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PRETERM BIRTH IN WOMEN WITH DIABETES MELLITUS

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▪ ***Hypothesis/aims of study.*** Diabetes mellitus (DM) is associated with an increased risk of obstetric complications, including preterm birth (PB). The incidence rate of PB in women with DM is higher than in the general population and amounts to 30–40%. Nevertheless, there are still open questions on the structure of PB, pharmacological approaches to its prevention and treatment, as well as the feasibility of prolonging the timing of glucocorticoid therapy to reduce perinatal morbidity and mortality. The objective of this study was to research the features of structure and clinical approaches in the case of PB in women with different types of DM, based on a literature review.

Study design, materials and methods. The study was performed using literature search, screening, data extraction, and analysis of publications collected in world databases such as MEDLINE, EMBASE, CNKI, and Cochrane.

Results. The rate of PB is the highest in women with pregestational DM: 21–30% in type 1 DM and 19–40% in type 2 DM. The incidence of PB in gestational DM (7–10%) is almost equal to the general population level (7–9%) and depends on the type of diabetes therapy: insulin — 16%, diet — 7%. Risk factors for PB in women with DM are poor glycaemic control, microvascular complications of DM, hypertension, obesity, infection, age, fetal macrosomia, polyhydramnios, and congenital malformations. Adequate glycemic control from early gestation is an important condition for PB prevention. The structure of PB in patients with pregestational DM changes due to an increase in both spontaneous and induced PB proportions. The most common indications for early delivery in DM are preeclampsia, premature placental abruption, impaired renal function in diabetic nephropathy, severe forms of carbohydrate metabolism disorders, diabetic fetopathy, and fetal distress. The risk of fetal respiratory distress syndrome in newborns of mothers with DM is higher than in the general population. The maturity of the lungs of a newborn may be insufficient, even in the case of term delivery. The use of antenatal corticosteroids is effective prophylaxis of respiratory disorders. However, these corticosteroids can increase the risk of neonatal hypoglycemia.

Conclusion. Despite the "term" weight and height, the newborn of a mother with DM may remain immature, therefore, delivery at term is recommended. The gestational age, until which it is advisable to prescribe corticosteroids for pregnant women with DM, and the mode of delivery in the case of PB, remain a matter of debate.

▪ **Keywords:** preterm birth; diabetes mellitus; gestational diabetes; macrosomia.

ПРЕЖДЕВРЕМЕННЫЕ РОДЫ У ЖЕНЩИН С САХАРНЫМ ДИАБЕТОМ

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▪ ***Актуальность.*** Наличие у матери сахарного диабета ассоциировано с повышенным риском развития акушерских осложнений, одним из которых являются преждевременные роды. Частота преждевременных родов у женщин с сахарным диабетом превышает таковую в общей популяции и составляет до 30–40 %. Тем не менее открытыми остаются вопросы структуры преждевременных родов, фармакологических подходов их профилактики и лечения, целесообразности пролонгирования сроков проведения терапии глюкокортикоидами для снижения перинатальной заболеваемости и смертности.

Цель. На основании литературного обзора уточнить особенности структуры и клинические подходы при преждевременных родах у женщин с различными типами сахарного диабета.

Материалы и методы. Литературный обзор и анализ исследований, полученных из ведущих информационных баз данных (MEDLINE, EMBASE, CNKI, Cochrane) за последнее десятилетие.

Результаты исследования. Наибольший вклад в структуру преждевременных родов у женщин с сахарным диабетом вносят прегестационные типы диабета: сахарный диабет 1-го (21–30 %) и 2-го (19–40 %) типов. При гестационном сахарном диабете частота преждевременных родов (7–10 %) незначительно превышает общепопуляционный уровень (7–9 %) и зависит от типа коррекции сахарного диабета: инсулинотерапия — 16 %, диетотерапия — 7 %. Детерминанты как со стороны матери (компенсация углеводного обмена, микрососудистые осложнения сахарного диабета, гипертензия, ожирение, инфекция, возраст), так и со стороны плода (макросомия, многоводие, диабетическая фетопатия, врожденные пороки развития) могут выступать факторами риска преждевременных родов у пациенток с нарушениями углеводного обмена. Адекватный гликемический контроль с ранних сроков гестации — важное условие профилактики преждевременных родов. Структура преждевременных родов у пациенток с прегестационными типами сахарного диабета меняется за счет увеличения доли как спонтанных, так и индуцированных преждевременных родов. Наиболее часто показаниями для досрочного родоразрешения при сахарном диабете являются преэклампсия, преждевременная отслойка плаценты, нарушение функции почек при диабетической нефропатии, тяжелые формы нарушений углеводного обмена, диабетическая фетопатия и дистресс плода. Риск развития респираторного дистресс-синдрома новорожденных от матерей с сахарным диабетом выше общепопуляционного. Глюкокортикостероиды эффективны в качестве профилактики развития дыхательных расстройств, но могут повысить риск развития неонатальной гипогликемии.

Выводы. Несмотря на «доношенные» весо-ростовые показатели, плод на фоне сахарного диабета у матери остается морфофункционально незрелым, поэтому предпочтительно пролонгирование беременности до доношенного срока. Вопросы максимальных сроков гестации, до которых целесообразно назначение глюкокортикостероидов беременным с сахарным диабетом, и выбора оптимального метода родоразрешения в случае преждевременных родов остаются дискутабельными.

▪ **Ключевые слова:** преждевременные роды; сахарный диабет; гестационный сахарный диабет; макросомия.

Background

Over the past decades, there has been a significant increase in the incidence rate of diabetes mellitus (DM) among women of reproductive age [1–4]. The prevalence of pregestational types of DM (PGDM) among pregnant women is 0.2–2.0% [1, 5, 6], and gestational DM (GDM) is from 4.6% to 17.8% [7]. This is characterized by an increase in the incidence of GDM (84% of all pregnant women with impaired carbohydrate metabolism) [8]. The presence of various types of DM in mothers is associated with an increased risk of obstetric complications, and one of which is preterm birth (PB) [1, 7, 9–17].

The frequency of PB in the global population varies depending on the level of welfare and medical and social protection of the state. The frequency of PB in developed countries is 7–9% and in Africa and Southeast Asia up to 12% [10]. The frequency of PB in women with DM is higher at 30–40%. Furthermore, there is a direct relationship between PB indicators and regional characteristics [5, 9, 11–14].

The greatest contribution to the structure of PB in women with impaired carbohydrate metabolism is made by PGDM and types 1 and 2 DM [5, 9, 11–14]. The proportion of PB is from 21% (Sweden and Great Britain) to 30% (Russia and France) in type 1 DM and from 19% (Russia and France) to 40% (Great Britain) in type 2 DM [9, 11–13]. For GDM, the frequency of PB slightly exceeds the general population level at 7–10% [9, 13–15]. The frequency of PB depends on the GDM correction type: insulin therapy is 16% and diet therapy 7% (Table 1) [9, 13].

Risk factors for premature birth of women with DM

Risk factors for PB in patients with impaired carbohydrate metabolism are determinants of both the mother and fetus.

By the mother:

- The compensation criterion of carbohydrate metabolism is an important factor for the successful end of pregnancy in women with various types of DM. Achieving the euglycemic state of pregnant women with various types of DM significantly reduces the incidence of obstetric and perinatal complications. The rates of miscarriages are 17.7%, 33%, and 57–60% when the levels of glycated hemoglobin (HbA1c) are less than 6.5%, between 6.5%

Prevalence of preterm birth in women with different types of diabetes mellitus in different countries
Частота преждевременных родов при различных типах сахарного диабета в зависимости от страны

Country	The study period	Number of patients	The frequency of premature birth						
			type 1 diabetes mellitus		type 2 diabetes mellitus		gestational diabetes mellitus		without disorders of carbohydrate metabolism
		diabetes mellitus/ control	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%
Russia	[9]		35.3%		18.9%		GDM (d) — 9.0%; GDM (I) — 16%		–
Norway	1985–2004 [14]	1307 (DM1) / 1 161 092 (control)	26.4%	4.9 (4.3–5.5)	–	–	–	–	6.8%
France	2012 [13]	1291 (DM1) / 1907 (DM2) / 57 629 (GDM) / 735 519 (control)	30.4%	5.8 (5.2–6.6)	19.0%	3.1 (2.7–3.4)	8.4%	1.2 (1.2–1.3)	7.0%
							Premature birth after 28 weeks of gestation		
							8.0% (OR 1.3); GDM (d) — 7.6%; GDM (I) — 9.2%		6.1%
The Great Britain	2015 [12]	3036 (PGDM)	27.7%	–	39.7%	–	–	–	–
Sweden	1991–2003 [11]	5089 (DM1) / 1 260 207 (control)	21%	5.27 (4.88–5.71)	–	–	–	–	–
Israel	1996–2004 [5]	448 (PGDM) / 17 370 (control)	27.5%	–	23.9%	–	–	–	6.0%

N o t e: 95% CI, 95% confidence interval; OR, odds ratio; DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; PGDM, pregestational types of diabetes mellitus; GDM, gestational diabetes mellitus; (d), diet therapy; (I), insulin therapy.

and 8.0%, and greater than 8.0%, respectively [18].

- Diabetic nephropathy, a microvascular complication of DM, is a significant predictor of PB development because of the high risk of both preeclampsia and placental insufficiency [1].
- Hypertension is associated with a two-fold risk of developing preeclampsia and an increase in the frequency of early delivery [1].
- Obesity is a comorbid condition that causes the development of obstetric complications. The value of the body mass index is directly proportional to the frequency of preeclampsia (odds ratio [OR] 2.37; 95% confidence interval [CI] 1.72–4.12). The presence of obesity and DM is a significant risk factor for PB [2, 3].
- Infection — DM is associated with a high risk of developing infectious complications [19]. Immunosuppression caused by hyperglycemia increases in opportunistic microflora and proinflammatory cytokine and prostaglandin production, which increases the risk of PB [9, 17].
- An age of over 35 years is associated with a high risk of developing preeclampsia and increased incidence of extragenital diseases and use of assisted reproductive technologies. These factors are associated with an increase in the frequency of PB [9].

By the fetal side:

- Fetal macrosomia is the most common complication of pregnancy in mothers with DM. The large size of the fetus causes an overgrowth of the uterus, which is one factor that initiates labor [1, 17].
- Polyhydramnios is a common complication of pregnancy when mothers' carbohydrate metabolism is disrupted. It occurs in 30–40% of cases, especially in the presence of PGDM [1, 9, 19]. The main link in the pathogenesis of polyhydramnios in DM is excessive urination of the fetus due to hyperglycemia. Meanwhile,

the presence of an infection that damages the amniocytes contributes to the active fluid secretion. Overgrowth of the uterus leads to premature outpouring of amniotic fluid or the early beginning of labor. Thus, polyhydramnios affects the increase in PB frequency [17].

- Diabetic fetopathy is a pathological morpho-functional condition of a fetus due to its development in unfavorable hyperglycemic conditions. Diabetic fetopathy is associated with a four-fold risk of hypoxia and antenatal fetal death [9]. The functional state deformity of a fetus in women with uncompensated DM leads to the need for early delivery and increases the frequency of PB [9].
- Congenital anomalies–PGDM in women during pregnancy is associated with a five-fold risk of developing fetal congenital anomalies for an HbA1c level greater than 7% [20]. More than 90% of these defects are detected in the first trimester of pregnancy during the first prenatal screening, which reduces the number of births of children with congenital malformations. However, some women with fetal malformations carry pregnancy up to 22 eeks, which contributes to the structure of PB [1].

Glycemic level as a predictor of a preterm birth

No significant link was found between preprandial or postprandial glycemic level and the PB frequency in women who have physiological indicators of carbohydrate metabolism [21]. However, for mothers with DM, hyperglycemia that existed earlier or occurred during pregnancy is directly associated with an increasing risk of PB [7, 12, 15, 22]. According to the hyperglycemia and unfavorable pregnancy outcome study, the ratio of chances of PB risk increases when the reference values of glycaemia exceeded 1 (OR 1.18; 95% CI 1.12–1.25) and 2 h (OR 1.16; 95% CI 1.10–1.23) after an oral glucose tolerance test with 75 g glucose. There was no such law for fasting glycaemia (OR 1.05; 95% CI 0.99–1.11) [7].

Interestingly, the HbA1c level before pregnancy did not show a predictive value in relation to the risk of PB [22] in a study by Lauszus et al. (2006). However, it revealed an increase in the HbA1c value of more than 7.7% at 8 weeks during gestation, and the risk of premature termination of pregnancy increased sharply to more than 40% [22]. In contrast, if the HbA1c target values are reached and maintained at less than 6.5%, the risk of PB is significantly reduced (from 48.0% to 30.4% in type 1 DM and from 35.7% to 21.6% in type 2 DM) [12].

Structure of PB in DM

The structure of PB in DM significantly depends on many parameters: DM type, correction method, obstetric complications, and fetus state.

According to Köck et al. (2009), the proportion of PB was higher (17.7%) in the PGDM and GDM groups than in the control group (7.3%) [23]. The frequency of induced labor (including delivery by a Cesarean operation) was 35.5% in all PB with DM compared with 14% in the control group [23]. A study by Melamed et al. (2008) revealed that the frequency of PB in patients with PGDM increases up to 26.6% compared with the indicators in the control group at only 6%. This is due to an increase in the proportion of both spontaneous (6.9% vs. 4.8%) and induced (19.6% vs. 1.2%) births [5]. It was found that a greater number of PB in PGDM (73.6%) is due to the need for early pregnancy termination by a surgery. In the group without carbohydrate metabolism disorders, spontaneous labor prevails in the structure of PB (79.9%) [5]. Women with GDM have a slightly higher risk of spontaneous PB than patients without carbohydrate metabolism disorders (relative risk [RR] 1.42; 95% CI 1.15–1.77), but the risk is significantly lower than patients with types 1 and 2 DM [15].

The most common indications for early delivery of the mother at DM are preeclampsia, premature placental abruption, impaired kidney function in diabetic nephropathy, and severe carbohydrate metabolism disorder forms. The most frequently observed indications from the fetal side are diabetic fetopathy and fetal distress [1, 5]. A severe preeclampsia is the main indication for termination of pregnancy up to 37 weeks for women with PGDM in almost half of cases (45%).

The risk of spontaneous PB increases with an inadequate control of glycemic level. Kovilam et al. (2002) showed that a 1% increase in HbA1c levels during pregnancy increases the risk of spontaneous PB by 37% in type 1 DM [24].

Respiratory distress syndrome (RDS) in newborns from mothers with DM

Contribution of maternal DM to the pathogenesis of RDS in newborn

The risk of developing RDS among newborns from mothers with DM is higher than that among the general population of the same gestational terms [13, 25, 26]. Carbohydrate metabolism disorders in pregnant women are an independent factor that has an intrauterine impact on fetal respiratory system development. Because of maternal hyperglycemia, fetal hyperglycemia develops, which causes hyperinsulinemia of the fetus. Inadequate control of carbohydrate metabolism in mothers can result in the fetal lungs to remain morphofunctionally immature even after 34 weeks of gestation [4, 25–27]. In experimental DM models of rats and rabbits, it was shown that the number of type II alveolocytes in the lungs decreases in fetuses against the background of hyperglycemia [28], the synthesis of phosphatidylcholine [29], and the expression of surfactant proteins [30]. Inadequate glycemic control during pregnancy is also associated with low phospholipid levels in the amniotic fluid [31, 32] and late fetal lung maturation [34, 35]. Differences in the surfactant composition of the lungs of fetuses from mothers with and without DM are the most expressed at the gestation period from 36 to 37 + 6 weeks [32].

Other organs that are most affected by metabolic disorders in DM are the fetal heart and liver. As a result of the anabolic action of insulin, myocardial hypertrophy develops antenatally, especially in the interventricular septum area, where the concentration of insulin receptors is increased. Lung immaturity increases the degree of obstruction of the outflow tract of the left ventricle, thereby aggravating the decrease in cardiac output and the phenomenon of congestive heart failure in newborns [4, 33]. Delayed fetal lung maturation increases the risk of developing RDS in newborns with DM, not only in the late PB case [27] but also at full-term birth.

Interestingly, the use of insulin therapy for mothers with DM increases the risk of developing RDS in newborns [13, 25]. This law is valid for both PGDM and GDM. However, the negative impact is not the method of correction of glycaemia but the degree of metabolic disorders, which need an insulin drug prescription.

According to Billionnet et al. (2017), newborns from mothers with GDM on insulin therapy have a higher risk of developing RDS (OR 1.1; 95% CI 1.0–1.3); in addition, there is an increased risk of birth trauma (OR 1.3; 95% CI 1.1–1.5) and cardiomyopathy (OR 1.3; 95% CI 1.1–1.4) [13]. A large French study by Becquet et al. (2015) analyzed more than 18,000 births at a period of more than 34 weeks and found that 2.2% of newborns from mothers without carbohydrate metabolism required treatment in the intensive care unit, 2.1% from mothers with DM on diet therapy, and 5.7% from mothers with DM on insulin therapy [25]. The group of DM on insulin therapy was heterogeneous in relation to the frequency of RDS development in newborns: 9.7% for type 1 and 4.7% for type 2 DM [25].

Thus, the course of GDM, in which it is not possible to compensate for metabolic disorders with the help of diet and need to prescribe insulin therapy, is a predictor of RDS development RDS and newborn maladaptation (hazard ratio [HR] 1.44; 95% CI 1.00–2.08) [25].

Prevention of RDS in newborns from mothers with DM

Antenatal use of glucocorticosteroids (GC) is the main method for preventing RDS in newborns [4, 34, 35]. GC help with the maturation of the fetal lung surfactant system and have several systemic effects. Antenatal use of exogenous GC leads to suppression of the hypothalamus-hypophyseal-adrenal axis of both the mother and fetus [36]. The adrenocorticotropic hormone (ACTH) level of the fetus decreases by almost 50% and is restored only after a week. During ACTH reduction, the fetus and newborn retain the ability to increase the production of cortisol by the adrenal glands in response to stress or exogenous ACTH stimulation [39]. After RDS prevention, the exogenous GC level in the cord blood is increased, and cortisol is reduced [37]. Concentrations of dehydroepiandrosterone sulfate and 17-alpha-oxyprogesterone in the cord blood also transiently decrease after GC use [36]. The fetal cardiovascular system reacts to antenatal GC use by increasing myocardial contractility, cardiac output, and blood pressure [36]. Long-term GC use improves renal blood flow and increases glomerular filtration rate [36].

A serious side effect of GC use is the development of neonatal hypoglycemia (24.0% vs. 14.9% in the placebo group; HR 1.61; 95% CI 1.38–1.88) [41]. After GC use in the fetal cord blood, the concentrations of glucose (3.47 vs. 3.11 mmol/L in the control group) and C-peptide (2.85 vs. 1.19 mcg/L in the control group) increases [37] that increase the risk of fetal hyperinsulinemia and neonatal hypoglycemia.

In hyperglycemic conditions, fetal insulin is actively synthesized in the fetus from mothers with DM. At the moment of crossing the umbilical cord, glucose transport from the mother to the fetus stops. However, it takes time to reduce the production of endogenous insulin, and since gluconeogenesis of the newborn is not yet sufficiently developed, an imbalance between glucose and insulin concentrations in the fetal blood leads to hypoglycemia. In premature newborns, the risk of hypoglycemia increases, which is associated with high energy demand, defective gluconeogenesis, and low glycogen and fat reserves [38]. If the probability of developing neonatal hypoglycemia is about 15% in a population of relatively healthy children, it can reach between 30% and 60% in high-risk populations [38].

The problem of expediency and timing of prolongation of antenatal GC use to prevent the development of respiratory disorders in newborns at risk of developing RDS (pregnant women with DM, planned Cesarean operation, macrosomia, and fetal hypotrophy) remains urgent. This is due to the morphofunctional immaturity of the fetal lungs of newborns from mothers DM. In this case, the need to prolong GC use remains relevant up to 36 weeks, and possibly until delivery [4, 34, 35].

An antenatal late preterm steroid trial showed that GC use between 34 and 36 + 6 weeks in 2827 patients was effective to prevent respiratory disorders in newborns from high-risk groups including DM. The incidence of RDS in newborns after the prevention decreased from 14.5% to 11.6% [39]. However, GC use in this group naturally increased the frequency of neonatal hypoglycemia.

Since GC use increases the maternal glycemic level, GC therapy in women with DM should be made along with an endocrinologist for timely correction of insulin doses.

Pharmacotherapy features for threatening premature birth in women with DM

Gestagens remains to be the main drug in the prevention and treatment of miscarriage. Meta-analyzes show a positive link between the use of all known progesterone medications and reduction of PB risk [40]. However, the influence of gestagens on the level of glycaemia and the risk of developing GDM is relevant.

There is evidence that the use of 17-hydroxyprogesterone is significantly associated with the risk of developing GDM [41]. In the second trimester, the use of micronized natural progesterone to prevent PB does not increase the risk of developing DM in pregnant women [41, 42]. The question of the effect of didrogesterone remains open because of restrictions on its use after 22 weeks of pregnancy [41].

Tocolytic drugs are widely prescribed for treating threatening PB. Meta-analyzes show similar efficacy of beta-adrenomimetics, calcium channel antagonists, and oxytocin receptor blockers for a prolonging pregnancy [43]. Nevertheless, beta-adrenomimetics should be used with caution in the case of mothers with DM because of the greater frequency of development of such a side effect as hyperglycemia [16]. Here, it is preferable to use calcium channel blockers or oxytocin receptors [16].

Invasive manipulations aimed to prevent PB, such as applying a circular suture to the cervix and installing a discharge obstetric peccary, should be made with caution in DM because of the higher risk of infectious complications [9]. Circulate for pregnant women with DM should be used against the background of compensation for the deformity of carbohydrate metabolism and necessary antibiotic prophylaxis [9].

Conclusion

A distinctive feature of the structure of PB in DM compared with the general population is a significant increase in the number of induced PB, which predominates over spontaneous ones.

Adequate glycemic control from early gestation is an important condition to prevent PB of women with DM. High postprandial glycemic values and HbA1c levels of more than 7.7% in early pregnancy are predictive of PB in PGDM [7, 22].

Despite the "full-term" weight–growth indicators, fetus against the background of mothers with DM remains morphofunctionally immature because of the late appearance of surfactant components. For this reason, it is preferable to prolong the pregnancy until a full term. Unfortunately, even after 37 weeks, the lungs of the newborn may be immature, which leads to the development of RDS and an increase in perinatal mortality in DM, not only in premature but also in urgent deliveries. The question of the maximum gestation period before which it is advisable to prescribe GC to pregnant women with DM is still being discussed. GC use in late gestation periods up to 36 + 6 weeks may be effective to prevent respiratory disorders but may increase neonatal hypoglycemia risk.

The optimal method of delivery in the case of PB in pregnant women with DM has not yet been determined. Morphofunctional immaturity of the fetus against the background of DM makes it difficult to solve the issue of delivery in early full term and especially in premature pregnancy. At the moment, there are not enough data on the reliable advantages of one method over another. There is evidence in favor of delivery by a Cesarean operation only in the case of PB in the pelvic presentation of the fetus [44, 45]. Nevertheless, the course of labor in the case of PB in the presence of DM in mothers is not fundamentally different from the course of labor in women without violations of carbohydrate metabolism. Thus, the act of delivery of these women should be conducted in accordance with the accepted norms.

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