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Original Article

Association of maternal diabetes during pregnancy with attention deficit hyperactivity disorder in offspring in an Iranian population: A case-control study

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Abstract

Background and aims: Gestational diabetes has long-term adverse consequences for both the mother and child and seems to be a risk factor for attention deficit hyperactivity disorder (ADHD) in children. However, no research has been conducted in this regard in Iran.

Methods: This was a case-control study. The sample consisted of 225 children who were referred to the general and psychiatric clinic of Besat Hospital in Sanandaj and were evaluated for a history of maternal diabetes in the fetal period. The diagnosis of ADHD in children was based on a structured clinical interview with Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) by a psychiatrist and a short and revised form of Conners' parent scale. The data were analyzed using Stata 14.

Results: The results showed that 25.3% of the mothers of children with ADHD had gestational diabetes during pregnancy, and 17.3% were taking diabetes medication. However, the results revealed that there is no statistically significant relationship between the history of gestational diabetes and ADHD ($P=0.427$). Furthermore, the logistic regression results demonstrated that the place of residence ($P<0.027$, OR=8.351) increases the probability of suffering from ADHD in children, while the age of the mother during pregnancy ($P<0.031$, OR=0.907) decreases the probability of the child suffering from ADHD.

Conclusion: Although cohort studies have associated gestational diabetes with an increased risk of ADHD in children, the results of this case-control study do not support this association.

Keywords: Gestational diabetes, Attention deficit hyperactivity disorder, ADHD, Maternal diabetes

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder affecting many children and adolescents. According to the Fifth Edition Diagnostic and Statistical Manual of Mental Disorders, Revised Text (DSM-5-TR), the early features of ADHD are characterized by a persistent pattern of inattention and impulsivity-hyperactivity, impairing a person's performance or growth (1).

The possible causes of ADHD include viral infection, smoking, alcohol use, maternal stress during pregnancy, changes in the intrauterine environment, preterm delivery, low birth weight, poor nutrition, prescription of specific medications, and exposure to various toxins such as lead contamination (2,3). Children born from high-risk pregnancies are more prone to neurodevelopmental disorders. Studies have shown that there is a relationship between gestational diabetes and externalizing disorders, including ADHD (4,5). The research indicates that gestational diabetes predisposes people to a wide range of psychiatric disorders. In a 39-year follow-up, 6.4% of the children of mothers with diabetes, before or during pregnancy, developed a psychiatric disorder (6).

Gestational diabetes, which is first diagnosed during pregnancy, is one of the most common types of metabolic disorders, the prevalence of which has been reported to vary from 1% to 14% in different communities (7). In such cases, the fetus is placed in a completely different environment. Glucose, alanine, and free fatty acids are transferred to the fetus in large quantities through the mother's bloodstream. Following an increase in insulin concentration, the amniotic fluid increases, indicating a fetal response to the increase in these substances (8). Animal and human studies have demonstrated the adverse

effects of gestational diabetes on brain development and child behavior (9). This type of diabetes leads to long-term adverse outcomes such as cognitive, motor, intelligence, language, and hyperactivity disorders (10). Ornoy (5) concluded that the offspring of mothers with gestational diabetes have a lower performance in the gross and fine motor functions than the children of healthy mothers and have a higher rate of ADHD.

A systematic and meta-analysis study demonstrated that the children of mothers with gestational diabetes had a lower intelligence quotient than those of healthy mothers (11). Some studies reported that maternal diabetes (type 1, 2, and gestational diabetes) is associated with an increased risk of ADHD in children (10,12,13). In a large population-based cohort study, Chen et al (14) found that exposure to maternal diabetes was associated with an increased risk of developing autism spectrum disorders, mental retardation, and ADHD in offspring. In addition, learning difficulties have been observed among the children of mothers with gestational diabetes (2). The prevalence of gestational diabetes varies in different countries and ethnicities. Various people are annually diagnosed with diabetes. The growing prevalence of this trend and its adverse effects on children's future health have caused great concern from a global perspective. Despite the increased risk of developing ADHD in the children of mothers with diabetes during pregnancy and the risks threatening children with ADHD, according to our knowledge, no research has been conducted in this field in Iran. Therefore, the present study was performed considering the 5.88% prevalence of gestational diabetes in Iran (15) and its adverse effects on the mother and child, especially the probability of children developing ADHD.

Materials and Methods

This study examined children with ADHD referred to Besat hospital in Sanandaj for maternal diabetes during pregnancy. The inclusion criteria were children aged 3-12 years old with ADHD. On the other hand, the exclusion criteria were reluctance of parents and children to participate in research, a family history of ADHD, smoking and alcohol use in the mother, preterm delivery, low birth weight, congenital anomalies, thyroid disease, seizures, mental retardation, and history of mental disorders according to history and clinical interviews. Based on a study by Bytoft et al (16), considering the prevalence of diabetes is 36% and 15% in the case and control groups, respectively, as well as an alpha of 5% and a beta of 20%, the sample size of 75 people was calculated using the following formula:

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 (p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

For a better estimation of the study results, two individuals were selected as the control group for each case. Thus, 75 and 150 children were assigned to the case and control groups, respectively. A total of 225 children aged 3-12 years referred to the general and psychiatric clinic of Besat hospital in Sanandaj were selected by convenience sampling. ADHD in children was diagnosed by a child and adolescent psychiatrist based on a semi-structured interview K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version). After diagnosing ADHD, patients entered the study after explaining the research process and obtaining written consent from their mothers. Then, the demographic information, researcher-made checklist about pregnancy, and short and revised forms of Conners' parent scale were completed by the parents of the case group. A control group was selected from the mothers of peers referred to the general clinic of the hospital without ADHD symptoms Demographic information and a pregnancy researcher-made checklist were completed in this group. During the study, the necessary precautions were taken to maintain the confidentiality of patients' information.

Demographic information checklist

A researcher-made checklist, including age, gender, type of maternal diabetes, type of antidiabetic drug, family history of ADHD, and the like, was used to examine the personal information.

The short and revised form of Conners' parent scale

This 27-item questionnaire was completed by parents; it had four subscales of opposition, cognitive/inattention problems, hyperactivity, and ADHD index. The subject's raw score in each subscale is calculated from the total of the parents' ratings (from 0 to 3) in the expressions related to that subscale, and then it is converted to the standard score based on their age and gender. A standard score equal to or greater than 65 usually indicates significant clinical problems in that subscale. The age range used in the Connors scale is 3-17 years, with separate age norms for girls and boys at 3-year intervals. The completion of this questionnaire took 5-10 minutes. The internal reliability coefficient and test reliability coefficient in 8 weeks were reported to be in the range of 75%-90% and 0.60-0.90, respectively. In addition, Connors forms were validated using factor analysis methods, and their differential validity was confirmed by statistically examining the questionnaire's ability to distinguish people with ADHD from normal and other clinical groups. The reliability of the six-week retest in the Persian version was 0.60 (17).

Frequency and frequency percentage, as well as odds ratio (OR) and confidence interval (CI), were calculated for qualitative and quantitative variables, respectively. Chi-square and Wilcoxon rank tests were used to compare qualitative variables in case and control groups. In addition, *t* tests and equivalent non-parametric tests were applied to compare quantitative variables. The OR and CI of 95% were determined for all factors using the logistic regression model. All the demographic variables of the

questionnaire were selected as predictor variables, and the group with ADHD was considered the response variable. The variables investigated in this research were selected according to the review of similar studies conducted in this field and after consultation with clinical experts. Data were analyzed using Stata14 software, and the significance level was considered $P<0.05$.

Results

Based on the results, 24% of mothers in the case group and 69.3% of other family members in the control group reported a history of diabetes. In addition, 17.3% and 12.7% of mothers in the case and control groups were taking diabetes medication, respectively (Table 1).

Based on the data (Table 1), there was a significant difference between the two groups in terms of the place of birth ($P=0.02$). However, there was no significant difference between the two groups with regard to the other indicators such as developmental disorders, gender, place of residence, history of diabetes in the family, gestational diabetes, and taking diabetes medication ($P=0.18$, $P=0.58$, $P=0.29$, $P=0.42$, $P=0.34$, and $P=0.25$, respectively).

The results demonstrated a significant difference in the age of the mother and child between the two groups ($P=0.009$ and $P=0.016$, respectively) (Table 2). However, no significant difference was found regarding the other indicators such as duration of pregnancy (month), birth weight (g), and duration of diabetes medication between the two groups ($P=0.665$, $P=0.830$, and $P=0.463$, respectively).

The logistic regression results represented that the OR of ADHD was obtained for children living in the village compared to urban children ($P<0.027$, OR=8.351), indicating that living in the village increases the probability of ADHD in children (Table 3). Furthermore, the OR was achieved for older mothers in comparison to younger mothers ($P<0.031$, OR=0.907), implying that the mother's old age reduces the possibility of the child suffering from ADHD.

Discussion

This study aimed to investigate the relationship between maternal diabetes during pregnancy with ADHD in children. The results demonstrated no significant relationship between gestational diabetes and ADHD in children. This finding could be because the relationship between gestational diabetes and ADHD in children was

Table 1. Chi-square test to compare demographic variables in case and control groups

Variable		Case group	Control group	χ^2	*P* value
		No. (%)	No. (%)		
Gender	Boy	30 (40)	74 (49.3)	1.75	0.18
	Girl	45 (60)	76 (50.7)		
Birthplace	City	66 (88)	113 (75.3)	4.93	0.02
	Village	9 (12)	37 (24.7)		
Place of residence	City	66 (88)	128 (85.3)	0.29	0.58
	Village	9 (12)	22 (14.7)		
History of diabetes except for the mother	Yes	18 (24)	46 (30.7)	10.9	0.29
	No	57 (76)	104 (69.3)		
History of gestational diabetes	Yes	19 (25.3)	31 (20.7)	0.63	0.42
	No	56 (74.7)	119 (79.3)		
Taking diabetes medication	Yes	13 (17.3)	19 (12.7)	0.89	0.34
	No	62 (82.7)	131 (87.3)		
Developmental disorders	Yes	12 (16)	16 (10.7)	1.3	0.25
	No	63 (84)	134 (89.3)		

Table 2. Comparison of the mean and SD of demographic variables by group

Variable	Case Group	Control Group	*P* value
	Mean (±SD)		
Child age (y)	8.27 (±2.17)	7.36 (±2.59)	0.009
Birth order	1.65 (±0.93)	1.69 (±0.8)	-
Age of the child at diagnosis (y)	6.47 (±2.38)	-	-
Maternal age at the pregnancy (y)	26.09 (±4.43)	28.01 (±6.11)	0.016
Duration of pregnancy (months)	8.94 (±0.15)	8.93 (±0.16)	0.665
Birth weight (g)	3219.33 (±422.26)	3205.68 (±463.84)	0.830
Duration of diabetes medication	1.08 (±2.68)	0.82 (±2.40)	0.463

Note. SD: Standard deviation.

Table 3. Logistic regression results for ADHD

Variable	B	*P* value	OR	(95% CI)	
				Lower	Upper
Child age	0.125	0.452	1.133	0.818	1.570
Group	2.153	0.080	8.609	0.772	96.042
Gender	0.359	0.428	1.431	0.590	3.472
Birth order	-0.051	0.842	0.951	0.578	1.564
Child education	0.252	0.731	1.287	0.305	5.425
Birthplace	-1.009	0.178	0.364	0.084	1.585
Place of residence	2.122	0.027	8.351	1.281	54.460
Disease history	-0.576	0.394	0.562	0.149	2.114
Age of child at diagnosis	0.080	0.645	1.083	0.770	1.523
Father's education	0.336	0.374	1.399	0.668	2.931
mother's education	-0.148	0.754	0.863	0.343	2.173
Father's job	0.233	0.485	1.263	0.657	2.428
Mother's job	-0.041	0.860	0.960	0.611	1.509
Marital status of parents	-0.686	0.268	0.503	0.149	1.697
Mother's age during pregnancy	-0.097	0.031	0.907	0.831	0.991
Duration of pregnancy	-1.097	0.483	0.334	0.016	7.152
Birth weight	0.000	0.916	1.000	0.999	1.001
History of diabetes except for the mother	-0.301	0.553	0.740	0.274	1.999
History of gestational diabetes	1.963	0.726	7.123	000	419.165
Type of diabetes	0.335	0.857	1.399	0.036	54.351
Taking diabetes medication	0.614	0.747	1.847	0.044	77.095
Duration of diabetes medication	0.300	0.547	1.350	0.508	3.589
Developmental disorders	0.961	0.203	0.382	0.087	1.681

Note. ADHD: Attention deficit hyperactivity disorder; OR: Odds ratio; CI: Confidence interval.

more in the 27-30th week of pregnancy (14), the timing of gestational diabetes was not considered in the present study. This could be considered an interfering factor. Furthermore, in some studies (14), body mass index and pregnancy weight gain were considered intervening factors, increasing the risk of developing ADHD in children, while they were not controlled in the current study.

A review of the research background represents contradictory findings in this regard. Some studies have reported the negative impact of gestational diabetes on children's cognitive functions. For example, Bolaños et al (18) investigated the effect of gestational diabetes on the delay in the cognitive-neurodevelopment of children aged 7-9 years and compared the cognitive characteristics of children born from mothers with and without gestational diabetes. Their findings revealed a lower cognitive function in the diabetic group. In contrast, other studies, including Veena et al (19), showed that children of diabetic mothers scored higher in long-term learning, storage and retrieval, reasoning, attention and concentration, spatial vision, and practical abilities than children of healthy mothers. A meta-analysis on a Caucasian sample demonstrated that in case-control studies, children of diabetic mothers are not at high risk for ADHD, while old age and maternal obesity are the risk factors for ADHD (13).

On the other hand, cohort studies indicated that gestational diabetes is a risk factor for ADHD. Xiang et al (20) reported that there is no significant relationship between gestational diabetes and ADHD, even when considering the timing of exposure to maternal diabetes. Ji et al (12) study excluded children with ADHD who were simultaneously diagnosed with mental retardation, autism spectrum disorders, and Tourette's syndrome. However, the prevalence of ADHD in children of mothers with gestational diabetes remained high. Some of these discrepancies seem to be due to differences in research methodology (in many case-control studies, no significant relationship was found between gestational diabetes and ADHD in children, while Cohort studies reported a significant relationship); the difference is due to how this disorder is diagnosed and evaluated (based on clinical interview or behavior rating scales), age of diagnosis of the disorder, cultural issues, leading to the lack of visiting a psychiatrist, and parents' desire to report fewer symptoms of the disorder for their children.

In his study, Ornoy (5) examined the cognitive and motor characteristics of children born to mothers with gestational diabetes and concluded that nephropathy and hypertension are the mediating variables for ADHD in children born to mothers with gestational diabetes. In other words, since there was no difference in physical diseases such as hypertension and nephropathy in the

two groups of mothers in the present study, no difference was found between the case and control groups in the prevalence of ADHD.

Additionally, it seems that the living environment and socioeconomic conditions could lead to neurodevelopmental disorders in children (21). It could be mentioned that ADHD is not diagnosed immediately after birth, and it may not be diagnosed until the age of 12 years (1). Therefore, it seems that due to problems related to maternal diabetes, these children face poor health care and more stress (5). Thus, they are at risk for ADHD due to environmental conditions, not just gestational diabetes. The socioeconomic status (SES) of the family, including parents' income, occupation, and education, is an intervening variable affecting the research results in this field. One study considered the socioeconomic problems of parents as a risk factor for ADHD in children (22). Diabetic mothers, especially those with low SES, are less likely able to work. Thus, they provide a relatively disadvantaged environment for their children due to their lower income. ADHD is more prevalent in people with low SES (23), thus one of the risk factors for ADHD in the participants in the present study was their low SES.

In addition to socioeconomic deprivation, lifestyle, access to healthy food, regular physical activity, and other factors are associated with glycemic control as well (24). Accordingly, it is recommended future researchers consider them as interfering factors when examining the actual effect of maternal diabetes on ADHD in children. Socioeconomic factors and maternal lifestyle may play a role in children developing ADHD, along with gestational diabetes. In the present study, the mothers of the case and control groups both belonged to the lower socioeconomic level of society, and no difference was found between both groups in this regard.

The findings of the present study indicated a significant difference between the two groups in terms of maternal age during pregnancy, and the mother's age was less in the case group, which is consistent with the findings of Hvolgaard Mikkelsen et al (25). Their results revealed that the young age of both parents is associated with ADHD in children, and this relationship is more significant when both parents are under 26 years old. They found no relationship between parental age and ADHD in half or all siblings. Thus, the difference may be due to family-related factors, not just the parents' age. Further, adolescents with ADHD engage in sexual behaviors and get a sexual partner earlier than their peers (26), raising the possibility of genetic susceptibility in their children. The younger mothers also have more negative reactions to their children, are more restrictive (27), and have more family conflicts (22), which are all associated with ADHD in their children. Furthermore, as the mother ages, children are less likely to develop ADHD. This trend may be due to improved parenting skills and maternal maturity, leading to a more accepting attitude toward the second child's behaviors, thereby reducing the symptoms of ADHD in the following siblings.

Despite an 85% improvement in the survival rate of preterm infants (less than 32 weeks of pregnancy) and extremely low birth weight, which accounts for almost 2% of all live births, half of them suffer from cognitive and neurodevelopmental disabilities (28). However, the findings of the current study showed no difference between infant weight at birth and duration of pregnancy in both groups. This finding contradicts the results of Kessenich (29) and Shum et al (30). Low birth weight was one of the exclusion criteria, and children under 2500 g were excluded from this study; thus, no significant difference was observed between the two groups.

Based on our findings, the prevalence of ADHD was higher in low-income and low-educated families, which is also in line with the results of Ji et al (12). However, this relationship was not significant in our study, which could be due to the small number of samples compared to the study of Ji et al. Moreover, in the present study, the mothers of the case and control groups both belonged to the lower socio-economic class of society.

In this study, no difference was observed in the duration of diabetes medication in the two groups. Xiang et al (20) reported that in 26% of cases, the children of mothers with gestational diabetes develop ADHD. They further stated that gestational diabetes with no need for treatment with anti-diabetic drugs does not increase children's risk of developing this disorder. However, in mothers with gestational diabetes who need to take anti-diabetic medication, the risk of its development increases, thus 29% of them develop ADHD. They found no relationship between gestational diabetes and the risk of developing ADHD through controlling interfering factors while reporting that types 1 (57%) and 2 (43%) diabetes increased the risk.

The findings of the present study represented that 32% of mothers who had a child with ADHD had a history of physical illness, but this difference between the two groups was not significant. Instanes et al (31) concluded that immune system diseases such as multiple sclerosis, rheumatoid arthritis, asthma, and hypothyroidism are more common among mothers of children with ADHD than those of healthy children.

Our findings and the existing literature clearly show that further studies, especially population-based prospective cohort studies, are required to investigate the relationship between gestational diabetes and neurodevelopmental disorders. It is suggested that in future research, the age of parents and not only the mother, as well as economic and social conditions and family environment after birth, be considered risk factors for this disorder. One of the limitations of the current study was the defect in recording maternal and infant information in health records. Another limitation was that this research was conducted in a limited area. Thus, it is impossible to generalize its findings to other communities. In addition, we had no information on the effectiveness of hyperglycemic

treatment and blood glucose control biomarkers, which could be a significant limitation.

Conclusion

The results of this case-control research do not support the relationship between gestational diabetes and an increased risk of ADHD in children. It appears that elements other than gestational diabetes, including the mother's age and the setting in which the newborns are raised, may contribute to the emergence of this condition. Children who live in low social and economic conditions or have young, inexperienced moms have the most significant risk of acquiring this disorder.

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Conflict of Interests

The authors declare that they have no conflict of interests.

Ethical Approval

The Ethics Committee of Kurdistan University of Medical Sciences approved the protocol of the study (IR.MUK.REC.1398.238).

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