СОВРЕМЕННЫЙ ВЗГЛЯД НА РЕПРОДУКТИВНУЮ ФУНКЦИЮ У ЖЕНЩИН С ИНСУЛИНОЗАВИСИМЫМ САХАРНЫМ ДИАБЕТОМ ОБЗОР ЛИТЕРАТУРЫ

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Аннотация: В последние годы во всем мире наблюдается растущий научный интерес к изучению нарушений репродуктивной функции у пациентов с сахарным диабетом (СД). Это связано с достижениями в лечении заболевания, что, в свою очередь, значительно увеличивает продолжительность жизни пациентов с СД, максимально задерживая начало и развитие тяжелых осложнений заболевания. Одной из актуальных проблем медицины является изучение особенностей протекания репродуктивной функции, особенно у пациенток с СД 1-го типа. В литературе доказано, что нарушения менструального цикла, бесплодие, повышенная патология беременности и родов, значительное сокращение фертильного периода у женщин с сахарным диабетом по сравнению со здоровыми женщинами очень высоки.
Ключевые слова: *сахарный диабет, репродуктивная функция, беременность.*

ИНСУЛИНГА БОҒЛИҚ ҚАНДЛИ ДИАБЕТ КАСАЛЛИГИ БИЛАН ОҒРИГАН АЁЛЛАРДАГИ РЕПРОДУКТИВ ФУНКЦИЯГА ЗАМОНАВИЙ НАЗАР АДАБИЁТЛАРИ ШАРҲИ

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ИНСУЛИНГА БОҒЛИҚ ҚАНДЛИ ДИАБЕТ КАСАЛЛИГИ БИЛАН ОҒРИГАН АЁЛЛАРДАГИ РЕПРОДУКТИВ ФУНКЦИЯГА ЗАМОНАВИЙ НАЗАР.KPTJ.-2023-T.2-№2-M
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Аннотация: Охирги йилларда дунё бўйича қандли диабет (ҚД) билан оғриган беморларда репродуктив функция бузилишларини ўрганишга илмий қизиқиш ортиб бормоқда. Бу касалликни даволашдаги ютуқлар билан боғлиқ бўлиб, ўз навбатида ҚД билан оғриган беморларнинг умр кўриш давомийлигини сезиларли даражада оширади, касалликнинг оғир асоратларининг бошланиши ва ривожланишини максимал даражада кечиктиради. Айниқса ҚД 1-тур билан оғриган беморларда репродуктив функцияни ўзига хос кечишини ўрганиш тиббиётнинг долзарб муаммоларидан бири булиб келмоқда. Адабиётларда ҳайз давринининг бузилиши, бепуштлик, ҳомиладорлик ва туғиш патологиясининг кучайиши, соғлом аёллар билан солиштирганда диабетга чалинган аёлларда туғилиш давринининг сезиларли даражада пасайиши жуда юқори эканлиги исботланган.
Калит сўзлар: *қандли диабет, репродуктив функция, ҳомиладорлик.*

A CONTEMPORARY VIEW OF REPRODUCTIVE FUNCTION IN WOMEN WITH INSULIN-DEPENDENT DIABETES MELLITUS REVIEW OF LITERATURE

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Annotation: In recent years, there has been an increasing scientific interest in the study of reproductive function disorders in patients with Diabetes Mellitus (DM). This is due to advances in the treatment of the disease, which in turn significantly increases the life expectancy of patients with QD, maximally delays the onset and development of severe complications of the disease. Studying the specific course of reproductive function, especially in patients with type 1 CD, is one of the urgent problems of medicine. In the literature, menstrual disorders, infertility, increased pregnancy and childbirth pathology, a significant decrease in the fertility period in women with diabetes compared to healthy women proved to be very high.
Keywords: *diabetes, reproductive function, pregnancy.*

Foreword: Amenorrhea is observed twice as often in women with QD of reproductive age than in healthy women [39]. Spontaneous abortions were reported 1.3 times more often, with a birth rate of 1.59% in female patients with QD and 1.89% in general. The question of the state of sexual function is much better studied in men with IQD than in women. According to some data, sexual disorders occur in 35% of women of reproductive age with IQD, that is, 6 times more often than in the general population, and the frequency of is positively related to the these disorders duration of the disease, insulin doses, and the presence of diabetes complications [40]. Data from other studies show the same frequency of sexual disorders in IQD and healthy women [42,43]. No significant differences were found between subjective and objective parameters of the response to erotic visual stimulation in healthy and IQD patients [57]. The frequency of disorders was not related to the duration of the disease, but the most important factor of self-remission seems to be the improvement of the social situation [43]. Type 2 diabetes (non-insulin-dependent) affects women's sexual sphere (orgasm, love, sexual activity, satisfaction) more than IQQD [55].

Before the introduction of insulin in the treatment of diabetes, pregnancy was excluded in women with diabetes. Until 1922, only 103 reports of diabetic mothers were found in the world literature [24]. Pregnancy, occurring in 2-5% of women with diabetes, resulted in maternal and/or infant death in half of the cases. Naynun's file (1906) recorded only one case of pregnancy with diabetes, and between 1898 and 1922, Joslin observed only 108 cases of pregnancy with diabetes, with a stillbirth rate of 44% [16]. With the improvement of insulin therapy, the situation changed rapidly. In the late 50s, there was an opinion that there were no significant differences in fertility between healthy and diabetic women. According to recent literature, pregnancy IQD observed in 70.5% of women infected with Stillbirths are more common in pregnant women with diabetes (6.3% versus 1.5% in healthy women). There is a difference in the number of women with diabetes who do not want to have children (22.7%) and healthy women (7.5%; data on patients with diabetes were obtained based on a survey of 337 women). The authors probably rightly explain the reluctance of women with IQD to have children due to the fear of pregnancy complications24. It is interesting to hear about the possibility of successful conception in vitro and subsequent embryo transfer to women with QD [50]. According to the majority of researchers, the frequency and severity of various disorders of menstrual function depend on the duration of QD and its level of compensation [4,11]. It is suggested to consider the possibility of pre-diabetes even in women with menstrual disorders of unknown etiology [4]. Other authors deny the existence of complete parallelism between the severity of diabetic diseases, the duration of the disease and the frequency of amenorrhea [13].

There are also ambiguous opinions about the role of diabetes in the formation of sexual function in adolescents. Some authors argue that the age at onset of childhood diabetes is not critical for the timing and physiology of adulthood, as biological maturation with compensated diabetes occurring even at the earliest ages is normal [20,41]. Other authors distinguish the duration of the disease and the severity of diabetes as the leading factors of the disorder of puberty in children with diabetes [6,12]. If the onset of diabetes is long before puberty, then physical and puberty are delayed, but if the onset of diabetes occurs during puberty, it is believed that secondary sexual development proceeds more quickly [14]. In patients older than 14.5 years with average or definite puberty delay, this delay is compensated by 15-16 years [16]. Uterine growth rates were compared in 9-20 year old girls with IQD and their healthy peers. A jump in the growth of the uterus occurred during menarche. In diabetic girls, however, uterine development was slightly delayed, but this leveled off by late puberty [36]. There is evidence that the development of the uterus and ovaries is delayed more often (2-2, 5 times) in patients with severe diabetes compared to patients with moderate diabetes. The duration of the course of the disease was observed from 2.5 to 4 years 29.3% of patients had a significant decrease in the size of the uterus, and in 33% of the ovaries. It was 54.6 and 61.1%, respectively, in patients for more than 5 years16. A number of researchers note a late onset of menarche in girls with diabetes compared to healthy peers [12,24]. Long-term dysmenorrhea is also characteristic for some teenage girls. During the period of long-term decompensation of girls, the cessation of menstruation is observed in the form of secondary amenorrhea. In other data, diabetic girls with dysmenorrhea have preserved their reproductive function [46]. Girls with diabetes duration of less than 5 years had a slight delay in sexual development with menarche. The absence of menstruation was observed in most of the girls whose

duration of diabetes was more than 5 years12. In girls with diabetes, the onset of menarche occurs at an average age of 13.4 years34. Compared to healthy menarche, their appearance is delayed by 0.4-1.3 years. According to a number of authors, the greatest delay is found in patients with diabetes in the period from 5 to 9 years [24,34]. There was a difference of 0.8-2 years in the onset of menarche in girls with onset of diabetes during puberty and after puberty. The frequency of primary amenorrhea was 3.6% in early-onset diabetes, 1.5% in late-onset diabetes and control groups. The frequency of secondary amenorrhea was higher in the group of girls with late onset of diabetes than in the group of girls who developed diabetes before menarche [24].

There are various assumptions about the reasons for the relatively frequent violation of the normal course of puberty in adulthood. Perhaps these disorders are associated with changes in protein homeostasis. Some patients have hypoalbuminemia and hyperglobulinemia6. Enlargement of the liver is not only a sign of decompensation of diabetes, but also a symptom that indicates a high probability of the formation of physical and sexual infantilism syndrome in adulthood [15,27]. Since the metabolism of sex hormones and the synthesis of sex hormone-binding globulin take place in the liver, its condition plays an important role in the development of sexual dysfunction. The effect of QD on gonadal function is particularly clearly illustrated by experimental data. Violation of the estrous cycle was noted in 100% of cases with streptozotocin diabetes in rats [33]. In parallel with progressive hyperglycemia, atrophy of the uterus, follicles and weakening of stereoidogenesis were observed. Alloxan diabetes in rats Due to the absence of the peak of LG when called, the anovulatory cycle can be observed. In the experiment, the relationship between the pancreatic islet apparatus and the gonads was shown. Estrogens have been shown to induce hypertrophy and hyperplasia of pancreatic beta cells and increase insulin production1. In ovariectomized rats, estradiol increased pancreatic islet dry mass and increased total insulin and proinsulin [17]. These data indicate a direct effect of estrogens on the islet apparatus of the pancreas. In rats, marked hyperglycemia and a decrease in body insulin reserves were noted after castration. Resection of the pancreas caused degenerative and atrophic changes in the testicular stroma [18,21]. Insulin has a specific effect on the regulation of testosterone production by Leydig cells. Excess insulin increases testosterone response to LG and stimulates testosterone secretion [35]. It can be assumed that the decrease in the level of sex hormones has a significant effect on the course of diabetes in patients. There is no consensus on the pathogenesis of sexual dysfunction in QD. Many authors believe that sexual disorders in patients with diabetes are a polyetiological disease that includes hormonal, metabolic, vascular and innervation mechanisms. At present, it is not possible to make a clear conclusion whether the sexual dysfunction caused by QD is mainly due to ovarian or secondary hypogonadism due to disturbances in the hypothalamus-pituitary system. The case of primary ovarian genesis is supported, for example, by the fact that ovarian response to LG in rats with alloxan diabetes is lower than in healthy animals [48], possibly due to a decrease in the concentration of cellular LG receptors. However, in humans and experimental animals, there is evidence that exogenous gonadotropins and pituitary gland maintain normal ovarian reactivity to LG-releasing hormone (LGRG).

Estradiol levels are lower in diabetic women with menstrual cycle disorders, and estradiol levels are lower than in diabetic women with normal menstrual cycles. [29,31]. At the same time, a significant decrease in the concentration of estradiol in all phases of the menstrual cycle, menstruation it is also observed in women with diabetes whose cycle is preserved [10,11,58]. Puberty girls with a short duration of diabetes and a regular menstrual cycle have the same cycle in the release of different fractions of estrogens as in healthy women, but the amount of estrogens is observed at a lower level. In girls with QD for more than 5 years, the content of all estrogen fractions in urine is significantly reduced [7,12]. A hypoestrogenic reaction is observed in vaginal cytological smear examinations of women with a menstrual cycle disorder and teenage girls with amenorrhea [39,47]. At the same time, an increase in the level of conjugine in blood serum and a decrease in the level of progesterone in the follicular phase were found in women with normal menstrual cycle. This study was conducted in a small number of young women to identify possible hormonal shifts as causes of increased susceptibility to myocardial infarction [60]. A number of researchers studied the state of gonadotropic function of the pituitary gland in patients with QD and concluded that sexual dysfunction is associated with changes in the secretion of gonadotropins and, first of

all, leutropin. Many studies have found a significant decrease in prolactin (PRL) and lutropin levels in QD patients with various menstrual disorders compared to a group of women with functional amenorrhea without carbohydrate metabolism disorders [31,32]. Data on FSG secretion are unclear. In the literature, there are data on normal and low levels of basal follitropin in QD women [28]. Cyclic secretion of gonadotropins and sex hormones is disturbed during menstruation. Violation of cyclic secretion of gonadotropin and sex hormones was observed during the menstrual cycle. The LG/FSG ratio is significantly reduced in the 2nd half of the menstrual cycle [14]. According to the same author, the increase in the amount of progesterone in the luteal phase of the cycle has a bilateral nature, which is the result of a shift in the secretion of LG, while the maximum concentration of progesterone is almost lower than in healthy women. In both phases of the cycle, the raw estradiol/progesterone ratio decreases significantly.

Many researchers have found a decrease in basal PRL levels in patients with menstrual disorders, but there are reports of a decrease in PRL levels in all women with IQD, regardless of menstrual cycle status, compared to healthy women [14,30,36,58]. The degree of violation of gonadotropin secretion their reaction to LG-RG was studied to determine. It was observed that the response of pituitary gland cells to LG-RG was decreased in IQD women regardless of their menstrual cycle status [30]. No correlation was found between the response of LG to LG-RG and plasma glucose levels, on the basis of which the authors concluded that IQD and reduced LG content in amenorrhoeic patients , suggest that there is no correlation between the level of diabetes compensation. There is also no relationship between the duration of diabetes and the decreased response of lutropin to luliberin30,31, although there is evidence to the contrary. For LG-RG and naloxone, LG response duration was similar in women with less than 10 years of QD and control women, but significantly lower in women with more than 10 years of QD (range 11-20 years). The maximal peak of LG secretion in response to stimulants was negatively correlated with the duration of diabetes [26]. In an experiment conducted on diabetic rats, no differences were found between the levels of gonadotropins in the basal pituitary gland and blood serum between animals in the insulin-treated, insulin-treated, and control groups. At the same time, hypothalamus LG-RG concentrations in rats with QD during diestrus were significantly lower than in the control group, which gave the authors reason to assume hypothalamic-pituitary-ovarian system disorders in animals, changes at the hypothalamic level [25]. The effect of dopamine on the secretion of gonadotropins in humans has not been sufficiently studied. In recent years, clinical observations of patients treated with parlodel in persistent galactorrhea-amenorrhea syndrome have been collected, suggesting that dopamine may play an important role in the implementation of a positive mechanism along the estrogen-LG axis, as well as restore the spontaneous impulse secretion of the LG. The effect of dopamine on gonadotropic function is determined by the level of estrogens in the peripheral blood [5].

A study of episodic or pulsatile gonadotropin secretion in QD patients with preserved menstrual function and amenorrhea revealed a decrease in the frequency and amplitude of LG secretion in patients w ith amenorrhea at a low basal LG level, which allowed the authors to consider the presence of an inhibitory effect of dopamine [30]. The basal level of FSG and its pulsatile secretion did not differ in both groups of patients. Pulsatile secretion of FSG and PRL was not synchronous with GH. Intravenous administration of 10 mg metoclopramide (MTK)— a central dopamine receptor blocker caused an increase in LG and FSG secretion at 30, 45, 60, and 90 min, respectively. Basal and MTK-stimulated levels of PRG were lower in amenorrhoeic diabetic women than in menstruating women. In 6 amenorrhoeic women, oral administration of MTK for 10 weeks resulted in a significant increase in FSG and PRL levels, but no significant changes in LG and estradiol levels. These data differ from the data obtained during the examination of patients with functional amenorrhea (normoprolactinemic) without violation of carbohydrate metabolism, in which increased secretion of LG, FSG and estradiol was observed against the background of long-term oral administration of MTK. It is possible that dopaminergic inhibition of LG-RG secretion is more pronounced in QD patients with amenorrhea. In amenorrhoeic patients, the increase in FSG secretion against the background of long-term oral administration of MTK did not lead to an increase in estradiol secretion, which may indicate a decrease in the sensitivity of the ovaries to the stimulating effect of FSG and, therefore, a violation of the positive feedback mechanism of FSG [30]. Interestingly, cortisol and ACTG levels are significantly increased in normoprolactinemic

amenorrhoeic IQD women and in amenorrhoeic women after MTK D-2 receptor dopamine blockade [23]. It cannot be ruled out that LG secretion can be suppressed as a result of disruption of other neurotransmitter systems besides dopamine. In experimental diabetes in rats, a change in the function of a special neurotransmitter system, in particular, a decrease in the level of serotonin in the hypothalamus, which is involved in the regulation of gonadotropin secretion, was found [44]. The response of PRL to the introduction of specific stimulators of thyrotropin-releasing hormone and MTK secretion turned out to be different. The response of PRL to thyroliberin was the same in QD patients with preserved menstrual function and in QD patients with amenorrhoea, despite a decrease in the basal level of PRL in the latter. In QD patients with amenorrhoea, the response of PRL to MTK was significantly reduced compared to patients with normal menstrual cycles[38,47]. The normal response of PRL to TRG and the reduced response to MTK may be due in part to an increase in hypothalamic dopaminergic activity leading to suppression of pituitary ovulatory mechanisms. Authors suggest that only dopamine receptors and TRG receptors in lactotrophs are affected. This may be primarily the result of a deterioration in the regulation of the number and/or sensitivity (affinity) of receptors as a result of prolonged exposure to high concentrations of dopamine in lactotrophs. Second, the PRL response to MTK and TRG may be mediated by different intracellular transmitters. If so, the intracellular pathway from the dopamine receptor to the PRL pool may be damaged. Third, the rapidly released PRL pool for a dopamine antagonist may be reduced in amenorrhoeic patients due to long-term inhibition by dopamine. A combination of these factors cannot be excluded. The cause of the possible increase in central dopaminergic activity remains unclear [30]. The authors consider ovarian hypofunction to be unlikely given the normal response of the gonads to stimulation of gonadotropin therapy.

Other authors noted a sharp increase in the response of PRL to TRG in 13-19-year-old girls with QD, regardless of the presence of menstrual disorders [47]. Increased activity of hypothalamic opiates inhibiting LG secretion is suggested as a cause of hypogonadotropic amenorrhea in patients with QD. However, studies have been conducted to disprove this hypothesis. Thus, serum levels of gonadotropins were measured during a 4-h infusion of the specific opiate antagonist naloxone against a background of varying degrees of QD compensation. There were no changes in LG or FSG levels, on the basis of which the authors concluded that secondary hypogonadotropic amenorrhea in IQD patients cannot be mediated by increased central opiate tone31. In addition, met-enkephalin and β-endorphin are known to increase PRL secretion, but this was not observed in these patients. Studies have been conducted to determine the relationship between residual pancreatic insulin secretion and hypothalamic-pituitary function in patients with IQD. QD patients with secondary amenorrhea were divided into C-peptide-positive (with residual islet insulin secretion) and C-peptide-negative groups. The nature of secondary amenorrhea in these groups turned out to be different. In the group of C-peptide-positive women, the hormonal profile was consistent with polycystic ovary syndrome: increased levels of LG/FSG, serum an increase in testosterone level, a decrease in the amount of sex hormone-binding globulin, as well as oligomenorrhea and excess weight were observed before diabetes. On the other hand, women in the C-peptide negative group had decreased LG content, LG/FSG ratio, and testosterone content. These results suggest that hypothalamic-pituitary function is affected by the absence of pancreatic beta cell activity in CKD. The authors conclude that polycystic ovary syndrome is independent of diabetes, amenorrhoea with low LG levels is a consequence of diabetes and is strongly associated with the absence of residual insulin secretion [54]. The inconsistency of literature data on the level of gonadotropins in women with IQD and normal menstrual cycle is explained by the same authors by the heterogeneity of the group in the presence of residual secretion of beta cells. As a proof of this position, a study was conducted on the pulsation of LG secretion and its reaction to baserelin (LG-RG) in women with IQD and preserved menstrual cycle. Pulsation of LG secretion was assessed every 10 minutes during the early follicular phase for 4 hours. A lower level of secretion and amplitude of LG pulsation was found in the C-peptide negative group, and a significant weakness of the LG to baserelin compared to the C-peptide positive group was found [53].

In another study, the authors compared the response of LG to LG-RG in the above groups after the improvement of glycemic indicators, the response was lower in C-peptide negative patients. PRL secretion in response to TRG stimulation was independent of residual β-cell function and improved metabolic metabolism [59]. The results,

according to the researchers, reveal a link between residual insulin secretion and hypothalamic-pituitary function, possibly reflecting central insulin secretion. The literature describes the effect of insulin on the production of androgens in ovarian theca-interna cells [22]. Clinical observations and experimental data confirm the hypothesis that insulin has gonadotropic activity independently or in combination with LG and FSG. Insulin is found in follicular fluid. Ovarian hypofunction in patients with IQD (primary amenorrhea, later menarche, anovulation, reduced pregnancy rate) is explained by the lack of insulin secretion sufficient to achieve full steroidogenic potential, the conversion of androgens into estrogens in granulosa cells [52]. Clinical hyperinsulinemia is manifested by hyperandrogenism. Taking into account the effect of insulin on ovarian steroidogenesis, it is possible to explain the frequent combination of hyperandrogenism with various insulin-resistant conditions (genetic defect in the number of insulin receptors, the formation of antibodies to insulin receptors, obesity, sometimes type 2 diabetes). Long-term exposure to hyperinsulinemia can cause morphological changes in the ovaries, such as hypertecosis or polycystosis. The main mechanisms of insulin gonadotropin activity include the direct effect of steroidogenic enzymes, the number of FSG or LG receptors increases, FSG or LG synergism, or nonspecific functional increase of cells [22,52].

Based on the autoimmune genesis of insulin-dependent diabetes, it is impossible to exclude autoimmune damage to ovarian tissue in some cases of amenorrhea. Organ-specific autobodies have been found in many organs and tissues (pancreas, skin, lungs, stomach, cortical layers of kidneys and brain) in patients with QD [3]. In the literature available to us, there are no studies on the detection of autoantibodies specific to ovarian tissue in patients with QD. However, such studies using the ELISA (immobilized antigen immunoassay) method for premature ovarian failure (reduction) syndrome are noteworthy. The authors observed 2 cases of pregnancy with immunosuppressant therapy and a decrease in the titer of antibodies and ovarian tissue [49]. There is no unity in the views of different authors on the way to correct reproductive diseases in QD. Some authors point to a clear delay in sexual and physical development, the need for a clear correction, and recommend anabolic steroids, sex hormones or anabolic agents together with thyroid hormones in addition to antidiabetic treatment [8,9]. However, researchers do not give universal recommendations, which indicates that the problem should be solved individually in each case. Other authors do not consider specific therapy to be effective. Thus, patients with QD between the ages of 13 and 17 underwent 3 months of microfolin therapy without a positive effect, and therefore the authors recommended treatment with multivitamins, general strengthening and physiotherapy [19].

There is also a debate on the medical tactics of menstrual disorders in women of reproductive age. Some authors believe that only long-term permanent compensation of diabetes is necessary, others recommend special stimulation of ovulation. The effect of improving carbohydrate metabolism on menstrual function in women with IQD with secondary hypogonadotropic amenorrhea was studied. After 6 months of intensive insulin therapy, a decrease in the level of glycated hemoglobin, weight gain, menstruation was not seen in any of the patients, there were no significant changes in the serum levels of estradiol, progesterone, dihydroxyepiandrosterone, testosterone, basal PRL and LG-RG stimulated LG or FSG [51]. The data of various researchers show that the circadian rhythm of gonadotropins is not normalized, the response of LG to the administration of LG-RG after the improvement of carbohydrate metabolism [31,56], although the rhythm of a number of other pituitary hormones (STG, ACTG) is leveled against this background [56]. Recognizing the concept of hypothalamus-pituitary level of reproductive function disorders in IQD women, it is necessary to agree with the expediency of specific stimulation of ovulation, in addition to achieving compensation for the disease. At the same time, the authors observed the spontaneous onset of menstruation only with the improvement of QD passage, not reporting a decrease in the amount of glycated hemoglobin. At this stage, an individual approach seems reasonable.

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