

PRENATAL MONITORING OF PREGNANCIES COMPLICATED BY DIABETES MELLITUS

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Abstract: Preconception and prenatal monitoring evaluate the condition of the mother's underlying disease and possible complications during pregnancy. Before conception, patients with diabetes should be informed that suboptimal glycoregulation is associated with reduced fertility and pregnancy losses. The task of the perinatologist in pregnancies affected by diabetes mellitus is to prevent complications of the underlying disease, such as hypoglycemic crises. Another important component of prenatal care in diabetic pregnancies is the recognition and prevention of pregnancy complications such as preeclampsia, polyhydramnios, congenital malformations, fetal macrosomia, and infections.

Keywords: diabetes mellitus, pregnancy, complications, preeclampsia, polyhydramnios.

INTRODUCTION

There are two main problems in planning a pregnancy in women with diabetes. First is how diabetes will affect the pregnancy and the child's health, and the second is how will the pregnancy affect the course of diabetes. Therefore, proper planning of all available procedures is crucial to minimize perinatal and maternal morbidity and mortality (1).

Preconception and prenatal monitoring evaluate the condition of the mother's underlying disease and possible complications. Most patients, according to the experience of clinicians, do not achieve satisfactory glycoregulation preconceptionally, and a large part of pregnant women has undiagnosed diabetes. Before pregnancy, it is important to:

1. Assess glycoregulation and glycosylated hemoglobin, and train the patient to determine the value 5 to 7 times a day with a glycemic meter.

2. Assess normal values of arterial blood pressure.

3. Assess kidney function by biochemical laboratory findings, determination of creatinine and urea clearance, and determination of proteinuria. If proteinuria is present, examine the urine bacteriologically.

4. Assess the state of the retina with an ophthalmological examination of the state of the retina performed by an ophthalmologist specializing in retinal diseases.

5. ECG should be done for women over 35 years old, those with hypertension, nephropathy or peripheral vascular disease, obese, with hypercholesterolemia, as well as if diabetes lasts longer than 10 years. In the case of pathological ECG findings or suspicious clinical circumstances, a stress test should be performed.

6. Assess peripheral and autonomic neuropathy, i.e. loss of sensorium on the lower extremities, heat intolerance, postural hypotension, and gastroparesis.

7. Assess hypoglycemia frequency, severity, and manifestations.

8. Assess any elements of peripheral vascular disease that may be present.

9. Evaluate the function of the thyroid gland (TSH and free T4) in patients with type I diabetes (1, 2).

After assessing the patient's condition, it should be emphasized that strict glycoregulation is the basis of a good pregnancy outcome and the patient should be provided with information, advice, and support.

Pregnancy planning and contraception

From the adolescent period, education about fertility control is especially important for patients with diabetes. Women who have diabetes and are planning to become pregnant should be offered the information:

- what are the risks of complications in pregnancy with diabetes concerning the duration of the disease;
- contraception use until good glycoregulation is established;
- glycemic goals, glucose monitoring, diabetes medications, and diabetes complications must be reviewed before and during pregnancy;
- more time and effort that is needed to keep diabetes under control during pregnancy

Nutrition, nutritional supplements, body mass, and physical activity

Dietary advice is especially important for these patients. If the body mass index is above 27 kg/m², it should be recommended to reduce the body mass according to the established protocol. It is important to highlight the importance of folic acid intake (5 mg per day) until the 12th week of pregnancy to reduce the risk of congenital anomalies of the nervous system (3, 4).

Target preconception glycemic values

Individual glycemic target values should be determined and self-monitoring should be enabled to avoid hypoglycemia. The goal is to maintain HbA1c below 6.1%. It is important to explain the importance of this to the patient (5). If glycosylated hemoglobin is above 10%, pregnancy should be avoided, and reducing this value towards the target of 6.1%, significantly reduces the risk of congenital anomalies. It is preferable that, in the case of planning a pregnancy, the level of HbA1c is determined once a month, and that, if they have not done so by then, they should be trained in self-measurement of blood glucose. If there is a need for more intensive therapy, a more frequent measurement of glycemia is recommended. In patients with type I diabetes, it is necessary to periodically detect ketonemia and ketonuria with test strips (6).

Safety of diabetes medications before and during pregnancy

Metformin can be used safely as sole or adjunctive therapy and can serve as a substitute for insulin. As a rule, other oral medications from the hypoglycemic group are already replaced by insulin in the preconception period. On the other hand, clinical research data indicate the safety of fast-acting insulin analogs (aspart and lispro) for fetuses and neonates. Regarding long-acting insulin analogues, there are in-

sufficient data at this time to make explicit statements (7). Before conception, as well as when pregnancy is confirmed, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists must be stopped, which must be replaced by alternative antihypertensive drugs that are safe to use. The same applies to statins (8).

The most common questions and dilemmas of patients and questions asked:

Does diabetes affect a woman's ability to conceive?

Various abnormalities of the reproductive function of women with diabetes are described. These include delayed menarche and early menopause, delayed ovulation, and an increased incidence of irregular menstrual cycles that occur twice as often compared to control subjects. A positive relationship between the duration of diabetes and delayed menarche was shown, even when maternal menarche was taken into account (9, 10).

The mechanisms that compromise fertility in women with diabetes are not fully understood. They may originate from a reduced response of luteinizing hormone to gonadotropins, a decrease in basal levels of LH and FSH, a decrease in thyrotropin that leads to a drop in circulating thyroxine and a decrease in the synthesis and release of prolactin, or a decreased synthesis of corticosterone. A decrease in ovarian mass has been proven in animal models, in animals where diabetes may have induced a reduced ovarian response to gonadotropins. Decreased insulin-induced progesterone synthesis in granulosa cells in women with diabetes has also been observed, even in cases of good disease control. Improving glycoregulation should improve fertility (11, 12, 13).

Does diabetes increase the risk of early termination of pregnancy?

The risk of spontaneous abortions (SAB) in diabetes is not fully specified. According to some research, SAB rates in diabetic pregnancies are no different from the SAB rates in the general population (14). Several scientists have found a link between increased HbA1c concentrations (an indicator of poor glycemic control) in the first trimester and SAB. Furthermore, SAB is associated with glycemic control in the immediate pre-pregnancy period, more so than in the immediate post-abortion period (15).

The increased risk of SAB in diabetes is most likely related to the adverse environment to which the developing fetus is exposed. This results in dam-

age to the fertilized ovum or the fetus itself, as well as congenital anomalies incompatible with life. Potential mechanisms of SAB may be due to inadequate placentation and vascularization as a result of poor glycemic control, as well as an increased incidence of chromosomal aberrations (16). Whether there is a threshold of hyperglycemia above which the risk of SAB is increased in women with diabetes is a controversial issue. The Diabetes in Early Pregnancy (DIEP) study (17) showed that higher HbA1c concentrations in the first trimester were associated with increased rates of SAB.

Does diabetes increase the risk of congenital malformations?

Congenital malformations (CM) are the leading cause of perinatal mortality in diabetes, accounting for 50%, compared to 20% to 30% in the general population. Children whose mothers are preconception diabetics (type I and type II) have an increased risk for congenital anomalies (18).

Some authors indicate that elevated HbA1c values in the first trimester are associated with a higher risk for CM. Diabetic vasculopathy has also been linked to an increased risk of CM in some studies (18).

Does pregnancy increase the risk of maternal hypoglycemia?

Intensive insulin therapy can worsen the counterregulatory response to hypoglycemia. Patients with long-term insulin therapy can sometimes tolerate suboptimal plasma glucose levels without any symptoms of hypoglycemia. In such patients, symptoms and a hormonal counterregulatory response become noticeable at significantly lower glucose concentrations (19).

Pregnant women are often on intensive insulin therapy, and hypoglycemia occurs as a common complication. In addition to the previously described mechanism, it has been shown that during pregnancy the counterregulatory response decreases even more (20).

Coustan et al. (21) noticed a rate of moderate hypoglycemia of 72% and severe hypoglycemia of 46% in 22 pregnant women with type I diabetes who were randomized to either an insulin pump or intensive conventional therapy.

Steel and Johnson (22), as well as Hellmuth et al. (23), measured hourly nighttime glucose levels in pregnant women during the first trimester and reported that 37% had hypoglycemia, which was asymptomatic in 42 out of 43 patients.

Kitzmilller et al. (24) reported that 58% of 84 women who became pregnant after preconception test-

ing had 1 to 17 episodes of hypoglycemia per week in the first 7 weeks of pregnancy.

Kimmerle et al. (25) also noticed severe hypoglycemia in 41% of 77 women with type I diabetes, especially in the first half of pregnancy. Likewise, Rosenn et al. (26) found that significant hypoglycemia, occurred in 71% with a peak incidence between weeks 10 and 15; 34% of 84 patients had at least one episode of hypoglycemia accompanied by convulsions, loss of consciousness, injury, emergency administration of glucagon or intravenous glucose.

Gabbe et al. (27) demonstrated that women who used an insulin pump during pregnancy had no episodes of significant hypoglycemia, and those who switched to an insulin pump during pregnancy had a reduction in episodes of severe hypoglycemia.

Bjorklund et al. (28) reported an increase in the number of fetal movements and an increased heart rate, while there was no effect on the speed and appearance of blood flow through the umbilical artery during moderate hypoglycemia.

Does diabetes increase the risk of preeclampsia?

The incidence of preeclampsia in women with diabetes is 5% to 7% higher than in the general population. In a prospective study of 491 women with type I diabetes, Hanson and Persson (29) found preeclampsia or pregnancy-induced hypertension in 21%, four times more than in the general population in Sweden. The frequency of preeclampsia increases with the increase in the class of diabetes in pregnancy according to White.

Finally, in women with diabetic nephropathy, most authors found a high incidence of preeclampsia/pregnancy-induced hypertension or threatened preeclampsia of about 30%.

Sidiqqi et al. (30) found a frequency of pregnancy-induced hypertension of 15.4% in 175 women with type I diabetes, closely related to nulliparity, poor glycoregulation, the first and second trimesters of pregnancy, as well as a higher class according to P. White. Kitzmilller et al. (24) showed that the rate of pregnancy-induced hypertension in their diabetic population was 5%, which was not significantly different from 3.8% in the general population. Martinet et al. (31) found a frequency of pregnancy-induced hypertension of 20% in diabetics (twice as much as in the general population), but no connection with glycoregulation was found.

Several studies have examined the relationship between microalbuminuria and preeclampsia. Combs et al. (32) found an increase in the risk of preeclampsia

if microalbuminuria increased to 190 mg in 24 hours. Similarly, Ekblom et al. (33) have noted that microalbuminuria before pregnancy is the strongest predictor of preeclampsia in type I diabetes.

It is unclear how diabetes affects the risk of preeclampsia. Although the etiology of preeclampsia is unknown, it appears to be related to impaired adaptation of the maternal vasculature to pregnancy. Poor glycoregulation is associated with a state of compromised vascular adaptation in pregnancy and the induction of preeclampsia in a positive relationship with the severity of the disease in pregnancy.

Does diabetes increase the risk of preterm delivery?

Premature birth is one of the most significant obstetric syndromes having a frequency of about 10%. It is responsible for 75% of perinatal morbidity and mortality. There are different data on the incidence of spontaneous preterm births in diabetes. In the studies published so far, the share of iatrogenic prematurity is especially emphasized, considering that part of the therapy in certain situations is planned preterm birth. Not so long ago, premature birth was undertaken to avoid the risk of intrauterine fetal death, especially after the 37th week of gestation (34).

Green et al. (35) demonstrated that 26.2% of women with type I diabetes had a preterm delivery, in comparison to 9.7% of women without diabetes, and that the most important risk factor associated with giving birth before the 37th week of gestation was preeclampsia. These results are in accordance with those reported by Rosenn et al. (26) which showed that improved glycemic control was associated with a lower risk of preterm birth. Kovilam et al. (36) even proved that an increase in the HbA1c levels by 1% increases the risk of premature birth by 37%.

Sibai et al. (37) reported that women with diabetes had a significantly higher rate of spontaneous (16.1% vs. 10.5%) and induced (21.9% vs. 3.4%) preterm deliveries in comparison to the control group.

Weiss et al. (38) measured umbilical vein insulin levels in infants of diabetic mothers and found that among children who had high insulin levels, the preterm birth rate was 71% compared to 5% among children whose levels were normal.

The association between preterm birth and poor glycemic control requires a rational explanation. Although the etiology of preterm labor is still not clearly defined, different pathophysiological conditions may play an independent role and trigger a common mechanism that leads to preterm labor, such as the local release of prostaglandins in the uterine muscle.

Prostaglandin production is increased in the platelets of diabetics, but no data show an increase in prostaglandin production in the uterus or amnion of pregnant women with diabetes. Furthermore, it is impossible to conclude whether lifestyle and other factors may increase the risk of preterm birth in patients with poor glycemic control (39).

Does diabetes increase the risk of polyhydramnios?

Polyhydramnios is common in diabetic pregnancies. Cousins (40) determined a frequency of 17.6% in classes B and C, according to White, and 18.6% in classes D, R, and F. Higher rates of polyhydramnios were also determined by Lufkin et al. (41) (29% compared to 0.9% in the control group), as well as Kitzmiller et al. (24) (31%) and Rosenn et al. (26) (26.4% to 0.6%).

Although the diagnosis of polyhydramnios is also related to the subjective assessment of the sonographer, the use of the amniotic fluid index (AFI) improves the objectivity of data on the amniotic fluid volume. The frequency of polyhydramnios in the control population may be underestimated because sonographic examinations are performed less often in healthy pregnant women. Polyhydramnios in diabetes can be a consequence of a higher concentration of glucose in the amniotic fluid, which increases the osmotic pressure, and when the balance is restored, it leads to an increase in the volume of the amniotic fluid. Additionally, maternal hyperglycemia causes fetal hyperglycemia, which further leads to fetal polyuria and increased amniotic fluid.

Does diabetes increase the risk for infections?

Diabetics are known to have an increased risk for infections. Deficiency of the immune system and reduced activity of lymphocytes and leukocytes can explain the tendency to infection. These abnormalities appear to be associated with poor glycemic control. As part of the body's adaptation to pregnancy, immunomodulation occurs, which is necessary for the survival of the fetus's allograft. As part of this, there is a depression of cellular immunity, which in diabetes is an additional risk for infection.

Vejlsogaards (42) found an increase in the frequency of urinary tract infections in pregnant women with diabetes. Diamond et al. (43) reported that wound infections, endometritis, or both, are more common in postpartum diabetic women. Cousins, Pedersen and Molsted-Pedersen (40, 44) found that pyelonephritis

was more common in diabetic pregnancies and was associated with increased perinatal mortality.

Stamler et al. (45) reported that 86% of women with diabetes had at least one infection antenatally, compared with 26% of women without diabetes. During pregnancy, these patients had a five times higher frequency of various infections.

CONCLUSION

Improving glycoregulation should improve fertility. The increased risk of SAB and CM in diabetes is most likely related to the unfavorable environment to which the developing fetus is exposed. Disturbances in fetal growth and the amount of amniotic fluid in-

dex are also present in diabetic pregnancies. The same applies to the development of preeclampsia and infections. Prenatal monitoring is of great importance in pregnancies complicated by diabetes mellitus.

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Sažetak

PRENATALNI NADZOR TRUDNOĆA KOMPLIKOVANIH DIJABETES MELITUSOM

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Prekonceptijski i prenatalni nadzor evaluiraju stanje osnovne bolesti majke i eventualne komplikacije tokom trudnoće. Pre začeća potrebno je pacijentkinjama sa dijabetesom predočiti da je suboptimalna glikoregulacija skopčana sa smanjenim fertilitetom i gubicima trudnoće. Zadatak perinatologa kod trudnoća opterećenih dijabetes melitusom je da predupredi komplikacije osnovne bole-

sti kao što su hipoglikemijske krize. Druga važna komponenta prenatalnog nadzora u dijabetičnim trudnoćama je prepoznavanje i sprečavanje komplikacija trudnoće kao što su preeklampsija, polihidramnion, kongenitalne malformacije, fetalna makrozomija i infekcije.

Ključne reči: dijabetes melitus, trudnoća, komplikacije, preeklampsija, polihidramnion.

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