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REVIEW

CENTRAL NERVOUS SYSTEM MALFORMATIONS ASSOCIATED WITH DIABETIC EMBRYOPATHY IN LATIN AMERICAN MOTHERS WITHOUT GLYCEMIC CONTROL: A REVIEW

Gilson Jabel Zelada-Bran [1], Ana Sofía Celada-Barrios [1], Jarmila Liska de León [2], Adrián Esteban Salatino-Diaz [1]

Filiation:
[1] Universidad de San Carlos de Guatemala, Facultad de Ciencias Médicas, Ciudad de Guatemala, Guatemala
[2] Hospital de Gineco-Obstetricia, Instituto Guatemalteco de Seguridad Social, Ciudad de Guatemala, Guatemala

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Correspondence:
Gilson Jabel Zelada Bran
Email: gilsonjabel23@gmail.com

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ABSTRACT

Objective: Describe the malformations of the nervous system associated with diabetic embryopathy in mothers without adequate glycemic control in Latin America. **Material and methods:** A thorough review of publications in recognized online databases in Spanish and English was conducted. The search engines used included MEDLINE, PubMed, Scielo, BVS, HINARI, EBSCO, Google Scholar. We found descriptive, observational, retrospective, clinical practice guidelines, systematic review, case-control, and meta-analysis. **Results:** Through a systematic review of articles, it was found that malformations of the central nervous system secondary to diabetic embryopathy are closely related to various risk factors in Latin American women. **Conclusions:** An association was found between the multifactorial epidemiological characteristics of Latin American women and the development of central nervous system malformations secondary to diabetic embryopathy, resulting from multiple pathophysiological processes triggered by maternal hypoglycemia.

Key words: Syphilis, Congenital syphilis, Social determinants of health, Logistic models (Source: MeSH NLM)

INTRODUCTION

Worldwide, according to data from the World Health Organization (WHO) and the Pan American Health Organization (PAHO), it is estimated that 1 in 10 pregnant women are diagnosed with diabetes. 90% of them have gestational diabetes and 10% of pregnant women who had pregestational diabetes did not know their diagnosis; with Latin America being the most susceptible region. To be more specific, Mexico reports 10% to 15% of pregnant women with diabetes, in South America, countries such as Argentina, Brazil and Peru report 7%, 9% and 16% respectively, of diabetic pregnant women. (1-4)

Diabetes Mellitus is a group of metabolic disorders characterized by chronic hyperglycemia that results from the alteration in the proper secretion of insulin or in the uptake of insulin in the different tissues at the level of the body. This pathology can be classified into types 1 and 2 according to its epidemiology, clinical presentation, and underlying metabolic aberrations. (5-7)

The presence of diabetes mellitus diagnosed prior to pregnancy and its persistence during pregnancy increases the risk of maternal-fetal morbidity. The fetus is affected by maternal hyperglycemia, causing sequelae in its intrauterine development. In the embryological period it can cause congenital malformations, the latter encompasses a spectrum of malformations directly linked to a state of maternal hyperglycemia called diabetic embryopathy. (6-8)

Diabetic embryopathy is characterized by a teratogenic environment caused by maternal hyperglycemia. This leads to an increase in the formation of free radicals that come from various metabolic pathways, which increases the concentration of glycosylation and its end products, leading to genetic dysregulation and apoptosis. The consequence is a set of congenital anomalies of the cardiac, musculoskeletal, renal and central nervous system types, the latter being the object of study of the present work. Of these, the most prevalent are: neural tube defects, caudal regression syndrome, anencephaly, encephalocele and holoprosencephaly. (7, 9–13)

In Latin America, diabetic embryopathy is an issue of high social importance since it is one of several complications related to diabetes mellitus, due to the fact that it affects the embryogenesis of the human being and conditions the quality of life of the newborn.

MATERIAL AND METHODS

A thorough review of publications in recognized online databases in Spanish and English was carried out to obtain reliable sources of information. Observational, descriptive, retrospective, clinical practice guidelines, systematic review, case-control, and meta-analysis were used. The search engines used included MEDLINE, PubMed, Scielo, BVS, HINARI, EBSCO, Google Scholar.

After the compilation of different sources of information through the aforementioned search engines, they were filtered and grouped according to their type of source to favor their analysis and ensure that they are sources with greater relevance and validity for the development of this study.

RESULTS

Prevalence and incidence of diabetes in pregnant women in Latin America

Gestational diabetes mellitus (GDM) is a disorder that occurs in pregnancy caused by carbohydrate intolerance. It is said to occur in approximately 3-10% of pregnancies. This metabolic disease is the most common one during pregnancy, occupying the third place as a chronic disease that can affect a pregnancy. (14, 15)

According to the WHO, the prevalence of gestational diabetes varies from 1 to 14% worldwide, which is why it has been determined as a public health problem, because it is an important cause of maternal and perinatal morbidity. In Latin America and the Caribbean, gestational diabetes is a disorder that has high prevalence rates, depending on the different characteristics of the population and diagnostic criteria used by different specialists. (16)

In the different regions of Latin America and the Caribbean, different data on prevalence have been reported. It is worth mentioning examples from

different countries in this region, Mexico for 2022 showed 22.7% prevalence. In the Central American region, studies conducted by PAHO and WHO showed a prevalence of 11.4% in 2010. The International Diabetes Federation (IDF) for the year 2019 indicates that in South and Central America there was a prevalence of gestational diabetes of 16.14%. (17-20)

In Mexico, according to the Ministry of Health through the Unified Information System for Epidemiological Surveillance (SUIVE) mentions that for 2016 the incidence of new cases of prenatal diabetes mellitus is 26.73 cases per 100,000 inhabitants. The SUIVE refers to the fact that women with GDM face complications such as hypertension, newborns with macrosomia, challenging deliveries and malformations. (21)

The variability in the incidence of gestational diabetes in different regions of Latin America could be attributed to divergences in the diagnostic criteria and characteristics of the populations analyzed in each country. However, it should be noted that, in some subregions, the lack of epidemiological surveillance on the part of the public institutions of each country on gestational diabetes makes it difficult to obtain accurate and up-to-date information on its incidence.

Risk Factors for Diabetes in Pregnant Women in Latin America

According to the American Diabetes Association (ADA) and the Latin American Diabetes Association (ALAD), the risk factors for gestational diabetes are the following:

- Age over 30 years
- History of Diabetes in First-Degree Relatives
- Body mass index (BMI) greater than 30kg/m2.
- Fasting blood glucose greater than 85mg/dl,
- History of GDM in previous pregnancy
- History of macrosomia in previous pregnancy, birth weight greater than 4,000gr
- Pre-pregnancy signs of insulin-resistance (acanthosis nigracans)
- History of high or low birth weight (greater than 4,000g or less than 2,500g),
- Ethnicity (Latino, Native American, and African American)
- Hypertensive Disorder With Drug Therapy That Is Not Effective
- Hypercholesterolemia
- Hypertriglyceridemia
- Polycystic ovary syndrome
- Physical inactivity. (22, 23)

In several studies carried out in different Latin American countries, it has been observed that the most prevalent, significant and common risk factor in pregnant women with gestational diabetes is BMI greater than 25 kg/m2. It has been found that pregnant women who are overweight and obese have a higher chance of developing gestational diabetes compared to those who have a normal BMI or suffer from malnutrition. It was also observed that pregnant women with obesity were three times more likely to have gestational diabetes. (24–30).

One of the most relevant risk factors identified in the studies was clinical and family history. The results demonstrated that a family history of diabetes mellitus, as well as a personal history of diabetes mellitus and gestational diabetes in previous pregnancies play a significant role in the development of gestational diabetes. (28, 30-32)

In the context of studies carried out in different Latin American countries on gestational diabetes and its risk factors, it was observed that age affects the development of this condition. Within this group, it has been identified that the most prevalent age range to develop this condition is between 30 and 35 years old. These findings are consistent with the risk factors mentioned by different medical associations, such as the ADA and ALAD. (24, 26, 27, 33)

Pathophysiology of Diabetic Embryopathy

Teratogenic maternal environment

Diabetic embryopathy is characterized by a state of maternal hyperglycemia that triggers the formation of a teratogenic environment for embryonic development and causes mutations that prevent the adequate expression of different genes important for normal embryogenesis, which can delay DNA duplication, therefore, cell replication, which would interrupt the different processes to carry out organogenesis. (8, 10, 34, 35)

This teratogenic environment is characterized by decreased or excessive DNA methylation, specifically of different genes related to neuroepithelial differentiation, especially genes ANKRD11, B3GNT1, BRF1, Srebf2, TRIO and PAX3. (8, 10, 36-41)

Other characteristics of the teratogenic environment are the state of hyperglycosylation to proteins, many of the detrimental effects of hyperglycemia and the high bioavailability of glucose are mediated by increased flow through the hexosamine pathway. Another effect of hyperglycosylation is DNA damage at the histone level, in response to such injury, several repair factors are repositioned at the damaged site, this dynamic repositioning is induced after the modifications in translation in the histones and at their binding sites or near the sites where the DNA was damaged. (42)

Acetylation of certain proteins due to maternal hyperglycemia disrupts normal embryogenesis, especially those proteins that are related to neurulation. Specifically, the myriscoylated alanine rich kinase C (MARCKS) substrate, whose acetylation is regulated through the interactive protein Tat 60, the latter is activated by oxidative stress generated by hyperglycemia, which induces DNA damage. In addition, MARCKS, its own acetylation, is necessary for its phosphorylation, which inhibits the protective factors of this protein on the mitochondria and the endoplasmic reticulum, which induces stress in these organelles and promotes the inadequate synthesis of proteins, especially those necessary for neurulation. Inhibition of this protein has been shown to be associated with defects such as encephalocele and holoprosencephaly. (13, 43)

Oxidative stress and loss of the embryo's antioxidant defenses

The hyperglycemic environment to which embryonic tissues are exposed before the circulatory system is formed, causes the oxidative metabolism of glucose to increase with increased oxygen consumption. This state of hypoxia can stimulate the production of mitochondrial super oxide radical, establishing a state of oxidative stress, which is embryotoxic. Mitochondrial dysfunction is the major producer of free radicals such as superoxide and hydrogen peroxide, which come from the electron transport chain, specifically, produced in complex I and III of the chain. (36, 37)

Loss of autophagy regulation and pro-apoptotic state

Maternal diabetes has been shown to suppress the autophagosome. Its function is to engulf dysfunctional proteins and cellular organelles. It plays an important role in the formation of neuroepithelial cells during neurulation. Impairment of autophagy induced by maternal hyperglycemia causes apoptosis of neuroepithelial cells. (45)

The endoplasmic reticulum response to hyperglycemia-induced stress is the abnormal folding of certain proteins. Likewise, signaling cascades involving pro-apoptotic proteins are activated, and that favor the development of neural tube malformations; "C/EBP homologous protein" (CHOP), "inositol requiring enzyme 1alpha" (IRE1α), "protein kinase R- similar to endoplasmic reticulum kinase" (PERK) and eukaryotic initiation factor 2α" (eIF2α), and collectively referred to as "unfolded protein response" (UPR). (46)

Pro-inflammatory state

Diabetes during pregnancy is also characterized by the alteration of lipid metabolism, and that impacts on the modulation of the immune response, leading to a chronic inflammatory state. (35)

In the hyperglycemic state, a decrease in phosphoinositol 2 and 3 (PIP2 and 3) and diacylglycerol has been demonstrated, due to the decrease in the formation of inositol, which is a precursor of these 3. PIP2 is one of the precursors of phospholipids essential for embryonic tissues, it also stimulates the activity of phospholipase A2. By decreasing PIP2, the activity of phospholipase A2 decreases, the formation of arachidonic acid decreases, which decreases the production and metabolism of prostaglandins, especially prostaglandin E2, which is essential during embryogenesis. (37, 38)

At the placental level, in giant trophoblasts, it has been shown that the SR-B1 receptor participates in the maternal-embryonic exchange of cholesterol and vitamin E uptake during neural tube closure; The deficiency of this receptor due to the oxidative

environment to which its formation is exposed has been related to the presence of malformations of the central nervous system. (36)

Cell division cycle-like protein 5 (CDC5L) is a marker of embryopathy with low tissue specificity, but is mostly expressed in the cerebral cortex, cerebellum, thalamus and hippocampus. This is associated with direct interaction with cells of the immune system such as type 1 neutrophils, complement factor C2, defensin 1. CDC5L has been shown to be associated with neuronal differentiation during embryogenesis, as it has been associated with cell division, DNA repair, and guiding messenger RNA assembly and maturation. (11)

Central Nervous System Malformations Associated with Diabetic Embryopathy in Latin America

Caudal regression syndrome

This syndrome can be classified as "pathognomonic" of diabetic embryopathy, it has been described as the malformation or group of malformations that has been most associated with maternal diabetes, the risk of the fetus developing this condition is 200 to 250 times greater than if it were associated with another cause other than diabetes, especially in those that do not have adequate glycemic control. This is the name given to the clinical picture in which sensory and motor alterations are found, caused by the poor development of the caudal portion of the body, which involves a spectrum of spinal, lumbosacral, pelvic, genitourinary, gastrointestinal and lower limb malformations. At the vertebral level, 60% of cases present scoliosis and 40% are associated with spinal cord malformations. (40, 41, 47, 48)

It has an incidence between 0.01 and 0.05 per 1,000 live births, but it is believed that this is due to underreporting or underdiagnosis. In Central American countries, such as Costa Rica, an incidence of 0.07 per 1000 live births has been reported, figures higher than the world average. 85, 86 This syndrome is more prevalent in males, with a ratio of 2:1. (40)

The most associated malformations of the nervous system or spinal cord are vertebral hypoplasia, vertebral fusion, hemivertebra or butterfly-shaped vertebra, misalignment of the spinal cord, abrupt termination of the spinal cord at different levels, tied or coiled spinal cord and anterior meningocele. (48)

The diagnosis and detection of this syndrome begins in the first trimester, by ultrasound between 11 and 13 weeks of gestation, this pathology is suspected because the crown-rump length is short, the nuchal translucency is wider, and a protrusion is detected in the lower part of the spine. But the definitive diagnosis is made in the second trimester, during the structural ultrasound, it is detected that the spine ends abruptly, in the lower extremities deformity can be observed in the angles of flexion and angulation of the feet, which is known as "Buddha position", since both legs are in abduction, Knees bent and legs crossed. (41, 49)

The prognosis of this syndrome depends on the severity of the vertebral anomalies and other associated malformations. Genitourinary abnormalities are associated with a worse prognosis, as well as signs of neurological deficits such as muscle atrophy or inability to mobilize the lower extremities, further worsening the condition. (49)

Myelomeningocele

It is characterized by a defect in the spinal cord and vertebral arches, the meninges, medulla and cerebrospinal fluid, they herniate and protrude through the spine, 90% of cases are associated with hydrocephalus. It is classified as open or cystic spina bifida, occurring at any level of the neuroaxis. It can represent motor, urological, orthopedic, and cognitive compromise. It is the most common of the open neural tube defects. They are more common in women than in men. (50–53)

In developing countries the prevalence is high, the Congenital Malformations Registry Center of Costa Rica, for 2019, reported a prevalence of 5.44 cases per 10,000 live births, in the period of time of the last 10 years. In Honduras, this defect accounts for 44% of children with congenital malformations. This malformation is not specific and has a specific relationship with maternal diabetes, but it does increase its incidence, from 2 per 1000 live births, in women who are diabetic and have some degree of obesity. (50, 52, 53)

Its diagnosis is prenatal, the tests of choice are: ultrasound, alpha fetoprotein and magnetic resonance imaging. During the second trimester ultrasound, it has a diagnostic effectiveness of 92 to 95%. At the time of the structural evaluation of the spine, it is possible to observe a cystic formation, relatively voluminous, which is located on the medullary axis at any level of the spine, although its most frequent location is in the lumbo-sacral region in 45% of cases. (52)

The symptoms and degree of neurological deficit will depend on the location of the defect, the higher the level in the spinal cord, the greater the sensory and motor deficit of the patient. The main neurological clinical features that occur are: muscle weakness, paresis, paresthesia or hypoesthesias, trophic changes, gait disorders and sphincter control. Depending on the size of the defect, its location and the involvement of neural structures, partial or toral paralysis in the lower limbs, loss of superficial and deep sensation may occur. (53, 54)

Once the prenatal diagnosis is confirmed, there are three options, the first is prenatal treatment and surgery, the second is post-birth treatment, and the third is termination of pregnancy. Timely treatment is vital, as it prevents infections of the central nervous system, reduces the incidence of motor and intellectual disabilities, and improves the patient's prognosis and quality of life. (52, 53)

Anencephaly

It is the most serious malformation of the central nervous system, it begins at the beginning of embryonic development, it is characterized by the absence of a scalp, without parts of the cranial vault, without meninges, without part of the cerebral hemispheres and without cerebellum, although if the back part of the brain and nerve stem is formed, all this makes it incompatible with life. (55)

This malformation is one of the most frequent neural tube closure defects, with an incidence of 1 child per 1,000 live births, and its frequency varies from 0.5 to two per 1000 births, especially in populations of low socioeconomic status such as Latin American countries. (55)

It results from a defect in the fusion of several sites of neural tube closure between day 23 and 26 of gestation. This can be categorized into two; meroacrania, which is characterized by a small defect in the cranial chamber covered by the brain-vasculous region, i.e. the foramen magnum is not involved; and holoacranium, in which the brain is completely absent, i.e., the defect goes beyond the foramen magnum. (55)

The diagnosis is made by ultrasound, it begins during the first trimester, between 11 and 13 weeks of gestation, although about 100% of cases are diagnosed during the second trimester. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), recommends that in the first trimester the evaluation and detection of the fetal head with third ventricle, choroid plexus, thalamus, posterior fossa and measurement of nuchal translucency, and could give an early diagnosis of anencephaly. The method of choice for definitive diagnosis is structural ultrasound performed between the 18th and 23rd week of gestation. (51, 56)

This malformation is incompatible with life, although on some occasions the structures found in the brain stem are preserved, allowing certain vital functions to develop such as spontaneous breathing, some primitive reflexes such as sucking, but these are maintained for a limited time, and the newborn dies in the next hours or days. although most commonly it dies during labor. (55)

Holoprosencephaly

This malformation is characterized by the absence of division of the forebrain between the third and fifth week of pregnancy, which causes the total or partial absence of separation of the cerebral hemispheres, accompanied by facial and non-facial malformations. The most associated facial defects are: premaxillary agenesis, cyclopia and cebocephaly; and non-facial malformations; transposition of great vessels, postaxial polydactyly, genital, vertebral, and shortened limb defects. (57, 58)

It is the most common malformation of the forebrain, occurring in 1 per 10,000 live births, although other authors mention an incidence of 1 per 8,000 live births or up to 1 in every 16,000 live births, which depends on the sociocultural context of each population. (59, 87)

For the diagnosis of holoprosencephaly, especially its most severe presentations, which are semilobar and alobar, it is performed during the first trimester of pregnancy. The findings show the partial or complete absence of the interhemispheric fissure, distorted appearance of the choroid plexuses in a transventricular axial plane, the fused thalamus, and sometimes facial malformations over the midline are also observed. (59)

The management of these cases must always be multidisciplinary, a team made up of different specialists such as gastroenterologists, neurologists, neurosurgeons, plastic surgeons, among others. The newborn with this malformation should receive follow-up focused on his neurodevelopment. Among the most frequent complications are: inability to chew and swallow, bronchoaspiration, endocrine dysfunction, hydrocephalus, convulsive syndrome, hypothalamic and cerebral dysfunction, the latter manifest as difficulty and instability in regulating body temperature, heart rate and respiration. (59, 60)

The prognosis of these patients is more favorable than is believed, since most survive beyond 12 months of life, even surviving to adulthood. This long survival is attributed to recent advances and diagnostic methods, including imaging methods for the early detection of severe or moderate malformations. (60)

Encephalocele

It is a malformation of the neural tube caused by herniation, through a defect in the skull, cranial contents, specifically the meninges, brain mass and part of the ventricles, and some parts of the brain mass go through a defect on the midline of the vault or base of the skull. It is defined as a mesodermal abnormality that results in the failed separation of the ectoderm surface from the neuroectoderm. This results because the cranial part of the neural tube does not close during embryogenesis, between 8 and 12 weeks of gestation. (61- 63)

This is the least common malformation of neural tube defects, occurring in 0.8 to 5 in every 10,000 live births. 1 in 3 die, and 76% of deaths occur during the first day of life. (62)

Diagnosis is made by ultrasound during the second trimester of pregnancy. Craniofacial defects can be seen as a cystic structure with or without echogenicity, depending on the content of the herniation. Magnetic resonance imaging is the preferred imaging method for categorizing the contents of the herniation and defining the specific location of the bony cleft. (64)

The clinical features of this malformation vary according to its location and severity; Syncytial or frontoethmoidal encephaloceles may present hidden or with craniofacial deformities; Baseline encephalocele may or may not be detectable on external evaluation, but may present with a widened nasal bridge or other mid-facial abnormalities or with a nasal, epipharyngeal mass, shortness of breath, recurrent upper respiratory tract infections, recurrent meningitis, or cerebrospinal fluid leakage; Occipital encephalocele, which is evident at birth and can be diagnosed at prenatal control by ultrasound, is characterized by being covered with skin, if it is large it is associated with cranial nerve deficit, poor sucking and feeding, spasticity, blindness, seizures and developmental delay. (51)

The treatment of this malformation is surgical, this consists of the incision of the sac, amputation of the excess tissue up to the level of the surrounding skull, the dura mater and skin are closed. In general, the location and content of the encephalocele are the best predictors of prognosis. Patients with occipital encephalocele have the worst prognosis, and in the different presentations of this malformation, if the lesion is large, the prognosis is poor in the long term. (62)

Existing preconception and prenatal preventive measures to decrease maternal-fetal morbidity and central nervous system malformations

Diagnosis and preconception care of diabetes mellitus

For the diagnosis of any of the aforementioned situations, the WHO states that the patient must present a typical clinical picture of diabetes mellitus associated with laboratory findings that confirm morbidity. The typical clinical symptoms of diabetes mellitus are characterized by; polydipsia, polyuria, polyphagia, and weight reduction or gain. (66)

The laboratory data, which the WHO recommends to have to establish and confirm the diagnosis are; random blood glucose greater than or equal to 200mg/dL unrelated to the time at last intake, venous plasma fasting blood glucose greater than or equal to 126mg/dL and confirmed by a second test during the same week, or blood glucose greater than or equal to 200mg/dL two hours after an oral load of 75 grams of glucose, This is known as an oral glucose tolerance test. (37, 67, 68)

After establishing the diagnosis, it is important to plan the pregnancy, take measures prior to gestation in order to reduce the risk of maternal and fetal morbidity. Women with diabetes must understand the importance of their morbidity and the risks they run when they become pregnant, the repercussions it would have on the evolution of their disease, and the results on the development of the fetus, in this case the increased risk of developing congenital malformations between 6 and 10%. (51)

During this pre-pregnancy check-up, it is desired to achieve adequate control of carbohydrate and lipid metabolism, achieving optimal nutritional status by changing eating habits, directing a food plan according to the patient's habits and economic possibility with the aim of maintaining a healthy weight, evaluated by BMI. Another important aspect is physical activity, which has been shown to favor the metabolic control of the patient. (65)

One of the markers most closely related to the development of diabetic embryopathy is glycosylated hemoglobin, which is expected to be below 7%. Pregnancy is strongly discouraged when it is above 10%. It has been established that for every 1% increase in glycosylated hemoglobin, the risk of malformations increases by 5 to 6%. (65)

Diagnosis and prenatal care of pregnant women with diabetes mellitus

For its diagnosis, the WHO and the ADA recommend that the first screening should be performed at the first visit of the pregnancy control, a random glycemia is performed to make an initial evaluation, if the visit is before 24 weeks, the screening and diagnosis is carried out as mentioned in the previous section. (69)

If the first visit is made after week 24 or the patient continues to be followed up and already exceeds this gestational age, fasting blood glucose should be performed, if she has values between 92 and 126mg/dl, it is thought that she is starting with gestational diabetes and does not need confirmatory testing. (69)

Another proposed diagnostic method, known as universal screening, refers to the oral glucose tolerance test, with a load of 75 grams of fasting glucose. This should preferably be performed between 24 to 28 weeks of gestation, and can be performed in the first trimester if the patient meets some of the risk factors mentioned in the previous paragraphs. Prior to oral loading, a venous sample is taken on an empty stomach, 8 to 14 hours of previous fasting, which must be less than 92 mg/dl, then, the oral load with 75 grams of glucose is administered, an hour later, a second sample is taken, this one must be less than 180 mg/dl. After two hours, a third sample is taken, this one should be less than 153 mg/dl. The test is described as positive if at least one of the values is above the mentioned value and establishes the diagnosis of gestational diabetes, so it is described as the "one-step" test. Some authors recommend performing a second test if it was performed in the first trimester, repeating it between 24 and 28 weeks, and subsequently, a new one 3 or 4 weeks after the latter, until reaching the 34th week of gestation, after this period it is no longer prudent to repeat the test. (43, 69-72)

There are other methods, Carpenter and Coustan, propose the "two-step" test, which consists of the O'Sullivan test, is a traditional oral load of 50 grams at any time of the day and is independent of the previous intake, to be carried out between 24 to 28 weeks, and can also be performed between the 13th to 23rd week of gestation if the patient meets the risk factors already mentioned. It is said that it is positive if the glycemia after one hour is greater than 140mg/dl and after two hours it is greater than 120 mg/dl, it is confirmed with an oral glucose tolerance test with a load of 100 grams of glucose, this if it is done with previous fasting. But if the initial measurement is greater than 180mg/dl, the diagnosis of gestational diabetes is established. (71, 73)

Prenatal Care for the Pregnant Patient with Gestational Diabetes

An important and fundamental part of the prenatal care of these patients is metabolic control and is established with self-monitoring of blood glucose levels on an outpatient basis and body weight. Glycemia control is the main objective of metabolic control, it is considered to have reached the goal when glycemia has been within normal ranges in 80% of the measurements and hypoglycemia has not been demonstrated, for which it is essential that the patient is provided with a glucometer and that she is guided in its proper use. To be specific, fasting blood glucose levels should be between 70 and 90 mg/dl, one hour postprandial between 90 and 140 mg/dl, and two hours postprandial between 90 and 120 mg/dl; and in none should it be below 60 mg/dl. (73)

During the first trimester it is important to assess the risk factors already mentioned above and thus decide which laboratories to perform aimed at the study of the patient's carbohydrate tolerance, in this period the first ultrasound evaluation is also performed, specifically between 11 to 13 weeks of gestation for the early evaluation of risk of chromosomal abnormalities. In the second trimester, universal screening is carried out or screening can be performed in "two steps", likewise, the second ultrasound evaluation is performed, between 18 and 22 weeks for the evaluation of gross structural anomalies, in this case to rule out malformations of the neural tube or central nervous system. Part of this evaluation is the performance of a fetal echocardiogram between the 24th and 28th week of gestation, likewise, different authors recommend an early evaluation of fetal growth by ultrasound between the 28th to 32nd week of gestation to evaluate early complications such as macrosomia. And finally, in the third trimester, start the monitoring of fetal well-being, control tests, assess the performance of oral tolerance test again, and the third evaluation between 32 and 36 weeks for the evaluation of fetal growth. (73, 74)

Nutritional status for pregnant women with diabetes mellitus

The main objective of establishing a healthy diet for the diabetic patient is to prevent excessive weight gain. Several studies have shown that women with a BMI between 25 and 29 kg/m2, which is classified as overweight, have shown a higher risk of developing gestational diabetes. In obese women, BMI greater than 30 kg/m2, the risk of gestational diabetes has been shown to be even higher. In both cases, there is a relationship with the appearance not only of maternal malformations, but also of fetal malformations. (75)

Approximately 75 to 80% of pregnant women with diabetes achieve the therapeutic goal by applying only a strict diet with the advice of an experienced nutritionist. Theoretically, the diet to be followed by these pregnant women can be calculated according to their ideal weight or their actual weight, as well as according to their basal energy expenditure. This diet should be normocaloric, not restrictive, that is, the patient should eat three meals and a snack among them, with the aim of distributing the recommended glucose schedule and thus avoid hypoglycemia during the fasting time and postprandial hyperglycemias, which would lead to more and more metabolic control of the patient. (76)

It is important to provide micronutrients, which are essential in any pregnancy, but in the case of diabetic patients, they play an important role as antioxidants. Among the most important and proven to be antioxidant are vitamin A, C, D, E, B vitamins and folates. (65, 77, 78)

Physical activity for pregnant women with diabetes mellitus

One of the important pillars as part of prenatal control in these women is physical activity since, together with the oriented diet, it favors to improve glycemic control, excessive weight gain and lipid control, improves insulin sensitivity, and, therefore, metabolic control. If there are no contraindications to physical exercise, it should be aerobic of mild to moderate intensity, with periods of time of 30 to 45 minutes a day and 3 to 4 times a week, or a total of 150 to 300 minutes a week. Exercises such as stationary cycling, aerobic dancing, swimming, or aerobic activity inside a pool are recommended. (79-81)

In the same way, other studies have proposed resistance physical activity, this refers to activity in which the contraction of long muscle groups is prioritized to overcome external resistance from a

resting state, this helps the progression of muscle strength and reduces the volume of adipose tissue. This routine, in addition to having the same effects as aerobic activity, is believed to regulate adiponectin and leptin levels. In addition, this routine facilitates the utilization of glucose by facilitating its transport into the muscle cell, and also increases the sensitivity of the muscle cell to insulin, prioritizing that the energy needed for contraction comes from glucose. The frequency with which it is performed is the same as aerobic activity. It is recommended that this activity be performed with light weights, using only the weight of the same body or using elastic bands. (81)

It is important to stop all physical activity when vaginal bleeding, amniotic fluid leakage through the vaginal canal, abdominal pain, onset of shortness of breath that does not improve after rest, headache, severe chest pain, muscle weakness or dizziness. (80, 81)

DISCUSSION

Diabetic embryopathy is a syndromic condition characterized by the set of congenital malformations associated with diabetes mellitus in pregnant women. Malformations can encompass different systems and organs, in isolation but often in a multisystemic manner, mainly including cardiac, genitourinary, musculoskeletal and central nervous system malformations, the latter being the most frequent of this pathology. It has been shown that, at the Latin American level, diabetic embryopathy has an incidence of 18.7%, it is the result of multiple causes that interact at the same time, conditioning the state of health of the pregnant woman and interrupting the normal development of embryogenesis. (7, 82)

The prevalence of gestational diabetes in Latin America and the Caribbean represents an important public health challenge, and it is relevant to compare it with other regions of the world such as North Africa and the Middle East, where a lower prevalence is observed compared to our region, however, it is crucial to highlight that the prevalence varies considerably in each country. This can be attributed to various factors, such as the methodology used for diagnosis, inclusion criteria, and the particular characteristics of the population studied. This significant variability of the data reported by different countries highlights the need for broader and more standardized epidemiological surveillance in the region, which will allow a better understanding of the prevalence of gestational diabetes and a more effective implementation of each country's prevention and treatment strategy. (14–20, 83–85)

The risk factors associated with gestational diabetes in Latin America vary across studies and medical associations, but some shared elements have been identified. The most prevalent risk factors include a high BMI, first-degree family history, previous history of gestational diabetes, an age >25 years. These factors highlight the importance of careful evaluation and follow-up of pregnant women who may have risk factors as they are prone to developing diabetes during pregnancy. (16, 19, 22, 23)

The pathogenesis of diabetic embryopathy is multifactorial but triggered by maternal hyperglycemia, although various mechanisms are in constant study and analysis, it has been possible to determine the bases of the different processes involved in congenital defects, in this case, of the central nervous system. Maternal hyperglycemia triggers the excessive formation of free radicals, which exposes the embryo to an environment of oxidative stress. The latter is key to triggering a pro-inflammatory, pro-apoptotic environment, in which the antioxidant defenses of the embryo itself are not sufficient and there is no regulation of autophagy, therefore, initiates a teratogenic maternal environment. (8, 10, 34, 35, 38, 42, 45, 70)

The teratogenic environment involves aberrant methylation, increased glycosylation, and acetylation of transcriptional factors and proteins, which activates responses that promote DNA or histone damage. The oxidative environment generates stress in the cellular organelles, especially in the mitochondria and endoplasmic rhetic, which generates the misfolding of proteins necessary for the proliferation of the neuroepithelium. (8, 10, 34, 35)

At the Latin American level, malformations of the central nervous system associated with diabetic embryopathy tend to have a greater impact on those that do not have glycemic control, in addition to the conditioning factors mentioned above. Of

these defects, the one that most presents or is characteristic of diabetic embryopathy is caudal regression syndrome, which is characterized by neural tube, lumbosacral, pelvic, genitourinary and lower limb defects. This syndrome is characterized by varying in its presentation and severity, and is directly associated with high glycemic values, greater uncontrol of maternal diabetes, and greater severity in the presentation of caudal regression syndrome. (7, 40, 41, 48, 49)

Likewise, other defects are associated with maternal diabetes, such as neural tube defects, anencephaly, holoprosencephaly and encephalocele, which have a lesser impact. All of them have a greater quantity and severity with a greater glycemic imbalance. If these are not lethal for the fetus, in the post-birth period they impact the physical and social aspects of the newborn, since the development and growth of the baby is not only limited in the cognitive aspect, but also in neurodevelopment, motor and aesthetic development. The latter is because, despite the fact that certain defects can receive surgical therapy, this treatment does not ensure that all the aspects already mentioned are fully restored and guarantee a life and growth like that of the majority of the totally healthy population. (7, 53, 59, 62, 64)

During the preconception period, the diagnosis and screening to rule out diabetes mellitus is a set of variables to be taken into account, ranging from the patient's medical, obstetric and family history, classic symptoms (polydipsia, polyphagia, polyuria, weight reduction or gain), to laboratory data (random glycemia, fasting glycemia and glycosylated hemoglobin). After making the diagnosis, the objective of planning the pregnancy is that the future mother and her partner understand the risks that pregnancy entails for both the patient and the fetus, in the case of congenital malformations, the risk of these in a hyperglycemic state increases from 6 to 10%. Therefore, it is essential that prior to pregnancy, glycemic control, metabolic control, reducing weight gain, initiation of pharmacological treatment, supported by individualized nutritional follow-up and aerobic or resistance physical activity are achieved. (37, 73, 65, 67, 68)

The prenatal care of the diabetic pregnant woman should be multidisciplinary, with the sole objective of bringing blood glucose levels to normal values, reducing excessive weight gain, which are the two variables that have been mostly associated with the development of congenital malformations, in this case, of the central nervous system. For this, nutritional follow-up with individualized diet and intake of antioxidant factors is essential, which have been shown to exert some benefit in counteracting the pathophysiological mechanisms that characterize diabetic embryopathy. Also, physical activity with aerobic or resistance exercises has been shown to reduce excessive weight gain in these patients. Together, diet and physical activity have been shown to be sufficient to improve blood glucose in 75 to 80% of cases, decreasing the risk of maternal and fetal complications, such as congenital defects of the central nervous system. (65, 73–75, 78, 86)

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All authors: Conceptualization, methodology, manuscript selection, design, research, project management, funding, data analysis, generation of graphs and figures, writing of the first draft, writing, review, approval of the final version of the manuscript.