Middle East Current Psychiatry

RESEARCH

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Maternal- and child-related risk factors for autism during the perinatal period

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Abstract

Background Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder commonly prevalent in children worldwide including KSA. It causes disability in social interaction, communication, and restrictive and repetitive behaviors. Detecting risk factors for ASD could help initiate screening and risk prevention approaches. Herein, this study aimed to detect several maternal and neonatal risk factors for ASD in KSA.

Results Ninety-four cases and 282 control completed an online survey tool. The survey items were close-ended questions. Participants were asked about maternal-related risk factors for autism during perinatal period. The logistic regression model revealed having a child diagnosed with autism with two predictors: factors related to the mother and factors related to the baby during perinatal period. The whole model was sig ($p < 0.0001$). The factors related to the baby have more impact on developing autism than maternal factors (*OR* is 3 vs 2.3, respectively, $p < 0.01$ for both).

Conclusion The findings of this study will be beneficial for subsequent nationwide screenings and educational programs. The study brought to light the potential for identifying children in need of early intervention.

Keywords Maternal, Risk factors, Autism

Introduction

Autism, often known as autism spectrum disorder, is a neurodevelopmental condition that affects a person's capacity for social interaction, communication, and the ability to react to environmental cues. Males are more likely than females to have the illness, which is detected by the age of 3 in both sexes [1]. It was previously thought that 5 out of every 10,000 children had autism; however, prevalence rates may have dramatically increased during the past 10 years [2]. An increase from the prior estimate of 14.7 per 1000 children aged 8 having autism is reported by the Autism and Developmental Disabilities Monitoring (ADDM) (roughly 1 in 189 girls and 1 in 42 boys) [3]. Between the ages of 2 and 14, the projected average yearly percent increases in prevalence ranged from 9.7 to 14.6% in Canada, where the incidence had jumped by 63% in just 2 years [4]. With 1 in 88 children impacted in the USA, the frequency has climbed by 18 to 26% annually (5 times higher in males) [5].

In KSA, the overall prevalence of autism in the primary school of Taif district whose age ranged from 7 to 12 years was 0.035% from a sample population of 22,950 student; the prevalence of autism in male (0.031%) was greater than female (0.004%) [6]. Reports state that 42,500 children in KSA's various areas were diagnosed with the disease in 2002, but sadly, no estimates of incidence rates could be made [7].

Although the etiology of these illnesses is not fully understood, twin and family studies indicate that genetic factors are likely to be a major contributing factor [8]. The modifiable risk factors for autism spectrum diseases,

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however, are poorly understood (ASDs) [9]. Several studies indicated the presence of one or more unfavorable obstetric circumstances, such as breech presentation, gestational age at birth 35 weeks, and parental mental history, has been linked to an elevated risk for autism [8].

Additionally, factors to having a child with autism included giving birth early and having a mother who is at least 35 years old [10], whereas prenatal risk factors included older parents, a short gestation period, low birth weight, hyperbilirubinemia, breech presentation, and drug usage during pregnancy [11]. However, the most significant risk factors to having a child with autism were extensively researched during pregnancy and child labor. These risk factors include fetal presentation, umbilical cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, low birth weight, small for gestational age, low 5-min Apgar score, meconium aspiration, ABO or Rh incompatibility, and neonatal anemia; the authors discovered a number of potential risk factors in a different meta-analysis that focused on the perinatal and neonatal period [12].

The relationship between pregnancy, birth problems, and other maternal factors and the onset of autism have been the subject of extensive research, although the exact cause of these interactions is still unknown.

The purpose of this study is to identify factors that, in Saudi Arabia, enhance a child's likelihood of developing an autism spectrum disorder.

Compare pregnancy and delivery concerns between mothers of children with autism and mothers of children who are normally developing to better understand this interaction.

Methods

Study type

It is a matched case–control study.

Study setting

The study was conducted in different regions of Saudi Arabia.

Study population

They are mothers of children with or without autism living in Saudi Arabia.

Inclusion criteria

The population of the study consisted of mothers of children with autism (considered as cases) and mothers of children without autism (considered as control), aged 18. Both groups of cases and controls were matched as regard family history of autism and working status of the mother.

Exclusion criteria

They are females without children or under the age of 18 years.

Sample size

Calculated sample size was minimum of 94 cases and 282 control based on 30% proportion of exposure to complications during delivery in Saudi population in 2015 [13]. Calculating sample size was done by *N4studies* application for a matched case–control study with 95% *CI* and 80% power, and least extreme odds ratio to be detected is 2. The present study eventually collected 103 cases and 567 controls. With this sample size, the statistical power of our study increased from 80 to 97%.

Sampling technique

It was a convenience sampling.

Materials and tools

The data was collected using an online survey tool consisting of three sections where volunteers were asked to sign an online consent before filling in the questionnaire. The survey items were close-ended questions. Participants were asked about demographic factors as well as maternal-related risk factors for autism during perinatal period such as suffering from diseases during pregnancy, Rh status, hospital admission during pregnancy, and type of labor. The third section was about child-related risk factors such as the following: baby distress during labor, high bilirubin level after birth, and low birth weight. Diagnosis of autism in the children was confirmed by mothers who confirmed that their children were diagnosed with autism by a doctor in their healthcare center. A pilot study was carried out to ensure high level of validity for the study, and the required changes for the questionnaire were done.

Statistical analysis

JMP version 14 was used for data analysis. Fisher's exact test was used to ensure proper matching of cases and controls as regard the required variables. Odds ratio was conducted to get the significant risk factors for autism. Additionally, logistic regression was performed to illicit predictors for autism. The cutoff point of significance was set to be 0.05.

Ethics approval and consent to participate

Before taking the survey, participants were asked to sign the consent form and were assured that all information will be kept confidential and anonymous.

The electronic analytic dataset included a unique study ID number for each participant with no personal

identifier. The electronic dataset was stored on a computer connected to secure server that is password protected. Data were accessed, managed, and analyzed only by the IRB-approved researchers. The ethical approval (IRB log number: 17–0254) was obtained from the Princess Nourah Bint Abdulrahman University before conducting the research.

Result

Table 1 reveals the sociodemographic characteristics of studied sample in both cases and control groups. Total sample size was 670 mothers, with 103 of them having a child with autism and 567 do not. A total of 13% of mothers with at least one child with autism reported positive family history compared to 8% of control group, and about half of the sample of mothers in both cases and control groups were not working. Both groups have no significant differences as regard family history of autism and working status of the mother ($p > 0.05$ for both variables). There was also no significant difference in nationality of both groups ($p > 0.05$). Regrading educational level of both parents, there was a significant difference between cases and control groups as the proportions of less educated mother and father were higher among cases than control groups (35% and 44% vs 11% and 23%, respectively, $p < 0.05$).

Table 1 Sociodemographic characteristics of studied sample in both cases and control groups

Variables	Having a child diagnosed with autism				Fisher's exact test
	Yes		No		
	N	%	*N*	%	
Family history					$p = 0.08$
Yes	14	13.86%	46	8.13%	
No	87	86.14%	520	91.87%	
Maternal education					***p* < 0.0001***
Less than college	36	35.64%	63	11.19%	
College or post-graduate	65	64.36%	500	88.81%	
Maternal working status					$p = 1.00$
Housewife	55	56.12%	297	56.36%	
Working	43	43.88%	230	43.64%	
Nationality					$p = 0.31$
Non-Saudi	13	12.62%	97	17.17%	
Saudi	90	87.38%	468	82.83%	
Husband education					***p* < 0.0001***
Less than college	41	44.09%	128	23.84%	
College degree or more	52	55.91%	409	76.16%	

* $p < 0.05$

Table 2 shows the maternal risk factors of having a child diagnosed with autism related to perinatal period. It was found that suffering from any disease during pregnancy was significantly associated with 2.5 times risk of having a child with autism (*CI*: 1.5–4.2, $p < 0.05$). The table also demonstrates that when the mother suffers from diabetes mellitus during pregnancy, she is at high risk of having a child with autism. This was found either for gestational diabetes (higher risk by 3 times) or type 2 diabetes (higher risk by 11 times than others), with $p < 0.05$ in both conditions. Other conditions during pregnancy were not significantly associated with having a child with autism such as administration of folic acid, calcium, or iron, hospital admission, and being Rh negative ($p > 0.05$ for all of these factors). Neither premature labor nor cesarian section was associated with higher risk of having a child diagnosed with autism ($p > 0.05$ for both).

Table 3 reveals the risk factors of autism related to the child condition during perinatal period. When the umbilical cord surrounds the child's neck, the risk of developing autism is 4.6 times higher (*CI*: 2.4–9, $p < 0.05$). It was also found that if the baby is distressed during labor, he is more likely to have autism by 5 times than others. The odds of autism were 7 times more if the baby is subjected to any injury during labor ($p < 0.05$ in both conditions). Another significant risk factor of developing autism among newly born babies is having a low birth weight (*CI*: 1.4–4.4, $p < 0.05$). Other factors that were not associated with a significant higher risk of autism include the following: baby high bilirubin level after birth and abnormal position of fetus in utero ($p > 0.05$ for both conditions).

In Table 4, the logistic regression model is presented. It predicts having a child diagnosed with autism with two predictors: factors related to the mother and factors related to the baby during perinatal period. Maternal factors are considered existing if the mother suffered from one or more of the followings during pregnancy: any disease during pregnancy, gestational diabetes, and type 2 diabetes. Factors related to the child are considered existing if the child had one or more of the followings during perinatal period: umbilical cord around the neck during labor, baby distress during labor, baby injury during labor, and low birth weight. The whole model was sig ($p < 0.0001$). The table also reveals that both factors are significantly associated with developing autism ($p < 0.01$ for both); however, the factors related to the baby have more impact on developing autism than maternal factors (*OR* is 3 vs 2.3, respectively, $p < 0.01$ for both).

Table 2 Maternal risk factors of having a child with autism related to perinatal period

	Having a child with autism				OR (95% *CI*)
	Yes		No		
Disease during pregnancy	***N***	**%**	***N***	**%**	**2.5 (1.5–4.2)***
Yes	27	30.68%	73	14.78%	
No	61	69.32%	421	85.22%	
Folic acid administration during pregnancy					1.2 (0.6–2.7)
No	9	9.89%	40	7.86%	
Yes	82	90.11%	469	92.14%	
Iron administration during pregnancy					1.2 (0.6–2.4)
No	12	13.33%	55	11.02%	
Yes	78	86.67%	444	88.98%	
Ca administration during pregnancy					1.6 (0.9–2.7)
No	25	28.74%	95	19.63%	
Yes	62	71.26%	389	80.37%	
Hospital admission during pregnancy					1.6 (0.9–3.1)
Yes	15	16.67%	54	10.55%	
No	75	83.33%	458	89.45%	
Rh -ive					1.6 (0.7–3.6)
Yes	10	15.87%	31	10.00%	
No	53	84.13%	279	90.00%	
Gestational diabetes					**3.1 (1.7–5.4)***
Yes	23	25.00%	50	9.65%	
No	69	75.00%	468	90.35%	
DM					**11.2 (4.9–25.4)***
Yes	17	18.09%	10	1.93%	
No	77	81.91%	509	98.07%	
Premature labor					1.5 (0.9–2.7)
Yes	20	21.28%	76	14.67%	
No	74	78.72%	442	85.33%	
Type of labor					1.2 (0.7–1.9)
CS	33	35.11%	157	30.19%	
Normal	61	64.89%	363	69.81%	

* $p < 0.05$

Discussion

The present findings are consistent with the growing research on risk factors associated with having an offspring diagnosed with autism. A systematic review assessing risk factors leading to having a child diagnosed with autism showed similar results to our findings [12].

When looking at the first component related to having a child with autism which is suffering from disease during pregnancy, many studies have shown that having a physical or mental disease or having any kind of infection during pregnancy can increase the possibility of having a child with autism [14, 15]. Moreover, taking medication to treat or manage these diseases during pregnancy can also increase the risk of having an offspring diagnosed with autism [12, 15].

For example, a study on mothers with a viral infection in first trimester and bacterial infection in second trimester had a significant association with having a child with autism [16, 17], whereas having a viral infection was not associated with having a child with autism [15]. Furthermore, findings from a systematic review suggested that pregnant women diagnosed with different autoimmune diseases demonstrated a 34% increased risk of having a child with autism [12].

The strong association between having diabetes during pregnancy and delivering an offspring with autism is apparent in many studies [18–20]. Specifically, in a retrospective cohort longitudinal study on children diagnosed with autism, it was found that autism diagnosis in offspring was significantly associated with mothers with

Table 3 Risk factors of having a child with autism related to the child condition during perinatal period

	Having a child with autism				*OR* (95% *CI*)
	Yes		No		
Umbilical cord around child's neck at labor	***N***	**%**	***N***	**%**	**4.6 (2.4–9)***
Yes	18	19.57%	25	4.93%	
No	74	80.43%	482	95.07%	
Distressed baby during labor					**4.9 (2.9–8)***
Yes	36	39.56%	61	11.73%	
No	55	60.44%	459	88.27%	
Baby injury during labor					**7 (3.4–14.4)***
Yes	17	19.32%	17	3.29%	
No	71	80.68%	500	96.71%	
Baby high bilirubin level after birth					1 (0.6–1.6)
Yes	30	34.48%	173	34.46%	
No	57	65.52%	329	65.54%	
Low birth weight					**2.5 (1.4–4.4)***
Yes	22	23.66%	55	10.81%	
No	71	76.34%	454	89.19%	
Abnormal position of fetus in utero					1.7 (0.8–3.3)
Yes	13	14.29%	46	8.88%	
No	78	85.71%	472	91.12%	

* $p < 0.05$

Table 4 Logistic regression model to predict having a child with autism

Term	Estimate	Std. error	Chi-square	Prob > ChiSq	OR (95% *CI*)
Intercept	− 1.431086	0.1295841	121.96	< .0001**	
Maternal factors (absent)[a]	− 0.4187875	0.1306783	10.27	0.0014**	2.3 (1.3–3.8)**
Factors related to the child (absent)[a]	− 0.5500026	0.124676	19.46	< .0001**	3 (1.8–4.8)**

[a] For log odds of yes/no

** $p < 0.01$

preexisting condition of diabetes or with gestational diabetes [20].

On the other hand, our findings verified that deficiency in iron, calcium, or folic acid did not increase the risk of having children with autism which was in line with [21, 22]. However, number of studies indicated that taking prenatal vitamins during pregnancy especially during the 3 months before and during the first month of first trimester decreased the risk of having a child with autism [23, 24]. Differences in the timing of prenatal vitamin inquiries and folate biomarker level tests during pregnancy may account for the observed discrepancy between our findings and those of other studies. We did not specify in the study questionnaire the time when the mother took folic acid or vitamins. If the availability of folate during specific developmental windows plays a role in determining the likelihood of an ASD or autistic behaviors. For instance, like our findings, a large prospective cohort study's results [24] showed that emotional and behavioral problems in young children at the age of 18 months were not related to variations in maternal serum folate measured between 10 and 17 weeks of pregnancy when levels were suggestive of an adequate intake of folate. Even though this study did not show a protective relationship between maternal serum folate levels and emotional disorders, the authors noticed that prenatal folic acid supplementation was connected to a lower incidence of emotional difficulties in children. This has important implications for future research. First, the effects of prenatal use of folic acid and vitamins on child ASD or autistic behaviors should be further investigated in prospective studies that can more robustly measure dosage and frequency of folic acid and vitamins as well as child development in various domains. These studies should collect adequate data to adjust for self-selection and confounding.

Looking at type of labor, our findings did not show any significant association between having a child with autism and vaginal vs. C-section delivery which is not in line with the literature. Based on a systematic review and a meta-analysis done by Curran [25] which affirm that cesarean section deliveries were more significant among women with children diagnosed with autism.

Although our research did not corroborate past findings that children born via cesarean section (CS) have a 20% higher prevalence of ASD diagnoses, the earlier studies revealed that the connection disappeared when sibling controls were used, indicating that family confounding by genetic and/or environmental factors is the reason for this association [26].

Regarding the risk factors of autism related to the child condition during perinatal period. When the umbilical cord surrounds the child's neck, the risk of developing autism is 4.6 times higher (*CI*: 2.4–9, $p < 0.05$). It was also found that if the baby is distressed during labor, he is more likely to have autism by 5 times than others. The odds of autism were 7 times more if the baby is subjected to any injury during labor ($p < 0.05$ in both conditions). The body of research and our findings were in agreement. According to a previous study using a sizable retrospective cohort analysis of 594,638 newborns from California, ASD risk factors include placental abruption, fetal dystocia, prolapsed cord, and birth hypoxia [27].

Previous studies have also shown that poor intrauterine circumstances are a risk factor for neuropsychiatric disorders including autism spectrum disorder (ASD) [28]. Complications during birth may have an adverse effect on neurodevelopment later and result in the appearance of ASD as a result of this unfavorable environment [29]. These problems may cause hypoxia and fetal discomfort, which have been associated with a higher incidence of ASD. Fetal distress is one of the urgent circumstances that necessitates a CS in the healthcare system. Due to an unfavorable prenatal environment, the association between ASD and fetal distress that this study found may actually be related to the underlying causes of CS deliveries.

Another significant risk factor of developing autism among newly born babies is having a low birth weight (*CI*: 1.4–4.4, $p < 0.05$). Similar conclusions were made by Karimi et al. [30], who identified postnatal infection and low birth weight as some of the most significant risk factors. There are three potential causes of a newborn with a birth weight of less than 2500 g, which is termed low birth weight and associated with a twofold greater risk of autism [12, 31]. Low birth weight, however, had contradictory effects; whereas some studies found it to be a strong predictor, others found no link between it and ASD [32].

Postnatal jaundice has been related to mental illness, specifically a fourfold increase in autism if the child survives or to mortality during a sensitive phase. Low hepatic excretory capacity brought on by general liver immaturity and elevated bilirubin generation as a result of accelerated fetal erythrocyte breakdown are the two factors that contribute to it [33, 34]. However, this was different from our study, which found baby high bilirubin level after birth, and abnormal position of fetus in utero ($p > 0.05$ for both conditions) was not associated with a significant higher risk of autism. This variation may be explained by the research participants' varied geographic areas and ages. For the majority of these cases, a combination and interaction of obstetric, environmental, and genetic factors are most likely responsible.

Conclusion

The present study found significant risk factors for autism during perinatal period. These risk factors are of two main types: maternal- and child-related risk factors. The maternal risk factors are as follows: suffering from a disease during pregnancy and having diabetes (either gestational or type 2 diabetes). The child-related risk factors are as follows: low birth weight, if the umbilical cord surrounds the child's neck, baby distress during labor, and if the baby is subjected to any injury during labor. Finally, the present study documented that both factors are significantly associated with developing autism ($p < 0.01$ for both); however, the factors related to the baby have more impact on developing autism than maternal factors (*OR* is 3 vs 2.3, respectively, $p < 0.01$ for both). Understanding these risk factors can contribute significantly to developing detecting and personalized follow-up health plan for population at higher risks of having children with ASD. Moreover, our study findings can shed the light on the relevance of different mother/child risk factors to determine the best approach to design diagnosis and treatment plan for each family and monitor pregnancy and birth closely to avoid complications. Finally, gasping key elements that could lead to having a child with ASD will help in imposing protective measures for at high-risk mothers-to-be in all clinical settings like emphasizing what to avoid and what to consume from the get-go to minimize the risk of having a child with ASD.

Limitation and recommendations

Notably, our study used a standardized technique for autism diagnosis and looked at a number of maternal- and child-related risk factors for autism in the Riyadh community during the perinatal period; nonetheless, it is vital to be aware of the limitations of our study. First, additional prospective investigations are needed to corroborate our findings because the retrospective

technique used in this study cannot establish causality. The information on maternal- and child-related variables was acquired via a self-administered questionnaire and was not linked to hospital records, making information and misclassification bias types of bias possible. It is probable that the results will contain some recall bias due to the lengthy nature of the questionnaire and the demand that women recall and report information going back as far as 5 years. Despite the questions being simple and direct, recall bias may have had an impact on how accurate the answers were.

Finally, we discovered several maternal and child-related risk factors for ASD in a sample from Riyadh. The findings of this study, in our opinion, will be beneficial for subsequent nationwide screenings and educational programs. Longitudinal studies linking hospital records to details about Saudi women's and their children's health are required. Our study brought to light the potential for identifying children in need of early intervention. Additional research studying genetic and environmental components and their interactions is required to build on current findings and help in the contextual knowledge of the disorder and the causes leading to it.

Abbreviations

ASD	Autism spectrum disorder
KSA	Kingdom of Saudi Arabia
PNU	Princess Nourah Bint Abdulrahman University

Acknowledgements
Not applicable.

Authors' contributions
The idea for the study was developed by SM. SM, SA, and SE designed the study. SM, SA, and SE all contributed equally to data collection. Once SM had examined the data, SA and HA offered the interpretation. All writers contributed equally to the writing and revision of the work. The authors consented to take full responsibility for their individual contributions and to ensure that any doubts about the truthfulness or integrity of any aspect of the work, even those in which they had no direct involvement, were thoroughly investigated, answered, and the answer documented in the literature. All of the writers have read and approved the final draft of the work.

Funding
The current research is funded by the Deanship of Scientific Research at Princess Nourah Bint Abdulrahman University through the Fast-track Research Funding program. Funds cover the overall costs of the project.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Approval was granted by the Princess Nourah Bint Abdulrahman University (PNU) Institutional Research Board under proposal code number HAP-01-R-059 IRB log number: 17–0254. Informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 3 March 2023 Accepted: 29 April 2023
Published online: 30 June 2023

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