WOLSZCZAK, Marta, WOŁODKIEWICZ, Hanna and SZMIT, Jakub. The Impact of GLP-1 Receptor Agonists on Women's Reproductive Health: A Review. Journal of Education, Health and Sport. 2025;82:60194. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.82.60194
https://apcz.umk.pl/JEHS/article/view/60194

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 09.04.2025. Revised: 25.04.2025. Accepted: 01.06.2025. Published: 05.06.2025.

The Impact of GLP-1 Receptor Agonists on Women's Reproductive Health: A Review

Authors:

Marta Wolszczak (MW)

Affiliation: Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

ORCiD https://orcid.org/0009-0005-6072-8524

Mail: wol.marta97@gmail.com

Hanna Wołodkiewicz (HW)

Affiliation: Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland ORCiD https://orcid.org/0009-0000-5166-6855

Mail: hwolodkiewicz@gmail.com

Jakub Szmit (JS)

Affiliation: Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

ORCiD https://orcid.org/0009-0000-0001-7425

Mail: s082739@student.wum.edu.pl

Abstract

Introduction:

GLP-1 receptor agonists (GLP-1RAs) were originally intended for the treatment of type 2 diabetes. However, they quickly proved to be effective in weight reduction and became an option for obesity therapy. A large group of patients using GLP-1RAs are women of reproductive age struggling with obesity, PCOS, or type 2 diabetes. Unfortunately, the safety of these substances in pregnancy and their influence on fertility, fetal health, and lactation remains unclear.

Aim of the study: The aim of this review is to assess the effects of GLP-1RAs on women's reproductive health, particularly on fertility, pregnancy outcomes, teratogenicity, lactation, IVF procedures, PCOS, and sexual function. The review aims to identify both potential benefits and risks associated with GLP-1RAs therapy in women.

Materials and methods: This narrative review was conducted using PubMed and PMC databases with the following search terms: ' 'GLP-1 receptor agonists' ', ' 'GLP-1RAs gynaecology' ', ' 'GLP-1RAs pregnancy' ', ' 'GLP-1RAs fertility' '.

Conclusion: Available data suggest that GLP-1RAs may improve fertility in women, especially in patients with PCOS, by reducing body weight and improving metabolic profile. The insufficient evidence for the safe use of these drugs in pregnancy and reports of teratogenic effects in animals encourage caution. It is recommended to use effective contraception during therapy with GLP-1RAs and to discontinue these drugs several weeks before pregnancy. Further studies are necessary to determine the long-term effects of GLP-1RAs and to formulate treatment guidelines for women of reproductive age.

Key words: GLP-1; GLP-1 receptor agonists; semaglutide; fertility; pregnancy; lactation

Introduction:

Although GLP-1 receptor agonists were originally developed to treat type 2 diabetes, they quickly proved to be much more effective in controlling body weight than other available anti-obesity therapies. Since then, their use in weight loss has grown rapidly, and the media has been paying more and more attention to them (1). A large group of patients using GLP-1RAs are women of reproductive age struggling with obesity, polycystic ovary syndrome (PCOS), and type 2 diabetes. Moreover, it cannot be overlooked that many patients use this therapy as a supplement to diet and physical activity to reduce excess weight and achieve their dream figure. GLP-1RAs used in obesity therapy include semaglutide (Ozempic, Wegovy, Rybelsus), liraglutide (Victoza, Saxenda), exenatide (Byetta, Bydureon), and tirzepatide (Mounjaro) (2). According to the current state of knowledge, there is insufficient evidence to confirm the safety of GLP-1 receptor agonists in pregnancy, which is why it is so important to

raise awareness of this topic among women and educate patients about the use of effective contraception to avoid accidental exposure to the drug during pregnancy. There is a great need for research that would help better understand and clarify the effects of these drugs on fetal development, including the risk of teratogenicity, miscarriage, fetal growth retradation, preterm birth and placental and breast milk drug passage, as well as on the metabolic status of the mother during pregnancy and her glycemic control (3). The aim of this literature review is to comprehensively assess the effects of GLP-1 receptor agonists on women's reproductive health, with particular emphasis on aspects such as fertility, pregnancy outcomes, risk of congenital defects, lactation, effectiveness of IVF procedures, PCOS, and sexual function. The review aims to identify both potential benefits and risks associated with GLP-1RAs therapy in women, mainly of reproductive age.

Methods:

This narrative review was conducted using PubMed and PMC databases with the following search terms: ' 'GLP-1 receptor agonists' ', ' 'GLP-1 gynecology' ', ' 'GLP-1 pregnancy' ', ' 'GLP-1 fertility' '. Relevant publications were analyzed. Only articles in English were considered. Publications regarding the effect of GLP-1RAs on metabolic, hormonal, and reproductive parameters in women were analyzed, and data on teratogenicity, drug transfer through the placenta, and into breast milk were also assessed.

Results and Discussion:

1. Overview of GLP-1 Receptor Agonists (GLP-1 RAs)

GLP-1 is a molecule that occurs naturally in our body and is an endogenous incretin hormone secreted in response to food intake by enteroendocrine L-cells located in the small intestine (4). Incretin hormones are secreted at a constant low level, stimulating the beta cells of the pancreas to secrete insulin and control sugar levels in the body. Incretin hormones are secreted at a constant low level, stimulating the beta cells of the pancreas to secrete insulin and control the body's sugar levels while inhibiting the release of glucagon and gastric emptying (5). GLP-1 receptor agonists directly activate areas of the brain involved in appetite regulation, food intake, food preferences, the reward system, and meal completion associated with early satiety and weight loss (6, 7). Currently, GLP-1RAs used in obesity therapy include semaglutide, liraglutide, exenatide, and tirzepatide, which is a dual GLP-1 and GIP receptor agonist (1). These drugs differ in dosing, administration frequency, and potency. The advantages and disadvantages of each of these drugs are not yet fully defined, and the impact of the adverse effects of these drugs still needs to be studied (8). Börchers and Skibicka (9) in their literature review report that both clinical and preclinical studies indicate that women respond more strongly to GLP-1RAs therapy and often achieve greater weight loss than men, although this does not always translate into better glycemic control. This difference may be since estrogens can enhance the effects of GLP-1 on insulin sensitivity and appetite suppression. This has been supported by preclinical studies in animal models, where removal of the source of estrogen by ovariectomy in females attenuated the effects of GLP-1 in

controlling hunger and satiety. The same phenomenon can be noticed in post-menopausal women, who often gain weight. It turns out that GLP-1 receptors can also be found in the reproductive system of mammals. GLP-1 has anti-inflammatory and anti-fibrotic effects on the testes and endometrium, which may counteract disorders related to obesity, diabetes, and PCOS. What is more, GLP-1RAs can improve ovarian morphology in women with PCOS and lower their androgen levels. Common side effects of GLP-1RAs include gastrointestinal tract symptoms such as nausea, vomiting, and diarrhea (10). It turns out that women are more likely than men to experience side effects of GLP-1 analogues, especially those related to the gastrointestinal tract, such as nausea and vomiting, which more often results in discontinuation of therapy in this group of patients. Preliminary studies also suggest that women may be more susceptible to the adverse effects of GLP-1RAs related to depression, anxiety, and eating disorders such as bulimia or anorexia. Due to these noticeable sex differences, additional studies are needed, especially with clearly separated sex groups, both in animal models and in humans (9).

2. Impact of GLP-1 RAs on Fertility

It has been shown that weight loss in general, as a standalone prognostic factor, can improve fertility. For women struggling with conception, a 5-10% weight loss is recommended (11). For this reason, it can be concluded that GLP-1RAs use, due to their effect on weight loss, leads to improved fertility, which makes it possible to assess the risk to the mother, fetus, and newborn after exposure to these drugs (12). However, the website of the manufacturer of the drug containing semaglutide still contains information recommending discontinuation of semaglutide 2 months before a planned pregnancy, due to the unknown outcome on the unborn baby or lactation (12, 13). A meta-analysis conducted by Zhou et al. (14) showed a significant improvement in natural pregnancies after GLP-1RA intervention, and longer duration of GLP-1RA use led to better menstrual cycle regularity, which can also be considered a beneficial factor in improving fertility. Interestingly, semaglutide may also improve reproductive outcomes in men. In the study by Gregoricˇ et al. (15), semaglutide treatment in a group of men with obesity, type 2 diabetes, and functional hypogonadism, in addition to improving metabolic status, also significantly improved sperm morphology. Improved physical and mental well-being was also observed. Similarly to women, losing weight in men is crucial for improving hormonal parameters, but it seems that semaglutide may have an additional, direct effect on spermatogenesis, through anti-inflammatory effects and better energy expenditure of Sertoli cells.

3. Use During Pregnancy and Pregnancy Outcomes

Unintentional exposure to GLP-1 receptor agonists has been increasing significantly recently due to the high popularity of these drugs among women of reproductive age. Simultaneously, the use of semaglutide may improve fertility in these women through weight loss. Discontinuation of the GLP-1 receptor agonists during pregnancy may cause rapid maternal weight gain and result in obstetric complications. Unfortunately, medical care for such women is difficult due to limited scientific evidence related to the effect of these drugs on pregnancy

outcomes (16). In March 2025, Kolding et al. (16) published the results of their study on a cohort of 100,000 pregnancies and presented the effect of semaglutide on pregnancy and neonatal health. Semaglutide-exposed pregnancies did not show an increased risk of malformations compared to solely insulin-exposed groups and unexposed pregnancies. However, semaglutide-exposed pregnancies showed an increased risk of preterm birth, macropsia, neonatal hypoglycemia, and jaundice compared to pregnancies not exposed to either semaglutide or insulin. The risk in the semaglutide-exposed group was similar to that in insulin-exposed pregnancies, which may have been due to the concomitant use of semaglutide and insulin and the generally higher age and BMI among these women.

In 2023, Skov et al. (17) presented a case of a 31-year-old woman who was exposed to semaglutide in early pregnancy. The mother was treated up until GW 3+4, and since the half-life of semaglutide is approximately 1 week, it is assumed that there was exposure to semaglutide for several weeks during her pregnancy. However, the semaglutide therapy used in the patient was aimed at treating PCOS, and the doses were lower than those used in the treatment of obesity, reaching 1 mg/week one month before conception. Thanks to preconception therapy, the patient lost 27 kg, reaching a body mass index (BMI) of 29, then gained a lot of weight during pregnancy at a rate of 1 kg/week, reaching +35 kg on the day of delivery. All prenatal screening tests were normal, and the patient did not have gestational diabetes. The baby's birth weight was 5.32 kg (+38%). The authors predict that the fetal macropsia could have been influenced by the high and very rapid maternal weight gain caused by discontinuation of semaglutide therapy. On the other hand, preclinical studies in animal models suggest that rapid weight loss in mothers may influence the risk of pregnancy loss and low birth weight of the fetus.

A condition associated with high-risk pregnancy is preeclampsia (PE) and eclampsia. To date, there is no specific treatment for PE if it has already developed. For this reason, the main medical intervention in this area is prophylaxis and prevention of the development of PE,and reducing the risk of maternal morbidity and mortality. It is believed that achieving a normal BMI of 18.5–24.9 kg/ m2 may prevent the disease. Due to the lack of sufficient data to clearly determine the effect of GLP-1RAs on the course of pregnancy and fetal development, these patients are advised to maintain weight with an appropriate diet and exercise, if possible (18). Currently, it is recommended to discontinue semaglutide two months before the planned conception. Perhaps in the future, the use of GLP-1RAs for the treatment of obesity may also prove to be a preventive measure in the development of preeclampsia and eclampsia and the risk associated with it.

Nausea and vomiting in pregnancy (NVP) is a common complaint in pregnant women, especially in the first trimester. The severe form of NVP is called hyperemesis gravidarum (HG). Okeke et al. (19) published the first documented case report of HG caused by semaglutide. A 34-year-old patient experienced extreme symptoms of nausea, vomiting, and abdominal pain after self-administration of a high dose of 2 mg semaglutide before she knew she was pregnant. Symptoms resolved within 6 days, which is consistent with the half-life of

semaglutide and suggests a direct relationship between the severity of symptoms and the drug. This case provides an alternative reason why GLP-1 analogues should not be used by pregnant women, especially without medical supervision.

4. Teratogenicity and Congenital Anomalies

Animal studies have shown that exendin-4, the synthetic equivalent of exenatide, does not cross the placenta in healthy mice. Exposure to other GLP-1RAs in mice resulted in dose-dependent effects, leading to reduced fetal weight and growth, delayed ossification, skeletal malformations, internal organ anomalies, and an increased risk of fetal death (12, 20). These defects are thought to be related to reduced maternal food intake, poorer nutrition, and reduced body weight rather than a direct teratogenic effect of GLP-1 analogues (20). In rats and rabbits exposed to doses of liraglutide much higher than the human dose, fetal malformations and fetal growth retardation occurred, often resulting in fetal death at the highest doses (12, 20). In a systematic review by Muller et al. (20), among the reports of GLP-1 analogues used in pregnancy, there is a case report of a woman taking liraglutide throughout pregnancy, whose cord blood levels were measured 3.5 hours after the last dose. The results indicate that there is no significant maternal transfer of liraglutide to the fetus, at least 3.5 hours after administration. Another case report of a woman taking exenatide during the period of fetal organogenesis stated that she gave birth to an anatomically healthy child. Ex vivo experiments also confirm that placental transfer of the drug is negligible.

According to Zipursky et al. (21), patients should stop taking GLP-1 receptor agonists 1-2 months before planned pregnancy because of the preclinical studies in animal models that have shown teratogenic effects of these drugs at doses similar to those used in humans. At the same time, two small observational studies in humans have not shown an increased risk of major birth defects in newborns taking these drugs before conception or in the early weeks of pregnancy. However, the data is limited. Dao et al. (22) published the results of a multicenter, observational, prospective cohort study of the effects of GLP-1RAs in early pregnancy. Their study found no specific pattern of birth defects in a group of 168 women exposed to GLP-1RAs in the first trimester, and the rate of major defects was comparable to a reference group of women with diabetes. The study did not find an increased risk of miscarriage, but did note a higher rate of abortion in the GLP-1RA group, which may be related to concerns about the potential risk to the fetus in unplanned pregnancies. Cesta et al. (23) also reported that in their study, there was no increased risk of major congenital malformations in children of mothers with type 2 diabetes treated with GLP-1RAs compared with the insulin-treated group.

5. Influence on Maternal Metabolic Health

Discontinuation of GLP-1RAs may lead to a rebound effect and rapid and significant weight gain. Given that obesity in pregnant women is associated with additional adverse pregnancy complications such as gestational diabetes, gestational hypertension, and even pregnancy loss, the goal of cooperation between the physician and the women of reproductive age is to

achieve optimal body weight in the period before planned conception and to ensure controlled and adequate weight gain during pregnancy (21).

6. Lactation and Breastfeeding

Pregnancy is associated with excessive weight gain in many women. With the growing popularity of GLP-1 analogues in obesity therapy, we can expect the use of these drugs in postpartum women who want to return to their pre-pregnancy weight. Interestingly, human GLP-1 is naturally found in breast milk (24), but the use of GLP-1 analogues by nursing mothers raises concerns about the transmission of these substances into the milk and their impact on the health of the newborn.

The conclusion of the review by Muller et al. (20), based on the data from animal models that showed that GLP-1 analogues can pass into breast milk and cause systemic symptoms in neonates, supports the current recommendation to limit the use of GLP-1RAs in pregnancy and lactation. Until there are results from reliable multicenter randomized trials in humans, they recommend the use of alternative therapies such as metformin or insulin analogues in mothers who require this kind of treatment.

Diab et al. (25) conducted a study examining the transmission of semaglutide into breast milk during lactation in humans. In the study, milk samples from 8 breastfeeding women were analyzed using liquid chromatography and mass spectrometry, which provided highly sensitive results. All samples had drug levels below the lower limit of quantification (LLOQ). The results suggest that the risk of infant exposure to semaglutide through breastfeeding is negligible, which may also be indicated by the fact that children evaluated in this study achieved expected developmental milestones and there was no negative impact on child weight gain, despite an isolated case of decreased appetite and diarrhea in one child. The results of this study support the belief that maternal use of semaglutide is associated with insignificant transfer of semaglutide into breast milk. Nevertheless, it is important to monitor the diet and nutrition of mothers during semaglutide treatment to avoid negative effects on milk production and its composition. Zipursky et al. (21) in their recommendations also pay attention to the low probability of passage of large molecules of GLP-1 analogues into breast milk in high concentrations. However, due to limited data on the human population, experts suggest avoiding GLP-1RAs during breastfeeding.

7. PCOS

Polycystic ovary syndrome (PCOS) is the most prevalent hormonal disorder in young women of reproductive age and stands as one of the primary causes of reduced fertility or infertility (26). PCOS is characterized by great heterogeneity, affecting up to 15% of women of reproductive age (27). The key elements of PCOS pathophysiology are ovulatory dysfunction, insulin resistance, hyperandrogenism, and gonadotropin secretion disorders (28). Due to the occurrence of the chronic anovulatory cycle, PCOS is associated with infertility, early miscarriages, and a higher risk of preterm birth. Currently, metformin, thanks to its multidirectional effect on the hormonal balance, is an important element of PCOS therapy. It

works most effectively in combination with lifestyle changes and, in some cases, with clomiphene therapy (28). GLP-1RA receptor agonists (exenatide, liraglutide, semaglutide) have emerged as a promising therapeutic option for PCOS, due to their beneficial effects on glycemic control, weight loss, lipid profile, fertility, and mental wellbeing (28, 29). In their study, Liu et al. (30) proved that GLP-1 analogue therapy results in more effective weight loss compared to metformin monotherapy, which is also associated with a significant improvement in the general symptoms of people struggling with PCOS. In terms of fertility, using exenatide or low-dose liraglutide before planned conception increased the likelihood of natural conception and improved the success of IVF procedures compared to metformin monotherapy. Moreover, exenatide monotherapy was associated with a higher rate of natural pregnancy, whereas in a study reported by Jenstrele et al. (31), exenatide in combination with metformin has been shown to be more effective than metformin monotherapy in improving cycle regularity, ovulation rate and glucose tolerance (28, 32, 33). Previously mentioned study by Liu et al. (30) also showed that exenatide treatment led to lower levels of inflammatory markers and increased natural pregnancy rates. This may suggest that reducing inflammation in patients is a key factor in improving ovulation regularity and successful pregnancy (29). The researchers also speculate that weight loss, appropriate BMI, and improved metabolic status of the patients, seems to be the main reason for this increase in fertility in patients treated with GLP-1 analogues, but at the same time, the hypothesis of their direct influence on the hypothalamic-pituitary-gonadal axis cannot be ruled out (28). However, when taking care of patients with PCOS, it is particularly important to limit the negative impact of obesity on the reproductive system, due to the fact that excess adipose tissue and substances secreted by it reduce the amplitude and concentration of luteinizing hormone LH, which disrupts the maturation of ovarian follicles. It cannot be denied that GLP-1RAs reduce the calorie intake and body weight of patients, thus reducing these negative effects (29, 34). Maslin et al. (35) also point out that improving cycle regularity and effective ovulation in PCOS patients in whom GLP-1RAs contributed to weight loss may increase the risk of unplanned pregnancies. Despite promising results of studies on GLP-1RAs in patients with PCOS, there is a need for randomized clinical trials using higher doses of drugs and a more diverse group of patients. Expanding knowledge in this area is crucial to fully exploit the potential of GLP-1RAs in PCOS therapy (28, 32, 36).

9. IVF

Obesity in women often worsens the outcome of the IVF procedure, with lower implantation, pregnancy, and live birth rates, as well as higher rates of miscarriage. Losing weight before the procedure may improve outcomes and reduce the number of conception attempts needed (37). In women with PCOS, a massive problem they struggle with is infertility and difficulties with natural conception or IVF procedures. Obesity and insulin resistance, closely related to PCOS, especially in women with a body mass index (BMI) >25 kg/m2, are the cause of IVF failures. In these women, fewer oocytes are obtained in IVF cycles, there is a lower risk of embryo implantation in the IVF procedure, and they require higher doses of gonadotropins and have more miscarriages (28, 32, 36, 38). Salamun et al. (37), in the first study of its kind,

showed that short-term liraglutide therapy in combination with metformin before conception was more effective than metformin monotherapy in increasing pregnancy rates per embryo transfer and the cumulative pregnancy rate in obese women with PCOS who had not previously responded to other weight loss and infertility treatments. Interestingly, despite comparable reductions in body weight and body fat in both groups (average 7 kg per 12 weeks), patients taking liraglutide achieved a significantly higher rate of successful embryo transfers. This may suggest that liraglutide has some additional, as yet unexplained effect on the reproductive system, although data from animal studies suggest it may affect the hypothalamic-pituitary-ovarian axis. Short-term liraglutide therapy before conception may be acceptable, but larger and longer-term studies are needed to confirm the efficacy and safety of GLP-1 agonists in improving reproductive outcomes in women with PCOS and obesity (37).

10. Sexual function

It may seem that achieving a desired body, through calorie deficit, exercising, or with the help of GLP-1RAs, will correlate with increased sexual function and desire. Unfortunately, there is insufficient support in the literature regarding the effect of GLP-1RAs on sex life in both men and women. In early 2025, Tveit et al. (39) in their article proposed a novel perspective on the effect of GLP-1RAs drugs on sexual desire. In their work, they consider an alternative hypothesis that the use of GLP-1RAs may, on the contrary, lead to a decrease in libido and sexual desire. This hypothesis is based on serotonergic neural circuitry. The effect of GLP-1RAs on sexual function is related to the interaction between the activity of GLP-1 analogues and serotonin, particularly through the effect on the 5-HT2C receptor. Increased activation of 5-HT2C receptors may have a negative effect on sexual behaviour and, similarly to the use of SSRIs, may lead to decreased sexual drive and anorgasmia (39). Certainly, further long-term studies are needed to confirm the effect of GLP-1 analogues on sexual function. In order to optimize the care of patients using these drugs, a comprehensive biopsychosocial approach is necessary, taking into account gender differences, individual and genetic variability of GLP-1 receptors. A meta-analysis by Chen et al. (40) showed that GLP-1RAs have a positive antidepressant effect in adults, especially in patients with type 2 diabetes. However, the specific mechanism of action of GLP-1RAs in the context of depression remains unclear, and further high-quality clinical studies are needed.

11. Gynecologic Oncology

Although obesity is a risk factor for the development of many cancers, endometrial cancer is the malignancy most often associated with obesity (41). Moreover, prediction models show that obesity-related factors such as anovulation, nulliparity, polycystic ovary syndrome,

insulin resistance, and diabetes increase the risk of atypical endometrial hyperplasia (AEH) in premenopausal women (42). For premenopausal women with AEH or early-stage endometrial cancer who wish to preserve their fertility, synthetic progesterone mimetics - progestins- are being studied as a therapy for endometrial cancer. They act similarly to natural progesterone by promoting differentiation of cancer cells and inhibiting their division, and inducing apoptosis (43). Unfortunately, despite the initial response to this treatment, some patients experience cancer relapse, suggesting that further research is needed to optimize hormonal treatment for endometrial cancer. Hagemann et al. (44) in their study demonstrated that GLP-1RAs such as semaglutide can enhance the effect of progestins in inhibiting the growth of endometrial cancer cells. The use of GLP-1RAs increases the expression of the GLP-1 receptor in cancer cells and simultaneously increases the expression of progesterone receptors, leading to a so-called positive feedback loop, thus endometrial cells become more sensitive to progesterone. Studies have shown that the combination of semaglutide with levonorgestrel is more effective in inhibiting cancer cell viability and reducing their growth than either substance alone. The article suggests that adding a GLP-1RA drug to progestin hormone therapy can extend the relapse-free period and also support weight loss, offering patients a better prognosis while maintaining fertility (44).

Conclusions:

The literature suggests that GLP-1RAs may have a beneficial effect on reproductive function in women. Weight loss, improving metabolic and hormonal parameters, in some studies, has been associated with improved menstrual cycle regularity, especially in women with PCOS. Available data have not shown a clear association between exposure to GLP-1RAs in the first trimester and an increased risk of major congenital malformations in the fetus. Despite this, due to the teratogenicity of these drugs shown in animal models, GLP-1RAs are in category C, and withdrawal of these drugs several weeks before conception is recommended. Literature supports the thesis that due to their high molecular weight, GLP-1RAs should not cross the placenta or be secreted into breast milk. However, due to the limited knowledge and scientific evidence in this area, further studies are needed to establish clear recommendations for use. Given that GLP-1RAs are currently contraindicated for use in pregnancy, this is an obvious barrier that limits the possibilities of their assessment and testing in people planning to have children or in early pregnancy. For the same reason, it is impossible to create uniform guidelines that could guide the use of GLP-1RAs in women of reproductive age. However, women of reproductive age should not be discriminated against in access to effective obesity therapies, and the task of the physicians, especially the gynecologists, is to provide appropriate care for the patient in terms of contraceptive advice. Considering the rapidly growing popularity of drugs that are analogues of the GLP-1 receptor in the treatment of type

2 diabetes, but also PCOS or obesity, there is a great need for clinical trials examining the effects of these drugs on the health of pregnant woman, fetus and newborns, including short-term and long-term effects on reproductive health.

AEH - atypical endometrial hyperplasia

BMI – body mass index

GLP-1 – glucagon-like peptide-1

GLP-1R – GLP-1 receptor

GLP-1RA(s) – GLP-1 receptor agonist(s)

GW – gestational week

HG – hyperemesis gravidarum

IVF – in vitro fertilization

LLOQ - lower limit of quantification

LH - luteinizing hormone

NVP – nausea and vomiting in pregnancy

PCOS – polycystic ovary syndrome

PE – preeclampsia

Disclosure

Author's contribution:

Conceptualisation and Methodology: MW, HW, JS

Software: Not applicable

Check: HW, JS

Formal analysis: MW, HW, JS

Investigation: MW, HW, JS

Resources: Not applicable

Data curation: MW

Writing-rough preparation: MW, HW, JS

Writing review and editing: MW, HW, JS

Visualisation: MW

Supervision: MW

Project administration: MW

All authors have read and agreed with the published version of the manuscript.

Funding Statement: The Study Did Not Receive Special Funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Conflict Of Interest: The authors declare no conflict of interest.

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