Advances in Health Sciences Research, volume 31
Proceedings of the 1st International Scientific Meeting on Public Health and Sports (ISMOPHS 2019)

Prenatal Risk Factors and Autism Incidence in Malang City, Indonesia

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ABSTRACT
The purpose of this study is to understand the relationship of prenatal factors on the risk of an autism incidence in Malang City. This is an unmatched case- control study design which is used in multivariate analysis. The case group consisted of 35 mothers of affected children in Autism Service Center (ASC) Malang selected using a total sampling while the control group consisted of 35 mothers of normally developing children from Universitas Negeri Malang Laboratory Elementary School selected using a quota sampling. The prenatal risk factors data were collected using a questionnaire and analyzed by a binary logistic regression. The results showed that the trimester of having any prenatal complication, prenatal period, smoker/s in the house during pregnancy, and maternal age were all giving effects about 59,9% of autism occurrences. Based on this research, women in their pregnancy period should be more cautious in their first trimester of pregnancy.

Keywords: *Autism risks, Prenatal risk factors, Neurodevelopmental disorders.*

1. INTRODUCTION

Autism is a brain developmental disorder that emerges as a behavioural disorder on social interaction, communication, or the use of both verbal and nonverbal language, as well as there is a very limited behavioural pattern, activities, and interest on a subject specifically and repeatedly [1]. A person with autism can show symptoms from mild to severe and can be identified since two years old (Blumberg, S. J. et.al., 2013:1). In several countries, autism has been considered as a development disorder that needs to be aware of due to the increasing number of the prevalence. Based on the report from the national survey of CDC (Center of Disease Control and Prevention) in 2011-2012, the prevalence of autism on 6-17 years old children was 2% (1 per 50 children) and significantly greater than the prevalence in 2007 in the same age group (1,16% or 1 per 86 children) (Blumberg, S. J. et.al., 2013:2). A systematic review of the prevalence of autism on various parts of the world such as Europe, America, Western Pacific Region, South East Asia, Mediterranean, and Africa. In 2000-2012, the prevalence of autism reached 0,62% [2]. Unfortunately, in Indonesia autism is still considered rare because screening and surveillance of this disease have not been carried out, causing a lack of official data on the number of autism sufferers in Indonesia. Even though accurate and official data has not been found, it is estimated that the number of people with autism has also increased as in other countries. In 2000, it was estimated that autism in Indonesia was 1 per 500 children, then increased in 2010 to 1 per 300 children, and in 2015 it was estimated to have reached 1 per 250 children [3]. The Indonesian Ministry of Health reports that there are around 475,000 children in Indonesia who might be born with autism in 2009 (0.67%) and the Indonesian Ministry of Education also estimates that the prevalence of autistic children in Indonesia increases by around 15% annually, based on the number of children diagnosed with autism registered in special schools that also continue to increase every year [4]. Malang city is the first city that has the autism services center also recorded that there is an increased number of students annually around 4%-6% since established in 2012 [5].

The significant increase number of the prevalence of autism triggered the importance of immediate autism countermeasures. The most common countermeasure is the establishment of special schools for autism by the government as well as the guidance for the family

members of autistic sufferers. Autism is a brain disorder that occurs for life, therefore by knowing the cause of autism will greatly help the appropriate countermeasures so that the prevalence of autism can decline in the future.

Unfortunately, until now the main cause for the autism incidence cannot be determined. However, as a brain disorder that occurs since birth, the experts have long estimated that autism can occur since the pregnancy period, particularly at the brain formation. This is because the prenatal period (pregnancy) is a very important period in the formation of the fetal brain and is a vulnerable period for the fetus to experience autism. The various brain abnormalities found in autism suffer during the prenatal period [6]. Some previous studies on neuroanatomy also indicated that the biological process causes the emerge of autism begins in the fetal development period or during the prenatal [7]. In people with autism, disorders during the neurogenesis period (neuron formation), neural migration (neuron migration), and neural maturation (maturation of neurons) in the brain are common brain formation processes in the first semester of pregnancy [8].

Based on the aforementioned, the causes of autism are estimated to occur during the prenatal period. The genetic factors are thought to be the cause of the autism incidence and are influenced by three things, namely: (1) genetic abnormalities associated with the occurrence of autism such as fragile X syndrome or tuberous sclerosis, (2) heredity and (3) environmental factors such as exposure to hazardous chemicals, drugs, viruses and bacteria during the pregnancy (Yearwood, Pearson, Newland, 2012:240). In addition, research reveals that genetic factors which are affected by heredity and its relationship to other genetic disorders only describe 37% of the risk of autism, while environmental factors cause 55% of the risk of developing autism in children (Shaw, et al., 2014:4). Therefore, this research intended to investigate various prenatal factors causing autism in Malang city, mainly those from the environments such as prone to cigarette exposure, major pregnancy disorder, as well as other common factors which can be prevented.

2. METHOD

This study is an analytical descriptive research. The method used was an unmatched case-control study with the case and control ratio of 1:1.

The case population was the 41 mothers of the students enrolled in the Autism Services Center in Malang City, Indonesia in the second semester of the 2016/2017 academic year. Meanwhile, the control population was the 569 mothers of Universitas Negeri Malang Laboratory Elementary School in the second semester of the 2016/2017 academic year who do not encounter autism or have had a history of autism. Thus, the total population in this study was 610 people.

A large number of samples was calculated using Fleiss formula and generated a minimal number of samples of 25 people with P2 = 0,5 and OR = 6,33 [9]. Samples from the case group were selected using total sampling and those who were willing to sign the willingness to be the research respondents (informed consent). The exclusion criteria from the case group are that there are questions in the questionnaire that have not been answered and cannot be confirmed to the person concerned, for example, because the respondent is hesitant in answering, forgetting, or cannot be contacted. The final number of sample cases in this study was 35 people. While the sample from the control group was chosen by the quota sampling method following the number of samples from the case group and signing informed consent. Exclusion criteria from the control group were no return of the questionnaire to the researcher. The number of control samples was 35 people.

The data collection instrument in this research was a questionnaire consisting of 35 question items with various prenatal factors being tested. The questions in the questionnaire were developed based on those proposed in Autism Genetic Resource Exchange (AGRE) entitled “Temporality of Risk Factors and the Gender Differential Related to Autism Spectrum Disorder Diagnosis” [10] and the questions in the data recording of therapist participants of Malang City Autism Services Center in Indonesia were then adjusted to the objectives and conditions in this study. The test of content validity was done through a questionnaire study. While the construct validity test was done through an expert judgment (expert judgment) through the calculation of the CVR (Content Validity Ratio) and for three (3) experts, the minimum CVR value for each question is 1 [11] so that all questions in the questionnaire are stated as valid. The instrument reliability was conducted through retest test on the 10 research sample with 4 months of the interval after the research was conducted. This time interval was considered to have fulfilled the requirement, as well as the result of the reliability, is higher than the critical points ($df = 8$; $\alpha = 0,05$) which is 0,549, therefore the questionairre is considered as reliable [12].

The data collection began on January 18 2017 until February 28 2017. The questionnaires were distributed directly to the case group directly by the researchers, while the questionnaires were distributed to the control group by the school after being given guidance by the researcher.

After the data collection, data processing was carried out in the form of editing, coding, processing, and cleaning. Editing is checking the contents that have not been filled and the number of questionnaires distributed.

Coding for independent variables is coded 0 for no answer choices, while other choices are given codes 1, 2, 3 and so on according to the choice of answers. Whereas for the dependent variable, the control group is given code 0 and group case code 1.

The data analysis in this research used a computer program with the significant value of $p < 0.05$ through logistic regression method with backward Wald test..

3. RESULTS AND DISCUSSION

3.1. Respondents' Characteristics

Based on the conducted research on the 35 respondents from the case group and 35 respondents from the control group, the finding revealed as follows.

Table 1. The general characteristics of respondents.

Variable	Case		Control	
	n	%	n	%
Respondent's occupation:				
Housewife	21	60,00	13	37,14
Entrepreneur	9	25,71	2	5,71
Civil servant	4	11,43	15	42,86
Private employee	1	2,86	4	11,43
Doctor	0	0	1	2,86
Respondent's husband occupation:				
Civil servant	2	5,71	8	22,86
Entrepreneur	22	62,86	15	42,86
Private employee	8	22,86	7	20
Police/military forces	3	8,57	3	8,57
Doctor	0	0	2	5,71
Birth order of the child				
The 1st	19	54,3	15	42,9
The 2nd	11	31,4	12	34,3
The 3rd	5	14,3	8	22,9
Child's sex				
Male	26	74,29	18	51,43
Female	9	25,71	17	48,57

Based on Table 1, the majority of the respondents in the case group were housewives with the percentage of 60% (21 respondents). While in the control group, the majority of the respondents' occupation was the civil servant with 15 respondents (42, 86%). Based on the results of observations and interviews by researchers, this was due to the fact that the mothers of the case groups preferred not to work and to become housewives to take care of their sons/daughters better. As is known, a child with autism has unusual behavior and needs more attention when compared to other children who develop normally, especially these children have different behaviors and cannot be predicted, like suddenly hurting themselves, interested in dangerous things like fire, etc. [13].

The occupations of the respondents' husband show the economy level of the family and based on the research result, the type of husband' job in both groups have almost the same percentage except for the civil servant occupation which is more on the control group (22,86%) than on the case group (5,71%). There is no difference in the economic status showed that the control group in the economic status have described that the population in this research was taken and can decrease the bias in the selecting the research control. [14].

The sex in the case group is dominated by male children (74.29%), compared to the female children (25.71%) with the ratio of 3:1. While in the control group, the comparison between the number of boys and girls was almost 1:1. This is consistent with the prevalence data from a meta-analysis study, it was found that the ratio of autistic children of boys to girls varied between 1.33 to 16, with an average ratio of 4:1 [15].

There is a theory that girls with autism experience underdiagnosis or are less able to be diagnosed because of differences such as the presence of several symptoms of autism that are not found in girls such as hyperactivity and aggression, besides girls with autism who have High IQ (Intelligence Quotient) tends to have better language skills than boys with the same IQ [16].

Furthermore, on the case group, children with the first birth order have more frequency because indeed in a meta-analysis study found that autistic children tend to be the first child and have a higher risk of developing autism than children with the next birth sequences [17] This is still doubtful in its clinical relationship and is believed to be more due to the reluctance of parents to have subsequent children if they find out that their child has autism [18].

3.2. Volunteers organizing strategy

The followings are the research results on the prenatal factors:

Table 2. Gravidity, parity, and history of respondent' miscarriage

Variable	Case		Control		p-value	OR (95% CI)
	n	%	n	%		
Gravidity					0.227	0.74 (0.45-1.21)
1	9	25.7	5	14.3		
2	16	45.7	14	40.0		
3	6	17.1	12	34.3		
4	3	8.6	3	8.6		
5	1	2.9	1	2.9		
Parity					0.14	0.63 (0.34-1.16)
1	10	28.6	5	14.3		
2	17	48.6	16	45.7		
3	6	17.1	13	37.1		
4	2	5.7	1	2.9		
Miscarriage history					0.576	1.38
0	30	85.7	32	91.4		
1	4	11.4	2	5.7		
2	1	2.9	1	2.9		

*OR < 1 = Research variables become protective factors; OR > 1= Research variables become risk factors

As in Table 2, both on case group and control group, the majority of the gravidity was 2 with the percentage of 45.7% and 42.8% respectively. The majority of factors are 2 that can be influenced by several things, such as the existence of a Family Planning program which in this case the achievement of the number of active family planning providers in Malang in 2015 has increased compared to 2014, from 103,302 people to 104,436 people (public health office Malang City, 2015:33). The P-value was 0.227 thus the gravidity does not significantly influence the incidence of autism. Then, (number of pregnancy > 1) is the protective number on the autism incidence (OR = 0.737, 95% IK = 0.45-1.209), thus the primigravidity becomes the risk factor for autism. Primigravidity or first pregnancy (gravidity 1) is often associated with several complications of pregnancy such as preeclampsia [19] and anxiety in pregnancy [20]. Gravidity is rarely directly associated with autism, but gravidity is suspected to affect several pregnancy complications that are harmful to the fetus such as preeclampsia that affect the incidence of autism [21].

The highest number of parity based on Table 2 was 2 (48.6% on the case group and 45.7% on control group). Based on the results of the analysis, the amount of parity does not significantly affect the incidence of autism (p-value = 0.14). Parity also tends to be a protective factor for the occurrence of autism with OR =

0.63 (IK = 0.34-1.16). The amount of parity in this study can also draw on family planning programs and services that are already running well and skilled health workers, because there is no prevalence of grand multiparity (birth ≥ 5) so that the high parity value no longer becomes a risk factor for disorders in pregnancy, especially disorders of pregnancy that can cause autism [22].

The history of miscarriage does not significantly influence the risk of autism incidence. This is in line with the results of a study conducted on 40 studies of prenatal factors and the presence of a history of miscarriage did not significantly influence the incidence of autism [23]. However, the risk for someone who has experienced a one-time loss in a previous pregnancy to give birth to an autistic child is 1,383 times greater than someone who has never had a miscarriage and the risk increases comparably with the amount of miscarriage experienced previously

Table 3. Pregnancy disorders, clinical care and pregnancy trimester disorders

Variable	Case		Control		p-value	OR (95% CI)
	n	%	n	%		
Pregnancy disorders						
Bleeding	3	8.6	2	5.7	0.482	1.96 (0.3-12.7)
Excessive nausea	3	8.6	2	5.7	0.482	1.96 (0.30-12.7)
Infection diseases	4	11.4	0	0	0.999	uncountable
Others	2	5.7	1	2.9	0.445	2.61 (0.22-30.6)
Clinical Treatment						
Not seeing a doctor	2	16.7	0	0		
Outpatient with regular activity	2	16.7	2	40.0	0.860	1.2 (0.16-9.1)
Outpatients with bed rest	5	41.7	2	40.0	0.212	3 (0.53-16.8)
Inpatients	3	25.0	1	20,0	0,280	3,6 (0,3-36,8)
Disorder Trimester						
No disorder	21	60	29	82.9		
Trimester I	11	31.4	3	8.6	0.023*	5.06 (1.26-20.4)
Trimester II	1	2.9	1	2.9	0.823	1.38 (0.08-23.4)

Variable	Case		Control		p-value	OR (95% CI)
	n	%	n	%		
Trimester III	2	5.7	2	5.7	0.756	1.38 (0.18-10.6)

**the occurrence of pregnancy disorder on the Trimester I significantly influences the autism incidence (p-value < 0,05)*

***OR < 1 = research variable becomes protective factor OR > 1= research variable becomes risk factor*

Based on Table 3, the p-value for each pregnancy disorder valued > α thus the existence of the pregnancy disorder does not significantly influence the autism incidence. Other disorders (other than bleeding, excessive nausea, infection disease) during pregnancy are at 2.609 times the risk of suffering from autism. Excessive bleeding and nausea during pregnancy are at risk of being twice as large as to give birth to children with autism than those who do not experience pregnancy problems at all. The results of research on bleeding disorders in this study are inaccordance with research conducted by Burstyn et. al. that bleeding does not affect the incidence of autism [21]. However, some studies suggest that bleeding has a significant effect on the incidence of autism [24]. it can be caused by the influence of a different sampling method or study type. On the pregnancy disorder in the form of excessive nausea was also stated that it does not influence the autism incidence as aligned with the research by Lubis [25]. Infectious diseases in this study were not specifically mentioned, but based on research conducted by Zerbo, et.al. that there is an infection during pregnancy does not significantly influence the autism incidence, however the infection on the urinary tract infection during pregnancy risks in increasing the autism incidence [26].

The type of treatment during the pregnancy disorder does not influence significantly on the autism incidence, but the type of treatment used during the pregnancy disorder can increase the risk of autism incidence. Someone who had to be inpatients is around 3.6 times greater for giving birth to children with autism, while mothers who get total rest outpatients during pregnancy disorders have a three times risk of giving birth to autistic children compared to someone who does not undergo any treatment at all when a pregnancy disorder occurs. The level of clinical care, in this case, can indicate the severity of pregnancy complications indirectly. This is according to research done by Atladóttir, et. al. who stated that inpatient treatment does not influence the autism incidence [27].

Next, the occurrence of pregnancy disorders on the Trimester I influences significantly on autism incidence (p-value = 0.023) and a five-time increase in risk to give birth to children with autism compared to those who do not experience pregnancy disorders. The majority process of brain formation in the fetus is in the first trimester of pregnancy so that the occurrence of various disorders at that time will be able to affect the fetal brain development process [9]. This is in accordance with the results of research showing that the presence of disorders in the first trimester of pregnancy affects the incidence of autism. The results are basically also in line with several studies regarding the pregnancy disorders and autism, which suggest a viral infection in the first trimester of pregnancy [27] and the bleeding occurred i < 20 weeks of pregnancy will increase the risk of autism (RR = 1,34; IK 95% = 1,08-1,67) [21]. As well as a study that shows that excessive nausea during pregnancy (hyperemesis gravidarum) at week 1-8 of pregnancy is significantly associated with the development of brain disorders in the fetus that can be caused by abnormal hormone levels during fetal development, maternal stress, malnutrition and vitamin deficiency [28] and those can cause autism.

Table 4. Pregnancy period, birth method, and the existence of close relatives with brain development disorders

Variable	Case		Control		p-value	OR (95% CI)
	n	%	n	%		
Pregnancy period						
7 months	0	0	1	2.9	0.04*	
8 months	1	2.9	5	14.3		8.60 (1.11-66.8)
9 months	31	88.6	29	82.9		
10 months	3	5.7	0	0		
Birth Method						
Normal	22	62.8	22	62.8	1	1 (0.06-17.01)
Vacuum	1	2.9	1	2.9		1 (0.37-2.70)
Caesarean	12	34.3	12	34.3		1 (0.06-17.02)
Close Relatives with Brain Development Disorders						
None	30	85.7	35	100	0.54	
Present	5	14.3	0	0		Uncountable

*significant test results

Based on the research results, it can be seen that the pregnancy period can influence significantly on the autism incidence (p-value = 0,04) and can increase the risk of up to 8.6 times the risk of giving birth to children with autism at every increase pregnancy period. A study that examined the relationship between pregnancy and autism showed that a pregnancy period of 39-41 weeks increased the risk of autism. (95% IK, RR = 1.16) [29]. The fetus has an optimal growth period, which is about

9 months and in some references, it is known that more or less development from that period will risk bad effects on the body and risk giving birth to autism sufferers [30]. A fetus who has a shorter pregnancy period is at risk of suffering from many pregnancy disorders and the fetus will not develop optimally. However, fetuses who have a longer pregnancy period will also be more susceptible to various types of exposure because of the number of pregnancies, the risk of placental failure, and the increased likelihood of birth with assistance (cesarean section, vacuum, or forceps) [30]. The length of the pregnancy period can also indicate a delay in the process of developing the fetus (when compared to those that develop normally) that can begin at the beginning of the pregnancy and affect the process of brain development that should occur in the right time, such as the process of neuronal migration which if it occurs in an inappropriate time will cause a brain malformation that affects the cognitive abilities of the fetus [31].

The birth method does not significantly influence autism incidence (p-value = 1) and not give effects on the autism incidence (OR = 1). This result is in accordance with research which states that there is no relationship between birth methods and autism [32]. Basically, the birth method has a greater influence maternal morbidity than fetus conditions such as post-partum bleeding, trauma, and even significantly affects the risk of maternal death [33].

The results also showed that brain development disorders in close relatives had no influence the autism incidence, whereas OR could not be calculated because these variables were not found in the control group.

Table 5. Paternal and matetnal age

Variable	Case		Control		p- value	OR (95% CI)
	n	%	n	%		
Paternal age						
≤ 30 years old	13	37,1	13	37,1	1	
> 30 years old	22	62,9	22	62,9		1 (0,38-2,64)
Maternal age						
≤ 30 years old	24	68,6	5	14,3	<0,001*	
> 30 years old	11	31,4	30	85,7		0,08 (0,02-0,25)

*significant test results

Based on Table 5, the paternal age does not significantly influence the autism incidence, while the maternal age of > 30 years old significantly influence with OR = 0.076.

The maternal age on the case group is dominated by ≤ 30 years old (68,6%), while the control group is dominated by > 30years old (85,7%). The results also indicate that maternal age > 30 years is a protective factor for the occurrence of autism. The results of this study are in accordance with the results of the meta-analysis study which states that maternal age> 30 years is a protective factor of the incidence of autism [34]. However, the hypothesis which states that maternal and paternal age factors in the incidence of autism are influenced by the de novo mutation seems to have not been proven through this study. If indeed the de novo mutation is a major cause of an increased risk of the occurrence of autism (many gamete cell gene mutations that occur mostly at older age), then the older the age of the father and mother will increase the risk of autism, however, in this study and research conducted by Parner which states that the older the age of the father, mother, or both did not significantly influence the incidence of autism(Parner et. al., 2012:148).

In this research, it can be concluded that the existence of gene mutations in gamete cells is not a major cause of the increased risk of autism incidence. The existence of complications during pregnancy has a greater tendency to influence the increased risk of developing autism than the occurrence of gene mutation in father and mother gamete cells. This requires further research.

Table 6. Active and passive cigarette exposure during pregnancy

Variable	Case		Control		p-value	OR (95% CI)
	n	%	n	%		
Active cigarette Exposure						
Duration of smoking						
Not smoking	34	97.1	35	100	1	uncountable
Before pregnancy Trimester 1	1	2.9	0	0		
Smoking Frequency						
Not Smoking	34	97.1	35	100	1	uncountable
Not smoking daily	1	2.9	0	0		
Passive cigarette Exposure						
Number of people smoking in the house						
none	15	42.9	27	77.1	0.004 *	4,5 (1.6-12.7)
1-3 people	20	57.1	8	22.9		
Duration of exposure in the house						
none	15	42.9	27	77.1		
Not always in a day (occasional ly)	9	25.7	8	22.9	0.226	2.025 (0.646-6,348)
< 1 hour/day	4	11.4	0	0	0.999	uncountable
1-4 hour/day	7	20	0	0	0.999	
Number of smoker in the working place						
Not exposed	27	77.1	31	88,6		
1-3 people	6	17.1	2	5.7	0.149	3.444 (0.641-

Variable	Case		Control		p-value	OR (95% CI)
	n	%	n	%		
						18.508)
≥ 4 people	2	5.8	2	5.7	0.894	1.148 (0.151-8.714)
Duration of exposure in the working place						
Not exposed	27	77.1	31	88.6		
Occasionaly	2	5.7	2	5,7	0.894	1.148 (0.151-8.714)
< 1 hour/day	1	2.9	2	5.7	0.658	0.574 (0.049-6.688)
1-4 hours/day	4	11.4	0	0	0.999	uncountable
≥ 4 hours/day	1	2.9	0	0	1	
Passive smoking exposureplace						
Not exposed	14	40	25	71.4		
Only at working place	1	2.9	2	5.7	0.666	0.595 (0.056-6.278)
Only in the house	13	37.1	6	17,1	0.009*	5 (1.487-16.813)
Both	7	20	2	5,7	0.057	5.357 (0.951-30.184)

*significant test results

The active exposure of cigarette during pregnancy is very rare to find and only one respondent in the case group who smoke during the pregnancy, thus the analysis is not significant. The low number of sample who smoke in this study was basically more influenced by the presence of cultural factors in the study population who thought that women who smoked were not in accordance with social norms, so this caused the number of women who smoked was very low and women know better the fact that smoking will adversely affect the condition of the fetus they carry, this is the same as what happens in China because of the normal social and economic equality [36]. Regales the fact, based on meta-analysis it was found that there is less strong proof which connects the active exposure of cigarette [37].

Furthermore, the passive cigarette exposure was divided into the cigarette in the house and working place. There are 1-3 people who smoke in the house during pregnancy can increase the risk of autism significantly (p-value = 0.004) with OR of 4.5.While the length of exposure to cigarettes in the house has no significant effect on the autism incidence but is able to increase the risk of autism by two times of autism incidence. This is in accordance with the results of research conducted by Kin-sang who stated that the number of smokers in the house during pregnancy can significantly influence the risk of autism incidence (p-value = 0.022 and OR = 2.96), while the duration of the cigarette exposure daily does not affect significantly on the autism incidence (p-value > 0,05) but increases the risk of autism along with the increased duration of smoke exposure (OR > 1) [38]. The passive exposure of cigarette smoke contains hydrocarbon polycyclic aromatic, metal and hazardous chemical substance which are known to cause bad effects on health, and also cause hypoxia on the fetus and affect the fetus's brain development during the prenatal period [36].

The research results showed that the number of smokers in the working place does not affect significantly on the risk of autism influence (p-value > 0.05). However, this increases the risk of autism by 3.4 times with 1-3 smokers in the workplace and 1.148 times as many as 4 or more smokers. An anomaly is seen in the results of this analysis because based on the hypothesis, it should be the more exposure from smokers the higher the risk of autism. This can occur because of the space in the workplace, the distance between the smoker and the respondent, and the duration of cigarette exposure from each smoker who is not the same and has not been identified in this study. The exposure to cigarette smoke during pregnancy can increase levels of carboxyhemoglobin which causes decreased oxygen to the fetus and it is also possible to influence gene coding through DNA methylation or chromatin modification which can trigger autism [38]. Therefore, the existence of an anomaly in the research result was possibly caused by the low number of samples. Thus, to make sure the cigarette exposure in the working space on autism there needs a research with a greater number of samples.

The exposure of cigarettes in the working place can be seen based on the type of work during the pregnancy as explained in Table 7.

Table 7. Distribution of respondents' occupation during pregnancy

Variable	Case		Control		p-value	OR (95% CI)
	n	%	n	%		
Housewives	23	65.7	17	48.6		
Entrepreneur	6	17.1	3	8.6	0.615	1.48 (0.32-6.77)
Civil Servant	4	11.4	6	17.1	0.326	0.49 (0.12-2.02)
Private Employee	2	5.7	7	20	0.072	0.21 (0.04- 1.15)
Others	0	0	2	5.7	0.999	0

Based on the place of passive cigarette smoke exposure, it can be seen that the cigarette smoke in the house significantly affected on the autism incidence (p-

value = 0.009) and increased the risk of autism by 5 times (OR = 1.487-16.813) compared to those not exposed to cigarette smoke at all. While being exposed to a cigarette smoke at home and workplace is also able to increase the risk of autism by 5 to 30 times, even though it has no significant effect. When linked to the results in table 7, the majority of respondents who chose not to work during pregnancy (65.7% in the case group and 48.6% in the control group), showed that respondents would spend more time at home during pregnancy so causing exposure to cigarette smoke in the home more significantly influences the autism incidence. The results were in line with the survey result by Global Adult Tobacco Survey which shows that women in Indonesia are more exposed to cigarette smoke in the house rather than in workplace [39].

Then, the type of occupation during pregnancy indeed does not affect the autism incidence ($p > 0,05$), but working as an entrepreneur while pregnant increases the risk of autism 1.478 times compared to those who do not work while pregnant. This is in line with the results of a survey conducted on cigarette consumption in Indonesia which concluded that cigarette exposure in the workplace is more experienced by self-employed compared to civil servants and private employees [39]. Besides that, the civil servants and the private employees also tend to have a higher socio-economy status compared to the entrepreneur. Further research is needed to support such a statement.

Table 8. Analisis result of multivariate

Prenatal Factors	B	S.E.	Wald	*p-value* Wald	*Adjusted* OR (95% CI)
Maternal age > 30 years old	-0.23	0.067	11.647	0.001*	0,79 (0,69-0,91)
Number of smokers in the house during pregnancy 1-3 people	1.634	0.760	4.616	0.032*	5,12 (1,15-22,74)
Pregnancy disorder in the first trimester	3.069	1.164	6.955	0.008*	21,52 (2,20-210,5)
Passive exposure in the house only	-0.873	1.222	0.510	0.475	0,42 (0,04-4,59)
Period of pregnancy	2.587	1.137	5.177	0.023*	13.29 (1.43-123.49)
Constanta	16.957	10.099	2.819	0.093	

*significant results

Based on Table 8, it can be seen that it has been referred to various previous variables. There are four prenatal factors which significantly affect autism incidence, they are maternal age > 30 years old (adj. OR = 0.794), number of smokers in the house 1- 3 people (adj. OR = 5.123), disorder during the first trimester of pregnancy (adj. OR = 21.516), and pregnancy period (adj. OR = 13.294).

4. CONCLUSION

The occurrence of interference in the first tri-semester of the pregnancy increases the highest risk of autism incidence. Meanwhile, the maternal age > 30 becomes the protective factor in autism incidence. This further supports the conclusion that maternal age has more influence the incidence of autism because of the presence or absence of pregnancy complications when compared to de novo mutations. Pregnancy complications in the population of this study were more prevalent in mothers who experienced first pregnancy (primigravidity 1) at a young age, so the hypothesis that the older the maternal age the higher the risk of autism was rejected based on the results of this study. The pregnancy period and the cigarette smoke exposure in the house from 1-3 smokers during pregnancy also increases a fairly high risk of autism incidence, it is caused by the amount of exposure to hazardous substances for fetus are greater and longer.

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