



## Risk Factors of Autism Spectrum Disorder (ASD)

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### Abstract

There were 112,000 ASD sufferers in Indonesia in 2012 and in 2015 it was estimated that there were 1 per 250 children or 134,000 sufferers. The proportion of ASD was 62.8% and in 2016 it was 1.28 out of 1000 children in 2015. This study aimed to determine the risk factors for the incidence of ASD in Pontianak City. The research method was analytic observational with a control case study design. The sample was 70 people (35 cases and 35 controls) taken by purposive sampling technique. Data analysis used Chi-Square test ( $\alpha = 0,05$ ). The results showed that the factors associated with the incidence of ASD were father's age ( $p = 0,03$ ; OR = 4,00; CI = 1,250-12,804), stress history during pregnancy ( $p = 0,04$ ; OR = 3,18; CI = 1,13-8,93) and insufficient months of birth ( $p = 0,036$ ; OR = 4,88; CI = 1,22-19,4), while age of mother during pregnancy, passive smoker, antenatal hemorrhage and pregnancy interval were not associated with the incidence of ASD ( $p > 0,05$ ). The conclusion of this study is father's age, the presence of a history of stress during pregnancy and insufficient months of birth associated with the incidence of ASD.

### Abstrak

Autism Spectrum Disorder (ASD) dikenal sebagai triad of impairments yaitu adanya gangguan perkembangan pada aspek komunikasi, adanya perilaku yang diulang-ulang dan gangguan dalam berinteraksi dengan lingkungan. Pada tahun 2012 dilaporkan sebanyak 112.000 penderita ASD di Indonesia, tahun 2015 diperkirakan terdapat 1 per 250 anak atau 134.000 penderita. Data dari UPTD Autis Center Kota Pontianak tahun 2015 proporsi ASD sebesar 62,8% dan pada tahun 2016 sebesar 1,28 dari 1000 anak. Penelitian ini bertujuan untuk mengetahui faktor risiko kejadian ASD di Kota Pontianak. Metode penelitian adalah observasional analitik dengan desain studi kasus kontrol. Sampel penelitian berjumlah 70 orang (35 kasus dan 35 kontrol) yang diambil dengan teknik purposive sampling. Analisis data menggunakan uji Chi-Square ( $\alpha = 0,05$ ). Hasil penelitian menunjukkan faktor yang berhubungan dengan kejadian ASD adalah usia ayah ( $p = 0,03$ ; OR = 4,00; CI = 1,250-12,804), riwayat stres saat hamil ( $p = 0,04$ ; OR = 3,18; CI = 1,13-8,93) dan lahir belum cukup bulan ( $p = 0,036$ ; OR = 4,88; CI = 1,22-19,4), sedangkan usia ibu saat hamil, perokok pasif, perdarahan antenatal dan jarak kehamilan tidak berhubungan dengan kejadian ASD ( $p > 0,05$ ). Simpulan penelitian ini adalah faktor usia ayah, adanya riwayat stres saat hamil dan kelahiran belum cukup bulan berhubungan dengan kejadian ASD.

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## INTRODUCTION

Child growth and development occur from the prenatal period, the natal period until the child is born. The optimal period is influenced by various factors both internal and external so that in the process, the child is vulnerable to experiencing various health problems (Chamidah, 2009). One of them is the occurrence of developmental disorders in the brain which leads to obstruction of the development of interaction, communication, and behavior. This disorder is known as autism spectrum disorder or ASD.

Autism spectrum disorder (ASD) is a developmental disorder with characteristics of weak ability to socialize and communicate, often accompanied by stereotypical behavior and the background of limited interest and behavior that occurs before the age of 3 years.

ASD limits the capacity of individuals to be able to carry out daily activities and live productively. Some individuals can live freely independently and productively but most others live in limitations, discrimination, and deprivation of the right to obtain health and education services. Children with ASD even have a high risk of becoming victims of violence, bullying, and torture. Based on the existing symptoms, the incidence of ASD also affects aspects of development, learning, and health. The impact on aspects of development and learning for children who suffer from ASD begins at the age of 1 year. Children with ASD read words but they are unable to speak directly when they meet their peers, do not respond when their names are called, there is no eye contact or gesture, no smiles spontaneously to people who see them or say goodbye without being asked (WHO, 2016 )

Children with ASD are rigid in how to learn and are unable to move information in different situations. They have difficulty in seeing object as a whole object. They generally focus on certain aspects of an object, for example, children with ASD see a toy car for only a wheel or a door. They focus on parts of a tool in a room, for example, table legs or small pieces of paper on the floor. Health impacts can also be felt for ASD sufferers based on Croen's study (2015) which known the health effects are allergies, asthma, metabolic disorders such as diabetes and heart and even ASD sufferers have a 1.4 times risk of being obese and 3 times at risk for constipation.

The number of ASD cases in the world experienced a significant increase, based on UNESCO data in 2011 as many as 35 million cases of ASD worldwide which mean that there were 6 out of 1000 people in the world who suffer from ASD. Identifi-

cation of data from the CDC (Center for Disease Control and Prevention) revealed an increase in the number of ASD cases from 2000 to 2016. In 2000-2002 cases of ASD occurred was 1 in 150, whereas in 2004 there was an increase in cases 1 per 125 children, the next two years, the cases increased by a ratio of 1 to 110 children. In 2008 the ASD case increased with a ratio of 1 to 88 and in 2010 to 2016 cases of ASD were reported to increase again with a ratio of 1 in 68 children.

The number of children with ASD in Indonesia is still not well documented and it is difficult to know clearly because there is no accurate ASD data collection. In 2012 the prevalence of children suffering from ASD was 1.68 per 1000, which means that more than 112,000 people with ASD in Indonesia were aged > 5 years. This number continues to increase from year to year. Based on the data of outpatient children in the Bangkong River Mental Hospital, West Kalimantan Province, the number of autistic patient visits from 2012 was 426, in 2013 it was 335 and for 2014 was 256. The average number of visits was one patient had three visits in a week, in the last three years in West Kalimantan there have been around 21 autistic children who are doing therapy (Suharningsih, 2015). Based on data collection in all clinics, both clinics and special schools in various parts of Pontianak City, the number of ASD cases in 2016 in Pontianak City was 137 cases (Secondary data, 2016). The proportion of ASD from Bina Anak Bangsa Special School data in 2014 was 39% and in 2015 amounted to 37.8% of cases. The proportion of cases based on data from the Pontianak City Autism Center Service Center in 2015 was 62.8% and in 2016 the prevalence of ASD cases in Pontianak City was 1.28 out of 1000 children.

The cause of ASD is multifactorial, namely the presence of genetic factors and the presence of influential environmental factors (Ganaie et al., 2014). The CDC stated that the cause of ASD in children is the presence of a gene disorder, having twin siblings, consumption of valproic drugs and thalidomide during pregnancy and the age of both parents who are getting older. The most potential causes of ASD that have been studied in recent years are genetic, biological, perinatal, neuroanatomy, immunology, biochemical, environmental, psychosocial and family factors (Elwardany et al., 2013). Preliminary survey results with interviews conducted by researchers on 10 mothers in two Special Schools in Pontianak City there were 8 people who had children with ASD, as many as 62.5% had husbands aged > 40 years, 50% of respondents aged > 35 years while pregnant, Respondents who were exposed to cigarette smoke from their husbands during pregnancy were 100%, respondents who experien-

ced pregnancy hemorrhage as much as 50%, had a pregnancy interval with previous children <2 years as much as 37.5%, experienced stress during pregnancy as much as 25%, respondents who gave birth on insufficient months as much as 37.5%. This study aimed to obtain information on the dominant risk factors with the incidence of Autism Spectrum Disorder (ASD) and to determine how much risk between the relationship of various determinant factors with the occurrence of ASD.

## METHOD

The type of research used was analytic observational research with a case-control study design. The study was conducted by retrospective observation of the role of the independent variables studied, namely father's age, maternal age during pregnancy, passive smoking, antenatal hemorrhage, gestational distance, history of stress during pregnancy and insufficient months of birth on the dependent variable, the incidence of ASD.

The sample in this study consisted of case and control groups. Case group was children diagnosed with ASD by health professionals (pediatricians, psychiatrists, and psychologists) who are recorded as therapy participants in two therapeutic facilities with the highest number of ASD cases, namely UPTD Autism Center and Bina Anak Bangsa Foundation with ages ranging from 2 to 5 years. Meanwhile, the control group was taken from children who were not affected by ASD who had almost the same sex and age characteristics as the case group, namely male and aged 2 to 5 years. Minimum sample size calculation was obtained as many as 35 samples with a comparison of the sample size between 1: 1 case and control that is 35 cases and 35 controls, so the total sample was 70 people.

The sampling technique used was purposive sampling technique using inclusion and exclusion criteria. The inclusion criteria of the case groups in this study were those with ASD aged 2-5 years who had live biological mothers, live in Pontianak City, male sex and enrolled in therapy in Pontianak City, while the exclusion criteria for the case group were respondents whose biological mothers not in Pontianak City; working outside the area or dying, respondents suffer from other diseases such as mute and deafness and respondents who were born at home. Data collection in this study consisted of primary and secondary data, primary data obtained through interviews with mothers of respondents who were guided by the research questionnaire and secondary data obtained from register data and medical records. Data analysis was carried out by univariate and bivariate through Chi-Square test ( $\alpha =$

0.05; CI = 95%) to find out how much the risk (odds ratio) of the factors studied on the incidence of ASD.

## RESULTS AND DISCUSSION

Characteristics of respondents in this study consisted of age, birth order, parental education, parental work, history of trauma or accident, labor and history of complications. The characteristics of each respondent can be seen in Table 1

The univariate analysis described all independent variables, namely father's age, mother's during pregnancy, passive smoking, antenatal hemorrhage, pregnancy interval, history of stress during pregnancy and insufficient months of birth by calculating frequency and percentage. Table 2 shows that the proportion of the tendency of respondents surveyed was 40% more in the case group who had father aged 40 years old and over, the proportion of respondents in the case group who had mother aged 35 years and over was 28.6% more than those in the control group. However, based on the condition of passive smokers the proportion of the tendency of respondents exposed to cigarette smoke during pregnancy was more experienced in the control group, which was 68.6%. Based on the history of antenatal hemorrhage, the tendency of respondents in the case group to experience antenatal hemorrhage was 25.7% greater than the control group, while the proportion of the tendency of respondents whose risk of pregnancy was more experienced in the control group was 8.6%. The proportion of the tendency of respondents who had a history of stress during pregnancy was higher in the case group by 48.6% and by 31.4%, the case group had more insufficient months of birth compared to the control group.

Bivariate analysis is an analysis that is used to see the relationship between independent variables, namely father's age, mother's age during pregnancy, passive smoker, antenatal hemorrhage, pregnancy interval, history of stress during pregnancy and insufficient months of birth with the dependent variable, the incidence of ASD.

The results of the bivariate analysis showed that there was a relationship between father aged  $\geq 40$  years with the incidence of ASD, from the calculation of Chi Square statistical tests obtained a p-value of 0.03 ( $p \leq 0.05$ ) and it was found that father aged  $\geq 40$  years are at risk 4 times greater for their child to experience ASD compared to fathers who are <40 years old when the mother experiences pregnancy. This study is in accordance with Budi's study (2015) that there was a significant relationship between father aged  $\geq 40$  years and the incidence of ASD and 6.3 times greater risk for children to be born with ASD compared to father aged <40 years old. This is

Table 1. Characteristics of Respodents

Characteristics	Case		Control	
	N	%	N	%
1. Birth order				
First child	24	68.6	16	45.7
Second child	8	22.8	10	28.5
Third child	3	8.6	9	25.7
Total	35	100	35	100
2. Education of Father				
Junior High School	1	2.9	1	2.9
Senior High School	14	40.0	21	60.0
College	20	57.1	13	37.1
Total	35	100	35	100
3. Job of Father				
Civil Servant	11	31.4	3	8.6
Private sector	24	68.5	32	91.4
Total	35	100	35	100
4. Education of Mother				
Elementary School	0	0	2	5.7
Junior High School	2	5.7	2	5.7
Senior High School	10	28.6	19	54.3
College	23	65.7	12	34.3
Total	35	100	35	100
5. Job of Mother				
Civil Servant	4	11.4	2	5.7
Private sector	6	17.1	9	25.7
Unemployment	25	71.4	24	68.6
Total	35	100	35	100
6. Trauma/Accident History				
Yes	7	20.0	3	8.6
No.	28	80.0	32	91.4
Total	35	100	35	100
7. Labor Process				
Caesar	17	48.6	6	17.1
Normal	18	51.4	29	82.9
Total	35	100	35	100
8. Complication History				
Yes	14	40	3	8.6
No.	21	60	32	91.4
Total	35	100	35	100

because the body DNA of a man that is copied from one cell to another in the sperm allows for an error, in terms of genetics called “copy error”. The copying process will be increasingly tired and less efficient so that the sperm produced will form abnormal

chromosomal structures (de novo mutation), these sperm mutations are then used to control the development of the fetal brain which can eventually cause children to become autistic (Hultman et al., 2011). The 2012 New York Times article on research

Table 2. Results of Univariate Analysis

No.	Variable	Case		Control	
		N	%	N	%
1.	Age of Father				
	≥ 40 years old	14	40	5	14.3
	< 40 years old	21	60	30	85.7
2.	Age of Mother				
	≥ 35 years old	10	28.6	3	8.6
	< 35 years old	25	71.4	32	91.4
3.	Passive smoker				
	Yes	23	65.7	24	68.6
	No	12	34.3	11	31.4
4.	Antenatal Hemorrhage				
	Yes	9	25.7	5	14.3
	No	26	74.3	30	85.7
5.	Pregnancy Interval				
	Risky	2	5.7	3	8.6
	Not Risky	33	94.3	32	91.4
6.	Stress history during pregnancy				
	Yes	17	48.6	8	22.9
	No	18	51.4	27	77.1
7.	Birth at insufficient month				
	<37 weeks	11	31.4	3	8.6
	≥37 weeks	24	68.6	32	91.4

conducted by deCode Genetics Company (a gene-based disease research firm) on population DNA in Iceland suggests that older men increase the risk of developing mental illnesses such as schizophrenia and ASD compared to the younger one. This is due to random mutations that become more common with increasing age by contributing to a 2% risk of mutation. De novo mutation plays a very large role in the occurrence of brain disorders because there are approximately 50% active genes in them that play a role in the development of the brain's nerves.

The results of bivariate analysis showed that there was no significant relationship between mother aged ≥ 35 years during pregnancy with the incidence of ASD p-value obtained at 0.065 ( $p > 0.05$ ). This study is in line with the results of Arulita's (2014) study that there was no relationship between mother aged ≥ 35 years during pregnancy with the incidence of ASD ( $p = 1.000$ ). The results of a study conducted by Budi (2015) showed similarities that mother aged ≥ 35 years during pregnancy did not have a significant relationship to the incidence of ASD ( $p = 0.261$ ). Although the result of the study showed no significant relationship to the incidence of ASD, the age of pregnant mother of ≥ 35 years

old is a high-risk gestational age. More difficult and long-term deliveries, and stillbirths are other problems that can be found in pregnancy and childbirth of mother aged ≥ 35 years old (Sibuea et al, 2013). High-risk pregnancy is the pregnancy that can cause pregnant women and babies to become ill or die before labor takes place (Sinsin, 2008). This age group has not entered the safe age for pregnancy, that is between the ages of 20-34 years, where in this age range the physical and psychological conditions of the mother are in prime condition to receive pregnancy (Hardiyanti, 2014). The unrelated results of the study were influenced by most of the case respondents having mothers aged <35 years, amounting to 71.4%, consisting of 30-34 years old of 34.2%, aged 28-29 years of 28.6% and age 20-24 years of 8.6%, this caused the tendency of probability value that did not have statistical relationship.

The results of the bivariate analysis showed that there was no significant relationship between passive smoker and the incidence of ASD with a p-value of 0.801 ( $p > 0.05$ ). This is similar to the results of Nurbayatin's (2015) study which suggested that pregnant women as passive smokers were not associated with the incidence of ASD ( $p = 1,000$ ).

Table 3. Bivariate Analysis Result

No.	Variable	Autism Spectrum Disorder (ASD) Case				p-value
		Case		Control		
		N	%	N	%	
1.	Age of Father					
	≥ 40 years old	14	40	5	14.3	0.03
	< 40 years old	21	60	30	85.7	
2.	Age of Mother					
	≥ 35 years old	10	28.6	3	8.6	0.065
	< 35 years old	25	71.4	32	91.4	
3.	Passive smoker					
	Yes	23	65.7	24	68.6	0.801
	No	12	34.3	11	31.4	
4.	Antenatal Hemorrhage					
	Yes	9	25.7	5	14.3	0.155
	No	26	74.3	30	85.7	
5.	Pregnancy Interval					
	Risky	2	5.7	3	8.6	0.5
	Not Risky	33	94.3	32	91.4	
6.	Stress history during pregnancy					
	Yes	17	48.6	8	22.9	0.04
	No	18	51.4	27	77.1	
7.	Birth at insufficient month					
	<37 weeks	11	31.4	3	8.6	0.036
	≥37 weeks	24	68.6	32	91.4	

Exposure to cigarette smoke, especially in pregnant women as dangerous as people who smoke cigarettes directly, nicotine contained in cigarette smoke is a vasoconstrictor substance that will cause vasoconstriction of blood vessels and increase heart contraction, consequently will affect the supply of oxygen and nutrients to the fetus. The supply of oxygen to the fetus becomes inadequate that will cause hypoxia and fetal growth to be disrupted. In addition, a decrease in nutrient supply will cause the fetus to be deficient in nutrients and interfere with growth in the fetus (Hanum, 2017). The result of the study was not related to the incidence of ASD because the proportion of respondents exposed to cigarette smoke at home was more experienced by control respondents, it was also influenced by the existence of confounding, namely the presence of pregnant mother that is not only in the house so that exposure to cigarette smoke is possible to be obtained from other environments such as places work or public area.

The results of the bivariate analysis showed that there was no significant relationship between

antenatal hemorrhage and the incidence of ASD with obtained p-value of 0.155 ( $p > 0.05$ ), the result of this study is in accordance with research conducted by Zahra (2014) that antenatal hemorrhage is not a risk factor for ASD in children. A study by Arulita (2014) also stated that the antenatal hemorrhage in pregnant women is not related to the incidence of ASD ( $p = 0.145$ ). Antenatal hemorrhage is a condition of pregnant women who experience vaginal bleeding during pregnancy over 28 weeks or more because of a disturbance in the placenta. Bleeding during pregnancy is one of several complications of pregnancy that will cause the fetus to experience hypoxia (Gardener et al., 2009). Unrelated research results caused the case respondents who had experienced bleeding during pregnancy were only 25.7%, other causes there were other factors that influence the occurrence of antenatal hemorrhage such as blood pressure during pregnancy, history of anemia and hypertension.

The results of the bivariate analysis showed that there was no significant relationship between the interval of pregnancy with the incidence of ASD

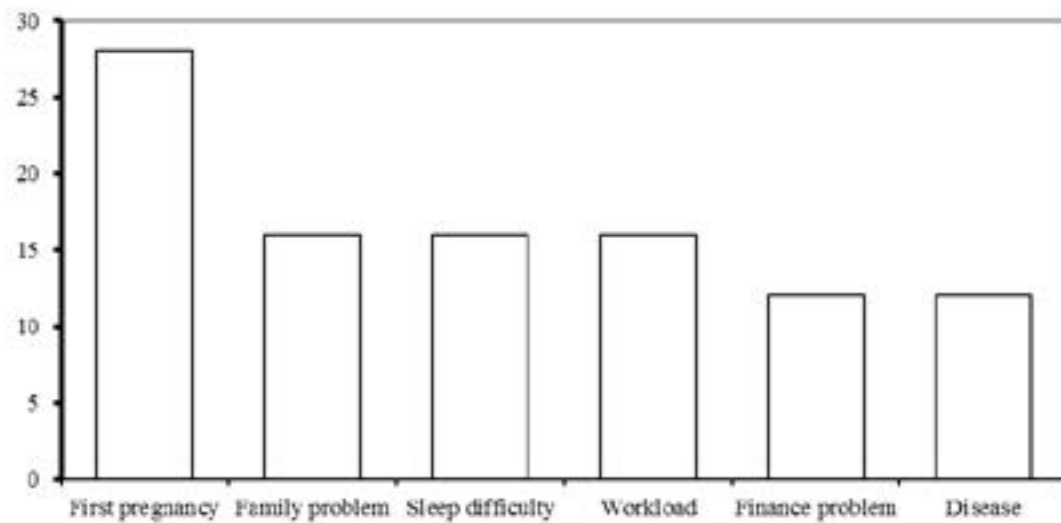


Figure 1. Prenatal Stress Type

obtained by p-value of 0.5 ( $p > 0.05$ ), the result of this study is in line with the research of Co0 (2015) which stated that there was no significant relationship between pregnancy interval and ASD events ( $p = 0.20$ ). Although the results of this study showed no significant association with the incidence of ASD, the two-year pregnancy interval was the age of determination that had been recommended by the National Population and Family Planning Board (*Badan Kependudukan dan Keluarga Berencana Nasional* or *BKKBN*) to reduce the increase in maternal mortality rates and infant mortality. The interval between pregnancies that are too close can endanger the baby to be born because the physical condition of the mother's uterus is not perfect. Too short interval causes the mother does not have time to recover, which is at risk of anemia due to iron deficiency in pregnancy (Ningrum, 2014). Too close pregnancy interval will increase the risk of bleeding, complications of pregnancy, premature babies and the risk of bleeding during childbirth (Sawitri, 2014). The result of the study was not related due to differences in the characteristics of the study sample, the majority of respondents who had siblings from previous births tended to be less than the respondents whose birth order was the first child, the proportion of the first child in the case respondents was 68.6% or the difference in proportion difference was two times compared to the proportion of second and third children.

The results of the bivariate analysis showed that there was a relationship between the history of stress during pregnancy and the incidence of ASD, from the calculation of Chi-Square statistical test, obtained p-value of 0.04 ( $p \leq 0.05$ ) and it was known that mothers who had a history of stress while

pregnant were 3.18 times greater for children with ASD than for mothers who had no history of stress during pregnancy. The result of this study is in line with the research conducted by Zhang (2010) that history of stress during pregnancy has a relationship with the incidence of ASD in children with an odds ratio of 4.08. The results of Salman's research (2016) show similar things that stress during pregnancy affects the incidence of ASD. The stressors commonly experienced by respondents in this study can be seen in Figure 1.

Figure 1 shows that the majority of respondents experienced stress due to first pregnancy with a distribution of 28%, having problems with family members, cousins, in-laws or divorce by 16%, having sleep trouble due to changes in sleep hours during pregnancy by 16% and stress due to workload by 16%, while the distribution of respondents who experienced stress due to financial problems by 12% and respondents who suffered from the disease at pregnancy by 12%. History of stress during pregnancy can increase the level of adrenaline in the mother's body, resulting in placental vasoconstriction and disrupt the flow of blood to the brain directly to the fetus (Zhang et al., 2010). Research conducted by Mulder in Kinney (2008) found that prenatal stress can damage a child's brain development with some damage that interferes with circulation in the flow of the placenta and uterine, causes hypoxia in the fetus, stimulates the release of stress hormones that can spread through the placenta, increases complications of pregnancy and childbirth, changes the response of genes and disrupts hormonal patterns that are important in the development of brain structure and function.

The results of the bivariate analysis showed

that there was a relationship between insufficient months of birth and the incidence of ASD, from the calculation of Chi-Square statistical tests obtained p-value of 0.036 ( $p \leq 0.05$ ) and the result of the study is also known that insufficient months of birth had a risk of 4.88 that is greater for experiencing ASD. The result of this study is in line with research conducted by Arulita (2014) that insufficient months of birth have a risk of 9.75 times greater for ASD. Generally, pregnancy is called at enough months if it lasts between 37-41 weeks, while labor that occurs before 37 weeks is called preterm labor. Prematurity is associated with infant morbidity and mortality and is one of the biggest contributors to perinatal mortality and neonatal morbidity, both short and long-term. Problems that can arise by preterm birth are neurological development problems that vary from severe to mild, such as behavioral abnormalities, difficulties in learning and understanding language, concentration/attention and hyperactivity disturbances (Sulistiari, 2016). Babies born prematurely are found to have fewer parts on the surface of the cortical gray box which causes inhibition of child development such as cognitive development, barriers in social relations and language and communication disability (Goldin, 2015).

## CONCLUSION

Risk factors for the incidence of ASD in Pontianak City in 2017 were the age of the father, history of stress during pregnancy and insufficient months of birth. Further research is needed to determine the determinant factors that are thought to influence the incidence of ASD, such as the environment, history of trauma or accident, LBW (Low Birth Weight), hyper bilirubin, anemia during pregnancy, drug consumption, history of fever during pregnancy, diabetes mellitus, history of cosmetic use, history of amalgam use on teeth, consumption of folic acid, birth of postmature and asphyxia.

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