

Fetal and neonatal complications of diabetic pregnancy

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Abstract

Background: There is currently convincing clinical and experimental evidence that a hyperglycemic intrauterine environment is responsible not only for significant short-term outcomes in the fetus and newborn infant, but it is also an increased risk for long-term outcomes, such as developing diabetes mellitus and other chronic diseases in adulthood. Short-term complications can occur in utero (i. e. diabetic fetopathy, fetal macrosomia, intrauterine growth restriction, congenital malformations, intrauterine fetal death); during labor (shoulder dystocia, birth injuries, intranatal death) and during the neonatal period (respiratory distress syndrome, metabolic, electrolytic and hematological disorders, hypertrophic cardiomyopathy, neonatal mortality). The risk of adverse outcomes is greater in pre-gestational diabetes, but undiagnosed and / or poorly controlled gestational diabetes can lead to similar consequences. Although there is currently a relatively clear view on the pathogenesis of fetal and neonatal complications of maternal diabetes and their interconnections, the deep molecular mechanisms are far from being clearly understood. Furthermore, there has been an unexpected increase in the incidence of gestational diabetes worldwide during the last decades, in association with the obesity pandemic and type 2 diabetes.

Conclusions: Maternal diabetes, especially pre-gestational diabetes has a significant impact on the incidence of fetal and neonatal complications with both short and long-term outcomes.

Key words: pregnancy, diabetes mellitus, gestational diabetes, diabetic fetopathy.

Introduction

All the types of diabetes mellitus (DM) in pregnancy – pre-gestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM) are associated with a significantly increased risk of short and long-term maternal, fetal and neonatal adverse outcomes [1, 2, 3]. The risk of developing pregnancy complications is associated with increased maternal blood glucose levels and it is 2 to 5 times higher in women with type 1 diabetes mellitus (T1DM) compared to the general population. Furthermore, there is evidence that type 2 diabetes mellitus (T2DM) in pregnancy has a similar impact on infants as T1DM [4, 5], and PGDM has a greater negative impact on pregnancy outcomes compared to pregnancies complicated with GDM [2].

Despite the significant progress achieved in glycemic control in pregnant women with DM, pregnancy complications are still very common, especially in case of PGDM [6].

Short-term adverse outcomes can be divided into complications that occur: in utero (diabetic fetopathy, fetal macrosomia, intrauterine growth restriction, congenital malformations, antenatal fetal death); during labor (shoulder dystocia, birth injuries, intranatal death) and during the neonatal period (respiratory distress syndrome, metabolic, electrolytic and hematological disorders, hypertrophic cardiomyopathy, neonatal mortality). Long-term fetal outcomes include: overweight and obesity, impaired glucose tolerance or T2DM, metabolic syndrome with increased risk of cardiovascular disease and subtle neurophysiological dysfunctions.

Adverse fetal outcomes of a diabetic pregnancy can also be classified according to trimesters:

- First trimester – congenital malformations, fetal loss, intrauterine growth restriction;
- Second trimester – hypertrophic cardiomyopathy, erythremia, fetal loss, low intelligence coefficient;
- Third trimester – hypoglycemia, hypocalcaemia, hyperbilirubinemia, respiratory distress syndrome, macrosomia, hypomagnesaemia, intrauterine fetal death [48].

Adverse fetal outcomes of diabetic pregnancy

Diabetic Fetopathy (DF) is a complex and heterogeneous syndrome that develops in the fetus during the intrauterine period and is induced by genetic or acquired disorders of insulin secretion and / or peripheral cell resistance to insulin action and is characterized by specific phenotypic changes, congenital defects, significant metabolic and functional disorders of the newborn [7].

The definition of “diabetic fetopathy” is mainly used in Russian specialty literature and it is uncommon in Anglo-American literature, being partly replaced by the term of “diabetic macrosomia”, with emphasis on birth complications such as shoulder dystocia, hypoxia and others, without counting the metabolic changes in this context [8].

The carbohydrate metabolism disorders during pregnancy contribute to the development of DF, which is most frequently characterized by macrosomia or intrauterine growth restriction (IUGR) and is one of the most serious and specific manifestations of maternal DM in the newborn, which increases the risk of birth trauma, perinatal morbidity and mortality [9].

The literature data on the frequency of DF is contradic-

tory. The incidence of DF ranges between 5.7% and 75.5% and depends on the type and degree of compensation of the maternal DM, the presence of vascular complications, associated obstetrical and extra-genital disorders, and the population that is subject to research. According to some authors, most newborns from mothers with T1DM (96%) and T2DM (85%) show signs of DF and only 49% of infants from mothers with GDM will develop these signs.[11].

Macrosomia. The concept of excessive fetal growth is expressed either by “macrosomia” or “large for gestational age” [12, 14, 15].

There is no general consensus on the definition of macrosomia or the underlying principles of diagnosis. Most recent studies and meta-analyses define macrosomia as birth weight $\geq 4,000$ g. The American College of Obstetricians and Gynecologists recommends as a reference the weight of $\geq 4,500$ g due to substantial increase of the rate of maternal, fetal and neonatal complications. Nevertheless, there is considerable variation in the definition of macrosomia ($\geq 4,000$ g, $\geq 4,100$ g, $\geq 4,200$ g, $\geq 4,500$ g, $\geq 4,536$ g regardless of gestational age, > 90 th percentile, > 95 th percentile or 2 deviations standard above the mean weight for corrected gestational age, gender and ethnicity) [12, 14, 15, 17, 23, 24].

Defining macrosomia with an absolute fixed birth weight has the advantage of making it easier to determine and remember, but does not take into account the influences of gestational age on the birth weight. Defining it as a newborn large for gestational age offers a potential solution for this problem. However, infants that are large for gestational age are also defined differently: infants with a body weight above the 90th percentile or the 95th percentile or greater than 2 standard deviations for the gestational age corrected for sex and ethnicity [6, 12, 18, 25].

Fetal macrosomia is the most common consequence of diabetic pregnancy, that usually becomes obvious from the 26-28th gestational week [26, 27] and its severity is mainly influenced by the maternal blood glucose level [14, 27]. Literature data on macrosomia frequency differs significantly by country and type of DM [16]. The prevalence of macrosomia in developed countries varies from 5% to 20% [15], and in developing countries - from 0.5% to 14.9% [14].

The prevalence of macrosomia studied in many countries of the world significantly varies from 1% (Taiwan) to 28% (Denmark), with the highest rates (20%) in Northern countries [16].

According to a recent study, the overall rate of macrosomia for the non-diabetic population is 7-9%, increasing to 20-45% in GDM [3]. Fetal macrosomia (birth weight $\geq 4,000$ g) is found in 15-45% of newborns from mothers with GDM, 47% of mothers with T1DM compared to 12% of neonates from pregnant women without DM. In the last 2-3 decades, the incidence of macrosomia increased by 15-25% and is worldwide associated with increased rates of obesity and maternal DM [15, 19, 29, 30].

Fetal macrosomia can be estimated using clinical data (assessment of uterine height and maternal medical his-

tory), determination of insulin levels in the amniotic fluid, requiring an invasive procedure – amniocentesis, and ultrasound scans. Fetal ultrasound scan became an indispensable part of an obstetrical examination and is the elective method for the antenatal estimation of fetal weight [12]. Some studies demonstrated that the Ott, Hadlock IV and Coombs formulas are preferred for estimating fetal weight in fetuses $< 2,500$ g and $> 4,000$ g. Formulas that combine all three parameters (bi-parietal diameter, femur length and abdomen circumference) provide the best estimation of fetal weight in terms of general accuracy and do not indicate a tendency to overestimate or underestimate real weight [12, 17, 23, 31].

There is evidence that serial biometric ultrasound scan throughout pregnancy, especially the evaluation of fetal abdomen circumference in the third trimester, can improve the predictive accuracy of fetal macrosomia in pregnant women with DM [24, 32, 33]. The majority of macrosomia prediction studies are based on ultrasound measurements of one parameter (abdominal circumference or subcutaneous tissue thickness) or combinations of measurements (abdominal circumference, biparietal diameter, femur length, and head circumference) to estimate fetal weight [12, 17, 23, 31]. Although the combined fetal biometric parameters or serial evaluation throughout pregnancy provide the best estimation of fetal weight, a recent meta-analysis revealed the utility, safety, and sufficiency of fetal abdominal circumference measurement only after 24 weeks of gestation for the estimation of newborns as large or small for gestational age [12].

Despite the fact that DM modifies the parameters of fetal biometry with the increase of the thoracic-abdominal parameter, there is still a lack of precision of the antenatal diagnosis of macrosomia using the ultrasound scan – insufficient method with a positive predictive value of only 65% for the detection of a fetus $\geq 4,000$ g [16].

The effectiveness of three-dimensional ultrasound in the estimation of fetal weight is contradictory. Some authors have demonstrated that this method improves the estimation of fetal weight [12, 23, 24] and other studies have found the superiority of two-dimensional ultrasound performed 2 weeks before birth in predicting the birth weight of the newborn and fetal macrosomia in pregnant women with DM [24, 34].

Therefore, scientific literature confirms that the prediction of fetal macrosomia is complicated. Ultrasound scan was recognized as the most accurate method of estimating fetal weight. Unfortunately, the average error varies within a 300-550 g range, and ultrasound assessment of fetal weight adds some useful additional information to clinicians in estimating macrosomia [33].

Multiple conclusive clinical and experimental studies showed the association of PGDM (T1DM and T2DM) or GDM with macrosomia. DM remains a major cause of macrosomia despite improved obstetrical care [1, 12, 18]. Glycemic parameters of diabetic pregnant women in the third trimester are stronger predictors of fetal growth than blood

glucose levels in the I and II trimesters or in preconception period, the latter being more commonly associated with lower birth weight [35,36,37].

The first meta-analysis of epidemiological studies published in 2015, which explored the significance of GDM as an independent risk factor for macrosomia, included 5 cohort studies and 7 case-control studies. The authors found that GDM was associated with macrosomia independently from other risk factors (pre-gestational body mass index, pre-pregnancy obesity, pathological weight gain in pregnancy) [39]. Each type of DM is an independent risk factor for macrosomia [1, 12, 18], and effective treatment of hyperglycemia in pregnancy significantly reduces the rate of fetal macrosomia [14, 38].

According to Pedersen's hypothesis, the macrosomia observed in pregnant women with DM is a consequence of fetal hyperinsulinemia, a secondary condition of maternal hyperglycemia. Fetal hyperinsulinemia causes an increased use of cellular glucose, which contributes to hepatic glycogen deposit formation, decreases lipid mobilization and increases protein production. Insulin stimulates the incorporation of amino acids into proteins and in diabetic pregnancy it increases the assimilation of amino acids and protein synthesis and decreases protein catabolism. During the last 12 weeks of gestation, the fetus of a diabetic mother stores 50-60% more fat than the fetus of a mother without DM [19].

Fetal growth is the result of maternal hyperglycemia with increased trans-placental transfer of maternal glucose leading to fetal hyperglycemia (glucose being an important anabolic nutrient), the stimulation of insulin release by fetal β -pancreatic cells (hyperinsulinemia, insulin being an important anabolic hormone) and, as insulin is a major factor in fetal growth, it leads to macrosomia and other complications with an increased risk of developing obesity, T2DM and cardiovascular disease in adolescence or youth years. Pederson's hypothesis is fundamental for understanding the physiopathological consequences of DM during pregnancy. Subsequently, this theory has been modified to include the contributions of other nutrients in increased concentrations (amino acids, lipids, insulin growth factor) that may contribute to fetal hyperinsulinemia [3, 15, 19, 28, 51, 52].

Fetal hyperinsulinemia has the following effects:

- Excessive growth of insulin-sensitive tissues such as adipose tissue (especially around the chest, shoulders and abdomen), organomegalia (especially of the liver, spleen and heart) and accelerated maturation of the skeleton, which increases the risk of shoulder dystocia, perinatal mortality, birth trauma and the rate of cesarean section surgeries;
- Neonatal metabolic, electrolytic and hematological complications: hypoglycemia, hypocalcemia, hyperphosphatemia, hypomagnesemia, polycythemia, hyperbilirubinemia;
- In utero hypoxemia develops, which may increase the risk of antenatal mortality, polycythemia, hyperbilirubinemia and venous renal thrombosis of the fetus;

- Increased risk of long-term outcomes such as obesity and DM in childhood [6, 12].

Experimental and clinical studies found that fetal hyperinsulinemia is strongly associated with fetal macrosomia and increased adipose tissue. However, the high frequency of fetal macrosomia in diabetic pregnant women with adequate glycemia control and in pregnant women without DM confirms the involvement of factors other than maternal hyperglycemia and fetal hyperinsulinemia, in the development of fetal macrosomia [19].

While maternal hyperglycemia and fetal hyperinsulinemia are considered the main causes for excessive fetal growth, the exact aspects of the underlying mechanisms of macrosomia remain less clear. Not only poor glycemic control before and throughout pregnancy is a cause of fetal macrosomia but also hormonal, genetic, environmental, and constitutional factors, an angiopathy of utero-placental vessels with fetal subsequent hypoxia contributes to the development of fetal macrosomia. DM and poor glycemic control, pre-gestational obesity, pathological weight gain in pregnancy, a history of macrosomia, and parity are the main risk factors for macrosomia. Despite all these risk factors, many aspects of the weight at birth remain inexplicable [12, 40, 41, 42, 43].

For practical reasons, the causes of fetal macrosomia can be divided into non-modifiable factors (genetic factors, male gender, parity, age and maternal height) and modifiable maternal factors (pre-pregnancy body mass index, pathological weight gain, nutritional intake, the level of physical activity, smoking and metabolic parameters, especially DM and dyslipidemia) [32].

Although DM and maternal obesity are independently associated with pregnancy complications, the combination of T2DM or GDM with pre-gestational obesity has a greater effect on macrosomia and is associated with higher perinatal morbidity rates [6, 19].

Macrosomia, regardless of the cause, is associated with a higher risk for maternal complications (prolonged labor, birth assisted with forceps or vacuum, caesarean delivery, maternal trauma, postpartum hemorrhage) and neonatal complications: premature birth and complications associated with prematurity (respiratory distress syndrome, infection, jaundice, transfer to neonatal intensive care unit and perinatal mortality), birth injuries (shoulder dystocia, brachial plexus palsy, clavicle and humerus fractures), neonatal hypoglycemia, perinatal asphyxia, meconium aspiration, congenital abnormalities [12, 14, 18, 19, 20].

Therefore, fetal macrosomia is an obstetrical condition that affects an average of 10% of all pregnancies and may be associated with severe maternal, fetal and neonatal adverse outcomes. An early identification of risk factors (pre-gestational obesity, pathological weight gain, PGDM and GDM) allows applying the measures needed to prevent perinatal complications.

Intrauterine growth restriction (IUGR)

Infants with a birth weight below the 10th percentile are

considered small for gestational age. IUGR is more rarely associated with DM, and it occurs in about 20% of diabetic pregnancies, more frequently in pregnant women with T1DM with severe renal-vascular complications compared to a 10% incidence in infants born to mothers without DM. Maternal renal-vascular disorder is a common cause of the impairment of fetal growth in pregnancies complicated with DM. The newborns considered small for gestational age have an increased risk of low Apgar score at birth, respiratory distress syndrome, neonatal death, cardiovascular and metabolic disorders during the life [20].

Congenital malformations of neonates from diabetic pregnant women are the main cause of perinatal and infantile death. The risk of major congenital malformations in pregnancies complicated with DM is 2-5 times higher than in the general population, congenital abnormalities occur in 4-12% of cases [16,20], and in pregnant women with decompensated forms of DM the risk increases up to 20% [14, 20].

The most common congenital anomalies are the following [15, 26, 45, 46]:

- Cardiac: transposition of the great vessels, atrial septal defect or ventricular septum defect, aortic co-actation, persistent truncus arteriosus, single ventricle;
- Of the central nervous system: anencephaly, microcephaly, encephalocele, meningomyelocele, holoprosencephaly, spina bifida;
- Skeletal: caudal regression syndrome (agenesia or hypoplasia of the sacral and coccygeal bone, sometimes of lumbar vertebrae), femoral dysplasia;
- Renal: renal agenesis, hydronephrosis, duplicated ureter;
- Gastro-intestinal: duodenal atresia, anorectal atresia;
- Others: palatoschisis, microftalmia, intestinal atresia.

Newborns of mothers with PGDM are more likely to develop congenital malformations, with a similar incidence in both types of PGDM, and the development risk is highly associated with the length of DM before pregnancy [15, 20, 44, 45, 46].

Several authors reported an association between GDM and the same types of congenital malformations diagnosed in the descendants of women with PGDM, although some studies found a limited association of GDM with some congenital defects. The risk of congenital abnormalities in neonates of mothers with GDM is lower than the risk for neonates of mothers with PGDM [15, 44, 47]. The risk of congenital malformations does not significantly vary in women with T1DM and T2DM, being 1.9-10 times higher in the PGDM, 1.7-3 times higher in T1DM compared to the general population. In the case of GDM, the risk of congenital malformations is moderate and is slightly increased (1.1-1.3 times higher) compared to the general population, but is much lower than in women with PGDM and is probably also determined by cases of undiagnosed T2DM in patients with GDM [15, 44]. In newborns of mothers with PGDM, the incidence of heart defects varies from 2 to 34 cases per 1,000 births, central nervous system abnormalities – from 1 to 5 cases per 1,000 births, musculoskeletal malformations

– from 2 up to 20 cases per 1000 births, genital-urinary abnormalities – from 2 to 32 cases per 1,000 births and gastrointestinal defects – from 1 to 5 cases per 1,000 births [44, 49].

It is difficult to compare the frequency of congenital abnormalities associated with maternal DM due to the differences in diagnostic criteria of DM in different countries. It is also difficult to compare maternal DM rates among populations where the screening of the disease is not similar in all centers.

The results of several studies on the risk of congenital anomalies in neonates of mothers with GDM showed the 1.2-fold increase in congenital malformations for GDM compared to the general population. Pregnant women with GDM with a basal hyperglycemia > 120 mg / dl (> 6.7 mmol / l) or HbA1c $\geq 7.0\%$ have a 3.4-fold higher risk, and for women with GDM with normal basal glucose there is no difference of risk compared to women without DM. It was found that there is a small, but statistically significant increase in the frequency of holoprosencephaly, bone abnormalities and genitourinary system malformations in children of mothers with GDM compared to non-diabetic pregnant women [44].

The pathogenesis of fetal malformations associated with PGDM is partially understood, but it is multi-factorial and correlates with several deficiencies of toxic nutrients or metabolites. Hyperglycemia, hypoxia, ketonemia, amino acid abnormalities and protein glycosylation were reported as potential teratogenic factors that may affect molecular signaling pathways with adverse effects on embryogenesis [15, 18, 20].

Embryo-developmental disorders during pregnancy complicated with DM were extensively explored in experimental and clinical studies. Available data indicate that there are many changes in the embryonic environment capable of inducing teratogenic development. The most important change is the increase in glucose concentration, which has a number of direct metabolic consequences on the embryo. However, there are other modifications with teratogenic effects - the excess of reactive oxygen molecules, elevated levels of ketone bodies and branched chain amino acids in the tissues of different fetal organs, but their mechanism of action still has to be elucidated. Likewise, newborn rats from mothers with chemically induced DM have an increased oxidative stress in different tissues, and there is an increase in reactive oxygen molecules and lipid peroxidation in the liver, kidney, brain and skin, and elevated levels of lipid peroxides in plasma [8, 14, 20].

Therefore, maternal DM, especially PGDM, has colossal consequences on the incidence of congenital anomalies [14, 16, 20].

Intrauterine fetal death. Approximately 50% of the cases of dead fetus births are related to uncontrolled maternal hyperglycemia, and the other cases are caused by fetal congenital infections or anomalies, placental insufficiency, maternal diseases. This increased risk is most commonly associated with T1DM, but it can also be encountered in other forms of DM. Compared with the general population, the risk of fetal mortality is 3-5 times higher in pregnant women

with T1DM, 2-3 times higher in women with T2DM, and pregnant women with GDM have a lower risk than women with PGDM. The birth of a dead fetus in pregnant women with DZG is more common at gestational age, suggesting that maternal hyperglycemia causes hyperinsulinemia and fetal lactic acidosis – the main causes of intrauterine death [13]. Antenatal fetal death in pregnant women with GDM is more common for gestational age fetus, suggesting that maternal hyperglycemia causes hyperinsulinemia and fetal lactic acidosis – the causes of intrauterine death [13]. Hypoxia and fetal heart failure, secondary to poor glycemic control, are probably the most important factors for antenatal mortality among pregnant women with DM [13].

Complications related to labor and delivery

Shoulder dystocia is a rare but serious obstetric complication that occurs in neonates with macrosomia and may lead to paralysis of the brachial plexus, fracture of the clavicle or of the humerus [15, 20]. In Denmark, the risk of shoulder dystocia among vaginal births is 6% at women with T1DM. A quarter of these neonates need resuscitation at birth, and some suffer from lesions of the bones and nerves. The incidence of brachial plexus paralysis and fractures of neonates born alive from mothers with PGDM is 10 times higher than in the general population [8, 20].

Preterm birth, being one of the major causes of fetal death, is found in about 10% of the pregnancies, in 50% of women with DM and is 4.8 times higher in pregnant women with DM than in the general population [21]. Patients with T1DM have an increased risk of premature birth. Recent cohort studies demonstrated that premature birth rates were 24-33.9% in pregnant women with T1DM, and previous studies reported values ranging from 26.2% to 31.1% [22].

Cesarean section. Women with DM generally have higher cesarean section rates. The frequency of this procedure in pregnant women with DM worldwide is about 42.7-78%, compared to a much lower rate in the general population (20%). The number of cesarean sections does not significantly vary in pregnant women with T1DM and T2DM. A number of DM-induced factors (maternal obesity, fetal macrosomia, polyhydramnios and diabetic microvascular complications) are also associated with an increased risk of surgery. Simultaneously with the protection of the newborn from hypoxic-ischemic cerebral lesions and the complications related to macrosomia by avoiding vaginal birth, the potential side effects of a cesarean surgery are delayed or discontinued breastfeeding and respiratory morbidity (transient tachypnea of the newborn or surfactant deficiency). These complications frequently lead to the admission of the newborn to the neonatal intensive care unit or resuscitation unit and separation of the mother from the child [21, 22].

Neonatal adverse outcomes

Respiratory distress syndrome. Neonates from mothers with DM have an increased risk of respiratory disorders. The incidence of respiratory distress syndrome is 5-6 times higher for any gestational age compared to non-diabetic

pregnancies. Respiratory distress syndrome is typical in newborns with DF, with a frequency of 13-40% in neonates of mothers with PGDM and up to 5% in neonates of mothers with GDM [3, 8, 14, 15, 18, 20].

The pathogenesis of respiratory distress syndrome in neonates from mothers with DM is poorly understood, but several theories are possible. First, hyperinsulinemia inhibits the synthesis and secretion of surfactant by type 2 pneumocytes with a delayed pulmonary maturation. Secondly, these children are often prematurely born with surfactant deficiency. Therefore, there is a direct adverse impact of hyperglycemia on the fetal metabolism of lung surfactant. Third, cesarean delivery due to macrosomia increases the risk of transient tachypnea in the newborn, while polycythemia predisposes the neonate to persistent lung hypertension. Finally, the cause of respiratory distress syndrome may also be meconium aspiration syndrome and hypertrophic cardiomyopathy. Nevertheless, respiratory distress syndrome affects newborns in pregnancies with severe PGDM. Frequency and risk of respiratory distress syndrome in GDM cannot be accurately determined due to insufficient data [3, 7, 8, 14, 15, 18, 20].

Metabolic, electrolytic and hematological neonatal disorders are associated with fetal hyperinsulinemia [18].

Hypoglycemia is the most common metabolic complication secondary to fetal hyperinsulinemia with a prevalence ranging from 25% to 76% depending on the definition of hypoglycemia threshold and maternal glycemic control at birth. However, in the vast majority of cases it is biochemical hypoglycemia, i.e. asymptomatic neonatal hypoglycemia. Pregnant women with the highest basal glucose level have infants with the highest frequency of neonatal clinical hypoglycemia – 5-7%. The risk of hypoglycemia is the highest in large for gestational age infants and premature newborns [3, 15, 18, 25, 50].

A recent study defined capillary blood glucose levels as normal (≥ 2.5 mmol / l), mild hypoglycemia (2.2-2.4 mmol / l), moderate hypoglycemia (1.6-2.1 mmol / l) and severe hypoglycemia (< 1.6 mmol / l). Among newborns from pregnant women with GDM, the prevalence of hypoglycemia was 25%: 12.1% had mild hypoglycemia, 10.5% moderate hypoglycemia and only 2.6% severe hypoglycemia [50].

Hypocalcaemia is detected at a calcium concentration of < 2 mmol / l (< 7 mg / dl) or ionized calcium concentration that is < 1.1 mmol / l (< 4 mg / dl) [14]. These complications occur up to 50% of cases, being usually associated with hyperphosphataemia and occasionally with hypomagnesaemia, all of which rarely have clinical significance. The etiology of neonatal hypocalcaemia is unclear, but severe DM and neonatal hypoparathyroidism may be possible causes [3, 18, 20].

Polycythemia (a hematocrit that is $> 65\%$) occurs in 13-33% of cases [14, 18, 20], is more commonly determined in neonates from mothers with DM. Relative cell hypoxia determines an increased erythropoietin secretion, which in return increases fetal erythrocyte production. Neonatal polycythemia can cause excessive neonatal jaundice by red

cell lysis and blood clotting syndrome with complications caused by vascular stasis [3, 18, 20]. Hyperbilirubinaemia occurs in 11-29% of cases [14, 15, 18, 20].

Hypertrophic cardiomyopathy

DM in pregnant women affects the fetal heart structurally (cardiac malformations, hypertrophic cardiomyopathy) and functionally (even in the absence of structural changes) with long-term consequences. Fetal hyperinsulinemia, as a result of abnormal maternal glycemic control, causes hyperplasia and hypertrophy of the fetal myocardium with the development of hypertrophic cardiomyopathy - interventricular septal hypertrophy and, to a lesser extent, ventricular hypertrophy with left ventricular outflow tract obstruction. However, clinical experience shows that even infants of DM women with adequate glycemic control may have septal hypertrophy. Therefore, other maternal major risk factors that affect the fetal heart were identified, such as hypertriglyceridemia, obesity, increased oxidative stress and placental factors [8, 14, 20].

Hypertrophic cardiomyopathy occurs in 25-35% of infants born to mothers with DM and sometimes it leads to significant morbidity and mortality, depending on the severity and extent of cardiac hypertrophy and aortic obstruction. Fortunately, most cases of hypertrophic cardiomyopathy are transient and asymptomatic, do not require treatment and have a spontaneous echocardiographic resolution in the first months after birth [8, 14, 20].

Perinatal mortality. Until the discovery of insulin, pregnancies in women with DM were often associated with perinatal mortality. The perinatal mortality rate was around 65%, and maternal mortality was up to 30%. Insulin reduced maternal mortality by reducing the frequency of diabetic ketoacidosis, improving the fertility of women with DM, but perinatal mortality, although reduced, remained high [13,22].

Perinatal mortality in pregnant women with T1DM is 5 times higher, with PGDM - 4 times higher and neonatal mortality in pregnant women with DM of any type - 15 times higher compared to the general population [18, 20, 21]. One of the largest recent population-based studies revealed that perinatal mortality is 3 times higher and infant mortality 9 times higher in pregnant women with PGDM compared to those without DM. Major congenital abnormalities, maternal hypertension, and premature birth are important factors in increasing the mortality of children born of diabetic mothers. Overall, the perinatal mortality rate is almost identical for mothers with T1DM and T2DM [18].

Studies with fetal blood sampling confirm that hyperglycemia is associated with fetal hypoxia and acidosis. In all types of DM there are additional risk factors associated with perinatal mortality - diabetic angiopathy, hypertension and IUGR. In T2DM and GDM, compared to pregnant women without DM, there is a so-called "triad" of factors for intrauterine death - the relatively greater age of pregnant women, higher incidence of obesity and high blood pressure [13]. Although several factors may influence the perinatal mortality rate, the blood glucose threshold <6.1 mmol

/l (<110 mg / dl) is possibly a major factor in preventing this complication. However, unlike PGDM, the increase in the fetal death rate in the 2nd and 3rd trimesters of pregnancy is questionable in GDM and can be attributed to previously undiagnosed T2DM [14].

A systematic review of the literature and meta-analysis of 33 observational studies, published in 2009, that compared maternal and fetal outcomes in pregnant women with T1DM and T2DM, found that pregnant women with T2DM had a lower level of HbA1c at the first OB visit, but a higher incidence of perinatal mortality, with no significant differences in major congenital malformations, antenatal, and neonatal mortality. Therefore, despite lower glycemic disorders, women with T2DM, compared to women with T1DM, did not show better perinatal outcomes [10].

The complications described above are short-term adverse outcomes, but long-term consequences may also occur. Children born from pregnancies complicated with GDM are at a higher risk of developing obesity, glucose intolerance and DM in adolescence and early adulthood. The lifetime risk to develop T1DM for children of diabetic mothers is 1.3%, and for children of diabetic fathers is 5.7%, while the risk of developing T1DM is much higher - about 50% [18].

Conclusions

1. Maternal diabetes, predominantly PGDM, has a significant impact on the incidence of both short-and-long-term complications in the fetus and newborn.

2. Short-term adverse outcomes include fetal complications (diabetic fetopathy, macrosomia, IUGR, congenital malformations, fetal antenatal death), complications related to labor and delivery (shoulder dystocia, birth injuries, intranatal death) and neonatal adverse outcomes (respiratory distress syndrome, metabolic, electrolytic and hematological neonatal disorders, hypertrophic cardiomyopathy, perinatal mortality).

3. Long-term fetal outcomes include overweight and obesity, impaired glucose tolerance or

T2DM, metabolic syndromes with an increased risk of cardiovascular disease and subtle neurophysiologic dysfunction.

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