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RESEARCH

AUTISM SPECTRUM DISORDER AND PRENATAL FACTORS: A CONTROL CASE STUDY

TRANSTORNO DO ESPECTRO AUTISTA E FATORES PRÉ-NATAIS: UM ESTUDO DE CASO CONTROLE

TRASTORNO DEL ESPECTRO AUTISTA Y FACTORES PRENATALES: UN ESTUDIO DE CASOS Y CONTROLES

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ABSTRACT

Objective: to investigate the association between Autism Spectrum Disorder (ASD) and prenatal factors. **Methods**: a control case study was conducted with the responsible adults of 248 children/teenagers diagnosed with ASD (case group) and 886 neurotypical participants (control group). A semi structured questionnaire was used to collect data and logistic regression model was adopted to estimate the crude and adjusted odds ratio (OR). **Results**: it was identified significant ASD association with the following prenatal factors: prenatal done in private care (OR=1,59); pre-eclampsia or eclampsia (OR=1,61); bleeding in pregnancy (OR=1,54); Absence of ferrous sulphate/iron supplement in pregnancy (OR=1,52); In the adjusted model, the variables of confounding factors also presented a positive association with ASD: very low weight when born, gender of the child, age of mother when giving birth, mother's color of skin and ASD family history. **Conclusions**: this study suggests that prenatal done in private care, occurrence of pre-eclampsia or eclampsia, bleeding in pregnancy e absence of ferrous sulphate/iron supplement in pregnancy presents an association with a high chance of ASD. The results found can be useful for prenatal advice over modifiable risk factors and early diagnosis.

Keywords: Autism Spectrum Disorder; Prenatal Care; Pregnancy; Risk Factors.

RESUMO

Objetivo: *investigar a associação entre o Transtorno do Espectro Autista (TEA) e fatores relacionados ao pré-natal.* ***Métodos:*** *estudo caso-controle realizado com os responsáveis por 248 crianças/adolescentes diagnosticadas com TEA (grupo caso) e 886 participantes neurotípicos (grupo controle). Utilizou-se um questionário semiestruturado para a coleta de dados, e foi adotado o modelo de regressão logística para estimar a razão de chances (odds ratio, OR) bruta e ajustada.* ***Resultados:*** *identificou-se associação significativa entre o TEA e os seguintes fatores pré-natais: realização do pré-natal em serviço privado (OR=1,59); ocorrência de pré-eclâmpsia ou eclâmpsia (OR=1,61); sangramento durante a gestação (OR=1,54); e ausência de suplementação com sulfato ferroso/ferro na gestação (OR=1,52). No modelo ajustado, os fatores de confusão também apresentaram associação positiva com o TEA: peso muito baixo ao nascer, sexo da criança, idade materna ao dar à luz, cor da pele da mãe e histórico familiar de TEA.* ***Conclusões:*** *este estudo sugere que a realização do pré-natal em serviço privado, a ocorrência de pré-eclâmpsia ou eclâmpsia, o sangramento gestacional e a ausência de suplementação com sulfato ferroso/ferro estão associados a uma maior chance de TEA. Os resultados encontrados podem ser úteis na orientação pré-natal quanto a fatores de risco modificáveis e no diagnóstico precoce .*

Palavras-chave: *Transtorno do Espectro Autista; Cuidado Pré-Natal; Gravidez; Fatores de Risco.*

RESUMEN

Objetivo: *investigar la asociación entre el trastorno del espectro autista (TEA) y factores relacionados con el período prenatal.* ***Métodos:*** *estudio de casos y controles realizado con tutores de 248 niños/adolescentes diagnosticados con TEA (grupo caso) y 886 participantes neurotípicos (grupo control). Para la recolección de datos se utilizó un cuestionario semiestructurado y se adoptó el modelo de regresión logística para estimar el odds ratio (OR) bruto y ajustado.* ***Resultados:*** *se identificó asociación significativa entre el TEA y los siguientes factores prenatales: atención prenatal en un servicio privado (OR=1,59); aparición de preeclampsia o eclampsia (OR=1,61); sangrado durante el embarazo (OR=1,54); y ausencia de suplementación con sulfato ferroso/hierro durante el embarazo (OR=1,52). En el modelo ajustado, los factores de confusión también mostraron una asociación positiva con el TEA: muy bajo peso al nacer, sexo del niño, edad materna al nacer, color de piel de la madre y antecedentes familiares de TEA.* ***Conclusiones:*** *este estudio sugiere que la atención prenatal en un servicio privado, la ocurrencia de preeclampsia o eclampsia, sangrado gestacional y la ausencia de suplementación con sulfato ferroso/hierro se asocian con mayor probabilidad de TEA. Los resultados encontrados pueden ser útiles en la orientación prenatal respecto a factores de riesgo modificables y diagnóstico precoz.*

Palabras clave: *Trastorno del Espectro Autista; Atención Prenatal; Embarazo; Factores de Riesgo.*

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BACKGROUND

Autism spectrum disorder (ASD) is a disorder that involves the neurologic development and that presents itself, albeit diverse in manners and degree, with deficits in social interaction, repetitive behavior and interest restrictions of a specific subject.[1]

The majority of epidemiological studies on autism are from developed countries as the USA. The prevalence of ASD in the USA in about 278 over 10,000 (1 in 36) when established the participant's age of eight years old[2]. Yet there are variations of prevalence referring to the gender of the child, being the chance of a boy presenting the diagnosis four times greater than observed in girls[2].

The origins of the increase of the autism prevalence are questioned, with debate centering on whether it is due to an expansion of the autism spectrum or increased awareness and access to information among parents[3]. Love et al. suggests that advancements in diagnosis are undoubtedly contributing to the higher prevalence, as professionals from various fields, along with parents, have become more engaged in identifying cases, coupled with increased societal acceptance. However, attention is drawn to the potential involvement of environmental factors in the pathophysiology of autism[4].

Due to its multifactorial perspective, it is not known the exact boundaries that permeate the etiology of ASD, including the idiosyncrasies of each one of the prototypes that is presented in the spectrum. Nevertheless, the most likely is a polygenic etiology, with epistatic potential and of great susceptibility towards genetic factors. Another fundamental aspect is that it justifies the importance of researching the circumstances occurring in the pregnancy period and the advent of the autistic offspring are findings that point to encephalic macro and microscopic abnormalities, besides the functional, suggestive intrauterine occurrences[5].

This paper had as scope to identify which are the factors associated to the high risk of ASD during the prenatal phase. It is assumed that further studies in the field will enable the knowledge of factors that have relevant association to the disorder, contributing to the prenatal advice over modifiable risk factors and early diagnosis.

METHODS

Data from a case-control study titled "Autism Spectrum Disorder in Montes Claros: A Case-Control Study" were utilized. Other referenced articles included variables such as postnatal factors of ASD patients[6] and parental age[7]. This study was methodologically guided by the Strengthening the reporting of observational studies in epidemiology (STROBE) instrument.

The sample size was planned as an independent case control study aiming to estimate an *Odds ratio* (OR) of 1.9, due to an exposure among the control's probability of 0.18[8]. In this study, an analysis of several exposure factors was planned, hence, values related to the exposure factor considered the mother's age in birth ≥ 35 years old, as it was found as a biggest part in the sample among the others that were tested. The strength of the study was defined as 0.80, a significant level of 0.05 and four participants of the control group for each one of the case group. There was an increase of 10% with the objective of compensating possible losses, and a deff of 1.5 was adopted for the correction of the design effect. The size of the sample was set at a minimum of 213 cases and 852 controls.

Participants in the case group were recruited from eight clinics serving individuals suspected of or diagnosed with ASD in the city, including two public clinics and the Autism Support *Associação de Apoio aos Autistas do Norte de Minas* (ASANM). Telephone calls were made to mothers of patients who had medical certificates of ASD obtained from these institutions. In addition to the medical certificate, mothers were required to affirmatively respond to inquiries regarding their child's ASD diagnosis as an inclusion criterion.

The control group was constituted by neurotypical children and adolescents without autistic traces. A search was done in 63 public, philanthropic and private regular schools of Montes Claros, the same ones also studied the cases. Taking into consideration that 14 children of the case group were not in school age, 66 neurotypical children in identical age range of the Family Health Strategy Units were recruited. In order to identify eventual ASD cases or to identify participants with traces in the control group, a Modified Checklist for Autism in Toddlers (M-chat) was applied.

After reviewing the LILACS, MEDLINE, and PubMed databases from 2000 to 2014, a questionnaire comprising 213 questions regarding pre-, peri-, and postnatal factors associated with ASD was developed. The questionnaire underwent revision by a specialized ASD team. Data collection occurred between August 2015 and January 2016 for cases, and February to September 2016 for controls. A trained team of healthcare students conducted the data collection process in person, at predetermined times and locations arranged by mothers or responsible adults of the children/adolescents.

The prenatal variables analyzed in this study included: prenatal care location, occurrence of pre-eclampsia or eclampsia, presence of bleeding, infection, use of ferrous sulfate, and medication. Additionally, to control potential confounding factors, the following variables were analyzed: child characteristics (gender, age, and very low birth weight), maternal characteristics (age at childbirth and self-reported skin color), and family history (history of ASD in first-degree relatives).

The frequency distribution of all variables was done, according to the case and control groups. A chi-square test was used for the bivariate analysis, and those variables that presented a descriptive level (value-*p*) lower tan 0.20 were selected for multiple analysis. The logistic regression model was used in the multiple analysis, where the strength of the association among the outcome (case/control) and the variables related to prenatal were estimated by *Odds Ratio* (OR), with their respective confidence intervals at 95%, adjusted by the child's characteristics, maternal's characteristics and family history variables. Individuals with missing data were excluded from bivariate and multiple analyzes (4.0% in the case group and 3.8% in the control group). The statistical data analysis was done through the statistical software Statistical Package for the Social Sciences (SPSS), version 23.0 (IBM, Chicago, United States).

The referred study was approved by the Ethics Committee in Research (ECR) of the *Universidade Estadual de Montes Claros* / UNIMONTES (number of the opinion 534,000/14), and all responsible adults of the children/adolescents signed an informed consent form.

RESULTS

E A total of 398 children/adolescents with ASD were identified in the clinics investigated. After contacting the 398 mothers via telephone, 332 answered the call and 278 agreed to participate. However, after the interview, 25 children/adolescents whose mothers did not respond positively to the question about the diagnosis of ASD were excluded from the case group, two children with Down syndrome, one with Rett syndrome and two with fragile X syndrome. Thus, the case group consisted of 248 children diagnosed with ASD (Figure 1). A total of 1,006 mothers of neurotypical children and adolescents agreed to participate in the study, however 120 with ASD signs or symptoms were identified, resulting in the exclusion of the study. Thereby, the control group was constituted of 886 participants.

The groups did not present significant difference (p=0.521) related to average age, presenting the average age of 6.4 years old (±3.6) in the case control and 6.6 years old (DP±3.4) in the control group. The age range distribution was similar between the groups (p=0.132), which, in the total sample (case and control), 44.0% were from two to five years old, 41.4% were six to 10 years old and 14.6% were over 10 years old. The case and control groups, respectively, were constituted by 81.0% and 50.7% of children and adolescents of the male gender, with significant difference (p<0.001) (Table 1).

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The results of the multiple analysis are presented in Table 3, which presents the crude and adjusted strength of associations estimations (OR). Hosmer and Lemeshow tests indicated that the model presented adjusted quality [$\chi2(8) = 6.20$; value-p= 0.668; R2N=0.246]. After the adjustment, the following relative variables to post-natal presented positive and significant associations to ASD: location of the private prenatal care; pre-eclampsia or eclampsia; bleeding; and absence of ferrous sulphate/iron supplement. The final model was adjusted by the child's gender, very low weight when born, age of mother when giving birth, self-declared mother's skin color and ASD history in first degree relatives.

DISCUSSION

Autism's etiology and physiopathology still present themselves as a challenge to science. The factors that permeate the disorder is object of questionings, especially due to the emotional and financial impact caused by ASD. Studies point to the positive associations between events/circumstances of the prenatal period and autism[9,10], as well as this study that, in identical direction, found positive association in diverse variables related to prenatal.

A significant association was observed between the location of prenatal care and ASD, with a higher likelihood of cases receiving prenatal care in private facilities. However, while it is not feasible to ignore this finding, it is inferred to be linked to socioeconomic factors, as it implies greater access to diagnosis and treatment for ASD. It is recognized that better socioeconomic status facilitates

Figure 1 - Flowchart of the case group sample selection process:

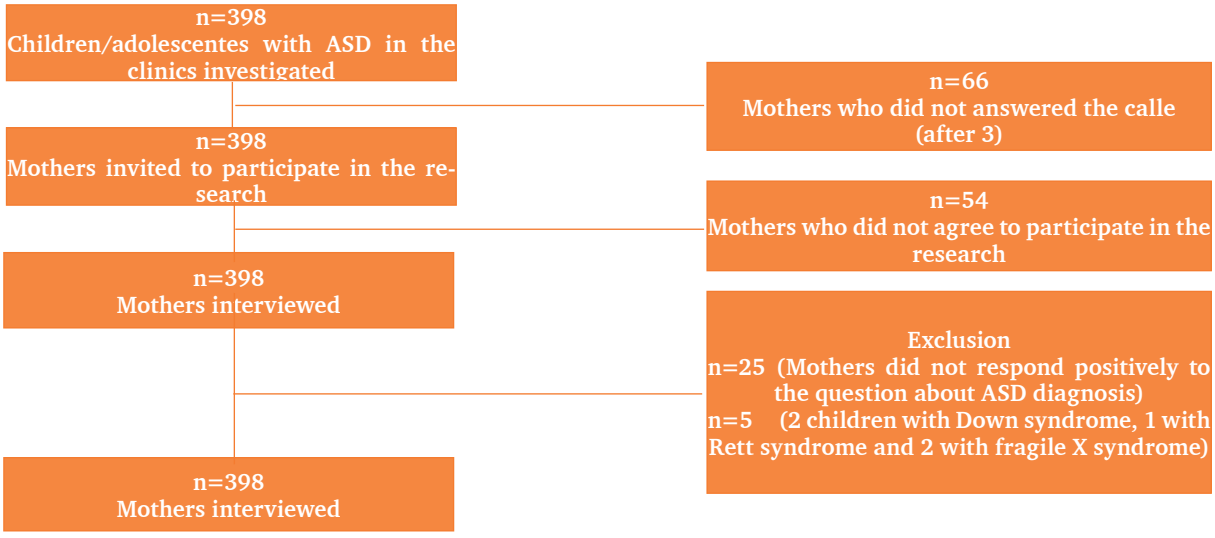

Table 1 - Distribution of the Case and Control participants according to the children/adolescents' characteristics, maternal characteristics and ASD Family history in Montes Claros - MG, Brazil, 2015-2016.

Variable	Case n (%)	Control n (%)	Total n (%)	p-value*
Children/adolescentes Characteristics				
Gender				<0.001
Male	201 (81.0)	449(50.7)	650 (57,3)	
Female	47 (19.0)	437(49.3)	484 (42.7)	
Age range				0.132
2 – 5 years old	121 (48.8)	378 (42.7)	499 (44,0)	
6 – 10 years old	89 (35.9)	380 (42.9)	469 (41,4)	
11 – 15 years old	38 (15.3)	128 (14.4)	166 (14,6)	
Very low weight when born				0.001
Yes (< 1500g)	13 (5.2)	14 (1.6)	27 (2,4)	
No (> 1500g)	235 (94.8)	872(98.4)	1107 (97,6)	
Maternal Characteristics				
Age of mother when giving birth				<0.001
≥35 years old	53 (21.4)	149(16.8)	202 (17.8)	
25 – 34 years old	149 (60.1)	443(50.0)	592 (52.3)	
< 25 years old	46 (18.5)	294 (33.2)	340 (29.9)	
Self-declared skin color				0.001
White	66 (26.6)	149(16.8)	215 (18.9)	
Non White	182 (73.4)	737(83.2)	919 (81.1)	
ASD Family History				
ASD history in 1º degree relatives				<0.001
Yes	59 (24.8)	63 (7.4)	122 (11.2)	
No	179 (75.2)	788 (92.6)	967 (88.8)	

* Chi-square Test. Number of missing data, in the case and control groups, respectively: Gender (10 and 35), ASD Family History (10 and 35).

Table 2 - Distribution of the Case and Control participants according to prenatal factors in Montes Claros - MG, Brazil, 2015-2016.

Prenatal Factors	Case n (%)	Control n (%)	Total n (%)	p-value*
Location of the prenatal				0.015
Private Care	149 (60.1)	366(41.7)	515 (45.7)	
Public Health Care	99(39.9)	511(58.3)	610 (54.3)	
Number of appointments				0.285
≥ 6 appointments	239(96.4)	839(94.7)	1078 (95.0)	
< 6 appointments	9(3.6)	47(5.3)	56 (5.0)	
Pre-eclampia or eclampsia event				0.003
Yes	33(13.4)	65(7.4)	98(8.8)	
No	214(86.6)	811(92.6)	1025 (91.2)	
Presence of bleeding				0.001
Yes	60(24.3)	132(15.2)	192(17.1)	
No	187(75.7%)	739(84.8)	926(82.9)	
Presence of Infeccion				0.039
Yes	67(28.5)	190(22.1)	257(23.4)	
No	168(71.5)	671(77.9)	839(76.6)	
Use of ferrous sulphate				<0.001
No	52(21.2)	115(13.5)	167(15.2)	
Yes	193(78.8)	740(86.5)	933(84.8)	
Use of medication				<0.001
Yes	310(35.3)	433(38.5)	433(38.5)	
No	568(64.7)	691(61.5)	691(61.5)	

* Chi-square Test. Number of missing data, in the case and control groups, respectively: Pre-eclampia or eclampsia event (1 and 10), Presence of bleeding (1 and 15), Presence of Infeccion (13 and 25), Use of ferrous sulfate (3 and 31), Use of medication (0 and 8).

access to specialists across various fields, potentially enabling earlier diagnosis. Moreover, the majority of users in the private healthcare system belong to families with higher socioeconomic status. It is worth noting that local factors, such as acceptance of a potential diagnosis, may introduce variations in study results, thus explaining the observed differences[11].

A positive association between ASD and pre-eclampsia and/or eclampsia events was also evidenced. Carter et al.[12] explains that pre-eclampsia or eclampsia is a result of superficial placentation, with inadequate cervix blood supply, as well as oxidative stress of placental tissue, causing hypoxia and interfering in the neurodevelopment. The placenta, present in viviparous mammals, is responsible for the exchange of substances, among which the oxygen, other gases, nutrients and secretions, accountable for the flow between pregnant woman and the unborn child. The placental insufficiency results, inexorably, in negative hemodynamic repercussions as much for the mother, as for the fetus[13].

Regarding the association found in this study between ASD and the presence of bleeding in pregnancy, this concatenates with the result of a metanalysis of 17 studies, in a total of 37,634 autistic children and 12,081,416 non autistic children. The metanalysis in question, demonstrated the association between antepartum hemorrhage and the increase risk of the occurrence of the autism spectrum disorder. Bleeding episodes are strictly connected to the reduction of perfusion and consequently hypoxia, leading to functional and structural lesions in brain tissue[14].

The absence of iron supplementation also showed a positive association with ASD in this study. Brynge et al. concluded that maternal iron intake during pregnancy may reduce the risk of ASD in children. Maternal iron deficiency is the most common cause of anemia, and the latter is associated with various adverse birth-related and behavioral outcomes, including autism[15].

This study has limitations, among them the fact that the diagnosis of the members of the case group was carried out by different teams, and it is not possible to verify

Table 3 - Strength of Associations among ASD and children/adolescents' characteristics, maternal characteristics and prenatal: crude and adjusted Odds ratio, with respective confidence internals of 95%. Montes Claros - MG, Brazil, 2015-2016.

Variable	ORcrude (IC 95%)	ORajustado (IC 95%)	Value-p*
Children/adolescents Charateristics			
Gender			< 0.001
Male	4.16 (2.95 – 5.87)	3.84 (2.65 – 5.56)	
Female	1,00	1,00	
Vey low weight when born			0.041
Yes (< 1500g)	3.45 (1.60-7.43)	2.49 (1.04 – 5.98)	
No (≥1500g)	1.00	1.00	
Maternal Characteristics			
Age when giving birth (in Years)	1.05 (1.02 – 1.7)	1,03 (1.00-1.06)	0.046
Self-declared skin color			0.046
White	1.79 (1.98 – 2.50)	1.49 (1.01- 2.19)	
Non white	1.00	1.00	
ASD Family History			
ASD history in 1º degree relatives			< 0.001
Yes	4.13 (2.79 – 6.09)	3.81 (2.46 – 5.89)	
No	1.00	1.00	
Prenatal Factors			
Location of the prenatal			0.008
Private care	2.10 (1.58-2.80)	1.59 (1.13-2.23)	
Public care	1.00	1.00	
Presence of Pre-eclampsia or eclampsia			0.089
Present	1.92 (1.23-3.00)	1.61 (0.93 – 2.77)	
Absent	1.00	1.00	
Presence of bleeding			0.034
Present	1,80 (1,27-2,54)	1.54 (1.03 – 2.30)	
Absent	1,00	1.00	
Use of ferrous sulphate			0.051
Did not use	1.73 (1.21-2.50)	1.52 (1.00 – 2.30)	
Used	1.00	1.00	

the criteria used for the diagnosis or the classification within the spectrum with a greater or lesser degree of impairment. However, according to a Diagnostic and Statistical Manual of Mental Disorders (DSM-5), all diagnosed individuals are part of the spectrum. It should be noted that all cases included in this study were being followed up by a team of qualified professionals specialized in ASD, which ensured that they had the disorder.

Another limitation in the present study is indicated in the memory bias, as it relies on the mothers' reports, especially in the variables related to mental disorders such as stress, depression, sadness and anxiety. Thus, the associations identified should be analyzed with caution. Considering that, in this sample about 56% of children/adolescents already were in the age range of 6 to 15 years old, it is assumed that a considerable amount of time had gone from pregnancy to data collection. Yet, it must be emphasized the considerable strength of the sample, consisting of 1,134 participants (248 cases and 886 controls). It is pointed out that the statistical analysis was adjusted by variables of ASD remarkable association, as well as factors related to the investigated prenatals. These variables

also revealed themselves associated to ASD in the present study, such as: male gender, very low weight when born; mother age when giving birth, self-declared white skin and family ASD history.

In this study, high chances of ASD in children/adolescents being of the male gender was observed. Worsham et al.[16] believes that the ASD physiopathology in boys involves the uterine exposure to hormones, especially testosterone, as well as their sensitive levels, once they have more receptors. Li et al.[17] explains that male genders generally suffer more of neurological disjunctions in comparison to the female gender, and are more susceptible to complications during pregnancy, among which bleeding, infection and brain trauma while in labor in comparison to women. The biological explanation would be on the fact that fetal testosterone is in key areas of behavior and cognition in the general population (in social development, language development, empathy, systemization and attention to details), as well as the influence to brain struture[18].

Another variable, referring to the child's characteristic, and that presented statistical significance was very low weight when born. The weight is in relation to the fetal growth and development, which can lead to a higher risk for autism and for other neuropsychiatric disorders. Association with very low weight when born with high risk for autism refers to the fact that many times the newborn's encephalon with very low weight is still too much vulnerable to clinical and environmental factors. Furthermore, the newborn in such condition, as a general rule, is submitted to longer hospital stays and therapeutic interventions capable of leading to an interruption of the adequate neurodevelopment by excessive exposure to stressful agents[19].

Regarding the association between maternal advanced age and ASD, it is understood due to the woman's gamete and ovum's genetic mutation over the years; higher tendency to obstetric complications as advancing in age, among which brain hypoxia[20].

Regarding to skin color, it is believed that a high ASD prevalence in mothers self-declared as white is due to its association to socioeconomic aspects, implying a greater access to diagnosis, as the white population represents a more economical privileged portion in most countries. Others studies point to an identical direction, finding positive association between ASD and white maternal skin color[21,22]. It was found that having a white maternal skin color is one of the factors that facilitates access to health services, playing a decisive role in the diagnosis of ASD and, consequently, in the increase in the number of reported cases[11].

Still stressing the importance of genetic load surrounding ASD, it was observed in this study a positive association between ASD and first-degree relatives with an ASD history. Several genetic mechanisms are involved not only in the origin of autism, but also in its own intergenerational transmission capacity. Previous study stated the excess sharing of the father is highly significant, with less significance for the mother[21]. Thus, several neurobiology explanations base the genetically strong physiopathology component of autism.

CONCLUSION

In conclusion, this study identified significant associations between ASD and variables related to prenatal as location of prenatal private care; pre-eclampsia or eclampsia; bleeding; and absence of ferrous sulphate/iron supplement. These variables represent relevant aspects to be observed when thinking about the etiology range of ASD. The results obtained may provide orientation on practices/care in the prenatal follow-up, once many of the analyzed factors are potentially modified, as well as be a potential diagnosis tool in retrospective assessments.

Despite advances in prenatal care practices, ASD is still rarely addressed systematically during this period, both in Brazil and in other countries. Generally, there is a greater focus on screening for genetic syndromes and conditions associated with parental age, while issues related to neurodevelopment are often overlooked. Considering that early signs of ASD involve alterations in child development, particularly in the achievement of age-appropriate milestones—which often do not occur or present atypically—it is essential that healthcare professionals include this topic in their guidance to expectant parents whenever possible. This approach may contribute not only to increased awareness but also to the early recognition of warning signs, facilitating timely referral for evaluation and intervention.

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