

Special Edition  
"Obesity and Infertility and  
Pregnancy Outcomes"

## Review

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# A Review of the Impact of Obesity on Reproduction and Potential Barriers In Conveying the Message

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## INTRODUCTION

*"Knowledge is power and it can command obedience. A man of knowledge during his lifetime can make people obey and follow him and he is praised and venerated after his death. Remember that knowledge is a ruler and wealth is its subject."*

- Imam Ali Bin Abi Taleb (600-661), Saying 146 from Nahj Al-Balagha

For centuries the adage "*Knowledge is Power*" has assured us that the accumulation of knowledge is the key to having more options, influence, and success. As physicians, we take pride and comfort in the fact that our knowledge and training will equip us with the necessary power to heal our patients.

However, what we are learning is that knowledge simply may not be enough. It has become increasingly clear that the manner in which we relay our knowledge is just as important. This concept especially applies to areas of health care that are particularly sensitive and emotionally charged, including obesity and reproduction.

The evidence is overwhelming that we are facing an obesity epidemic that has serious health consequences. Moreover, from a reproductive health standpoint, the consequences include reduced menstrual function, fertility, success rates utilizing Assisted Reproductive Technology (ART), and lower live birth rates.<sup>1</sup>

To handle obesity and promote fertility, the American Society for Reproductive Medicine (ASRM) advocates that physicians need to counsel their obese infertile patients about the harms of excess weight on reproduction, and advise them on dietary modification, physical activity, and weight loss.<sup>2</sup> To manage overweight and obesity in the primary care setting, the American College of Cardiology, the American Heart Association Task Force on Practice Guidelines, and the Obesity Society recommend shaping recommendations on diet, lifestyle intervention, and bariatric surgery around each individual patient's preferences and risk factors.<sup>3</sup> This requires a complex, individualized approach for which most physicians have not been trained. In addition, a significant barrier to addressing obesity is physician and medical staff bias—whether conscious or not—against people affected by obesity. This bias is perceived by patients, who then delay or forgo essential care.<sup>4</sup> Somewhere in our vast vacuum of knowledge, we forgot to provide physician training in discussing sensitive issues regarding weight loss in an effective and appropriate manner.<sup>5</sup>

This Open Journal Special Edition reviews the epidemiology of obesity and its impact on reproduction, as well as potential barriers including physician bias in communicating the message related to the obesity.

**THE OBESITY EPIDEMIC**

Obesity has become the most prevalent chronic disease in the United States and worldwide.<sup>6</sup> Over two-thirds of American adults are overweight or obese, defined as having a Body Mass Index (BMI)>25 kg/m<sup>2</sup> or more, over a third are obese (BMI>30 kg/m<sup>2</sup>), and 4% are morbidly obese (BMI>40 kg/m<sup>2</sup>).<sup>7,8</sup> Worldwide, obesity affects over 600 million adults.<sup>6</sup> According to the Global Burden of Disease 2013 Obesity Collaboration, 37% of men and 38% of women worldwide had a BMI>25kg/m<sup>2</sup> in 2013.<sup>9</sup> Obesity also impacts the pediatric population. In 2009-2010, nearly 10% of infants and toddlers through two years of age were considered obese<sup>10</sup> and close to 17% of children and adolescents aged two through 19 years were defined as obese.<sup>10</sup>

The negative consequences of obesity are identifiable in every organ system and include increased risk of diabetes, hypertension, cardiovascular disease, cerebrovascular disease, pancreatitis, sleep apnea, cancer, and musculoskeletal disease.<sup>11</sup> Obese women also experience inferior outcomes in all aspects of reproduction including irregular menstruation, decreased ovulation, and reduced fertility.<sup>12</sup> Obesity is also associated with reduced success rates related to infertility treatment including ovulation induction and *In Vitro* fertilization (IVF).<sup>13</sup>

Obesity is currently the most common complication of pregnancy worldwide<sup>14,15</sup> and leads to complications including gestational diabetes, pre-eclampsia, preterm birth, neonatal morbidity, birth defects and childhood obesity.<sup>16,17</sup>

**Adverse Health Effects Associated with Obesity**

General Adverse Effects

- Diabetes
- Hypertension
- Cardiovascular disease
- Cerebrovascular disease
- Pancreatitis
- Sleep apnea
- Cancer
- Musculoskeletal disease

Fertility-Related Adverse Effects

- Decreased pregnancy rates
- Decreased live birth rates
- Impaired outcomes to assisted reproductive technology
- Gestational diabetes
- Pre-eclampsia
- Preterm birth
- Neonatal morbidity
- Birth defects
- Childhood obesity

**A REVIEW OF OUR CURRENT KNOWLEDGE OF OBESITY AND REPRODUCTION**

The consequences of altered hormone physiology in obesity on reproductive function include an ovulation, reduced pregnancy rates, increased miscarriage rates, and increased pregnancy complications in both natural and assisted reproduction conceptions.<sup>1</sup>

Obese women are three to four times more likely to have menstrual disturbances than women of healthy weight.<sup>18,19</sup> A case-control study by Rich-Edwards et al found that the risk of an ovulatory infertility significantly increased with increasing BMI over 23.9 kg/m<sup>2</sup> in 18-year-old women.<sup>20</sup> The most common cause of infertility due to an ovulation is Polycystic Ovarian Syndrome (PCOS)<sup>13</sup>; 30-75% of PCOS women are obese.<sup>21</sup>

Studies reveal that obese women require a longer duration of time to achieve a spontaneous pregnancy and pregnancy rates are decreased even in ovulatory obese women.<sup>1,22</sup> Moreover, for each BMI unit above 29 kg/m<sup>2</sup>, there appears to be a 5% decrease in the likelihood of achieving pregnancy.<sup>22</sup> Data from the 2002 National Survey of Family Growth suggest that women with a BMI of ≥30 kg/m<sup>2</sup> are more likely to report seeking fertility services than women with a BMI <29.9 kg/m<sup>2</sup>.<sup>23</sup>

The association between obesity and miscarriage has also been reported in a number of studies in both the general population and in women undergoing assisted reproduction.<sup>1</sup> The risk of miscarriage in obese women has been reported to be as high as 40% higher than women of healthy BMI.<sup>24</sup> Miscarriage rates in obese women with PCOS after either spontaneous or assisted conception have been reported up to 30% to 50% which is threefold higher than in women of healthy weight without PCOS.<sup>25</sup> In those undergoing assisted reproduction, studies reported that miscarriage occurred in 38% of obese women compared to 13% of women with a healthy BMI.<sup>26</sup>

A number of studies have reported women with obesity are more likely to have reduced pregnancy outcomes following infertility therapy including clomiphene-induced ovulation induction, gonadotrophin-induced ovulation induction, and in IVF.<sup>1,12,27</sup> With increasing adiposity there is a need for prolonged ovarian stimulation and higher doses of gonadotropins, as well as reduced number of retrieved mature oocytes, embryo quality, the number of transferred embryos,<sup>28,29</sup> and increased cycle cancellation.<sup>1,30</sup> With respect to cycle outcomes, as BMI increases, favorable outcomes following ART decrease. In one study of 48,000 treatment cycles, obese women had significantly reduced clinical pregnancy and live birth rates following IVF (RR=0.87, 95% CI: 0.80-0.95, p=0.002; RR=0.80, 95% CI: 0.71-0.90, p=0.0002).<sup>31</sup> In a meta-analysis of 37 studies, women with BMI ≥ 25 kg/m<sup>2</sup> are 0.71 times as likely (95% CI: 0.62-0.81) to achieve pregnancy following IVF than women of healthy weight.<sup>27</sup> Another meta-analysis of 27 studies revealed the live birthrate following IVF was 10% lower in overweight women compared to healthy

weight women (OR=0.09; 95% CI: 0.82-1.0,  $p=0.04$ ).<sup>32</sup>

Egg donation, which allows one to separately assess the egg from the uterus, has revealed conflicting results. Styne-Gross et al reported that no association between increased BMI and impaired implantation in 536 cycles.<sup>33</sup> In a review of the Society for Assisted Reproductive Technology national registry, in over 40,000 autologous embryo transfers, as maternal BMI increased, clinical pregnancy significantly decreased: obese women with BMI 30-34.9 were more likely than women of healthy weight to fail to achieve clinical intrauterine pregnancy (OR: 1.13, 95% CI: 1.05-1.21,  $p<0.05$ ).<sup>34</sup> However, there was no difference in clinical pregnancy rates when donated oocytes were used (OR: 0.99, 95% CI: 0.80-1.24,  $p>0.05$ ).<sup>34</sup> The authors suggested that the adverse effects of obesity appeared to primarily impact embryo quality, but not endometrial receptivity.<sup>34</sup> In contrast, Bellver et al reported that when donor oocytes from healthy women were given to overweight women ( $n=1,770$ ) and obese women ( $n=663$ ), as maternal BMI increased, the risk of spontaneous abortion significantly increased (OR: 1.20, 95% CI: 0.59-2.44,  $PNS$ ; OR: 4.02, 95% CI: 1.53-10.57,  $p=0.005$  respectively), suggesting increased BMI is an independent risk factor for spontaneous abortion.<sup>26</sup> To further corroborate this, Goldman et al demonstrated no differences in aneuploidy rates in women using their autologous oocytes<sup>35</sup> indicating that the adverse effects of increased BMI on reproductive outcomes may not be due to an oocyte factor, but rather are at the level of the endometrium.

#### Pathophysiology: The Effects of Obesity on Reproduction

- Hormonal imbalance:
  - Hyperinsulinemia
  - Hyperandrogenemia
  - Hyperleptinemia
  - Decreased adiponectin levels
- Disturbances of hypothalamic-pituitary-ovarian axis
- Oligoovulation and anovulation

#### **PATHOPHYSIOLOGY**

The adverse effect of obesity on fertility is multifactorial and appears to involve multiple overlapping pathways.<sup>1</sup> The negative impact is believed to be linked primarily to insulin resistance, insulin excess, androgen excess, and changes in the levels of various adipokines.<sup>1,12,13</sup> Excess insulin working through Insulin-like growth factor-binding protein (IGF-BP) receptors over-stimulates ovarian androgen production<sup>13,30</sup> while inhibiting Sex Hormone Binding Globulin (SHBG) production. This leads to increased free estrogen levels,<sup>13</sup> which have a negative feedback on hypothalamic-pituitary function, altering the menstrual cycle while reducing ovulation.<sup>30</sup> Obesity is also associated with increased luteinizing hormone levels, which has negative effects on normal folliculogenesis.<sup>30</sup> Increased leptin levels are also noted and stimulate the hypothalamic-pituitary-ovarian

axis, disturbing ovarian function and leading to oligoovulation and anovulation.<sup>30</sup> Conversely, leptin has inhibitory effects in ovarian steroid production, normally stimulated by insulin, and a reduction in ovarian estradiol production, normally stimulated by luteinizing hormone.<sup>1</sup> Obesity also leads to reduced adiponectin levels, which normally inhibits gluconeogenesis by the liver, improves insulin sensitivity, and inhibits fatty acid synthesis.<sup>1</sup>

#### **TRANSLATING KNOWLEDGE INTO POWER—WEIGHT RELATED BIAS**

Obstetrician-gynecologists and reproductive endocrine infertility specialists undoubtedly are aware and understand the pathophysiologic mechanisms related to obesity including the clinical sequelae, and the need for intervention prior to conception. However, similar to other areas of medicine, there is a high likelihood that the message could be lost in translation at the bedside.

Weight-related stigma has been well-documented in all areas of life including the workplace. Studies show that as an individual's BMI increases, their likelihood of being hired, earning the appropriate salary, or receiving promotions decreases.<sup>36</sup> Recent studies show that weight-related bias affects women even more significantly than in men.<sup>37</sup>

Weight-based bias is also an issue in the medical arena. More than half of overweight and obese patients have received discourteous comments from doctors about their weight.<sup>36</sup> Furthermore, after family members, physicians are reported to be the second most common source of weight-based stigma.<sup>36</sup> Bias from any source can lead to depression, anxiety, and decreased self-esteem. Just as important, this bias is associated with delayed care-seeking and appointment cancellations.<sup>38,39</sup> One study found that almost a fifth of physicians were reluctant to perform a pelvic exam on an obese patient, and the majority of obese women reported reluctance to receive a pelvic exam.<sup>40</sup> By reducing healthcare utilization, this bias experienced by overweight and obese women further contributes to the overall adverse health effects including reproductive related issues for which they are already at an increased risk. Additionally, weight discrimination has been shown to exacerbate the effects of higher waist-to-hip ratio on HbA<sub>1c</sub> levels.<sup>41</sup>

Since many physicians are uncomfortable with weight loss discussions, these discussions are often inadequate or avoided altogether. A recent study of 28 primary care physicians and 588 overweight or obese patients found that only 50% of visits included a weight loss discussion.<sup>42</sup> Of the visits where weight was discussed, only 35% included a plan for assessment and treatment.<sup>42</sup> In contrast, another study of pediatricians caring for overweight Latino patients ( $n=26$ ) found more promising results, where 81% of visits included a discussion about weight, and 50% included a management plan.<sup>43</sup> However, in this study a lack of Spanish proficiency by providers was a contributing

factor.<sup>43</sup> These weight-related discussions are sentinel as they have the potential to have a real impact on patients' health and well-being as best demonstrated in a 2014 National Health and Nutritional Examination Survey of 5,5054 overweight and obese patients. In this study, self-reported weight loss was significantly related to a physician telling the patient in the past year that they were overweight (adjusted OR: 1.88, 95% CI: 1.45-2.44) or obese (adjusted OR: 1.79, 95% CI: 1.30-2.46).<sup>44</sup> By assuming that overweight and obese patients are already aware of the need to lose weight, physicians miss out on a critical opportunity for health improvement.

As physicians, we must ensure that we treat overweight and obese women with respect and provide appropriate care including weight loss counseling. Part of respectful and appropriate medical care includes weight-sensitive language, something of which many providers are not even cognizant. For example, overweight and obese women report that they prefer "weight", "excess weight", and "BMI" to refer to excess weight of 50 pounds or more. Conversely they would rather not use terms such as "weight problem", "unhealthy weight", "unhealthy BMI", "heaviness", "large size", "obesity", "excess fat", or "fatness".<sup>45</sup>

Physician-patient communication is crucial for appropriate medical care of all patients. However, a negative association between patient BMI and several facets of physician-patient communication, including physician's respect, listening practices, and the amount of time spent with the patient has been reported. In a study of 6,628 patients, obese patients were significantly less likely to report feeling respected by their physicians (OR: 0.77, 95% CI: 0.61-0.98), or feeling that their physician spent enough time with them (OR: 0.80, 95% CI: 0.61-0.98).<sup>5</sup> Even more alarming is that more than two-thirds of obstetrician-gynecologists (OB-GYNs) and family practitioners surveyed stated that discussions of gestational weight gain with obese women was "unpleasant," while almost a third admitted to making derogatory statements to their obese patients, and 92% acknowledged the need to improve their communication skills.<sup>46</sup>

Weight-related bias can also be expressed non-verbally throughout the medical office environment. The lack of necessary equipment such as appropriate-sized blood pressure cuffs, gowns, vaginal speculums, exam tables, scales, and waiting room chairs, as well as weight-unfriendly magazines or other reading materials are non-verbal biases.<sup>47-49</sup>

Often at the root of weight stigma is the assumption that people with obesity are personally responsible for their weight because of laziness, lack of exercise, overeating, etc.<sup>50</sup> Experimentally, when patients are provided with information that emphasizes personal responsibility for obesity, negative stereotypes increase. Conversely, when provided with information about the complex etiology of obesity, their stereotypes improve.<sup>51</sup> Helping physicians and health care providers to understand the complexity of obesity and the multitude of causes, many of which

are outside of individual patients' control,<sup>52</sup> may help providers view their patients with more compassion.

With all this said, obesity bias studies have not addressed the impact on fertility and assisted reproduction. While we may have the knowledge of the negative impact of obesity on reproduction, we very likely as providers fail in the ability to translate this knowledge as many other disciplines. As reproductive infertility specialists, we must acknowledge the potential bias and take necessary steps to eliminate it. This includes improving the sensitivity, communication skills, and medical office environment that affect the reproductive care and health of women with overweight and obesity. If we expect to have a significant impact on obesity and fertility issues, then we too must recognize these potential failures. If we don't, then the knowledge to positively impact patient outcomes will most certainly be lost in translation.

#### Recommendations for Management of the Patient with Obesity

- Preconception counseling is recommended for all couples affected by obesity
- Preconception weight management programs are the treatment of choice and include diet and exercise interventions
- Pharmacotherapy and bariatric surgery are reserved for patients with obesity that is refractory to behavioral modification
- Physician and patient should work together to make personalized decisions based on an individual patient's needs, risk factors, and goals

#### RECOMMENDATIONS

The ASRM recommends that in addition to discussing obesity treatment options, preconception counseling for couples affected by obesity should include a discussion of the adverse health effects of obesity on mother and child.<sup>2</sup> The first line treatment for obesity is a preconception weight management program. Comprehensive guidelines for assessment and treatment of overweight and obesity are available from the American College of Cardiology, the American Heart Association Task Force on Practice Guidelines, and the Obesity Society.<sup>3</sup> An individualized approach that takes into consideration medical risks and patient readiness is best. Patient and physician should arrive at a plan together and specialized interventionists should be included in the treatment.<sup>3</sup>

Height, weight and BMI should be obtained at least annually in all adults, and waist circumference should be measured at least annually in patients with an overweight or obese BMI.<sup>3</sup> Overweight and obese adults with cardiovascular risk factors such as hypertension and dyslipidemia should be advised that even modest weight loss of 3-5% of body weight is proven to produce health benefits and lower risk factors.<sup>3</sup> Weight loss strategies should include a comprehensive lifestyle intervention with a low-calorie diet and increased physical activity.<sup>3</sup> Patients should aim to achieve a BMI < 35 kg/m<sup>2</sup> before pregnancy, and to avoid excess gestational weight gain.<sup>2</sup>

Behavioral change approaches alone are not sufficient for many patients attempting weight loss. In such circumstances, pharmacotherapy and/or bariatric surgery may be considered. Many new weight loss medications have been recently approved.<sup>2,3</sup> In patients hoping to conceive, these medications can be used for weight loss, but should then be discontinued prior to conception.<sup>2</sup> Patients should be counseled regarding the risk of weight regain following weight loss and encouraged to participate in a comprehensive program to ensure healthy gestational weight gain.<sup>2</sup> Bariatric surgery serves as adjunctive treatment to both behavioral modification and pharmacotherapy. Bariatric surgery should be considered in adults with BMI $\geq$ 40, or with BMI $\geq$ 35 with co-morbidities, who have not achieved weight loss targets using behavioral modification and/or pharmacotherapy.<sup>3</sup> Pregnancy should be delayed for a year following bariatric surgery.<sup>2</sup>

Physician and patient should work together in making the personalized decision of delaying pregnancy for pre-conception weight loss, *versus* conceiving before fertility decreases with age.<sup>2</sup> Additional recommendations that should be considered for health care providers to improve their communication skills and weight-related sensitivity include monitoring their vocabulary during discussions about weight, explaining the multifactorial causes of obesity to their patients, and ensuring their office environment is free of stigmatizing materials. Providers should avoid using pejorative terms for excess weight, such as “fatness,” and instead use terms like “excess weight” and “BMI”.<sup>45</sup> In addition to discussing behavioral contributors to obesity such as nutrient-dense diet and sedentary lifestyle, providers should explain to their patients the pathophysiological basis for obesity as a disease.<sup>51</sup> By focusing on the multi-modal basis of obesity, it may help providers to decrease feelings of shame and stigma experienced by their patients. Improving the office environment includes maintaining adequate supplies of all necessary equipment in appropriate sizes for many body types, and promoting weight-friendly attitudes among all office personnel.<sup>47-49</sup>

The success of behavioral modification and weight loss varies depending on a multitude of factors including an individual's body type, resources, and motivations. A 2001 study of the National Weight Control Registry found that only 20% of overweight and obese people were able to maintain a weight loss of 10% of body weight for at least one year using behavioral strategies.<sup>53</sup> However more invasive means may be necessary for many to achieve success. A recent systematic review and meta-analysis revealed that 58% of obese infertile women (n=589) achieved spontaneous pregnancy after bariatric surgery.<sup>54</sup> There is currently a randomized control trial underway to assess the cost-effectiveness of a lifestyle modification program for obese infertile women to use before and during pregnancy.<sup>55</sup>

## CONCLUSION

While we as providers, in particular as reproductive infertility specialists, know the significant impact on reproductive risks related to obesity, we must recognize there are a number of

potential barriers in translating this information. These include the ability to effectively communicate the negative impact on reproductive outcomes and the inherent bias that may be present towards overweight and obese patients. As we strive for better medical and surgical treatments, we must also work on communication skills to better improve fertility related outcomes.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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