27 kg per week) during pregnancy, are associated with prematurity, low birth weight and maternal delivery complications (81).

Women with a high BMI and their babies experience difficulties during and after labour, including increased chance of labour induction or of caesarean delivery, prolonged labour, difficulty in monitoring the baby's heartbeat, postpartum hemorrhage and breathing difficulties in the newborn (82). For example in a historical cohort study of 6,949 low risk presenting a singleton birth at term, and a vaginal delivery attempt by spontaneous labour, maternal BMI ≥ 30 kg/m² in nulliparous women of maternal age ≥ 30 years was associated with increased rate of cesarean section delivery due to dystocia (82). Other prospective cohort studies and meta-analyses agree that BMI in this range is associated with a high risk of caesarean section (40,83). High BMI is also associated with increased chance of induction of labour, but also with reduced chance of successful response. In a retrospective cohort study based on the Aberdeen Maternity and Neonatal Databank, morbid obesity was associated with induced labour (46). A secondary analysis of data from 1273 patients collected during the Misoprostol Vaginal Insert Trial, a multisite, double-blind, randomized trial of women requiring cervical ripening before labour induction revealed that obesity and morbid obesity were associated with adverse labour and delivery outcomes including prolonged labour, oxytocin requirements and cesarean delivery rates (84).

Conclusion

It is evident that high BMI has an adverse impact on fertility in both women and men, as well as on pregnancy and delivery. Obese and overweight women are associated with reduced fecundity and waiting time to pregnancy, which may be exacerbated if both partners in a couple are obese (58,59). The impact of BMI on chances of conception during IVF are more conflicting and further research should focus on other adiposity measures to help inform clinical decisions (47-49). Weight loss may improve chances of conception and would be recommended prior to IVF, particularly in patients under the age of 36 years. For older prospective parents, a more prompt and aggressive approach to ART may be justified. Lifestyle changes such as dietary modulation to achieve such weight loss may be beneficial in achieving pregnancy without IVF. For example, consumption of a high energy diet has in itself been implicated in adverse effects on testicular metabolism and sperm parameters in men (24). Given the impact on pregnancy and delivery outcomes of high or low maternal BMI, maternal health promotion programs should be aimed towards improving mothers' nutrition before and during pregnancies. Obese women may gain from low weight gain during gestation. The need for such interventions is further highlighted by the reported long-term effects of pregnancy complications such as gestational diabetes, which has been associated with increased risk of developing chronic diabetes and/or CVD for the mother (68) and child

insulin resistance for the baby (69). Maternal obesity has also been implicated in other consequences for offspring such as foetal macrosomia and malformation (64) and pre-implantation phenotypic changes in embryos (37). It is clear that the reduction of body weight should be suggested to patients both for maximising their fertility potential and for safeguarding long-term health of both parents and children.

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