

## Effect of Intrinsic Factors on the Incidence of Preterm Birth in Mothers with High-Risk Pregnancies

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### KEYWORDS

Intrinsic factors, Preterm birth, High risk pregnancy.

### ABSTRACT

One of the problems caused by high-risk pregnancies is that babies are born preterm. Preterm birth is currently not known for sure, but it is thought to be triggered by a variety of mechanisms, including infection or inflammation, uteroplacental ischemic or bleeding, uterine overdistension, stress, and other immunological processes. Various factors are also associated with the occurrence of premature delivery, but the route of the mechanism is still being sought. The purpose of this study is to analyze the influence of intrinsic factors on the incidence of preterm birth in mothers with high-risk pregnancies at Waluyo Jati Hospital, Probolinggo Regency. This study is quantitative research with a cross-sectional approach. Sampling took place from January to June 2024 at Waluyo Jati Hospital, Probolinggo Regency. Sampling used the accidental sampling technique with a sample of 222 respondents who participated in this study. The results of this study showed that the most respondents with the criteria of the age range of 26-35 years were 103 respondents (46.4%), the last education was junior high school as many as 115 respondents (51.8%), the first pregnancy as many as 64 respondents (28.8%), never had an abortion as many as 183 respondents (82.4%), spontaneous childbirth as many as 114 respondents (51.4%), had a history of previous comorbidities as many as 139 respondents (62.6%), normal BMI as many as 94 respondents (42.3%), normal Hb levels were 168 respondents (75.7%), and preterm labor was 150 respondents (67.6%). The results of the double liner regression statistical test obtained a P-value of 0.000. The conclusion of this study is that there is an influence of intrinsic factors on the incidence of preterm birth in mothers with high-risk pregnancies at Waluyo Jati Hospital, Probolinggo Regency.

### 1. Introduction

A real and possible risk for the mother and the fetus during pregnancy is called high-risk pregnancies. [1]. One of the problems caused by high-risk pregnancies is that babies are born preterm [2]. Preterm birth occurs before the 37th week of pregnancy, although there are variations in different countries on low gestational age limits that distinguish it from spontaneous abortion [3].

The incidence of high-risk pregnancies varies across countries, ranging from 25.6% to 75.6%. [4]. The prevalence of preterm births varies across countries. When comparing developed and developing nations, it is evident that the rate is significantly higher in developing countries, with figures reaching 31% in Sudan, 30% in India, and 15% in South Africa. In contrast, developed countries report lower rates, ranging from 5-11% in Europe and 11.5% in the United States. [5]. On average, worldwide, 1(one) baby dies every 30 seconds, leading to the conclusion that over 1 million babies die each year as a result of premature births. [6].

Babies with low birth weight may (LBW) be used as an indicator for estimating the number of premature births. At the hospital, the national incident of low-born babies (LBW) registered at 27.9% [7], Compared to 2013, the number of low birth weight (LBW) babies increased in 2-15 years, which was around 13.03%. The distribution of the three highest regions is 20.27% in Papua, 19.77% in North Maluku, and West Kalimantan 19.79% while the lowest percentage is located in the Riau Islands, DI Yogyakarta and Bali with percentages of 8.38%, 8.9% and 9.08% respectively. There is another data released by the who in 2018 that indicates that some 675,700 babies were born prematurely. In other words, the rate of premature births in Indonesia is 15.5 percent of every 100,000 births. [9].

Preterm birth is not yet fully understood, but it is suspected to be triggered by various mechanisms, including infection or inflammation, ischemia or bleeding in the uterine and placental tissues, excessive uterine distension, stress, and other immunological processes. Various factors are also associated with the occurrence of less than a month of labor, but the pathway of the mechanism is still being sought [10]. The causes of preterm birth can be caused by anatomical, biochemical, immunological, endocrinological and genetic changes [11]. Shapiro et al. (2017) stated that although biological risk factors are not very specific and the accuracy level of its prediction

is quite low, the fact is that only half of preterm births have risk factors [12].

The risk of preterm birth can be lowered through the use of progesterone, aspirin, and cervical circulatory therapy. Vaginal progesterone may decrease the likelihood of preterm labor in women who have a short cervical length [13]. Low-dose aspirin administration can prevent preterm labor due to pre-eclampsia [14]. NICE (2015) noted that circulation is advantageous in lowering the incidence of premature birth, morbidity, and a perinatal mortality among patients who have a history of premature births and a short cervical length as observed through transvaginal ultrasound examination. [15].

## 2. Research Method

The study employed a descriptive analytical research design utilizing a cross-sectional approach. Data collection was carried out for mothers with pregnancies at elevated risk from January to June 2024 in the Rosela room of Waluyo Jati Hospital, Probolinggo Regency with a population of 498 pregnant women. Sampling was carried out using an accidental sampling technique on 222 respondents participating in this study. The research instrument used a checklist observation sheet filled out by the researcher derived from the outcomes of interviews, height also weight examinations and the findings of the respondents' Hb laboratory examination. The statistical test within this research uses a multiple linear regression test.

## 3. Result and Discussion

### Results

**Table 1. Characteristics of Respondents**

Characteristic	N	%
<b>Age</b>		
15-25 Years	82	36.9
26-35 Years	103	46.4
36-45 Years	36	16.2
> 45 years	1	0.5
Total	222	100
<b>Education</b>		
Not in school	0	0.0
Elementary School	15	6.8
Junior High School	115	51.8
Secondary School	86	38.7
College	6	2.7
Total	222	100
<b>Pregnancy History</b>		
1st pregnancy	64	28.8
2nd pregnancy	60	27.0
3rd pregnancy	62	27.9
4th pregnancy	27	12.2
5th pregnancy	8	3.6
6 <sup>th</sup> pregnancy	1	0.5
Total	222	100
<b>History of Abortion</b>		
Never	183	82.4
Ever Abortion	39	17.6
Total	222	100
<b>Childbirth History</b>		
Never	71	32.0
Spontaneous	114	51.4
Caesarean	37	16.7
Total	222	100
<b>Disease History</b>		
None	83	37.4
Have a history of illness	139	62.6
Total	222	100
<b>Body height</b>		
< 145 cm	32	14.4
> 145 cm	190	85.6
Total	222	100
<b>IMT</b>		
Underweight	12	5.4

Normal range	94	42.3
Overweight	65	29.3
Obese calass I	34	15.3
Obese calass II	13	5.9
Obese calass III	4	1.8
<b>Total</b>	<b>222</b>	<b>100</b>
<b>Up to Hb</b>		
< 11 g/dL	54	24.3
> 11 g/dL	168	75.7
<b>Total</b>	<b>222</b>	<b>100</b>
<b>Labor</b>		
Preterm	150	67.6
Aterm	72	32.4
<b>Total</b>	<b>222</b>	<b>100</b>

The number of respondents to mothers with high-risk disabilities was obtained as many as 222 respondents in the research period in the Rosela room of Waluyo Jati Hospital. Table 1 indicates that most respondents fall within the age group of 26 to 35 years (46.4%), the last education is junior high school (51.8%), first pregnancy (28.8%), never had an abortion (82.4%), spontaneous delivery (51.4%), have a history of previous comorbidities (62.6%), normal BMI (42.3%), normal Hb levels (75.7), preterm delivery (67.6%).

**Table 2 Statistical Test Results of Multiple Linear Regression Test Model Summary**

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.478a	.228	.199	.420

Table 2 presents an R value of 0.478, suggesting a significant relationship among intrinsic factors and the rate of preterm birth among mothers with elevated-risk pregnancies. The R Square value of 0.228 shows that the intrinsic factor can explain the occurrence of premature birth by 22.8%. The Standard Error value of 0.420 shows that the linear regression error rate is quite small.

**Table 3. Statistical Test Results of Coefficientsa Multiple Linear Regression Test**

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Mr.
1	(Constant)	-.064	.157		-4.10	.682
	Patient's pregnancy history	.006	.039	.015	.156	.876
	History of abortion	.148	.087	.120	1.701	.090
	Previous labor history	.010	.055	.015	.185	.853
	Respondent's disease history	.239	.064	.247	3.742	.000
	Respondent's height	.087	.083	.066	1.050	.295
	IMT Respond	-.060	.029	-.136	-2.049	.042
	Up to HB respondent	.435	.067	.399	6.483	.000
	Age of respondents	-.026	.053	-.040	-.492	.624

Table 3 shows the Sig value (P-value) in the variable categories of disease history, BMI, and Hb levels  $< \alpha = 0.05$  which means that independently the variables of disease history, BMI, and Hb levels have an effect regarding the occurrence of premature birth in mothers alongside high-risk pregnancies. Other variables such as pregnancy history, abortion history, childbirth history, disease history, height, and age of the respondents showed a Sig value (P-value)  $> \alpha = 0.05$  that indicates independently the variables of pregnancy history, abortion history, childbirth history, disease history, height, and age of the respondents made no difference to the incidence Regarding premature birth in mothers with high-risk pregnancies.

**Table 4 Statistical Test Results of Anova Multiple Linear Regression Test**

Model		Sum of Squares	Df	Mean Square	F	Mr.
1	Regression	11.113	8	1.389	7.883	.000b
	Residual	37.536	213	.176		
	<b>Total</b>	<b>48.649</b>	<b>221</b>			

Table 4 shows the Sig value (P-value) = 0.000  $< \alpha = 0.05$  that indicates intrinsic factors in simultaneously affect the occurrence of premature birth in mothers experiencing elevated-risk pregnancies.

## Discussion

The findings of this research indicated that the majority respondents with the criteria of the age range regarding 26-35 years were 103 respondents (46.4%), the most recent educational attainment was the number of junior

high schools reaching 115 respondents (51.8%), the first pregnancy as many as 64 respondents (28.8%), never had an abortion as many as 183 respondents (82.4%), spontaneous childbirth as many as 114 respondents (51.4%), had a history of previous comorbidities as many as 139 respondents (62.6%), normal BMI as many as 94 respondents (42.3%), normal Hb levels were 168 respondents (75.7%), and preterm labor was 150 respondents (67.6%). The Sig value (P-value) in the variable categories of disease history, BMI, and Hb levels shows a value of  $< \alpha = 0.05$  which means that independently these three variables Impact the rate of premature birth in mothers with high-risk pregnancies. Different values were indicated in the variables of pregnancy history, abortion history, childbirth history, disease history, height, and age of the respondents showing a Sig value (P-value) of  $> \alpha = 0.05$  that indicates these six variables independently have no effect on Impact the rate of premature birth mothers with high-risk pregnancies. The conclusions from multiple linear regression hypothesis test obtained a P-value of 0.000 which means that simultaneously intrinsic factors affect the occurrence of premature birth among mothers with elevated-risk pregnancies.

The occurrence of high-risk pregnancies varies across countries, ranging between 25.6% and 75.6%. [4]. The prevalence of preterm births varies across countries. When comparing developed and developing nations, it is evident that the rate is significantly higher in developing countries, with figures reaching 31% in Sudan, 30% in India, and 15% in South Africa. In contrast, developed countries report lower rates, ranging from 5-11% in Europe and 11.5% in the United States [5].

Preterm birth is the birth of a baby at 22 weeks to 36 weeks of gestation (ACOG, 2016) [16]. Based on clinical circumstances, preterm birth can be split into two classifications, namely, spontaneous preterm birth or indicated preterm birth. Spontaneous preterm birth occurs due to the spontaneous activation of one or more of the labor processes (maturation of the cervix, activation of membranes, and decidua, as well as uterine contractions). Preterm birth due to indications is a preterm pregnancy that is deliberately terminated due to maternal or fetal indications [17].

The identification of preterm labor involves established determined by clinical criteria within the form belonging to rhythmic uterine muscle contractions accompanied by cervical changes such as dilation and/or cervical thinning. Using these criteria, overdiagnosis is frequent (40-70%), and only less than 10% of patients go into labor within 7 days of symptoms appearing. The American College of Obstetricians and Gynecologists proposes the criteria for preterm labor, namely (1) contractions happen four times within 20 minutes or eight times in 60 minutes, along with changes in the cervix; (2) cervical dilation of more than 1 cm, thinning of more than or equal to 80% [16,17].

Prawirohardjo (2016) explained that several factors have a role in the occurrence of preterm labor, including maternal factors such as severe maternal disease, preeclampsia or hypertension, diabetes mellitus, trauma, cervical incompetence, fetal and placental factors such as antepartum hemorrhage, twin/amenorrhea, Low-lying placenta, Abruptio placentae, preterm rupture of membranes (PROM), polyhydramnios, or other factors such as socio-economic factors such as low education and low employment. too heavy [18].

Adequate nutrition and normal BMI will have better pregnancy outcomes than others. Some evidence has supported the hypothesis that malnourished mothers during pregnancy will have preterm births. Pregnant women with adequate nutrition need to be done during the conception period to prevent cases of preterm birth [19]. Maternal nutritional conditions greatly affect pregnancy outcomes [20].

Women with overweight and fatness have the highest risk for extremely preterm birth. According to NICE recommendations, Women according to their body mass index (BMI)  $>30$  kg/m<sup>2</sup> need to plan a weight loss program before conception. Expectant mothers with excess weight are educated at the time of the first antenatal interested in the perks of weight reduction throughout pregnancy [21].

Based on a meta-analysis study, 42.7% of women experience anemia in pregnant women in low- and middle-income economies. As many as 19% of cases of preterm labor are related to maternal anemia. Anemia during the first or second trimester notably raises the likelihood of preterm labor [22]. Anemia is strongly associated with a heightened risk of preterm labor, BBLR and child mortality as well as a predisposition to infection in women who are pregnant [23]. The occurrence associated with anemia within pregnancy ranges from 24.1% in the United States and 48.2% in Southeast Asia [24].

Previous disease history also affects the incidence of preterm birth, such as hypertension and diabetes mellitus. According to Tehranian et al, (2016) Maternal complications such as infectious diseases and hypertension most often cause premature labor in general [25]. Chronic hypertension causes complications in up to 10% of

pregnancies [26]. The likelihood of preterm labor is heightened among women with chronic hypertension and gestational hypertension; Women suffering from chronic hypertension experience a high rate of preterm labor [27].

Diabetes mellitus causes complications in 6% to 9% of pregnancies. The likelihood of preterm labor is elevated in women alongside diabetes mellitus [27]. In patients with diabetes mellitus, preterm birth can occur due to iatrogenic due to maternal deterioration or spontaneous preterm birth. In a study based on observation, it was discovered that women who have diabetes mellitus or gestational diabetes had an augmented risk of preterm birth as opposed to normal women (Kock et al. 2010) [28].

Robinson and Nortwitz (2019) revealed that an experience of preterm birth represents the principal risk element for recurrence, along with recurrence frequently occurs at the equivalent gestational age. In one study of more than 1 million pregnant women, there was a significant increased risk for premature birth among women expecting who have experienced abortion in the past, but not for those who experienced medical termination of pregnancy [19]. Hidayati's research, 2016 found having a history of preterm labor in mothers increases the likelihood of future premature labor that represents a risk that is 17.8 times greater than that faced by mothers who do not have a history of early labor [29].

Research by Rao (2017) states that pregnant women with a height of < 145 cm have a high probability of preterm delivery [30]. Pregnant women with a taller stature often have a reduced risk (Ganchimeg et al. 2014) [31].

Pregnant women aged 10 to 19 years will face a chance of early birth in contrast with women who become pregnant between the ages of 20 and 24. Some teenage pregnancies occur because they are planned or desired. As many as 15 million women are married under the age of 18, and 90% give birth between the ages of 15 and 19. However, most teenage pregnancies are not planned or desired. (Ganchimeg et al. 2014) [31]. Several studies mention that pregnant women with the age of less than 19 years have a probability of preterm delivery (Azevedo et al. 2015) [32].

According to researchers, intrinsic factors affect the frequency of early birth in mothers classified as high-risk because in this intrinsic fact there are variables that have a direct contribution to the prevalence of preterm labor, namely elements of history of comorbidities, Hb levels and BMI of pregnant women. The history of these comorbidities has a great influence with respect to the prevalence of preterm labor because the presence of comorbidities will cause vulnerability to the mother and fetus being conceived. Low Hb levels will also interfere with oxygen circulation to the mother and fetus, aggravating the condition of both. Meanwhile, BMI in pregnant women affects the nutritional intake received by the mother and fetus. Mothers with underweight BMI will reduce nutrients to the fetus so that it interferes with fetal growth and development, while obese mothers with excess nutrition can also interfere with normal fetal growth and development.

Other variables also affect the occurrence of preterm birth if it occurs simultaneously between several variables, including variables such as multiple pregnancy history, abortion history, history of spontaneous birth, height < 145 cm, and childbirth age that is too young or too old.

#### **4. Conclusion**

Simultaneously, intrinsic factors affect the frequency of early birth in mothers Involving significant risk pregnancies, while independently only variables, disease history, BMI, and Hb levels Affect the occurrence of premature birth among mothers with elevated-risk pregnancies.

#### **Reference**

- [1] Holness N. High-risk pregnancy. *Nursing Clinics*. 2018;53(2):241–51.10.1016/j.cnur.2018.01.010
- [2] Berek JS. Berk And Novak's Gynecology. 16th Ed. Philadelphia: Lippincott Williams And Wilkins; 2020
- [3] Vivekanand Khandre, Jyotsana Potdar, and Akshunna Keerti. Preterm Birth: An Overview. *Journal Cureus*.V.14(12); 2022 Dec PMC9879350
- [4] Bajalan Z, Sabzevariha Z, Abdollahi F, Qolizadeh A. Prevalence Of High-Risk Pregnancies And The Correlation Between The Method Of Delivery And The Maternal And Neonatal Outcomes. *Journal Of Pediatric Nursing*. 2019;5:52–8.
- [5] Osterman MJK, Kochanej KD, MacDorman MF, Strobino DM, Guyer B, 2015. Annual summary of vital statistics: 2012-

- 2013, Pediatrics, pp. 1115-1125
- [6] Berghella V, 2017. Obstetric evidence based guidelines third edition, CRC Press, Philadelphia, Pennsylvania USA.
- [7] POGI Cabang Bandung, 2011. Panduan pengelolaan persalinan preterm nasional, Perkumpulan Obstetri dan Ginekologi Indonesia, Bandung.
- [8] Riskesdas, 2013. Riset kesehatan dasar (Riskesdas 2013), Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan, Jakarta.
- [9] WHO, 2018. Preterm birth, WHO news 19 February 2018, downloaded 20 July 2024.
- [10] Matthew J, Allen D, Myrna G, Serrano, Lindsey P, Pflugner BS, Jennifer MF, Prestosa MA, Vishal NK, Brooks JP, Strauss JF, Romero R, Chaiworapongsa T, Eschenbach DA, Gregory AB, & Kimberl, 2015. Identification of a gene in mycoplasma hominis associated with preterm birth and microbial burden in intra-amniotic infection. *Am J Obstet Gynecol*, pp. 1-13.
- [11] Lockwood CJ. Pathogenesis of spontaneous preterm birth. Berghella V, Barss VA (ed), UpToDate, downloaded 27 Agustus 2019, <https://www.uptodate.com/contents/pathogenesis-of-spontaneous-preterm-birth>
- [12] Shapiro GD, Fraser WD and Séguin JR, 2017. Biopsychosocial Factors in Preterm Labor and Delivery. Edozien LC, O'Brien PM (eds). *Biopsychosocial Factors in Obstetrics and Gynaecology*. Cambridge: Cambridge University Press.
- [13] Romero R, Conde-Agudelo A, El-Refaie W, Rode L, Brizot ML, Cetingoz E, et al. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. *Ultrasound Obstet Gynecol*. 2017;49 (3):303-14.
- [14] Xu TT, Zhou F, Deng CY, Huang GQ, Li JK, Wang XD. Low-Dose Aspirin for Preventing Preeclampsia and Its Complications: A Meta-Analysis. *J Clin Hypertens (Greenwich)*. 2015;17(7):567-73.
- [15] NICE Guideline 25: Preterm labour and birth. 2015.
- [16] ACOG Practice Bulletin No. 171: Management of Preterm Labor. *Obstetrics and gynecology*. 2016;128(4): e155-64.
- [17] Simhan HN, Berghela V. Preterm Labour and Birth. In: Creasy RK, Resnik R, Iams JD, Lockwood CJ, Moore T, Greene MF, editors. *Creasy and Resnik's MaternalFetal Medicine: Principles and Practice*: Elsevier Health Science: 2014
- [18] Prawirohadjo. S, 2016, Buku Acuan Nasional Kesehatan Maternal Dan Neonatal Edisi 5. Jakarta. Hal 667-675
- [19] Robinson JN, Norwitz ER, 2019. Preterm birth: Risk factors, interventions for risk reduction, and maternal prognosis, CharLockwood CJ (ed.),
- [20] Ota E, Hori H, Mori R, Tobe-Gai R, Farrar D. Antenatal dietary education and supplementation to increase energy and protein intake. *Cochrane Database Syst Rev*. 2015(6):CD000032.
- [21] Furber CM, McGowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. Antenatal interventions for reducing weight in obese women for improving pregnancy outcome. *Cochrane Database Syst Rev*. 2013(1):CD009334.
- [22] Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW, et al. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 2013; 346: f3443.
- [23] Kassebaum NJ, 2016. The global burden of anemia, Seattle USA, *Hematol Oncol Clin N Am*, vol. 30, pp. 247–308.
- [24] Agustina T, 2012. Faktor-faktor yang berhubungan dengan persalinan prematur di Indonesia tahun 2010 (analisis data Riskesdas 2010), Skripsi, Jakarta: Fakultas Kesehatan Masyarakat Universitas Indonesia
- [25] Tehranian, N., Ranjbar M., Shoebeiri, F. 2016. The Prevalence Rate and Risk Factors Preterm Delivery in Teran, Iran : *J. Midwifery Health* : 4 (2) : 600 600 – 604.
- [26] Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. *Am J Clin Nutr*. 2016;103(2):495-504.
- [27] Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 2014;348:g2301
- [28] Kock K, Kock F, Klein K, Bancher-Todesca D, Helmer H. Diabetes mellitus and the risk of preterm birth with regard to the risk of spontaneous preterm birth. *J Matern Fetal Neonatal Med*. 2010;23(9):1004-8
- [29] Hidayati L, 2016. Faktor risiko terjadinya persalinan prematur mengancam di RSUD DR. Soetomo Surabaya, Skripsi, Fakultas Kedokteran Universitas Airlangga, Surabaya.
- [30] Raoa CR, Parvati B, Vandana KEc, Veena K, Asha K, Dinesh N, Revathi PS, Shashikala KB, 2017. Assessment of risk

factors and predictors for spontaneous pre-term birth in a South Indian antenatal cohort ." *Clinical Epidemiology and Global Health*, p2213-3984 <http://dx.doi.org/10.1016/j.cegh.2017.07.001>

- [31] Ganchimeg T, Ota E, Morisaki N, Laopaiboon M, Lumbiganon P, Zhang J, et al. Pregnancy and childbirth outcomes among adolescent mothers: a World Health Organization multicountry study. *BJOG*. 2014;121 Suppl 1:40-8
- [32] Azevedo WF, Diniz MB, Fonseca ES, Azevedo LM, Evangelista CB. Complications in adolescent pregnancy: systematic review of the literature. *Einstein (Sao Paulo)*. 2015;13(4):618-26.