



Case Report

The Impact of Obesity on Fertility

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Abstract

Introduction: The rising prevalence of child obesity has a profound impact on worldwide health. Children who have an increased body mass index associated with diet, sedentarism and genetic influence, results in obesity since early ages. From the embryo stage, the uterine environment promotes expression of genes that predispose degenerative diseases such as diabetes, hypertension and obesity. Obesity during childhood continues at puberty, creating a proinflammatory microenvironment that impacts germ cells directly. Male obesity is associated with altered spermatogenesis and spermiogenesis due to modifications on hormone levels. Female obesity is associated with ovulatory disorders and poor outcomes in fertility treatment, requiring higher doses of medications for ovulation induction. Pregnancy rates vary among studies; however, there is a clear association between obesity and early pregnancy loss. There are several mechanisms explaining how obesity causes fertility problems. The increase in leptin concentration, decrease in adiponectin levels and a variation in kisspeptin expression to reach puberty, all affect the hormonal level and influence germ cell development.

Objectives: To describe the impact of obesity in childhood and the possible negative prognosis on future fertility.

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Methods: Literature search was performed in PubMed from January 2000 to March 2017 using the search terms child obesity, infertility, spermiogenesis, spermatogenesis, ovulation, oocyte and pregnancy rates.

Conclusion: Obesity affects fertility from intrauterine development all the way through adult life. Obesity has multiple effects with respect to fertility and creates a constant pro-inflammatory microenvironment in germ cells, which in turn has a negative impact on reproduction in adulthood of both sexes.

Keywords: Child obesity; Fertility prognosis; Germ cells

Introduction

Obesity is defined as an abnormal or excessive fat accumulation that may impair health in many ways including fertility. The most common method to evaluate fat accumulation is through the Body Mass Index (BMI) which is calculated by using a person's weight in kilograms divided by the square of his/her height in meters (kg/m²) [1].

The classification by age group is:

- **Adults:** WHO defines obesity as a BMI greater than or equal to 30
- **Children under 5 years of age:** Obesity is weight-for-height greater than 3 standard deviations above the WHO child growth standards median
- **Children aged between 5-19 years:** Obesity is greater than 2 standard deviations above the WHO growth reference median

New studies report that the microenvironment in the uterus defines the obesity of the future newborn affecting males in a higher proportion [2,3]. Animal models have demonstrated the expression and suppression of genes associated with the mother's diet that affects the placental microenvironment and promotes obesity [4-6]. These states correlate with the chronic low-grade inflammation and immune system activation accompanied by insulin resistance [7-9]. In the long term, there is a long (intrauterine-pre-puberty-puberty-post puberty) proinflammatory environment on germ cells [10].

Childhood and Puberty

Obesity in childhood is associated with a higher chance of obesity in adulthood, premature death and disability [11]. Obese children are associated with endocrine abnormalities, such as exaggerated adrenarche and hyperandrogenism as well as an increased risk of polycystic ovary syndrome. These events have an important impact at the hypothalamus-hypophysis-gonadal axis and fertility [12,13]. There is also extensive evidence suggesting that excessive adiposity during childhood influences development at a pubertal stage [14]. Excess body weight during childhood has an influence on pubertal development on a timing effect of pubertal onset and hormone levels related to kisspeptin and metabolism [15]. Puberty appearance in obese boys and girls has also been associated with abnormal levels of adrenal and gonadal hormones. Levels of Dehydroepiandrosterone Sulphate

(DHEAS) have been directly associated with body weight in 8-year-old children, where they could contribute to the association between early growth and adult disease risk by enhancing insulin resistance and central fat deposition [16]. Obese peripubertal girls have shown significant hyperandrogenism, by increased levels of total testosterone and free testosterone and decreased Sex Steroid-Binding Globulin (SSBG) compared with non-obese patients [17].

Insulin and Luteinizing Hormone (LH) contribute to increased levels of testosterone in obese peripubertal adolescents, although other factors associated with obesity may also mediate this association. Obesity is associated with low overnight LH pulse frequency in prepubertal and early pubertal girls, whereas by Tanner stages 3-5, LH frequency is abnormally elevated in obese girls, possibly reflecting the effects of hyperandrogenism and resembling findings of adult polycystic ovary syndrome. Interestingly, weight loss has been associated with a significant decrease in testosterone concentrations in obese boys and girls [17]. These suggest that childhood obesity contribute to the appearance of endocrine disturbances during adolescence and increase the risk of developing infertility later in life.

Adult male fertility effects associated with obesity

The adult age male needs to complete a functional spermatogenesis. This process is highly complex and specialized, involving several mechanisms (hypothalamus, pituitary, Leydig cells, Sertoli cells and sex steroids) [18]. Hypothalamic Pituitary Gonadal (HPG) axis is vital for the reproductive function and can be dysregulated with obesity. There is a direct correlation between hypogonadism and obesity, due to higher estrogen levels and hypoandrogenemia, affecting aromatase receptors and Leydig and Sertoli behavior [19,20]. In obesity, testosterone is metabolized to Estradiol via the cytochrome P450 enzyme aromatase in adipose tissue, which elevates estrogen levels [21]. The increase of estrogens has a negative feedback upon the HPG axis via kisspeptin neurons, resulting in a down-regulation of testosterone and thus spermatogenesis [19,22]. Obesity promotes expression of proinflammatory cytokines such as Tumor Necrosis Factor (TNF) and Interleukin (IL)-6 that down-regulates testosterone levels while endocrine changes modify concentration of insulin, Sex Hormone Binding Globulin (SHBG), leptin and inhibin B, all affecting free testosterone levels.

Testosterone is involved in insulin regulation, metabolism of lipids and body composition. Hyperinsulinemia has been shown to have a negative effect on spermatogenesis with a significantly higher level of nuclear and mitochondrial DNA damage. At the same time, increased concentration of estrogen diminishes SHBG levels [23]. Leptin is a hormone secreted by adipocytes to regulate satiety but is also involved in sexual maturation and reproduction [21]. Leptin stimulates Gonadotropin Releasing Hormone (GnRH) secretion; in obesity, excess leptin causes a resistance later in life [20]. The production of inhibin B by Sertoli cells is the most effective marker for normal spermatogenesis. Inhibin B is a growth-like factor which acts in the testes to inhibit Follicle Stimulating Hormone (FSH) production and to stimulate testosterone production by Leydig cells [24]. The reduced levels of inhibin B found in obese males are indicative of seminiferous tubule dysfunction and it is hypothesized to be due to a lower number of Sertoli cells [22]. However, a compensatory increase in FSH levels in response to low inhibin B has not been observed, indicating potential partial dysregulation of the HPG axis [24].

Obesity causes a chronic inflammatory state resulting in formation of Reactive Oxygen Species (ROS) which can induce damage to sperm DNA and membrane, as well as increase stress on the testicular environment [21]. Obesity during childhood increases the insult time creating more profound damage on DNA fragmentation that affects fertilization and embryo development [23].

Adult female fertility effects associated with obesity

In adulthood, females need to complete multiple reproductive functions, such as liberation of the oocyte, completion of meiosis, fertilization, implantation and pregnancy development. All these processes are affected by obesity secondary to a dysregulation at the HPG axis. It is associated with a higher level of proinflammatory cytokines in the follicular fluid [25]. A direct correlation has been established between hypogonadism and obesity due to higher levels of estrogen and hypoandrogenemia that affect aromatase receptors and granulosa cell behavior, causing anovulation and abnormal endometrial receptivity [19].

Ovulation disorders: Most of the ovulation disorders in obese patients are oligo or anovulation. The endocrine activity of the hypothalamus-hypophysis-ovary axis in the prepubertal female will remain dormant until she reaches a critical weight and composition, liberating pulses of kisspeptin and secondly FSH-LH activation that marks the onset of puberty continuing into their reproductive lives [26]. Obesity is associated with Polycystic Ovarian Syndrome (PCOS) which is marked by hyperandrogenemia. Hyperandrogenemia induces apoptosis in granulosa cells, dysregulating pituitary function due to increased aromatase activity in peripheral tissues and an increased negative feedback on gonadotrophin secretion. At the same time, insulin resistance is associated with ovarian steroidogenesis and a decrease of sex hormone-binding globulin and leptin levels [27].

Hormonal alterations associated with obesity affects the endometrium with a higher incidence of endometrial cancer in obese patients [11]. Animal models have shown that leptin and Leptin Receptor (LEPR) play a relevant role in the regulation of implantation. Obesity disrupts leptin/LEPR which may disturb endometrial receptivity and implantation leading to impaired fecundity. The effects of leptin on reproduction are not homogenous and both stimulatory and inhibitory functions have been described [28]. Although it is known that leptin has a complex role in endometrium functionality, basic science and clinical studies are necessary to comprehend the effect of obesity on implantation and early pregnancy.

Conclusion

Obesity is a worldwide problem that affects all ages and the impact on obesity and fertility involves multiples variants that create a constant proinflammatory microenvironment in germ cell that have a negative impact on reproduction. We need to emphasize the role of the hormone axis in both sexes. In males, increased BMI affects the testosterone levels and elevated ROS that damages sperm membrane and DNA. In women, obesity modifies the hormonal axis presenting ovulatory dysfunction and a decreasing endometrial receptivity affecting fertilization rates. Lifestyle modification is important to diminish inflammatory exposure and avoid long microenvironment dysregulation on germ cells.

References

1. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, et al. (2017) Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 377: 13-27.
2. Oken E, Gillman MW (2003) Fetal origins of obesity. *Obes Res* 11: 496-506.
3. Kozyrskyj AL, Kalu R, Koleva PT, Bridgman SL (2016) Fetal programming of overweight through the microbiome: boys are disproportionately affected. *J Dev Orig Health Dis* 7: 25-34.
4. Jennings TD, Gonda MG, Underwood KR, Wertz-Lutz AE, Blair AD (2016) The influence of maternal nutrition on expression of genes responsible for adipogenesis and myogenesis in the bovine fetus. *Animal* 10: 1697-1705.
5. Qiao L, Yoo HS, Madon A, Kinney B, Hay WW Jr, et al. (2012) Adiponectin enhances mouse fetal fat deposition. *Diabetes* 61: 3199-3207.
6. Lewis RM, Demmelmair H, Gaillard R, Godfrey KM, Hauguel-de Mouzon S, et al. (2013) The placental exposome: placental determinants of fetal adiposity and postnatal body composition. *Ann Nutr Metab* 63: 208-215.
7. Carolan E, Hogan AE, Corrigan M, Gaotswe G, O'Connell J, et al. (2014) The impact of childhood obesity on inflammation, innate immune cell frequency, and metabolic microRNA expression. *J Clin Endocrinol Metab* 99: 474-478.
8. Sackeck J (2008) Pediatric obesity: an inflammatory condition? *J Parenter Enteral Nutr* 32: 633-637.
9. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N (2014) Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract* 105: 141-150.
10. Burt Solorzano CM, McCartney CR (2010) Obesity and the pubertal transition in girls and boys. *Reproduction* 140: 399-410.
11. Yanovski JA (2015) Pediatric obesity. An introduction. *Appetite* 93: 3-12.
12. Davidson LM, Millar K, Jones C, Fatum M, Coward K (2015) Deleterious effects of obesity upon the hormonal and molecular mechanisms controlling spermatogenesis and male fertility. *Hum Fertil (Camb)* 18: 184-193.
13. Pandey S, Pandey S, Maheshwari A, Bhattacharya S (2010) The impact of female obesity on the outcome of fertility treatment. *J Hum Reprod Sci* 3: 62-67.
14. Unni JC (2016) Onset of Puberty in Relation to Obesity. *Indian Pediatr* 53: 379-380.
15. Seminara SB (2014) Fatness and fertility: which direction? *J Clin Invest* 124: 2853-2854.
16. Dai YL, Fu JF, Liang L, Gong CX, Xiong F, et al. (2014) Association between obesity and sexual maturation in Chinese children: a multicenter study. *Int J Obes (Lond)* 38: 1312-1316.
17. Marcovecchio ML, Chiarelli F (2013) Obesity and growth during childhood and puberty. *World Rev Nutr Diet* 106: 135-141.
18. Ruwanpura SM, McLachlan RI, Meachem SJ (2010) Hormonal regulation of male germ cell development. *J Endocrinol* 205: 117-131.
19. Rao PM, Kelly DM, Jones TH (2013) Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. *Nat Rev Endocrinol* 9: 479-493.
20. Reis LO, Dias FG (2012) Male fertility, obesity, and bariatric surgery. *Reprod Sci* 19: 778-785.
21. Du Plessis SS, Cabler S, McAlister DA, Sabanegh E, Agarwal A (2010) The effect of obesity on sperm disorders and male infertility. *Nat Rev Urol* 7: 153-161.
22. MacDonald AA, Herbison GP, Showell M, Farquhar CM (2010) The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. *Hum Reprod Update* 16: 293-311.
23. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R (2010) Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril* 93: 2222-2231.
24. Palmer NO, Bakos HW, Fullston T, Lane M (2012) Impact of obesity on male fertility, sperm function and molecular composition. *Spermatogenesis* 2: 253-263.
25. La Vignera S, Condorelli R, Bellanca S, La Rosa B, Mousavi A, et al. (2011) Obesity is associated with a higher level of pro-inflammatory cytokines in follicular fluid of women undergoing medically assisted procreation (PMA) programs. *Eur Rev Med Pharmacol Sci* 15: 267-273.
26. Hussain MA, Song WJ, Wolfe A (2015) There is Kisspeptin - And Then There is Kisspeptin. *Trends Endocrinol Metab* 26: 564-572.
27. Schisterman EF, Mumford SL, Browne RW, Barr DB, Chen Z, et al. (2014) Lipid concentrations and couple fecundity: the LIFE study. *J Clin Endocrinol Metab* 99: 2786-2794.
28. Lin XH, Liu ME, Xu HY, Chen XJ, Wang H, et al. (2015) Leptin down-regulates γ -ENaC expression: a novel mechanism involved in low endometrial receptivity. *Fertil Steril* 103: 228-235.