



# Successful Pregnancy in Morbidly Obese Women of Polycystic Ovary Syndrome With Various Treatment Options With Individual Consequences: Case Series

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**Abbreviations:** IVF: In-vitro fertilization; PCOS: Polycystic ovary syndrome; WHO: World Health Organization; BMI: Body mass index; IOM: Institute of Medicine guidelines; GWG: Gestational weight gain; GDM: Gestational diabetes mellitus; BS: Bariatric Surgery; ESG: Endoscopic sleeve gastroplasty

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## Abstract

**Objective:** The objective of the study was to compare the effectiveness of different treatment options in the management of infertility across three cases in morbidly obese women with polycystic ovary syndrome (PCOS).

**Case study & results:** The first case is 30 years old with secondary infertility for two years with two abortions and a body mass index (BMI) is 69, she tried all lifestyle modifications with no response to weight reduction and she was conceived spontaneously without fertility treatment and subsequent antenatal care progressed without any complications until 36 weeks complicated with raised blood sugar beyond the normal level but not so high and intrauterine fetal death one week later ended by spontaneous normal vaginal delivery. The second case is 24 years old with BMI 66 is undergone weight reduction, ovulation induction with clomiphene citrate and gonadotropin injections with good ovulation response but no pregnancy, in vitro fertilization was performed but aborted at 8 weeks gestation, one year later after the use of metformin and ovulation induction with injections patient conceived and her pregnancy complicated by pre-eclampsia, gestational diabetes treated with insulin and preterm delivery. The third case is 40 years old with primary infertility for 5 years with BMI 70, she is known case diabetes mellitus 10 years back controlled with insulin, and hypertension on treatment, undergone bariatric surgery and one year later IVF was done after the failure of multiple ovulation induction, her diabetes mellitus and hypertension control well with treatment and delivered at 39 weeks by elective cesarean section with a birth weight of 4.5 kg.

**Discussion:** PCOS is a genetic condition, worsened by obesity. The prevalence of obesity in PCOS women is up to 80%. There is a strong relationship between PCOS and obesity making the condition more complex. The majority of women with PCOS are either overweight or obese and the pathogenesis of obesity in PCOS has not yet been exactly identified. Obesity has adverse effects on fertility through anovulation, poor implantation, and quality oocyte.

**Conclusion:** The ideal treatment of infertility in morbidly obese PCOS women has not been defined, but generally, before deciding which treatment option is preferred, proper weight loss and control of the metabolic state are carried out for successful pregnancy.

## Introduction

Obesity is becoming more prevalent worldwide [1]. Abnormal or excessive white fat accumulation in the adipose tissue causes overweight and obesity, which detrimental affects the health status [2]. The World Health Organization [3] and the National Institutes of Health [4] defined overweight as a body mass index (BMI, kg/m<sup>2</sup>) of 25 to 29.9, and obesity as a BMI of  $\geq 30$ . Further, obesity is characterized by BMI (kg/m<sup>2</sup>) into 3 classes: Class I (30-34.9), Class II (35-39.9), and Class III ( $\geq 40$ ). Body mass index (BMI) is defined as the ratio of human body weight in kilograms to squared height in meters (kg/m<sup>2</sup>). And those with values of 40 kg/m<sup>2</sup> and above are accepted as morbidly obese.

The classification of overweight and obesity in adults as proposed by WHO (1998)

is shown in Table 1.

**Table 1.** Classification of weight status in adults according to Body Mass Index (BMI)

Classification	BMI (kg/m <sup>2</sup> )	Risk of co-morbidities
Underweight	< 18.5	Low (but the risk of other clinical problems increased)
Normal range	18.5 – 24.9	Average
Overweight:	$\geq 25$	
Pre-obese	25 – 29.9	Increased
Obese class I	30.0 – 34.9	Moderate
Obese class II	35.0 – 39.9	Severe
Obese class III	$\geq 40.0$	Very severe

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There is proof that comorbidities such as diabetes mellitus, high blood pressure, dyslipidemia, cardiovascular disease, obstructive sleep apnea, and overall mortality are more likely to occur in women with higher BMIs [5]. Additionally, a high body mass index (BMI) has a negative impact on female fecundity [6]. All the components of the reproductive system can be affected by obesity, from oocyte competence, and embryo quality to the uterine environment [7]. In natural conception cycles, the like hood of a spontaneous pregnancy decreased linearly as a BMI above 29 kg/m<sup>2</sup> [8]. And the risk of the first trimester and recurrent miscarriage is also raised [9]. With IVF treatment, women with higher BMI had a significantly greater risk of miscarriage rate and significantly lower clinical pregnancy and live birth rates [10].

### Case report

The first case is 30 years old, morbidly obese polycystic ovary syndrome woman with secondary infertility for two years and two abortions at 8 weeks gestation, she had never been a known case of hypertension or diabetes or any medical illness, and she had been overweight in childhood and adolescence. She is not interested in her weight and had tried many weight loss efforts with diet and exercise but failed in weight reduction. She is seeking pregnancy at the outpatient clinic; she was fully aware of the relationship between obesity and related health problems and receive folic acid supplementation of 5 mg daily to avoid fetal complications, and she was conceived spontaneously without fertility treatment. Her weight and Height measured at the first visit include a weight of 166 kg with a height of 1.55 m, these measures use to calculate her body mass index, which classifies her as morbidly obese (69kg/m<sup>2</sup>) and starts an aspirin tablet of 75mg daily. And advised to moderate physical activity like fast walking and limit her gestational weight gain to approximately 5-9 kg according to the Institute of Medicine guidelines (IOM) advised by her doctor to reduce the risk of adverse pregnancy outcome, and her investigations were normal and her antenatal care passed without any complications despite of close monitoring with some difficulties in ultrasound resolution and measurement of blood pressure which need special large cuff fit to arm circumference until 36 weeks complicated with raised blood sugar beyond the normal level but not so high and intrauterine fetal death one week later ended by spontaneous normal vaginal delivery.

The second case is 24 years old with BMI 66 kg/m<sup>2</sup>, she had been obese as adolescent and gradually gaining weight until three years of married her weight becomes morbid and is undergone weight reduction by diet and exercise, she lost only 1-2kg over two months. Making many trials of weight loss but still morbidly obese, after lifestyle modification and evaluation, the decision to start ovulation induction with clomiphene citrate and higher doses of gonadotropins injections (150 IU/day) for a long time with good ovulation response but no pregnancy, in vitro fertilization, performed but aborted at 8 weeks gestation, one year later after use of metformin and ovulation induction with injections. The patient conceived and her pregnancy was complicated by pre-eclampsia at 28 weeks and treated with double antihypertensive agents, and at 32 weeks complicated by gestational diabetes treated with insulin in three doses regime with metformin and preterm delivery at 35 weeks.

The third case is a 40-year-old with primary infertility for 5 years with a BMI of 70, presented with abnormality in the menstrual cycle varied from amenorrhea to oligomenorrhea, she is known case of diabetes mellitus 10 years back controlled

with insulin, and hypertension on treatment making many trials for ovulation induction with oral tablets and injections but no good follicle development was been seen. She had tried many years for weight loss with diet but failed in weight reduction. Undergone laparoscopic bariatric surgery (laparoscopic gastric resection), eight-month of surgery her BMI became 60 one year later, underwent ovulation induction with gonadotrophin injections (75 IU/day) two times but no improvement in ovulatory status, IVF was performed as requested by the patient due to advanced age immediately after the failure of multiple ovulation induction, the patient gets pregnant and her antenatal care was complicated with nausea and vomiting treated with intravenous fluids with anti-emetics up to 15 weeks gestation and her diabetes was good control with insulin and hypertension was good control with antihypertensive treatment and delivered at 39 weeks by elective cesarean section with a birth weight of 4.5 kg.

### Discussion

The prevalence of obesity has increased in developed countries because of a change in lifestyle, including reduced physical activity, changes in nutrition style, and an increased calorie intake [11]. However, some other factors such as endocrine disorders, hormonal disorders, psychological disorders, and the use of some drugs such as steroids and antidepressants may lead to obesity [12].

White adipose tissue is an organ with different functions and serves as an energy reserve and is considered as a significant endocrine organ that secretes adipokines to control metabolism. These adipokines, which are cytokines mostly released by adipocytes, play significant roles in the control of several physiological processes, including reproduction. Cell metabolism and function deteriorate as a result of any abnormality in adipokines [13]. Adipose tissue is therefore essential for healthy development and reproduction. It is widely known that excessive white adipose tissue leads to reproductive disorders [14]. Which is associated with different obstetrics and gynecological disorders including, irregular menstrual cycles, reduced ovarian follicular development, oocyte development in both qualitative and quantitative terms, fertilization, embryo development, and implantation [15], as well as challenges with assisted reproduction, miscarriage, and poor pregnancy outcomes.

Gonadotropin secretion becomes abnormal in obese women, due to increased peripheral aromatization of androgens to estrogens. In obese women, there is a lot of hormone disturbance, including insulin resistance and hyperinsulinemia leading to hyperandrogenemia. The sex hormone-binding globulin (SHBG), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP) are diminished and leptin levels are elevated results in deterioration in the neuroregulation of the hypothalamic-pituitary-gonadal (HPG) axis [16]. This deterioration may explain irregular or an-ovulatory cycles and impaired reproductive health. Overweight and obese women have a higher incidence of anovulation and menstrual disturbance. Rogers and Mitchell [17] found that menstrual disturbances are about fourfold more common in obese women.

In addition, insulin resistance and type 2 diabetes mellitus have been demonstrated to be associated with abnormal levels of adipokines [18]. The metabolic syndrome and obesity are strongly related [19]. This connection either directly through adipokines secretion or indirectly, through the enhancement of insulin resistance which is considered a pathological condition.

As well as a number of pathogenic disorders, including Type 2 diabetes, atherosclerosis, stroke, hypertension, and several malignancies (including breast and colon cancers), have also been associated with obesity [20]. Pregnancy is already a period of insulin resistance, even for mothers with a normal BMI, and this may be an unusual mechanism to ensure proper nutrition for the developing fetus. Gestational diabetes mellitus (GDM) is the result of an imbalance between pregnancy-associated insulin resistance (exacerbated by obesity) and inappropriate compensatory secretion/action of insulin. Obesity may be characterized by a state of low-grade chronic inflammation, as excess adipose tissue is a source of inflammatory cytokines and other metabolically active chemical mediators [21]. GDM is usually diagnosed by an oral glucose tolerance test at 24 weeks of gestation, but in obese women, the GDM can develop much earlier and remain undetected until it is too late for optimal treatment [22]. GDM also predisposes a woman to type II diabetes later in life. Therefore, appropriate treatment should be initiated as early as possible to prevent future health risks associated with GDM. The higher incidence of gestational diabetes in women with PCOS may be explained by the higher incidence of obesity in these women [23]. On the one hand, obesity appears to put women with PCOS at an additional risk of gestational diabetes.

Obesity, insulin resistance (such as GDM), hypertriglyceridemia, and endothelial dysfunction are all important factors in the development of pre-eclampsia [24]. Pre-eclampsia is a rapidly progressing condition characterized by maternal hypertension, oedema and proteinuria that may lead to maternal and fetal death.

In a recent study, Jungheim et al. showed that morbid obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) in PCOS patients was associated with significantly lower pregnancy rates than non-morbidly obese patients, even after IVF [25]. A significantly lower pregnancy rate which is manifested by miscarriage, macrosomia, fetal distress, and unexplained fetal death.

There are studies that have found no association between obesity and miscarriage [26,27]. Other studies have reported an association between obesity and miscarriage [9]. An association between obesity and miscarriage has been reported for both normal pregnancy and in vitro fertilization (IVF), Belber et al. [28]. The mechanisms leading to miscarriage in obese women are still unknown. But the possible cause may be due to obesity which may affect the embryo, the endometrium, or both [29].

According to Huang et al. [30] a rise in maternal obesity prior to conception was the factor most strongly linked to unexplained fetal death. Although the exact mechanism of fetal compromise is unknown, it is likely caused by a variety of causes, such as placental insufficiency, relative fetal hypoxia, and organ malfunction [31]. Also, maternal obesity and macrosomia have been strongly linked in a number of studies [31-33].

Gestational weight gain (GWG) usually occurs during pregnancy, but in pregnant women with morbidly obese, it is preferable to limit that GWG according to guidelines which provide weight gain ranges according to pre-pregnancy BMI [34,35]. These guidelines were recommended by the US National Academy of Sciences Institute of Medicine [36] to prevent the prevalence of low birth-weight infants and prevent conditions such as macrosomia, caesarean delivery, and post-partum weight retention associated with gaining too much weight during gestation [34,35]. The Institute of Medicine published GWG guidelines in 1990 and these guidelines

were re-examined and updated in 2009 (IOM, 2009). The recommended amount of GWG in the 2009 IOM guidelines was 12.5-18 kg, 11.5-16 kg, 7-11.5 kg, and 5-9 kg for women with pre-pregnancy BMI classified as underweight (< 18.5 kg/m<sup>2</sup>), normal weight (18.5-24.9 kg/m<sup>2</sup>); overweight (25-29.9 kg/m<sup>2</sup>) and obese ( $\geq 30$  kg/m<sup>2</sup>) respectively.

Limitation of gestational weight gain either by diet restriction, physical exercise or drugs. Some experts believe that it is not desirable for women to lose weight during pregnancy because of calorie restriction [37]. Severe caloric restriction (restricted to 50% or more) has been shown to increase ketonuria and ketonemia in pregnant women and may impair fetal brain development [38]. However, to control weight gain without inducing ketosis, a 33% reduction in caloric intake is recommended [39]. When energy intake is reduced, it is important that pregnant women be provided with adequate amounts of high-quality protein, vitamins, and minerals from diets. Lack of physical activity increases the risk of excess fat gain during pregnancy [40,41]. Exercise has been found to be an effective treatment option for improving pregnancy outcomes. A decrease in physical activity has been observed in some women during pregnancy, possibly reflecting the assumption that all forms of physical activity are contraindicated during pregnancy [41]. However, it is now accepted that exercise during pregnancy is safe for both mother and fetus [35].

The effect of metformin on body weight and fat distribution in PCOS patients is unclear, as some studies have shown a decrease in weight and waist circumference, while others have not [42]. However, metformin appears to improve the effectiveness of lifestyle modifications leading to weight loss and visceral fat reduction [43, 44]. There is evidence of the beneficial effects of metformin on menstrual cycle and hormone levels in PCOS patients [44, 45].

Obese women are recommended to lose weight prior to becoming pregnant since obesity is linked to challenges in conceiving and elevated risks during pregnancy and delivery. However, despite therapeutic support many morbidly obese women with PCOS fail to lose weight in order to meet the necessary BMI of less than 35 prior to reproductive therapy [46,47]. Bariatric surgery (BS) appears to be the most effective in treating patients with PCOS with morbid obesity resulting in constant weight loss, improvement of PCOS symptoms and improved fertility [48,49] it has therefore been suggested that BS should be considered as first-line treatment in patients with PCOS with severe obesity. Based on the clinical practice guidelines of the American Society of Clinical Endocrinology, the Obesity Society, and the American Society of Metabolic and Bariatric Surgery, it is recommended to delay pregnancy for at least 12-18 months after BS [50]. This is also supported by the Obesity Management Task Force of the European Association for Obesity Research [51]. On the other hand, the Royal College of Obstetricians and Gynecologists proposes an individualized approach depending on the age of the woman and its effect on fertility delay in older women [52]. After BS, a waiting period of at least 12 to 18 months is recommended, before trying to conceive so that weight can stabilize and any potential nutritional deficiencies not apparent in the first few months can be correctly identified and managed. BS can be divided into restrictive and malabsorption processes or a combination of both. The most common surgical procedures are Roux-en-Y gastric bypass (RYGB), gastric sleeve surgery,



and adjustable gastric banding [53]. Sleeve gastrectomy is a restrictive procedure and is performed as a laparoscopic gastric resection, which creates a small stomach. There is study showed that endoscopic sleeve gastroplasty (ESG) produced beneficial changes in obesity-related comorbidities and metabolic complications which result in significant improvements in insulin resistance. The mechanisms that cause weight loss and improvements in metabolic parameters after ESG remain poorly understood [54]. Additionally, obesity-related fertility problems and poor pregnancy outcomes appear to be reduced by BS [55]. Pregnant women after bariatric surgery should be screened for nutritional deficiencies at least once every trimester [56]. Especially ferritin, vitamin B12, folate, and vitamin D [57]. Supplementation should follow routine pregnancy recommendations and according to the level of deficiency.

### Conclusion

Despite the limitations in the trial of weight loss over three cases of morbidly obese pregnancy occurred, complications arose, as seen in the first case the pregnancy ended by sudden intrauterine fetal death and other two cases complicated by metabolic state disturbance, we believe that the optimal treatment of infertility in morbidly obese women with or without polycystic ovary syndrome has not been defined, but generally, before deciding which treatment option is preferred, proper weight loss and control of the metabolic state are carried out for successful pregnancy.

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