

# Gestational diabetes mellitus and its complications, role of desynchronosis in pathogenesis (a review)

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Diabetes mellitus is the most common metabolic disorder during pregnancy. The International Diabetes Federation estimates that one in six pregnant women (16.8 %) has diabetes. The prevalence of this disease in the human population is striking and, according to various sources, accounts for 14–25 % of all pregnant women. Most cases of hyperglycemia during pregnancy (75–90 %) is due to gestational diabetes mellitus (GDM).

Risk factors, etiology and pathophysiology of GDM are being actively studied, but there are still some controversial issues. For example, the development of GDM in the aspect of circadian rhythm disorders. This problem is especially relevant in connection with pregnancy. After all, there is a two-way relationship here – circadian rhythm disorders affect the course of pregnancy, and pregnancy can be the cause of these disorders. In addition, this problem is relevant for women with a history of endocrine disorders, including diabetes mellitus, as there is a clear link between circadian rhythms and the production of hormones, including insulin.

**The aim** of this review was to show the relationship between the development of GDM, its complications, and circadian rhythm disorders in women.

Pregnancy complicated by GDM can have a negative effect on the myocardium and liver. Moreover, this disease has a significant impact on the myocardium of the offspring. GDM also can cause other complications for the mother's health and fetus or newborn. Scientists have identified a fairly significant number of risk factors for GDM. However, circadian rhythm disorders accompanying pregnancy are often underestimated as a risk factor.

In general, there are many controversies regarding the relationship between long / short sleep duration and quality and the risk of developing diabetes, as well as how melatonin and its precursor serotonin affect metabolism in critical organs. Thus, the role of circadian rhythm disorders in the development of diabetes and its consequences is not yet fully understood. It is likely that solving the problem of circadian rhythm disorders will be the key to overcoming a significant proportion of cases of GDM. Therefore, there is an urgent need for further, larger-scale studies to investigate the causal links between circadian rhythm disorders, diabetes mellitus, and pregnancy.

**Key words:**  
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## Гестаційний цукровий діабет і його ускладнення, роль десинхронозу в патогенезі (огляд літератури)

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Цукровий діабет – найпоширеніше порушення обміну речовин під час вагітності. За оцінками Міжнародної діабетичної федерації, в кожній шостій вагітній жінки (16,8 %) виникає діабет. Поширеність цього захворювання в популяції вражає і, за різними даними, становить 14–25 % від усіх вагітних жінок. Більшість випадків гіперглікемії під час вагітності (75–90 %) зумовлена гестаційним цукровим діабетом (ГЦД).

Фактори ризику, етіологію та патофізіологію ГЦД активно вивчають, але окремі питання залишаються дискусійними, як-от щодо розвитку ГЦД внаслідок порушення циркадних ритмів. Особливо актуальною ця проблема є в аспекті вагітності, коли визначають двобічний зв'язок: порушення добового ритму впливають на перебіг вагітності, а вагітність може бути причиною цих порушень. Крім того, ця проблема актуальна для жінок, які мають в анамнезі ендокринні захворювання, зокрема цукровий діабет, оскільки є чіткий зв'язок між циркадними ритмами та продукцією гормонів, як-от інсуліну.

**Мета роботи** – показати зв'язок між розвитком ГЦД, його ускладненнями та порушеннями циркадного ритму в жінок.

Вагітність, ускладнена ГЦД, може мати негативний вплив на міокард і печінку. Це захворювання має значущий вплив і на міокард потомства. ГЦД також може спричинити інші ускладнення для здоров'я матері та плода чи новонародженого. Встановлено чимало факторів ризику ГЦД, але порушення циркадних ритмів, що супроводжують вагітність, часто недооцінюють як фактор ризику.

Дискусійним залишається питання щодо зв'язку між тривалістю сну (довгий чи короткий), його якістю та ризиком розвитку діабету, а також щодо того, як мелатонін і його попередник серотонін впливають на метаболізм у критичних органах. Отже, роль порушення циркадних ритмів у виникненні діабету та його наслідків остаточно не з'ясована. Імовірно, вирішення проблеми розладів циркадних ритмів відкриє шляхи до запобігання й подолання багатьох випадків ГЦД. Тому необхідні наступні масштабні дослідження для вивчення причинно-наслідкових зв'язків між порушеннями циркадних ритмів, цукровим діабетом і вагітністю.

**Ключові слова:**  
десинхроноз, гестаційний цукровий діабет, діабетична кардіоміопатія, печінка.

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Diabetes mellitus (DM) is the most common metabolic disorder during pregnancy. Pregnant women can have either pregestational diabetes or gestational diabetes (GDM). The International Diabetes Federation estimates that one in six pregnant women (16.8 %) has diabetes. Of this number, 13.6 % suffer from pregestational diabetes, Gestational diabetes mellitus (GDM) is a disorder of glucose tolerance of any type of gestational age, ICD-10 code O.24.4) is a disorder of glucose tolerance of any degree that occurred or was first detected during pregnancy. The prevalence of this disease in the human population is striking and, according to various sources, accounts for 14–25 % of all pregnant women. Most cases of hyperglycemia during pregnancy (75–90 %) is due to GDM [1,2]. Risk factors, etiology and pathophysiology of GDM are being actively studied, but there are still some controversial issues. For example, the development of GDM in the aspect of circadian rhythm disorders.

Shift work, sleep / wake disturbances, frequent traveling across time zones – all of these are at the root of circadian rhythm disorders. It follows that this is an inevitable consequence of the modern lifestyle. Given that such a lifestyle is inherent in modern society, it is advisable to study this problem in more depth to further develop methods to prevent negative consequences. This problem is especially relevant in connection with pregnancy. After all, there is a two-way relationship here – circadian rhythm disorders affect the course of pregnancy, and pregnancy can be the cause of these disorders. In addition, this problem is relevant for women with a history of endocrine disorders, including diabetes mellitus, as there is a clear link between circadian rhythms and the production of hormones, including insulin.

## Aim

Therefore, the purpose of this review was to show the relationship between the development of GDM, its complications, and circadian rhythm disorders in women.

PubMed and Google Scholar were searched to make this review.

Gestational diabetes mellitus is glucose intolerance that first occurs or is first diagnosed during pregnancy. This type of diabetes may first appear during the second [3] or third trimester of pregnancy [4]. During pregnancy, the mother's metabolism undergoes significant changes, which affects insulin sensitivity. This effect increases in the second half of pregnancy due to insulin resistance and subsequent hyperglycemia [5].

The main function of the pancreatic  $\beta$ -cells is to produce and secrete insulin in response to elevated blood glucose levels. However, when  $\beta$ -cells lose sensitivity to serum glucose concentrations or become unable to properly secrete insulin,  $\beta$ -cell dysfunction occurs. Thus, GDM is a consequence of  $\beta$ -cell dysfunction in the setting of chronic insulin resistance during pregnancy. Therefore, these processes are crucial in the pathophysiology of GDM. In addition, as a result of chronic hyperglycemia, which is inevitably present in diabetes,  $\beta$  cells suffer even more. The decreased ability of pancreatic cells to hyperplasm also plays a role in the pathophysiology of GDM. During normal pregnancy,  $\beta$ -cells undergo hyperplasia and hypertrophy to ensure the metabolic demands that increase during pregnancy. Since

tissue sensitivity to insulin decreases, blood glucose levels rise. As insulin sensitivity is restored after childbirth and glucose levels decrease,  $\beta$ -cells return to normal. In contrast, in GDM, the mass and number of  $\beta$ -cells do not increase significantly during pregnancy, and therefore the pancreas is unable to meet the increased metabolic needs. When this inability is combined with reduced insulin sensitivity, persistent hyperglycemia develops, which can be leveled after childbirth or develop into type 2 diabetes [6,7].

The dysfunction of the neurohormonal system is also involved in the pathogenesis of GDM. This system controls the body's metabolism and activity. The most important hormones involved in this process are leptin and adiponectin. In addition, the circadian clock has an important impact on the neurohormonal system [8,9].

Oxidative stress and inflammation are also important components in the pathophysiology of GDM. It was found that GDM is characterized by excessive formation of free radicals and impaired mechanisms of their neutralization. Reactive oxygen species (ROS) inhibit insulin-stimulated glucose uptake by tissues. This leads to even more severe hyperglycemia. Under these conditions, the level of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor- $\alpha$  increases. Thus, oxidative stress leads to inflammation, and hyperglycemia mediates between these links [10].

It is important that some organs other than the pancreas can also be involved in the development of GDM and suffer from it. These include the liver, skeletal muscle and myocardium, placenta, and adipose tissue.

**Effect of GDM on the myocardium.** A meta-analysis of data from more than 5 million women showed that GDM remains closely associated with the risk of future cardiovascular events, even in women who did not develop type 2 diabetes after childbirth [11]. Prospective studies have reported that women with GDM have greater relative thickness and mass of the left ventricular wall compared to women with normal pregnancies at 34–39 weeks [12,13]. Physiological hypertrophy of the heart, which occurs during normal pregnancy, is the result of overloading the heart with an increased volume of circulating blood, endocrine changes caused by elevated levels of progesterone and estrogen.

The molecular mechanisms underlying cardiac hypertrophy during pregnancy include activation of the PI3K / Akt (phosphatidylinositol 3-kinase / protein kinase B) and MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) pathways [14]. In the short term, cardiac hypertrophy is a physiological adaptive response of the body. However, in the long term, this becomes a sign of pathology associated with diastolic and systolic dysfunction, arrhythmias, and the development of heart failure. It is important that in healthy women, the size of the heart returns to the pre-pregnancy level within a few months after delivery, whereas pathological hypertrophy is the main manifestation of heart disease in people with type 2 diabetes mellitus (DM2) and occurs even in the absence of vascular complications [15]. Studies on pregnant animals have shown that cardiac hypertrophy is Ca-dependent, which implies activation of the calcineurin-NFAT (nuclear factor of activated T-cells) signaling pathway during normal pregnancy [14,16]. In pregnant animals with DM2, two signaling pathways are activated – CaMKII / HDAC (calci-

um-calmodulin dependent kinase II / histone deacetylase) and calcineurin / NFAT) [15]. It is important that the signaling is initiated in the pre-diabetic, insulin-resistant phase, before the onset of overt hyperglycemia.

Although the mechanisms underlying myocardial hypertrophy during and after pregnancy complicated by GDM are not well known, it can be assumed that some mechanisms are common to hypertrophy in normal pregnancy and DM2. Since calcineurin / NFAT pathway hypertrophy is activated both in type 2 diabetes and in the early stages of normal pregnancy, Nirmal Verma et al. (2021) investigated whether enhanced calcineurin / NFAT signaling contributes to cardiac hypertrophy after GDM-associated pregnancy [17]. Female rats heterozygous for the expression of the human isoform of the pancreatic hormone amylin, in particular in  $\beta$ -cells (HIP-rat), were used as a model of GDM. Under these conditions,  $Ca^{2+}$  / calmodulin-dependent activation of calcineurin phosphatase leads to dephosphorylation of NFAT, causing its translocation to the nucleus, where it activates the transcription of the corresponding gene. The study of calcineurin / NFAT signaling pathway activity in isolated cardiomyocytes, including nuclear and cytosolic localization of NFATc4 (nuclear factor of activated T-cells 4), showed a tendency to decrease the nuclear-cytosolic ratio of NFATc4 immediately (within 1 day) after delivery, which is consistent with data indicating a downregulation of this signaling pathway in late pregnancy [14, 16].

In a normal pregnancy, the activity of this pathway returns to its original level within two months after delivery. It is important to note the significant role of calcipressin-1 (also known as RCAN1 or MCIP1), which is an endogenous calcineurin inhibitor, in activating the calcineurin / NFAT signaling pathway. Its expression in the HIP myocardium of female rats remains significantly elevated even two months after delivery [18]. This may indicate a prolongation of the period of myocardial remodeling in the setting of GDM, because the decrease in calcium content in cardiomyocytes in the postpartum period is much slower [17]. Another calcium-dependent activation pathway, CaMKII / HDAC, plays an important role in the development of myocardial hypertrophy during pregnancy. It involves the release of HDACs from the nucleus after phosphorylation by CaMKII through the expression of the corresponding genes. This mechanism is activated both in normal pregnancy and in GDM. However, in both variants of pregnancy (normal and GDM), the activity of this pathway normalizes two months after delivery in females of both groups [17], which suggests that it is not involved in postpartum myocardial remodeling in animals with GDM.

There is ambiguity in the interpretation of the impact of GDM on the risk of developing heart failure. Some data indicate a positive correlation between GDM and cardiac dysfunction [19], while others deny such a relationship [20]. The denial of such a connection is based on research shortcomings. These shortcomings include the diagnosis of GDM not based on biochemical data, lack of differentiation between perinatal cardiomyopathy and long-term heart failure, neglect of comorbidities (postpartum diabetes mellitus, postpartum hypertension, postpartum coronary artery disease), and insufficient data on cardiovascular risk factors (lipid levels and body mass index, smoking, alcohol consumption, and physical activity). The lack of data on the

subtype of heart failure (HF) for the diagnosis of perinatal cardiomyopathy negatively affects the results of correlation analysis, because the clinical signs and symptoms of HF often coincide with the symptoms of normal pregnancy. There are often no detailed data on the use of medications related to diabetes and HF during and/or after childbirth [21].

Endothelial damage is one of the first consequences of diabetes and a precursor to cardiac damage / dysfunction. Endothelial changes associated with diabetes/hyperglycemia include increased ROS production, impaired nitric oxide (NO) release, and a shift to a proinflammatory phenotype. NO deficiency causes impaired endothelium-mediated vasorelaxation, which can result in diastolic heart failure [22]. A key factor in endothelial damage is mitochondrial dysfunction. In addition to the formation of ROS in endothelial cells through glycolysis, mitochondria play a central role in intracellular signal transduction, calcium homeostasis, amino acid synthesis, and meeting energy needs during proliferation or stress [23]. Mitochondria are also the main source of oxidative stress in endothelial cells due to the formation of superoxide anion during oxidative phosphorylation. In diabetes, mitochondrial ROS production increases, leading to dysfunction, inflammation, and apoptosis [24]. These effects are balanced by the activation of pathways that provide resistance to oxidative stress, such as nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent deacetylases [25]. An additional mechanism by which mitochondria can disrupt endothelial function is the release of mitochondrial DNA (mtDNA) and inflammatory reactions [26].

One of the new ways to investigate the mechanisms of endothelial damage / dysfunction is to study extracellular vesicles (EV). EV are the membrane vesicles that are formed ubiquitously under physiological conditions and under stress. Their subpopulations are micro EV, ecosomes, and apoptotic bodies, which differentiate by their biogenesis, release pathway, size, content, and function. EV of different origin are found in biological fluids and their levels change in pathological conditions, including type 1 and type 2 diabetes [27]. In a study of rats with GDM induced by a diet that mirrored several aspects of human pregnancy with GDM, including excessive weight gain during pregnancy, impaired glucose tolerance, and beta-cell dysfunction, the level of circulating endothelial EV and von Willebrand factor was found to increase more than 3-fold. This was indicative of endothelial stress and was confirmed by a deficiency of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) in the aorta and increased levels of EV-related mtDNA. These data prove that mitochondrial damage may play a causal role in vascular damage associated with GDM. A positive correlation between signs of remodeling, diastolic myocardial dysfunction, and endothelial EV levels demonstrates the important role of vascular factor in the development of heart failure [28].

Interestingly, according to [28,29], an increase in the level of circulating EV of endothelial origin was not accompanied by changes in the total EV index. However, C. Salomon et al. (2016) and M. Arias et al. (2019) reported an increase in the rate of all circulating EV in women with GDM [30,31]. The authors of the study used approaches that focused specifically on small EVs. This may mean that GDM may affect different subpopulations of EVs differently. In the context of the analysis, it is noteworthy to report an

increase in the activity of  $Ca^{2+}$  / calmodulin-dependent protein kinase II beta, which is involved in mitochondrial fragmentation in hyperglycemia [32].

GDM has a significant impact on the myocardium of the offspring. The offspring of mothers with GDM are 20.6 times more likely to demonstrate cardiovascular pathology than the offspring of mothers who had a normal pregnancy. The main cardiac manifestation in such newborns is myocardial hypertrophy, which in severe cases can lead to transient subaortic stenosis and congestive heart failure. Also, the offspring of mothers with GDM have a more significant impairment of cardiac function (biventricular systolic dysfunction), their hearts are rounder. Moreover, the effect of GDM on the morphology and function of the fetal heart is manifested from the second trimester [33].

**The effect of GDM on the liver.** Non-alcoholic fatty liver disease (NAFLD) is defined as an increase in the fat content of hepatocytes in the absence of any secondary cause of steatosis. The prevalence of NAFLD is increasing in parallel with the increase in the prevalence of obesity, metabolic syndrome, and type 2 diabetes [34]. In general, there are few scientific studies on the effect of GDM on the liver. Nevertheless, the literature we have analyzed has revealed some patterns. NAFLD was found to be an independent risk factor for the development of type 2 diabetes. However, NAFLD and type 2 diabetes have a common pathophysiological basis – insulin resistance. An insulin-resistant fatty liver overproduces glucose and very low-density lipoprotein. This activates mechanisms that lead to the depletion of the pancreatic beta-cell reserve, which ultimately leads to the development of diabetes. The steatotic and inflamed liver secretes hepatokines such as fetuin-A, fetuin-B, angiotensin-like proteins, fibroblast growth factor 21, and selenoprotein P, which perform endocrine functions in the extrahepatic space, causing insulin resistance and other adverse effects on glucose homeostasis. It is known that there is a link between a history of GDM and NAFLD in women. However, there are few data on whether pre-pregnancy NAFLD can be a risk factor for the development of GDM. You S. Y. et al. (2021) demonstrated that the presence of NAFLD before pregnancy was associated with an increased risk of GDM, in which patients required insulin therapy. Moreover, a stronger correlation was found in the cohort of women without metabolic syndrome before pregnancy. This confirms the hypothesis that NAFLD is an independent risk factor for CKD, regardless of the presence or absence of metabolic syndrome [35].

**GDM and other complications.** In addition to all the risks described above, GDM can cause other threatening conditions. Among the possible negative consequences for the mother's health are preeclampsia, postpartum bleeding, premature rupture of membranes, and the need for labor induction, cesarean section, and instrumental delivery. For the fetus or newborn, GDM is fraught with antenatal and neonatal death, congenital malformations, preterm birth, macrosomia, neonatal hypoglycemia, neonatal jaundice, respiratory distress syndrome, low Apgar score, and hospitalization in the neonatal intensive care unit [36]. Zhu H. et al. (2019) demonstrated that even a short-term exposure of the fetus to maternal T1D in the early stages of development is sufficient to induce permanent changes in DNA methylation and expression of genes that control insulin secretion. This

suggests a methylation-mediated epigenetic mechanism of GDM-induced intergenerational glucose intolerance. In addition, their findings provide experimental evidence of the long-term positive effect of insulin therapy in GDM on the health of offspring [37].

**The role of circadian rhythm disorders in the development of GDM.** Scientists have identified a fairly significant number of risk factors for GDM. The greatest epidemiologic value is body mass index of 25 and above, pregnant woman's age of 25 years and older, hypothyroidism, polycystic ovary syndrome, and family history of diabetes [38,39]. However, circadian rhythm disorders accompanying pregnancy are often underestimated as a risk factor.

**Circadian rhythms.** The rhythmic control of physiological and behavioral processes is carried out by an endogenous molecular clock located inside the suprachiasmatic nucleus. Afferent neuronal pathways, i.e., those that start from light-sensitive retinal ganglion cells, travel to the suprachiasmatic nucleus, where the circadian oscillator is synchronized with the surrounding signals. In this way, autonomous oscillations are generated that have an approximate 24-hour period, which are circadian rhythms. External signals, such as light-dark cycles, are the triggers for the circadian clock to work, ensuring its synchronization with a sunny day [40]. An autonomous molecular oscillator transmits signals to the body's organs and tissues to ensure vital functions. There are many genes that control the circadian clock. They include *Bmal1*, *Clock*, *periodic (Per)*, and *cryptochrome (Cry)*. The expression of these genes is regulated by the principle of negative feedback [41]. Melatonin plays a key role in synchronizing the internal environment with the external environment (namely, with light-dark cycles), which is formed mainly in the pineal gland. Altered sleep patterns disrupt melatonin secretion and can impair reproductive function. For example, high levels of melatonin are associated with delayed puberty and impaired ovulation, while low levels of melatonin are associated with premature puberty. In addition, melatonin, which is found in ovarian follicular fluid, is believed to protect eggs from oxidative stress due to its antioxidant properties [42]. Sleep deprivation suppresses the secretion of endogenous melatonin, which reduces the level of melatonin in the follicular fluid and exposes the follicles to ROS. This reduces the quality and quantity of eggs, which can lead to infertility. This is confirmed by a study in which scientists report that women with idiopathic infertility had significantly lower levels of follicular melatonin compared to controls, which is associated with increased levels of oxidative stress markers [43].

Given the link between melatonin and reproductive function, scientists have tried to assess the possible therapeutic effects of exogenous melatonin. There is evidence that taking melatonin improves the redox balance inside the follicles, and as a result, improves the results of assisted reproductive technologies [43]. Despite this, the use of exogenous melatonin does not always have a positive effect on sleep disorders in women with infertility. A study of 116 women who underwent in vitro fertilization found that melatonin supplementation did not have a dose-response effect on objective sleep measures in these women [44].

A study conducted on mice found that circadian rhythm disorders can affect fertility independently of the hypothalamic-pituitary-gonadal axis.

lamic-pituitary axis. For example, mice deficient in the Clock and Bmal1 genes suffer from ovulatory dysfunction and reduced fertility [45]. In an experiment using a Clock transgenic mouse model, the formation of the Bmal1-Clock dimer occurred, but the regulation of Per and Cry transcription was lost. This was manifested by a loss of circadian rhythm, as well as an increased incidence of miscarriage. In addition, mice with Per1-Per2 deficiency have a premature decrease in ovarian reserve, irregular estrous cycles, and reduced reproductive performance [46].

The synthesis, secretion, and metabolism of various hormones are synchronized with circadian rhythms and regulated by sleep patterns [47]. For example, gonadotropins, sex steroids, and sex hormone binding globulin (SHBG) show diurnal rhythms in women of reproductive age [48,49]. In the follicular phase of the menstrual cycle, follicle-stimulating hormone (FSH) and luteinizing hormone, estrogen, progesterone, and sex hormone binding globulin are released rhythmically, while in the luteal phase only FSH and SHBG are rhythmic [49]. Disruption of the suprachiasmatic nucleus rhythm, which can occur in sleep disorders, leads to changes in the hypothalamic-pituitary-gonadal axis, resulting in the loss of synchronization of sex hormone release [40], which can contribute to changes in reproductive processes [50]. For example, it can affect puberty, ovarian function, fertility, the success of assisted reproductive technologies, and pregnancy.

The occurrence of circadian rhythm disorders may not be related to pregnancy, for example, working in shifts or frequent changes in time zones. Although in some cases, circadian rhythm disorders are caused by pregnancy. For example, in a study by Mindell et al. (2015), 17 % of early pregnant women and 33 % of late pregnant women reported a total sleep duration of 6 hours or less. This study also shows a significant frequency of complaints such as low back pain, reflux, and difficulty finding a comfortable position. Moreover, these complaints increased with each subsequent trimester of pregnancy [51]. Other studies also indicate that sleep quality often deteriorates during pregnancy due to reduced total sleep duration and non-restorative sleep [52]. In the first trimester, the causes include morning sickness, vomiting, and diarrhea. In the second trimester, fetal movements and esophageal reflux usually occur for the first time. And in the third trimester, pregnant women are most often concerned about nocturia, difficulty finding a comfortable position, back and pelvic pain, symptoms of restless legs syndrome, and sleep apnea. In addition, many women experience sleep disturbances due to anxiety about their baby and childbirth [51]. Thus, a combination of psychosocial, biological, and physical factors can lead to insufficient sleep during pregnancy and circadian rhythm disorders.

Wai Man G. C. et al. (2017) found that the coordinated functioning of the circadian clock is important during pregnancy, as it has a positive effect by suppressing the development of inflammatory diseases, including GDM [53]. Reduced sleep duration and/or quality leads to dysregulation of melatonin secretion and can have a negative impact on health. Importantly, melatonin penetrates the placental barrier and has the ability to accelerate the formation of the fetal suprachiasmatic nucleus and reduce fetal oxidative stress. Since the placenta has the ability to produce

melatonin, the level of this hormone in pregnant women is higher than in non-pregnant women. Moreover, with each trimester of pregnancy, the concentration of melatonin in the blood serum increases, and after childbirth it decreases sharply [54].

Some researchers report that polymorphisms in the genes responsible for melatonin receptor expression can affect insulin secretion and pancreatic glucose sensitivity, causing T2D [55,56]. That is, a decrease in melatonin levels is positively correlated with an increased risk of hyperglycemia. Importantly, melatonin supplementation reduces this risk [57]. At the same time, other studies evaluating the association between sleep duration during pregnancy and the risk of developing GDM indicate that extreme sleep duration (not only too little but also too much) during the first and second trimesters of pregnancy was positively correlated with the incidence of GDM [58].

For example, a study was conducted among pregnant women, of whom 7.3 % suffered from GDM [59]. In this experiment, three groups of pregnant women were compared: 1) women who slept 9 hours/day or more (55 %), 2) women who slept less than 7 hours/day (2 %), and 3) women who slept 7-9 hours/day (43 %). Pregnant women who slept 9 hours or more per day had an increased risk of GDM, while those who slept less than 7 hours had a slightly increased risk [59]. Data from other studies, including large-scale prospective cohort studies, also note that both short and long sleep duration, accompanied by sleep-disordered breathing, positively correlate with the incidence of GDM [60,61,62]. In a study involving 46 women with newly diagnosed GDM and 46 healthy pregnant women matched for age, gestational age, body mass index, and race, women with obstructive sleep apnea had a higher risk of GDM [63]. In addition, the severity of sleep apnea in women with GDM correlates with higher glucose levels at night and in the morning [64].

As you know, impaired glucose tolerance can first appear during pregnancy (GDM) or exist before conception (prediabetes). However, there are little data on the pathogenesis of the latter. Asuaje Pfeifer M. et al. (2022) conducted a study using female New Zealand obese (NZO) mice as a model of GDM. It has been shown that GDM is associated with increased levels of serotonin (5-hydroxytryptamine, 5-HT) in the urine, but the role of this biogenic amine in subpopulations with pre-diabetes remains unclear. 5-HT is synthesized in various tissues, including the islets of Langerhans during pregnancy. In addition, 5-HT receptors are expressed in tissues important for the regulation of glucose homeostasis, such as the liver and pancreas. Interestingly, the researchers found elevated concentrations of 5-HT in the plasma and islets of Langerhans of NZO mice, as well as impaired glucose-stimulated 5-HT secretion. Incubation of isolated islets of NZO females with 5-HT revealed an inhibitory effect on insulin and glucagon secretion. In hepatocytes of NZO females, 5-HT enhances glucose synthesis in the liver, reduces glucose uptake and glycogen content. Treatment with a serotonin receptor antagonist reduced the 5-HT-mediated deterioration in metabolic status. These data indicate that 5-HT is a potential indicator of GDM in mice before conception [65]. Since serotonin is a precursor to melatonin, dissonance arises again. After all, even though melatonin has organ-protective properties, serotonin has a number of the above-described

negative effects on the liver. There is evidence of the negative effect of light desynchronization on myocardial function in pathological conditions.

Given the negative impact of diabetes on the myocardium, especially during pregnancy, it is worth noting that light disturbance also has a negative impact on myocardial metabolism and functional activity. In a rat experiment, it was shown that dark deprivation significantly enhances the pathogenic effect of epinephrine on the myocardium of animals, as evidenced by an increase in the area of cardiomyocyte damage in the model of epinephrine necrosis, high free radical oxidation activity, and a deficiency of antioxidant protection [66], while simultaneously reducing the vagal control of cardiac activity [67].

## Conclusions

1. All these controversies regarding the relationship between long/short sleep duration and quality and the risk of developing diabetes, as well as how melatonin and its precursor serotonin affect metabolism in critical organs, indicate that the role of circadian rhythm disorders in the development of diabetes and its consequences is not yet fully understood. It is likely that solving the problem of circadian rhythm disorders will be the key to overcoming a significant proportion of cases of GDM.

2. Scientists have already investigated main pathophysiology links of GDM development. Also they realize that this disease can impact myocardium, liver and other mother's and fetus' organs. Moreover, scientists have discovered relation between GDM, its complications and desynchronization. Despite many controversial issues regarding the role of circadian rhythm disorders in the development of GDM, there is clear understanding that desynchronization can influence this process.

3. Understanding of cause-effect relations and ability to see and select the main link of pathogenesis will allow to liquidate a pathological process and accelerate the offensive of favorable consequences of illness. Therefore, there is an urgent need for further, larger-scale studies to investigate the causal links between circadian rhythm disorders, diabetes mellitus, and pregnancy.

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