

## Obesity as an Epidemic: Causes, Morbidities and Reproductive Performance

E. Hakan Duran, M.D.<sup>1</sup>

**Key Words:** Obesity

### Abstract

*Obesity is an epidemic causing significant morbidity and mortality in United States. It is facilitated by many factors including sedentary life style, abundance of food, and unhealthy dietary habits. This review aims to briefly address causes and conditions associated with obesity, with a special emphasis on reproductive performance for Obstetricians and Gynecologists.*

<sup>1</sup>*Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Carver College of Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA*

### Definition of Obesity

Obesity is defined by both National Institutes of Health (NIH) and World Health Organization (WHO) as having a body mass index (BMI) equal to or greater than 30 kg/m<sup>2</sup>.<sup>1,2</sup> The degree of obesity is significantly associated with metabolic and cardiovascular comorbidities, including type 2 diabetes mellitus, hypertension, coronary heart disease, and sleep apnea (Table 1). Coexistence of these conditions will

place patients in a very high-risk category for subsequent mortality.<sup>3</sup> Other morbidities associated with obesity include osteoarthritis, cholelithiasis, and impaired quality of life. Overall, obesity is associated with a striking reduction in life expectancy for both men and women, in younger and older ages.<sup>4,5</sup>

Obesity is a chronic disease with increasing prevalence in adults, adolescents and children. It is now considered a global epidemic. In the United States, the lifetime risk of becoming overweight and obese is approximately 50% and 25%, respectively.<sup>6</sup> As of 2009, overall self-reported obesity prevalence in the United States was 26.7%, disproportionately affecting non-Hispanic blacks (36.8%), Hispanics (30.7%), those who did not graduate from high school (32.9%), and people aged 50-59 years (31.1%) and 60-69 years (30.9%) (Figure 1).<sup>7</sup> Healthcare expenses are significantly higher for overweight and obese individuals, and on average, obese people have medical costs that

*Please cite this paper as:* Duran, EH. Obesity as an Epidemic: Causes, Morbidities and Reproductive Performance Proc Obstet Gynecol. 2011 Apr;1(3):Article 8[16 p.]. Available from: <http://ir.uiowa.edu/pog/>. Free full text article.

**Corresponding author:** E. Hakan Duran. Department of Obstetrics and Gynecology, University of Iowa, 31322 PFP, 200 Hawkins Drive, Iowa City, IA, 52242. Telephone( 319)356-4119. [hakan-duran@uiowa.edu](mailto:hakan-duran@uiowa.edu)

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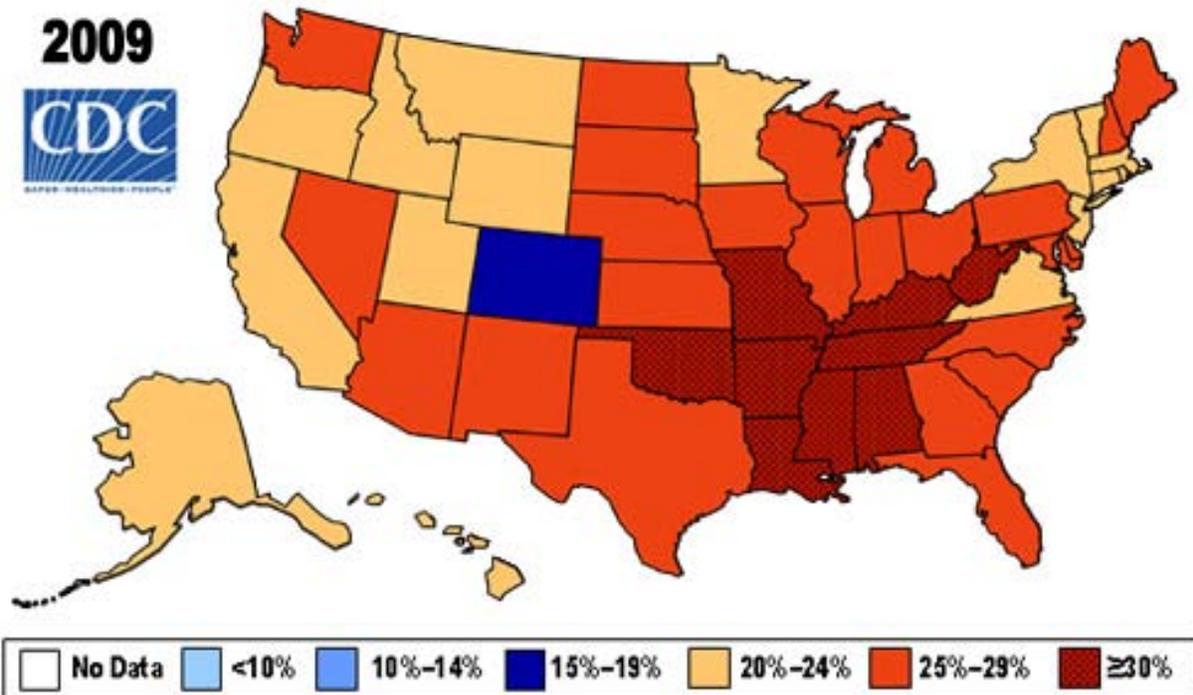
are \$1,429 more than non-obese people, translating to an estimated

annual cost of \$147 billion in the United States.

Table 1: Classification of obesity

WHO Class	Popular Description	BMI (kg/m <sup>2</sup> )	Co-morbidities
Underweight	Thin	<18.5	Other clinical problems
Normal range	Normal	18.5-24.9	Average
<b>Overweight</b>			
Pre-obese	Overweight	25.0-29.9	Increased
Obese Class I	Obese	30.0-34.9	Moderate
Obese Class II	Obese	35.0-39.9	Severe
Obese Class III	Morbidly obese	>40.0	Very severe

Figure 1: Prevalence of obesity in US adults by state in 2009<sup>1</sup>



<sup>1</sup>Centers for Disease Control and Prevention. U.S. Obesity Trends: Trends by State 1985–2009. <http://www.cdc.gov/obesity/data/trends.html>. March 2011.

### Physiologic Basis for Obesity

Simply put, energy intake needs to be higher than energy expenditure for an increase in body fat. However, there is a feedback between energy intake and expenditure in biological systems, which is affected by several factors including

intrauterine growth and growth and reproductive hormones. This complicated modulation of energy utilization and storage reduces the initial statement of the first law of thermodynamics to an oversimplification. The body typically responds to a 10-20% loss in weight by

decreasing total and resting energy expenditures; weight gain is associated with an increase in energy expenditure, which retards further weight gain.<sup>8</sup> Therefore, organisms seem to have a mechanism that tries to maintain bodyweight, indicating that behavior may not be the sole determinant of obesity.

Approximately 70% of energy expenditure is utilized for basal or resting metabolic processes, 10% is dissipated through the thermic responses to food, and the remaining component is attributed to activity and exercise.<sup>9</sup> Spontaneous activity (fidgeting) can account for an expenditure of up to 800 kcal daily and, along with the genetic factors, is responsible for much of the variance in energy expenditure among individuals.

A simplified schematic representation of energy regulation is presented in Figure 2.<sup>10</sup> Afferent signals provide information about the deficits or excesses of nutrients and also include neural circuits and circulating hormones, such as leptin, ghrelin, obestatin, and glucagon-like-peptide-1. Regions of the brain that process this information are the nucleus of the tractus solitarius, the arcuate nucleus, the paraventricular nucleus, the ventromedial hypothalamus, the lateral hypothalamus, and selected regions of the amygdala. A variety of monoamines, including norepinephrine and serotonin, and hormones play various roles in this system. Among these, neuropeptide Y, ghrelin, dynorphin, melanin-concentrating hormone, growth hormone-releasing hormone, norepinephrine, orexin-A, and orexin-B act as appetite enhancers. In contrast, cholecystokinin, enterostatin, and peptide YY 3-36 suppress food intake.

The sympathetic nervous system and glucocorticoids also act as components of the efferent signaling system, affecting food intake and adipose tissue metabolism. Leptin is the principal afferent signal that provides information about the amount of stored energy in adipose tissue.

### **Pathogenesis of Obesity**

Obesity has many causes with variable genetic components.<sup>11</sup> Twins raised separately still inherit obesity, although to a lesser extent than when raised together.<sup>12</sup> Similarly, adoptees' BMIs correlate with that of their biological parents rather than that of their adoptive parents.<sup>13</sup> In addition to weight, metabolic rate, thermic response to food, and spontaneous physical activity are to some extent heritable.<sup>14</sup>

Several genetic disorders present with obesity; some are inherited as autosomal dominant, some are autosomal recessive, whereas others are X-linked.<sup>11</sup> The Bardet-Biedl and Prader-Willi syndromes are probably the best known examples of these traits. Bardet-Beidl syndrome is an autosomal recessive disorder characterized by obesity, hypogenitalism in men, mental retardation, retinal dystrophy, polydactyly, and renal malformations.<sup>15</sup> At least 10 genetic loci have been identified in patients with this syndrome. Prader-Willi syndrome, on the other hand, is caused either by a deletion of paternal DNA in the long arm of chromosome 15 (q11-13), or by the presence of two copies of maternal chromosome 15 (uniparental disomy).<sup>16,17</sup> Affected patients have poor muscle tone, a history of poor feeding in the newborn period, a voracious appetite later in life,

behavioral problems (irritability, tantrums), delayed development, short stature, and hypogonadotropic hypogonadism with a common occurrence of cryptorchidism in boys and primary amenorrhea in girls.<sup>18</sup> Despite the well-defined nature of these genetic syndromes, they are rare and genes contributing to the more common forms of obesity are yet to be determined. Several candidate genes have been identified and are currently under investigation with the hopes of understanding the causes of the more common types of obesity.

### Obesity Risk Factors

The risk factors associated with a high risk of obesity can be roughly categorized as metabolic and socioeconomic. Metabolic factors include a low metabolic rate, increased

carbohydrate oxidation, insulin resistance, and low sympathetic activity. Socioeconomic factors include a lower socioeconomic class, a lower education level, and cessation of smoking.<sup>19,20</sup>

There are several predictors of obesity starting from the prenatal period to adulthood. Infants born to women with diabetes and infants born to women who smoked during pregnancy are at greater risk for obesity later in life. Similarly, both infants born small for gestational age and those in the top 10<sup>th</sup> percentile of birth weight are at greater risk for obesity. Breastfeeding for three or more months seems to be a good preventive strategy to prevent obesity later in life.<sup>21</sup> A list of risk factors identified to predict development of obesity is presented in Box 1.<sup>22</sup>

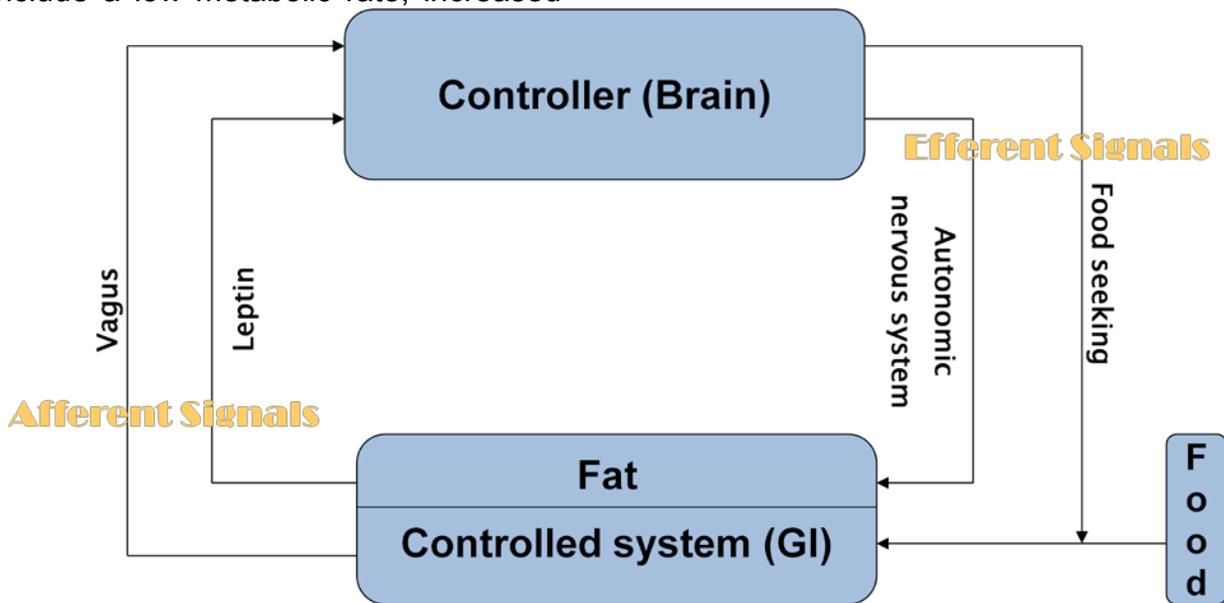


Figure 2: Feedback model for body energy regulation (modified from reference (10))

**Table 2: Drugs causing weight gain and their alternatives**

<b>Category</b>	<b>Drug</b>	<b>Alternative</b>
Neuroleptics	Thioridazine, olanzapine, quetiapine, risperidone, clozapine	Molindone, haloperidol, aripiprazole
Antidepressants		
Tricyclics	Amitriptyline, nortriptyline, imipramine	Protriptyline
SSRI	Paroxetine	Sertraline, fluoxetine
Other	Mitrazapine	Bupropion, nefazodone
Anticonvulsants	Valproate, carbamazepine, gabapentin	Topiramate, lamotrigine, zonisamide
Antidiabetics	Insulin, sulfonylureas, thiazolidinediones	Acarbose, miglitol, metformin, pramlintide, exenatide
Antiserotonins	Pizotifen	-
Antihistamines	Cyproheptadine	Inhalers, decongestants
β-blockers	Propranolol, atenolol, metoprolol	ACE inhibitors, Ca channel blockers
α-blockers	Terazosin	ACE inhibitors, Ca channel blockers
Steroid hormones	Corticosteroids, progestins	-

Adapted from (22). Abbreviations: MOA, monoamine oxidase; SSRI, selective serotonin uptake inhibitors

**Box 1: Risk factors for development of obesity**

<b>Risk Factors</b>
• Infants born to women who smoked during pregnancy
• Infants born to women with diabetes
• Multiple births
• Premature births
• Small for gestational age infants
• Large for gestational age infants
• Recent marriage
• Smoking cessation
• Parental overweight
• Lower socioeconomic status
• Overweight during childhood or adolescence
• Lack of maternal knowledge of child’s sweet-eating habits
• Low level of physical activity
• High intake of dietary fat
• Infants breastfed for less than 3 months
• Pregnancy
• Menopause

## Conditions Causing Obesity

Other than the well-defined genetic syndromes some of which were stated above, there are several clinical entities that may result in obesity without producing distinctive phenotypes.

### 1. Neuroendocrine Obesity

#### a) Hypothalamic Obesity

Hypothalamic obesity may be produced in animals by injuring the ventromedial or paraventricular region of the hypothalamus or the amygdala, but it is rare in humans. It may be caused in humans by trauma, tumor, inflammatory disease, surgery in the posterior fossa or increased intracranial pressure.

#### b) Cushing's syndrome

Obesity is a major feature of Cushing's syndrome. However, a variety of conditions may mimic Cushing's syndrome by distorting the hypothalamic-pituitary-adrenal axis; manifestations include depression, anxiety disorder, obsessive-compulsive disorder, poorly controlled diabetes, and alcoholism, and the condition is referred to as pseudo-Cushing's syndrome. Although it may be challenging at times to differentiate these two conditions from each other, it is necessary to address the underlying problem appropriately.

#### c) Hypothyroidism

Weight gain associated with hypothyroidism is secondary to the slowing metabolic activity and typically does not lead to marked obesity. It is more prevalent in older women.

#### a) Polycystic Ovary Syndrome

Polycystic ovarian syndrome (PCOS) is a spectrum of conditions characterized by menstrual irregularities,

hyperandrogenism and/or ultrasonographic appearance of polycystic ovaries.<sup>23</sup> It is believed to affect 6-8% of all women.<sup>24,25</sup> Approximately 60% of women in United States with PCOS are obese.<sup>26</sup> Similarly, 50-70% of women with PCOS have clinically measurable insulin resistance in vivo, which is more than what is determined by their body weight. It is clear that environmental factors play part in determining the presence and degree of obesity in PCOS; however it is also possible that PCOS is associated with a greater propensity for obesity and weight gain.

#### d) Growth Hormone Deficiency

Growth hormone selectively decreases visceral fat and may be a factor in the age-related increase in visceral fat since the level of growth hormone gradually decreases with age. Women and children with growth hormone deficiency exhibit an increase in visceral fat, although this increase does not lead to clinical obesity.

### 2. Drug Induced Weight Gain

A brief list of drugs that may cause weight gain is presented in Table 2.<sup>22</sup> Most of these medications are not sufficient to cause obesity on their own, except high dose corticosteroids, psychoactive drugs or valproate.

### 3. Cessation of Smoking

Weight gain after cessation of smoking is common and at least partly mediated by nicotine withdrawal.<sup>27,28</sup> The odds ratio of obesity by smoking cessation is estimated to be 2.4 in men and 2.0 in women. Therefore, all patients who plan to quit smoking should consider an exercise program and decreased caloric intake.

#### 4. Sedentary Life Style

Restriction of physical activity is probably the most important contributor to obesity, even more so than increased food intake. The highest frequency of overweight individuals occurs in those persons with sedentary occupations. Low levels of physical activity and recreation are related to weight gain.<sup>29</sup> In addition, high levels of physical activity are required to maintain normal body weight in middle age years.<sup>30</sup> Similarly, BMI of children is positively correlated with the hours spent watching television.<sup>31</sup> Just reducing TV viewing, without any other intervention, significantly reduces BMI in children.<sup>32</sup>

#### 5. Dietary Factors

Excess energy intake in relation to energy expenditure is the basis for development of obesity. Several dietary factors that may impact this balance are listed below.

##### a) Overeating

Voluntary overeating is one cause of excess energy intake. Some individuals may actually lose all the weight they have gained once they stop overeating, whereas for others weight gain can reach a rate of nearly 25 kg/year and is sustained until death.

##### b) Fat Intake

High fat content in a diet is associated with obesity, as indicated by a positive correlation between relative weight in several populations and the percentage of fat in their diets.<sup>33</sup> A high-fat diet provides a high energy density (i.e., lesser weight of food for the same amount of calories), which makes overconsumption more likely.

##### c) Carbohydrate and Fiber Intake

The glycemic index is a measure of the effects of carbohydrates on blood sugar levels. Carbohydrates that break down quickly during digestion and release glucose rapidly into the bloodstream have a high glycemic index; carbohydrates that break down more slowly, releasing glucose more gradually into the bloodstream, have a low glycemic index. It has been documented that the consumption of foods with a high glycemic index is associated with higher energy intake than when the foods have a low glycemic index.<sup>34</sup> Foods with low glycemic index also stimulate less food intake. Consumption of sugar-sweetened beverages, which typically have a high glycemic index, by children may enhance the risk of rapid weight gain.<sup>35</sup>

##### d) Calcium Intake

Low calcium intake may facilitate weight gain. Increasing supplemental calcium from 0 mg to nearly 2,000 mg daily was associated with a reduction in BMI of approximately 5 units.<sup>36</sup>

##### e) Frequency of Eating

Although not completely established, eating bigger portions less often seems to cause weight gain more than eating smaller portions more frequently. One explanation to this observation may be the greater insulin secretion associated with eating larger meals.

##### f) Restrained Eating

Restrained eating is a common practice in many, if not most, middle-aged women of normal weight, characterized by conscious limitation of food intake. Greater increases in restraint correlate with greater weight loss but also with a higher risk of lapses, loss of control, and overeating.

### **g) Binge Eating Disorder**

Binge eating disorder is a psychiatric illness that primarily affects women. It is characterized by uncontrolled episodes of usually evening time eating.

### **h) Night-Eating Syndrome**

Night-eating syndrome is the consumption of at least 25% of the total daily energy consumed between the evening meal and the following morning. It may be related to sleep disturbances, and may be a component of sleep apnea.

## **6. Psychological and Social Factors**

Seasonal affective disorder is a type of depression that occurs during the winter in some individuals living in the north, possibly associated with shorter days. Patients with this condition have a tendency to gain weight during the winter. It can be treated effectively by high intensity artificial light in the winter. Attempts to link a personality type to the development of obesity have been unsuccessful.

## **7. Socioeconomic and Ethnic Factors**

Obesity is more prevalent in lower socioeconomic groups in the United States. Although African-American women of all ages are more obese than Caucasian women, the association between socioeconomic status and being overweight or obese is much greater in the latter group. The relationship between the socioeconomic status and obesity is generally far less pronounced in men.<sup>37</sup>

### **Conditions Associated with Obesity**

Obesity is estimated to be responsible for approximately 100,000-300,000

deaths annually in the United States. A Prospective Studies Collaboration analysis of 57 prospective studies, where 894,000 individuals were followed for a mean of eight years, showed that mortality is lowest among men and women with a BMI between 22.5 and 25 kg/m<sup>2</sup>, and there is a 30% increase in overall mortality for each 5 kg/m<sup>2</sup> increase in BMI.<sup>3</sup> Obesity-related deaths are mostly caused by increased deaths from heart disease, diabetes, hypertension and cancer.

### **1. Morbidity Related to Adipose Tissue Hyperplasia / Hypertrophy**

These conditions can be listed as metabolic syndrome, diabetes, cardiovascular disease and hypertension, gallbladder disease, and cancer. Specifically, central obesity has been associated with an inflammatory milieu, which may lead to insulin resistance, impaired glucose tolerance or diabetes, dyslipidemia, including high levels of triglycerides and markers of inflammation (e.g. C-reactive protein), hyperuricemia, hypertension, impaired coagulation, and vasculoendothelial dysfunction. Weight loss of ~16% in obese individuals dramatically increases recovery from many of these conditions,<sup>38</sup> and beneficial effects start to be seen by losing as low as 10 lbs. In addition, the prevalence of gall stones sharply increases with weight gain, which may be a product of increased cholesterol levels and excretions serving as nidation factors for stone formation in the gallbladder. Furthermore, rates of cancer of the endometrium, breast, colon, and gallbladder are increased in obese women. This is explained in part by increased aromatization of androgens into estrogens, which serve

as a mitogenic factor for some of these tissues, by the adipose tissue.

## **2. Morbidity Attributed Directly to Fat Tissue**

Sleep apnea is prevalent in overweight/obese individuals, characterized by intermittent airway obstruction that interrupts sleep and causes hypoxemia. Increased fat mass in the pharyngeal area is one explanation for this condition. Degenerative osteoarthritis is one of the most costly and debilitating consequences of obesity, and generally progresses with age. Social stigmatization is another direct consequence of obesity, which probably affects women more than men, creating self-confidence and quality of life problems.

### **Reproductive Performance**

Many studies have reported an association between increased BMI and infertility, most commonly related to ovulatory dysfunction, although decreased spontaneous pregnancy rates and increased time to pregnancy was also reported even among ovulatory obese women.<sup>39, 40, 41</sup> Obesity may also have a negative impact on the outcome of treatment of infertility. Some studies show poorer outcomes of infertility treatment in these women,<sup>42</sup> while others suggest that outcomes are comparable to non-obese women but higher doses of ovulation-inducing agents need to be used.<sup>43,44</sup> A systematic review of 11 observational studies addressed the impact of obesity on the outcome of assisted reproductive technologies, i.e., in vitro fertilization. Overall, overweight women had a lower likelihood of pregnancy, increased risk

of miscarriage, reduced number of oocytes retrieved, and higher doses of gonadotropins were needed. In this review, there was insufficient evidence for a correlation between obesity and live birth and cycle cancellation rates, as well as ovarian hyperstimulation syndrome development rate,<sup>45</sup> although individual studies reported conflicting results.<sup>46,47,48</sup>

Obesity is associated with various complications during pregnancy, including gestational and overt diabetes, pregnancy associated hypertension, preterm delivery, postterm pregnancy, urinary tract infections, and sleep apnea. It is logical to consider the combination of two hypercoagulable states, pregnancy and obesity, as a compounded hypercoagulable and prothrombotic state.<sup>49</sup> Obese women have longer labors characterized by prolongation of the active phase of labor, are more likely to have labor induction,<sup>50,51,52</sup> are more likely to fail vaginal birth attempt after cesarean delivery with an increased risk of uterine dehiscence/rupture,<sup>53,54,55,56</sup> and are more likely to have macrosomic infants with associated intrapartum complications (shoulder dystocia, malpresentation, hemorrhage, and fourth degree laceration).<sup>57,58,59,60</sup> There are many intra- and post-operative concerns surrounding cesarean delivery with obese women, including emergency delivery, prolonged incision-to-delivery interval, blood loss >1000 ml, longer operative times, among others.<sup>53,57,58,61,62</sup> The type of incision should be decided carefully secondary to the presence of large pannus and caudal displacement of umbilicus. Complications due to anesthesia are more common, both for regional

(challenging placement of spinal anesthesia or epidural catheter) or general anesthesia (challenging endotracheal intubation, increased risk of aspirating stomach contents, avoiding premature extubation).<sup>62,63,64,65</sup> Obese gravid is at higher risk for postpartum infection (wound, episiotomy, and endometritis) regardless of the mode of delivery and despite the use of antibiotic prophylaxis.<sup>57,58,59,62,66,67</sup> There are conflicting data about the effect of obesity on lactation and postpartum bleeding. Some studies suggested an increased risk of failure to initiate lactation and a decreased duration of lactation in obese women,<sup>68,69,70,71,72</sup> whereas others failed to identify a similar relationship.<sup>73,74</sup> Similarly, a large population-based cohort study reported a 44% increased risk for major postpartum hemorrhage in obese gravidas,<sup>57</sup> whereas several small studies did not find such an association.<sup>59,75,76</sup>

Maternal obesity is associated with a small increase in the absolute rate of some congenital anomalies, including neural tube defects, cardiovascular anomalies, cleft lip and palate, anorectal atresia, hydrocephaly, and limb reduction anomalies, whereas the risk of gastroschisis was significantly reduced.<sup>77,78,79</sup> Also, the typical reduction in neural tube defect risk associated with standard doses of folic acid supplementation was reported to not occur in obese women.<sup>80</sup> There are several confounders that may have an impact on these findings. Among those are increased prevalence of diabetes among obese women, and increased difficulty in diagnosing congenital anomalies in obese women, probably leading to more affected liveborns in this population. Risk of stillbirth and neonatal

death were also reported to be higher in obese women.<sup>81,82</sup> In addition to shoulder dystocia, fetal macrosomia may also predispose the neonate to obesity later in life, based on epidemiologic studies.<sup>83,84,85,86</sup>

For prevention of obesity-related complications during pregnancy, the best strategy is weight loss before conception. Despite the challenges associated with weight loss, it should continue to be encouraged as a primary preventive strategy in this population.

### **Conclusions and Comments**

Obesity is an epidemic fueled by sedentary life style, abundance of food, unhealthy dietary habits, and other factors. Epidemiologic indicators predict worsening of the situation in the forthcoming years, leading to a chain reaction of increases in several morbidities and mortality. Prevention is the best strategy to avoid morbidity and mortality associated with obesity. Obstetricians and gynecologists have a unique position in this respect. As a primary care provider, he/she can not only use the regular office visit as an opportunity to screen for obesity and encourage proper diet, physical activity, and weight control, but also help manage underlying disorders that lead to obesity. Preconceptional visits are another excellent opportunity to help an overweight woman begin a weight loss program before she gets pregnant. By doing so, both maternal and fetal health may be protected and improved, allowing a better start and a healthier life for future generations.

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