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Medical and surgical interventions to improve outcomes in obese women planning for pregnancy

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Obesity is a known risk factor for infertility in women. The exact mechanism through which obesity is linked to infertility is still not fully understood. Hyperleptinaemia, hyperinsulinaemia and resultant hyperandrogenism are all thought to play a role. Various medical and surgical interventions have been attempted to improve fertility rates in obese women. Encouraging evidence for pharmacotherapy, bariatric surgery and assisted reproduction are yet to be seen. In this chapter, we review the hormonal changes in obesity and the evidence behind medical and surgical interventions to improve fertility in obese women.

Introduction

Per the World Health Organization (WHO) guidelines, overweight is defined as a body mass index (BMI) of 25–29.9 kg/m^2 and obesity as a BMI of ≥30 kg/m^2. Obesity is further subcategorized into class 1 (BMI 30–34.9 kg/m^2), class 2 (BMI 35–39.9 kg/m^2) and class 3 or severe obesity (BMI ≥ 40 kg/m^2) [1]. According to the Health Survey for England in 2012 [2], the prevalence of obesity among adults rose from 15% to 25% between 1993 and 2012 with women having a higher prevalence of severe obesity compared to men [2]. Obesity in women has been linked to infertility through a variety of mechanisms including anovulation, increased rate of miscarriage, both mechanical and medical complications in pregnancy and difficulties in performing assisted reproduction [3,4]. In this section, we review the

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pathophysiology and medical and surgical management of obesity as it relates to reproductive outcome.

Epidemiology of obesity and obesity-related infertility

Worldwide, obesity has nearly doubled since 1980 [5]. "A majority of the US population is overweight, a third obese and nearly 5% morbidly obese" [6], and high rates have similarly been demonstrated in Europe and many other countries of the world [7]. Obesity is associated with considerable morbidity, and infertility is a prevalent issue among women of childbearing age. Worldwide, almost 14% of women are obese [8] and several population studies have clearly demonstrated an increased risk of infertility associated with elevated BMI [9]. The Nurses' Health Study II suggested that in the United States as much as 25% of ovulatory infertility may be attributable to BMI $\geq$25 kg/m^2 [10], and another study demonstrated a 3.1 times higher relative risk of ovulatory infertility in women with BMI >27 kg/m^2 compared to primiparous controls [9]. Obesity is also strongly correlated with polycystic ovary syndrome (PCOS). It is estimated that as many as 5–10% of women of reproductive age have PCOS [11] and that between 38% and 88% of women with PCOS are overweight or obese [12].

Hormonal changes in obesity and their impact on fertility

Adipose tissue is an active endocrine organ that releases adipocyte-specific factors called adipokines as well as cytokines, which may enable the body to adapt to complex metabolic challenges [13,14]. Obesity is characterized by an expanded adipose tissue mass, and it has been suggested that a sustained state of energy excess is unusual in evolutionary terms and that adipose tissue signalling adapts poorly [14]. In this section, we discuss the proposed mechanisms by which excess adiposity can impair fertility.

Endocrine effects of adipose tissue: leptin and insulin resistance

The adipocyte hormone leptin is secreted in proportion to fat content, and it plays a crucial role in regulating appetite, body weight and metabolism [12,15]. It acts as a negative feedback signal relaying the magnitude of peripheral energy stores to the hypothalamus to alter energy expenditure and food intake [9,13]. Apart from this, however, leptin may directly influence reproductive capacity in women. It acts as a signal of a nutritional status suitable for conception and pregnancy, and it is important in activating the hypothalamic–pituitary–ovarian (HPO) axis [12,16]. In states of metabolic stress such as starvation or anorexia, a decline in circulating leptin may deactivate the HPO axis [16].

Obesity is a state characterized by hyperleptinaemia. However, in spite of these high levels of leptin, obesity "promotes multiple cellular processes that attenuate leptin signalling" [17] leading to a leptin-resistant state, thereby increasing the risk of HPO axis deactivation, irregular menses and anovulation [16,18]. Hyperleptinaemia itself may also directly inhibit ovarian granulosa and thecal cell steroidogenesis and "high leptin concentrations in the ovary may interfere with the development of a dominant follicle and oocyte maturation" [19].

Insulin resistance and its associated hyperinsulinaemia is another important feature of obesity, especially central obesity, that impacts fertility, and although the mechanisms are not fully elucidated, many aspects of adipocyte activity have been linked to its development. The adipocyte hormone adiponectin has been shown to increase insulin sensitivity but its concentration is negatively correlated with fat mass [13]. Adipocyte proteins, resistin and retinol-binding protein-4 (RBP-4), have been implicated in the development of insulin resistance and they are positively correlated with adiposity [13]. Inflammatory cytokines tumour necrosis factor alpha (TNF-α) and interleukin (IL)-6 are produced by adipose tissue macrophages and "increase in circulating levels of these macrophage-derived factors in obesity leads to a chronic low-grade inflammatory state that has been linked to the development of insulin resistance" [13].

Insulin resistance is associated with compensatory hyperinsulinaemia, and these elevated levels of insulin can contribute to subfertility in several ways. One of the major effects is hyperandrogenism arising from ovarian and other sources. At the level of the ovary, hyperinsulinaemia increases androgen