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History of Pregnancy and Birth of Children with Autism Syndrome Disorder (ASD)

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Abstract— Children with ASD have a form of social interaction disorder, have limited communication, and repeatedly fidget. In Indonesia, it is estimated ASD occurs in 1 in 88 children. This research aims to find out more about the correlation between the history of pregnancy, birth and baby characteristics, and children with ASD. Researchers analyzed 112 children with ASD below the age of 10 based on inclusive and exclusive criteria from 3 therapy centers, Bina Autis Mandiri, YPAC, and SDLB in October and November of 2017. The Case-Control method was used in this research. Samples of some ASD cases have been taken from a therapy center in Palembang recently. From 112 samples (35.7% girls, 64.3% boys), we can conclude that gender, mother's occupation, and race are factors of ASD ($p < 0.005$). History of pregnancy such as age during the marriage, bleeding, APGAR score, age during pregnancy, the weight of the newborn and history of the birth of twins. The factors that lead to the birth of children with ASD are the mother's age during the first pregnancy, bleeding, the birth process, age of pregnancy of the child with ASD, the weight of the newborn with ASD, APGAR score, and birth disorder. Having a checkup before pregnancy and antenatal care are some of the ways to prevent a child from getting ASD.

Keywords— History of pregnancy, birth and ASD (Autism Syndrome Disorder)

Introduction

The child's growth and development process determine the quality of the child. Growth and development experience a rapid increase at an early age, which is from 0 to 5 years and is often referred to as the "golden age" phase. The quality of a child in life independently and socially can be disrupted if the process of growth and development is not perfect.¹ One of disorders that can affect children's growth and development. Autism Spectrum Disorder (ASD) or Autistic Disorder (AD) in children⁴ is defined by the American Psychiatric Association (APA) in 2013 as a developmental disability or disorder characterized by social interaction disorders, verbal and nonverbal communication disorders and behavioral repetition.² Children with ASD experience impairments / disabilities in social interaction, limited communication, and repetition of behavior.³ Children with ASD are also more at risk for developing language disorders, ADHD, and cognitive delays than in the general population.⁴ The prevalence of autism is increasing from 3.3 case in 10,000 children in 1980s to 1 in 59 children in 2014 among US children.^{5,6} Although genetic factors are an important factor in the incidence of ASD, environmental factors are no less important in the incidence of ASD. Environmental factors play a role in the development of ASD such as the use of drugs during the prenatal period and maternal immunological influences such as the incidence of infection during pregnancy also influence the increased incidence of ASD in children.⁷ Early intervention is needed as it has the potential to reduce core and related ASD feature and may even allow children with ASD to catch up the development of their peers.^{2,8} According to data released by the Indonesian Central Agency² Statistics, the number of autistic disorders in Indonesia in 2010 is estimated to reach 2.4 million. In that year the population of Indonesia² reached 237.5 million people with a growth rate of 1.14%. The number of autistic disorders every year is estimated to increase by about 500 people each year, more men than women, with a ratio of 4: 1.3.⁹ Although ASD is not a disease that causes death, ASD is still a big problem because of its massive effects that affect children and their families now and in the future.

This applies specially to prevent the increasing number of cases of ASD. Another problem is treatment of children with ASD is also a challenge because there is a risk of complications due to higher sensitivity to

side effects of treatment.^{10,11} Based on these findings, the researchers aimed to look for risk factors and a history of pregnancy against ASD findings.

Subjects and Methods

The researchers used a case-control study to analyze data between children with ASD and children without ASD according to their mother's pregnancy and birth history. Researchers analyzed 112 children with ASD under the age of 10 years based on inclusive and exclusive criteria from 3 therapy centers, Bina Autis Mandiri, YPAC and SDLB in October and November 2017. Control was taken from children without ASD living in environments the same as children with ASD. All research samples live in Palembang. Research data were collected from secondary sources at the 3 therapy centers, including general characteristics, maternal characteristics, pregnancy history, birth complications and child characteristic data during infancy.

General Characteristics

The researcher collected data about the sample and the characteristics of the respondents namely the age of the child, the education of the respondent, work and race. Education of respondents is categorized into Elementary School, Middle School, High School and Bachelor. The mother occupations are categorized as housewives, civil servants, employees and entrepreneurs. Race includes Palembangnese, Batakese, Padangnese, Javanese and Chinese.

Risk Factor

Researchers chose respondents based on prenatal history, which included characteristics of maternal pregnancy and complications of childbirth as well as child characteristics during infancy.

Maternal Characteristics

Maternal characteristics include the age of the mother during labor, parity (number of children the mother gave birth to), history of smoking behavior during pregnancy (categorized as daily, not every day and not smoking).

Pregnancy and birth complication

The researchers collected data on diseases in pregnancy and birth complications, which included history of hypertension in pregnancy, history of diabetes before and after pregnancy, history of bleeding during labor, and birth process. (normal, use of equipment or sectio caesaria)

Child Characteristics during Infancy

Characteristics of the child during infancy include the duration of the pregnancy (calculated since the last menstruation), newborn body weight (in grams), APGAR score in the first 5 minutes and birth with a disability.

Statistical Analysis

Statistical analysis using SPSS version 22. Significance level: $p < 0.05$. The variable weight scale data categories were analyzed by the Chi-Square Method. The researcher will find out the difference in the mean of each variable for the ASD and non-ASD groups.

Result:

On Table 1, the majority of ASD are made up of male (64.3%) with a significance ($p < 0.05$) compared to children in the non ASD group. Employed mother related to ASD ($p < 0.05$) have similar proportion on ASD or non ASD (36%) more than on non ASD children group. Race has contributed to ASD ($p < 0.005$), with Chinese 33% and Palembangese 32.1% as shown in Table 1.

Table 1. General Characteristics

Characteristics	Case <i>n</i> = 112 (100%)	Control <i>n</i> = 112 (100%)	<i>p</i> value
<i>Sex</i>			
<i>Female</i>	40 (35.7)	41 (36.6)	0.004*
<i>Male</i>	72 (64.3)	71 (63.4)	
<i>Education</i>			
<i>Low</i>	11 (9.8)	20 (17.9)	0.567
<i>Middle</i>	62 (55.4)	69 (61.6)	
<i>High</i>	39 (34.8)	23 (20.5)	
<i>Mother's Occupation</i>			
<i>Housewife</i>	32 (28.6)	20 (17.9)	0.047*
<i>Government employees</i>	30 (26.8)	40 (35.7)	
<i>Private employees</i>	40 (35.7)	41 (36.6)	
<i>Entrepreneur</i>	10 (8.9)	11 (9.8)	
<i>Father's Occupation</i>			
<i>Government employees</i>	24 (21.4)	53 (47.3)	0.342
<i>Private employees</i>	45 (40.2)	50 (44.6)	
<i>Entrepreneur</i>	43 (38.4)	9 (8.1)	
<i>Race</i>			
<i>Palembang</i>	36 (32.1)	60 (53.6)	0.042*
<i>Batak</i>	5 (0.5)	5 (4.5)	
<i>Padang</i>	8 (0.7)	10 (8.9)	
<i>Jawa</i>	26 (2.3)	30 (26.8)	
<i>Cina</i>	37 (33.0)	7 (6.3)	

Table 2 shows result of bivariate analysis. Mother's age during pregnancy (≤ 19 years of age (64.7%) and ≥ 35 years of age (80%)), bleeding (66.7%) and history of twin birth has a risk of childbirth with ASD in 3 therapy centres in Palembang ($p < 0.05$). The delivery process, the duration of pregnancy, the newborn's weight, APGAR score and congenital disorder are the risk factors of a child with ASD in 3 therapy centres in Palembang ($p < 0.05$). Delivery process are differentiated by vaginal, vaginal with equipment assistance and Sectio Caesaria.

The proportion of a child with ASD from mother that deliver the baby with equipment are more than the proportion of a child without ASD (64.3%). The proportion of APGAR score between 0 to 6, the children with ASD have higher proportions compared to children without ASD.

Table 2. Mother's pregnancy and delivery history

Characteristics	Case <i>n</i> =112	Control <i>n</i> = 112	Total <i>n</i> =224	<i>p</i> value	Odd Ratio CI 95%
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<i>First Age of Pregnant (yr)</i>						
≤19	11 (64.7)	6 (35.3)	17	0.010	2.28 (0.81– 6.44)	
20 -34	81 (44.5)	101 (55.5)	182			
≥ 35	20 (80)	5 (20)	25	0.001	5 (1.79 – 14.4)	
<i>Parity</i>						
1	53 (57)	40 (43)	93	0.063	1.62 (1.09-3.25)	
2-3	50 (41.3)	71 (58.7)	121			
≥ 4	9 (90)	1 (10)	10	0.103	12.82 (1.56 – 100)	
<i>Smoking habits during pregnancy</i>						
Every day	69 (59.5)	47 (40.5)	116	0.230	2.64 (1.36 -5.11)	
Not everyday	20 (35.7)	36 (64.3)	56			
No smoking	23 (44.2)	29 (55.8)	52	0.401	1.42 (0.83 – 5.53)	
<i>Diabetes Mellitus</i>						
Yes	2 (333.3)	4 (66.7)	6			
No	110 (52.4)	108 (49.5)	218	0,091	1.88 (1.09-3.25)	
<i>Hypertension</i>						
Yes	25 (43.9)	32 (56.14)	57	0.109	2.14 (0.83-5.53)	
No	87 (52.1)	80 (47.9)	167			
<i>Bleeding during pregnancy</i>						
Yes	14 (66.7)	7 (33.3)	21	0.001	5.30 (0.255-11.02)	
No	98 (48.3)	105 (51.7)	203			
<i>The process of giving birth</i>						
Vaginal	47 (40.5)	69 (59.5)	116	0.003	2.28 (0.81– 6.44)	
Vacuum	36 (64.3)	20 (35.7)	56			
Sectio Caesaria	29 (55.8)	23 (44.2)	52	0.001	1.24 (0.83 – 5.53)	
<i>Age of pregnancy (weeks)</i>						
≤ 36	30 (73.1)	11 (64.7)	41	0.001	2.01 (1.36 -5.11)	
37 – 41	90 (52.6)	81 (44.5)	171			
≥ 42	2 (9.1)	20 (80)	22	0.044		
<i>Birth Weight</i>						
<2,500	52 (49.5)	53 (57)	105	0.001	1.23 (1.09-3.25)	
2,500 – 4.499	59 (54.1)	50 (41.3)	109			
>4,500	1 (10)	9 (90)	10	0.056		
<i>Apgar Score for 5 minutes</i>						
0-6	57 (93.4)	4 (6.6)	61	0.012	2.14 (0.83-5.53)	
7-10	46 (31.7)	99 (68.3)	145			
Unknown	9 (50)	9 (50)	18	0.104		
<i>Congenital abnormalities</i>						
Yes	30 (85.7)	5 (14.3)	35	0.000	1.30 (0.255-11.02)	
No	82 (43.4)	107 (56.6)	189			

Discussion:

Based on table 2, there is a significant relationship between maternal age at birth and the incidence of ASD in children. Maternal age ≥35 years may increase the risk of children diagnosed with ASD by 5 times compared to mothers aged 20-34 years. This finding is consistent with the results of previous studies by Cheng which stated there was a significant relationship between maternal age and ASD.¹² A meta-analysis in 2012 showed the significance of mothers with a minimum age of 35 years for the incidence of ASD with increasing maternal age.¹³ A 2017 meta-analysis showed the highest maternal age category was associated with an increased risk of ASD by 1.4 times higher.¹⁴ A cohort study of 30,000 children from 5 different countries in 2016 showed a significant relationship between maternal age and an increased risk of ASD.¹⁵

One explanation that can be given is that maternal age affects the increased presence of genomic alteration. Maternal age is an important factor in the aetiology of chromosomal anomalies and genomic modification. Another explanation is the effect of maternal age affecting epigenetic dysfunction. "Epigenetic" is the regulation of gene expression inherited but can be changed. Epigenetic dysfunction is related to various neuropsychiatric disorders and can affect the incidence of single-gene disorders. Advanced maternal age can also be associated with the accumulation of toxin exposure over the course of life causing genomic and/or epigenetic alterations of germ cells from older people. Toxins have shown the ability to damage DNA, cause cell mutations and have long-term developmental consequences. Increased maternal age can also be related to hormonal and endocrine factors, not only to age but also to maternal stress factors, which can increase the risk of infertility and the use of reproductive medicine.¹³

Gestational age has a significant relationship with the incidence of ASD where pregnancies <36 weeks of age are more than 2.01 times more likely to experience ASD than gestational ages above 37 weeks. This is consistent with the findings of Weisman and Yip who stated preterm birth as one of the risk factors for ASD.^{16,17} This result is also supported by meta-analysis in 2017 with similar research results.⁷ This fact can be caused by one of the causes of preterm birth is a fetal distress condition complication during pregnancy.¹²

There is a **significant relationship between birth weight and** the incidence of ASD. Children with birth weight <2,500 grams have a risk of 1.23 times higher to experience ASD than children with birth weight of 2,500 grams and above. This finding is in accordance with a meta-analysis by Modabbernia which shows LBW as a risk factor for ASD in children.⁸ Another study by Hisle-Gorman showed that LBW increased the risk of ASD by 1.23 times. These findings support the concept that an increase in the prevalence of ASD may partly be associated with an increase in the survival of babies born with LBW.¹⁸

Bleeding during pregnancy is significantly related to the incidence of ASD with a risk of occurrence 5.3 times higher than mothers without bleeding during pregnancy. This is consistent with Oerlemans' findings in 2016 which suggest bleeding in pregnancy was observed in the ASD group compared to controls.¹⁹ Malla in his research in 2017 also stated that there was an increase in the incidence of ASD in women who experience bleeding during pregnancy up to three times higher.²⁰ Another study that supports is a meta-analysis by Modabbernia in 2017 with similar results.⁸ Bleeding during pregnancy can be associated with the incidence of preterm birth.

There is a significant relationship between the process of giving birth and the incidence of ASD in children. This finding is supported by previous research which shows an increased risk of ASD by 1.26 times in children of mothers undergoing CS procedure.¹⁶ Other findings show a 36% increase in the risk of ASD after undergoing CS.⁷ These findings are associated with other complications during labor that can lead to fetal stress such as prematurity, prolonged labor, perinatal asphyxia and other findings that indicate emergency CS.¹²

Apgar score has a significant relationship to the incidence of ASD. Children born with an APGAR score of 0-6 are 2.14 times more likely to experience ASD than children born with an APGAR score above. Alibek's research findings in 2019 showed the same findings where the prevalence of asphyxia in the group of children with ASD was significantly higher than the normal group of children.²¹ Another findings stated that ASD was significantly associated with the incidence of asphyxia at birth and was associated with the incidence of complications during labor.^{18, 22} Other meta-analyzes prove the relationship between ASD and APGAR scores <6 and <7 at minute 1 and <7, <8 and <9 at minute 5.⁸ Anoxia caused by asphyxia at birth can cause excessive activation of the dopaminergic system and cause dopaminergic hyperactivity found in some children with ASD. Perinatal asphyxia can explain the tendency of men to experience ASD, because male babies are usually more likely to experience neurological dysfunction due to cerebral hypoxia than girls.²³

Congenital abnormalities have a significant effect on the incidence of ASD in children. Children with congenital abnormalities are 1.3 times more likely to develop ASD. Meta-analysis by modabbernia

successfully links congenital malformations to the incidence of ASD.⁸ another study by Rotem showed a significant association of specific congenital malformations namely cryptorchidism and hypospadias to the incidence of ASD with an increased risk of 1.55 and 1.65, respectively. This is supported by the theory that androgen has an influence on brain development in parts that are relevant to ASD, although the mechanism is not yet known with certainty.²⁴ Another finding by Danzer in his research in 2018 stated an increased risk of the incidence of ASD in children with congenital diaphragmatic hernias. This is supported by findings that suggest that central nervous system acquired and congenital malformations in children with congenital diaphragmatic hernias. Brain development in children with congenital diaphragmatic hernias is structurally delayed resulting in delayed maturation associated with neurocognitive function and language.²⁵

Conclusion:

There are 112 children with ASD as a sample, the majorities are boys, and their mother are employee and they are chinese and Palembangese. From 11 variables, 7 risk factor variables of ASD have correlated with mother's age during her first pregnancy, bleeding, delivery process, duration of pregnancy, newborn's weight, apgar score and congenital disorder. And next, thoroughly checkup before pregnancy and Antenatal Care are one of prevention way to avoid birth with ASD.

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