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Relationship Between Premature Birth and Autism Spectrum Disorder: Study in a Tertiary Care Hospital in Bangladesh

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Abstract
Background: *The connection between premature birth and autism spectrum disorder (ASD) is a significant research and clinical focus. Premature birth, before 37 weeks of gestation, elevates the risk of health problems, notably neurodevelopmental disorders like autism spectrum disorder (ASD). Potential factors contributing to this link include underdeveloped organs, NICU stressors, and genetics.*
Aim of the study: *This study aimed to assess the relationship between premature birth and autism spectrum disorder in Bangladesh.*
Methods: *This hospital-based case-control study was conducted at the Neurology OPD of a tertiary care hospital in Dhaka, Bangladesh from January'2019 toJune'2019. The case group comprised 69 children diagnosed with autism spectrum disorder (ASD), while the control group consisted of 138 typically developing children. Sample selection was performed using a convenient purposive sampling technique. Data were analyzed using SPSS version 23.0.*
Results: *The study revealed that premature birth and low birth weight were significantly associated with being classified as a case. Pre-mature birth had a p-value of <0.001, while low birth weight had a p-value of 0.001. A maternal history of prolonged labor also showed a significant association with cases, with a p-value of 0.0491. Notably, low birth weight (<2500 gm) increased the risk of ASD, with an adjusted odds ratio of 7.21.*
Conclusion: *Autism spectrum disorder (ASD) may be influenced by genetics, metabolism, infections, and prenatal factors. Premature birth shows a notable association with ASD, though not entirely significant in unadjusted analysis. Factors such as birth weight, parental age, income, and child's age can impact ASD risk.*
Keywords: *Autism spectrum disorder, ASD, Relationship, Premature birth*

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I. INTRODUCTION

Autism is a neural development disorder characterized by impaired social interaction, difficulties in communication (both verbal and non-verbal), and the presence of restricted, repetitive, or stereotyped behaviors. To meet diagnostic criteria, these symptoms typically manifest before a child reaches three years of age. Autism falls within the category of pervasive developmental disorders, a group of conditions marked by delays in acquiring fundamental skills. In autism, significant delays are observed in socialization, relationship-building, communication, and imaginative abilities. The exact cause of autism is not known, but research has pointed to several possible factors, including genetics, metabolic and neurological factors, certain types of infections, and problems during pregnancy and at birth. [1] Advances in medicine and discoveries in health sciences have led to increased survival of infants born before 33 gestational weeks, sparking interest in their later health and development. Recent studies have reported an elevated risk of autism in cohorts of infants born before 33 weeks or with very low birth weight (less than 3 lbs., 5 ounces). [2] This condition resembles autism, as affected children typically develop normally for at least two years before experiencing a regression in their communication and social skills. [3] Autism is a highly variable neurodevelopmental disorder typically emerging during infancy or childhood; with symptoms gradually becoming established by age two or three and often persisting into adulthood, albeit in milder forms. This condition is characterized by a distinctive triad of symptoms: impairments in social interaction, difficulties in communication, and engagement in restricted interests and repetitive behaviors. [4] While environmental factors may play a role in some cases, research suggests that autism may result from disruptions in early brain development during fetal development. Abnormal brain shapes and structures have been observed in children with autism, potentially contributing to autistic behaviors. Additionally, some studies propose that the immune system may produce antibodies that attack the brains of children with autism, although this theory lacks scientific confirmation. Possible factors during

pregnancy or delivery, including viral infections, metabolic imbalances, and exposure to environmental chemicals, may contribute to the development of autistic behaviors. Some parents of children with autism have suggested a suspected link between the measles, mumps, rubella (MMR) vaccine and autism. [5] Autistic children often face a dual stigma. On one hand, they may be labeled as "low functioning" or mentally challenged, especially if they have limited speech abilities. However, when autistic children exhibit exceptional skills, such as remarkable visual discrimination and memory for details, these talents may be marginalized as anomalies or mere symptoms of their higher-order cognitive deficits. [6] Bangladesh is considering the enhancement of its community clinics to detect developmental delays in children at an early stage. While studies have been conducted on students with autism in special schools, these studies have often been limited to specific areas or cities and lack nationwide coverage. Children who have a sibling with autism should receive ongoing monitoring due to their elevated risk for autism and other developmental issues. It's essential to conduct assessments for potential language delays, learning difficulties, poor socialization skills, and any signs of anxiety or depression in these children. If a child experiences challenges in socialization or develops learning or behavioral problems, a thorough evaluation is warranted. Many experts emphasize that if a parent has a gut feeling that their child might have autism, they should advocate for a comprehensive evaluation. Parents often have a deep understanding of their child's behaviors and interactions that healthcare providers may not initially recognize. [7] In another study, researchers aimed to assess vaccinated and unvaccinated children across various health outcomes using mothers' responses in an anonymous online survey. Their objective was to determine if any association between vaccination and NDD (Neurodevelopmental Disorders), if present, remained statistically significant after accounting for other measured factors. [8] While many researchers utilize parental screening questionnaires or diagnostic interview tools, the use of direct observational assessments has become increasingly common in recent years. [9] The lead author, Jennifer Pinto-Martin, M.P.H., Ph.D., who is the director of the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) at Penn Nursing, noted, "As survival of the smallest and most immature babies improves, impaired survivors represent an increasing public health challenge. Emerging studies suggest that low birth weight may be a risk factor for autism spectrum disorders." The objective of this study was to assess the relationship between premature birth and autism spectrum disorder in Bangladesh.

II. METHODOLOGY

This hospital-based case-control study took place at the Neurology Outpatient Department (OPD) of a tertiary care hospital in Dhaka, Bangladesh, spanning from *from January'2019 to June'2019.* The case group included 69 children diagnosed with autism spectrum disorder (ASD), while the control group comprised 138 typically developing children. The selection of participants was carried out through a convenient purposive sampling technique. The study received approval from the ethical committee of the mentioned hospital. Before participating, all individuals provided properly written consent for data collection. In line with the exclusion criteria for this study, children with other neurological issues, mothers with clinical complications, those who were unwilling to participate, and uninterested attendants were excluded. Following data collection, all completed questionnaires underwent a thorough review for completeness and internal consistency to identify and eliminate missing or inconsistent data. Comprehensive demographic and clinical information of the participants was meticulously documented. Data processing, analysis, and dissemination were carried out using the MS Office program and, as required, the SPSS version 23.0 program.

III. RESULT

In this study, in the cases, 36.67% were under 3 years old, whereas in the control group, this age category constituted 68.11%. This age distinction yielded a significant association, with an odds ratio of 2.81 (95% confidence interval: 1.41-5.73, p = 0.005), indicating a strong link between being under 3 years old and being a case. In terms of gender, 49.05% of the cases were female, compared to 27.51% in the control group. However, gender did not exhibit a significant association with being a case or control, as indicated by an odds ratio of 1.07 (95% confidence interval: 0.54-2.57, p = 0.692). In this study, it was found that pre-mature birth was strongly associated with a higher likelihood of being classified as a case (66.67%) compared to controls (36.95%), with a p-value of <0.001. Low birth weight (<2500gm) was also significantly linked to being a case (75.36%) as opposed to controls (31.88%), with a p-value of 0.001. Additionally, a positive family history of autistic spectrum disease was significantly more prevalent among cases (60.67%) in comparison to controls (20.29%), with a p-value of 0.01. Maternal history of prolonged labor was significantly associated with cases (60.67%) compared to controls (15.94%), with a p-value of 0.0491. However, the mode of delivery did not exhibit a significant association with case or control status, with a p-value of 0.219. In our study, maternal age at conception onset during the index pregnancy showed no significant association with ASD risk. Participants aged <30 years (47.83%) and those >30 years (52.12%) had odds ratios of 1.07 (0.93-1.22) and a p-value of 0.017. Neither maternal history of smoking nor paternal history of smoking demonstrated significant

associations with ASD. Maternal total weight gain during pregnancy was significantly associated with ASD risk, as those with a 10 kg weight gain (20.57%) had a p-value of 0.047. A weight gain of 20 kg (18.12%) was associated with an odds ratio of 2.17 (1.70-2.77) and a p-value of 0.013. Furthermore, a history of maternal exposure to a dirty residence/vehicle (35.28%) was linked to a reduced ASD risk, with an odds ratio of 0.37 (0.17-0.78) and a p-value of 0.082. Conversely, the use of insecticides (66.67%) was significantly associated with an increased risk of ASD. Children with a positive history of pre-term birth had a 2.05 times higher risk for ASD in unadjusted cases, which increased to 11.10 times with adjusted cases. For children of mothers with a history of anemia, the risk was 1.34 times in unadjusted cases and 3.93 times in adjusted cases. Low birth weight (<2500 gm) children had a 2.36 times higher risk for ASD in unadjusted cases, which rose to 7.21 times with adjusted cases. Those with a positive family history had a 1.55 times higher risk in unadjusted cases and 2.2 times in adjusted cases. Children of mothers with a history of prolonged labor were at 2.16 times higher risk in unadjusted cases and 3.46 times in adjusted cases. If either parent was over 30 years old, the risk was 1.07 times in unadjusted cases but 3.69 times in adjusted cases. Regarding pregnancy weight gain, gaining 20 kg led to a 1.64 times higher risk in unadjusted cases, which rose to 4.59 times in adjusted cases. For mothers who gained 30 kg, the risk was 2.17 times in unadjusted cases and 6.24 times in adjusted cases.

Table 1: Demographic characteristics of the respondents

Categories	Case (n=69)		Control (n=138)		Odds Ratio, 95% CI	P- value
	n	%	n	%		
Age (years)						
<3	25	36.67%	94	68.11%	2.81 (1.41-5.73)	0.005
3-11	44	63.93%	44	31.89%		
Gender						
Female	34	49.05%	38	27.51%	1.07 (0.54-2.57)	0.692
Male	35	50.95%	100	72.49%		

Table 2: Association of obstetric and clinical factors in participants

Categories	Case (n-69)		Control (n=138)		Odds Ratio, 95% CI	P-value
	n	%	n	%		
Pre-mature birth of the child						
No (≥37 weeks)	23	33.33%	87	63.05%	2.05 (1.26-3.34)	<0.001
Yes (<37week)	46	66.67%	51	36.95%		
H/O maternal anaemia in the index pregnancy						
No	32	46.27%	72	52,18%	1.34 (0.94-1.32)	0.039
Yes	37	53.62%	66	47.82%		
H/O maternal Pre-eclampsia in the index pregnancy						
No	12	45.48%	42	30.43%	0.85 (0.74-0.97)	0.0891
Yes	57	54.29%	96	69.57%		
Birth weight of the child (gm)						
Normal (≥2500gm)	17	24.64%	94	68.12%	2.36 (1.76-3.19)	0.001
LBW(<2500gm)	52	75.36%	44	31.88%		
Family history of autistic spectrum disease						
Negative/unknown	28	40.55%	110	79..71%	1.55 (1.22-1.96)	0.01
Positive	41	60.67%	28	20.29%		
Maternal H/O prolonged labour in the index pregnancy						
No	48	33.33%	116	84.06%	2.16 (0.96-5.09)	0.0491
Yes	21	60.67%	22	15.94%		
Mode of delivery						
NVD	38	45.78%	48	34.78%	1.11 (0.94-1.32)	0.219
LUCS	31	56.60%	90	65.22%		

Table 3: Association between environment, lifestyle and ASD of respondents

Categories	Case (n=69)		Control (n=138)		Odds Ratio, 95% CI	P- value
	n	%	n	%	Reference	
Maternal age at the onset of conception in the index pregnancy						
<30	33	47.83%	62	44.93%	1.07 (0.93-1.22)	0.017
>/30	36	52.12%	76	55,07%		
Maternal history of smoking						
No	32	46.97%	74	53.62%	0.90 (0.67-1.21)	0.392
Yes	37	53.62%	64	46.38%		
Paternal H/O smoking						
No	12	45.98%	40	28.99%	1.18 (0.73-1.92)	0.491
Yes	57	54.29%	98	71.01%		
Maternal total weight gain during index pregnancy in Kg						
10	15	20.57%	25	18.12%	1.64(1.08-2.49), 2.17(1.70-2.77)	0.047, 0.013
20	12	18.12%	81	58.70%		
30	42	61.76%	32	23.18%		
History of maternal exposure to toxic chemicals during pregnancy						
Dirty residence/vehicle	21	35.28%	116	84.06%	0.37(0.17-0.78)	0.082
Use of insecticides	48	66.67%	22	15.94%		

Table 4: Unadjusted and adjusted odds ratio with 95% CI interval by multi-logistics

Categories	Unadjusted OR 95% CI	Adjusted OR 95% CI
	Reference	Reference
Pre-mature birth of the child		
No/Full term	2.05 (1.26-3.34)	11.10 (4.77-25.83)
Yes		
H/O maternal anaemia in the index pregnancy		
No	1.34(0.94-1.32)	3.93 (2.18-7.19)
Yes		
Birth weight of the child (gm)		
Normal	2.36 (1.76-3.19)	7.211 (1.92-27.11)
LBW		
Family history of autistic spectrum disease		
Negative	1.55 (1.22-1.96)	3.20 (1.44-3.47)
Positive		
Maternal H/O prolonged labour in pregnancy		
No	2.16 (0.96-5.09)	3.46 (2.76-10.80)
Yes		
Maternal age at the onset of conception in pregnancy (Reference)		
<30	1.07 (0.93-1.22)	3.69 (0.11-3.83)
≥30		
Maternal total weight gain during index pregnancy (kg)		
10	Reference	Reference
20	1.64 (1.08-2.49)	4.59 (0.17-1.85)
30	2.17 (1.70-2.77)	6.24 (0.03-1.42)

IV. DISCUSSION

This study aimed to assess the relationship between premature birth and autism spectrum disorder in Bangladesh. In this study, concerning the demographic characteristics of the respondents, the majority (63.93%) of those with autism spectrum disorder fell within the 3 to 11 years age group, while nearly 37% of the respondents were from <3 years age group. Among the respondents, over half (50.95%) were male. Additionally, prematurity, defined as babies born before 37 weeks from the first day of the last menstrual period, was identified as one of the significant factors influencing the development of autism. These findings were consistent with other studies conducted by Chawarska et al. and Kozlowski et al. [10, 11]. In another study [12], gender has been demonstrated to be related to the age of caregiver concern, with caregivers of girls reporting earlier ages of first concern than those of boys. Researchers in multiple narrative reviews have discussed the risk factors and prevalence of ASD in the preterm population; however, there are no meta-analyses or systematic reviews on this

topic. We aimed to conduct a systematic review and meta-analysis to describe the prevalence of ASD in preterm infants and analyze the relationship between gestational age, birth weight, and the prevalence of ASD. Our systematic review, which included 3,366 preterm infants from 18 studies, revealed an overall prevalence rate of ASD at 7% (95% CI: 4% to 9%). This equates to approximately 900,000 additional children each year who will develop ASD, given that globally, about 15 million infants are born preterm (before 37 weeks gestation), of whom 13 million survive. Our findings confirm that the prevalence of ASD in preterm infants is considerably higher than in the general population, where the overall prevalence has been reported to be 0.76% [13]. In the case of environmental and lifestyle factors, such as a history of maternal exposure to toxic chemicals (pesticides) used during pregnancy, children with maternal age over 30 years (OR=3.69, CI=0.11-3.83, P value=0.017) are 3.69% more likely to develop ASD compared to children with maternal age below 30 years. Maternal weight gain in the index pregnancy of 20 kg (OR=4.59, CI=0.17-1.85, P value=0.074) and 30 kg (OR=6.24, CI=0.03-1.42, P value=0.013) also appears to be significant. In a recent systematic review, researchers identified 28 studies from LMICs in which they reported on 18 different screening tools used to assess children for ASD. None of the included studies in that review specifically focused on preterm infants. Given that approximately 90% of preterm deliveries occur in LMICs, and the survival of preterm infants in those countries is increasing rapidly, the number of children who will need assessment and management of ASD is expected to rise in the coming years. Hence, the implementation of optimal strategies in LMICs is urgently needed [14]. Certain findings indicate that the risk of autism spectrum disorder increases after prenatal exposure to pesticides or chemical substances within 2000 meters of their mother's residence during pregnancy, in comparison to the offspring of women from the same agricultural region without such exposure [15]. In our study, it was observed that mothers with anemia during pregnancy (OR=3.93, CI= 2.18-7.19, P value= 0.039) had a 3.93% higher chance of having a child with ASD compared to women without anemia. Similarly, women with a history of prolonged labor also showed significance (OR=3.46, CI=2.76-10.80, P value=0.0491) as significant variables. In another case-control study, a comparison was made with infants born at term, revealing that the unadjusted odds ratios (ORs) for autistic disorders among very and moderately preterm infants were 2.05 and 1.55, respectively. After controlling for maternal, pregnancy, and birth characteristics, the ORs were reduced to 1.48 and 1.33, respectively. It was observed that the increased risk of autistic disorders related to preterm birth is primarily mediated by prenatal and neonatal complications that occur more commonly among preterm infants [16,17]. In this current study, a strong association was found between prematurity (P<0.001) and low birth weight (P<0.01) with autism spectrum disorder (ASD) [2]. As a next step for research, enhancing the understanding of brain development in late preterm infants may further improve our understanding of outcomes for individuals with ASD.

Limitation of the study:

This study was conducted at a single center with a relatively small sample size. Additionally, the study had a relatively short duration. Therefore, it's important to note that the findings of this study may not be fully representative of the broader population and should be interpreted within the context of these limitations.

V. CONCLUSION & RECOMMENDATION

Determining the precise cause of autism spectrum disorder (ASD) in children is challenging due to its multifactorial nature. Factors that may contribute to ASD include genetics, metabolic and neurological factors, certain infections, and prenatal and birth-related issues. Detecting these risk factors can serve as early warning signs, facilitating early ASD diagnosis through screening tests. After adjusting for various factors, our findings concluded a significant relationship between premature birth and ASD, even though in unadjusted analysis, the relationship was nearly significant. Additionally, the study suggests that factors like birth weight, parental age, family income, and child's age may influence the risk of ASD. Further research is required to better comprehend the intricate interplay of environmental, obstetric, and genetic elements contributing to ASD's etiology in Bangladesh. It is crucial for public health agencies and relevant organizations to promote ASD awareness programs, plan for children's future opportunities, and provide necessary services with the support of the government and non-governmental organizations (NGOs). This study can assist policymakers and administrators in understanding the status of children with ASD in comparison to their neurotypical peers and contribute to developing strategies for enhancing the health and well-being of children with ASD.

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