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Maternal Risk Factors for Autism Spectrum Disorder

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Abstract

Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by deficits in social communication, restricted interests, and repetitive behaviors. The etiology of ASD is multifactorial, involving genetic, environmental, and maternal factors. Recent studies have suggested maternal factors, such as advanced maternal age, high BMI, smoking, and depression during pregnancy, as significant risk factors for ASD.

Objective: This study aims to investigate the maternal risk factors that contribute to ASD in children at Diyala, Iraq.

Patients and Methods: This case-control study was conducted on 150 children, comprising 75 children diagnosed with ASD and 75 healthy children as a control group. The study was carried out from August 2023 to May 2024 in Diyala, Iraq. Data collection included comprehensive demographic, social, obstetric, and maternal health histories. ASD diagnosis was confirmed using the Childhood Autism Rating Scale 2 (CARS-2). A logistic regression analysis was performed to assess the association between maternal risk factors and ASD.

Results: The study revealed several significant maternal risk factors for ASD. Advanced maternal age at pregnancy (mean age 28.1 years in cases vs. 22.9 years in controls, p=0.001), high maternal BMI (mean BMI 26.9 in cases vs. 24.4 in controls, p=0.0001), maternal smoking (6.7% in cases vs. 0% in controls, p=0.023), and maternal depression during pregnancy (22.7% in cases vs. 0% in controls, p=0.0001) were all significantly associated with an increased risk of ASD. The use of stimulating hormones before pregnancy also showed a significant association (21.3% in cases vs. 4% in controls, p=0.001). Parity, particularly having 1-2 pregnancies, was also a significant risk factor (p=0.002).

Conclusion: This study identifies advanced maternal age, high BMI, smoking, depression, and the use of stimulating hormones before pregnancy as significant maternal risk factors for ASD in children.

Keywords: Autism, ASD, maternal age and autism, maternal illness and autism.

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Introduction

Autism spectrum disorder (ASD) is a term referring to a constellation of early-appearing deficits in social, emotional, and nonverbal communications in addition to strict or repetitive behaviors. The disorder, which has a global prevalence of 0.5% to 2%, results in a substantial social and

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economic burden (1). These children with ASD become distressed when their surroundings change because their adaptive abilities are limited, the symptoms appear in early childhood and impair daily functioning. Since early diagnosis and behavioral intervention in ASD could effectively improve prognosis, detecting ASD risk factors to identify at-risk children should be encouraged (2). Several prenatal risk factors, including maternal age, interpregnancy_ interval, immune issues (such as autoimmune diseases and infections that occur during pregnancy), medication use (particularly antidepressants, anti–asthmatics, and anti-epileptics), maternal metabolic conditions (like hypertension and diabetes), and maternal fever during pregnancy is a risk factor for ASD in offspring (3,4). Maternal exposure to smoking and pollutants during pregnancy is a risk factor for ASD. Additionally, maternal exposure to stressful life events during pregnancy is a potential risk factor for ASD (4,5,6). The presenting symptoms of ASD depend on age, language levels (from nonverbal to fully fluent), cognitive abilities, and sex. In the first 2 years of life, common features include poor acquisition of or declines in language skills and communicative gestures or failure to learn or adopt these skills. ASD is also characterized by diminished responsiveness in social interactions and presence of repetitive behaviors, such as no response to name when called, hand flapping, and lining up toys in a particular way. Savant abilities are exceptional abilities that appear to be beyond the normal range of human ability, and they are more common in people with ASD. These abilities frequently show up in domains such as memory, creativity, music, mental math, and calendar skills, which include the ability to determine the day of the week for any historical date (7). Behavioral or cognitive rigidity (e.g., insisting that routines are precisely followed or that others adhere to specific verbal scripts), lack of interest in socializing, restricted interests, and lack of imaginative play typically become more apparent as a child develops. Children with visual and/or hearing impairment may have delays in attaining developmental milestones (eg, deficits in nonverbal communication due to blindness) compared with those without sensory impairment and exhibit behaviors that overlap with ASD symptoms (eg, stereotyped, repetitive motor movements), requiring careful assessment to determine whether behaviors these children exhibit are part of the symptoms of ASD (8). The American Academy of Pediatrics recommends screening all children for ASD at 18 and 24 months of age, on the other hand, the US Preventive Services Task Force concluded in 2016 that there was insufficient data to suggest routine screening for young children in the absence of parental concerns. The Modified Checklist for Autism in Toddlers Revised (M–CHAT–R) is a widely Used 20 items screening tool in primary care to identify children ((aged 16 to 30 months)) who may be at risk for ASD. In order to improve the specificity of the tool, a total score of more than two denotes a risk and prompts medical professionals to inquire further about the items the child failed (9).

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Patients and Methods

Study design: A case-control study that included 150 individuals divided in to two groups; case group and control group, each contains 75 population categorized as Autistic and healthy children, respectively. Case group taken from the Institutions for Autistic Children in Diyala from 1st of August 2023 to 31st of May 2024.

Study population: Seventy-five (75) children with ASD considered as case group along with 75 healthy children included as control group.

Inclusion Criteria: The study included patients with following criteria:

1- Patients diagnosed with ASD.
2- Live mothers.

Exclusion criteria:

• Mothers who refused to participate in the study.

• Mothers who were not able to remember.

ASD diagnosis

The diagnosis of ASD was made based on CARS-2 (Childhood Autism Rating Scale -2) (10).

Statistical Analysis

The statistical package for social sciences (SPSS) software version 23 had been used for data entry and analysis. In the descriptive statistics for socio-demographic characteristics, the means, standard deviations, min, max values were used for continuous data. Numbers and percentage values were used for countable data. Chi-square test; or Fisher-Exact test for small frequency cells; was performed for comparison between categorical variables. Independent T-test of the two means was used for comparison between quantitative parameters. A logistic regression analysis has been used for factors that showed a significant association with ASD in univariate analysis to assess its' as confounder for ASD child. P-values ≤ 0.05 were considered statistically significant.

Results

The study included 150 individuals divided into two groups; group A, which included 75 children diagnosed with autism spectrum disorder, and group B, which included healthy children as a control group.

Demographic characteristics

The maternal age is significantly higher in the case group, with a mean of 28.1 years (± 6.6) compared to 22.9 years (± 5.4) in the control group (p=0.001). The distribution of residency shows no significant difference, with 30.7% of cases and 28.0% of controls residing in rural areas (p=0.85). Regarding the education of mothers, there are no significant differences, though the distribution varies slightly across categories: 16.0% of cases and 17.3% of controls have no formal education; 28.0% of cases and 40.0% of controls have primary education; 28.0% of cases and 22.7% of controls have high school education; and 28.0% of cases and 20.0% of controls have higher education (p=0.34). It was found that 22.7% of mothers in the case group are employed compared to 12.0% in the control group (p=0.084), while 77.3% of mothers in the case group are housewives compared to 88.0% in the control group as found in Table 1.

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Table (1): Demographic criteria of cases and control groups.

Variables		Cases N=75	Control N=75	P value
Age of Mother	Mean ± SD	28.1 ± 6.6	22.9 ± 5.4	**0.001**
	Range	26	23	
Residency	Rural	23 (30.7%)	21 (28.0%)	0.85
	Urban	52 (69.3%)	54 (72.0%)	
Education of mother	No Formal	12 (16.0%)	13 (17.3%)	0.34
	Primary	21 (28.0%)	30 (40.0%)	
	High school	21 (28.0%)	17 (22.7%)	
	Higher	21 (28.0%)	15 (20.0%)	
Occupation of mother	Employee	17 (22.7%)	9 (12.0%)	0.084
	Housewife	58 (77.3%)	66 (88.0%)	
Parent consanguinity	Yes	35 (46.7%)	37 (49.3%)	0.74
	No	40 (53.3%)	38 (50.7%)	

Social history

The comparison between cases and controls reveals significant differences in maternal BMI and smoking habits. The mean BMI of mothers in the case group is significantly higher at 26.9 (± 4) compared to 24.4 (± 3.3) in the control group (p=0.0001). The range of BMI values is also broader in the case group (18) than in the control group (16). There is a significant difference in smoking habits, with 6.7% of mothers in the case group subject to passive smoking, while none in the control group face such exposure (p=0.023). Animal contact shows no significant difference, with 14.7% of cases and 12% of controls having animal contact, while 85.3% of cases and 88% of controls have no animal contact (p=0.63), as found in Table 2.

Table (2): Maternal social history of cases and control groups.

Variables		Cases N=75	Control N=75	p value
BMI of mother	Mean ± SD	26.9 ± 4	24.4 ± 3.3	**0.0001**
	Range	18	16	
Smoking	Passive	5 (6.7%)	0	0.023
	No	70 (93.3%)	75 (100%)	
Animal contact	Yes	11 (14.7%)	9 (12%)	0.63
	No	64 (85.3%)	66 (88%)	

* BMI; Body Mass Index.

Obstetric history

Parity showed a notable distinction, with a higher proportion of mothers in the case group having 1-2 pregnancies (48% vs. 24%) and a lower proportion having 3-4 pregnancies (32% vs. 49.3%) compared to the control group (p=0.009). There is no significant difference in the history of abortion, with

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42.7% of cases and 41.3% of controls reporting abortion history (p=0.89). Similarly, twin pregnancies do not significantly differ, with 2.7% of cases and 6.7% of controls having twin pregnancies (p=0.26). Normal conception rates are nearly identical, with 100% of cases and 97.3% of controls reporting normal conception (p=0.15). The type of delivery shows no significant difference, with 62.7% of cases and 54.7% of controls having caesarean sections, and 37.3% of cases and 45.3% of controls having normal vaginal deliveries (p=0.32). A slightly higher, but not statistically significant, percentage of cases experienced delayed labor (4% vs. 0%, p=0.08). Both groups report no birth trauma. Antenatal care quality is similar, with 96% of cases and 98.7% of controls receiving good antenatal care (p=0.31). Close spacing between pregnancies shows no significant difference, with 6.7% of cases and 12% of controls having closely spaced pregnancies (p=0.26), as found in Table 3.

Table (3): Obstetric history of cases and control groups.

Variables		Cases N=75	Control N=75	p value
Abortion history	Yes	32 (42.7%)	31 (41.3%)	0.89
	No	43 (57.3%)	44 (58.7%)	
Parity	1-2	36 (48%)	18 (24%)	**0.009**
	3-4	24 (32%)	37 (49.3%)	
	≥ 5	15 (20%)	20 (26.7%)	
Twin pregnancy	Single	73 (97.3%)	70 (93.3%)	0.26
	Twin	2 (2.7%)	5 (6.7%)	
Normal conception	Yes	75 (100%)	73 (97.3%)	0.15
	No	0	2 (2.7%)	
Type of Delivery	C/S	47 (62.7%)	41 (54.7%)	0.32
	NVD	28 (37.3%)	34 (45.3%)	
Delay of labor	Yes	3 (4%)	0	0.08
	No	72 (96%)	75 (100%)	
Birth trauma	No	75 (100%)	75 (100%)	----
Antenatal care	Poor	3 (4%)	1 (1.3%)	0.31
	Good	72 (96%)	74 (98.7%)	
Close space between pregnancy	Yes	5 (6.7%)	9 (12%)	0.26
	No	70 (93.3%)	66 (88%)	

*C/S; caesarean sections, NVD; Normal Vaginal Delivery

Maternal illness during pregnancy

Gestational diabetes mellitus is equally prevalent in both groups, with 2.7% in each group having it (p=0.99). Similarly, the prevalence of gestational hypertension (HTN) shows no significant difference, with 12% of cases and 10.7% of controls having it (p=0.79). A notable difference is observed in the incidence of mood disorders during pregnancy. A significant proportion of mothers in the case group (22.7%) reported

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depression, compared to none in the control group (p=0.0001). Regarding TORCH infections, there were 2 cases (2.7%) of rubella infection in the case group and no one in the control group (p=0.15), as found in Table 4.

Table (4): Maternal illness during pregnancy for cases and control groups.

Variable		Cases N=75	Control N=75	p value
Gestational DM	Yes	2 (2.7%)	2 (2.7%)	0.99
	No	73 (97.3%)	73 (97.3%)	
Gestational HTN	Yes	9 (12%)	8 (10.7%)	0.79
	No	66 (88%)	67 (89.3%)	
Depression	Yes	17 (22.7%)	0	**0.0001**
	No	58 (77.3%)	75 (100%)	
TORCH	Yes	2 (2.7%)	0	0.15
	No	73 (97.3%)	75 (100%)	

* DM; Diabetics Miletus, HTN; Hypertension, TORCH; (Toxoplasmosis, Other, Rubella, Cytomegalovirus, and Herpes simplex virus)

Drugs before and during pregnancy

The use of contraceptive pills (combined oral contraceptive pills) shows no significant difference, with 12% of cases and 6.7% of controls using them (p=0.15). There is a significant difference in the use of ovulation-stimulating hormones, with 21.3% of cases using them compared to only 4% of controls (p=0.001). The use of folic acid is higher among cases, with 89.3% of cases taking folic acid compared to 70.7% of controls (p=0.058). Acetaminophen use is very similar between the groups, with 1.3% of cases and 2.7% of controls using it (p=0.31). There are no cases of anti-epileptic or anti-depressant drug use in either group. The use of tonics (multivitamins) is identical in both groups, with 2.7% of cases and controls using them (p=0.99) Table 5.

Table (5): Drugs before and during pregnancy of cases and control groups.

Variables		Cases N=75	Control N=75	p value
Contraceptive pills	Yes	9 (12%)	5 (6.7%)	0.15
	No	66 (88%)	70 (93.3%)	
Ovulation-stimulating hormones	Yes	16 (21.3%)	3 (4%)	**0.001**
	No	59 (78.7%)	72 (96%)	
Folic acid	Yes	67 (89.3%)	53 (70.7%)	0.058
	No	8 (10.7%)	22 (29.3%)	
Acetaminophen	Yes	1 (1.3%)	2 (2.7%)	0.31
	No	74 (98.7%)	73 (97.3%)	
Anti-Epileptics	No	75 (100%)	75 (100%)	----
Anti-Depressant	No	75 (100%)	75 (100%)	----
Tonics	Yes	2 (2.7%)	2 (2.7%)	0.99
	No	73 (97.3%)	73 (97.3%)	

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Discussion

The study indicates that the mean maternal age is significantly higher in the case group compared to the control group (28.1 years vs. 22.9 years, p=0.001). In a large meta-analysis study by Wu S et al. (11), they found that an increase in the mother's age is associated with an increased risk of autism in the offspring. There were no significant differences in maternal education, although a higher percentage of mothers in the case group were employed. This contrasts with other studies suggesting lower maternal education levels associated with increased ASD risk in which in study from Egypt by Arafa A et al (12). The study showed, no significant role for parental consanguinity between the case and control groups, this finding is consistent with some studies, like a study from Qatar by Alshaban FA et al (13). The mean BMI of mothers in the case group was significantly higher compared to the control group (26.9 vs. 24.4, p=0.0001) a study by Krakowiak et al (14). It was shown that maternal obesity is associated with a higher risk of ASD. The study reports that 6.7% of mothers in the case group were exposed to passive smoking, while none in the control group were exposed (p=0.023). This suggests that passive smoking during pregnancy is a significant risk factor for ASD. A study by Visser JC et al. (15) found that maternal smoking during pregnancy was associated with a higher risk of ASD in children. The study shows no significant difference in animal contact between the groups. Parity showed a significant difference between the groups, with a higher proportion of mothers in the case group having 1-2 pregnancies (48% vs. 24%) and a lower proportion having 3-4 pregnancies (32% vs. 49.3%) compared to the control group (p=0.009). This was in line with previous study by Cheslack-Postava K et al. (16) that should decrease risk of ASD with increasing parity. Also, another study Burstyn I et al. (17) showed that ASDs decreased with increasing parity. Twin pregnancies did not show a significant difference between the groups in this study (p=0.26) while a study from Egypt by Arafa A et al (2). found that multiple pregnancy is a risk factor for ASD. The history of abortion was similar between groups (p=0.89), as were the rates of normal conception (p=0.15). The mode of delivery, whether a cesarean section or normal vaginal delivery, did not significantly differ between the groups (p=0.32), nor did the quality of antenatal care received (p=0.31). Additionally, close spacing between pregnancies (p=0.26) and the presence of birth trauma (both groups reported none) were also not significantly different. A notable difference was observed in the incidence of depression during pregnancy, with 22.7% of mothers in the case group reporting depression compared to none in the control group (p=0.0001). Studies, such as those of Caparros Gonzalez RA et al. (18). It was concluded that exposure to high levels of stress during pregnancy is associated with ASD. Another study by Ayano G et al (19). It was shown that depressive disorders increased the risk of ASD in offspring. Some studies suggest a modest increase in ASD risk associated with gestational diabetes; other studies, including this one, have not found a significant association (20). For instance, a large cohort study by Shao W et al. (21) found that gestational diabetes was associated with a

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higher risk of ASD. Furthermore, congenital heart disease may increase the risk of autism (22). Existing literature on gestational hypertension and ASD risk is limited, but some studies suggest a potential link, like a study by Wang LW et al. (23). TORCH infections are known to cause severe congenital abnormalities and neurodevelopmental disorders, including ASD (24). However, the low detection rate of rubella (n=2, 2.7%) in this study limits the ability to detect a significant association. Studies have suggested that the use of ovulation-stimulating hormones may be associated with an increased risk of ASD this study and a study by Robinson SL et al. (25) reported that assisted reproductive technologies, including ovulation-stimulating drugs, could be linked to a higher ASD risk. The use of contraceptive pills was similar among the groups in a study by Hargreave M et al. (26). It was shown that maternal use of hormonal contraception may be associated with ASD risk in children. The use of folic acid was higher among cases but not significantly different (89.3% vs. 70.7%, p=0.058), suggesting widespread adherence to prenatal guidelines. In a study by Surén P et al (27). It was found that prenatal folic acid supplements around the time of conception were associated with a lower risk of ASD. Acetaminophen use was also similar (1.3% vs. 2.7%, p=0.31), reflecting the low prevalence and possibly limited impact of occasional use on ASD risk. There were no reported cases of anti-epileptic or antidepressant drug use in both groups. Moreover, maternal intrahepatic cholestasis of pregnancy (ICP) is associated with children's risk of autism (28,29).

Conclusions

Based on the study results, we concluded the following:

Advanced Maternal Age, Maternal BMI, Smoking, Depression, use of Stimulating hormones before pregnancy, and Parity are all factors that are significantly associated with an increased risk of ASD.

Recommendations

Based on study results, we recommended the following: Provide comprehensive preconception counseling to older women planning to conceive, Implement nutritional and lifestyle interventions for women of childbearing age to manage BMI and promote healthy weight. Strengthen smoking cessation programs targeting pregnant women and their families to reduce exposure to secondhand smoke. Integrate mental health screenings and support into prenatal care to identify and treat depression and other mood disorders early in pregnancy. Closely monitor and evaluate the use of stimulating hormones and other fertility treatments, considering potential risks and benefits.

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Ethical Clearance: Official approval has been obtained to use data, and data were analyzed without the names to protect privacy. This study was conducted according to the approval of the College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of Ethical Committee of the College (Document no. 2024NAM890).

Conflict of Interest: Non

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عوامل الخطورة عند الامهات لاضطرابات طيف التوحد

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الملخص

خلفية الدراسة: اضطراب طيف التوحد هو اضطراب تطوري عصبي معقد يتميز بعيوب في التواصل الاجتماعي واهتمامات محدودة وسلوكيات متكررة. تعتبر مسببات اضطراب طيف التوحد متعددة العوامل، حيث تشمل العوامل الوراثية والبيئية والأمومية. أشارت الدراسات الحديثة إلى أن العوامل الأمومية مثل تقدم عمر الأم، ارتفاع مؤشر كتلة الجسم، التدخين والاكتئاب أثناء الحمل، هي عوامل خطر مهمة لتطور اضطراب طيف التوحد. تهدف هذه الدراسة إلى التحقيق في عوامل الخطر الأمومية المساهمة في المرض لدى الأطفال في ديالى، العراق.

اهداف الدراسة: ان الهدف من هذه الدراسة هو معرفة عوامل الخطورة عند الامهات المسببة لمرض اضطراب طيف التوحد.

المرضى والطرائق: اجريت هذه الدراسة من نوع الحالات والشواهد على ١٥٠ طفلًا، شملت ٧٥ طفلًا تم تشخيصهم باضطراب طيف التوحد و٧٥ طفلًا كمجموعة سليمة. بدأت الدراسة من شهر آب ٢٠٢٣ إلى شهر آيار ٢٠٢٤ في محافظة ديالى، العراق. حيث شمل جمع البيانات تاريخ شامل ديموغرافي، اجتماعي، توليدي، وصحي للأمهات. تم تأكيد تشخيص المرض باستخدام مقياس تقييم التوحد في مرحلة الطفولة ٢ (CARS-2) وتم إجراء تحليل الانحدار اللوجستي لتقييم العلاقة بين عوامل الخطر الأمومية واضطراب طيف التوحد.

النتائج: كشفت الدراسة عن عدة عوامل خطر أمومية مهمة للمرض، حيث كان عمر الأم المتقدم أثناء الحمل (متوسط العمر ٢٨,١ سنة) في مجموعة الحالات مقابل (٢٢,٩ سنة) في المجموعة السليمة(p=0.001) ، و متوسط ارتفاع مؤشر كتلة الجسم للأم (٢٦,٩ كغم/م^{٢}) في مجموعة الحالات مقابل (٢٤,٤ كغم/م^{٢}) في المجموعة السليمة (p=0.0001) والتدخين بين الأمهات (٦,٧٪) في الحالات، مقابل (٠٪) في المجموعة السليمة، (p=0.023)، والاكتئاب أثناء الحمل (٢٢,٧٪) في الحالات مقابل (٠٪) في المجموعة السليمة، (p=0.0001) كلها عوامل مرتبطة بشكل كبير بزيادة خطر حدوث المرض. كما أظهر استخدام الهرمونات المحفزة قبل الحمل ارتباطًا كبيرًا حيث بلغت النسبة (٢١,٣٪) في الحالات مقابل (٤٪) في المجموعة السليمة، (p=0.001).وكانت نسبة الولادات لها تأثير، خصوصا عند الأمهات اللاتي حملن مرة أو مرتين فقط، عامل خطر كبير أيضًا (p=0.002).

الاستنتاجات: تبين من خلال هذه الدراسة ان (العمر المتقدم للأم، ارتفاع مؤشر كتلة الجسم ، التدخين، الاكتئاب وعدد الولادات عند الامهات اللاتي حملن مرة او مرتين وايضا استخدام الهرمونات المحفزة قبل الحمل) جميعها تعتبر عوامل خطر عند الامهات لتطور مرض اضطراب طيف التوحد عند الأطفال.

الكلمات المفتاحية: التوحد، اضطراب طيف التوحد، عمر الأم وعلاقته بالتوحد، مرض الأم وعلاقته بالتوحد.

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