

Prenatal, Perinatal, and Other Risk Factors of Attention-Deficit Hyperactivity Disorder in Soerojo Hospital

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ABSTRACT

Background: Long-term negative effects on academic ability and social activities can persist into adulthood in children with neurodevelopmental disorders characterized by inattention, hyperactivity, and impulsivity (Attention Deficit Hyperactivity Disorder/ ADHD). Genetic, neurotransmitter, neurological, environmental, psychosocial, brain trauma, and addictive factors are some of the predisposing factors for ADHD. But theoretically, maternal risk factors often contribute to neuropsychiatric disorders, because of their potential influence on child brain development. This study aimed to assess the proportion of maternal risk factors consisting of prenatal, perinatal, and other factors of ADHD in Soerojo Hospital.

Subjects and Method: A descriptive-analytic study with a retrospective approach was conducted on April-June 2022 at Soerojo Hospital. A total of 90 subjects pediatric patients diagnosed with ADHD selected by purposive sampling. The data were collected using questionnaires. The data were described in frequency (n) and percent (%).

Results: The proportion of prenatal risk factors are mother's age at pregnancy (19%), maternal disease history (8%), hormonal contraception pre-pregnancy (24%), maternal psychopathology (34%), maternal excess weight (49%); the proportion of perinatal risk factors are premature birth (12%), operative abdominal and vaginal delivery (49%), low birth weight (13%), neonatal emergencies (34%); while other factors are hereditary factors (13%), exposure to cigarettes (47%), and marital conditions (23%).

Conclusion: The most common maternal risk factors were maternal excess weight, operative abdominal and vaginal delivery, exposure to cigarettes, maternal psychopathology, and neonatal emergencies.

Keywords: ADHD, maternal risk factor, prenatal, perinatal.

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BACKGROUND

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder in childhood characterized by hyperactive,

inattentive, and impulsive behavior. This adversely affects academic ability, social activities, and others (American Psychiatric Association, 2013). Long-term negative

effects can persist into adulthood, approximately 50-60% of children with ADHD continue to exhibit sequelae and difficulties growing up (Juniar and Setiawati, 2014). Children with ADHD have difficulties in all aspects of their lives, including difficulties in learning, difficulties in social interaction, and emotional problems (Nurinawati et al., 2021).

There are several factors that predispose to ADHD such as genetic factors, neurotransmitters, neurologic, environmental, psycho-social, brain trauma, and addictive substances. However, there is no single risk factor that considered the main cause of ADHD in individuals, but theoretically, maternal risk factors are often a contributing factor to neuropsychiatric disorders, due to their potential influence on brain development (Faraone et al., 2015). Exposure to environmental factors may also moderate genetic factors in ADHD, therefore genetic factors contribute to susceptibility of ADHD individuals to exposure to environmental risk factors. The interaction of genetic and environmental factors also contributes to the risk of ADHD, although the mechanism for the interaction of these two factors is not known for certain (Setiawati, 2017). In most cases, genetic factors play a major role influencing ADHD. However, problems during pregnancy and childbirth may increase the risk of ADHD. In previous studies, maternal risk factors were shown to increase the incidence of ADHD such as exposure to cigarettes during pregnancy, alcohol consumption during pregnancy, obese pregnant women, Low Birth Weight (LBW), premature birth, low APGAR scores, and history of cesarean section (SC) (Adiputra et al., 2021).

The studies related to maternal risk factors in pediatric patients with ADHD in Indonesia are limited. Therefore, Soerojo Hospital as a center for mental health ser-

vices for children and adolescents is deemed necessary to take the initiative to conduct research on maternal risk factors in order to determine the proportion of risk factors in mothers of children with ADHD. This is considering that the number of visits by ADHD patients at Soerojo Hospital is quite large, as many as 1098 patients in 2020 and 996 patients in 2021. Based on these considerations, this research was conducted in order to become the basis for planning and implementing ADHD promotion and prevention programs, therefore treatment can be carried out immediately and prevent long-term negative impacts of ADHD.

SUBJECTS AND METHOD

1. Study Design

The research design is a descriptive-analytic study with a retrospective approach and was conducted using a questionnaire between April and June 2022 in Mental Health Installation for Child and Adolescent, Soerojo Hospital.

1. Population and Sample

The target population in this study were all children with ADHD at Mental Health Installation for Child and Adolescent. Meanwhile, the accessible population consisted of 116 ADHD child patients who were undergoing outpatient care at Mental Health Installation for Child and Adolescent from 1 January 2020 to 31 March 2022. A total of 90 samples were taken by purposive sampling technique and were selected with eligible criteria: 1) pediatric patients who met DSM V for ADHD (F.90); 2) recorded in Soerojo Hospital's medical record in 2020-2022; 3) The mother of ADHD children willing to be a subject was filled out an informed consent.

2. Study Variables

The dependent variables were maternal excess weight, maternal psychopathology, hormonal contraception, mother's age at pregnancy, maternal disease history, alcohol

consumption, operative abdominal and vaginal delivery, neonatal emergencies, low birth weight, premature birth, exposure to cigarettes, marital conditions and hereditary factors.

3. Operational Definition of Variables

All variables in this study are maternal risk factors, divided into prenatal, perinatal and other risk factors. The maternal risk factors for ADHD were seen before and during pregnancy until delivery. Therefore, it can be ascertained that each subject can have 1 or more ADHD risk factors.

Prenatal risk factors consist of 6 risk factors with operational definitions as follows: Maternal excess weight (Mothers with BMI in the category of overweight and obesity before and/during pregnancy and mothers with an increase in weight during pregnancy >15kg), Maternal psychopathology (Mothers had anxiety/depression during pregnancy), Hormonal contraception (Mothers used contraception pills/ injections/ implants/ hormonal IUDs), Mother's age at pregnancy (<20 years and >35 years), Maternal disease history (Mother has a history of seizures or hypertension), Alcohol consumption (Mother consumed alcohol during pregnancy)

Perinatal risk factors consist of 4 risk factors with operational definitions as follows: Operative abdominal and vaginal delivery (Mothers with history of SC, induced and vacuum labor), Neonatal emergencies (Born with respiratory disorders, has an infection, treated with antibiotics, treated in the Neonatal Intensive Care Unit (NICU)), Low birth weight (LBW) (<2500 grams), Premature birth (Gestational age less than 37 weeks).

Other risk factors consist of 3 variables with operational definitions as follows: Exposure to cigarettes (mother is an active or passive smoker/ exposed to cigarette smoke during pregnancy), marital conditions (mother with inharmonious marriage, uncom-

fortable living with parents in-laws, pregnancy out of wedlock and long distance marriage), hereditary factors (there is a heredity of ADHD from the mother's/ father's family).

4. Study Instruments

Data collected by questionnaire that consists of three sections. The first section contains of informed consent. In the second section, we collected subject's socio-demographic profiles. The last section is the main questionnaire contained questions regarding maternal risk factor of ADHD that was adapted and modified from previous research and was validated by the experts. This questionnaire was filled out by mothers of children with ADHD. The mother of ADHD children willing to be a subject was given a detailed explanation of this study and filled out an informed consent.

5. Data analysis

Univariate analysis was carried out on each variable in this study to determine the proportion of maternal risk factors. The data was presented in frequency (n) and percentage (%) using tables and figures. Therefore, the number of maternal risk factors for ADHD at Soerojo Hospital can be obtained. Based on the results of the proportions, the most common risk factors in mothers with children with ADHD will also be obtained.

6. Research Ethics

The research has followed ethical issues including informed consent, anonymity, and confidentiality that have been determined at the research site. This research has been approved by the Ethics Committee, Soerojo Hospital, Magelang, Indonesia, No:10/KEH-/III/2022 was issued on March 7, 2022.

RESULTS

1. Sample Characteristics

In this study, there are 90 subjects willing to participate. Table 1 shows the character-

istics of children with ADHD and Table 2 shows the characteristics of mother.

Table 1. Demographic Characteristics of ADHD Children

Characteristics	Frequency (n)	Percentage (%)
Age (years)		
<5	16	18
5-11	55	61
≥ 12	19	21
Gender		
Male	78	87
Female	12	13
Birth Order		
First Child	58	64
Second Child or more	32	36
Siblings		
No Siblings	26	29
Have 1 sibling	37	41
Have more than 1 sibling	27	30
ADHD Onset		
< 7 years (<i>Pre-school</i>)	80	89
≥ 7 years (<i>School</i>)	10	11

Table 2. Demographic Characteristics of Mother

Characteristics	Frequency (n)	Percentage (%)
Age (years)		
18-25	3	3
26-35	37	41
≥ 36	50	56
Occupation		
Civil servant	12	13
Private employees	20	22
Entrepreneur	9	10
Housewife	42	47
Others	7	8
Education Level		
Primary School	1	1
Junior High School	9	10
Senior High School	31	34
Diploma Degree	10	11
Bachelor Degree	30	33
Magister Degree	9	10

2. Maternal Risk Factors of ADHD

The risk factors identified in this study are consistent with earlier studies that have been linked to higher incidence of ADHD in children, especially in terms of the maternal risk factor. In this study, maternal risk factors were divided into prenatal, perinatal and other risk factors. The prenatal risk

factors are those potentially result in ADHD before conception and up to 20 weeks gestation. Meanwhile, perinatal risk factors are those potentially result in ADHD starting from 20 weeks of gestation to 28 days postpartum. In addition, other risk factors for ADHD including hereditary factors,

exposure to cigarettes, and marital conditions were also examined in this study.

a. Prenatal Risk Factors

The Prenatal risk factors in this study consist of mother's age at pregnancy, maternal disease history, alcohol consumption, hormonal contraception, maternal psychopathology, maternal excess weight.

The proportion of prenatal risk factors shown in figure 1. Based on these results, the most common prenatal risk factor is maternal excess weight (n= 44; 49%). Meanwhile, the least prenatal risk factor is alcohol consumption (n=0; 0%).

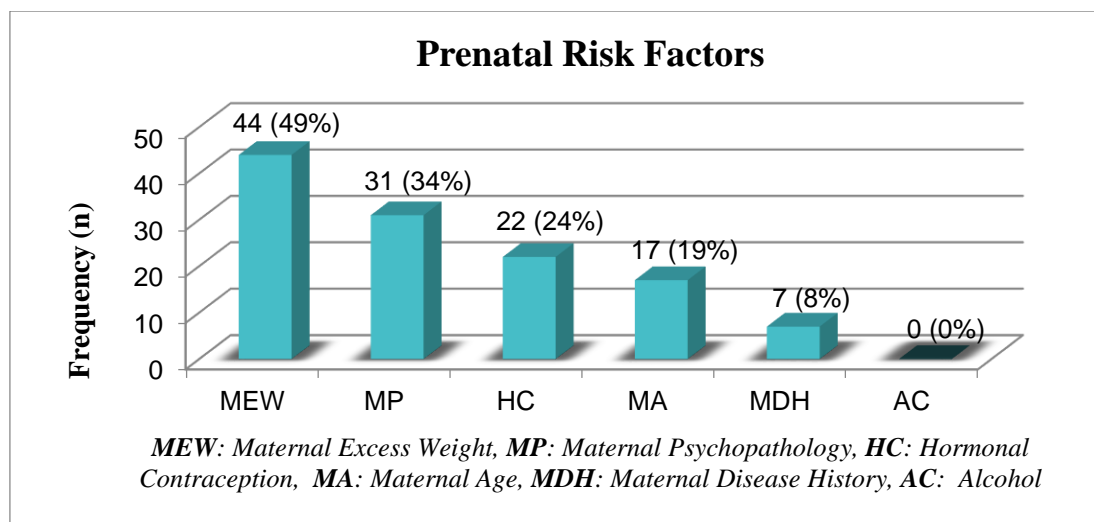


Figure 1. The proportion of prenatal risk factors

b. Perinatal Risk Factors

The perinatal risk factors consist of operative abdominal and vaginal delivery, neonatal emergencies, low birth weight, premature birth. Based on figure 2, the operative abdominal and vaginal delivery show the highest proportion (n=44;49%) compared to other perinatal factors. Meanwhile, premature birth (n=11;12%) is the least common risk factor.

c. Other Risk Factors

The other risk factors in this study consist of exposure to cigarettes, marital condition and hereditary factors. Based on figure 3, exposure to cigarettes during pregnancy is the highest percentage (47%) of other risk factors of ADHD.

3. Combination of maternal risk factors

Based on the results of the frequency distribution of maternal risk factors, data is obtained that there are risk factors that combine with each other. Therefore, subjects in this study may have one or more risk factors of ADHD. Table 3 shows the common combinations of maternal risk factors.

According to Table 3, the most combination of maternal ADHD risk factors is the combination of maternal excess weight and exposure to cigarette smoke (n= 22; 24%), followed by the combination of maternal excess weight and operative abdominal and vaginal delivery (n=20;22%) and the combination of marital conditions with maternal psychopathology (n=17;19%).

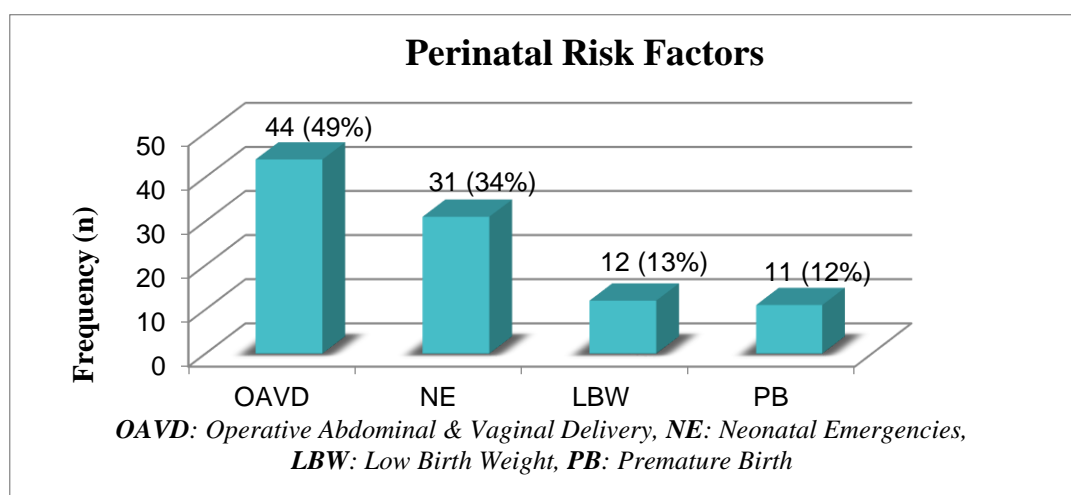


Figure 2. The proportion of perinatal risk factors

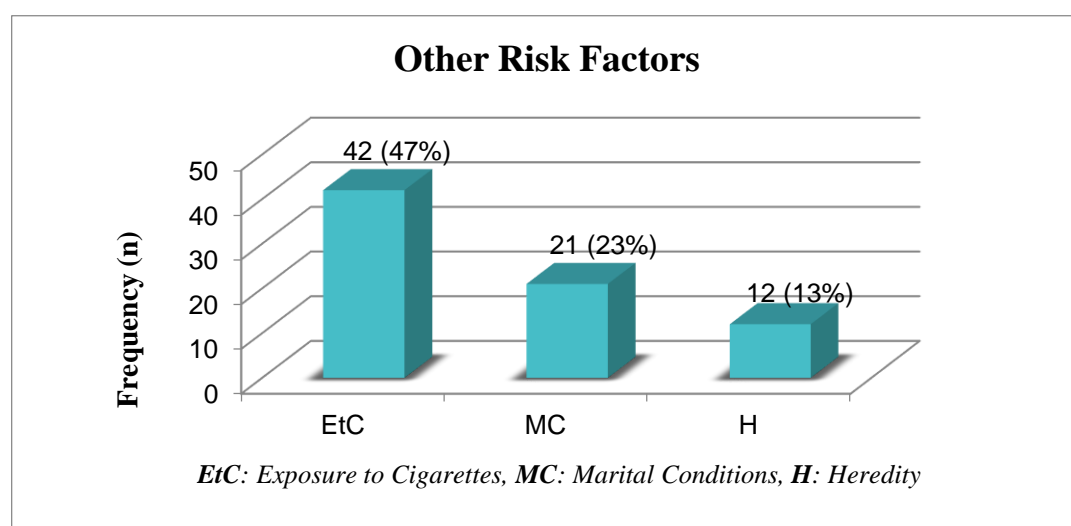


Figure 3. The proportion of other risk factors

Table 3. Combination of Maternal Risk Factors

Maternal Risk Factor	n	%
Maternal Excess Weight - Exposure to Cigarettes	22	24
Maternal Excess Weight - Operative Abdominal & Vaginal Delivery	20	22
Marital Conditions - Maternal Psychopathology	17	19
Maternal Excess Weight - Exposure to Cigarettes - Maternal Psychopathology	10	11
Marital Conditions - Maternal Psychopathology - Operative Abdominal & Vaginal Delivery	9	10
Maternal Excess Weight - Exposure to Cigarettes - Marital Conditions	8	9
Hormonal Contraception - Marital Conditions - Maternal Psychopathology - Operative Abdominal & Vaginal Delivery	3	3
Hormonal Contraception - Marital Conditions - Maternal Psychopathology - Operative Abdominal & Vaginal Delivery - LBW	2	2
Hormonal Contraception - Marital Conditions - Maternal Psychopathology - Operative Abdominal & Vaginal Delivery - Neonatal Emergencies	2	2

DISCUSSION

In this study, maternal excess weight is the most common prenatal risk factor, it was identified from the Body Mass Index (BMI) and maternal weight gain before and during pregnancy. Similar results were also obtained in a large cohort study of more than 12,000 children reported higher ADHD symptom scores in children aged 7-8 years born to mothers with both high pre-pregnancy BMI and excess gestational weight gain. Nutrient intake during developmental phase in the uterus influence epigenetic regulation, whereby maternal obesity affects the cognition and mental health of offspring. Among the classical epigenetic mechanisms, DNA methylation is the most interesting process to analyze. This is because levels of folic acid, a cofactor in the production of principal methyl donor methionine, are reduced in amniotic fluid of obese pregnant women. Offspring exposed the high-fat diet early in life can also reverse deficits in attentive behavior and motivation of adolescents regarding methyl supplementation in utero (Contu and Hawkes, 2017).

Based on the results in this study, maternal psychopathological is the second most common risk factor. There are 31 mothers (34%) had a history of mild anxiety/depression during pregnancy and did not take treatment. The majority of mothers stated that psychological disorders appeared in their first pregnancy in the first trimester. In addition, it turns out that mothers with mild anxiety/ depression had pressure during the pregnancy phase, such as lack of family support, husband's financial condition, and long-distance marriage. Maternal stress during pregnancy has an impact on the symptoms of ADHD that appear in their children (Grizenko et al., 2015). The Hypothalamus Pituitary Adrenal (HPA) axis which regulates the stress response in the offspring will be reprogrammed when the mother is

stressed. Thus, exposure to prenatal stress have impact on brain function of the offspring and may increase susceptibility to ADHD due to epigenetic modifications and alteration of the HPA axis (Udagawa and Hino, 2016).

Although further research is still needed, there is a study that states the use of hormonal contraceptives before or during pregnancy can increase the risk of ADHD in their offspring, especially in the use of non-oral hormonal contraceptives (Hemmingsen et al., 2020). In this study, 22 mothers used hormonal contraception (birth control pills, injections, implants, IUDs) three months before pregnancy. Meanwhile, maternal use of hormonal contraceptives affects the neurodevelopment of offspring by inducing epigenetic changes during follicular phase and interfering with action of endogenous hormones that control reproductive function. This pattern of increased risk for her ADHD in offspring was consistently seen for all forms of contraception, oral and non-oral, combined, and noncombined hormonal contraceptives (Tiemeier, 2020).

In terms of mother's age at pregnancy from the results of our research, it is shown that the proportion of mothers aged >36 years is 19%, higher than the age of younger parents. Based on a previous study by Kyo-ung Min Kim (Kim et al., 2020), the young and old age of both parents was associated with ADHD in children. Therefore, not only at a young age but advanced age of parents also increase the risk of offspring with ADHD. Advanced maternal age is also implicated with the risk of neurodevelopmental disorders through unknown mechanisms (Merikangas et al., 2016).

These findings shows that 8% of subjects with maternal disease history. The history of maternal diseases found in this study were epilepsy and hypertension. Mothers with epilepsy and/ or hypertension before or

during pregnancy were more likely to have child with ADHD. Consuming valproic acid as an epilepsy treatment during pregnancy increased the risk of having a child with ADHD (Christensen et al., 2019). Children born to mothers with preeclampsia have changes in cerebral vascular and neural connectivity and are exposed to abnormal levels of pro- and anti-angiogenic factors in utero, endorsing a possible causal role for preeclampsia. However, because the definitive treatment for preeclampsia is delivery, it is also a major cause of premature birth, which may adversely affect neurodevelopment (Sun et al., 2020).

In this study, there were no mothers who consumed alcohol during pregnancy. However, there were 2 mothers who consumed alcohol before becoming pregnant. Meanwhile, previous research stated that ADHD in childhood is associated with mothers who consume alcohol during pregnancy (Han et al., 2015).

A total of 44 subjects had operative abdominal and vaginal delivery, 33 mothers had a history of cesarean delivery, 9 mothers with induced labor, and 2 mothers with vacuum delivery. Based on these results, induced labor is known more common in cases of ADHD (Sciberras et al., 2017). Compared to vaginal delivery, C-section have a higher risk of delivering a child with ADHD (Zhang, 2022). A study conducted by Amiri et al, stated the psychological impact of C-section on mothers can affect the attitudes and behavior of mothers in relation to their children, in turn resulting in increased expression of ADHD symptoms in their offspring (Amiri et al., 2012). However, in a number of studies, known that ADHD is more frequent in problematic or complicated birth history (Yüksel et al., 2021).

The next highest number of perinatal factors is neonatal emergencies. It was identified based on a history of asphyxia, infect-

ion, use of antibiotics and have treated in Neonatal Intensive Care Unit (NICU). Overall there were 31 (34%) subjects had these factors, 19 of them received treatment in the NICU, 14 children received antibiotics, 9 children had asphyxia, and 4 children were exposed to neonatal infection. A history of asphyxia is predicted to increase the risk factors for ADHD (Serati et al., 2017). Newborn exposure to infections and antibiotics also associated with an increased risk of ADHD (Lavebratt et al., 2019). In addition, there was a greater risk of ADHD in newborns receiving intensive care experienced disorders or complications such as chronic stress in the womb, respiratory disorders, hypoxia, injuries to the central nervous system, and others (Baboli et al., 2017; Kittler et al., 2013). These findings are in line with the statement of Serati (Serati et al., 2017) that currently, complications during the perinatal period have significant implications on child's physical and mental health. Perinatal complications represent an important, but a modifiable risk factor for the future development of ADHD. But the other research results are also contrasting for complications during perinatal period so further studies must confirm this finding.

These findings indicate that 13% of subjects have a history of LBW. Newborns that weigh less than 2500 grams are more vulnerable. This risk can further interact with other risks such as inappropriate parenting methods that can cause disorders in children such as ADHD (Nigg and Song, 2018). LBW that are less than 2500 grams increase the risk of ADHD compared to infants with birth weights of 2500 grams or more (Halmøy et al., 2012). Furthermore, based on figure 2, preterm birth was the least common perinatal factor. Of the total 90 subjects, only 11 subjects were born prematurely (less than 37 weeks gestation). Although the proportion is not large, it has

been explained that preterm birth has negative consequences on the brain maturation process and immaturity may produce neurologic consequences and disruption in cortical development and brain connectivity (Perapoch et al., 2021). Therefore, a history of preterm birth is a risk for children to have neurodevelopmental disorders such as ADHD. The findings in this study confirm the results of previous research that stated the factor of preterm birth could be one of the causes of the incidence of ADHD (Chu et al., 2012; Sciberras et al., 2017).

Exposure to cigarettes during pregnancy is one of the factors that increase the risk of disorders in the fetus. In this study, there were 42 subjects exposed to cigarette smoke, in terms of the mother's smoking habits or exposure to cigarette smoke from the surrounding environment. Although the results obtained from subjects at risk of this matter are passive smokers, exposure to tobacco smoke in the womb can cause metabolites from tobacco smoke to cross the placenta, exposing the fetus to 15% higher concentrations of nicotine than the mother. This can cause teratological effects directly on the developing fetal brain in utero and immediately after birth (He et al., 2020). Essentially, fetal exposure to nicotine is related to different behavioral and neurological outcomes such as cognitive disorders, ADHD, and other psychiatric disorders (Amiri et al., 2012).

On the marital conditions, 21 subjects had dissatisfaction in marital-relationship either with their partners or families, therefore it could affect the mother's stress during pregnancy which could be a risk for children experiencing ADHD. Pressures in marriage such as poverty, discrimination, substandard housing, overcrowded households, and family turmoil can cause stress. Meanwhile, stress in pregnant women can have an impact on their child's neurobehavioral deve-

lopment through activation of the hypothalamus-pituitary-adrenal (HPA) axis (Okano et al., 2019).

Genetic factors are known to play an important role in occurrence of ADHD. It is explained that there can be no doubt that DNA variants in genes or regulatory regions increase the risk for ADHD. Regarding family history, it has been shown that ADHD is a polygenic disorder that can be inherited or hereditary (Faraone and Larsson, 2019). However, genetic factors are not the only major cause of ADHD. In this study, we did not prove the DNA variation, but we reviewed the history of ADHD in previous generations and there were 12 subjects stated that there were families of subjects that had a history of ADHD, both those had been diagnosed by a doctor, or only known from the symptoms that appeared.

Based on the results and discussion, this study concludes that the five most common maternal risk factors for ADHD are maternal excess weight (prenatal); operative abdominal and vaginal delivery (perinatal); exposure to cigarettes (other risk factors); maternal psychopathology (prenatal); and neonatal emergencies (perinatal). Most of the subjects had a high pre-pregnancy BMI and excess gestational weight gain, history of C-section, passive smokers, had moderate anxiety/ depression, and have received treatment in NICU. There is no subject that has a single ADHD risk factor. Although the proportion of other risk factors is small, previous studies has revealed that each of these factors is associated with ADHD. Therefore, we emphasize that this study did not examine the factors that influence ADHD. However, it examines the proportion of ADHD risk factors at Soerojo Hospital that were seen before and during pregnancy until delivery in mother with ADHD children. Accordingly that limitation of this study, further research is recommended to

involve non-ADHD children to prove the relationship between maternal risk factors and determine the most influential maternal risk factor for ADHD.

AUTHOR CONTRIBUTION

In this research, Doddy Sutanto and Susi Rutmalem Bangun collaborated to develop a conceptual framework, research methodology, and final approval of the research document. Doddy Sutanto and Ery Surya Sevriana collaborated on data interpretation. Rayi Citra Ayu Pangestuti and Yumna Nur Millati Hanifa collaborated to analyze the data. Ery Surya Sevriana, Rayi Citra Ayu Pangestuti and Yumna Nur Millati Hanifa collaborated to collect data, drafting the article and revising it critically.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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