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GLP-1 Receptor Agonists' Impact on Fertility – A Review

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ABSTRACT

Purpose of Research: The aim of the research is to summarize the impact of GLP-1 analogs on fertility according to clinical studies, particularly in obese or overweight women with PCOS.

Research Materials and Methods: The study is built upon an analysis of current literature, clinical trials, meta-analyses, and systematic reviews as well as press reports from various sources. Data were collected from studies examining the effects of obesity on fertility, as well as the impact of GLP-1 analogs on both fertility and obesity.

Basic Results: GLP-1 analogs promote weight management among obese and overweight patients leading to improvement in their fertility. Furthermore, they improve pregnancy rates in women with PCOS, although further examination is needed.

Conclusions: We observe, GLP-1 analogs are often used in regulation of type 2 diabetes. They have proven their ability to impact a variety of hormonal as well as metabolic pathways. They manage glucose metabolism, appetite, as well as insulin secretion. Alongside their metabolic influence, research demonstrates that GLP-1 analogs may have an effect on the reproductive system, involving fertility via metabolic and hormonal pathways.

Keywords: GLP-1 analogs, fertility, obesity, PCOS

Introduction

Glucagon-Like Peptide-1 receptor agonists (GLP-1RAs) represent quite a new drug class, used in the treatment of type 2 diabetes and obesity, with exenatide being the first one introduced in the treatment of DM 2 in 2005 (1). The mechanism of GLP-1RAs is based on increasing insulin secretion while simultaneously suppressing glucagon secretion, which leads to reducing hemoglobinA1c and fasting plasma glucose concentration, while also helping maintaining glucose homeostasis. These advantages are accomplished without causing hypoglycemia (2). It is confirmed that GLP-1RAs increase the sensitivity of peripheral tissues for insulin (3) (4). Furthermore, GLP-1RAs contribute to reducing body weight through the mechanism of delayed gastric emptying, which is being evidenced during paracetamol absorption tests (5) (6). This phenomenon is associated with reduced postprandial blood glucose in patients with type 2 diabetes mellitus. The postponement in gastric emptying leads to a prolonged sensation of satiety, loss of appetite and therefore lower calorie intake. Studies show, that the loss of appetite is also linked with the GLP-1 receptors' activation in the central nervous system, more specifically in the brainstem as well as the hypothalamus, causing a decrease in hunger (7) (8).

Obesity and fertility

Obesity is a condition characterized by an excessive accumulation of body fat, which is associated with various health complications such as diabetes, cardiovascular diseases, and particular types of cancer (9). In 2022, according to WHO data, 43% of the adult population were obese or overweight, reflecting a significant increase, compared to the 1990 statistic, where the percentage was 25% (43). Research demonstrates that obesity decreases the ability to conceive in both men and women (10) (11). Fertility is a state where it is possible to establish a clinical pregnancy after 12 months of unprotected and regular intercourse. In contrast, infertility is the inability to achieve such outcome after this time period. Among causes of infertility are parental age, hypogonadotropic hypogonadism, ciliary dysfunction, infections, hyperprolactinemia, polycystic ovary syndrome as well as systemic diseases and lifestyle related factors such as e.g. obesity (12).

Obesity impact on men’s fertility

Male obesity leads to hypogonadism. It is associated with a decreased production of sex hormone binding globulin (SHBG) in the liver. An increase in BMI may be inversely proportional to testosterone and SHBG levels. It is also linked to increased adipocyte aromatase activity, converting testosterone to estradiol. Due to these given mechanisms the hypothalamic-

pituitary feedback loop is disrupted leading to reduced release of gonadotropin-releasing hormone (GnRH) thereby lowering luteinizing hormone (LH) and testosterone levels. It is shown that significant weight loss leads to increase in testosterone, SHBG and LH levels (13). Among men, obesity causes significant decline in semen quality. Obese men exhibit reduced sperm concentration as well as total sperm count. For example, Danish military recruits with a BMI >25 kg/m² showed
a 21% and 23.9% reduction in sperm concentration and sperm count, which leads to oligospermia or even azoospermia, respectively (14). Meta-analyses have demonstrated that both, overweight and obese men are associated with reduced sperm quality which includes semen volume, sperm count, sperm concentration, sperm vitality, total motility and normal morphology (13) (15). When it comes to analyzing outcomes of IVF and ICSI methods, the data suggests that obese fathers are less likely to achieve live births. It may be connected with increased sperm DNA fragmentation and decreased mitochondrial activity, among obese and overweight men (13) (16). Another crucial factor affecting male fertility is erectile dysfunction, which is proven to be linked to obesity due to the obesity itself as well as concomitant metabolic disorders (17).

Obesity impact on women fertility

Excessive adipose tissue among women exerts a range of influences on fertility. First of all adipose tissue could be perceived as an active endocrine organ that secretes various hormones and adipokines, including leptin, adiponectin, and inflammatory cytokines (18). Adipose tissue produces aromatase which serves a critical function of converting androgens into estrogens. Elevated estrogen levels impair the feedback mechanism of the hypothalamic-pituitary-ovarian axis (HPO) by suppressing gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus (19). Leptin is a hormone which regulates appetite and affects HPO axis by stimulating the release of gonadotropin-releasing hormone (GnRH) in the hypothalamus, which causes the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland (20). During obesity, leptin resistance develops, impairing its ability to stimulate GnRH, consequently influencing the release of LH and FSH. Such disruption explains the irregular or even absent ovulation in obese women. Other factors interfering with the HPO axis produced by excessive adipose tissue are the above mentioned, inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). They are known to cause chronic low-grade inflammation thus disrupting proper ovarian function, HPO axis balance,

impairing proper ovulation, oocyte maturation and embryonic developmental competency (21) (22). Due to obesity, insulin resistance develops. There are a few mechanisms co-acting in this process such as chronic inflammation, the release of free fatty acids leading to lipotoxicity, as well as general metabolic dysregulations (23) (24) (25). Circulating free fatty acids have the ability to cause apoptosis of various cell types, including oocytes by boosting reactive oxygen species (ROS), which activate mitochondrial and ER stress (21). One of the consequences of insulin resistance is hyperinsulinemia, which has the potential to heighten androgen production in the ovaries. Hyperinsulinemia is strongly connected with Polycystic Ovary Syndrome (PCOS) and affects oocyte development thereby compromising embryo quality and decreasing endometrial tolerance that can lead to problems with embryo implantation, which could naturally lead to a decreased rate of clinical pregnancies. Studies have shown women overweight or obese undergoing IVF, have reduced chances of implantation and pregnancy (18) .

How PCOS affects woman fertility

Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrine disorder which affects an estimate of 4–18% of women during their reproductive years. PCOS is the leading cause of infertility, with 70–80% of affected women experiencing difficulties in conceiving._The mechanisms through which PCOS may accelerate the onset of infertility are complex, involving structural ovarian alterations, metabolic dysregulation as well as hormonal imbalances (26). Infertility in women with PCOS develops through a variety of mechanisms as described below. Women with PCOS exhibit hyperandrogenism. They present with higher testosterone levels, which interferes with ovarian follicle development, that can lead to anovulation. Without the occurrence of ovulation, an immature egg cell (also known as an oocyte), cannot be released, leading to infertility (27). PCOS is linked with an increased secretion of Luteinizing Hormone (LH), compared to follicle-stimulating hormone (FSH). This imbalance between the two hormones can disrupt ovulation as well as follicular development, further exacerbating challenges to fertility (28). Individuals diagnosed with PCOS, tend to display small follicles that unfortunately, are unable to mature and release oocyte, giving themselves a ‘polycystic’ appearance, which results from the arrested follicular development. This leads to infertility and anovulation (28). One of the outcomes of chronic anovulation includes endometrial hyperplasia. This is a consequence of prolonged estrogen levels, with progesterone not counterbalancing it. This interferes with the embryo’s ability to successfully implant itself in the uterine lining, thus preventing pregnancy from taking place (29). A substantial number of women affected by PCOS

have insulin resistance. A condition in which the body's cells become less responsive to the effects of insulin. In order to compensate for this dysfunction, the pancreas produces additional insulin, however this further leads to hyperinsulinemia. This phenomenon can cause hyperandrogenism as the ovarian androgen production is stimulated. In addition, inhibition of hepatic synthesis of sex hormone-binding globulin (SHBG) is observed, which all together increase free testosterone levels, ultimately disrupting ovulation (30). Another complication which occurs due to PCOS is low-grade inflammation in the endothelium, being the result of abnormal glucose and lipid metabolism (29).

Cooperation between GLP-1 analogs and the reproductive system

GLP-1 analogs are proven to have an effect on hypothalamus, which has GLP-1 receptors. GLP-1 analogs stimulate GnRH release, Kisspeptin neurons in the hypothalamus respond to GLP-1 stimulation which leads to pulsatile release of GnRH. During the pre-ovulatory period, expression of GLP-1 receptors in the hypothalamus is the highest, which leads to boosted reproductive ability (31). GLP-1 analogs have an influence on hormonal pathways, owing to their ability on regulating reproductive hormones including follicle-stimulating hormone (FSH) as well as luteinizing hormone (LH) which are both crucial in order to attain normal ovulation and most importantly, proper ovarian functioning. When it comes to pituitary gland, direct GLP-1 stimulation is less prevalent than in the hypothalamus. The LH release is mostly caused by GnRH secretion. Studies show, rats had experienced a notable rise in preovulatory LH levels as a result of acute GLP-1 treatment, strengthening its significance in regulating reproductive hormones (32). In a 16-week prospective, randomized, open-label study with 30 obese men treated with liraglutide 3.0 mg, results demonstrate fundamental elevation in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels (33). Study on rats with PCOS have shown that administration of GLP-1R agonists increases the number of granulosa cell layers, improves ovarian reserve and decreases dilated follicles, therefore it was able to reverse polycystic ovary morphology (34). In a meta-analysis on women with PCOS, a 90-day treatment with liraglutide led to a reduction of BMI −1.65 (0.72–2.58) Kg/m^2 and in approximately half of examined women, it led to decrease of serum testosterone concentration (35). Though it remains uncertain whether the impact of GLP-1 analogs on hyperandrogenism is due to a BMI reduction or their direct action on the ovaries (31). GLP-1 agonists exert anti-inflammatory effects in ovaries through their interaction with GLP-1 receptors as well as reducing body weight and adipose tissue, which are both responsible for inflammation (31). Women suffering from PCOS may present endometrial abnormalities that can result in

implantation impairment (36). Among rats with Streptozocin induced diabetes, exenatide decreased inflammation and oxidative stress in the endometrium leading to reduced histological degeneration and fibrosis (37). The key role of GLP-1 analogs is weight management, reducing adiposity and improving insulin sensitivity, three key factors for facilitating fertility and hormonal balance. Metabolic abnormalities and obesity have a significant impact on hormonal imbalances, therefore worsening fertility health. These analogs have been studied to improve insulin sensitivity, aid with weight management and maintain hormonal balance, that all together promotes fertility. A range of reproductive tissues, including uterine horns as well as ovaries, express GLP-1 Receptors, highlighting its role in regulating reproductive functions (38). Even though GLP-1 analogs are contraindicated during pregnancy, research suggest that GLP-1 administration, during preconception period in women with PCOS reported higher pregnancy rates following the discontinuation of GLP-1 analogs (39) (40).

Cases

Recently there have been more common press reports about a phenomenon of 'Ozempic babies', (44) (45) (46) regarding unexpected pregnancies among women with PCOS, who suffer from challenges in conceiving. Certainly the reports are anecdotal and further clinical validation is needed. The clinical study in 2008, examined 42 overweight women with PCOS as well as oligo-ovulation, after 24 weeks of exenatide, metformin or combination of both. All participants had shown an increase in their ovulation rate, however the biggest increase was observed in those who received the combination therapy - 86 %. (41) In 2017, a randomized clinical trial with 72 overweight women with PCOS was conducted where the data had demonstrated that after 26 weeks of liraglutide administration, the ovarian volume decreased by -1.6 ml and the bleeding ratio improved when compared with the placebo group (42). In a study involving 176 overweight/obese women with PCOS, who were treated for 12 weeks with either exenatide or metformin, pregnancy rates experienced a notable increase in those treated with exenatide (43,6%), when compared with those treated with metformin (18,7%) (39). Another research examined 28 obese women with PCOS. Before IVF procedure, they were treated with liraglutide and metformin or with metformin alone for 12 weeks. The results revealed that the cumulative pregnancy rate over 12 months of observation was 69%, in those receiving GLP-1 agonists and metformin at the same time, compared to 36% in those receiving metformin alone (40).

Summary

GLP-1 receptor agonists, used to treat obesity as well as type 2 diabetes, facilitate an increase in insulin secretion, delay gastric emptying and suppress glucagon, all leading to not only weight loss, but ultimately, improved metabolic health. Obesity notably impairs fertility in both women and men, disrupting hormone levels, ovulation, embryo implantation and sperm quality, oftentimes worsening certain conditions such as PCOS, which can involve hyperandrogenism, insulin resistance and hormonal imbalances, that all disrupt endometrial receptivity and ovulation. GLP-1 receptor agonists have a positive impact on fertility through enhancing insulin sensitivity, managing reproductive hormones, aiding weight loss and decreasing inflammation. Research reveals, women with PCOS who were treated with GLP-1 receptor agonists, display higher pregnancy rates and ovulation, especially when combined with metformin, making them favorable for preconception care, even though they are contraindicated during pregnancy.

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