Is cesarean section delivery associated with autism spectrum disorder?

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ABSTRACT

الأهداف: بحث العلاقة بين الولادة القيصرية والإصابة بطيف التوحد.

الطريقة: تم استخدام دراسة الشاهد والحالة بنسبه 2 إلى 1 في المدينة المنورة خلال عام 2016م، وقد تم اختيار الحالات بناء على معايير الأهلية المحددة مسبقاً كما تم اختيار الشواهد من الأطفال الذين يراجعون في عيادة الطفل السليم في نفس المستشفى. تم جمع البيانات من خلال السجلات الطبية و كذلك من خلال استبيان عن طريق مقابلة الأمهات. في التحليل الإحصائي تم استخدام اختبار مربع كاي للتحليل الثنائي وكذلك نموذج الانحدار اللوجستي متعدد المتغيرات لحساب نسبة العلاقة الخام و المنضبطة.

النتائج: كانت هناك 87 حالة طيف التوحد و 174 حالة شاهد في هذه الدراسة. تقريبا 39% من إجمالي 87 طفل مصاب بطيف التوحد تمت ولادته عن طريق الولاده القيصريه مقارنة مع 21% من إجمالى 174 طفل شاهد. بعد ضبط العوامل المشوشة المحتملة، أظهرت الدراسة الحالية علاقة مهمة إحصائياً بين الولادة القيصرية والإصابة بطيف التوحد.

الخاتمة: وجدت الدراسة الحالية علاقة مهمة إحصائياً بين الولادة القيصرية وطيف التوحد مما يؤكد نتائج الدراسات السابقة. توصي الدراسة باتخاذ الإجراءات الوقائية لتجنب الولادات القيصرية غير الضرورية.

Objectives: To investigate a correlation between birth by caesarean section and autism spectrum disorder (ASD).

Methods: A case-control study with a case to control ratio of 1:2 was performed in Al-Madina Al-Munawarah city, Kingdom of Saudi Arabia during the year 2016. The cases were selected according to the eligibility criteria and children attending a well-baby clinic in the same hospital, were chosen as the control group subjects. Data was collected from the medical records and an interview-based questionnaire was administered to the mothers. The chi-square test was used for bivariate analysis and logistic regression to estimate the crude and adjusted odds ratios (ORs).

Results: Eighty-seven cases of ASD and 174 control group subjects were included in the current study. Approximately 39% (n=34) of the 87 children with ASD were delivered by cesarean section compared to 21% (n=36) of the 174 children in the control group. After adjusting for potentially confounding factors, the adjusted OR was 2.9 (95% confidence interval [CI]: 1.57-5.35).

Conclusion: An association between delivery by cesarean section and ASD was found in this study, in support of the findings of other studies. It is recommended that preventive measures are adopted to avoid unnecessary cesarean sections.

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Autism spectrum disorder (ASD) comprises a range of conditions that are characterized by impaired social communication and interaction, as well as repetitive behavior. Autism spectrum disorder begins in childhood and continues into adulthood, leading to a significant psychological and financial burden on the caregiver and family. The worldwide prevalence of ASD is estimated to be 0.7%, although wide variability has been reported.[1] In addition, it has been reported in several studies that the prevalence of ASD is increasing worldwide. A real increase in ASD cannot be excluded

even though it might be explained by improvements in documentation and the diagnosis of milder cases.[2,3]

The pathophysiology of the disease is not well understood but multifactorial etiology is suggested by the current evidence.[1] Various genetic and environmental factors have been found to be associated with ASD, including, advanced paternal age and exposure to heavy metals such as lead and inorganic mercury.[4] As is the case with many other diseases, it is believed that ASD is caused by an interaction between genetic and environmental factors rather than attributable to a single cause. Deoxyribonucleic acid (DNA) methylation, which can be influenced by diet, stress, drugs, or environmental chemicals, has also been suggested as the mechanism involved in this interaction.[5]

Globally, cesarean section delivery is estimated to account for 19% of all births, ranging from 7% in Africa to 41% in Latin America and the Caribbean.[6] An average of 4% global increase in ASD has been reported annually over the last few decades.[6] Cesarean section is associated with various short and long-term health challenges, including respiratory morbidities,[7] hospitalization for asthma,[8] acute lymphoblastic leukemia,[9] and neurodevelopmental impairment.[10] Conflicting results have been reported in previous studies on an association between cesarean section delivery and the subsequent development of ASD in the infant.[11-13] Thus, the current study objective was to investigate the association of birth by cesarean section and the risk of ASD.

Methods. A case-control study was performed of ASD cases diagnosed in Al-Madina Al-Munawarah, Kingdom of Saudi Arabia. The recruitment of subjects and the data collection were carried out from March-May 2016.

Autism spectrum disorder cases. Cases were selected from 2 hospitals in Al-Madina Al-Munawarah, Kingdom of Saudi Arabia; the Mental Health Hospital and the Maternity and Children's Hospital. Each hospital has a registry of ASD cases that includes the basic data, file number, and contact information. Cases were eligible for inclusion based on an ASD diagnosis conferred within the last 2 years (between January 2014 and May 2016), confirmation of the diagnosis by psychiatric consultants using the international statistical classification of diseases and related health problem (ICD-10th revision) criteria, and being in the age range of 3-10 years. Cases of cerebral palsy, Down's syndrome, or epilepsy were excluded. All cases satisfying the above-mentioned inclusion criteria were included in the study.

Control subjects. Children attending well-baby clinics in the Madinah Maternity and Children's hospital were selected as subjects in the control group if they had no issues relating to neurodevelopmental or mental health problems. The control group subjects were frequently matched according to age and gender using a case to control ratio of 1:2 and were screened to exclude ASD. The screening test was developed by the National center for developmental & behavioral disorders and is endorsed by the Ministry of Health. It contains 3 sections (social interaction, social communication, and behavior), with a potential maximum score of 18 points. Children who scored ≥9 points were referred to the psychiatric clinic and were excluded from the study. Subjects in the control group were also excluded if any of the exclusion criteria that were applicable to the case subjects pertained to them too.

Data collection. Data on the cases was collected from the hospital medical records and an interview-based questionnaire that was administered to the mothers. Data collected from the medical records included the age of the child, gender, method of ASD diagnosis, and the date of diagnosis. Other data on exposure variables and covariates were obtained via the interview-based questionnaire that was developed based on others in the literature, then tested in the pilot study and modified accordingly. The questionnaire comprised 5 sections: i) sociodemographic data: age, gender, maternal-paternal age and education, family income, parity, and smoking; ii) familial factors: a history of ASD, mental illness, and consanguinity; iii) parental factors: maternal and paternal age at the time of birth, maternal and paternal educational levels, and the socioeconomic status of the family; iv) prenatal conditions: gestational diabetes, high blood pressure, infections, bleeding during the pregnancy, and fetal distress; and v) perinatal factors: premature membrane rupture, breech presentation, induced labor, and mode of delivery.

Statistical analysis. Stata® for Windows version 13.1 (SPSS Inc., Chicago, IL, USA) was used to perform the analysis. The covariates were categorized as maternal age (<30 years and ≥30 years) and paternal age <30 years and ≥30 years) at the birth of the child, the highest maternal and paternal educational achievement (≤9 years, 10-12 years, and ≥13 years), family income (<6000, 6000-10000, >10000 Saudi riyals), and parity (0, 1, 2, and ≥3 previous births). The proportions of ASD cases were calculated in various categories of the exposure variable as well as other independent variables.

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The *p*-value for the chi-square test was also calculated to determine if there was a significant relationship with the independent variables. Logistic regression models were used to estimate the crude and adjusted ORs and 95% CIs with respect to an association between a history of cesarean section delivery and an ASD diagnosis of the child. To estimate the adjusted OR, an adjustment was made for factors reported in the literature relating to ASD (namely, maternal age at birth, paternal age at birth, maternal education, paternal education, parity, and family income). Further adjustment was made in a second model for other maternal conditions during pregnancy A variance inflation factor was utilized to check for multicollinearity in the models.

The study was approved by the Ethics Committee of the directorate of health. The study was conducted according to the principles of Helsinki declaration. All the subjects provided informed written consent prior to participation. Participant anonymity and data security was ensured throughout the study.

Results. Overall, 87 ASD cases and 174 control group subjects were included in the study. The baseline characteristics of the subjects are presented in **Table 1**. Sixty-five (75%) male and 22 (25%) female subjects were included in the study, which corresponds with the internationally reported male preponderance of ASD.[14] The characteristics of the case and control group subjects were similar, except for the presence of hypertension during pregnancy. Thirty-nine percent (n=34) of the 87 children with ASD were delivered by cesarean section compared to 21% (n=36) of the 174 children in the control group (**Table 1**).

An association was demonstrated between cesarean delivery and subsequent ASD diagnosis of the child. Cesarean delivery was linked to an increased likelihood of ASD (crude OR=2.46, 95% CI: 1.40-4.33). The association remained statistically significant, even after adjusting the potential confounding factors (reported previously in the scientific literature) in the first model (adjusted OR=2.9, 95% CI: 1.57-5.35). The association persisted after further adjustment of the maternal factors during pregnancy in the second model (adjusted OR=3.41, 95% CI: 1.76-6.58) (**Table 2**).

Discussion. Delivery by cesarean section was associated with an increased risk of ASD in children in the current research, even after adjusting the potentially confounding factors. In fact, the effect estimate OR of the association increased after adjustment of the confounding variables which indicates a negative confounding effect. The study findings support those of previous studies in which a statistically significant association between ASD and cesarean section has been demonstrated. For example, an OR=1.23, 95% CI: 1.07-1.4 was reported in one study by Curran et al,[12] compared to a similar estimate of OR=1.26, 95% CI: 1.22-1.30 in other research conducted recently by Yip et al.[13] The Yip et al,[13] study also reported a stratified OR for various gestational weeks and a consistently increased risk of ASD was demonstrated for gestational weeks 36-42. They also reported no statistically significant difference in the ASD risk between planned and emergency caesarean section. Although the effect estimate in the current study was higher than

Table 1 - Basic characteristics of cases and control subjects.

Characteristics	Cases (N=87)	Controls (N=174)	*P*-value
	n (%)		
Gender			
Male	65 (74.71)	129 (74.14)	0.920
Female	22 (25.29)	45 (25.86)	
Maternal age			
<30	55 (63.22)	120 (68.97)	0.352
≥30	32 (36.78)	54 (31.03)	
Paternal age			
<30	24 (27.59)	59 (33.91)	0.301
≥30	63 (72.41)	115 (66.09)	
Father's education			
≤9	17 (19.54)	41 (23.56)	
10-12	27 (31.03)	40 (22.99)	0.356
≥13	43 (49.43)	93 (53.45)	
Mother's education			
≤9	39 (44.83)	57 (32.76)	
10-12	19 (21.84)	45 (25.86)	0.161
≥13	29 (33.33)	72 (41.38)	
Family's income (SR)			
<6000	39 (44.83)	75 (43.10)	
6000-10000	34 (39.08)	65 (37.36)	0.795
>10000	14 (16.09)	34 (19.54)	
Parity (previous births)			
0	28 (32.18)	56 (32.18)	
1	13 (14.94)	46 (26.44)	0.163
2	14 (16.09)	23 (13.22)	
≥3	32 (36.78)	49 (28.16)	
Maternal smoking			
Yes	0 (0.0)	0 (0.0)	-
No	87 (100)	174 (100)	
Maternal DM			
Yes	4 (4.65)	9 (5.17)	0.856
No	82 (95.35)	165 (94.83)	
Maternal HTN			
Yes	10 (11.63)	8 (4.60)	0.036
No	76 (88.37)	166 (95.40)	
Cesarean Section			
Yes	34 (39.08)	36 (20.69)	0.002
No	53 (60.92)	138 (79.31)	

SR - Saudi Riyals, DM - Diabetes mellitus, HTN - Hypertension

Table 2 - Multivariable analysis of the association between cesarean delivery and ASD.

Delivery type	Number of cases/controls	Odds ratio (95% CI)		
		Crude	Adjusted	
			*Model 1	†Model 2
Cesarean section				
Yes	34/36	2.46 (1.40-4.33)	2.9 (1.57-5.35)	3.41 (1.76-6.58)
No	53/138	Ref	Ref	Ref

ASD - autism spectrum disorder, OR - odds ratio, CI - confidence interval. *Model 1 adjusted for maternal and paternal age, maternal and paternal education, parity and family income. †Model 2 adjusted for the same factors in model 1 in addition to hypertension, UTI and fever during pregnancy

that reported by Yip et al,[13] the OR reported in the current study was similar to that described in previous case-control studies, namely, an OR=2.51, 95% CI: 1.12-5.63 was reported in the study by Al-Ansari et al.[15] The wide CI in the current study could be explained by the relatively small sample size. The rate of cesarean section for the control group subjects in our study was 21%, similar to that reported in previous studies at national level (namely, 19%), a finding that confirmed that the proportion of subjects selected for the control group in the current study was sound.[16]

Various theories have been proposed to explain the relationship between delivery by cesarean section and ASD, and include oxytocin dysregulation, the microbiota-gut-brain axis, and neurotoxicity due to general anesthesia administered during cesarean section.

Oxytocin is a peptide that is produced in the hypothalamus and is released into the bloodstream by the pituitary gland. It is known for its role in the stimulation of uterine contraction during labor and its ability to regulate breastfeeding. Oxytocin has also been demonstrated to be influential in social behavior, including mother-infant bonding, social interaction, and sexual behavior.[17,18] It has been shown that children with ASD have significantly lower plasma levels of oxytocin compared to non-autistic children.[19] During normal birth, oxytocin is secreted in pulses, in gradually increasing amounts; reaching a peak in the first hour after birth. However, this peak is absent when delivery occurs via planned cesarean section. It has been proposed that oxytocin dysregulation affects the brain development of the infant. The potentially therapeutic benefits of oxytocin in ASD cases have been investigated in various studies and although the results have been promising, the evidence remains inconclusive.[18]

The microbiota-gut-brain axis is another potential mechanism that has recently attracted increasing attention in the scientific literature. This axis represents the interaction between the gut microbiota, the neuroendocrine and neuroimmune systems, and the central and peripheral nervous systems; all of which form a complex network and influence one another.[20] The observation that approximately 70% of ASD patients also regularly experience gastrointestinal symptoms has led to the suggestion that the microbiota-gut-brain axis has a potential role to play in ASD.[21] The effects of microbiota alterations on social interaction have been reported in animal studies.[22] In addition, differences in the composition of gut microbiota between ASD patients and control group subjects were observed in clinical studies.[22] The mode of delivery (cesarean section vs. vaginal delivery) is known to change the acquisition and composition of microbiota in newborn infants.[23] Thus, it is biologically plausible that delivery via cesarean section has a link to ASD through the microbiota-gut-brain axis.

It has also been proposed that the neurotoxicity that is associated with general anesthesia administered to perform a cesarean section could explain the increased risk of ASD in infants who are delivered in this way. Chien et al,[24] reported a 52% increased risk of ASD in neonates born by cesarean section involving general anesthesia compared to those born by vaginal delivery. However, they also reported that an increased risk of ASD was not found for neonates born by cesarean section with regional anesthesia compared to vaginal delivery.[24] By contrast, a difference in the risk of acquiring ASD was not reported between cesarean section with general anesthesia and that with regional anesthesia in other research.[13]

Although an association between delivery by cesarean section and ASD is biologically plausible and is supported by the current study finding and those of others, a causal relationship has not yet been confirmed. The results of the current study could be owing to residual confounding or unmeasured bias. Cesarean section is associated with various prenatal conditions which might be connected to ASD. However, the evidence in the current and other studies warrants the adoption of preventive measures to avoid unnecessary cesarean sections.

Strengths and limitations of the study. A strength of the current study was that an adjustment was made for various confounding factors in order to obtain a

more realistic estimate of the association between ASD and cesarean section, in addition to its reliance on an evidence-based psychiatrist assessment and diagnosis of ASD to reduce diagnosis misclassification, as opposed to self-reporting used in other studies.

A study limitation was the case-control study design as this has potential for recall bias. However, the exposure factor (cesarean section) is a major event and is therefore unlikely to be affected by recall bias. Secondly, it was not possible to determine the indications for cesarean section and this could have had a confounding effect on the relationship between ASD and cesarean section.

In conclusion, the current study findings constitute further evidence of an association between delivery by cesarean section and a subsequent increased risk of ASD in the infant. Adjustment for confounding was not found to reduce the effect estimate. Preventive measures to reduce cesarean section deliveries without a strong medical indication should be implemented based on evidence of a correlation between the increased rate of cesarean section and ASD.

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