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Review Article

Diabetic Fetopathy

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ABSTRACT

The global incidence of diabetes mellitus, including gestational diabetes, has been increasing in recent years. Diabetes during pregnancy can have serious consequences on the fetus. Fetal complications can occur, with congenital malformations, macrosomia, and fetal death being the most frequent; complications during delivery such as prematurity, perinatal asphyxia and obstetric trauma; and neonatal complications, the most frequent being metabolic ones, in which hypoglycemia and hypocalcemia stand out. Current evidence has shown that glycemic control until the end of pregnancy is of the utmost importance in order to significantly reduce the appearance of these complications and achieve good fetal development.

Keywords

Diabetic fetopathy, Child of diabetic mother, Gestational diabetes, Fetal macrosomia.

Introduction

Around 366 million people worldwide suffer from diabetes mellitus (DM) and it is expected that this number will double by 2030 [1]. With the increase in the prevalence of Diabetes Mellitus, there has also been an increase in gestational diabetes mellitus (GDM), which is diagnosed during pregnancy, this in relation with the high prevalence of obesity and overweight in the world [1,2]. In the United States, it is estimated that 1-5% of pregnancies are complicated by DM and that around 0.2-0.3% of pregnant women have DM before pregnancy. In this country, for each year there can be up to 150,000 children born to diabetic mothers [3]. Likewise, fetal complications associated with diabetes, also known as diabetic fetopathy, are one of the leading causes of death in the United States, affecting 1 in every 33 babies [4]. Infants of diabetic

mothers (IDM) have a higher risk of perinatal morbidity and mortality, and the main abnormalities that can occur are macrosomia, hypocalcemia, hypoglycemia, respiratory disorders, polycythemia, thrombocytopenia and hyperbilirubinemia, which are estimated to be six times more frequent than in children of non-diabetic mothers (HMND) [5,6]. It is essential for the treating physician to be aware of the complications that can arise if the pregnant diabetic woman does not have a good glycemic control. Therefore, the aim of this narrative review is to present the risk factors, the etiopathogenesis and complications that can occur in the fetus, during labor and at childbirth in diabetes during pregnancy.

Risk Factors

Obesity and genetic predisposition for developing type 2 DM are the main risk factors for developing diabetes in pregnancy [7]. Patients with polycystic ovary syndrome (PCOS) and high blood pressure are also part of the group at highest risk for GDM [7]. Obstetric and perinatal risk is higher in GDM compared to non-diabetic women.

Risk factors for the development of diabetic embryopathy have been described, such as: poor glycemic control during the first period of pregnancy, especially in unintended pregnancies, advanced maternal age predisposes to type 2 diabetes mellitus de novo, which makes glycemic control not appropriate during the embryonic period and pregestational *diabetes* which is a significant risk for the development of congenital anomalies due to maternal hyperglycemia at the time of conception and during pregnancy [2,8]. Glycemic control during pregnancy is a determining factor in the development of birth defects associated with diabetes [1]. Studies have shown that the frequency of congenital malformations is proportional to the value of maternal glycated hemoglobin (HbA1c) in the first trimester (Table 1).

HbA1c (%)	<7,1	7,2 - 9,1	9,2 - 11,1	>11,2
Risk (%)	1-2	14	23	25

Tabla 1: Risk of developing congenital malformations depending on HbA1c levels during pregnancy. Table adapted from: Kallem VR, Pandita A, Pillai A. Infant of diabetic mother: what one needs to know? J Matern Fetal Neonatal Med. 1rst of February 2020;33(3):482-92.

One of the most frequent complications of Infants of diabetic mothers (IDM) is macrosomia and the main associated risk factors are maternal obesity, Diabetes Mellitus with poor metabolic control between weeks 20-30 of gestation, previous delivery of a child with macrosomia, multiparity, and weight gain during pregnancy (greater than 15 kg) (Table 2) [3]. Risk factors for perinatal asphyxia in pregnant diabetic patients, in addition to poor glycemic control during the third trimester which leads to hypoxia, are diabetic vascular disease during pregnancy which can lead to placental vascular disease and hypertension along with smoking during pregnancy, because both can lead to fetal hypoxemia [9].

Main Risk Factors For Diabetic Fetopathy
Poor glycemic control during pregnancy
Maternal obesity
Excessive maternal weight gain (> 15kg)

Table 2: Main Risk Factors for Diabetic Fetopathy (macrosomia). Adapted from: Danglot-Banck C, Gómez-Gómez M. Infants of Diabetic Mothers.

Ethiopathogenesis

During pregnancy, a progressive increase in insulin resistance occurs, due to the action of placental hormones (estrogen, cortisol, prolactin, human placental lactogen) [1,10]. The increase in the concentration of these hormones affects the way in which insulin is used, which tries to balance itself by reducing its clearance, however, during pregnancy weight gain, low mobility and high-calorie food intake can aggravate the condition [1]. As the pregnancy progresses, insulin decreases steadily, which leads to a greater production of it to compensate the insulin resistance. However, in this case, the β-cells of the pancreas could be damaged and not produce enough insulin levels to offset this demand, which would trigger hyperglycemia in pregnancy [1,11].

Pedersen's hypothesis suggests that abnormal metabolism in the maternal bloodstream is reflected in the fetal compartment, so that maternal hyperglycemia in turn produces fetal hyperglycemia due to glucose crossing the placenta [1,8]. *Likewise, uncontrolled fetal hyperglycemia produces hypertrophy of the fetal pancreatic islets and hyperinsulinemia, and this in turn promotes lipogenesis in fetal adipocytes, thus triggering pathological effects depending on the evolutionary stage: fetal, delivery or neonatal [3,8,12]* (Figure 1 and 2) (Table 3).

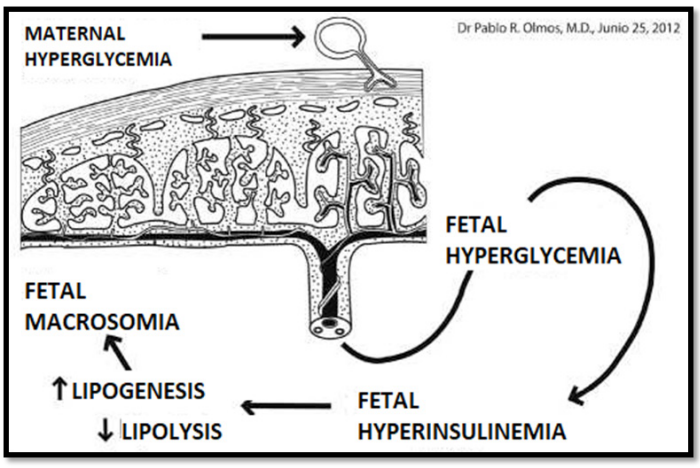

Figure 1: Pedersen hypothesis. Adapted from: Olmos P, Martelo G, Reimer V, Rigotti A, Busso D, Belmar C, et al. La hipótesis de Pedersen no es suficiente: Otros nutrientes además de la glucosa explicarían la macrosomía fetal en pacientes diabéticas gestacionales con sobrepeso y buen control glicémico. Rev Médica Chile. noviembre de 2013;141(11):1441-8.

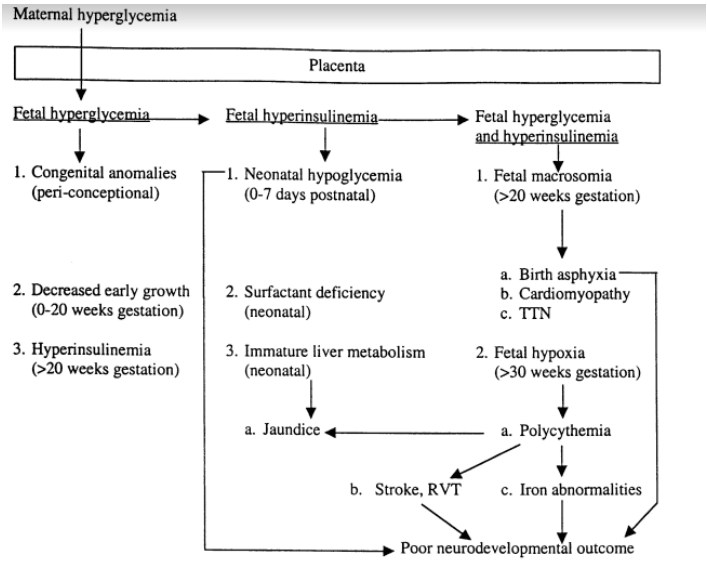

Figure 2: Fetal and neonatal effects attributable to fetal hyperglycemia and hyperinsulinemia. Adapted from: Nold JL, Georgieff MK. Infants of diabetic mothers. Pediatr Clin North Am. June 2004;51(3):619-37.

Fetal period	Childbirth	Neonatal period
Congenital malformations	Perinatal asphyxia	Metabolic: Hypoglycemia, hypocalcemia and hypomagnesemia
Macrosomia	Prematurity	Hematologic: Hyperbilirubinemia, polycythemia, iron deficiency, The Neonatal Small left colon syndrome (NSLCS)
Fetal death	Obstetric trauma	Cardiorespiratory: Respiratory Distress Syndrome, hypertrophic cardiomyopathy, congenital heart disease

Tabla 3: Complications of the infant of a diabetic mother according to evolutionary stage. Table adapted from: Danglot-Banck C, Gómez-Gómez M. Los hijos de madres diabéticas.

Fetal Effect

Congenital Malformations

The main mechanism involved is hyperglycemia due to poor control of DM in the first eight weeks of pregnancy [3]. Hyperglycemia promotes an overload of the mitochondria, which generates an increase in the formation of free radicals. The reduction of the activity of the glutathione antioxidant system and the biosynthesis of prostaglandins can generate mutations and apoptosis, therefore resulting in malformations [13]. *Likewise, chronic hyperglycemia in gestational diabetes induces embryopathic defects at the structural level through various mechanisms such as increased non-enzymatic glycosylation of embryonic proteins, arachidonic acid deficiency, functional decrease in catalase, and decrease in ascorbic acid intracellular with increased dehydroascorbic acid, which by inhibiting mitosis can be teratogenic in addition to the genetic predisposition of infants of diabetic mothers to present malformations [3,13].* Moreover, hyperglycemia plays a critical role in the proliferation and migration of neural crest cells, which are important in the development of the heart and brain [14]. Among congenital malformations, alterations of the central nervous system predominate, among them, defects in the closure of the neural tube such as anencephaly and myelomeningocele (2%, which corresponds to 10 times higher than in the general population); congenital heart diseases such as transposition of the great vessels, ventricular septal defect, atrial septal defect, aortic coarctation (1.7-4% of cases of Infants of Diabetic Mothers) and musculoskeletal alterations, the most frequent being the caudal regression syndrome (0.2-0.5%) [3].

Macrosomia

It is the result of fetal hyperinsulinism due to maternal and fetal hyperglycemia during pregnancy [15]. It has been defined as a birth weight greater than 4000 g or a weight greater than the 90th percentile for gestational age [16]. The classic characteristic phenotype of an infant of diabetic mother is: large, weight and height above the mean for gestational age, Cushing's facie, abundant fat pad, hump on the back of the neck (buffalo neck), facial hypertrichosis, globose abdomen with hepatomegaly and hypotonia, marked folds in the extremities, a thickening of the myocardium is also frequently found at the level of the interventricular septum (> 5 mm) that usually disappears between 2 and 6 months of birth (Table 4) [3,17]. Macrosomia can lead to complicated labor; Studies have shown that women who delivered macrosomic babies vaginally have a higher risk of developing postpartum hemorrhage or pelvic trauma, which is the main reason why various researchers consider that diabetic patients with macrosomic babies should be considered candidates for cesarean section [16,18,19]. Similarly, macrosomia predisposes the development of birth injuries, mainly shoulder dystocia [18], which occurs in almost a third of Infants of Diabetic Mothers with macrosomia [20] and this is associated with a greater risk of brachial plexus injury [18], so it is important to measure the abdominal circumference, especially in the third trimester of pregnancy [2]. A fetal abdominal circumference greater than 35 cm according to ultrasound allows detecting more than 90% of fetuses at high risk of macrosomia, in such a way that this parameter allows the physician to anticipate possible risks during delivery, and consider cesarean section as an option to avoid the development of injuries [2,21].

Characteristic Phenotype of the Child of a Diabetic Mother
Large, with weight and height above the average for gestational age
Cushing's rounded face
Buffalo neck
Abundant fat pad, globose abdomen with visceromegaly
Facial Hypertrichosis

Table 4: Characteristic phenotype of the child of a diabetic mother. Adapted from: Salvía MD, Alvarez E, Cerqueira MJ. *Neonatology service. Institut Clínic de Ginecología, Obstetrícia y Neonatologia. Hospital Clínic. Barcelona. **Servicio Obstetricia Hospitals Vall d'Hebron.

Fetal Death

Stillbirth is the medical term used to refer to the death of the fetus [22]. Gestational diabetes is a risk factor for stillbirth, approximately

half of stillbirths occur before week 30 of gestation, corresponding to 30 to 40% of perinatal deaths due to malformations, 20 to 30% due to asphyxia perinatal and another 20 to 30% due to prematurity [2]. In pregnant diabetic women it occurs in up to 10% of cases [3]. This is due to the increase in oxygen consumption produced by hyperglycemia and hyperinsulinemia, which lead to fetal hypoxia and subsequent death [23]. Patients with pre-gestational DM can also present complications such as utero-placental insufficiency, which implies a greater fetal risk due to lack of oxygen that can lead to fetal death in utero [24].

Childbirth

Perinatal asphyxia

Infants of Diabetic Mothers are at increased risk of intrapartum and perinatal asphyxia due to macrosomia, which leads to a difficult and traumatic delivery [1]. The need for resuscitation at birth increases with the presence of chronic intrauterine hypoxia, cardiomyopathy, and respiratory distress [1].

Prematurity

It is defined as the birth that takes place before the 37th week of gestation [25]. It is common in Infants of Diabetic Mothers and the main risks factors are premature rupture of membranes, arterial hypertension and multiple gestation [3].

Obstetric Trauma

The most frequent obstetric bone trauma in newborns is the clavicle fracture. Fetal macrosomia is one of the main risk factors associated with this trauma, with a frequency of appearance of 2.18% in the macrosomic fetus and whose risk increases as the increase in birth weight increases, being 7 to 14% when a weight of 4,000 to 4,999 g is present and between 15 and 50% in newborns weighing more than 4,500 g [26]. Second is brachial plexus paralysis caused by elongation of the brachial plexus at birth, and among the risk factors that can cause trauma in addition to macrosomia are obesity, multiparity, excessive weight gain during pregnancy, and advanced maternal age [27]. Therefore, during pregnancy a strict metabolic control must be followed, accompanied by the use of ultrasound. The evaluation of fetal weight prior to birth is also an important factor for the timely detection of macrosomia, so it is necessary to evaluate everything together to determine which route of birth is the most appropriate taking into account the conditions of each patient and thus be able to reduce the risk of developing an obstetric trauma [3,28].

Neonatal Effects

Metabolic complications

Hypoglycemia

It is the most frequent complication of IDMs, occurring in 10-50% of newborns, especially those with high weight and premature infants [17]. It is defined with blood glucose levels below 20 mg / Dl in the first 72 hours of births in premature infants and below 30 mg / dL in term infants and in both cases, if the blood glucose level is less than 40 mg / Dl after 72 hours of the birth [3]. It is secondary to hyperinsulinism, which, added to the absence of counter-regulation, produces a decrease in gluconeogenesis and an increase in peripheral glucose uptake, which causes neonatal hypoglycemia [17,29]. The clinical manifestations are paleness, cyanosis, sweating, apnea, hypotonia, tremors, and even coma [29]. To prevent hypoglycemia, early and frequent breastfeeding is essential, to the extent that the infant is able to feed independently [30].

Hypocalcemia and hypomagnesemia

Hypocalcemia is defined as a serum calcium concentration less than 8 mg / dL, while hypomagnesemia is defined as a serum magnesium concentration less than 1.5 mg / dL [31]. It occurs in approximately 50% of IDMs [3]. The etiology of these pathologies is not well known so far. However, it has been proposed that IDMs present hypomagnesemia due to the loss of magnesium in the mother due to gestational diabetes, and in turn that this magnesium deficiency could cause hypoparathyroidism functional leading to neonatal hypocalcemia when the newborn does not receive calcium through the placenta [31]. Furthermore, perinatal asphyxia and prematurity can lead to low calcium levels [32]. The clinical manifestations are: irritability, tremors, clonus, sucking and rarely seizures, likewise these signs and symptoms may take up to 24 to 72 hours after the onset of hypoglycemia [2,3,29].

Treatment consists of vitamin D 10,000 IU orally or intramuscularly, followed by 10% calcium gluconate of 100-300 mg / kg / dose, every eight hours for three to five days. Magnesium sulfate 50% is also given in Intramuscular or intravenous dose of 0.1-0.3 mg / kg / dose that can be repeated in eight to twelve hours (3).

Cardiorespiratory complications

Respiratory distress syndrome (RDS)

The Respiratory Distress Syndrome presents a clinical features composed of: tachypnea, expiratory grunts, rib and subcostal retractions, nasal flaring [33]. It occurs in 25-38% of cases [34]. It is more common in males [35]. It is suggested that the cause could be hyperinsulinism, which inhibits the synthesis of enzymes necessary for the production of phosphatidylcholine and phosphatidylglycerol, main phospholipids in the composition of the surfactant (lung surfactant) [36]. The most common complications associated with Respiratory Distress Syndrome are patent ductus arteriosus (PDA) in infants weighing less than 1500 grams and bronchopulmonary dysplasia [37]. The lecithin / sphingomyelin index (L / S) is one of the tests that is used as a predictor of lung maturity, when the value is greater than 2 at the end of the third trimester there is a high probability of lung maturity [38]. Also, the presence of prostaglandins in the amniotic fluid has been associated with lung maturity, if these are found in the amniotic fluid, Respiratory Distress Syndrome is generally absent [29,34,38].

On the other hand, IDMs have a higher risk of transient tachypnea of the newborn, and it is more likely to occur in babies with macrosomia and after cesarean section [39].

Hypertrophic cardiomyopathy

Several authors estimate that 10-20% of IDMs could present hypertrophic cardiomyopathy [40]. It is defined as a disease in which the myocardium thickens abnormally in the absence of other diseases that increase the workload (hypertension, valvular disease) with histological alteration of the muscle structure [41]. It is secondary to fetal hyperinsulinemia, which generates a thickening of the anterior wall of the right ventricle and the posterior wall of the left ventricle greater than 5 mm and a hypertrophy of the interventricular septum greater than or equal to 6 mm [42,43]. Also, it has been postulated that the inhibition of glycogen synthase kinase 3-beta by the action of insulin is a potential factor for the development of Hypertrophic Cardiomyopathy [44]. 20% of cases present with heart failure, which is why they present clinical manifestations such as tachycardia, congestive hepatomegaly and gallop rhythm [3]. In a descriptive cross-sectional study carried out in Guadalajara, it was found that 100% of patients with macrosomia developed Hypertrophic Cardiomyopathy, so there is an association between these two pathologies [45]. It is considered that hypertrophic cardiomyopathy in most cases does not need treatment because it has a benign natural history, in which there is a spontaneous regression of symptoms. If the use of drugs is necessary Propranolol is usually the choice [46]. The administration of digitalis is not recommended, especially if there is obstruction of ventricular outflow [47].

Congenital heart disease

Infants of Diabetic Mothers have a higher risk of developing congenital malformations, including congenital heart disease with an incidence of 5% [48]. The cardiac malformations that occur more frequently in IDMs are: transposition of great vessels, ventricular septal defects, aortic stenosis, pulmonary atresia, dextrocardia, tetralogy of Fallot, truncus arteriosus [49].

Hematologic complications

Hyperbilirubinemia

It is defined as an indirect bilirubin level greater than 4 mg / dL in umbilical cord blood; greater than 6 mg / dL in the first 12 hours of birth; above 10 mg / dL in 1 day; Indirect bilirubin above 13 mg / dL between day 1 and 2, and more than 15 mg / dL at any time [3]. It occurs in 25% of cases [38]. Infants diabetics mothers with poor glycemic control during pregnancy are at higher risk of developing hyperbilirubinemia, this could be attributed to polycythemia and ineffective erythropoiesis accompanied by increased red blood cell turnover, and immaturity of bilirubin conjugation and excretion liver [38].

Polycythemia and hyperviscosity

Polycythemia is defined as a hematocrit greater than 65% in the neonatal period, and has an incidence of 16% to 34% in IDM [50]. It is considered secondary to chronic intrauterine tissue hypoxia, which results in an increase in erythropoietin concentration [29]. Hyperviscosity can appear in IDM with a hematocrit less than 65% but rarely less than 60% [51]. The factors that influence the appearance of polycythemia are: smoking during pregnancy, congenital diseases such as hypothyroidism, adrenal hyperplasia, and genetic disorders such as trisomy 13, 18 and 21 [51]. Furthermore, an observational study conducted in Turkey observed a correlation between elevated maternal levels of β-hydroxybutyrate and polycythemia [52]. *Its clinical manifestations are neurological signs such as lethargy, irritability, hypotonia stand out, as well as respiratory distress, oliguria, and food intolerance [29,51]. Hypoglycemia is the most common metabolic problem associated with polycythemia in IDM, with an incidence of 12% to 40% of cases [51]. In asymptomatic neonates with a hematocrit greater than 70% and symptomatic neonates with a hematocrit greater than 65%, plasmapheresis is recommended [3].*

Thrombosis

Fetal polycythemia, hyperviscosity, and increased platelet aggregation are factors that could explain the increased incidence of intravascular thrombosis in IDMs [50]. The most common is renal venous thrombosis, it classic signs are hematuria and a palpable renal mass, and its management is based on fluid control and heparin to prevent the formation of additional clots [3,17]. Cerebral thrombosis and necrotizing enterocolitis are also common [17].

Iron Deficiency

Iron metabolism abnormalities have a prevalence greater than 90% in Infants of Diabetic Mothers (IDM) [53]. Iron deficiency alters the synthesis of cytochrome c and of proteins that contain iron and sulfur, thus affecting how tissues use oxygen and energy metabolism, generating a negative impact on cognitive development and on the behavior of IDMs, finally generating adverse effects on the muscle and the gastrointestinal function [2,53].

The Neonatal Small Left colon Syndrome (NSLCS)

It is defined as a disease in which there is a transitory functional obstruction of the colon in the newborn, similar to Hirschsprung's disease and meconium plug syndrome, and has a high association with maternal diabetes, with an incidence of 40 to 50% of cases. reported cases being Infants of Diabetic Mothers [54-56]. It is suggested that the cause is related to the release of glucagon by hypoglycemia, this hormone decreases the motility of the jejunum and the left colon and increases parasympathetic activity [57].

Long-Term Effects

Infants of diabetic mothers have a higher risk of type 2 diabetes mellitus, data from studies in Pima Indians showed that 45% of individuals between the ages of 20 and 24 with diabetic mothers during pregnancy developed the disease [58].

Inadequate insulin production and tissue insulin resistance are mechanisms that contribute to the development of long-term diabetes mellitus and obesity in Infants of diabetic mothers. However, obesity has multifactorial causes since other factors such as lifestyle, demographic, postnatal and intrauterine factors intervene [1,2]. Other long-term effects are hypertension and neurological deficit [1,3].

Conclusion

Diabetes during pregnancy is associated with an increased risk of embryonic, fetal, and neonatal complications, which means that Infants of Diabetic Mothers have a higher risk of morbidity and mortality compared to Infants of non-diabetic mothers. Therefore, their management must be anticipated through metabolic monitoring, with blood glucose measurements and ultrasound monitoring.

Abdominal circumference is the most important measure to predict the risk of macrosomia, measuring it at the beginning of the third trimester of pregnancy will reduce the risk of injuries, mainly shoulder dystocia and associated complications such as perinatal asphyxia and hypertrophic cardiomyopathy.

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