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Neurodevelopment at Two Years of Age in Newborn Infants of Diabetic Mothers

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ABSTRACT

Introduction: *The lack of brain maturity caused by hyperglycemia in children of diabetic mothers has repercussion on language, fine and gross motor skills and cerebral palsy, which seem to have a higher incidence due to an adverse intrauterine environment, characterized by hyperglycemia, maternal hypoglycemia, vascular abnormalities and hypoxemia, which profoundly affect neurodevelopment.*

Objective*: To describe neurodevelopment at two years of age of newborns born to diabetic mothers, who were admitted to the Pediatric Follow-up service of the National Institute of Perinatology in Mexico.*

Material and Methods*: It is a retrospective, observational, longitudinal, analytical study of a cohort of newborns born to diabetic mothers, at two years of age, from 1990-2010. Two hundred and forty four infants plus a 51control group met the criteria for admission to the Pediatric Follow-up service and had the evaluations from the different services. Statistic analysis; means, medians, frequencies, ANOVA, Ch2, SPSS version 21.*

Results: *295 infants met the criteria and four groups were formed; 1) control group, 2) diabetes mellitus type 1, 3) diabetes mellitus type 2 and 4) gestational diabetes. Perinatal morbidity was higher for the type 2 diabetes mellitus group, but the presence of cerebral palsy was higher in mothers with gestational diabetes 8.3%, the Bayley II assessment was lower for type 1 diabetes mellitus, problems of decreased language for the different groups.*

Conclusion: *There is a relationship between infants of diabetic mothers and the presence of neurodevelopmental problems, mainly cerebral palsy in gestational diabetes, Bayley II with normal mental and low motor scales.*

Keywords

Newborn, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Gestational diabetes mellitus, Neurodevelopment, Bayley II, Cerebral palsy.

Introduction

Diabetes Mellitus

It is a chronic metabolic disease, characterized by high blood glucose levels, where the pancreas does not use, or does not produce enough insulin. The most common is type 2 diabetes mellitus (DM2) in adults; the prevalence has increased in low-income countries. Juvenile type 1 diabetes mellitus (DM1) is a chronic condition in which the pancreas produces little or no insulin [1]. Currently, 62 million people in the Americas have type 2 diabetes, from 2000 to 2016 mortality increased by 5%, being the sixth cause of death in the world and the second for disability. The main factors for the development of DM2 are obesity, overweight and

physical inactivity. The prevalence of overweight in the Americas was double than that observed worldwide, 80.7% of young people are inactive [1,2]. The prevalence in Mexican population is 18% in those over 20 years [3]. In other countries, the prevalence for DM2 is 4.8% and 18.7% for DM1 in the general population. In pregnancy, the prevalence is 4.5% to 16.1% [4]. DM is the most common cause of end-stage renal disease and its prevalence is increasing [5].

Diabetes Mellitus during Pregnancy

Diabetes mellitus during pregnancy is divided into pregestational and gestational diabetes mellitus (GDM), due to insulin resistance and pancreatic beta cell dysfunction during pregnancy. Its presence has been reported in 9 to 25% of all pregnancies in the world [6]. More and more is known about how the adverse intrauterine environment influences neonatal neurodevelopment (ND) and its effects throughout life [7]. Because of this, there is a need to know and investigate the developmental origins of health and disease (DOHAD), which refers to the intrauterine environment and its effects on the health of the newborn later in life [8]. The intolerance to carbohydrates is of variable intensity; it begins or has its first manifestation during pregnancy. An adequate evaluation reduces maternal and fetal morbidity [6-8]. During pregnancy there is an increase in insulin resistance, this resistance is due to the secretion of diabetogenic hormones by the placenta, such as growth hormone, corticotropin releasing hormone, placental lactogen and progesterone [8].

Placenta

Insulin does not cross the placenta, but glucose does, hyperglycemic and hypoglycemic events affect the embryonic development of the fetus. Hypoxia, fetal acidemia, increased lactate and elevated placental weight, reflect an impaired metabolism in diabetic pregnancies due to poor glucose control [9]. Poor maternal vascular perfusion of the placental bed is a pathologic finding that results in abnormalities in oxygenation and flow dynamics in the intervillous space [10]. In diabetes mellitus, regardless of whether it is pre or gestational, the changes are the same. It presents villous immaturity, chorioangiogenesis, infarction, villous fibrinoid necrosis, nucleated fetal red blood cells and ischemia when compared to placentas from non-diabetic mothers [10,11].

Fetal Hypoglycemia

There is a relationship between maternal hypoglycemia during pregnancy with fetal growth retardation and perinatal mortality. When diabetes is undiagnosed or poorly controlled, it can cause fetal hypoglycemia and increased neonatal mortality [12]. During pregnancy, 45-71% of mothers may experience 3 to 5 times more severe hypoglycemia in the first trimester and less frequently in the second trimester, with teratogenic effects. Low glucose levels in the mother produces intrauterine growth retardation and low weight in the fetus [13].

Fetal hyperglycemia

Fetal hyperglycemia and hyperinsulinemia seem to be responsible for fetal and neonatal complications that increase morbidity and mortality, despite advances in diabetes management [14]. During the first trimester of pregnancy, maternal hyperglycemia can cause structural abnormalities, central nervous system abnormalities and abortions during the second and third trimesters of pregnancy as well as diabetic fetopathy with manifestations in the neonatal period [15,16].

Congenital Malformations

These occur in up to 13-30% of pregnancies with a frequency up to 10 times higher in pregnancies of diabetic mothers when compared to normal pregnancies. They cause up to 50% of perinatal deaths, caudal regression syndrome, and hypoplastic left colon, renal, skeletal muscle and central nervous system anomalies, cyanogenic congenital heart disease, and hypospadias. The risk being higher for pregestational than gestational diabetes [17-19].

Stillbirth

The prevalence for stillbirth is 3% in pregestational diabetes, increasing up to 4.5 times more [17,20]. It is believed that the fetus grows slowly in the uterus due to poor circulation, small and damaged blood vessels in women with poor metabolic control [21,22]. Worldwide, fetal death is around 3.9 million, with gestational diabetes mellitus being the second cause for this [23].

Neonatal Morbidity and Mortality

Children of mothers with GDM are at increased risk of developing macrosomia, short neck, and full moon fascies. From 10 to 50% present hypoglycemia secondary to hyperinsulinism that appears in the first two hours of life. Hypocalcemia occurs in 20-40% and appears in the first 72 hours of life, and is attributed to transient functional hypoparathyroidism. Polycythemia and hyperviscosity occur in 30-40%. Hyperglycemia and chronic hyperinsulinemia stimulate basal metabolism and oxygen consumption, with increased erythropoietin levels. Hyperbilirubinemia secondary to various factors occurs in 20-25%. Respiratory distress due to deficit in the production of surfactant by type II pneumocytes, as well as maternal hyperglycemia and fetal hyperinsulinism that inhibit proper surfactant production. Other causes of neonatal morbidity and mortality are: transient tachypnea of the newborn, intrauterine growth retardation in pregestational diabetics with vasculopathy and decreased placental flow, perinatal asphyxia, hypertrophic cardiomyopathy, shoulder dystocia, high weight for gestational age, macrosomia [15-17,24-16].

Maternal Morbidity and Mortality Associated with Diabetes Mellitus

Preeclampsia occurs in 15-20% for DM1 and 10-14% for DM2. GDM and preeclampsia share risk factors such as advanced maternal age, nulliparity, multiple pregnancies, race, diabetic ketoacidosis, and obesity [27]. Cardiovascular disease is the leading cause of pregnancy related maternal death, and hypertension is a risk factor attributable to women becoming pregnant at an older age [28]. These complications during pregnancy share similar risk factors and pathophysiological changes with negative neurodevelopmental outcomes [17,27,29].

Diabetes Mellitus and Neurodevelopment

The programming of pathologies during childhood and adult life have their origin during fetal development. In the case of diabetes mellitus, it is related to problems in neurodevelopment and fetal development of the central nervous system, with a wide variety of neurological pathologies [30]. During pregnancy, it is associated with a greater number of neurodevelopmental problems due to different biological alterations such as hyperglycemia, hyperinsulinemia, oxidative stress, hypoxia, iron deficiency, and affects the development of the central nervous system (CNS) of the fetus. Alterations in glucose and insulin in mothers and children are considered a teratogenic factor for the development of the CNS [30,31].

Neurodevelopment

It is the progressive differentiation of organs and systems as well as the dynamic processes between the child and the environment [32]. Changes in behavior produced by the maturation of the CNS functions, allow children to build schemes of greater complexity [33], adjust, develop abilities, psychomotor skills, affective relationships, socialization, and personality formation, with or without sensory problems [34]. Neurodevelopment begins in intrauterine life with the neurulation of the embryo's ectoderm and takes an average of 20 -25 years to mature. This prolonged process is necessary for experience-based maturation, and depends on the brain's ability to develop the neurological pathways responsible for normal human functioning [35].

Maturation of the Fetal and Postnatal Central Nervous System

The first half of gestation is dominated by cell multiplication and migration, the period of histogenesis or development of neuronal tissue, gives rise to the hundred billion neurons that the brain possesses. All neurons must move to their final place in the cortex during migration, a precise process that can be affected by hyperglycemia [36-38]. The second half of pregnancy is characterized by cell growth and differentiation. Encephalization occurs in the forebrain, the brain triples its weight and millions of synaptic connections appear. The germinal zone that gives rise to the germinal matrix and the subcortical plate that gives rise to the subcortical zone are transitory structures and occur between 32-33 weeks. Myelination is a specific maturational process, considered an essential phenomenon for the rapid conduction of the nerve impulse [35-38].

Biomarkers for Neurodevelopment in Diabetes Mellitus

Decosahexaenoic acid (DHA) is decreased in umbilical cord blood and has been associated with cognitive delays [39]. Variations in leptin levels in the umbilical cord are associated with neuromotor development [40]. Oxidative stress, oxidized glutathione, and catalase activity affect behavior, short-term memory and spatial work [41-44]. Interleukin-8 (IL-8) levels are associated with decreased fine motor skills and problem-solving abilities at two years [42]. Peroxisome proliferation activation receptors (PPARs) are involved in cognitive functions [43,44]. Brain-derived neurotrophic factor (BDNF) is lower in mothers with GDM [45].

Diabetes Mellitus and Neurodevelopmental Sequels

The adverse intrauterine environment increases the risk of neurodevelopmental delay by 1.30 to 2.36 times [46]. DHA levels in the umbilical cord are lower in GDM children and at 6 and 12 months are associated with low Bayley II (BSID II) Mental Scale Index (MDI) and Motor (PDI) scores with p 0.049 and p 0.043 [47]. BDNF levels may have a neuron protection factor against glucose metabolism lesions; at 6 and 12 months, the children of mothers with GDM had higher body weight p 0.04, height p <0.01, low language p 0.038. The BDNF is lower in the GDM group at 12 months, p 0.013 [45]. The levels of saturated fatty acids (SFA), DHA, changes in fasting glucose during the second half of pregnancy are related at 12 months with low scores in the Bayley scale compared with the control group without diabetes [48]. However, in the PREOBE study at 6 months the children of mothers with obesity presented an accelerated development in cognition and language with p 0.035, compared with the children of GDM [49,50]. The children of women with diabetes had lower language scores when compared to the children of mothers without diabetes [51]. Tertti in 2015 compared mothers with GDM treated with metformin versus insulin. At two years, the infants presented a normal Hammersmith neurological assessment and Bayley III without significant differences [52]. When comparing neurodevelopmental problems in children of mothers with DM1, DM2 and GDM, the negative effects on neurodevelopment are greater for DM1, which was associated with a higher risk of developmental delay and epilepsy/infantile spasms. DM2 is associated with developmental delay, cerebral palsy, and epilepsy/ spasms. GDM poses an increased risk of developmental delay [53]. In children of well-controlled insulin-dependent mothers, neurological development may be similar to that of a child of a mother without diabetes at 6, 12, 24, and 36 months. However, children of DM1 mothers presented low language, cerebral palsy < p 0.03 [54].

Little is mentioned about premature newborns born to mothers with DM and its effects on neurodevelopment. In 2021 in the USA, 122 children of mothers with DM were studied, and were evaluated at 2 years of corrected gestational age with Bayley III, the results were low in cognition and language in children of older diabetic mothers, with an abnormal neurological examination (11%) and sensory impairment (22%) [55]. In a study done in 2021 in our follow up service (INPer) the MDI at12 and 24months was normal, but PDI was below normal (79 and 80 points) [56].

Diabetes Mellitus and Cerebral Palsy

Mothers with diabetes mellitus are at increased risk for high rates of preterm births, sometimes with increased risk of hypoxia, which can trigger perinatal asphyxia, and thus brain injury associated with cerebral palsy [57]. Advanced maternal age (over 35 years), has a greater probability of presenting diabetes mellitus during pregnancy, with odds ratio 1.9 (95% CI 1.3-2.8), and this in turn is a risk factor for the presence of cerebral palsy [58,59]. A Norwegian study tried to correlate 17 maternal chronic pathologies during pregnancy with cerebral palsy and found that the highest risk for cerebral palsy was in DM2 RR 3.2; 95% CI 1.8-5.4), DM1

in third place with RR 2.2; (95% CI 1.4-3.4) [60,61]. We must not forget that obesity increases pregestational diabetes, and this in turn increases cerebral palsy with a RR 2.10 (95% CI 1.76-2.52), and gestational diabetes for paralysis brain with a RR 1.35 (95% CI 1.22-1.50) [62]. 35 children of mothers with DM1 were studied at an early age, searching for the diagnosis of CNS damage or dysfunction, 4 presented cerebral palsy and 9 presented soft neurological signs or minor neurological dysfunction at 18 months [63].

Objective

To describe the impact on neurodevelopment at two years of age in the children of type 1, 2 and gestational diabetic mothers, who attended the Pediatric Follow-up service of the National Institute of Perinatology.

Material and Methods

Observational, analytical, longitudinal, retrospective study of a cohort of infants of diabetic mothers at two years of age, carried out in the period of 1990-2010. A total of 6320 records of infants admitted to the Pediatric Follow-up Service (15-year Surveillance Program in neurodevelopment, (see Figure 1), were reviewed with the following criteria; Newborns less than or equal to 1500g, newborns less than or equal to 34 gestational weeks, mechanical ventilation for more than 3 days, bronchopulmonary dysplasia, surfactant application, intraventricular hemorrhage, posthemorrhagic hydrocephalus, seizures, neuroinfection, hypoxic ischemic encephalopathy, APGAR score less than 3 at one minute and 6 at 5 minutes, with a pH of 7.0, intrauterine growth retardation, multiple pregnancies and infants of mothers with immunodeficiency virus. All were patients from the National Institute of Perinatology, which cares only for high-risk pregnant women. Only 244 (3.8%) infants met the criteria for being children of a diabetic mother (it is important to clarify that all the mothers had control, except one), in addition to a control group without diabetes. Statistical analysis; measures of central tendency, parametric tests, ANOVA, Chi^2, statistical significance, statistical program SPSS version 21.

Definition of assessment instruments according to the multidisciplinary team of the Pediatric Follow-up service (Figure 1)

Amiel Tison Neurological Examination: Performed at 1,3,6,9 and 12 months of corrected gestational age by the Pediatric service. It assesses; clinical examination of the skull, elements collected from the mother, sensory development, posture and spontaneous motor activity, passive and active tone, primitive reflexes and postural reactions [64].

Neurological Abnormalities Classification

Mild; an altered maneuver in active and/or passive tone, reflex of the upper and/or lower extremities, no asymmetries, head control, independent sitting, balance reflexes. Moderate; upper/lower extremity asymmetries with altered passive and/or active tone, head control present, assistance in sitting down, sitting for 30 seconds, balance reflexes absent. Severe; abnormal motor activity, poor for age, no head control, absence of independent sitting position, scissor straightening of the lower limbs, opisthotonos [65].

Mayo Clinic Neurological Examination

It is a neurological examination that is applied from age 2, every 6 months, when the infant is seen at the Pediatric clinic. It allows interpreting the patient's muscle activity, understanding motor exploration through movement assessment, and briefly identifying cerebral palsy [66].

Infant Neurobehavioral Assessment

Screening instrument whose objective is the early detection of risks for delayed development. It is based on the direct observation and work with the child on relevant aspects of child development. It is applied by the Neuromotor Stimulation service at the age of 1,4,8,12,18 and 24 months. Includes 60 behaviors, 10 items by age. Mild delay is 2 months, moderate delay 4 months and severe delay 6 months of developmental delay [67].

Bayley II Development Scale

Is a child development scale that is applied by the Psychology department at 1 to 2 years of age. Evaluates the functional development that the child presents, diagnoses delay in development and planning intervention strategies. Mental and Motor Scale: determines the cognitive level, language, personal, social areas, fine and gross motor development. Mental Scale (MDI), Motor Scale (PDI) scores: 115 accelerated development, 85-114 normal development, 70-84 slight developmental delay, less than 69 significantly retarded performance [68].

Human Communication Department

Specialists in Human Communication assess infants from 3 months and then every 6 months. According to the international value system; normal hearing, international system 10-20 db, mild or superficial hearing loss 21-40 db, moderate or medium hearing loss 41-70 db, severe hearing loss 71-90 db, profound hearing loss or deafness greater than 91 db [69]. Language expressed in months according to the age.

Nutrition

A Nutrition specialist provides nutritional guidance starting at 6 months, then twice a year. Anthropometric measurements of weight, height and head circumference are recorded, using the CDC tables for girls and boys [70].

Results

295 infants who met the criteria were included for the present study. Four groups were formed as follows; group 1 the control group (CG) without diabetes 51-17.3%, group 2 (G2) 89-30.2% the group that corresponds to DM1, group 3 (G3) 71-24.1% which is DM2 group and group 4 (G4), the GDM 84-28.5%. In relation to sex, female 48.1% and male 51.9%, it was similar for all groups. Weight 1695g and gestational age of 33.3 weeks average, both being lower for GDM with $p = 0.00$. The weight-for-age ratio in premature infants was 59.5% and for full-term infants was 9.8%, the high weight for premature infants was 1.7% and none in term infants, low weight-for-age was 30.3% for DM1, statistically

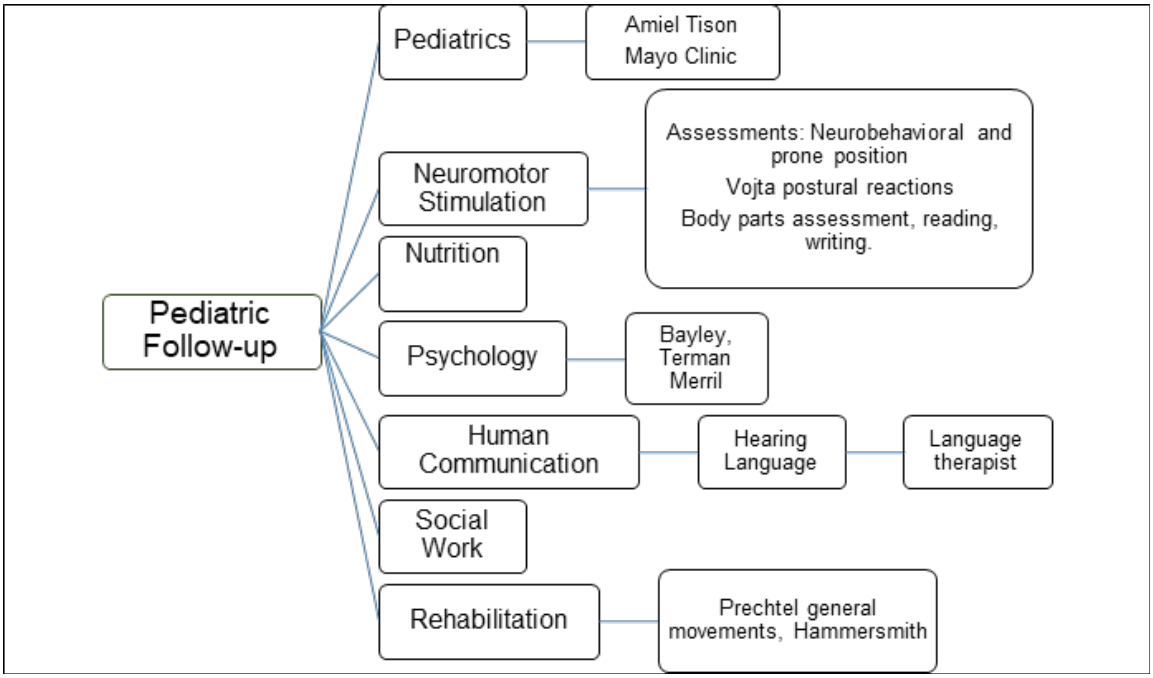

Figure 1: Pediatric Follow-up Program at 15 years of age, National Institute of Perinatology

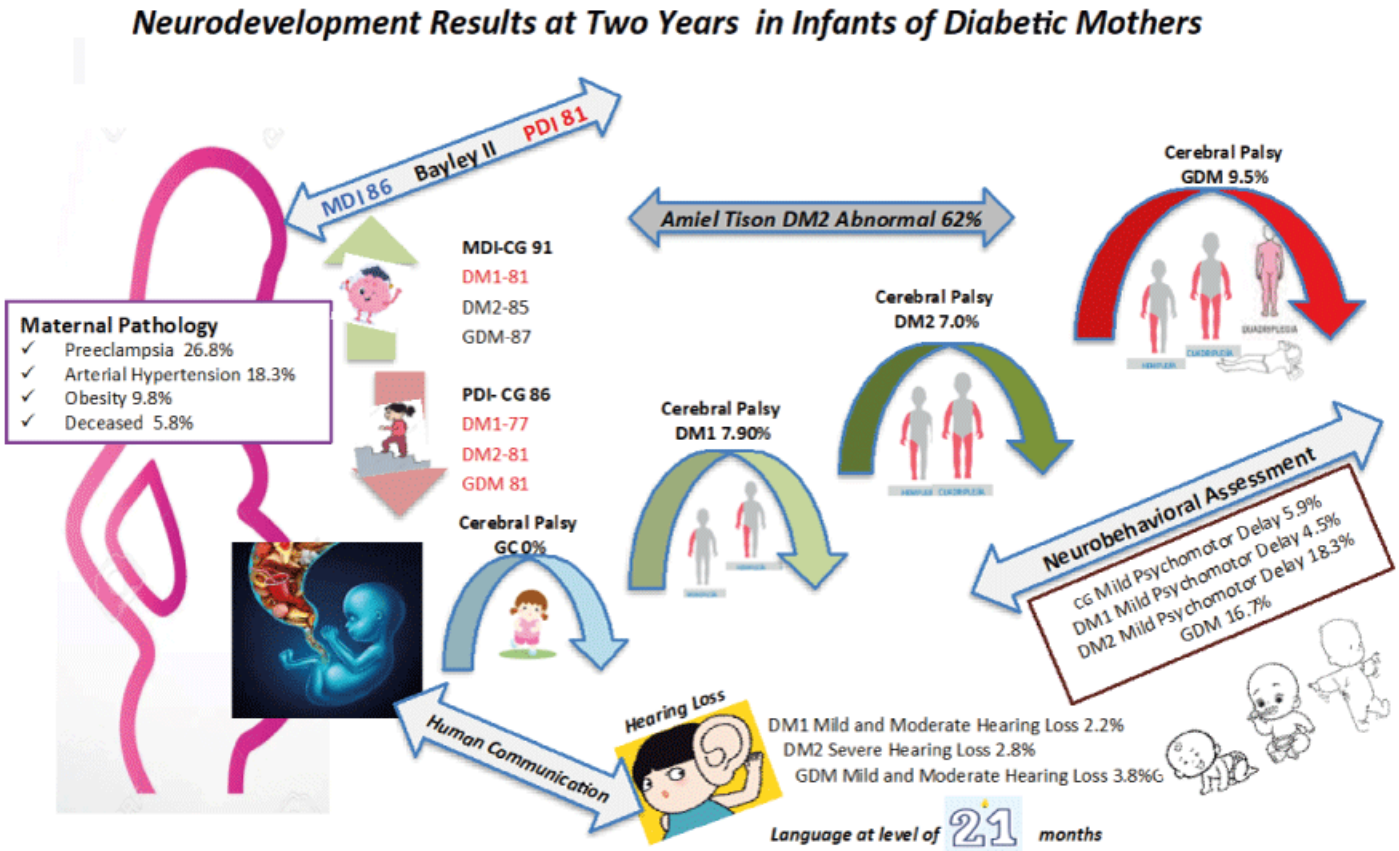

Figure 2: Maternal pathology associated to pregnancy of the diabetic mother; Preeclampsia, arterial hypertension, obesity, deceased during the study, were the most frequent. Bayley II developmental assessment, mental scale (MDI) was lower for type 1 diabetes mellitus (DM1), motor scale (PDI) below average for DM1, diabetes mellitus 2 (DM2), gestational diabetes (GDM), compared to the control group (CG). Amiel Tison with more abnormalities for DM2. The presence of cerebral palsy for CG was 0%, DM1 7.9% monoparesis, hemiparesis, DM2 7.0% hemiparesis and quadriparesis, and GDM 9.5% more cerebral palsy, greater severity and no functional ability. Human communication; Hearing loss: mild and moderate DM1, severe DM2, GDM mild and moderate for this group. Language was low according to age in all groups. Neurobehavioral assessment the slight delay was greater for the GDM.

different between the groups. Maternal age increased according to the groups, for GDM it was 35 years. Lung maturation protocol for the same group was p = 0.00. Drug addiction was higher in DM2. Maternal pathologies such as obesity 16.9%, arterial hypertension 25.4% and preeclampsia 38.0% were higher for DM2 with statistically deferent values. Seventeen mothers died during the course of the study, 12.1% for DM1. The delivery type was C-section 93.9% on average, similar for all groups. The lowest APGAR at one minute for DM2, with adequate recovery at five minutes, however the pH of the venous blood gases taken from the umbilical cord at birth was 7.20 with CO_2 of 53.4 with p=0.04 and 0.02. Positive pressure at birth 47.9% and orotracheal intubation 26.8% for DM2, without statistical relationship (Table 1).

In regards to metabolic problems, the most frequent ones were hyponatremia 7.1%, hypoglycemia, hypocalcemia, asymptomatic hyponatremia and potassium changes, which were 23.2% for DM2, not statistically significant. Neonatal sepsis was the most frequent neonatal pathology, 52.1% for DM2. Intrauterine growth retardation, patent ductus arteriosus, intraventricular hemorrhage and seizures were similar in all groups. Hyperbilirubinemia of multifactorial origin was 53.6% for GDM and only 4.8% had exchange transfusion, with statistical significance. Hyaline membrane disease 35.7% and the use of surfactant 38.1% for GDM, with p= 0.00. Conventional mechanical ventilation 37.1% for DM1, high-frequency ventilation 8.5%, CPAP 15.5%, oxygen hood 14.1% for DM2 with a statistically significant relationship. As for the days and oxygen concentration, it was similar for all groups, as well as for hospital stay (Table 2).

In relation to the neurodevelopmental results at 12 months of gestational age, we found only 47.5% normality on average, 58.3% with greater normality for GDM with p=0.03 and most of the mild abnormalities of 50.7% and 4.2% of severe neurological abnormalities, not statistically different. At two years, the neurological evaluation of the Mayo Clinic was normal 93.2% and 6.8% with some degree of cerebral palsy, DM1 presented mild cerebral palsy 7.9%, DM2 mild cerebral palsy 7.0% and GDM was the one that presented more cases of cerebral palsy 8.3%, with 6.0% mild, 2.4% severe and with no functional ability 1.2%, and with hypotonic syndrome. Neurobehavioral assessment, the majority with normal development, only 17.3% of the population

Table 1: Outcomes of perinatal morbidity of newborn infants born to diabetic mothers.

N=295-100%	Control Group 51-17.3%	Diabetes Mellitus 1 89-30.2%	Diabetes Mellitus 2 71-24.1%	Gestational Diabetes 84-28.5%	p
Sex					
Female 142-48.1%	27-52.9%	42-47.2%	34-47.9%	39-46.4%	*0,89
Male 153-51.9%	24-47.1%	47-52.8%	37-52.1%	45-53.6%	
Weight 1695g	2260g	1593g	1682g	1472g	**0,00
Gestational Age 33.3 wks	36.6 wks	32.8 wks	33.1 wks	32.2 wks	**0,00
Body Composition					
Preterm SGA 62-21.0%	3-5.9%	27-30.3%	13-18.3%	19-22.6%	**0,00
Preterm AGA 176-59.7%	18-35.3%	54-60.7%	46-64.8%	58-69.0%	
Preterm LGA 5-1.7%	1-2.0%	2-2.2%	2-2.8%	0-0.0%	
Term SGA 23-7.8%	15-29.4%	1-1.1%	3-4.2%	4-4.8%	
Term AGA 29-9.8%	14-27.5%	5-5.6%	7-9.9%	3-3.6%	
Maternal characteristics					
Maternal Age 31years	22 years	30 years	34 years	35 years	**0,00
Drug addiction 60-20.3%	10-9.6%	18-20.2%	19-26.8%	13-15.5%	*0,38
Lung Maturation 82-27.8%	2-3.9%	22-24.7%	25-35.2%	33-39.3%	*0,00
Obesity 29-9.8%	0-0.0%	9-10.1%	12-16.9%	8-9.5%	*0,02
Arterial Hypertension 54-18.3%	2-3.9%	20-22.5%	18-25.4%	14-16.7%	*0,01
Preeclampsia 79-26.8%	2-3.9%	23-25.8%	27-38.0%	27-32.1%	*0,00
deaths 17-5.8%	0-0.0%	11-12.1%	3-4.2%	3-3.6%	*0,01
Type of delivery					
Cesarean 277-93.9%	49-96.1%	80-89.9%	68-95.8%	80-95.2%	*0,51
Vaginal 16-5.4%	2-3.9%	8-9.0%	2-2.8%	4-4.8%	
forceps 2-0.7%	0-0.0%	1-1.1%	1-1.4%	0-0.0%	
Neonatal Resuscitation					
APGAR at 1 min 6.1	6.2	6.1	5.9	6.5	**0,63
APGAR at 5 min 8.4	8.6	8.4	8.3	8.5	**0,30
pH 7.23	7.26	7.24	7.20	7.24	**0,04
Co2 49.1	50.1	47.3	53.4	46.7	**0,02
Positive pressure at birth 120-40.7%	16-31.4%	34-38.2%	34-47.9%	36-42.9%	*0,29
Orotracheal intubation 67-22.7%	8-15.7%	18-20.2%	19-26.8%	22-26.4%	*0,39

*Ch2,** ANOVA of one factor

Table 2: Outcomes of perinatal morbidity of newborn infants born to diabetic mothers.

N=295-100%	Control Group 51-17.3%	Diabetes Mellitus 1 89-30.2%	Diabetes Mellitus 2 71-24.1%	Gestational Diabetes 84-28.5%	p
Metabolic Problems					
Asymptomatic hypoglicemia 17-5.8%	2-3.9%	5-5.6%	6-8.5%	4-4.8%	*0,70
Asymptomatic Hypocalcemia 4-1.4%	0-0.0%	1-1.1%	3-4.2%	0-0.0%	*0,10
Asymptomatic Hiponatremia 21-7.1%	6-11.8%	4-4.5%	6-8.5%	5-6.0%	*0,39
Potassium Alterations del 4-1.4%	0-0.0%	1-1.1%	2-2.0%	1-1.2%	*0,59
Neonatal Pathologies					
Intrauterine growth retardation 106-35.9%	24-47.15	28-31.5%	26-36.6%	28-33.3%	*0,28
Multifactorial hyperbilirubinemia 129-43.7%	5-9.8%	45-50.6%	34-47.9%	45-53.6%	*0,00
Exchange transfusion 4-1.4%	0-0.0%	0-0.0%	0-0.0%	4-4.8%	*0,01
Neonatal sepsis 146-49.5%	31-60.8%	38-42.7%	37-52.1%	40-47.6%	*0,20
Neuroinfection 4-1.4%	1-2.0%	2-2.2%	0,0%	1-1.2%	*0,64
Patent ductus arteriosus 35-11.9%	2-3.9%	12-13.5%	11-15.5%	10-11.9%	*0,24
Intraventricular Hemorrhage 27-9.2%	0-0.0%	11-12.4%	8-11.3%	8-9.5%	*0,08
Seizures 13-4.4%	2-3.9%	6-6.7%	2-2.8%	3-3.6%	*0,62
Respiratory					
Surfactant 84-28.5%	0-0.0%	28-31.5%	24-33.8%	32-38.1%	*0,00
Respiratory Distress 75-25.4%	0-0.0%	24-27.0%	21-29.6%	30-35.7%	*0,00
Ventilation Mode					
without ventilation 100-33.9%	0-0-0%	40-44.9%	21-32.4%	37-44.0%	*0,00
Conventional mechanical ventilation 125-42.4%	41-80.4%	33-37.1%	21-29.6%	30-35.7%	*0,00
High Frequency Ventilation 24-8.1%	10-19.6%	2-2.2%	6-8.5%	6-7.1%	*0,00
CPAP 22-7.5%	0-0.0%	7-7.9%	11-15.5%	4-4.8%	*0,00
Hood 24-8.1%	0-0.0%	7-7.9%	10-14.1%	7-8.3%	*0,00
Ventilation days 4.6 días	6.2 days	3.8 days	4.1 days	4.5 days	**0,22
Maximum % of oxygen 54%	62%	51%	53%	52%	**0,09
Days of hospital stay 34 days	34 days	30 days	35 days	37 days	**0,26

*Ch2, ** ANOVA of one factor

with some degree of delay in psychomotor development, mild delay 18.3% for DM2, moderate 5.6% for DM1 and severe 6.0% for GDM, with a statistically significant difference. Normal hearing 97.3%, some degree of hearing loss; DM1 2.2% one child with mild and one with moderate hearing loss, DM2 4.2% two patients with severe hearing loss, one with a successful cochlear implant and GDM 3.6% two infants with mild hearing loss and one with moderate hearing loss. Average language at a level of 21.4 months lower for DMG, not statistically significant (Table 3).

For the evaluation of Bayley II at two years, MDI 45.1% with normal development, 42.4% with development below the average and 12.5% not evaluated (it is important to clarify that they are patients who did attend their consults, but could not be evaluated for different reasons such as being asleep, irritable or the mothers needed some emotional support). With 86 average points within the normal range, we have that normal development was for DM2 49.3%, DMG 45.3% and DM1 35.9%, below average development was found in DM1 50.0%, DMG 41.6% and DM2 39.4%, without statistical relationship. This was not the case for the highest score in the control group of 91 points, and only DM1 with 81 points below the average with p=0.03. For the PDI, normal development was 39.0% and 48.5% below average, with 81 points below normal, normal DM2 motor development with 40.8%, followed by MDG and DM1, development below normal for DM1 was 52.8% followed by DMG and DM2, in relation to the score obtained 86 on average, the rest below the average without statistical relationship. Nutrition and anthropometry at the time of graphing both at 12 months and 24 months, were between the 25th and 50th percentile, with height at 24 months with p=0.04 (Table 4).

Discussion

In the present study, it was possible to verify the relationship that exists between the children of diabetic mothers (MD1, DM2 and DMG) and the repercussions that exist with the delay in development and cerebral palsy, which puts the child at risk in the environment that surrounds him. Therefore, the importance of knowing and recognizing the risk factors that present during pregnancy, the neonatal period and the rest of life. The limitation of this work was the control group, which we tried to make as close as possible to the study population but without diabetes, due to the characteristics of the service and the hospital, it was complex.

Table 3: Neurodevelopment outcomes of infants born to diabetic mothers at 2 years of age.

N=295-100%	Control Group 51-17.3%	Diabetes Mellitus 1 89-30.2%	Diabetes Mellitus 2 71-24.1%	Gestational Diabetes 84-28.5%	p
Amiel Tison Neurologic Assessment					
Normal 140-47.5%	27-52.9%	37-41.6%	27-38.0%	49-58.3%	*0,03
Abnormal 155-52.5%	24-47.1%	52-58.4%	44-62.0%	35-41.7%	
Neurologic Abnormalities					
Mild 129-43.7%	24-47.1%	43-48.3%	36-50.7%	26-31.0%	*0,09
Moderate 18-6.1%	0-0.0%	7-7.9%	5-7.0%	6-7.1%	
Severe 8-2.7%	0-0.0%	2-2.2%	3-4.2%	3-3.6%	
Mayo Clinic Neurological Assessment					
Normal 275-93.2%	51-100%	82-92.1%	66-93.0%	76-90.5%	*0,23
Cerebral Palsy 20-6.8%	0-0.0%	7-7.9%	5-7.0%	7-8.3%	
Mild 17-5.8%					
Monoparesia 2-0.75%	0-0.0%	2-2.2%	0-0.0%	0-0.0%	
Right Hemiparesis 5-1.7%	0-0.0%	3-3.4%	0-0.0%	2-2.4%	
Left Hemiparesis 5-1.7%	0-0.0%	2-2.2%	2-2.8%	1-1.2%	
Quadriparesis with independent gait	0-0.0%	0.0.0%	3-4.2%	2-2.4%	
5-1.7%	0-0.0%	0-0.0%	0-0.0%	2-2.4%	
Severe***NHF 2-0.7%	0-0.0%	0-0.0%	0-0.0%	1-1.2%	
Hypotonic Syndrome 1-0.3%					
Neurobehavioral Assessment	47-92.2%	80-89.9%	53-74.6%	64-76.2%	*0,00
Normal 244-82.7%	3-5.9%	4-4.5%	13-18.3%	14-16.7%	
Mild delay 34-11.5%	1-2.0%	5-5.6%	3-4.2%	1-1.2%	
Moderate delay 10-3.4%	0-0.0%	0-0.0%	2-2.8%	5-6.0%	
Severe delay 7-2.4%					
Hearing	51-100%	87-97.8%	68-95-8%	81-96.4%	*0,31
Normal 287-97.3%	0-0.0%	1-1.1%	0-0.0%	2-2.4%	
Mild hearing loss 3-1.0%	0-0.0%	1-1.1%	0-0.0%	1-1.2%	
Moderate Hearing loss 2-0.7%	0-0.0%	0-0.0%	2-2.8%	0-0.0%	
Severe hearing loss 2-0.7%	0-0.0%	0-0.0%	1-1.4%	0-0.0%	
Cochlear implant1-0.3%					
Language 21.4 months	22.1 months	21.8 months	21.2 months	20.8 months	**0,13

*Ch2, ** ANOVA of one factor. ***No functional ability

Table 4: Neurodevelopment outcomes of infants born to diabetic mothers at 2 years of age.

N=295-100%	Control Group 51-17.3%	Diabetes Mellitus 1 89-30.2%	Diabetes Mellitus 2 71-24.1%	Gestational Diabetes 84-28.5%	P
Bayley II Scale MDI					
Above Average Development					
12-4.1%	4-7.8%	1-1.1%	2-2.8%	5-6.0%	*0,24
Normal development 121-41.0%	24-47.1%	31-34.8%	33-46.5%	33-39.3%	
Developmental delay 69-23.4%	14-27.5%	35-28.1%	11-15.5%	19-22.6%	
Significantly Delayed					
56-19.0%	4-7.8%	19-21.9%	17-23.9%	16-19.0%	
Not evaluated 37-12.5%	5-9.8%	13-14.6%	8-11.3%	11-13.1%	
Average 86	91	81	85	87	**0,03
Bayley II Scale PDI					
Above Average Development	2-3.9%	1-1.1%	1-1.4%	4-4.8%	*0,73
8-2.7%	24-47.1%	28-31.5%	28-39.4%	27-32.1%	
Normal development 107-36.3%	12-23.5%	26-29.2%	16-22.5%	23-27.4%	
Developmental delay 77-26.1%					
Significantly Delayed 66-22.4%	8-15.7%	21-23.6%	18-25.4%	19-22.6%	
Not evaluated 37-12.5%	5-9.8%	13-14.6%	1-11.3%	11-13.1%	
Average 81	86	77	81	81	**0,06
Nutrition					
Weight at 12 months 8.270g	8.457g	8.279g	8.275g	8.143g	**0,65
Height at 12 months 71.4cm	71.8cm	71.1cm	71.2cm	71.5cm	**0,84
Head circumference at 12 months 44.9cm	45.2cm	44.8cm	44.7cm	44.9cm	**0,53
Weight at 24 months 10.942g	11.156g	11.032g	11.051g	10.626g	**0,18
Height at 24 months 83.5m	84.7cm	83.8cm	82.8cm	82.8cm	**0,04
Head circumference at 24 months 47.3cm	47.3cm	47.3cm	47.4cm	47.2cm	**0,87

*Ch2, ** ANOVA of one factor

The hospital only treats high-risk pregnancies and is a reference hospital for the interior of the country, which is why the mothers included in the present study, except one, had a pregnancy with good metabolic control, which the literature refers to [6-8,12,13], in addition to good prenatal control. Preeclampsia is associated with 15-20% of diabetics, in our case it was higher [27,28], followed by arterial hypertension and obesity. During the course of the study, 17 mothers died due to pathology secondary to DM, information provided by the family, higher for DM1. The majority of infants were born via caesarean section, body composition adequate for gestational age, without compromise of this at birth. Apgar with good recovery at 5 minutes, with pH < 7.35 and elevated CO2, with resuscitation maneuvers such as positive pressure and orotracheal intubation higher in DM2. Of the metabolic problems at birth in GDM the most frequent were hyponatremia, followed by hypoglycemia, hyperbilirubinemia, neonatal sepsis, intrauterine growth retardation, they were more frequent for DM2, however, neurological problems at birth were more frequent for the DM1. Respiratory morbidity was associated with being the infant of a diabetic mother, higher for DM2 [15-17,24].

In relation to neurodevelopment there is little evidence [49,50] of how a neurological assessment is used for the early detection of neurological abnormalities that could be transient or permanent [52,55] which reported abnormality 11%, in contrast to our study which was 62% for DM2. The presence of cerebral palsy is relevant despite presenting in a mild form, but disabling in its severe form. DM2 has a higher risk of presenting cerebral palsy followed by DM1 and GDM in third place [60-62]. However, in the present study it was the opposite, in GDM the mothers are older, with 8.3% cerebral palsy, mild 6.0% and 2.4% severe form, with no functional ability 1.2%, a hypotonic syndrome, and followed by DM1 7.9% mild forms and DM2 7.0% mild forms. We are a multidisciplinary team that has been working together for more than 20 years, so the neurodevelopment results are something relevant to share, mainly for cerebral palsy where we have the crucial support of a neurologist and neurophysiologist. In the consulted literature, as far as we know, we did not find information that refers to cerebral palsy as the present study, therefore the importance of these neurodevelopmental results.

The strength of this study is that there is greater consistency in relation to cerebral palsy, contrary to what has been reported in other studies. In the neurobehavioral assessment that reports delays, mild delays were more frequent for DM2 and severe delays for GDM, with a strong relationship and an easy and simple instrument applied. The hearing loss found in the present study was 2.7%, severe hearing loss was more common in DM2, a cochlear implant that was successful until discharge, and few speak of the sensoriality that can accompany these patients. Language at 24 months, all groups was low [55,56] at the level of 21.4 months, lower for GDM, reported by different authors. The Bayley II [52,55,56] assessment, which is the international gold standard for the assessment of neurodevelopment, found MD1 42.4% and PDI 48.5% below normal, so we have to pay attention to the different risk factors that interfere with neurodevelopment. Lowest MDI for DM1, followed by GDM, DM2, and lowest PDI for DM1 followed by DM2 and GDM, DM1 was lower in both and the motor scale was below normal for the other groups. Regarding weight, height, and head circumference at 12 months, weight and height at 24 months, were at 25-50 percentiles, head circumference at 24 months at 50, with normal growth velocity in relation to birth weight.

Conclusion

Perinatal morbidity is related to being an infant of a diabetic mother for DM1, DM2 and gestational diabetes, in relation to the control group. The presence of cerebral palsy in its severe form was for GDM, which is surprising, followed by DM1 and DM2 only for mild cerebral palsy. Screening tests such as neurobehavioral assessment are very useful, which is why they should be used more. Fortunately, sensoriality is minimal, with low language for all groups. The Bayley II Scale both mental and motor scale, low for DM1 followed by GDM and DM2. More clinical studies are required that can broaden the knowledge of how neurodevelopment is in the first years of life, in infants of diabetic mothers, as well as the expansion of the multidisciplinary teams that provide care, to monitor the impact of brain dysmaturity produced by hyperglycemia and hyperinsulinemia in these patients.

Contributions

The present work allows us to visualize that early surveillance of infants of diabetic mothers such as DM1, DM2 and GDM is necessary, since the results of various studies, including the present one, show that these children may have some degree of neurodevelopmental delay that requires early intervention. In the Pediatric Follow-up service of our hospital, we have the opportunity to carry out various assessments by the different medical specialists that allows the identification and classification of infants according to the type of diabetes presented by the mother. The novel contribution provided by our results is the description of cerebral palsy and the description of how it presented. It is disturbing that the severe form with no functional ability occurred in gestational diabetes, probably due to the lack of prenatal control in the early stages. Prenatal control continues to be the cornerstone for early detection. In Mexico, we do not have a similar study, so we hope that this work will be a great contribution to promote concern and generate knowledge, to improve the quality of life of infants and their families.

Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki, and approved by the Research, Ethics in Research Committees of the National Institute of Perinatology "Isidro Espinosa de los Reyes" (2022-1-17).

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