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The influence of gestational diabetes on fetal development. A review

Abstract

Gestational diabetes is a form of diabetes that starts during pregnancy and although is an affection which may regress after birth, it leaves its mark on the health of the mother and fetus in the perinatal period, but also on long-term and appropriate treatment initiated at the onset of the disease can reduce its effects. It is defined as carbohydrate intolerance of varying degrees of severity, occurring during pregnancy and that can complicate it (i.e. by increasing the risk of preeclamplsia, polyhydramnios, macrosomia, respiratory distress, hypoglycemia, hypocalcemia and hyperbilirubinemia and neonatal injury at birth). Although the diagnostic criteria varies from one guideline to another, the oral glucose tolerance test remains the gold standard method for the diagnosis of gestational diabetes. Underlying this article we have found significant studies and guidelines related to gestational diabetes published in PubMed and Cochrane databases. Gestational diabetes may be associated with repeated miscarriages, still births, pregnancy-induced hypertension, preeclampsia, premature detachment of the normally inserted placenta, trauma at birth, postpartum bleeding and infection immediately postpartum. Increased risk of maternal complications also increases the risk of premature births. The only modifiable factor in the emergence of all these complications is obesity. Gestational diabetes is a pathology that requires a multidisciplinary team and close monitoring of perinatal complications of pregnancy, in order to prevent and reduce these complications, both on short and long term.
Keywords: *gestational diabetes, complications, fetal development*

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Introduction

Gestational diabetes is a form of diabetes that appears during pregnancy and although the disorder may develop after birth, it has an impact on the health of the mother and the fetus both in the prenatal period and on long-term while appropriate treatment initiated at the onset of the disease can reduce these consequences[(1)].

This paper is intended to signal both the association between gestational diabetes and fetal development peculiarities and its consequences for mother and fetus, on both short and long term. The sources analyzed for this paper are relevant articles and guideline published on specialized sites regarding gestational diabetes published in PubMed and Cochrane databases.

The patients entered in the analyzed trials were either diagnosed with diabetes during the current pregnancy or prior to it[(2)].

Definition and diagnosis

Gestational diabetes is defined as intolerance to carbohydrates of various degrees of severity, occurs during pregnancy and that can complicate it by increasing the risk of preeclamplsia, polyhydramnios, macrosomia, respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia and neonatal injury at birth. Although gestational diabetes may remit after birth, complications of this disease may be encountered on long term[(1,2)].

Although the diagnostic criteria varies from one guideline to another, the oral glucose tolerance test remains the gold standard method for the diagnosis of gestational diabetes[(2)].

Pathophysiology

Insulin is secreted from pancreatic beta-cells in response to increasing blood sugar. The mechanism can be altered either by a problem of insulin secretion, or it is ineffectiveness, a situation known as insulin resistance. This latter mechanism is found in case of gestational diabetes, when hormones secreted by the placenta in the second trimester (i.e. progesterone, prolactin and cortisol) reduce the effectiveness of insulin action, which leads to increased transplacentar nutrient transport for the developing fetus which promote growth. In a normal pregnancy, the body tries to maintain balance by increasing insulin secretion[(3)]. Latest theories include in the pathogenesis of gestational diabetes an inflammatory component.

The inability of insulin to keep blood sugar levels within normal ranges is manifested by the transplacentar transfer from mother to child of glucose, which produces a fetal hyperinsulinemia in order to counter the glucose excess transferred[(3,4)].

Gestational diabetes is responsible for teratogenicity by high levels of glucose transferred to the embryo, leading to disturbances in the genes that control the development process. In theory, any system can be affected by glucose excess, but the most common malformations seen in clinical trials are neural tube defects (i.e. spina bifida) and heart malformations (i.e. outflow tract defects)[(4)]. There have also been cases of holoprozencephaly and sintelencephly[(5)].

Recognition of teratogenic effect of glucose, even episodic or transient, could explain the increased number

of birth defects, especially neural tube ones in obese women[5].

At the molecular level, increased levels of glucose up taken by cells in the embryo produces oxidative stress through a combination of increased oxidative metabolism in a stage of development where the balance of free radicals is immature and altered biochemical pathways. This leads to decreased expression of splotch (PAX3), a gene responsible for the neuroepithelisation and development of the neural crest. It can affect the expression of other genes involved in neural tube or other organs development, but in the absence of compensatory mechanisms Pax3 deficit in a vulnerable stage of development is sufficient for the occurrence of neural tube defects. PAX3 decodes the transcription of factors that inhibit apoptosis like tumor protein (p53). Therefore, a fall in PAX3 increases the expression of p53, which activates cell death, leading to the abandonment of neural tube closure process[6]. It should be noted that the same mechanism involved in the occurrence of neural tube defects, decreased PAX3 with increased p53 may occur in other conditions such as ionizing radiation and administration of anticonvulsant drugs[7].

Studies have shown that PAX3 gene expression is low in patients with type I/II diabetes, leading to increased incidence of neural tube defects in this population. It was also showed that neural tube defects occur because of the direct effect of glucose on the embryo and not due to hostile uterine environment. The role of folic acid is not fully understood in reducing neural tube defects, but folate increases the production of methionine, which prevents the buildup of homocysteine, which has a prooxidant role. In addition, folic acid may have antioxidant properties itself[8].

In the literature there are studies that focus on observing the relationship between first trimester markers used to assess the risk of chromosomal abnormalities and gestational diabetes. In the first trimester aneuploidy screening we consider the mother's age at conception, nuchal translucency size (TN), the level of β-human chorionic gonadotrophin (β-HCG) and pregnancy associated plasma protein A (PAPP-A) in maternal blood. β-HCG and PAPP-A are influenced by race, smoking, body weight and the method of conception, which is why they are therefore taken into account in calculating the risk by multiples of the median values. Most studies have concluded that the PAPP-A is lower in patients known to have diabetes compared to the general population, and should therefore be included among the markers of the first trimester, which would decrease the number of false-positive results[9]. Some studies have noted that the size of TN and β-HCG levels are not much altered in patients with pre-existing diabetes pregnancy or that will develop gestational diabetes. Other studies have reported a significant decrease in the levels of PAPP-A and β-HCG in a population which will develop diabetes during pregnancy, others just a drop in PAPP-A but not in the β-HCG value. One possible explanation for understanding these differences between studies could be the severity of gestational diabetes[10].

Maternal and fetal complications

Since 20 years ago it was found that the intrauterine environment plays an important role for epigenetic alterations and the effects can persist into adolescence, causing obesity and type II diabetes. As many countries have begun to adopt a Western lifestyle, it was observed an increase in the obese population. Increasing body mass index (BMI) in women also increases the risk of newborn macrosomia, newborn which will likely in the future develop type II diabetes[11]. Diet can influence the circultion of key hormones with secondary alteration of transplacentar transport of nutrients, resulting in excessive growth of the fetus[12].

Birth weight is an indicator of fetal growth, but may influence infant, adolescent and adult morbidity and mortality. It can be influenced by various genetic or constitutional or environmental factors. Studies comparing birth weight based on race, showed a lower weight in the South Asian and black population, while fetal macrosomia is more common in the white population considering non-diabetic pregnant women. Macrosomia has a similar prevalence in the European and color population in pregnant diabetics[13].

Newborn babies of pregnant women who have maintained a high-fat diet show altered messenger ribonucleic acid expression and protein levels for glucose transport, like glucokinase. Obesity of the father can also lead to pancreatic β cell dysfunction. Maternal obesity can lead to hepatic steatosis, increased expression of genes encoding pro-inflammatory proteins such as interleukin-6 and of phospholipase A2 and mast cell proteases in children[14].

Malnutrition also affects fetal growth and can lead to glucose intolerance in adolescence[15]. Obese children known with low birth weight, have a low insulin secretion capacity and exposed to a high calorie diet, are prone to develop various metabolic diseases[16,17]. Animal models exposed to a reduced calorie diet or a low-protein during pregnancy show a reduction in pancreatic β cells and low birth weight. In mice, the phenotype persists through adolescence, with the gradual appearance of glucose intolerance observed at about 4 months after birth and insulin resistance and type II diabetes in approximately 17 months after birth[17]. Timing of such diets is important: if exposure to a low-calorie or low-protein diet early in pregnancy hasn't important consequences for pancreatic cells, as opposed towards the end of pregnancy this exposure can be detrimental for the fetus[18]. A high fat diet during lactation could induce hyperinsulinemia and hyperglycemia to the newborn. Animal models show that chickens affected by a diet low in protein can reach a normal weight if they are breastfed by a normal mother, but have a shorter lifespan, supporting the hypothesis that early stimulation of pancreatic cells can overwork the regenerative capacity of pancreatic cells[19].

Uncontrolled gestational diabetes and obesity are correlated with neural tube defects and disorders in psychomotor and intellectual development in children[20].

Of the neural tube defects we mention spina bifida-variable defect of the vertebral arch which is incomplete

or absent, holoprozencephaly- incomplete cleavage of the forebrain in both hemispheres between day 18 and 28 of gestation and sintelencephaly, the absence of the separation between the frontal and parietal lobes, the absence of the corpus callosum and of the differentiation of hypothalamic and lentiform nuclei[21,22]. Holoprozencephaly is characterized in particular by craniofacial malformations[23].

The most severe of these are considered cyclopia, etmocephaly and cebocephaly which are found in about 2% of cases. Hypotelorism is a moderately severe malformation and is observed in 14% of cases. Coloboma of the iris is considered a minor malformation found in 36% of cases[24].

Clinical manifestations include, in addition to the central nervous system abnormalities and facial dysmorphism, and a number of neurological development disorders. Therefore, clinical panel may include a wide range of systemic diseases, endocrine and neurological disorders[25]. Therefore, these children may experience neuro-psychiatric disorders such as psychotic episodes since adolescence with risk of schizophrenia in adult life[26].

As previously mentioned, gestational diabetes can be diagnosed by performing oral glucose tolerance test between 24-28 weeks of pregnancy[27].

Central nervous system malformations and facial prenatal ultrasound can be evaluated in the first quarter inch of pregnancy[28]. The ultrasound can notice the presence of a single cerebral ventricle in the form of a horseshoe, the absence of the interemisphere fissure, the absence of corpus callosum and cavum septum pelucidum, fused thalamus, thin cerebral cortex, microcephaly or hydrocephaly, hypotelorism, cyclopia, malformed nasal pyramid, cleft lip or cleft palate[29]. Additional information can be provided by magnetic resonance imaging. Other diagnostic methods that we can be used are karyotyping and genetic study, for higher resolution karyotyping. This condition puts a significant imprint on pregnancy, both by malformations that may arise during it, and the consequences associated with them. Results can be seen in both the short and long term[30].

Fetuses of mothers with gestational diabetes can have various malformations of the central nervous system and heart, with varying degrees of severity, may suffer trauma at birth, neuro-psychiatric disorders, obesity and diabetes since adolescence, their repercussions and going up to death[30].

Gestational diabetes may be associated with repeated miscarriages, still births, pregnancy-induced hypertension, preeclampsia, premature normally inserted placental detachment, trauma at birth, postpartum bleeding and infection immediately postpartum[30]. Increased risk of maternal complications also increases the risk of premature births. The only modifiable factor in the emergence of all these complications is obesity[31].

Birth of a patient diagnosed with gestational diabetes is a challenge, even more if it presents one or more risk factors. Since the birth of macrosome babies increases the risk for dystocia shoulder, brachial plexus injuries, collarbone fracture, the likelihood is greater that they require birth by caesarean section or instrumental vaginal delivey[32]. The birth of such patients in emergency, by instrumental vaginal delivery or by caesarean section requires a multidisciplinary experienced team of presents more risks than the birth by planned cesarean section. Given this, we consider that patients with gestational diabetes might benefit from delivery by scheduled caesarean section. Various studies analyzing the benefits of a birth by elective caesarean section did not reveal a reduction of complications, except for shoulder dystocia[33].

Due to vulnerable ground in this period, women have an increased risk of developing gestational diabetes in subsequent pregnancies or diabetes in the future.

Therefore, it was found that women who were macrosomic at birth have an increased risk of developing breast cancer later in life because of increased levels of fetal insulin and insulin-like growth factor with mitogenic effect[34].

Breastfeeding was found to have a beneficial effect on the behavior of the patients diagnosed with gestational diabetes. It has been found that women who are breastfeeding have a lower prevalence of diabetes at 6-9 weeks postpartum compared to the the non-lactating. The duration of breastfeeding may influence the development of diabetes mean duration: 12.3 years compared to 2.3 years for not breastfeeding. The next factor that can predict the development of diabetes in a patient with a history of gestational diabetes, after BMI, is race. Insulin resistance varies between races, the black and Asian populations are known with a higher prevalence of it, hence the higher number of patients with cardiovascular disease and type II diabetes[35].

As we can see, gestational diabetes is a pathology that requires a multidisciplinary team and close monitoring of pregnancy. In order to decrease the number of complications due to fetal malformations and increased levels of glucose, it is necessary to conduct a pre-conception screening and to start an aggressive therapy during this period, followed by close monitoring of blood glucose during pregnancy[35]. Given this, it would be helpful for patients with diabetes type I/II to be counseled pre-conceptionally and if pregnancy should be planned. For patients with known diabetes it should be noted that altered production of hormones that regulate glucose homeostasis in pregnancy require dose adjustment of administered insulin, diet and exercise in order to maintain an acceptable level of blood sugar. It should also be explained that these patients singular treatment with insulin may decrease rates of complications compared with those of a patient who has diabetes and that additional measures may be needed. As the obesity prevalence in young population increses the role of fetal malformations by excess glucose exposure is an important area of future investigation[36]. The influence of other biological markers on course of pregnancy was studied in other studies[37-39].

Conclusions

Gestational diabetes is a form of diabetes that appears during pregnancy and although the condition can regress after birth, it leaves its mark on the health

of mother and fetus in the perinatal period and on long-term, while appropriate treatment, started at the onset of the disease may reduce its effects. Hormones secreted by the placenta starting with the second trimester reduce the effectiveness of insulin, which leads to increased transplacentar nutrient transport as the fetus develops and promotes its growth. Therefore, clinical symptoms can be complex and include a wide range of systemic diseases, endocrine and neurological disorders. This pathology has a significant influence on pregnancy, gestational diabetes consequences may be visible both in the short and long term. Therefore, the management of this disease requires a multidisciplinary team and close monitoring of pregnancy. ■

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