Risk factors associated with disease severity in autism spectrum disorder

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SUMMARY

Objective: This study aimed to evaluate prenatal-perinatal-postnatal risk factors, which are thought to have a role in the etiology of autism spectrum disorder, according to autism severity and to evaluate the relationship between maternal stress during pregnancy and the age difference between parents.

Method: 100 children between the ages of 18-72 months who were diagnosed with ASD according to DSM-V diagnostic criteria and were followed up were included in the study. By evaluating the clinical severity of autism with the childhood autism rating scale, children diagnosed with ASD were divided into two subgroups according to clinical severity. Sociodemographic data and risk factors were recorded in the clinical data form, and the characteristics of the two groups were compared. Birtchnell Spouse Evaluation Scale-female form was applied to mothers to evaluate marital-relationship problems.

Results: In our study, it was determined that premature birth and regression history were more common in the severe autism group than in the mild-moderate autism group (p=0.007, p=0.025). No significant relationship was found between the difference between the ages of the mother and father and the subscales of the Birtchnell Spouse Rating Scale. It was found that the disconnection subscale of the Birtchnell Spouse Assessment Scale was significantly higher in the severe autism group.

Discussion: Our study is one of the few studies conducted in this field and aims to contribute to the identification of preventable risk factors of autism. In the future, there is a need to confirm the data with larger studies in which maternal stress risk factors are also evaluated in the postnatal period and include other maternal stress factors besides marriage-relationship problems.

Key Words: Autism Spectrum Disorders, prenatal, perinatal, risk factors, stres, parental age

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by issues in interaction and communication, restricted/repetitive interests and behaviors, and it arises from a genetic basis through the interaction of multiple factors (1). The prevalence of ASD has been increasing, with a reported prevalence of 1 in 36 as of 2023 (2).

Although the etiology of ASD is not yet fully understood, studies focus on genetic and environmental factors, with emphasis on epigenetic mechanisms (3-5). The epigenetic effect of environmental factors, indirectly affecting brain development, may act through changes in gene function or regulation of gene expression during developmental stages (6,7). Considering that the prenatal-perinatal-postnatal periods are critical and vulnerable neurodevelopmental phases, it is important to evaluate whether the environmental factors a baby is exposed to during these periods are risk factors for the development of ASD. Among environmental factors, maternal infections during pregnancy, medical and psychiatric conditions, advanced parental age, maternal smoking/alcohol/drug use, emotional stress, delivery method and timing, birth complications such as hypoxia or hyperbilirubinemia, and vitamin D deficiency have been investigated in different studies with varying results (8). It has been emphasized that these data need further support, and advanced parental age has been identified as the most consistent and significant risk factor (9). Studies also suggest that age differences between parents might be a risk factor for the

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development of ASD, and further research on this topic is limited (9-11). Given that greater age differences between parents might increase familial stressors such as conflicts and misunderstandings, it could be valuable to examine the relationship between parental age difference and maternal stress. Prenatal maternal stress has recently been studied in ASD etiology, with research suggesting that maternal exposure to social, environmental, and familial stressors during pregnancy could negatively affect fetal brain development (12).

There is still much to learn about the factors predicting the severity of ASD. While some studies suggest that prenatal-perinatal-postnatal factors increase the risk of ASD, few have examined their effects on ASD severity. One study found no correlation between these risk factors and ASD severity (13). Other studies have identified predictors such as male gender, advanced parental age, maternal gestational diabetes, preeclampsia, parental depression, maternal stress, and preterm birth, though results vary across studies (14-16). In the literature, there are few studies evaluating these risk factors based on the clinical severity of autism (17).

In conclusion, studies suggest that complications during pregnancy, birth, and the postnatal period, as well as related negative factors, are more frequently observed in children diagnosed with ASD compared to normally developing children (8). Although these risk factors are not specific to ASD, identifying and supporting these factors through research is important for developing prevention strategies and understanding the etiology of ASD. Our study aims to compare prenatal, perinatal, and postnatal factors, as well as sociodemographic characteristics, based on autism severity. Additionally, we aim to evaluate the relationship between maternal stress and the age difference between parents, which is considered a possible risk factor for ASD. Ultimately, the goal is to contribute to identifying preventable risk factors for ASD.

METHOD

Sample

This study included 100 children aged 18-72 months who were diagnosed and followed up with ASD in our clinic between November 2022 and June 2023, according to DSM-V diagnostic criteria. Ethical approval was obtained from Muğla Sıtkı Koçman University Ethics Committee (Protocol No: 220088 Decision No: 77). Detailed informed consent was obtained from the families of the patients. The study group consisted of children diagnosed with ASD according to psychiatric evaluation, clinical observation, and DSM-V, without other neurodevelopmental disorders affecting cognitive development or diagnosed genetic/neurological/metabolic diseases. The study group included both newly diagnosed ASD cases and those with continued follow-up in the 18-72 month range. Newly diagnosed ASD cases were referred to the Ear-Nose-Throat department for routine hearing evaluations and to the pediatric neurology department for neurological examination.

A form prepared by the researchers was used to collect sociodemographic information, as well as questions about possible prenatal-perinatal-postnatal risk factors for ASD. The clinical data form included questions to evaluate parental age, the age difference between parents, education and employment status, and family characteristics, as well as to screen for risk factors during pregnancy, birth, and the postnatal period. Prenatal factors evaluated included threatened miscarriage, smoking/alcohol/substance use, infection history, medication use, physical illness history, trauma, history of surgery, maternal stress, psychiatric complaints/disorders, loss or bereavement, and marital/relationship problems. The presence of maternal stress was determined based on reports of relationship issues with the spouse, psychiatric complaints/disorders, or loss history. The presence of any of these factors was considered as maternal stress. Perinatal factors included delivery method, birth timing, birth weight, birth complications, hypoxia, and incubator/intensive care history. Postnatal factors included jaundice, blood transfusion, vaccinations, postnatal surgeries, trauma, ill-

nesses, and developmental regression. Regression was assessed through interviews with families. Due to families' inability to provide detailed early information, a broad definition of regression was used, without specifying severity or duration, and included any regression in language or social interaction skills (18).

The clinical severity of autism was assessed using the Childhood Autism Rating Scale (CARS), and children with ASD were divided into two subgroups based on severity. To ensure consistency among raters, CARS was administered by a single researcher for each child. To assess marital/relationship issues believed to impact maternal stress, the Birtchnell Partner Evaluation Scale – female form was administered to mothers. To evaluate relationship issues during pregnancy, mothers were asked to respond to the questions in the Birtchnell Partner Evaluation Scale while reflecting on the pregnancy period. To prevent interpretation errors, the researcher completed the questionnaire by asking the mothers the questions directly.

Childhood Autism Rating Scale (CARS): The CARS is a 15-item, clinician-administered behavioral assessment tool used to determine the clinical severity of autism, ranging from mild to moderate to severe. Scores range from 15 to 60, with a score above 30 supporting an autism diagnosis, and increasing scores indicating higher severity. Scores between 30-36.5 indicate mild to moderate severity, while scores of 37 and above indicate severe autism. The Turkish validity and reliability of the scale were established by İncekaş (19).

Birtchnell Partner Evaluation Scale (BPES): Developed by Birtchnell, the BPES consists of separate forms for men and women, assessing their evaluations of each other. The female form consists of 79 items, while the male form consists of 72 items. The evaluated dimensions are dependency (D), detachment (DP), control (C), and reliability (R). Participants are asked to respond with 'Yes', 'Undecided', or 'No'. Scores are obtained for each subscale, indicating the degree to which the relevant characteristics are present. The dependency subscale is related to a lack of self-confidence, a need for continuous help and support, and excessive attention. The control subscale is related to dominance over the spouse, relegating the spouse to a secondary role, and assuming excessive responsibility. The detachment subscale is related to emotional isolation and a desire to be alone. The reliability subscale is related to accepting the spouse as they are, supporting the spouse, and expressing emotions. The reliability subscale enhances marital harmony, while the control, detachment, and dependency subscales indicate traits that hinder a harmonious marriage. The Turkish validity and reliability of the scale were conducted by Kabakçı and colleagues (21).

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA) software. The distribution of the data was evaluated using skewness and kurtosis values, and the data were found to be normally distributed. Numerical variables with a normal distribution were presented as mean ± standard deviation. Categorical variables were presented as frequencies and percentages, and chi-square tests were used to determine the relationships between categorical variables. Independent t-tests were used for comparisons of normally distributed numerical data between groups. Pearson correlation analysis was used to assess the direction and strength of relationships for parametric data. A significance level of $p < 0.05$ was considered statistically significant, with a 95% confidence interval.

RESULTS

In our study, 22 girls (22%) and 78 boys (78%) were diagnosed with ASD. The average age of children in the mild-moderate ASD group was 46.64 ± 16.03 months, while it was 40.79 ± 14.27 months in the severe ASD group. Sociodemographic characteristics of the mothers and fathers of children diagnosed with ASD showed that 70% of the mothers (n=70) were not working, 95% of the fathers (n=95) were working, and most of the parents were high school or university graduates (mothers: n=60, 60%; fathers: n=56, 56%). Almost all families (n=96, 96%) had a nuclear family structure, and consanguineous marriage was observed in 12 families (12%). The rate of autism diagnosis among

Table 1: Comparison of Sociodemographic Data According to Autism Severity

	Mild-Moderate ASD (n=61)	Severe ASD (n=39)	p-value
Age (months), mean – SD	46.64 – 16.03	40.79 – 14.27	0.067*
Maternal age during pregnancy (years), mean – SD	29.77 – 5.94	29.85 – 6.43	0.952*
Paternal age during pregnancy (years), mean – SD	33.98 – 6.16	33.97 – 6.73	0.994*
Age difference between parents (years), mean – SD	4.62 – 3.46	5.72 – 3.83	0.142*
Gender (n, %)			
Male	49 (80.3%)	29 (74.4%)	0.482**
Female	12 (19.7%)	10 (25.6%)	
Maternal education level (n, %)			
Illiterate	0 (0%)	1 (2.6%)	0.145**
Primary school	15 (24.6%)	6 (15.4%)	
Middle school	7 (11.5%)	11 (28.2%)	
High school	18 (29.5%)	11 (28.2%)	
College/University	21 (34.4%)	10 (25.6%)	
Paternal education level (n, %)			
Illiterate	0 (0%)	0 (0%)	0.203**
Primary school	13 (21.3%)	8 (20.5%)	
Middle school	13 (16.4%)	13 (33.3%)	
High school	21 (34.4%)	8 (20.5%)	
College/University	17 (27.9%)	10 (25.6%)	
Marital status (n, %)			
Married	59 (96.7%)	37 (94.9%)	0.642***
Separated	2 (3.3%)	2 (5.1%)	
Family history of autism (n, %)			
Yes	14 (23.0%)	13 (33.3%)	0.254**
No	47 (77.0%)	26 (66.3%)	
Consanguineous marriage (n, %)			
Yes	9 (14.8%)	3 (7.7%)	0.358***
No	52 (85.2%)	36 (92.3%)	
Maternal employment status (n, %)			
Employed	18 (29.5%)	12 (30.8%)	0.893**
Unemployed	43 (70.5%)	27 (69.2%)	
Paternal employment status (n, %)			
Employed	57 (93.4%)	38 (97.4%)	0.646***
Unemployed	4 (6.6%)	1 (2.6%)	

*Independent t-test, **Chi-square test, ***Fisher s Exact Test
Mean – SD: Mean – Standard Deviation

the families and relatives was 27% (n=27).

The average age of mothers in the mild-moderate ASD group was 29.77 ± 5.94 years, while in the severe ASD group, it was 29.85 ± 6.43 years. The average age of fathers in the mild-moderate ASD group was 33.93 ± 6.16 years, and in the severe ASD group, it was 33.97 ± 6.73 years. There was no significant difference in parental age between the two groups (p=0.952 for mothers, p=0.994 for fathers). When the age difference between parents was compared between the two groups, the difference was 4.62 ± 3.46 years in the mild-moderate ASD group and 5.72 ± 3.83 years in the severe ASD group, with no statistically significant difference (p=0.142). Other sociodemographic data did not differ significantly between the groups, and these data are presented in Table 1.

When prenatal risk factors in children with ASD were evaluated, 25 mothers (25%) experienced threatened miscarriage during pregnancy, 25 mothers (25%) smoked during pregnancy, 58 mothers (58%) had a history of medication use during pregnancy, including painkillers, antibiotics, and hormone therapy (n=26, n=18, n=13, respectively), 28 mothers (28%) had a history of infections during pregnancy (9 upper respiratory infections, 14 urinary tract infections), 19 mothers (19%) had a history of significant physical illness (4 hypothyroidism, 3 diabetes mellitus, 4 hypertension, 5 migraine, 1 gastritis, 1 shingles, 1 fibromyalgia), 39 mothers (39%) reported psychiatric symptoms/disorders, 32 mothers (32%) experienced marital conflicts and communication problems, and 5 mothers (5%) had a history of loss or bereavement.

Regarding perinatal and postnatal risk factors, 26

Table 2: Comparison of Prenatal, Perinatal, and Postnatal Characteristics According to Autism Severity

	Mild-Moderate ASD (n=61)	Severe ASD (n=39)	p-value
Threatened miscarriage			
Yes	13 (21.3%)	12 (30.8%)	0.287
No	48 (78.7%)	27 (69.2%)	
Maternal smoking during pregnancy			
Yes	13 (21.3%)	12 (30.8%)	0.287
No	48 (78.7%)	27 (69.2%)	
Maternal medication use during pregnancy			
Yes	34 (55.7%)	24 (61.5%)	0.579
No	27 (44.3%)	15 (38.5%)	
Maternal infection history during pregnancy			
Yes	19 (31.1%)	9 (23.1%)	0.381
No	42 (68.9%)	30 (76.9%)	
Maternal physical illness during pregnancy			
Yes	12 (19.7%)	7 (17.9%)	0.830
No	48 (80.3%)	32 (82.1%)	
Maternal stress during pregnancy			
Yes	32 (52.5%)	19 (48.7%)	0.715
No	29 (47.5%)	20 (51.3%)	
Maternal psychiatric symptoms/disorders			
Yes	24 (39.3%)	15 (38.5%)	0.930
No	37 (60.7%)	24 (61.5%)	
Parental relationship issues during pregnancy			
Yes	23 (37.7%)	9 (23.1%)	0.126
No	38 (62.3%)	30 (76.9%)	
Maternal loss during pregnancy			
Yes	4 (6.6%)	1 (2.6%)	0.646
No	57 (93.49%)	38 (97.4%)	
Delivery method			
NSVD (normal vaginal delivery)	17 (27.9%)	9 (23.1%)	0.594
C/S (cesarean section)	44 (72.1%)	30 (76.9%)	
Birth timing			
Preterm	8 (13.1%)	14 (35.9%)	0.007
Term	53 (86.9%)	25 (64.1%)	
Birth weight			
Low birth weight	8 (13.1%)	9 (23.1%)	0.196
Normal birth weight	53 (86.9%)	30 (76.9%)	
Hypoxia/asphyxia during birth			
Yes	3 (4.9%)	2 (5.1%)	1.000
No	58 (95.1%)	37 (94.9%)	
Incubator/intensive care history			
Yes	12 (19.7%)	9 (23.1%)	0.683
No	49 (80.3%)	30 (76.9%)	
Jaundice history			
Yes	25 (41.0%)	17 (43.6%)	0.797 *
No	36 (59.0%)	22 (56.4%)	
Phototherapy history			
Yes	18 (29.5%)	12 (30.8%)	0.893
No	43 (70.5%)	27 (69.2%)	
Head trauma history			

children (26%) were born through normal spontaneous vaginal delivery, while 74 children (74%) were delivered via cesarean section. Preterm birth history was present in 22 children (22%), 17 children (17%) had low birth weight, 21 children (21%) had an incubator/intensive care history, and 42 children (42%) had a history of jaundice. A history of head trauma during the 0-18 month period was reported for 11 children (11%), and 12 children (12%) had a history of significant physical illness during the postnatal period. Regression, defined broadly, was identified in 33 children (33%).

When the mild-moderate and severe ASD groups were compared regarding prenatal, perinatal, and postnatal risk factors, preterm birth and regression history were found to be significantly higher in the severe ASD group (p=0.007 and p=0.025, respectively). Other prenatal, perinatal, and postnatal risk factors were similar between the two groups. No children in either group had undergone blood transfusion, and all postnatal vaccinations were completed. The comparison of prenatal, perinatal, and postnatal risk factors according to ASD severity is presented in Table 2.

When the relationship between the age difference between parents and marital/relationship problems was evaluated, no significant correlation was found (dependency subscale: p=-0.076, r=0.453; detachment subscale: p=0.070, r=0.487; control subscale: p=0.131, r=0.194; reliability subscale: p=-0.044, r=0.665). The results are presented in Table 3.

When BPES subscales were compared between the

Table 3: Relationship Between Age Difference Between Parents and BPES Subscales

BPES Subscale	Correlation Coefficient (r)	p-value
Dependency (BPES)	-0.076	0.453
Detachment (BPES)	0.070	0.487
Control (BPES)	0.131	0.194
Reliability (BPES)	-0.044	0.665

Pearson Correlation Analysis
BPES: Birtchnell Partner Evaluation Scale

Table 4: Comparison of BPES Subscales According to Autism Severity

BPES Subscale	Mild-Moderate ASD (n=61)	Severe ASD (n=39)	p-value
Dependency (BPES)	26.80 ± 6.247	24.87 ± 4.060	0.064*
Detachment (BPES)	25.26 ± 7.874	28.59 ± 8.197	0.045*
Control (BPES)	33.08 ± 11.104	32.10 ± 10.445	0.661*
Reliability (BPES)	56.70 ± 12.976	60.74 ± 11.180	0.113*

*Independent t-test
BPES: Birtchnell Partner Evaluation Scale

mild-moderate and severe ASD groups, the detachment subscale was significantly higher in the severe ASD group (p=0.045). The other BPES subscales did not differ significantly between the two groups. The comparison of BPES subscales according to ASD severity is shown in Table 4.

DISCUSSION

In our study, preterm birth and regression were found to be significantly more common in the severe ASD group compared to the mild-moderate group. No significant relationship was found between the age difference between parents and marital/relationship issues as assessed by the BPES subscales. However, the detachment subscale of BPES was significantly higher in the severe ASD group.

When examining the sociodemographic data in our study, no significant differences were found regarding autism severity. Studies have shown that increasing parental age raises the risk of ASD. Advanced paternal age is considered the most consistent environmental risk factor for ASD (22). One study found that both maternal and paternal age had similar effects on ASD risk, and a meta-analysis indicated that advanced maternal age increased ASD risk by 41%, while advanced paternal age increased it by 55% (23). Advanced maternal age may contribute to ASD risk through chromosomal and genomic changes and associated obstetric and fetal complications (24). However, some studies report no increased risk of ASD associated with advanced maternal age (25,26). The more pronounced effect of advanced paternal age on ASD risk might be due to the accumulation of de novo mutations, as men can have children later in life (9,27).

Although parental age has been studied as a risk factor for ASD for a long time, studies examining its relationship with ASD symptom severity are more limited. Some studies found that paternal age is a significant predictor of autism severity (17). In a retrospective study of 351 children, no relationship was found between increasing parental age and phenotypic severity of ASD (28). Another study investigating the relationship between maternal age and the severity of cognitive and social deficits in ASD also found no significant association between age and severity (29). In our study, when we evaluated parental age in mild-moderate and severe ASD groups, no significant differences were found. Some recent studies suggest that a large age difference between parents could also be a risk factor for ASD (9). One study reported that children of parents with smaller age differences had a lower risk of ASD, while those with larger age differences had a higher risk (10). A retrospective study in our country also reported that the age difference between parents was higher in the ASD group compared to the control group (11). However, no studies were found comparing the age difference between parents according to the severity of autism. In our study, when we evaluated the age difference between parents in the autism severity groups, no significant differences were observed. Given the inconsistent data, further studies are needed to evaluate these findings.

When prenatal risk factors were compared according to severity, preterm birth was found to be significantly more common in the severe ASD group. Previous research has reported that adverse factors during pregnancy are more frequently observed in children with ASD (30). Factors such as medication use during pregnancy, maternal physical illness, emotional stress, smoking, alcohol, and substance use, prematurity, hypoxia, and low birth weight have been associated with neurodevelopmental disruption and increased ASD risk, though further research is needed to support these findings (31,32).

In studies evaluating prenatal-perinatal-postnatal factors and their effects on ASD severity, one study found no relationship between these factors and

ASD severity (33). However, another study reported that conditions such as preeclampsia, polyhydramnios, oligohydramnios, and gestational diabetes were associated with more stereotyped behaviors and social communication difficulties (14). Another study found that maternal hypertension, preeclampsia, and parental depression were linked to more severe communication deficits and repetitive behaviors in children with ASD (15). In addition, maternal stress during the prenatal period has been reported to contribute to ASD symptom severity in some studies (34). A recent study also showed that preterm birth and obstetric complications were associated with more severe autism (16). Our study also found that preterm birth was significantly more common in the severe ASD group. Recent research suggests that ASD prevalence is higher in preterm infants and that a shorter gestational period is associated with greater neurodevelopmental vulnerability (35-37). A meta-analysis found that preterm children (gestational age < 37 weeks) had approximately a 30% higher risk of ASD compared to full-term children (38). The possible mechanism for the association between preterm birth and ASD risk has not been fully determined, though it may involve inflammatory pathways (39,40). Increased levels of pro-inflammatory cytokines, particularly IL-1, IL-6, and TNF, have been associated with uterine activation and the initiation of preterm labor. These increased cytokine levels in preterm infants may also negatively impact neurodevelopment during early childhood (41,42). Fetal brain development continues throughout the third trimester (43), so preterm birth may disrupt neurodevelopmental processes and increase the risk of neurodevelopmental disorders, motor, and sensory abnormalities. Although preterm birth has been identified as a risk factor for ASD, its effects on symptom severity remain unclear. Some studies have found that children born prematurely with ASD are at higher risk of poorer neurodevelopmental outcomes compared to full-term children with ASD. One study found that children with ASD born preterm had greater difficulties with non-verbal social interaction skills, such as social smiling and communicative facial expressions, compared to full-term children with ASD (44). Although some prenatal/perinatal factors may affect ASD severity, further studies are needed to confirm these findings.

When postnatal risk factors were compared according to severity, regression was found to be more common in the severe ASD group. In autism regression, language skills are most affected, and social interests and abilities, play, and rarely motor skills may also be impacted (45,46). Some researchers suggest that social skill loss may occur alone and might even be the more common type of regression (47). Regression is generally defined as the loss of learned developmental skills such as language, motor, or social abilities. However, retrospective assessment of regression through parent interviews can lead to varying results, limiting the validity and reliability of its identification (48). Studies have reported regression rates ranging from 10% to 50%, with an overall prevalence of 30% (49). The broad use of the term "regression" in different studies likely contributes to the wide range of reported rates. In our study, a broad definition of regression was used, and the regression rate was 31%, consistent with other studies in the field.

Little is known about the underlying causes of regression, and findings regarding the relationship between regression and ASD symptom severity are inconsistent. Most studies suggest that children with regression have more severe core ASD symptoms and more severe overall disease severity compared to children without regression (50,51). However, some studies have found no difference in disease severity between children with and without regression (52,53). In one study, no differences were found in obstetric and prenatal risk factors between children with and without regression (55). These inconsistent findings may be due to the small sample sizes and limited number of children included in the studies.

In our study, no significant relationship was found between the age difference between parents and marital/relationship issues as assessed by BPES subscales. Research suggests that maternal exposure to social, environmental, and familial stressors during pregnancy can negatively affect fetal brain development. One study found that children of mothers who experienced stress between the 25th and 28th weeks of pregnancy had a higher likelihood of developing autism (56). Another study reported that inappropriate psychological stress,

especially in mothers with severe and long-lasting psychiatric disorders, was associated with an increased risk of ASD (57). Increased maternal stress during the prenatal period can activate the hypothalamic-pituitary-adrenal axis, leading to the release of cortisol and norepinephrine. These stress hormones can cross the placenta and negatively affect fetal development (58,59). Stress during pregnancy may also increase ASD risk through other mechanisms, though this remains uncertain. Some studies suggest that stress affects inhibitory neuronal systems, serotonin pathways, and fetal testosterone levels, though more research is needed (60,61). Epigenetic mechanisms may also influence the expression of genes related to neurobiology, metabolism, and physiology, contributing to ASD etiology (62). Prenatal maternal stress is considered a non-specific risk factor, and high maternal stress during pregnancy may be associated with other risk factors (12). In our study, we evaluated the relationship between maternal stress and the age difference between parents, another potential risk factor, but no significant relationship was found. Maternal stress can be oxidative, psychological, or physical in nature, and in our study, we primarily assessed psychological stress through marital and relationship issues during pregnancy using the BPES. Whether parental age is an independent risk factor for ASD is not clear (63). The lack of a relationship between the age difference between parents and maternal stress in our study suggests that parental age may not be an independent risk factor and could be related to other factors. Given the lack of clarity regarding the relationship between maternal stress and ASD, it is possible that the interaction of maternal stress and parental age with multiple other risk factors is significant. More studies are needed to evaluate the relationship between marital/relationship issues, parental age differences, and other risk factors in larger samples.

There is evidence that maternal stress can increase the severity of ASD. One study found that exposure to stressful life events during pregnancy was a significant predictor of ASD symptom severity (34). Another study showed that children of mothers who experienced natural disasters during pregnancy had higher autism spectrum scores (60). In our study, the relationship between ASD severity and BPES subscales was evaluated, and the detachment subscale was found to be significantly higher in the severe ASD group. The dependency subscale of BPES reflects dependent traits in spouses, while the control subscale relates to control over the spouse. The detachment subscale is primarily related to emotional detachment. Thus, the detachment subscale may be more relevant for assessing emotional stress in relationships. In our study, mothers in the severe ASD group rated their relationships with their spouses during pregnancy as more emotionally detached and distant compared to mothers in the mild-moderate group. Emotional detachment from their spouses during pregnancy may have increased maternal stress, contributing to the severity of ASD. Our findings are consistent with the limited studies in the field.

One limitation of our study is that only marital/relationship issues were evaluated as a maternal stress factor using BPES subscales. Psychiatric evaluations and records during pregnancy, as well as postnatal maternal stress factors, were not included, which is another limitation.

The absence of a control group, the small number of participants, the lack of developmental assessments for the children, and the retrospective nature of the data collection using questionnaires are other important limitations of our study.

There is still much to learn about the factors predicting the severity of autism spectrum disorders. While studies suggest that prenatal-perinatal-postnatal factors increase the risk of ASD, few have examined their effects on ASD severity. Our study found that preterm birth and regression were more common in the severe ASD group. Given the limited number of studies evaluating potential risk factors based on ASD severity, our findings may contribute to the literature. Additionally, identifying and controlling preventable risk factors, such as preterm birth, could be important for the development and severity of neurodevelopmental disorders.

Prenatal maternal stress has recently been studied as a factor contributing to ASD etiology, and some studies suggest that it increases ASD severity. Our

study also found that mothers in the severe ASD group rated their relationship with their spouse during pregnancy as more emotionally detached. Emotional detachment from their spouse during pregnancy may have increased maternal stress, contributing to the severity of ASD. Recognizing, monitoring, and intervening in maternal stress during pregnancy may help reduce its potential negative effects on ASD severity. Future studies should include other maternal stress factors beyond marital/relationship issues, with larger sample sizes, to confirm these findings.

High maternal stress during pregnancy may be associated with other risk factors. In our study, no significant relationship was found between maternal stress and the age difference between parents. Since many risk factors for ASD remain unclear, it is possible that maternal stress and parental age may only be significant in interaction with multiple other risk factors.

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