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ORIGINAL ARTICLE

DOES CIGARETTE SMOKE EXPOSURE ON PREGNANT WOMEN INCREASE THE RISK OF AUTISM SPECTRUM DISORDERS IN THEIR CHILDREN?

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ABSTRACT

The prevalence of autism spectrum disorder (ASD) has increased over the last three decades. Although genetic factors have a big contribution to ASD, environmental factors, prenatal, and postnatal factors were also found to be related. According to past literature, exposure to cigarette smoke during pregnancy raises the risk of behavioral problems in children, including ASD. The purpose of this study was to determine the relationship between maternal exposure to cigarettes during pregnancy and the risk of having a child with ASD in Indonesia. This is a case-control study that was conducted in Banyumas, Indonesia. The study consisted of 47 children with ASD as the case group and 195 healthy children as the control group. The Chi-Square test was used to evaluate the relationship between exposure to cigarettes and ASD. The findings showed that exposure to cigarette smoke from active or passive smokers during pregnancy was associated with the occurrence of ASD in children ($p < 0.05$). Exposure to cigarette smoke during pregnancy raises the risk of ASD in children. Therefore, nurses should provide adequate education to the community about the dangers of exposure to cigarette smoke during pregnancy and the risks for ASD in their children.

Keywords: ASD; cigarette smoke; pregnancy

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INTRODUCTION

Autism spectrum disorder (ASD) is a disability that is concerned with impairments in communication and social interaction, and repetitive behavior (*American Psychiatric Association*, 2013). It was estimated that 1 of 68 children diagnosed with ASD had a heritability presentation chance of 0.5-0.9%. Studies have shown that 881 genes, at least one of each chromosome, are factors that affect ASD (Butler, Rafi, & Manzardo, 2015). It was estimated 62/10 000 children were diagnosed with ASD around the world (Elsabbagh et al., 2012). There were 14.7/1000 children in the USA (CDC, 2014) and 27.2/10 000 children in Japan that were diagnosed with ASD (Honda, Shimizu, & Rutter, 2005). Meanwhile, in Indonesia, research about ASD prevalence is still limited. In 1992, it was reported that 12/10 000 children are diagnosed with ASD in Indonesia (Wignyosumarto, Mukhlas, & Shirataki, 1992). Based on the Indonesian Ministry of Education report in 2009, 638,000 children were diagnosed with ASD, and this statistic would rise 15% every year (Riany, Cuskelly, & Meredith, 2016).

Many clinical manifestations appear in children with ASD, especially problems in social and interaction skills, as well as repetitive behavior or interests. Some children with ASD would also show other characteristics such as delayed language and cognitive skills (CDC, 2021). The multiple clinical manifestations that are present in ASD make it challenging to study the etiology and genetic mechanism of ASD. Diagnostic and statistical manual of mental disorders (DSM-5) has categorized ASD based on clinical manifestations such as persistence deficit in social communication and repetitive behavior, interest, or activity patterns (American Psychiatric Association, 2013).

Multiple factors contribute to ASD such as genetic, environmental, pregnancy, and behavioral factors (CDC, 2020). One of the factors that are still being investigated as a risk factor of ASD is maternal smoking status during pregnancy. A previous study from howed that smoking causes several problems during pregnancy. Banyumas is the second highest region in terms of the number of active smokers in Central Java after Cilacap with 32.98% of the

productive age population being smokers (25-34 years old) (Statistics Indonesia, 2019).

Numerous studies have proven that smoking during pregnancy has caused several disorders such as preterm birth, low birth weight, altered cardiorespiratory responses, birth defects, and more (CDC, 2020); (Knopik, 2013); (Kataoka, Carvalheira, & Ferrari, 2018). Furthermore, past literature has also reported that mothers who were active or passive smokers during pregnancy are likely to have children with ASD (Johani, Mohamed, Abd Majid, Ibrahim, & Md Isa, 2020); (Kim et al., 2021). Conversely, studies from Norway and the UK have shown that there was no relationship between smoking status during pregnancy and ASD (Moylan et al., 2015); (Caramaschi et al., 2018). Therefore, this study investigated the relationship between maternal exposure to cigarettes during pregnancy and the risk of having children with ASD in Indonesia.

METHOD

Study Design

This is a quantitative analytical study with a case-control design.The case group consisted of children diagnosed with ASD, where the diagnoses were examined by psychologists and pediatricians that specialize in neurology and the diagnoses were made based on DSM V. Meanwhile, the control group was children in the healthy category that showed no signs of behavioral disorders or other mental disorders.

Sample

The researchers did not calculate the sample size and used a purposive and consecutive sampling method of sample selection because ASD is a rare case. The inclusion criteria were mothers who were willing to become respondents within February-June 2018.

In this study, the case group consisted of 47 children diagnosed with ASD and 195 healthy children as the control group. The study was conducted in the region of Ex Regency of Banyumas Residency, namely, Banyumas, Cilacap, Purbalingga, and Kebumen Regencies.

Data Collection

Consecutive sampling was used over 4 months to collect study samples. Parents who have children with ASD were invited to the Banyumas Autism Care Project (BACP) and were asked for their informed consent for their children to become participants. Control groups were selected from healthy children who came with their parents and through our team's visitation of local schools.

Instrument

Demographic data that was measured in this research were the children's sex, newborn weight, gestational age, maternal age, maternal and paternal education status, and maternal and paternal smoking status.

The variables were measured in a questionnaire that consisted of 10 questions, namely, the name of the child and parents, gender and age of the child, and the child's weight and gestational age at birth. The questions for the parents were the age of the mother, the last education of the father and mother, and the smoking status of the father and mother.

The risk category of maternal smoking status included mothers that are active and passive smokers. Active smokers are defined as individuals who would smoke one or more cigarettes per day during pregnancy, while passive smokers were defined as individuals with a household member that regularly smoked cigarettes in their presence or if a co-worker smoked in the same indoor room in their presence during pregnancy (Bonita, Duncan, Truelsen, Jackson, & Beaglehole, 1999).

Data Analysis

The data analysis was conducted by univariate and bivariate analysis. The univariate analysis of variables was presented by frequency and percentage of proportions. The bivariate analysis used the Chi-square test to explore correlations between variables.

Ethical Consideration

This study has been approved by the Faculty of Medicine, Public Health and Nursing Ethics Committee of Universitas Gadjah Mada with number: KE/FK/0686/EC/2017.

RESULTS

Description of Respondent Characteristics

The respondents in this study were 242 respondents that divided into two groups, namely, the case group (N = 47, 36 boys and 11 girls) and the control group (N = 195, 72 boys and 123 girls). Most children were of school age. Most of the fathers' highest education levels in the case group were university level, and in the control group were high school level. The majority of both groups' highest level of education for mothers was high school level. The social demographic data are shown in Table 1.

Table 1. Distribution of children's characteristics (n=242)

Variables		Case group (n = 47)		Control group (n = 195)	
		f	%	f	%
Gender	Boys	36	76.6	72	36.9
	Girls	11	23.4	123	63.1
Age	Toddler (2-3 years old)	2	4.3	20	10.3
	Preschool (4-6 years old)	10	21.3	74	37.9
	School age (7-12 years old)	21	44.7	79	40.5
	Teenagers (13-18 years old)	14	29.8	22	11.3
Fathers' highest education level	< Elementary school	0	0	67	34.4
	Junior high school	8	17.0	35	17.9
	High school	15	31.9	66	33.8
	University	24	51.1	26	13.3
Mothers' highest education level	< Elementary school	0	0	61	31.3
	Junior high school	6	12.8	42	21.5
	High school	21	44.7	69	35.4
	University	20	42.6	23	11.8

For measurement, we used data of the children's sex, newborn weight, gestational age, and maternal age. Based on the analysis of the frequency distribution of sex between the case and control groups, a significant difference was obtained, as indicated by the value of p = 0.00 (p < 0.05) with a value of OR = 5.6, which means that boys have a 5.6 times higher risk for ASD compared with girls. There was also no strong significant relationship between newborn weight, gestational age, and maternal age to ASD in this study. The data is shown in Table 2.

Table 2. Characteristics of children with and without ASD (n=242)

		Cases group (n = 47)		Control group (n = 195)		*p*	OR	CI 95%	
		f	%	f	%			Min	Max
Gender	Boy	36	76.6	72	36.9	0.00	5.6	2.68	11.66
	Girl	11	23.4	123	63.1				
Newborn weight	Risky (< 2500 gr/> 4000 gr)	5	10.6	11	5.6	0.206	1.99	0.66	6.04
	Not risky (> 2500 gr-4000 gr)	42	89.4	184	94.4				
Gestational age	Risky (preterm/post-term)	12	25.5	29	14.9	0.125	1.96	0.9	4.22
	Not risky (aterm)	35	74.5	166	85.1				
Maternal age	Risky (< 20 years old/> 35 years old)	9	19.1	31	15.9	0.75	1.25	0.55	2.85
	Not risky (20-35 years old)	38	80.9	164	84.1				

Table 3 shows the association between exposure to cigarette smoke (active and passive smokers) and ASD. It was found that maternal and paternal smoking status is related to ASD with a *p*-value = 0.003 and 0.00, and OR value = 0.33 and 1.02.

Table 3. Analysis of the association of exposure to cigarette smoke with ASD

		Case group (n = 47)		Control group (n = 195)		*p*	OR	CI 95%	
		f	%	f	%			Min	Max
Maternal smoking status	Risky	12	25.5	99	50.8	0.03	0.33	0.16	0.68
	Not risky	35	74.5	96	49.2				
Paternal smoking status	Risky	27	57.4	111	56.9	0.00	1.02	0.54	1.95
	Not risky	20	42.6	84	43.1				

DISCUSSION

The number of children with ASD has continuously risen over the years (Baio et al., 2018) due to various etiologies including genetic and environmental factors (Hallmayer, 2011 and Sandin et al., 2014). Past literature has found that problems during the prenatal period could cause ASD in children in later life (Ben-Ari, 2015); (Stoner et al., 2014); (Willsey et al., 2013). This study found that sex and exposure to cigarettes during pregnancy are related to ASD.

Based on this study's demographic data measurement, boys have a higher possibility of having ASD than girls. Research in Egypt has shown a similar result where as many as 82 children out of 100 respondents were boys with ASD (82%) (El-Baz, Ismael, & El-Din, 2011). Similarly, Mandy et al. (2012) had more boys with ASD (N = 273) than girls (N = 52) as their participants. Furthermore, a study in Indonesia by Aditya, Dahliana, Widodo, & Sekartini (2021) also reported that boys have a significant association with ASD. Thus, these studies suggest that neurodevelopmental disorders are more common in the male gender. The mechanisms underlying higher vulnerability in men are unknown and are still being studied. Current research in the field of biology is examining why autism and other neurodevelopmental disorders are more prevalent in the male sex.

ASD is a complex neurodevelopmental disorder with a male-to-female occurrence ratio of 4:1 (Lai, Lombardo, & Baron-Cohen, 2014); (Zhang et al., 2020). Some researchers found that genes and hormones are associated with this gender risk factor in ASD (Zhang et al., 2020). One reason why the prevalence of ASD in males appears to be higher than females is that the signs and symptoms of ASD are more visible in males than females. Males with ASD show more externalizing behavior problems than females, such as aggressive behavior, hyperactivity, reduced prosocial behavior, and increased repetitive/restricted behaviors and interests. Females with ASD show more internal and emotional symptoms, such as anxiety or depression. Thus, it has been easier for ASD to be detected in boys (Werling & Geschwind, 2013). However, this sex-specific risk factor mechanism of ASD is still being investigated.

This research found that mothers that were exposed to cigarette smoke during pregnancy had a relationship with ASD. Hertz-Picciotto et al. (2021) and Ehrenstein et al. (2021) stated that mothers who actively smoked more than 20 cigarettes per day during pregnancy have a higher chance of having children with ASD. A meta-analysis study also found that mothers who were passive smokers have a risk of having children with ASD (Johani et al., 2020). Moreover, some studies have announced that smoking during pregnancy could raise the risk of hyperactive behavior and emotional problems in children (Lin et al., 2017); (Poole-Di Salvo, Liu, Brenner, & Weitzman, 2010). Additionally, smoking increases the risk of spontaneous abortus, premature labor, low birth weight, immunity problems such as asthma and allergy,

learning problems, attention deficit disorders, and mental disorders in children (Kiechl-Kohlendorfer et al., 2010).

This study also found that paternal smoking status during pregnancy is related to ASD. To our best knowledge, there are still limited studies about the relationship between fathers' smoking status with ASD. A study from South Korea discovered that prenatal paternal smoking significantly increased the risk of having children with ASD (Kim et al., 2021). Research from Japan also found that paternal smoking was related to short birth length and small head circumference (Inoue et al., 2017). However, research from Taiwan reported that there was an insignificant relationship between paternal smoking with low birth weight, small size for gestational age, and preterm birth infants (Ko et al., 2014).

Although the mechanism of ASD is still unclear, some studies believed that it could happen because of genetic mutations and cigarette exposure during pregnancy. This is because maternal cigarette smoking could alter the equilibrium between the oxidant and antioxidant systems in the mothers' body. This in turn causes oxidative stress and augments lipid peroxidation, which results in free radicals in the body and affects fetus development (Mund, Louwen, Klingelhoefer, & Gerber, 2013). Furthermore, toxins from cigarettes could also alter gene expression during fetus development (Joubert et al., 2012). Nicotine in cigarettes is also well-known for affecting the brain and neurological functions of the fetus (Cope, 2015).

The mechanism for paternal smoking status on fetus development is also still unclear. We assume that smoking fathers cause mothers to become passive smokers. Cigarette smoke is known to be riskier for passive smokers because it can spread damaging chemicals and toxins to the environment (American Cancer Society, 2020). Therefore, cigarette smoke inhaled by pregnant women could negatively impact the pregnancy and alter the fetus' development. However, further studies are needed to investigate the mechanism between paternal smoking status and ASD.

CONCLUSION AND RECOMMENDATION

Gender and exposure to cigarettes during pregnancy are risk factors for the development of ASD in children. Boys have a 5.6 times higher risk for ASD than girls. Therefore, it is recommended for nurses to provide education to the community, especially to couples of childbearing age, about the dangers of exposure to cigarette smoke on fetal growth and development and risk for ASD.

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