Obesity and Reproduction

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Obesity is the most common chronic condition in the United States and its impact on reproduction is significant. For over 100 years, the incidence of obesity has been increasing in the US secondary to an affluent society, a sedentary lifestyle, and high calorie foods. Obesity starts in childhood and continues into puberty and adulthood.

OBESITY AND REPRODUCTION IN WOMEN

The menstrual cycle is influenced by body fat, and obesity can lead to irregularities in the menstrual cycle. Studies have indicated that 30-47% of obese women have irregular cycles,[1,2] although the incidence of infertility among obese women is not that high. Infertility in this population seems to be related to ovulatory dysfunction. A large case-controlled study that compared obese, anovulatory women with fertile controls found a relationship between BMI at age 18 and subsequent anovulatory infertility.[3] The relative risk for anovulatory infertility was 1.3 (95% CI 1.2-1.6) in women with a BMI of 24 – 31 kg/m2, and 2.7 (95% CI 2.0 – 3.7) for those with a BMI > 32 kg/m2.

POLYCYSTIC OVARIAN SYNDROME

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy seen in relation to obesity. Clinical features include obesity, anovulation, hirsutism, androgen excess, increased waist-to-hip ratio, and menstrual irregularities. But the true spectrum of PCOS is a continuum; patients do not have to exhibit all of these features, including obesity.

To understand how body weight affects the menstrual cycle, it is first necessary to review the hormonal control of the normal functioning cycle. In an ovulatory cycle, follicle stimulating hormone (FSH) from the pituitary stimulates the growth of a follicle and the recruitment of granulosa cells which begin producing estradiol. The theca cells that surround the granulosa cells produce testosterone in response to luteinizing hormone (LH). Testosterone is the precursor to estradiol production. Insulin-like growth factor-II (IGF-II) is produced in the theca cells in response to gonadotropin stimulation, and this response is enhanced by estradiol and growth hormone. IGF-II increases luteinizing hormone stimulation of androgen production in the theca cells. As the follicle reaches full maturity and ovulates, there is more that transpires, but this will suffice to explain the impact of PCOS.

PCOS is an imbalance in the delicate feedback system that normally takes place during an ovulatory cycle to allow for a single developing follicle to reach maturity and be released. This system can be thwarted by obesity and PCOS in several ways. Fat cells are capable of making a weak estrogen, estrone, and releasing it into the circulation. Although weaker than estradiol, it is capable of suppressing FSH release and preventing the full development of a dominant follicle. When this occurs, developing follicles will progress to about 10 mm in size, add estradiol to the circulating pool of hormones, and be unable to grow further due to the decreasing levels of FSH occurring secondary to the negative feedback estrogens exert on FSH excretion. The ovaries will obtain a "polycystic appearance" due to the many small follicles present at the periphery which are unable to fully develop with the dropping FSH levels. Androgen levels rise with the falling FSH levels since FSH stimulates the aromatization of androgens to estrogens. A high androgen environment within the developing follicle leads to atresia. Elevated serum androgens exert an inhibitory effect on hepatic protein production, which leads to decreased production of sex hormone binding globulin (SHBG). SHBG binds estrogens and androgens in the serum making them less active. With less SHBG, the amount of free testosterone in the serum increases causing further atresia and hirsutism. Anovulation and unopposed estrogens can lead to endometrial hyperplasia and carcinoma.

Some patients with obesity will have insulin resistance, a condition where their cells do not respond adequately to insulin so they must maintain elevated serum insulin levels in order to regulate glucose. One theory for this disorder is an insulin receptor defect. Insulin is capable of activating the IGF-II receptor and stimulating the theca cells to produce excess amounts of androgens leading to PCOS. Therefore, patients with insulin resistance can develop PCOS.

OBESITY AND REPRODUCTION IN MEN

The effects of obesity on male reproduction have been less well studied than those on female reproduction, but there is a growing body of evidence suggesting that obesity has an adverse

effect on male reproduction. The incidence of oligospermia and azospermia increases as BMI increases, from 5.3% and 4.5% in normal weight men, to 9.5% and 8.9% in overweight men, and to 15.6% and 13.3% in obese men.[4] Fat cells in men can produce estrone (as in women) via aromatization which suppresses gonadotropin secretion. These endocrine abnormalities are present in obese men and more pronounced in infertile obese men. In addition, in obese men, the scrotum remains closer to surrounding tissue than thinner men causing a thermogenic effect on developing sperm.

TREATMENT OF REPRODUCTIVE DISORDERS IN THE OBESE

Treatments are aimed at correcting the imbalances that exist and allowing homeostasis to be restored. The first step is weight loss. Encouraging the patient to return to a more normal BMI often corrects the underlying hormonal imbalances allowing the menstrual cycle to restore itself. When the BMI moves closer to ideal, the peripheral production of estrone decreases, removing the inappropriate negative feedback on pituitary release of FSH. With the normal levels of FSH restored, ovulation can occur, or in the case of the male, normal spermatogenesis can commence or improve.

Alternatives to weight loss as a means of regulating the menstrual cycle include oral contraceptives or cyclic progestins. By placing an anovulatory patient on oral contraceptives or giving her progestins on a monthly basis, one replaces the progesterone that the ovary fails to make when the ovulatory cycle is disrupted, and it is possible to lower the incidence of endometrial hyperplasia and carcinoma. Oral contraceptives have the added advantage of lowering serum LH levels which lowers production of ovarian androgen. The estrogens in oral contraceptives stimulate the liver to increase production of SHBG and thereby lower the serum concentration of free androgens and improve hirsutism. Patients with insulin resistance can be placed on an insulin sensitizing agent to lower the serum level of insulin and alter its impact on ovarian androgen production through the IGF-II receptors.

If patients are interested in having children, ovulation induction can be pursued through use of an estrogen receptor blocker, e.g. clomiphene citrate, which will inhibit the negative feedback of estrogen on the hypothalamus and pituitary and allow for increased FSH release. If this fails, FSH itself can be injected to induce folliculogenesis. This can be combined with other therapies such as intrauterine insemination or in vitro fertilization (IVF).

Studies on the effect of obesity on the response to ovarian stimulation have shown conflicting results, but overall they suggest that obesity has adverse effects. A retrospective study evaluating the outcomes in 5,019 IVF cycles revealed that obesity was associated with longer duration of the cycles, increased amounts of medications used, increased frequency of cancelled cycles, and lower numbers of oocytes retrieved.[5] In another retrospective study of 3,586 IVF cycles, pregnancy rates were significantly lower in obese and very obese women compared to women who were not obese (OR 0.73, 95% CI 0.57 – 0.95 and 0.05, 95% CI 0.32 – 0.77 respectively).[6]

CONCLUSION

Obesity has profound effects on the reproductive systems of both women and men, mediated primarily through the endocrine system on multiple levels. Weight loss is the treatment of choice to restore the natural balance to these systems. When weight loss does not occur, oral contraceptives, progestins, and medications that induce ovulation can be utilized.

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