Perinatal and background

by Desiyani Nani

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Perinatal and background risk factors for children with autism spectrum disorder in Indonesia

Desiyani Nani[1]*, Ahmad Hamim Sadewa[2], Sri Hartini[2], Elisabeth Siti Herini[2]

[1]Nursing Program, Faculty of Health Sciences, Universitas Jenderal Soedirman, Purwokerto, Indonesia;[2]Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

ABSTRACT

Background: Indonesia has experienced an increased number of children with autism spectrum disorder (ASD). One of the challenges that Indonesia currently faces is how to reduce the perinatal and risk factors related with the incidence of autism. This study aimed to identify the perinatal and risk factors contributing to ASD.

Methods: This research was a case control study involving 52 children with ASD in the case group and 201 normal children in the control group in Banyumas district, Province of Central Java, Indonesia. Data collection used independently completed questionnaires, concerning perinatal factors such as maternal age at birthing, gestational age, labor method, fetus presentation in labor, and history of complications during labor.

Results: Stepwise logistic regression analysis indicated a higher risk of preterm gestational age among children in the ASD group with p=0.019 and OR:5.883. Abnormal delivery methods such as caesarean delivery or vacuum extraction also had association with the ASD group (p=0.001; OR=0.303). Abnormal fetus presentation during labor increased the risk of ASD (p=0.004; OR:6.908). Mother with complication during labor such as difficult labor, preeclampsia, and fetal distress correlated with ASD (p=0,.021; OR:2.101). Multivariate analysis also showed complications during labor became a risk factor for ASD (OR: 2.142 (1.904-4.196). There was no correlation between maternal age below 20 years (p=0.332; OR=1.871) or 31-40 years (p=0.115; OR=2.868) with ASD.

Conclusion: Labor method, fetus presentation, and complication during labor were significantly related with ASD.

Keywords: *Perinatal, labor, fetus, ASD, risk factors*

***Corresponding author:**

Desiyani Nani
Nursing Program,
Faculty of Health Sciences,
University of Jenderal Soedirman
Purwokerto, Central Java, Indonesia
Phone number.: +62-(281) 642838
Mobile: (+6281392021989)
Email: desiyani.fahrudin@gmail.com

INTRODUCTION

Autism Spectrum Disorder (ASD) is a type of neurodevelopmental disorder. ASD presents with a range of severity and impairments in social, communication skill, and behaviors[1] . Based on epidemiological data, it is estimated that the global prevalence of ASD is more than 7.6 million persons with various disabilities and has become 0.3% of the global burden of disease[2]. In many developing countries such as Indonesia, ASD receives little attention and this lack results in fewer available studies about ASD[2,3]. Consequently, Indonesia also has no current data about the exact national or provincial prevalence of ASD.

The cause of ASD is still unknown. A recent study showed that genetics account for only 35-40% of the contributing factors. The remaining 60-65% are likely due to a multi-factorial combination, involving prenatal, perinatal, and postnatal environmental factors. In a previous study, perinatal factors such as acute fetal distress, prematurity, exceeding the term, and difficult labor were found to be the most affecting factors in ASD[4]. Considering the potential risk about perinatal factors, we used a case control study to investigate the association between perinatal factors and ASD.

METHOD

Research design: This case control study was conducted in a community in Banyumas District, Province Central Java, Indonesia. It was conducted over a period of four months from October 2017 to January 2018.

Population and samples: The sample included 253 children in Banyumas District, Province of Central Java, Indonesia. The sample population was divided into case group and control group. The case group was composed of 52 autistic children previously identified by psychologists in the Banyumas Autism Care Project (BACP) event. The control group was composed of 201 normal children. Inclusion criteria were children with age between 3-18 years old and willing to be a respondent with parental approval. Whereas, exclusion criteria were children with known neurogenetic conditions such as Down Syndrome, Mental Retardation, and Neurofibromatosis.

Sample size: Using sex differences between ASD within boys and girls as a risk factor and aiming to detect an odds ratio (OR) of at least 2 with a power of 80% using a 5% level of significance, the recommended sample size was calculated to be 58 cases and 58 controls.

Sample type and selection: Consecutive cases were selected over 4 months, during which time every weekend was allocated to visit the school of special needs children. We invited parents who have children with ASD and independently confirmed their approval by completing the informed consent form to permit their children to become participants for this study. The location for sampling was in the Research Center of the Faculty of Medicine, Universitas Jenderal Soedirman, Banyumas District, Central Java Province, Indonesia. Controls were selected from normal children who came with their parents and also were visited by the research team at local schools, until the required sample size was reached.

Instruments: This study used a demographic tool with questions about perinatal history. It consisted of five questions about Maternal Age at Birthing, Gestational Age, Labor Method, Fetus Presentation in Labor, and Complications during labor.

Data collection: Data were collected from parents of children ages 2-18 years old who were currently diagnosed using DSM 4 and DSM 5 by professional practitioners and then grouped in the case group (children with ASD) and the control group (children in normal state) during a four month study period using an independently completed questionnaire consisting of demographic factors and risk factors for ASD.

Statistical Analysis: Analysis were first done to describe the data and then to describe the trends resulting from each item. Bivariate analysis used Chi-square to explore relationships between variables. This study also used logistic regression for multivariate analysis to determine the most affecting factors in ASD.

RESULTS

Two hundred and three respondents participated in this study. Maternal Age at Birthing, Gestational Age, Labor Method, Fetus Presentation in Labor, and Complications during labor together with the frequencies and presentation, P values and OR are shown in Table 1.

Table 1. Result of Risk Factors of ASD

Variable	Case Group (n = 52)		Control Group (n = 201)		*P*	OR	CI 95%	
	n	%	n	%			Min	Max
Maternal Age at Birthing (years)								
<20	3	1.18	24	9.48	0.332	1.871	0.527	6.639
20-30	29	11.47	124	49.01		ref		
31-40	19	7.51	53	20.96	0.115	2.868	0.774	10.625
>40	1	0.39	0		-	-	-	-
Gestational Age								
Preterm (<37 weeks)	10	3.95	12	4.74	0.019	5.883	1.338	25.429
At term (38-39 weeks)	39	15.41	168	66.41		ref		
Postterm (>39 weeks)	3	1.18	21	8.31	0.450	1.625	0.461	5.722
Labor method								
Abnormal (caesarean, vacuum, etc.)	15	5.92	22	8.69	0.001	0.303	0.144	0.639
Normal	37	14.63	179	70.76		ref		
Fetus Presentation during Labor								
Other	7	2.77	5	1.98	0.004	6.098	1.850	20.094
Occipital Presentation	45	17.78	196	77.47		ref		
Complications during labor								
Present	21	8.31	49	19.36	0.021	2.101	1.107	3.988
Not Present	31	12.25	152	60.08		ref		

Table 1 shows the the distribution of perinatal factors and relationship with ASD. Gestational age, labor method, fetus presentation in labor, and complications during labor were significantly correlated with ASD ($p<0.05$). Mother with preterm gestational age <37 weeks (OR: 5.883), fetus presentation (OR: 6.098), and complications during labor (OR: 2.101) had significantly increased risk for children with ASD. Meanwhile, abnormal labor method had a significant association with ASD, but it had a low relative risk (OR: 0.303). On the other hand, maternal age at birthing was not related significantly with ASD ($p>0.05$).

Table 2. Final Result of Multivariate Analysis

Variable	S.E.	Sig.	OR	CI 95%	
				Min	Max
Labor Method	0.430	0.081	0.472	0.203	1.096
Fetus Presentation in Labor	0.680	0.027	4.487	1.183	17.020
Complication during labor	0.343	0.026	2.142	1.094	4.196

Table 2 shows the final result of multivariate analysis with logistic regression. Gestational age was excluded from the multivariate final result because it had a *p*-value more than 0.05. These result show fetus presentation in labor and complication during labor were the most affecting perinatal factors of ASD with OR: 4.487 and OR: 2.142.

DISCUSSION

For the Indonesian population sample, the most common perinatal risk factors related with incidence of ASD were preterm gestational age, abnormal labor method, abnormal fetus presentation in labor, and complications during labor with ASD. There were was no significant relationship between maternal age at birthing and ASD. This result was the same with a recent study that showed an association between prematurity with ASD in Denmark[5]. Another study found there was a strong relationship between delivery circumstances such as labor method and fetus presentation with ASD in China[6]. A meta-analysis study also showed that history of complications such as difficult labor, preeclampsia, fetal distress, and other delivery problems significantly related with ASD[7]. Similar to this study, recent research found there was no relationship between maternal age at birthing with ASD[8].

Infants with premature gestation get a high exposure to stressors during a critical period and it may affect the brain development. One study reported there were cerebellar lesions in preterm infants at risk of developing autism[9]. Preterm infants also had the largest gray matter cluster that included the left angular gyri and the heteromodal association region involved in complex language functions. This brain structure is known to be affected in ASD[10].

Abnormal labor method also had a relationship with ASD. Studies have shown a strong relationship between abnormal delivery method with ASD[11, 12, 13]. Labor methods such as vacuum extraction pose a potential harm such as brain injury. This brain injury could be a predisposing factor in ASD[14]. Anesthesia in the caesarian method is also known have a potential risk as a brain injury agent and could contribute to abnormality in neurodevelopment in ASD. Infants with caesarian birthing history have been shown to have a lower APGAR's score, which shows fetal distress syndrome could affect the an infant's neurodevelopment[15].

The next finding also showed that abnormal fetus presentation during labor increased the risk of ASD. Fetus presentation such as breech presentation is also known to be one of the risk factors for ASD. A fetus with breech presentation will experience a difficult labor and may need an abnormal delivery method such as caesarian that are also risk factors of ASD. Previous study also had found that abnormal fetus presentation was related with ASD[16]. One meta-analysis study had a similar result showing a strong relationship between

fetus presentation with ASD[7]. Accordingly, breech presentation is also known as one of the risk factor in ASD. Breech presentation will conduct a difficult labor and need an abnormal labor method like caesarian. Other presentations such as placenta previa position also are known to cause delayed brain development and are potential risks for ASD[1].

History of complications during labor also could become a potential risk factor for ASD. Complications such as difficult labor, preeclampsia, and fetal distress can make infants susceptible to experience stress[18]. Research in Australia found that complications during labor increased the risk of ASD[22]. Another retrospective-cohort study in USA also found a potential risk of ASD related to the history of complications of intrapartum conditions[19]. Circumstances during complications made infant more susceptible to get stress[18]. These stressful complications potentially can cause infants to aspirate fluids into the respiratory system. Then, this impaired respiratory status of the neonate infant could be altered causing the brain to only get a little oxygen. In a lower oxygen conditions, the brain could be damaged causing a neurodevelopment disorder such as ASD[20] .

Study Limitations

Perinatal factors could be significant risk predictors of ASD. However, this study had some limitation because further detailed explanation could not be given about the factors which potentially became a risk for ASD. Some factors need to be explained and examined more completely such as labor method, fetus presentation during labor, and history of complications during labor. It is considered important for further study to provide more detailed data to clearly determine the mechanisms and the effect of perinatal factors on ASD.

CONCLUSION

The perinatal risk factors for ASD included gestational age, labor method, fetus presentation in labor, and complications during labor.

This study highlights the importance of improving access to quality health services, with special care given to young mothers. Efforts in the future need to additionally focus on implementing preconception education and counseling programs to ensure more widespread pregnancy and delivery planning, which will help in improving maternal health and reducing the potential risks for autism spectrum disorder.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Ethical Clearance

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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