

# White Paper

## Understanding How Obesity Affects Infertility

By Andrea M. Pampaloni, Ph.D.

Having a child is a defining moment in the life of many people. However, for a growing portion of the population, conceiving a child is increasingly difficult. One in eight heterosexual couples experience subfecundity and are unable to become pregnant within 12 months.<sup>1 2</sup> People with obesity, a body mass index (BMI) higher than 30 kg/m<sup>2</sup>, are more likely than those of a healthy weight to have trouble conceiving, even with the aid of fertility treatments. This affects females and males individually, and if both partners struggle with obesity the likelihood of infertility increases further.<sup>3</sup> Because nearly 40 percent of American adults are affected by obesity and the rate of childbirth in the United States is decreasing<sup>4</sup>, this has profound socio-economic implications.<sup>5</sup>

The impact of being unable to become pregnant extends far beyond physical outcomes. It affects would-be parents' emotional and psychosocial well-being. While some couples may grow closer together in their struggle to conceive, research finds that infertile couples are more dissatisfied with their marriage, themselves, the fertility treatments, and the level of stress related to infertility.<sup>6</sup> One study found that couples who were diagnosed as infertile were three times more likely to get divorced if the woman was unable to get pregnant and give birth.<sup>7</sup> Understanding the relationship between obesity and infertility and the possible impact of interventions can offer hope for infertile couples trying to conceive a child.

### CHALLENGES TO CONCEPTION FOR WOMEN WITH OBESITY

High reproductive health risks associated with obesity in women is well-established. Increased adipose tissue has direct and indirect deleterious effects on reproduction,<sup>8</sup> resulting in a myriad of challenges to becoming pregnant. Imbalances in the hypothalamic-pituitary-ovarian axis, a decrease in growth hormone and sex-hormone-binding globulin (SHBG),<sup>9 10</sup> conversion of androgens to estrogen,<sup>11</sup> and increases or decreases of several adipokines<sup>12</sup> represent only a few of the biochemical challenges that inhibit pregnancy. Further, these challenges prevent not only natural conception but also assisted methods including ovulation induction, in vitro fertilization, and ovum donation cycles. Among the issues frequently affecting women with obesity are greater occurrences of menstrual dysfunction and anovulation, which are both associated with subfecundity and infertility.<sup>13</sup> These and other issues contributing to infertility in women with obesity are discussed below.

#### ***Menstrual Dysfunction***

Women with obesity are more likely to experience irregularities in menstrual cycles with amenorrhea and oligomenorrhoea common occurrences.<sup>14</sup> The reduction of SHBG, along with increases in insulin and testosterone, disrupts hormonal balance and, as a result, the menstrual cycle — even women with obesity who experience regular menstrual cycles are more likely to be subfecund.<sup>15</sup> The age at which a woman becomes obese also has significant impact on menstrual irregularity. Obesity during adolescence causes menstrual problems and leads to anovulatory infertility.<sup>17</sup> Nearly 20 percent of children reaching adolescence are obese,<sup>18</sup> which affects menarche in young girls. Higher levels of body fat in adolescent girls trigger changes in estrogen level and leads to earlier activation of the pituitary

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gland and the onset of puberty.<sup>19</sup> As such, girls with obesity begin menstruation at an earlier age than girls of normal weight.<sup>20</sup> Among today's youth, higher weight can be attributed to decreased activity, higher calorie diet, and exposure to endocrine-disrupting chemicals used in many products (e.g. plastic bottles, furniture). This increases girls' "window of susceptibility," a critical time of development when events — such as environmental exposure — will more likely impact their general and reproductive health later in life.<sup>21</sup>

### ***Anovulation***

Obesity is associated with anovulation, the failure of the ovaries to release an oocyte during a menstrual cycle. Between 25 to 50 percent of female infertility is attributable to ovulatory disorders and occurs more frequently among women with obesity and those who have a higher body mass index.<sup>22</sup> Women with obesity can experience a five percent reduction in conception per unit increase in BMI over 29 kg/m<sup>2</sup>.<sup>23</sup>

### ***Polycystic Ovary Syndrome***

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women associated with anovulation. The triad comprising obesity, infertility, and PCOS is inextricably linked, and the prevalence of this hormonal imbalance is high with 80 percent of anovulatory infertility caused by PCOS.<sup>24</sup> Among women of reproductive age, 12 to 21 percent present with PCOS<sup>25</sup> and they typically, though not exclusively, are overweight. Women who struggle with obesity and have PCOS are more likely to experience congenital anomalies, hypertensive disorders, miscarriages, preterm birth, need for an intensive care unit, Caesarean delivery, and perinatal mortality.<sup>26</sup> They also typically are glucose intolerant with a high risk for developing type 2 diabetes mellitus and exhibit markers of hyperandrogenism.<sup>27</sup>

### ***Implantation Rate***

Studies yield mixed findings regarding the link between obesity and oocyte implantation. Some research has found that obesity is linked to lower implantation rates,<sup>28 29 30</sup> while other studies reveal neutral findings or successful implantation outcomes.<sup>31 32</sup> These inconclusive outcomes suggest the need for further research to better determine if implantation failure or success is linked with obesity.

### ***Miscarriage***

The likelihood of miscarriage increases for women with obesity regardless of how conception occurs, including natural methods, oocyte donation, or ovulation induction. Miscarriage is independent of other conditions, such as PCOS, which alone can cause the end of a pregnancy. Recurrent pregnancy loss also is experienced at a higher rate by women with obesity versus those at a normal weight.<sup>33 34</sup> Not only is the fetus at risk: in the United States, the maternal mortality rate has doubled since 1987, attributed to age, diabetes, and weight.<sup>35 36</sup>

## **CHALLENGES TO CONCEPTION FOR MEN WITH OBESITY**

As levels of obesity increase across populations, male infertility has increased and gained greater recognition. Male infertility rates are not tracked as rigorously as female infertility rates, though some estimates suggest that it affects 34 percent of the male population over the age of 20 and contributes to half of all infertility cases. Women with obese male partners have lower pregnancy rates when undergoing in vitro fertilization and have a significantly greater chance of having a nonviable pregnancy.<sup>37</sup>

Leptin, the hormone produced by the body's fat cells, generally neutralizes or decreases for males after puberty and body fat decreases as muscle mass increases. Among males with obesity, however, excess leptin and a

higher BMI are linked with decreased sperm counts and motility, increased sperm DNA fragmentation, lower testosterone levels, and higher estradiol and luteinizing hormone levels.<sup>38</sup> All of these contribute to infertility in men with obesity.

### ***Erectile Dysfunction***

The inability to maintain an erection severely limits the ability for natural conception. Erectile dysfunction (ED) is common among men who are infertile and men with obesity are at greater risk of experiencing ED<sup>39</sup> due to hormonal imbalance, insulin resistance, physical inactivity, and psychological issues. Obesity is an independent risk factor for ED and among men who experience it, 79 percent are obese. In the United States, ED affects over eight million men.<sup>40</sup>

### ***Change in Semen Parameters***

All men experience decline in semen quality as they age through decreased sperm concentration, motility, and morphology.<sup>41</sup> These defects contribute to infertility both individually and collectively. If fertilization does occur, the poor quality of sperm leads to a greater risk of miscarriage.<sup>42</sup> While some studies argue that BMI does not affect semen quality,<sup>43</sup> small sample size and other limitations suggest the need for further, reliable research.

Like women, men with obesity have decreased SHBG and androgen levels which can affect sperm maturation. Because around 80 percent of men with obesity are diagnosed with type 2 diabetes, SHBG is further inhibited due to higher insulin levels. If SHBG levels become too low, aromatase enzymes convert testosterone to estrogen.<sup>44</sup> This hormonal imbalance causes infertility. Men with obesity and diabetes also have greater levels of DNA damage.<sup>45</sup>

### ***Additional Factors Contributing to Male Infertility***

Obesity in men also is linked to sleep apnea which disrupts the nightly rise in testosterone. Oxidative stress, common in persons with obesity, can increase production of ROS, an independent marker of male infertility, and cause pathophysiological symptoms, such as ED.<sup>46</sup> Both of these conditions, as well as inflammation, contribute to male infertility. Men with obesity also have increased lower abdominal, thigh, and scrotal fat. This increases testicular temperature and negatively impacts testosterone synthesis and spermatogenesis.<sup>47</sup> Additionally, hypogonadism and ED are associated with decreased sexual desire,<sup>48</sup> which has both physiological and psychological effects.

## **RECOMMENDATIONS**

Many of the negative outcomes linked to obesity-related infertility in women and men can be mediated, and research recommends weight loss as the preferred preconception lifestyle change. Dietary modifications and regular exercise to restrict calories and increase energy “remain the first line and cornerstone of management of obesity.”<sup>49</sup> Further, weight loss prior to conception also helps negate many of the pregnancy risks identified here.<sup>50</sup>

### ***Preconception Weight Loss***

There is unequivocal agreement across medical literature in the view that pre-pregnancy weight loss is the best option for women who are overweight or suffer from obesity seeking to become pregnant, regardless of whether they are using natural or assisted methods of conception. A meta-analysis of nearly 200,000 women found that pre-pregnancy BMI was significantly associated with pregnancy

complications, obesity in the offspring, and gestational weight gain.<sup>51</sup> Dr. Romy Gaillard, who led the project, recommends that the medical community place a stronger emphasis on developing strategies to “optimize maternal weight before the start of pregnancy” to improve outcomes rather than focusing on gestational weight gain. This is important because when women become pregnant “there’s nothing they can do about it, because we consider losing weight during pregnancy to be unsafe.”<sup>52</sup> Also, women often classify their BMI as normal even when they are overweight or suffer from obesity,<sup>53</sup> which may make them reluctant to attempt weight loss. In addition to a wide range of health benefits, lifestyle changes to reduce weight prior to conception often restores regular menstrual cycles and ovulation, which improves the likelihood of conception.<sup>54</sup> A study of obese, infertile women who lost 10 percent of their body weight found that they were able to achieve a pregnancy rate of 77 percent and live birth rate of 67 percent, and the likelihood increased with greater weight loss.<sup>55</sup> In a study following women with obesity who participated in preconception lifestyle intervention, participants were tracked at six months and five-and-a-half years after initial changes to diet and physical activity.<sup>56</sup> The diet intervention was successful in changing lifestyle and reducing BMI at both times periods, though the activity intervention was positive only at six months. Although the frequency of vaginal births was significantly lower for the intervention group, significantly more women in that group had ongoing pregnancies from natural conception.<sup>57</sup> Men with obesity who lose weight show improvement in SHBG, testosterone levels, ED, and sperm motility.<sup>58</sup> A Very Low Calorie Diet (VLCD) and/or bariatric surgery are preconception weight loss options for women and men with obesity. All preconception interventions should be considered carefully and in close consultation with medical guidance.

### ***Very Low Calorie Diets***

A VLCD is safe and medically supervised. As such, patients and physicians are in frequent contact, allowing the physician to offer guidance to both female and male patients who are considering conception. Some findings indicate that the quicker weight loss associated with a VLCD may offer better long-term outcomes than more gradual weight loss.<sup>59</sup> Studies of women with obesity and PCOS who followed a VLCD supported by behavioral change therapy and group support found that most women achieved and maintained weight loss compared with other interventions.<sup>60</sup> They also experienced improved self-esteem.<sup>61</sup> Recent trials support the use of a VLCD for preconceptions weight loss. A study of women seeking fertility treatment who used a VLCD for six weeks followed by a hypocaloric diet found significant improvement in pregnancy and live birth rates.<sup>62</sup> Likewise, a systematic review of 62 articles specific to fertility and very-low calorie, very-low energy, and very-low carbohydrate diets were analyzed. The findings suggest that low calorie, specifically low-carbohydrate diets, optimize fertility for overweight and obese women, particularly those with PCOS.<sup>63</sup> Another study incorporating meal replacement products found similar results, with preconception weight loss leading to higher ovulation rates for women with PCOS.<sup>64</sup> The research also suggests that these lifestyle interventions are likely to benefit women who do not have PCOS.

### ***Bariatric Surgery***

For those who have struggled unsuccessfully to lose weight, bariatric surgery is an option if their BMI is over  $>40 \text{ kg/m}^2$  or over  $>35 \text{ kg/m}^2$  if they have two or more comorbidities. Women who undergo bariatric surgery in preparation for becoming pregnant should wait 12 to 18 months following the surgery to avoid complications from nutritional deficiencies<sup>65</sup> and continue with follow-up care for a minimum of two years following surgery.<sup>66</sup> Bariatric surgery also has been found to improve PCOS,<sup>67</sup> provide significant improvements to self-esteem, sexual functioning, and general health.<sup>68</sup> Another study found improvement in the number oocytes retrieved in women with obesity after bariatric surgery.<sup>69</sup> There are mixed results for men who undergo bariatric surgery. Some men increased their testosterone and sperm count, but sperm motility, morphology, and DNA fragmentation findings were inconsistent.<sup>70</sup> In a small study of three male patients who underwent bariatric surgery, sperm parameters .

## CONCLUSION

Many of the negative outcomes linked to obesity-related infertility in women and men can be mediated, and research recommends weight loss as the preferred preconception lifestyle change. Dietary modifications and regular exercise to restrict calories and increase energy “remain the first line and cornerstone of management of obesity.” Further, weight loss prior to conception also helps negate many of the pregnancy risks identified here.

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