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RISK FACTORS OF INTRAUTERINE FETAL DEATH IN CIPTO MANGUNKUSUMO GENERAL HOSPITAL, INDONESIA

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Abstract

Intra Uterine Fetal Death (IUFD) results from various disorders of the mother, fetus, and placenta. This study aimed to explore factors contributing to IUFD, knowing the risk factors will prevent this case in the future time. In 2016-2018, patients diagnosed with IUFD at 22 weeks of gestation were included. One hundred twenty-five patients with IUFD and 125 controls with alive fetuses were enrolled. Data were collected from the medical records of participants. Factors that may have contributed to IUFD were explored. Comparisons between various risk factors and outcomes of the two groups were made. P-value was statistically significant if ≤0.05. We found several factors that contribute to IUFD. Some factors like BMI, ANC provider, referred from tertiary health facility, and congenital anomaly increased the risk of IUFD by 2.86, 5.86, 6.26 and 9.45 times respectively. In contrast, some factors like a number of ANC ≥ 6 times and gestational age >36 weeks decrease the risk of IUFD. Regular and intensive ANC ≥ 6 times during pregnancy, number of pregnancy and gestational age ≥ 36 weeks significantly decreases the risk of IUFD with OR 0.12, 0.4, and 0.23 respectively. High-quality ANC to identify IUFD risk factors may lead to a significant decrease in its occurrences. Some factors like BMI, ANC provider, referred from tertiary health facility, and congenital anomaly increased the risk of IUFD, but Number of ANC≥ 6 times, number of pregnancy ≥2 and gestational age ≥36 weeks can reduce risk of IUFD.

Keyword: Intrauterine fetal death, risk factor

Introduction

The United State National Center for Health Statistics defines fetal death as the delivery of a fetus showing no signs of life as indicated by the absence of breathing, heartbeats, pulsation of the umbilical cord, or definite movements of voluntary muscles (MacDorman & Gregory, 2015). Every year worldwide, there are about 2.6 million IUFD cases at or above 28 gestational weeks, with an incidence ranging from 3.4 per thousand (‰) total births in high-income countries to 36 in The Sub-Sahara and Southern Asia regions (Blencowe et al., 2016). The rate of IUFD in low-income countries is much higher (about 21 deaths per 1000 births) than in high-income countries (about three deaths per 1000 births) (L.-C. Liu et al., 2014). In the United States, the dead birth rate is 2.84 per death per 1000 live births, about 50% of fetal deaths occur between 20 and 27 weeks (especially from 20 to 23 weeks of pregnancy), and another 50% occur at ≥ 28 weeks (Leal et al., 2020).

Intra-Uterine Fetal Death results from various disorders of the mother, fetus, and placenta. Sociodemographic factors affecting the fetal mortality rate are the black race, younger or advanced maternal age, and marital status. The lack of universal protocols inhibited the study of the specific cause of intrauterine death to evaluate and classify dead births and a decrease in the level of an autopsy (Man et al., 2016). These factors are as follows maternal factors (post-term pregnancy, advanced maternal age, diabetes mellitus, ascending infection, preeclampsia, eclampsia, birth trauma, maternal hemorrhage, maternal obesity, previous fetal loss, and preterm), fetal factors (Intrauterine retardation growth, congenital abnormalities, and twin complication) and placental factors (umbilical cord disorder, and placental abruption) (Maslovich MM, 2020).

Intrauterine fetal deaths in early pregnancy seem to be associated with congenital anomalies, infections and obstructed intrauterine growth. In addition, maternal medical condition such as chronic hypertension, obesity, and diabetes, while in the late pregnancy seems to be caused by maternal medical abnormalities and obstetric disorders, and the condition that develops around the time of childbirth, such as placental abruption, Stillbirth risk is increased by early and late-term gestational age. At 42 weeks, the risk of stillbirth is 1.08/1000. The relative risk for stillbirth is 7.7 for persistent polyhydramnios compared with pregnancies with resolved polyhydramnios, while the risk in oligohydramnios is 11.54 (95% CI: 4.05-32.9) (Maslovich MM, 2020).Regarding the high prevalence of IUFD rate in Indonesia, it is crucial to study the prevalence of intrauterine fetal death rate and the risk factors in tertiary hospitals to prevent these cases in the future time.

Research Methods

This research was a case-control study. The research was conducted at Cipto Mangunkusumo General Hospital (RSCM), Jakarta, Indonesia. Data collection was taken from 2016 to 2018. All patients diagnosed with IUFD at or beyond 22 weeks of gestation were included in the research. We also recruited a control group who had delivered alive babies at any gestational age at or beyond 22 weeks during the study period. We included 125 women with pre-labor IUFD confirmed by ultrasound examination, and 125 women were enrolled in the study as a control. Patients and controls data were collected from their medical records. The variables collected in this study were prevalence of intrauterine fetal death, demographic characteristics of the patients, including age, number of pregnancies, parity, body mass index, history of pregnancy, history of antenatal care, and antenatal care number. Risk factors of IUFD such as maternal risk factors, placental risk factors, fetal risk factors, and others had also been taken. The target population of the research is intrauterine fetal death that occurred in RSCM. The targeted population is pregnant women in RSCM. Research subjects are affordable populations that match the criteria of inclusion and exclusion. The inclusion criteria were intrauterine fetal death in RSCM in 2016-2018, while the exclusion criteria were intrauterine death under 22 weeks. Samples were taken using consecutive sampling. The Ethics Committee approved this study of the Faculty of Medicine, University of Indonesia number KET-657/EN.2F1/ETIK/PPM.00.02/2019 on 10th June 2019

Data Analysis

Data analysis was performed using Statistical Package for Social Services (SPSS) software, version 25.0 (IBM Corps., USA). All data collected in this study were presented descriptively. Descriptive analysis was conducted to assess the baseline characteristics of the study population and the prevalence of the IUFD in RSCM. The data will be presented as n and percentage (%). In order to identify the risk factors of IUFD, we calculated the multivariate logistic regression. The odds ratios were calculated with 95 % confidence intervals. Categorical variables were compared using corrected Chi-square and Fisher's exact test. Differences with a p-value ≤0.05 were considered statistically significant.

Results and Discussion

From 4.347 births in 2016-2018, there were 125 IUFD cases (2.87%), with the following distribution according to the year of IUFD occurrences: 41 cases in 2016 (2.34%); 48 cases in 2017 (3.15%), and 36 cases in 2018 (3.35%). (table 1)

Table 1. **Intrauterine Fetal Death in RSCM Year 2016-2018**

Year	Prevalence of Intrauterine fetal death cases n (%)	Total number of births
2016	41 (2.34)	1755
2017	48 (3.15)	1520
2018	36 (3.35)	1072
Total	125 (2.87)	4347

Demographic characteristics of patients with intrauterine fetal death are shown in Table 2. It can be seen that the most maternal age in the case of an intrauterine death is ≤35 years old by 94 (75%), while subjects with >35 years old are 31 (25%); this data is due to the maternal age range 20-35 years old being the best reproductive age and the most female population that comes to RSCM. In some number pregnancies characteristic, mostly ≥2 pregnancy as many as 68 subjects (54.4%), while mainly our subject had nullipara by 91 subjects (72.8%) In the variable body mass index (BMI), it has been obtained that most intrauterine death of the fetus occurs in patients with BMI ≥23 81(64.8%). The history of marriage mostly 1 time in 117 subjects (93.6%). Furthermore, most of the subject going to non-gynecologist for ANC, as many as 109 (87.2%). From a number of antenatal care (ANC), it is found that the most proportion in the case of intrauterine fetal death is experienced in mothers with antenatal care number <6 times 94(75.2%).

Table 2. Demographic Characteristics of Patients with Intra Uterine Fetal Death

Characteristic	N (%)
Age	

● ≤35 years old	94 (75)
● >35 years old	31 (25)
Number of pregnancies	
● 1	57 (45.6)
● ≥2	68 (54.4)
Parity	
● 1	91 (72.8)
● ≥2	34 (27.2)
Body Mass Index (Asia)	
● <23	44 (35.2)
● ≥23	81 (64.8)
Number of marriage	
● 1	117 (93.6)
● ≥2	8 (6.4)
Antenatalcare Provider	
● Gynaecologist	16 (12.8)
● Non- Gynaecologist	109 (87.2)
Number of Antenatal care	
● <6 times	94 (75.2)
● ≥6 times	31 (24.8)

Intrauterine fetal death risk factors include maternal, placental, and umbilical cord, fetal and other risk shown in table 3. In the results of the analysis of maternal risk factors from this study, it is found that the most maternal risk factor has with the case of intrauterine fetal death is preeclampsia by 48 subjects (38.4%). Based on fetal risk factors, congenital abnormalities, 23 cases (18.4%), are the most common risk factors experienced by the research subject. Placental abruption was the highest number in placental and umbilical Cord factors in 17 subjects (13.6%).

Table 3. Risk Factor of Intra-Uterine Fetal Death

Risk Factor	N (%)
Maternal	
Preeclampsia	48 (38.4)
Diabetes	5 (4)
Chronic disease	5 (4)
Autoimmune disease	6 (4.8)
Heart disease	4 (3.2)
Premature rupture of membrane(PROM)	15 (12)
Intrauterine infection	4 (3.2)
History of IUFD	8 (6.4)
History of Trauma	2 (1.6)
Placenta and umbilical cord (macroscopic)	

Placenta Previa	6 (4.8)
Placental abruption	17 (13.6)
Vasa Previa	1 (0.8)
Umbilical cord anomaly	5 (4)
Fetal	
Congenital anomaly	23 (18.4)

In bivariate analysis, from 24 variables, we obtained 10 variables that statistically significant correlated with IUFD, like ANC provider, number of ANC, referral origin, gestational age, preeclampsia, ruptured membranes, history of IUFD, placental abruption, umbilical cord entanglement, congenital abnormalities.

Table 4. Bivariate analysis of factors affecting IUFD.

Variables	**Control**	**Case**	**OR (95% CI)**	**p**
Age				
>35	29	31	1,02 (0.44-1.59)	0.968
<35	96	94		
Number of pregnancies				
≥2	78	65	1,16 (0.1-0.50)	0.154
1	49	57		
Parity				
≥2	36	34	0,98 (0.43-1.54)	0.949
1	91	91		
BMI				
≥23	63	81	1,34 (1.30-2.31)	0.140
<23	62	44		
Number of marriage				
2	12	8	0,95 (0.02-1.88)	0.507
1	115	117		
ANC Provider				
Non-gynecologist	86	108	1,48 (0.82-2.13)	0.000*
Gynecologist	41	15		
Number of Antenatal care			0.37(0.19-0.93)	0.000*
≥6	90	31		
<6	37	94		
Referral origin			2,02 (1.49-2.56)	
Tertiary care	41	78		0.000*

Non-Tertiary care	86	40		
Gestational age				
≥36	77	27	0,45 (0.11-2.83)	0.000*
<36	50	98		
Number of Fetus			6,24 (5.22-7.26)	0.474
Multiple	10	14		
Single	117	11		
Preeclampsia				
Yes	27	48	1,42 (0.87-1.98)	0.004*
No	100	77		
Diabetes melitus/gestational			1,07 (0.59-2.72)	0.392
Yes	2	5		
No	125	120		
Chronic disease				
Yes	1	5	1,08 (1.01-3.24)	0.167
No	126	120		
Autoimmune disease				
Yes	7	8	1,02 (0.02-2.07)	0.810
No	120	118		
Heart disease				
Yes	2	4	1,05 (0.67-2.76)	0.618
No	125	121		
Ruptured membrane				
Yes	0	15	1,29 (0.76-3.32)	0.000
No	127	110		
IUI				
Yes	3	4	1,03 (0.49-2.55)	0.976
No	124	121		
History of IUFD				
Yes	0	8	1,15 (0.95-3.24)	0.004
No	127	117		
History of Trauma				
Yes	0	2	1,05 (1.00-3.08)	0.311
No	127	123		
Placenta Previa				
Yes	1	6	1,10 (0.94-3.14)	0.092
No	126	119		
Placental abruption			1,27 (0.77-3.31)	0.001
Yes	3	17		

No	123	107		
Vasa Previa				
Yes	0	1	1,03 (1.01-3.07)	0.311
No	127	124		
Umbilical cord looping				
Yes	4	5	1,03 (1.01-3.07)	0.05
No	123	120		
Congenital anomalies				
Yes	9	23	1,27 (0.77-3.31)	0.001*
No	118	102		

We include 14 variables with p<0.25 to multivariate analysis. From 14 variables we obtained 7 variables that statistically significant affected the risk of IUFD. Several variables increase the risk of IUFD. BMI ≥23 increase the risk of IUFD by 2.86 times , antenatal care to non-gynecologist by 5.86 times, referred from tertiary health facilities by 6.26 times, congenital anomalies by 9.45 times with p value 0.015, 0.002, 0.001, 0.001 respectively.

Some variables show to decrease in the risk of IUFD. Number of pregnancy, number of antenatal care more than 6 times during pregnancy and gestational age more than 36 weeks significantly decrease the risk of IUFD with OR 0.41, 0.12, 0.23 and p value 0.033, 0.001, 0.001 respectively.

Table 5. Multivariate analysis of factors affecting IUFD.

Variable	OR	95% CI	p
Number of Pregnancy	0.41	0.17-0.93	0.033*
BMI	2.86	1.23-6.68	0.015*
ANC Provider	5.86	1.96-17.47	0.002*
Number of ANC	0.12	0.049-0.272	0.001*
Referral origin	6.26	2.59-15.13	0.001*
Gestational Age	0.23	0.09-0.533	0.001*
Preeclampsia	1.38	0.58-3.31	0.466
Chronic Disease	0.28	0.019-4.18	0.357
PROM	3993252590.13		0.998
History of IUFD	17321404423.35		0.999
Placenta Previa	15.76	0.46-539	0.126
Solution Placenta	3.41	0.50-23.24	0.209
Umbilical cord looping	0.95	0.127-7.40	0.960
Congenital Anomaly	9.45	2.77-32.17	0.001*

* Statistically significant p≤ 0.05

Discussion

In our study, the prevalence of IUFD was 125 subjects (2.87%), which was higher than the value obtained in the Indonesian Demographic and Health Survey (SKDI) 2017, which is 21

deaths per 1000 births (2.1%).[4] However, SKDI data were retrieved from all primary services to tertiary services. At the same time, RSCM is a tertiary hospital which is one of the national referrals in the healthcare system in Indonesia, so the case obtained has a higher level of difficulty than other healthcare services.

Compared to other tertiary health service centers, the numbers gained in this study are lower than the percentage of IUFD in China (35 per 1,000 births) and higher than in Pakistan (18 per 1,000 births). At the rate of growth of intrauterine death in RSCM annually, it can be assessed that the number of cases of intrauterine fetal mortality decreases. However, it is accompanied by a reduced number of births in the RSCM. This makes it as if there is a higher percentage of intrauterine death of the fetus each year. These findings may be due to factors not included in this study, such as a better health referral system each year (thus lowering the number of patients in tertiary services).

In our study, in the age group >35 years, there were 31 subjects (25%), which was slightly lower than data from SKDI 2017, which shows the prevalence of the highest perinatal death is the mother in the group age 40-49 years of 38 deaths per 1,000 births (3.8%). Our study showed that age >35 years old has a risk of IUFD 1.02 times more than ≤35 years old (OR 1.02, CI 0.44-1.59, p 0.968). It is similar with another study showed that increasing maternal age (aOR 1.0, 95 % CI 1.0–1.1) had an association with IUFD (Kc et al., 2015)

The subject who had BMI ≥23 were 81 (64.8%) higher than subjects with BMI<23 by 63 (53.4%) with OR 2.86. This is similar to research conducted in the UK in 2014, indicating the increase of risk by 2-5 times to experience intrauterine fetal death in the mother with excess body weight.[8] Obesity is associated with intrauterine fetal death through increased risk of preeclampsia, hypertension, diabetes, and thromboembolism during pregnancy. In addition, obesity is also associated with the delay of birth of spontaneous births, increased induction of labor, and cesarean section. Another theory shows that the incidence of hypoxia-apnea in mothers with obesity may increase the case of intrauterine fetal death (Yao et al., 2014).

Our study shows a mother with ANC number ≥6 times significantly lower risk of IUFD than mothers who have a number of ANC <6 times with OR 0.12. While routine ANC provided by a non-Gynecologist will increase the risk of IUFD by 5.86 fold than a mother who got ANC from Gynecologist. Mothers with high-risk pregnancies usually require a reference to tertiary health services. Our study shows that being referred from tertiary facilities increases the risk of IUFD by 6.26 fold more than a mother reffered from non-tertiary facilities. Because the frequency of ANC ≥6 and a history of antenatal care with a Gynecologist is the less proportion in this study, the IUFD incidence remains high due to the less frequency and antenatal care quality. Adequate antenatal care will reduce the intrauterine death rate due to the ability to prevent and avoid the majority of the previous risk factors where adequate antenatal care help in controlling a lot of factors (blood sugar level, blood pressure), earlier diagnosis of congenital anomalies, prescribe folic acid, which provide an excellent chance to early referral to good center for cesarean section in high-risk cases (Beauclair et al., 2014). Gestational age plays a significant role in determining IUFD. From our study, we found that IUFD usually does not happen at gestational age ≥36 weeks, the risk of IUFD at gestational age ≥36 weeks reduce with OR 0.23.

Preeclampsia is the highest maternal risk factor found in our study, with 48 subjects

(38.4%). It increases the risk of IUFD by 1.42 fold. This is similar to the research results conducted in 2015, which show that preeclampsia is one of the most risk factors for intrauterine fetal death, with a relative risk of 1.45 fold (Harmon et al., 2015). Balu et al. in a 2015 study in a tertiary hospital in India, expressed the same results that preeclampsia was the most common cause of IUFD (Divya et al., 2015). Preeclampsia begins to increase the risk of fetal death since clinical symptoms of preeclampsia present and the risk of fetal death will be reduced with appropriate and immediate management of the case of preeclampsia. Preeclampsia is also associated with excess body weight and hypoxia in the fetus (Y. Liu et al., 2017). Another maternal risk is an infection; 3 subjects (2.5%) had an intrauterine infection in our study. Stillbirths before 28 weeks seem to be strongly associated with an intrauterine bacterial infection. In contrast, later preterm stillbirths are less likely to be caused by such infection due to premature rupture of the membrane in the form of chorioamnionitis. Clinical chorioamnionitis affects 1-4% of pregnancies worldwide in developed countries. Data is lacking in developing nations but is likely higher than this rate. Maternal bacteremia occurs in 5-10 % of women with chorioamnionitis (Johnson et al., 2014).

We found that placental abruption is the highest placental risk factor among 17 subjects (13.6%). It increases the risk of IUFD by 3.41 fold. Placental abruption is the most risk factor for intrauterine fetal mortality. Placental abruption is an emergency case in obstetrics that requires immediate treatment to prevent the death of the fetus and mother. Globally, placental abruption is the common cause of intrauterine fetal mortality in developing countries, especially countries with complex health services access like Africa. In this research, access to health services can be influenced by external factors not examined in this study, such as the delay caused by patient ignorance.

Research conducted in Sri Lanka in 2014 showed an increased risk of intrauterine fetal death by 7.63 times in the fetus with congenital malformations (Fernando et al., 2014). It was similar to our study that found from the multivariate logistic regression that congenital abnormalities increased the risk of intrauterine fetal death 9.45 times.

This study has several limitations. First, the number of subjects in this study is relatively small, and the observation period is short (from 2016 to 2018 only). Further analytic research should be conducted with more subjects and a more extended observation period. Second, IUFD is a complex and multifactorial condition. The risk factors mentioned and studied in this research might not be able to represent all the variables that might cause IUFD. Therefore, it is possible that there were still lots of confounders that were left unaccounted for in this study.

Conclusion

High-quality ANC to identify IUFD risk factors may lead to a significant decrease in its occurrences. Some factor-like BMI, Number of Prgenancy, ANC provider, being referred from Tertiary Health Facility, and congenital anomaly increase the risk of IUFD. However, Number of ANC≥ 6 times and gestational age ≥36 weeks can reduce IUFD.

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