



# Stressful life events during pregnancy as risk factors for developing autistic disorder in children

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## Abstract

**Introduction:** This study aimed to examine the role of prenatal stressful events in mothers of children and adolescents with autistic disorder (AD).

**Methods:** This case-control study was conducted in 2014. A total number of 115 children and adolescents with AD were selected by convenience method from the autism rehabilitation centers in Tabriz, Iran. Moreover, 112 typically developing (TD) children and adolescents were selected from public schools using a random clustering method. Two groups were matched in terms of mother's and child's age and mother's educational level. The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) semi-structured diagnostic interview was used to evaluate the presence of psychiatric disorders. The diagnosis of AD was made based on the DSM-IV criteria during separate diagnostic interviews by two child and adolescent psychiatrists. The life stressful events' inventory was used to assess the presence of stressful events during pregnancy.

**Results:** According to Fisher's exact test, the frequency of stressful life events including failure to achieve life goals, high debt, frequent marital conflict, conflict with spouse's family, changes in sleeping habits, and sexual difficulties in the mothers of AD children during pregnancy was significantly higher than the mothers of TD children. Also, mothers of AD children reported significantly higher frequency for the positive stressful life events including the major job progress, starting or finishing education, change of education, location, and summer vacation during pregnancy.

**Conclusion:** Some stressful life events in mothers during pregnancy may be considered as risk factors for developing AD in their children. Further researches are needed to establish the results of this study.

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## Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), autistic disorder (AD) is characterized by disorder in social interaction, qualitative impairment in communication, significant limitation of activities and interests, and mental preoccupation with parts of objects.<sup>1</sup> The prevalence of autism spectrum disorders (ASD) in the social sample of children was

estimated between 0.75 and 2.64.<sup>2</sup> Moreover, the prevalence of ASD at the age of eight was estimated between 5.7 and 21.9 per thousand children.<sup>3</sup> The prevalence of autism disorders in a sample of five-year Iranian children was estimated to be 6.26 per ten thousand.<sup>4</sup>

The cost of supporting an individual with an ASD with and without intellectual disability during his or her lifespan was \$2.4 and \$1.4 million in the United States.<sup>5</sup> The

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high burden of AD<sup>1</sup> as well as its individual, familial, and social consequences<sup>6</sup> indicate the importance of identifying risk factors for AD which could have applications in the disease control and social education.

Today we are helpless in explaining the genetic cause of autism, despite numerous studies which have confirmed the fundamental role of the genome.<sup>7,8</sup> Although epidemiological studies and environmental risk factors associated with autism have increased,<sup>9,10</sup> autism etiology theories focus on the role of environment in three areas (characteristics of parents, family engagement, and early stress).<sup>11</sup> In this regard, researchers commonly report that families of children with ASD experience more parenting stresses than families of typically developing (TD) children or those diagnosed with other disabilities (e.g., Down syndrome, cerebral palsy, and intellectual disability).<sup>12</sup>

It appears that the stresses of parents, especially mothers, affect the interactions of mothers with family members and provide early stress.<sup>13</sup> However, these results cannot show the relationship between parental stress and the risk of autism because they were studied after birth. Parental stress after birth and assigning the diagnosis might be due to the consequences of condition of the children.

The study of the stressful life events during pregnancy could evaluate the existence of initial life stress, and show a temporal relationship between parental stress and AD. Previous research suggested that mothers of AD children report more family discord during pregnancy compared to controls.<sup>14</sup> It was also reported that mothers of AD children experience more stressful life events, such as job loss or death of spouse during their pregnancy.<sup>15</sup>

A study conducted in the US showed a higher prevalence of autism in children of mothers experienced hurricanes and severe tropical storms during their pregnancies from 1980 until 1996 in Louisiana. There has been a dose-response mode regarding the severity of storm exposure, especially for cohorts exposed near the middle or end of

gestation.<sup>16</sup> Inconsistent with previous reports, a population-based cohort study reported that maternal bereavement during the prenatal period was not associated with an increased risk of AD.<sup>17</sup>

Since few studies have been conducted on the risk factors relating to stressors during pregnancy and many stressors were investigated with less convergence, it is essential to examine them separately. Moreover, stressors are heavily influenced by the culture and geographical locations. Very few studies have been carried out in Iranian population. Thus, this study was conducted to evaluate prenatal stressful events as risk factors for AD.

### **Methods**

In this case-control study, a total number of 115 children and adolescents with AD were selected from the Autism Community Rehabilitation Centers in Tabriz, Iran. Moreover, 112 TD children and adolescents were selected from public schools with the random clustering method matched to the AD group in terms of age and education.

### *Exclusion and Inclusion Criteria*

Parental consent for participation, age below 18 years and a diagnosis of AD were the inclusion criteria for children with autism. Children were excluded in presence of any known medical, endocrine, metabolic or neurological disorder.

The control group needed parental consent to participate in the study and a maximum of 18 years of age and children were excluded in presence of any psychiatric disorder at that moment. The exclusion criteria for mothers were as follows: being a step-mother, having chronic and severe physical illness during pregnancy or at present, infertility or having the pregnancy through in vitro fertilization.

### *Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)*

K-SADS is a semi-structured diagnostic interview designed based on DSM-III-R and DSM-IV criteria, which is performed by a psychiatrist through interviews with parents

and children. K-SADS is scored using a 0-3 point rating scale. Zero score indicates lack of adequate information, 1 indicates presence of symptoms, 2 represents sub-threshold level of symptoms and 3 represents the threshold criteria. In Iran, Ghanizadeh<sup>18</sup> reported the reliability of the Persian version of K-SADS to be 0.81 through the test-retest method and 0.69 through inter-rater method. In this study, K-SADS was used to assess lack of psychiatric disorders associated with autism.

#### *Strengths and Difficulties Questionnaire (SDQ)*

The SDQ is a brief behavioral screening questionnaire for investigating the mental health of children and adolescents which contains 25 questions with 5 subscales (emotional problems, conduct problems, hyperactivity/inattention problems, peer problems, and pro-social behavior) each having 5 items.<sup>19</sup> The SDQ scoring method is as follows: 1 = not true, 2 = sometimes true, 3 = always true. In Iran, the Persian version of the SDQ has been validated among 3-17 years old individuals by Ghanizadeh and Izadpanah.<sup>20</sup> It has a good reliability with Cronbach's alpha of 0.73. In this study, the SDQ was used for screening and diagnosing normality of the control group.

#### *The Modified Holmes-Rahe Stress Inventory*

This inventory includes 50 stressful events designed based on the Social Readjustment Rating Scale<sup>21</sup> according to the cultural and social context of Iran by Malek et al.<sup>22</sup> Since this inventory is designed for general population, four items were removed as they were inappropriate with the conditions of pregnant women, and were replaced with an item based on the Prenatal Psychosocial Profile inventory.<sup>23</sup> Thus the inventory used in the study had 46 items that assessed life stress events in pregnant women with regard to culture and social conditions of Iran. The yes-no questions were used. This inventory was completed through interviews with mothers.

All statistical analyses were performed using SPSS (version 21, SPSS Inc., Chicago, IL, USA). The descriptive data are presented as frequency (percentage) or mean

[ $\pm$  standard deviation (SD)]. Fisher's exact test was used to compare the frequency of life stressors in the mothers of TD and AD children and odds ratios (OR) were calculated. For comparing the average age of mothers of AD children and controls, the independent Student's t-test was used. The significance level was set as less than 0.05.

#### **Results**

A total of 115 mothers of AD children and adolescents and 112 mothers of TD controls participated in the study. In the AD group, there were 68 boys and 42 girls. In the TD group, there were 70 boys and 39 girls.

According to the independent t-test results, the mean age of children in AD group and controls was  $6.94 \pm 3.55$  and  $7.63 \pm 3.52$  years, respectively ( $P = 0.330$ ,  $t$ -value = 0.96). The mean age of the mothers of AD children at the time of birth was  $27.8 \pm 4.96$  years which was not different from control group ( $28.5 \pm 4.67$ ,  $P = 0.230$ ,  $t$ -value = 1.20).

Based on the Fisher's exact test results, 32 cases (27.8%) of the mothers of AD children had education of high school, and 83 cases (72.2%) had academic education. In the control group, 26 cases (23.3%) of the mothers of TD children had education of high school, and 86 cases (76.8%) had academic education ( $P = 0.450$ ,  $\chi^2 = 0.63$ ).

Based on the Fisher's exact test results, 19 cases (16.5%) of the mothers of AD children worked and 96 cases (83.5%) were housewives. In the control group, 51 cases (45.5%) of the mothers of TD children worked and 61 cases (54.5%) were housewives [ $OR = 4.22$ , 95% Confidence interval (CI) = 2.27-7.82,  $P < 0.001$ ,  $\chi^2 = 22.39$ ], so that the incidence of autism in children of normal working mothers was 4.22 times lower than children of AD mothers.

According to Fisher's exact test results (Table 1), the frequency of stresses for failure to achieve life goals, high debt, frequent marital conflict, conflict with spouse's family, changes in sleeping habits and sexual difficulties in the mothers of AD children during pregnancy was significantly higher

than the mothers of TD children. The OR for risk of AD was 2.93 due to events relating to the failure to achieve life goals in mothers, 2.55 for high debt, 3.60 for frequent marital conflicts, 2.44 for conflict with spouse's family, 3.41 for changes in sleeping habits, and 3.84 for sexual difficulties.

Mothers of AD children reported significantly higher frequency for the positive stressful life events including the major job progress, starting or finishing education, change of education location and summer vacation during pregnancy. The OR for risk of AD was 5.53 due to major job progress of mother, 7.14 for starting or finishing education, 5.53 for change of study location, and 2.88 for summer vacation.

The most common negative stressful life events for mothers included changes in sleeping habits (42%), frequent marital conflict (40%), conflict with spouse's family (30%), and failure to achieve life goals (29%) (Table 1). Based on the results of Fisher's exact test, none of the life stressors examined in table 2 had significant difference between the mothers of AD children and the control group.

## Discussion

This study aimed to identify prenatal stressful events as risk factors for AD. these results showed that ten stressors can be identified as

risk factors for autism so that six types of negative stressors (including failure to achieve life goals, high debt, frequent marital conflict and spouse discord, conflict and discord with spouse's family, changes in sleeping habits, and sexual difficulties during pregnancy) in the mothers might increase the risk of autism.

Consistent with these findings, a previous study has shown that experiencing discord during their pregnancies is associated with the risk of autism in their children.<sup>14</sup> A study in China has shown that maternal unhappy emotional state is a risk factor of autism.<sup>24</sup> A study in Iran has also shown that the frequency and severity of exposure to stressful events in the mothers of AD children are higher than the mothers of the control group.<sup>25</sup>

According to this study, four good stressors (including major job progress, starting or finishing education, change of study location and summer vacation during pregnancy of the mothers) reduced the risk of autism in children. These findings indicated the importance of positive emotional experience in reducing the risk of autism. Although positive events are stressful, stress of positive events that do not cause great excitement and at the same time cause pleasure for the individual might increase mental health.

**Table 1.** Frequency (percentage) of life stressors during pregnancy for mothers of autistic disorder (AD) and typically developing (TD) children and results of Fisher's exact test

Variable	Autism (n = 115)		Control (n = 112)		OR (95% CI)	$\chi^2$	P
	No N (%)	Yes N (%)	No N (%)	Yes N (%)			
Failure to achieve life goals	81 (70.4)	34 (29.6)	98 (87.5)	14 (12.5)	2.93 (1.47-5.84)	9.91	0.002
Too much debt	92 (80.0)	23 (20.0)	102 (91.1)	10 (8.9)	2.55 (1.15-5.64)	5.59	0.020
Frequent marital conflicts	68 (59.1)	47 (40.9)	94 (83.9)	18 (16.1)	3.60 (1.92-6.75)	17.1	< 0.001
Conflict with spouse's family	80 (69.6)	35 (30.4)	95 (84.8)	17 (15.2)	2.44 (1.27-4.68)	7.47	0.007
Changes in sleeping habits	66 (57.4)	49 (42.6)	92 (82.1)	20 (17.9)	3.41 (1.85-6.27)	16.4	< 0.001
Sexual difficulties	104 (90.4)	11 (9.6)	109 (97.3)	3 (2.7)	3.84 (1.04-14.20)	4.65	0.049
Career progress	113 (98.3)	2 (1.7)	102 (91.1)	10 (8.9)	5.53 (1.18-25.90)	5.85	0.010
Starting or finishing education	112 (97.4)	3 (2.6)	94 (83.9)	18 (16.1)	7.14 (2.04-25.00)	12.30	< 0.001
Changing education location	113 (98.3)	2 (1.7)	102 (91.1)	10 (8.9)	5.53 (1.18-25.90)	5.85	0.010
Summer vacation	101 (78.8)	14 (12.2)	80 (71.4)	32 (28.6)	2.88 (1.44-5.77)	9.44	0.003

OR: Odds ratio; CI: Confidence interval

**Table 2.** Frequency (percentage) of life stressors during pregnancy in the mothers of autistic disorder (AD) and typically developing (TD) children and results of Fisher's exact test

Variable	Experience of stressor		$\chi^2$
	Autism (n = 115)	Control (n = 112)	
Death of a child	2 (1.7)	1 (0.9)	0.31
Death of spouse	0 (0)	1 (0.9)	1.01
Betrayed spouse	2 (1.7)	3 (2.7)	0.23
Imprisonment	3 (2.9)	0 (0)	2.96
Addiction of self or family	4 (3.5)	8 (7.1)	1.52
Divorce	2 (1.7)	7 (6.3)	3.03
To stand accused	7 (6.1)	2 (1.8)	2.75
Unhappy marriage	12 (10.4)	7 (6.3)	1.29
Son or daughter leaving home	3 (2.9)	2 (1.8)	0.17
Death of close relatives	13 (11.3)	19 (17.0)	1.50
Accident and incident	12 (10.4)	10 (8.9)	0.14
Separation without divorce	3 (2.6)	4 (3.6)	0.17
Behavioral and educational problems of children	16 (13.9)	9 (8.0)	2.00
Health problems of a family member	15 (13.0)	7 (6.3)	2.99
Dismissal from work	3 (2.9)	5 (4.5)	0.57
Change in financial state	20 (17.4)	11 (9.8)	2.75
Personal injury or illness	5 (4.3)	4 (3.6)	0.09
Academic failure of self or family member	8 (7.0)	9 (8.0)	0.09
Social security	12 (10.4)	5 (4.5)	2.91
Having to make lifestyle changes	14 (12.2)	7 (6.3)	2.37
Unwanted Pregnancy	16 (13.9)	16 (14.3)	0.007
Changes in job responsibilities	4 (3.5)	3 (2.7)	0.12
Change in housing conditions	33 (28.7)	27 (24.1)	0.61
Child marriage	2 (1.7)	1 (0.9)	0.31
Child away from home	2 (1.7)	1 (0.9)	0.31
Changes in the socio-religious activities	7 (6.1)	4 (3.6)	0.77
Reconciliation with spouse	18 (15.7)	9 (8.0)	3.14
Gain a new family member	2 (1.7)	7 (6.3)	3.03
Change to different line of work	3 (2.6)	3 (2.7)	0.001
Changes in recreational and social activities	20 (17.4)	13 (11.6)	1.52
New year	42 (36.5)	35 (31.3)	0.70
Retirement from work	1 (0.9)	4 (3.6)	1.92
Death of close friend	3 (2.6)	1 (0.9)	0.96
Spouse starts or stops work	6 (5.2)	6 (5.4)	0.002
Unwanted violation of the rights of others	1 (0.9)	0 (0)	0.97
Unfavorable workplace conditions	3 (2.6)	6 (5.4)	1.12

Based on our findings, 36 types of stressors namely death of a child, death of spouse, spouse betrayal, imprisonment, addiction of self or family member, divorce, stand accused, unhappy marriage, son or daughter leaving home, death of a close relative, accident and incident, separation from spouse without divorce, behavioral and educational problems of children, health problems of family members, dismissal from work, change in financial situation, personal disease, academic failure of self or family member, lack of social security, forced lifestyle changes, unwanted pregnancy, changes in job responsibilities (upgrade or

downgrade), changes in the conditions of the home location and neighborhood, offspring marriage, offspring away from home (marriage and education), changes in the socio-religious activities, reconciliation with spouse, gain a new family member, job change, change in social and recreational activities, new year, retirement, death of close friend, spouse starts or stops work, unwanted violation of the rights of others, and undesirable workplace conditions were not associated with the risk of autism.

Consistent with our findings, the previous reports showed that maternal bereavement during the prenatal period was not

associated with an increased risk of autism in the offspring.<sup>17</sup> But consistent with these findings, it was reported that mothers who experienced job loss or death of spouse during pregnancy had an increased risk of AD in their children.<sup>15</sup>

In general, these research findings in Tabriz, were consistent with studies in other countries that stress and stressful experiences during pregnancy are the risk factors for AD. Some studies reported that a higher incidence of prenatal stressors was found in autism at 21-32 weeks of gestation, with a peak at 25-28 weeks.<sup>15</sup> It was also reported that increased maternal stress at 4-7 months of gestation (weeks 14-32) was associated with increased risk of autism in the children. But the increased severity of stresses at 2-3 months of gestation (weeks 5-13) was associated with increased severity of autism.<sup>25</sup>

This does support the possibility of prenatal stressors as a potential contributor to autism, with the timing of stressors consistent with the embryological age suggested by neuroanatomical findings seen in the cerebellum in autism.<sup>15</sup>

Since the perception of stressors regardless of psychological ability of individuals has a negative impact on them,<sup>26,27</sup> a closer look at the findings cannot be achieved without considering the characteristics of people. Therefore, additional studies about the mediating role of personality traits on the perception of stressors can help to better understand the research findings.

Thus, combining the findings of previous studies about gene and maternal stress interaction can remind the importance of gene-environment interactions in the treatment and prevention of AD.<sup>28,29</sup>

The findings of any study are important considering its limitations. This study examined a sample of AD children and did not control the severity of autism disorder. Moreover, stressful events were based on self-report measures, and the severity of stress and stressful events and mediating

individual factors were not studied. The above limitations indicate the importance of further studies.

### **Conclusion**

Some stressful life events in mothers during pregnancy may be considered as risk factors for developing AD in their children. The most common stressful negative life events for mothers were the changes in sleeping habits, frequent marital conflicts, and conflict with spouse's family. Further studies are needed to establish the results of this study. The findings of this study may have some implications for policy makers regarding preventive strategies related to AD.

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### **Authors' Contribution**

Salman Abdi and Shahrokh Amiri drafted the manuscript; Afshin Razzaghi-Rezaii and Ayyoub Malek designed the study, performed evaluations and revisions, Habibeh Barzegar and Salman Abdi contributed to design and analysis. All authors approved the final draft.

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### **Conflict of Interest**

Authors have no conflict of interest.

### **Ethical Approval**

Research proposal was approved by regional ethical committee of Tabriz University of Medical Sciences.

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