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THE IMPACT OF GESTATIONAL DIABETES ON INFANTS' NEURODEVELOPMENTAL STATUS: A COHORT STUDY

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ABSTRACT

Objective: The prevalence of gestational diabetes is increasing worldwide. Several studies have indicated that gestational diabetes can cause neurodevelopmental disorders in children. None of them has examined all areas of neurodevelopment. We conducted this pilot study to compare the neurodevelopmental status in infants of mothers with and without gestational diabetes. **Materials and Methods:** Forty infants of mothers with gestational diabetes and 40 infants of healthy mothers were included and followed up at 6 and 12 months old of age. The primary data of the study were extracted from a cohort study (PERSIAN Birth Cohort) done in Yazd province, Iran. Ages and Stages Questionnaire (ASQ) was used as a standard test to assess all domains of neurodevelopment. Finally, the data obtained from the questionnaire were statistically analyzed using SPSS software.

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Results: Data analysis showed a significant relationship between gestational diabetes and neurodevelopment in the area of problem solving at one year old, but its relationship with other domains was not significant. In the case group, there was a significant relationship between the type of treatment (insulin therapy) and neurodevelopment in the area of gross motor skills at one year of age. **Conclusion:** Based on this study, it seems that infants' neurodevelopment in the area of problem solving has been affected by gestational diabetes. Thus, the role of physicians in follow up of the neurodevelopmental progress of infants of diabetic mothers is significant**.**

KEYWORDS: Gestational Diabetes; Neurodevelopment; ASQ.

EL IMPACTO DE LA DIABETES GESTACIONAL EN EL ESTADO DE NEURODESARROLLO DE LOS LACTANTES: UN ESTUDIO DE COHORTES

RESUMEN

Objetivo: La prevalencia de la diabetes gestacional está aumentando en todo el mundo. Varios estudios han indicado que la diabetes gestacional puede causar trastornos del neurodesarrollo en los niños. Ninguno de ellos ha examinado todas las áreas del neurodesarrollo. Realizamos este estudio piloto para comparar el estado del neurodesarrollo en niños de madres con y sin diabetes gestacional. **Materiales y métodos:** Se incluyeron 40 lactantes de madres con diabetes gestacional y 40 lactantes de madres

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sanas, a los que se realizó un seguimiento a los 6 y 12 meses de edad. Los datos primarios del estudio se extrajeron de un estudio de cohortes (PERSIAN Birth Cohort) realizado en la provincia de Yazd, Irán. Se utilizó el Cuestionario de Edades y Estadios (ASQ) como prueba estándar para evaluar todos los dominios del neurodesarrollo. Por último, los datos obtenidos a partir del cuestionario se analizaron estadísticamente mediante el programa SPSS. **Resultados:** El análisis de los datos mostró una relación significativa entre la diabetes gestacional y el neurodesarrollo en el área de resolución de problemas al año de edad, pero su relación con otros dominios no fue significativa. En el grupo de casos, hubo una relación significativa entre el tipo de tratamiento (insulinoterapia) y el neurodesarrollo en el área de motricidad gruesa al año de edad. **Conclusiones:** Sobre la base de este estudio, parece que el neurodesarrollo de los lactantes en el área de la resolución de problemas se ha visto afectado por la diabetes gestacional. Por lo tanto, el papel de los médicos en el seguimiento de la evolución del neurodesarrollo de los lactantes de madres diabéticas es importante.

PALABRAS CLAVE: Diabetes gestacional; neurodesarrollo; ASQ.

INTRODUCTION

The neurodevelopmental status of children is affected by many factors. Any

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problems throughout embryonic development and birth or even after birth can affect the growth and development of the infant. In a study conducted in 2017, possible maternal factors causing developmental disorders were evaluated. The results revealed that mothers' lifestyle (e.g. history of smoking, alcohol consumption, malnutrition, and high-fat diet as well as maternal age), metabolic issues (i.e. Gestational diabetes, hypothyroidism, and obesity), and viral and bacterial infections during pregnancy could cause brain damage and finally lead to neurodevelopmental disorders (1).

Gestational diabetes is one of the most common worldwide metabolic disorders during pregnancy (2). The prevalence of gestational diabetes varies from 1 to 14% in different communities (3). The prevalence of gestational diabetes was 12% in Yazd, Iran (4). The general outcome of diabetes during pregnancy depends on the time of onset, duration, and severity of maternal diabetes. If gestational diabetes is not completely treated, it can increase the risk of fetal, neonatal, and long-term complications, as a silent disease. Studies suggest that the side effects of hyperglycemia on the fetus and infant can be reduced by optimally controlling maternal blood sugar levels during pregnancy and even during childbirth(5).

Pregnancy hyperglycemia causes fetal hyperglycemia, and fetal pancreatic response to the high serum glucose concentration causes fetal hyperinsulinemia. Due to fetal hyperglycemia, glucose uptake into the liver increases and consequently glycogen synthesis, lipogenesis, and increased protein synthesis, resulting in the weight gain of the placenta, fetus, and internal organs (6). Hyperglycemia and hyperinsulinemia can cause fetal acidosis and increased stillbirth. Since the first trimester of pregnancy is a crucial time and organogenesis occurs in this period, the teratogenic effects of hyperglycemia in the first trimester are more prominent and may cause severe congenital

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anomalies (7). Hence, hyperglycemia, hyperinsulinemia, and macrosomia are among the fetal complications induced by gestational diabetes mellitus (8). Fetal macrosomia and organomegaly increase the need for oxygen and may cause fetal hypoxia. Chronic fetal hypoxia in pregnancy causes polycythemia, reduction of iron stores, and respiratory distress (9).In the long term, gestational diabetes can cause behavioral, cognitive, and memory disorders. Some studies have shown that gestational diabetes mellitus (GDM) is associated with neurodevelopmental disorders (10).

GDM has milder and less severe side effects than overt diabetes mellitus. Several studies have indicated that gestational diabetes can cause developmental disorders in the long term (11). However, there are conflicting findings in this regard. No study has investigated all the developmental indicators yet. The present study attempted to investigate the effect of GDM on neurodevelopment.

Material & Methods

Gestational diabetes mellitus is diagnosed in pregnancy screening and approved by a gynecologist and endocrinologist. Mothers' information was recorded in the cohort study (The Prospective Epidemiological Research Studies in Iran, Persian Birth Cohort) at Yazd province, Iran. The primary data of mothers was extracted from a cohort study. Mothers who met the inclusion criteria were selected. The children of these mothers were followed up at 6 months and 1 year.

The statistical population of the study included 6-month-old and 12-month-old infants who entered the study obtaining their parents' consent and meeting the inclusion criteria.

The inclusion criteria were:

1. Not to be preterm.
2. The mothers of the infants in both groups should have no history of alcohol consumption, smoking, and drug abuse.

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3. The mothers of infants in the case group have proven GDM (at least one abnormal value for fasting, one-hour and two-hour plasma glucose concentration: =92, 180, and 153 mg/dl, in routine screening tests of first and second trimester respectively). Mothers with GDM were treated with metformin or insulin therapy or diet modification.

4. For the control group, the mothers should be healthy without any other problems such as preeclampsia or gestational or overt diabetes (first and second trimester screenings).

5. The infants of both groups did not have another serious systemic disorder or major fetal abnormalities.

6. Infants had no history of moderate to severe asphyxia at birth, either Exclusion criteria were: lack of parental cooperation, family migration, and death.

These infants were divided into two groups: infants of mothers with GDM (case group) and infants of healthy mothers (control group). The sample size was determined to be 80 (40 infants of mothers with gestational diabetes and 40 infants of healthy mothers. Since no study evaluated all aspects of neurological development and the number of similar studies is very limited, we conducted a study to assess all neurodevelopmental domains. The Ages and Stages Questionnaires® (ASQ) was used as a standard test to assess different neurodevelopmental domains (12)

This questionnaire contains 30 questions in 5 developmental areas. Developmental areas include the following:

1. Establishing communication
2. Gross motor
3. Fine motor
4. Problem-solving area
5. Individual-social areas

The Questions in the field of communication are related to making noise, listening,

The questions in the field of the gross motor are related to the movements of the trunk and limbs.

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The Questions in the field of the fine motor are related to finger movements

The Questions in the field of Problem-solving are related to learning and playing with toys.

The Questions in the field of Individual-social are related to individual play, and social work.

A pediatric resident completed the ASQ with the cooperation of the infants 'parents. Based on the ASQ questionnaire scoring, scores higher than (-1) mean having normal neurodevelopment, and scores lower than (-2) mean having abnormal neurodevelopment. ASQ Scores between -1 and -2 should be repeated 2 weeks later and at this time according to the results, it is considered normal or abnormal. The data obtained were statistically analyzed by SPSS 20.

Results

Eighty infants (40 infants of mothers with GDM and 40 infants of healthy mothers) were included in the study and followed up. During the first year of life, infants who met the inclusion criteria entered the study. Of 80 studied cases, 48 were female and 32 were male. None of the studied infants were preterm. They did not have any other serious systemic illness, major fetal abnormalities, or a history of moderate to severe asphyxia at birth. The mothers of infants in the case group had proven GDM (at least one abnormal value for fasting, one-hour and two-hour plasma glucose concentration: =92, 180 and 153 mg/dl, respectively) and had no history of diseases other than GDM. Two groups had no statistical difference in term of gender. The results revealed no significant relationship between establishing communication, gross motor, fine motor, and individual-social areas and GDM.

However, a significant relationship was found between problem solving area and GDM in the case group, In the other words, the infants of diabetic mothers had more difficulty in solving the problem than infants of healthy ones (Table 1).

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Table 1. Frequency of neurodevelopmental changes in infants of healthy and gestational diabetic mothers

Establishing communication	Normal	Abnormal	P value
Infants of Gestational Diabetes Mothers	39	1	1.000
Infants of healthy mothers	40	0	
Total	79	1	
Gross motor skills			0.840
Infants with Gestational Diabetic Mothers	33	7	
Normal infants	33	7	
Total	66	14	
Fine motor skills			1.000
Infants of Gestational Diabetic Mothers	40	0	
Normal infants	40	0	
Total	80	0	
Problem solving area			*0.001
Infants of Gestational Diabetes Mothers	28	12	

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Infants of healthy mother	39	1	
Total	67	13	
Individual-social areas			1.000
Infants with Gestational Diabetic Mothers	40	0	
Infants of healthy mothers	39	1	
Total	79	1	

*P- value less than 0.05 was considered as significant.

The results revealed a significant relationship between the gross motor area and the type of GDM treatment. Infants whose mothers were treated with insulin had more impaired gross motor. The results also showed, no significant relationship between the fine motor, problem solving, and the individual-social areas and the type of GDM treatment (Insulin therapy, metformin and Diet modification) (Table 2).

Table 2. Frequency of neurodevelopmental changes in infants of healthy and gestational diabetic mothers based on the type of treatment.

Diabetic			Non-diabetic		P value
Establishing communication	Normal	Abnormal	Normal	Abnormal	1.000
Insulin therapy	9	0			

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Oral hypoglycemic agents	22	0	39	1	
Diet therapy	9	0			
Gross motor skills					*0.009
Insulin therapy	6	3	32	8	
Oral hypoglycemic agents	19	3			
Diet therapy	9	0			
Fine motor skills					1.000
Insulin therapy	9	0	40	0	
Oral hypoglycemic agents	22	0			
Diet therapy	9	0			
Problem solving area					*0.048
Insulin therapy	9	0	39	1	
Oral hypoglycemic agents	19	3			
Diet therapy	9	0			
Individual-social areas					1.000
Insulin therapy	9	0	39	1	
Oral hypoglycemic	22	0			

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agents					
Diet therapy	9	0			

*P- value less than 0.05 was considered as significant.

The difference of ASQ scores between 6-month-old and 12-month-old groups was significant in case group. It was revealed that neurodevelopment was better in 6-month-old group than 12-month-old group (Table 3).

Table 3. Frequency of ASQ score in neurodevelopmental changes in infants of healthy and gestational diabetic mothers

ASQ score			
P value	Diabetic	Normal	Neurodevelopment area in six months old
1.000	55.2	53.6	Establishing communication
1.000	54.6	50.7	Gross motor
0.49	57.4	56.9	Fine motor
0.36	57.5	54.6	Problem solving area
0.67	56.6	53.5	Individual-social areas
			Neurodevelopment area in one year old
1.000	53.7	52.07	Establishing communication
0.08	53.2	52.07	Gross motor

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1.000	56.9	55.8	Fine motor
0.001*	52.02	55.4	Problem solving area
1.000	53.40	54.02	Individual-social areas

*P- value less than 0.05 is considered as significant.

Discussion

The effect of GDM on neurodevelopment was significant at 12-month-old age. GDM affected the area of solving-problem in 12-month-old infants. Several studies investigated the effect of GDM on infants' neural function. Most of these studies confirmed the effect of overt DM on neural function, but less attention was paid to the effect of GDM (13-17). Overt DM patients were excluded from the statistical population of this study and this study emphasized the effect of GDM only on infants' developmental status. Since the first trimester of pregnancy is a critical period and organogenesis occurs during this period, the teratogenic effects of hyperglycemia in overt DM are significant (15). Since GDM occurs during the last trimester of pregnancy, its side effects are milder than overt DM. Two systematic reviews indicated the prominent neurological adverse effects of infants of mothers with gestational diabetes (18). Overt DM has been investigated in most studies and GDM studies have provided contradictory results, and there is disagreement in this regard. The results of a study conducted by Cai *et al*. showed that GDM mostly affects the left hemisphere (which is related to memory, concentration, and attention) and it reduces neural function in the face of sensory stimuli (19). Similarly, in our study, GDM affected the problem-solving area, which is related to concentration and attention, and probably the left hemisphere of the brain. The mechanism of action of GDM on brain function has not been clarified exactly. Based on previous studies, the most important complications of GDM are

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hyperglycemia, hyperinsulinemia, and macrosomia (20, 21). In the embryonic period, hyperglycemia can cause morphological changes in the presynaptic nerve terminals. Hyperglycemia-induced oxidative stress can cause vascular and neurological damage. The hippocampus is a sensitive area of the brain that will be damaged quickly by any stress such as hypoglycemia and finally impairs memory, learning, and problem-solving skills. In our study, GDM had a significant relationship only with the area of problem-solving and had no significant relationship with other areas of neurodevelopment. We also found that 12-month-old infants of mothers treated with insulin had a poorer motor performance. Tertti *et al*. investigated the neurodevelopment of GDM infants exposed to anti-diabetic drugs (metformin and insulin) and concluded that there was no significant difference between insulin-treated and metformin-treated groups in terms of neurodevelopment (23). The white classification was used to assess the severity of GDM in the past, but this classification is not currently in use, and the distinction between overt DM and GDM is more important (24). In GDM treatment, the drug of choice is insulin. Usually, those who need insulin have higher levels of hyperglycemia and do not respond well to diet modification and oral medications (25, 26). Thus, impaired development of the infants ‘gross motor in the present study can be attributed to the increase in blood glucose and requiring more insulin. Insulin administered to pregnant mothers does not pass through the placenta and it reduces fetal complications with the mechanism of regulating the mother's blood sugar (27). Therefore, it cannot be stated that the infant's neurological complications could be due to the adverse effects of insulin treatment. Several trials on the complications of treatment with metformin and insulin revealed that metformin was associated with milder infantile hypoglycemia, lower birth weight, and a lower rate of macrosomia. Since oral drugs pass through the placenta in higher doses, they increase the risk of

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hypoglycemia and the need for NICU care (28-30). Studies conducted so far to assess infants' neural function have used IQ tests, the Bayley-III questionnaire, and physical examination. None of the studies examined all the areas of neurodevelopment. In our study, the ASQ was used as a standard test to assess all the areas of neurodevelopment. In the present study, infants of mothers with GDM showed a significant difference in terms of ASQ scores at the ages of 6-month-old and 12-month-old, so they had a lower ASQ score at 12-month-old age than 6-month-old age. Birgitte *et al*. and Ornoy *et al*. also reported diabetes-related intelligence and cognitive developmental disorders (16, 22). Our results indicated that GDM might have a long-term effect on neural function, and it seems that neural function can be detected and measured more accurately with increasing age.

Conclusion

A significant relationship was found between GDM and neurodevelopmental progress in the area of problem-solving. One year after treatment, insulin-treated mothers' infants had lower gross motor scores than their peers. Neurodevelopmental scores were better in 6-month-old infants of diabetic mothers than in 12-month-old infants. It may indicate that GDM manifests its effects in the long term. Consequently, it is recommended that larger sample sizes and older infants be recruited for future studies.

Ethics approval

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE. REC.1399.17)5.

Conflict of interests

There is no conflict of interest in this research.

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None

Authors' Contribution

In this study, all authors contributed to design, management, and review of the manuscript. Hosein Eslamiye contributed to data collection and analysis. Habib Nikukar contributed to data collection. Mehran Karimi contributed to data analysis. Zahra Mohsenolhoseini did the data interpretation and managed and supervised the experiments and results.

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