The Correlation between Pregnancy and Delivery Characteristics and Autism Spectrum Disorder and Symptomatic Severity

Gebelik ve Doğum Özelliklerinin Otizm Spektrum Bozukluğu ve Belirti Şiddeti ile İlişkisi

İrem Damla Çimen

Darıca Farabi Training and Research Hospital, Child and Adolescent Psychiatry Department, Kocaeli

Yazışma Adresi / *Correspondence:*
İrem Damla Çimen

Department of Child and Adolescent Psychiatry, Darıca Farabi Training and Research Hospital, Kocaeli, Turkey, TR 41700
T: **+90 262 656 43 45 (d:1565)** E-mail: **damlamanga@gmail.com**

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Abstract

Objective Autism is a neurodevelopmental disorder. Although Autism is substantially hereditary, it has been associated with environmental factors as well. This study investigates the correlation between pregnancy period and delivery characteristics and Autism and to evaluate whether or not there is a correlation between the symptom severity and some factors in this period. ***(Sakarya Med J 2019, 9(1):30-37)***

Materials and Methods In the study, 35 children, who were admitted to the Child/Adolescent Psychiatry Clinic, diagnosed with Autism were taken as the study group, and their 35 siblings of the same gender with the closest age and without any mental disorder were taken as the control group. The diagnosis of Autism was made according to the Diagnostic and Statistical Manual of Mental Disorders-5 Diagnostic Criteria in the clinic interviews held. Characteristics of delivery and birth were questioned by sociodemographic data form. And the symptom severity of Autism was assessed by using the Autism Behavior Checklist.

Results The rate of unplanned pregnancy and stressful life events during pregnancy was found to be significantly higher in the cases with Autism. The social relating, body and object use, language skills and total scores of the Autism Behavior Checklist were found to be significantly higher in children with Autism who were born as a result of unplanned pregnancy.

Conclusion There are few studies on Autism etiology in our country. It is important to investigate the effects of environmental factors in the etiology of Autism, and that elucidation of the etiology can contribute to prevention studies of the disorder.

Keywords Autism Spectrum Disorder; gestation; unplanned pregnancy; birth

ÖZ

Amaç *Otizm Spektrum Bozukluğu nörogelişimsel bir bozukluk olup büyük oranda kalıtımsal olmakla birlikte çevresel faktörler de ilişkili bulunmuştur. Bu çalışmada gebelik süreci ve doğum özellikleri ile Otizm Spektrum Bozukluğu arasındaki ilişkinin incelenmesi ve Otizm Spektrum Bozukluğu belirti şiddeti ile bu süreçteki bazı faktörlerin ilişkisinin olup olmadığının değerlendirilmesi amaçlanmıştır.* **(Sakarya Tıp Dergisi 2019, 9(1):30-37)**.

Gereç ve Yöntemler: *Çalışmada araştırma grubu olarak Darıca Farabi Eğitim Araştırma Hastanesi çocuk psikiyatri polikliniğine başvuran, Otizm Spektrum Bozukluğu tanısı konulan 35 çocuk alınmış, kontrol grubu olarak ise bu çocuklar ile aynı cinsiyetteki, yaşı en yakın olan, herhangi bir ruhsal bozukluğu olmayan 35 kardeşi alınmıştır. Olguların gebelik süreci ve doğum özellikleri ile ilgili bilgiler sosyodemografik veri formu ile toplanmıştır. Otizm Spektrum Bozukluğu tanısı yapılan klinik görüşmelerde Psikiyatride Hastalıkların Tanımlanması ve Sınıflandırılması El Kitabı 5 tanı kriterlerine göre konulmuş, belirti şiddeti Otizm Davranış Kontrol Listesi ile değerlendirilmiştir.*

Bulgular *Otizm Spektrum Bozukluğu olan olgularda plansız gebelik ve gebelikte stresli yaşam olayı yaşama oranı anlamlı düzeyde yüksek bulunmuştur. Otizm Davranış Kontrol Listesini ilişki kurma, beden ve nesne kullanımı, dil becerileri ve toplam puanlarının, plansız gebelik sonucu doğan Otizm Spektrum Bozukluğu olan olgularda belirgin düzeyde yüksek olduğu saptanmıştır.*

Sonuç *Otizm Spektrum Bozukluğu etyolojisinde çevresel etmenlerin etkilerinin incelenmesinin önemli olduğu, etyolojinin aydınlatılmasının bozukluğu önleme çalışmalarına katkı sağlayabileceği düşünülmektedir.*

Anahtar Sözcükler *Otizm spektrum bozukluğu; gestasyon; planlanmamış gebelik; doğum*

INTRODUCTION

Autism Spectrum Disorders (ASD) is a neurodevelopmental disorder characterized by deficiencies in social communication and interaction, repetitive behavioral patterns, interests or activities, in which symptoms begin at an early stage of development.[1] The prevalence of the disease in developed countries is presumably reported as 1,5%.[2,3] Considering the prevalence according to gender, the male/female ratio is indicated as 4/1.[4]

The etiopathogenesis of ASD is quite complex and the etiologic factors can only be detected in 15-25% of the cases.[5] Although the underlying etiology of ASD has not been elucidated to a large extent, a progress has been made about the neurobiological and genetic basis and risk factors of this complex condition over the past decade. The family and twin studies have shown the effects of genetic factors. The fact that the diagnosis of autism is more common in siblings of children diagnosed with autism than in siblings of children with normal development and the concordance rate is greater in monozygotic twins than in dizygotic twins of the same gender has revealed the role of genetic factors in autism.[6-10]

Genetic factors as well as environmental factors have been reported to influence the subsequent cell generation by affecting the fetal programming in the prenatal period or by making changes in the control of gene expression.[11] Considering the studies on environmental factors, numerous studies report that the prenatal and perinatal risk factors are associated with autism.[12-18] The use of thalidomide during pregnancy, having rubella infection, vitamin D deficiency, smoking, elevated fever especially during the 2nd trimester, the use of antidepressant during the 2nd and/or 3rd trimester, air pollution due to traffic, advanced age of mother and father are also indicated to be the risk factors for ASD.[12,14,15,19-26] Experiencing hemorrhage or preeclampsia during pregnancy and breech presentation in the delivery process, cesarean delivery, fetal hypoxia and delivery before the 35th gestational week were found to be the risk factors in the studies conducted. Being the first child and low birth weight were also significantly associated with autism spectrum disorder.[13,14,18,27,28,29] It is also reported in the literature that mother's mental status during pregnancy and stressful life events experienced during pregnancy may be the risk factors for ASD.[16,30]

The aim of this study was to investigate the correlation between pregnancy period and delivery characteristics and autism spectrum disorder, and to evaluate whether or not there is a correlation between the symptom severity of autism spectrum disorder and some factors in this period.

MATERİALS and METHODS

Sample

This research is a case-control study. A total of 35 patients, who have sibling with the same gender, and without mental disorder, under 18 years were selected as the study group from the patients diagnosed with ASD who were admitted to the Child/Adolescent Psychiatry Clinic of the Darıca Farabi Training and Research Hospital between May to November 2017. And their 35 siblings of the same gender with the closest age and without any mental disorder were taken as the control group. The diagnosis of ASD was made according to the Diagnostic and Statistical Manual of Mental Disorders-5 Diagnostic Criteria in the clinic interviews held and the symptom severity was assessed by using the Autism Behavior Checklist. The mental statuses of the siblings of the children with ASD were also clinically evaluated. Those who did not agree to participate in the study and were not diagnosed with ASD and did not have a sibling of the same gender and had a sibling with mental disorder were excluded from the study. The study was approved by the Kocaeli Clinical Research Ethics Committee (Project Nr.: 2016/152).

Data collection tools:

Socio-demographic data form: It includes characteristics such as parental age/education level/marital status, way of getting pregnant, number of pregnancy, hospitalization

status during pregnancy/drug use/stressful event experienced/malnutrition/vitamin D deficiency/smoking/use of tap water, type/place/season of delivery, whether or not there is a problem during delivery.

Autism Behavior Checklist (ABC): It is one of the scales used for the assessment and screening of ASD. ABC is a 57-item assessment tool consisting of a total of five sub-scales which are sensory behavior, social relating, body and object use, language and social and adaptive skills. The lowest score that can be got from the scale is 0, the highest score is 159.[31] The validity and reliability of the Turkish version of the Autism Behavior Checklist were done by Yılmaz Irmak et al. The cut-off score of the Turkish version of the scale was determined as 39.[32] The data were analyzed using the Statistical Package for the Social Sciences 22.0 software. The Kolmogorov-Smirnov test for normality of the distribution was carried out prior to the analysis of the numerical data. The MannWhitney U test was used for the analysis of the quantitative independent data. The chi-square test was used for the analysis of qualitative independent data, and the Fischer test was used when the conditions were not met for the Chi-square test. The statistical significance level was accepted as $p < 0,05$.

RESULTS

A total of 70 cases, 8 (11,4%) females and 62 (88,6%) males, were included in the study. The mean age of the cases diagnosed with ASD is 83,4±30,6 months and the mean age of the siblings is 111,8±58,5 months. The sociodemographic characteristics of the cases participating in the study are defined in Table 1.

Table 1. Sociodemographic characteristics of individuals families

Characteristics	Groups	N (%)
Mother's education level	No education	2 (5,7)
	Primary school	14 (40,0)
	Secondary school	8 (22,9)
	High school	10 (28,6)
	University	1 (2,8)
Father's education level	Primary school	12 (34,3)
	Secondary school	7 (20,0)
	High school	15 (42,9)
	University	1 (2,8)
Father's job	Private	19 (54,3)
	Employee	16 (45,7)
Monthly income	1000-1500	16 (45,7)
	1501-2000	11 (31,4)
	2001-2500	2 (5,7)
	2501-3000	2 (5,7)
	3001-3500	1 (2,9)
	3501 and more	3 (8,6)
Marital status	Together	35 (100,0)
	Divorced	0 (0,0)
Kinship between parents	Yes	9 (25,7)
	No	26 (74,3)
N: Number		

Table 2. Comparison of the characteristics of the ASD and control group's mothers's pregnancy period					
Characteristics	Groups	Control group N (%)	ASD group N (%)	Ki square P value	Post hoc Power analyses
Pregnancy order	Second (after abort/curettage)	4 (11,4)	6 (17,1)		% 10
	1	16 (45,7)	6 (17,1)	0,055	% 73
	2 (after healthy birth)	11 (31,4)	13 (37,1)		% 7
	3	3 (8,6)	7 (20,0)		% 28
	4	1 (2,9)	3 (8,6)		% 17
Multiple pregnancy	No	34 (97,1)	35 (100,0)	1,000	% 17
	Yes (twin)	1 (2,9)	0 (0,0)		
Planned pregnancy	Yes	29 (82,9)	21 (60,0)	**0,034***	**% 56**
	No	6 (17,1)	14 (40,0)		
Use of oral contraceptive before pregnancy	Yes	0 (0,0)	2 (5,7)	1,000	% 30
	No	6 (17,1)	14 (40,0)		
Type of conception	By natural ways	35 (100,0)	34 (97,1)	0,314	% 17
	Other	0 (0,0)	1 (2,9)		
Regular doctor check in pregnancy	Yes	32 (91,4)	31 (88,6)	0,690	% 6
	No	3 (8,6)	4 (11,4)		
Hospitalization in pregnancy	No	30 (85,7)	33 (94,3)	0,232	% 22
	Due to non-febrile disease	4 (11,4)	1 (2,9)		% 28
	Due to fever disease	1 (2,9)	1 (2,9)		% 3
Drug use in pregnancy	Yes	10 (28,6)	7 (20,0)	0,403	% 13
	No	25 (71,4)	28 (80,0)		
Stressful life event in pregnancy	Yes	8 (22,9)	16 (45,7)	**0,044***	**% 52**
	No	27 (77,1)	19 (54,3)		
Malnutrition in pregnancy	Yes	6 (17,1)	6 (17,1)	1,000	% 3
	No	29 (82,9)	29 (82,9)		
Problems in pregnancy	Yes	12 (34,3)	13 (37,1)	0,803	% 4
	No	23 (65,7)	22 (62,9)		
Weight gain during pregnancy	≤ 5 kg	4 (11,4)	3 (8,6)	0,849	% 6
	6-17 kg	26 (74,3)	28 (80,0)		% 8
	≥ 18 kg	5 (14,3)	4 (11,4)		% 6
Vitamin D deficiency in pregnancy	Yes	11 (31,4)	7 (20,0)	0,389	% 19
	No	18 (51,4)	18 (51,4)		% 3
	Unknown	6 (17,1)	10 (28,6)		% 21
Smoking in pregnancy	Yes	2 (5,7)	1 (2,9)	1,000	% 8
	No	33 (94,3)	34 (97,1)		
Smoker at home during pregnancy	Yes	19 (54,3)	15 (42,9)	0,339	% 16
	No	16 (45,7)	20 (57,1)		
Tap water usage in pregnancy	Yes	30 (85,7)	27 (77,1)	0,356	% 15
	No	5 (14,3)	8 (22,9)		
ASD: Autism Spectrum Disorders, **N:** Number, **Kg:** Kilograms, *P < 0,05.					

The pregnancy and delivery characteristics of the cases with ASD diagnosis and the control group are seen in Table 2 and Table 3, and the rate of unplanned pregnancy and stressful life events during pregnancy was found to be significantly higher in the cases with ASD (p <0,05).

In the ASD group, the correlation between the subscores and total scores of the ABC scale and parental educational level, parental age during delivery, monthly income level, experiencing a stressful event during pregnancy, birth order of the child and whether or not the pregnancy was planned were investigated. The social relating, body and object use, language skills and total scores of the ABC scale were found to be significantly higher in those with ASD who were born as a result of unplanned pregnancy (p <0,05) (Table 4). There was no significant correlation between the subscores of the ABC scale and other characteristics (p >0,05).

Table 3. Comparison of birth characteristics of ASD diagnosed cases and control group

Characteristics	Groups	Control group N (%)	ASD group N (%)	Ki square P value
Birth time	Term	30 (85,7)	28 (80,0)	0,526
	Preterm	4 (11,4)	3 (8,6)	
	Post-term	1 (2,9)	4 (11,4)	
Birth season	Spring	7 (20,0)	7 (20,0)	1,000
	Summer	10 (28,6)	10 (28,6)	
	Autumn	7 (20,0)	7 (20,0)	
	Winter	11 (31,4)	11 (31,4)	
Birth weight	1500-2000 gr	1 (2,9)	0 (0,0)	0,445
	2001-2500 gr	4 (11,4)	2 (5,7)	
	2501-3000 gr	7 (20,0)	8 (22,9)	
	3001-3500 gr	11 (31,4)	15 (42,9)	
	3501 gr and more	11 (31,4)	10 (28,6)	
Delivery method	Normal	17 (48,6)	17 (48,6)	1,000
	Caesarean	18 (51,4)	18 (51,4)	
Problems in birth	Yes	6 (17,1)	10 (28,6)	0,255
	No	29 (82,9)	25 (71,4)	
Place of birth	Hospital	34 (97,1)	35 (100,0)	1,000
	Home	1 (2,9)	0 (0,0)	

ASD: Autism Spectrum Disorders, N: Number

Table 4. Comparison of ABC scores according to whether the pregnancy is planned or not

Subscales	Unplanned pregnancy		Planned pregnancy		Mann-Whitney U test P value
	Mean ±SD	Median	Mean ±SD	Median	
Sensory Behavior	12,5 ± 6,1	12,0	10,4 ± 4,7	11,0	0,311
Social Relating	19,6 ± 8,1	20,0	10,9 ± 6,2	11,0	**0,003***
Body and Object Use	14,4 ± 7,8	19,5	10,0 ± 6,1	8,0	**0,006***
Language Skills	18,1 ± 9,1	23,0	12,5 ± 5,2	14,0	**0,040***
Social and Adaptive Skills	16,9 ± 9,2	16,5	12,1 ± 7,3	11,0	0,117
Total	84,4 ± 34,9	94,0	55,8 ± 21,5	55,0	**0,018***

ABC: Autism Behavior Checklist, **SD:** Standard Deviation, *P < 0,05.

DISCUSSION

35 children/adolescents with diagnosed with ASD were taken as the study group, and their 35 siblings were taken as the control groups in the study. Whether some of the factors during the pregnancy and delivery period contributed to the etiology of ASD and some factors that are predicted to affect the severity of autism symptoms were investigated in the study.

In the literature, there are conclusions that ASD may be linked to numerous factors like Vitamin D deficiency, fever, air pollution during pregnancy and delivery period.[21,22,23], In the study conducted, many factors thought to play a role in the etiology of ASD related to pregnancy and delivery period were questioned. Among these factors, only unplanned pregnancy and stressful life events during pregnancy were found to be significantly higher in children with ASD, and no correlation was found between ASD and other factors.

Stress, natural disasters such as earthquakes, floods, storms, unavoidable events such war and terrorism, or domestic violence can be caused by problems in human relations in the home or business environment. Considering the literature, there are studies reporting a significant correlation between encountering stressful events and experiencing stress before delivery and the increased risk for ASD, similar to the conclusion of the study.[16,33-35] It has been reported that stress is involved in the etiology of ASD through various mechanisms. One of these mechanisms is in the form of impairments in the negative feedback system of the hypothalamic-pituitary-adrenocortical (HPA) axis caused by stress, and an increase in the glucocorticoid levels. Psychological stress experienced during pregnancy increases the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus and regulates the HPA axis and also affects the programming of the fetal HPA axis. Thus, early life stress increases the susceptibility of individuals to mental disorders in later stages by causing an increase in stress response.[36] Some human and animal studies proved the significant effects of prenatal stress activating the HPA axis on postnatal behavior. Elevated plasma CRH levels have been associated with preterm labor and anxiety in the preconception period. It has also been reported that acute stress increased the level of serum interleukin-6 level, which is secreted by the mast cell and is responsible for the neuroinflammatory response, thereby contributing the pathogenesis and symptoms of autism by the impairing the permeability of the blood-gut barrier and blood-brain barrier and increasing the penetration of neurotoxic molecules into the brain.[37] Changes in the Gamma-aminobütirik asitergic, serotoninergic, and dopaminergic pathways and changes secondary to increased activity in the sympathoadrenal system have also been reported to be other mechanisms of action of stress in the etiology of ASD.[38-41] It has been suggested by the animal studies conducted that prenatal stress negatively affected the neurodevelopment of infant and led to behaviors resembling autism symptoms.[17] It has been suggested that psychological stress may affect the neurodevelopment through mechanisms such as Deoxiribo Nucleic Acid methylation or the programming of the HPA axis.[17,42] It has been indicated that in Rhesus apes, exposure of mother to prenatal stress hormones or psychological stress resulted in abnormalities in the immune function that occur in the postnatal period and continues in the late childhood period.[43] It has been indicated that impaired immune functions, such as lymphocyte proliferation, natural killer cell activity and cytokine production, may reduce the ability to resist viral and bacterial infections, and may therefore be associated with an increased risk of autism, suggesting that the pathological mechanisms of prenatal stress are linked to prenatal infections.[44] Although the conclusions of this mentioned study are biologically reasonable, the evidence supporting the correlation between psychological stress during pregnancy and ASD is limited and inconsistent in human studies.[45] Experiencing a stressful event during pregnancy may also cause mother to have an unhappy mood during pregnancy. It has been reported by the studies that there were significant correlations between mother's unhappy mood

and ASD. It has been suggested that the unhappy mood of mother may increase the maternal hormone levels, such as adrenaline, and that the adrenalin may affect the cerebral blood flow of infant as a result of causing placental vasoconduction or may alter the fetal hormone levels, so as to affect the development of infant.[30]

In the study conducted, unplanned pregnancy was associated with ASD. It has been suggested that unplanned pregnancy may result in mother's not being ready mentally and a major source of stress for pregnancy and perceptions for subsequent processes, and may affect this process similar to stress experienced during pregnancy period. Furthermore, this association may also have been caused by not taking care of the environmental factors or nutritional process that may be effective in terms of the development of ASD during pregnancy period, or by not performing necessary medical follow-ups. The ABC total score, social relating, body and object use and language skills of children with ASD who were born as a result of unplanned pregnancy were found to be significantly higher. Considering the studies, the women who had unplanned pregnancy were found to have a higher level of postnatal depression.[46,47] It has been thought that depression symptoms such as turning in upon himself/herself, not wanting to communicate with people may have caused mother to interact less with child, thus child's ability to communicate, body and object use and language development may be negatively affected. There are also studies in the literature revealing a strong correlation between the oral responsiveness levels, interaction styles and frequency of parents, and the language skills of autistic children.[48,49]

The study has various strengths and limitations. There are few studies on the pregnancy and delivery period of ASD cases in our country. It has been thought that inclusion of the siblings of the same gender with the closest age to that of patients diagnosed with ASD as the control group reduced the effect of the genetic factor, known to be important in the etiology of ASD, to lower levels. The low number of samples in the study and control groups limits the generalization of the study results and control of confounding factors. Moreover, the fact that some of the patients were in the adolescence period may have caused a problem in recalling the answers to questions asked retrospectively so bias probability is high. In case-control studies, it is not known which of the "Cause and Result" started first.

In this study, the stress experienced during pregnancy and the unplanned pregnancy were found to be correlated with ASD. It was determined that the patients with ASD, who were born as a result of unplanned pregnancy, had more symptoms of autism, such as social relating, body and object use, language skills, and a higher total symptom severity. It has been thought that getting pregnant by planning and living stress-free may allow mother to adapt to pregnancy, delivery and subsequent processes easier, and may reduce the possibility of the ASD development, and may lead the symptom severity to be lower, even if ASD develops.

It is reported that the prevalence of ASD has increased in recent years. Although it is indicated that this may be due to causes such as increased awareness of both clinicians and parents about the disease, better record-keeping and increased use of screening scales, these causes cannot exactly explain the increase in the prevalence.[50] Therefore, it is thought that it is also important to investigate the effects of environmental factors in the etiology of ASD, and that elucidation of the etiology can contribute to prevention studies of the disorder.

Conflict of interest

The authors declare they have no actual or potential competing financial interests.

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