**Research Article**

# Anemia in Pregnancy and Its Maternal Perinatal Outcome

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## Abstract

**Objective:** To investigate the relationship between anemia in pregnancy and maternal perinatal outcomes.

**Methods:** This was a retrospective cohort study. This research was held at Prof. Dr. R. D. Kandou General Hospital Manado. Data was taken from January 2021 to December 2022.

**Results:** There were 1953 deliveries which 1304 subjects (66.7%) with anemia 649 subjects with anemia (33.3%), 489 subjects with mild anemia, and 160 subjects with moderate-severe anemia. The median maternal age was 28 years for mild anemia. The majority of mothers have a high school education. A total of 326 study subjects were multigravidas with mild anemia. The results of severe preeclampsia with mild anemia were 30 subjects. Prolonged labor tends to be higher in the mild anemia group. The highest distribution was observed in the mild anemia group, with 12 cases of maternal mortality, 88 cases of premature birth, 78 cases of low birth weight (LBW), 75 cases of disorders leading to decreased scores, and 24 cases of fetal mortality. In research subjects, IUGR tends to be more common in groups with moderate-severe anemia with 14 subjects (8.8%). Hemoglobin levels showed a median of 11.6 g/dL with a distribution midway between 10.5 and 12.6 g/dL. The mean MCV value is 76.1 fL (SD 8 fL). The mean MCH value was 24.8 + 3.6 pg. The MCHC value is 32.5%. Conclusions: There are no significant relation in pregnant women with anemia with preeclampsia, prolonged labor, maternal mortality rate and IUGR, but there are significant relation between anemia in pregnancy with increase rate of caesarean section, premature delivery, low birth weight, low APGAR score and fetal death.

**Keywords:** anemia in pregnancy, maternal outcome, neonatal outcome.

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## INTRODUCTION

Anemia is a global health issue that also affects pregnant women. The prevalence of anemia varies according to socioeconomic status and lifestyle factors. It is primarily caused by iron deficiency, followed by other micronutrient deficiencies, infections, and hereditary hemoglobinopathies.[1] Forty percent of pregnant women worldwide are anemic, with 56% of women in low- to moderate-income countries affected.[2,3] Indonesia has shown an upward trend in the prevalence of anemia from 2015 to 2019. Among ASEAN countries, Indonesia ranked fourth highest in the prevalence of anemia during pregnancy in 2019, with a rate of 44.2%, while Cambodia had the highest rate at 47.8%.[4] Anemia in pregnancy in North Sulawesi in 2018 was 455 cases and this is increased from 2017 which are 339 cases, while in Manado itself there was 11% pregnant women with anemia[5].

Anemia in pregnancy is related to adverse outcomes and increases the risk of maternal and perinatal mortality rates. Various research shows that anemia in pregnancy contributes to 23% indirect cause of maternal mortality rate in developing countries.[5-7] Maternal outcomes of anemia in pregnancy are preeclampsia, hemorrhagic postpartum, and maternal mortality. Research showed that severe anemia in pregnancy has 3 times the risk of preeclampsia.[8-11] Perinatal outcomes that can happen in anemia in pregnancy are premature delivery, low birth weight, intrauterine fetal death (IUFD), low APGAR score, and intrauterine growth restriction

(IUGR).[9,12-15] Similar results show that anemia in pregnancy has lower birth weight outcomes.15 This research aimed to analyze the relation between anemia in pregnancy and maternal and perinatal outcomes, and further quantify the risk.

## METHODS

This was a retrospective cohort study with primary data from blood work and secondary data from pregnant women who delivered at the research site. This research was held at Prof. Dr. R. D. Kandou General Hospital Manado, and the data taken was from January 2021 to December 2022 with the number of ethical clearance No. 239/EC/KEPK-KANDOU/XI/2022. The inclusion criteria for this research were women with a gestational age of > 20 weeks and blood works of hemoglobin level, MCV, MCH, and MCHC. Women with chronic diseases like tuberculosis and malignancy were excluded. Data taken was then analyzed using Fisher's test and the Kruskal-Wallis test according to the variable. At the same time, the correlation of anemia in pregnancy with the outcomes was analyzed with a logistic regression model.

## RESULTS

There were 1953 deliveries with 1304 subjects (66.7%) with non anemia and 649 subjects with anemia (33.3%), with 489 subjects with mild anemia and 160 subjects with moderate-severe anemia Table 1 showed the characteristics of research subjects.

**Table 1.** Characteristic of Research Subjects

| Characteristics | Mild Anemia | | Moderate-Severe Anemia | |
|---|---|---|---|---|
| | n (%) | Median (Q1;Q2) | n (%) | Median (Q1;Q2) |
| **Maternal age** | | 28 (23-33) | | 26 (22-32) |
| < 20 | 63 (12.8) | | 21 (13.1) | |
| 20-35 | 338 (69.2) | | 115 (71.9) | |
| > 35 | 88 (18) | | 24 (15) | |
| **Maternal educational level** | | | | |
| Junior high/lower | 105 (21.5) | | 46 (28.8) | |
| Senior high | 268 (54.8) | | 85 (53.1) | |
| Diplome/Bachelor | 116 (23.7) | | 29 (18.1 | |
| **Parity** | | | | |
| Primigravida | 163 (33.3) | | 51 (31.9) | |
| Multigravida | 326 (66.7) | | 109 (68.1) | |
| Total ANC | | 5 (2-7) | | 3 (1-5) |
| Never | 76 (15.5) | | 32 (20) | |
| 1-3 | 94 (9.2) | | 50 (31.3) | |
| > 4 | 319 (65.3) | | 78 (48.7) | |
| **ANC provider** | | | | |
| General practitioner/Clinic | 16 (3.3) | | 4 (2.5) | |
| Primary Health Care/Midwife | 125 (25.6) | | 48 (30) | |
| Obgyin/Hospital | 272 (55.6) | | 76 (47.5) | |
| Never | 76 (15.5) | | 32 (20) | |

*NOTE:* Characteristic and distribution of research subjects

From all the deliveries taken within the period, we obtained 649 subjects with anemia, where 489 and 160 subjects had mild anemia and moderate-severe anemia respectively. There were 338 (69,2%) research subjects who delivered at 20 – 35 years old in the mild anemia group and 115 (71.9%) in the moderate-severe anemia group. Most of the research subjects (348/649 research subjects, 53.6%) did antenatal in hospital with an OBGYN specialist, and more than 60% of subjects went for antenatal care > 4x visits. Table 2. describes the distribution of maternal and perinatal outcomes for research subjects with mild and moderate-severe anemia. Maternal and perinatal outcomes are categorized as preeclampsia, prolonged labor, cesarean section, maternal mortality, premature delivery, low birth weight, low APGAR score, IUGR, and IUFD.

**Table 2.** Maternal and Perinatal Outcome

| Characteristics | Mild Anemia | Moderate-Severe Anemia |
|---|---|---|
| | n (%) | n (%) |
| **Preeclampsia/Eclampsia** | | |
| Not preeclampsia | 434 (88.8) | 143 (89.4) |
| Preeclampsia | 6 (1.2) | 1 (0.6) |
| Severe Preeclampsia | 30 (6.1) | 13 (8.1) |
| I mpending eclampsia – eclampsia | 19 (3.9) | 3 (1.9 |
| Prolonged labor | 20 (4) | 9 (5.6) |
| **Delivery method** | | |
| Vaginal delivery | 166 (33.9) | 50 (31.3) |
| Cesarean section | 323 (66.1) | 108 (67.5) |
| Maternal Mortality | 12 (2.5) | 0 |
| Premature Delivery | 88 (18) | 38 (23.7) |
| Low Birth Weight | 78 (16) | 41 (25.6) |
| APGAR 5' | 75 (15.3) | 47 (29.4) |
| IUGR | 12 (2.5) | 14 (8.8) |
| IUFD | 24 (4.9) | 22 (13.8) |

*Notes:* SD standard deviation, Q1 quartile I, Q3 quartile III, Low Birth Weight (< 2500 g), IUGR *intrauterine growth restriction* according to Lubchenco

Table 2 shows that prolonged labor tends to occur in the mild anemia group. In contrast, IUGR tend to occur more in the moderate-severe group.

**Table 3.** Classification and Degree of Anemia

| Characteristics | *n* (%) | Mean ± SD | Med (Q1; Q3) | |
|---|---|---|---|---|
| **Hemoglobin (g/dL)** | | | 11.6 | (10.5 ; 12.6) |
| MCV (fL) | | 76.1 + 8 | | |
| Normocytic | 169 (9) | | | |
| Microcytic | 303 (16) | | | |
| MCH (pg) | | 24.8 + 3.6 | | |
| Normochromic | 175 (9) | | | |
| Hypochromic | 297 (15) | | | |
| MCHC (%) | | | | |
| **Anemia status** | | | 32.5 | (31 ; 33,7) |
| Non-Anemia (Hb > 11 g/dL) | 1304 (67) | | | |
| Mild (Hb 9 – 10.9 g/dL) | 489 (25) | | | |
| Moderate (Hb 7 – 8.9 g/dL) | 125 (6.3) | | | |
| Severe (Hb < 7 g/dL) | 35 (1.7) | | | |
| Classification of Anemia | | | | |
| Normocytic Normochromic | 139 (7) | | | |
| Normocytic Hypochromic | 30 (1.5) | | | |
| Microcytic Normochromic | 36 (1.8) | | | |
| Microcytic Hypochromic | 267 (13.7) | | | |

*Notes:* SD standard deviation, Q1 quartile I, Q3 quartile III, MCV mean corpuscular volume, MCH mean corpuscular hemoglobin, MCHC mean corpuscular hemoglobin concentration

Hemoglobin concentration showed a median of 11.6 g/dL with a range of 10.5 and 12.6 g/dL. The average MCV value was 76.1 fL (SD 8 fL). MCV value showed the result was below normal value, indicating that the erythrocytes tend to be smaller in size (mycrocytic). The MCH value was 27-35pg. In this research mean MCH values were 24.8 + 3.6 pg with MCHC value 32.5%. Table 4 describes the relation between anemia in pregnancy and maternal and perinatal outcomes with univariate and multivariate regression models to analyze the odds ratio.

**Table 4.** Maternal and Perinatal Outcome in Relation of Anemia in Pregnancy with Non-Anemia on Univariate and Multivariate Regression Model

| Outcome | Univariate | | Multivariate | |
|---|---|---|---|---|
| | ***OR* (95% CI)** | ***P-value*** | ***OR* (95% CI)** | ***P-value*** |
| Preeclampsia/ Eclampsia | 0.52 ( 0.40 ; 0.68) | < 0,001 | 0.53 ( 0.40 ; 0.69) | < 0.001 |
| Prolonged Labor | 0.72 ( 0.43 ; 1.20) | 0.208 | 0.68 ( 0.41 ; 1.14) | 0.146 |
| Caesarean Section | 1.04 ( 0.85 ; 1.27) | 0.708 | 4.33 ( 2.70 ; 6.96) | < 0.001 |
| Maternal Mortality | 1.06 ( 0.45 ; 251) | 0.899 | 0.00 ( 0.00 ; 0.0) | 0.985 |
| Prematurity | 1.03 ( 0.78 ; 1.34) | 0.848 | 1.79 ( 1.20 ; 2.67) | 0.004 |
| Low Birth Weight | 1.01 ( 0.80 ; 1.27) | 0.953 | 1.60 ( 1.12 ; 2.27) | 0.009 |
| APGAR 5' (β )* | -0.28 (-0.47 ; -0.09) | 0.003 | -0.65 (-0.96 ; -0.34) | < 0.001 |
| IUGR | 1.15 ( 0.84 ; 1.56) | 0.384 | 1.10 ( 0.80 ; 1.50) | 0.557 |
| Fetal Death | 1.59 ( 1.04 ; 2.43) | 0.032 | 1.62 ( 1.06 ; 2.48) | 0.026 |

NOTES: CI *confidence interval,* OR odds rasio, Low Birth Weight (< 2500 g), IUGR *(intrauterine growth restriction)* according to Lubchenco. * Linear coefficient regression to evaluate APGAR score

Table 4 showed there is no significant relation between anemia in pregnancy and preeclampsia/ eclampsia (p<0.001) and prolonged labor (p<0.146). Anemia in pregnancy related with increase rate of caesarean section by almost 4.33 times in compared with non anemic patient (OR 4.33, p<0.001). there is significant relation between anemia in pregnancy and the incidence of premature delivery (p<0.004). low birth weight (p<0.009), low APGAR score (p<0.001) and fetal death (p<0.026). While there is no significant relation between IUGR and anemia in pregnancy (p<0.557).

## DISCUSSION

This research showed no relation between anemia in pregnancy and preeclampsia (Univariate OR 0.52 %, 95% CI 0.4 – 0.68, P < 0.001 vs multivariate OR 0.53 %, 95% CI 0.4 – 0.69, P < 0.001). The mechanism of preeclampsia in anemia in pregnancy is caused by micronutrient deficiency. In this mechanism, norepinephrine induces the synthesis of corticotropin-releasing hormone (CRH) which is produced by the placenta. CRH stimulates inflammatory cytokines, glucocorticoid, and oxidative stress. Oxidative stress stimulates angiotensin receptor 1-autoantibodies (AT1-AAs) which induce sFlt-1 and sEng which bind to vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). This condition affects systemic vascular resistance.

A previous study described the relationship between anemia in pregnancy with preeclampsia. Severe anemia has the tendency of preeclampsia up to 3 times higher. Another research was done at Airlangga University Hospital Surabaya where there was no significant relation between anemia in pregnancy and preeclampsia. This relation might be due to an increase in plasma volume with a reduction of hemoglobin level which causes hemodilution while MCV, MCH, and MCHC tend to increase. [16,17]

In this research, there is no relation between anemia in pregnancy with prolonged labor (Univariate OR 0.72%, 95% CI 0.43 – 1.20, P 0.208 vs Multivariate OR 0.68%, 95% CI 0.41 – 1.14, P 0.146). This result differs from several studies that support anemia in pregnancy related to the progressivity of delivery during stage one labor and weakening of contraction at stage two. Prolonged stage one might happen because of low hemoglobin levels causing the reduction of the circulating oxygen level to the brain. Hence the oxygen level to the uterus is also reduced causing weakening of uterine contraction, causing cervical ripening to become prolonged.[18,19] This difference might be because of most of our research subjects have mild anemia. Several studies showed that moderate-severe anemia may cause prolonged labor. Mothers with moderate-severe anemia tend to prolong the labor compared with mild anemia (OR 4.681).[20]

This research found that there is no significant relation between anemia in pregnancy and maternal mortality (Univariate OR 1.06%, 95% CI 0.45 – 2.51, P 0.899 vs multivariate OR 0.00, 95% CI 0.00 – ∞, P 0.985). There is a discrepancy between the univariate and multivariate tests. During this study period, 17 out of a total of 23 subjects (73.91%) were affected. At least the total sample and cause of date is COVID-19 which might affect the sample. Severe anemia reduces the availability of oxygen in tissue, reduces iron for DNA synthesis, and changes enzyme function

all of which contribute to the association of anemia in pregnancy and maternal mortality. Severe anemia gives a 2.36 times higher chance mother with severe anemia death.

There is significant relation between anemia in pregnancy and premature delivery. In this study the chance of premature delivery increase as high as 1.79 times compared to non anemic patient (Univariate OR 1.03%, 95% CI 0.78 – 1.34, P 0.848 vs multivariate OR 1.79, 95% CI 1.20 – 2.67, P 0.004). Anemia cause tissue hypoxia and directly increase corticotropin hormone (CRH) release, which induce delivery. CRH also can inhibit fetal growth.[21-23] This result is in accordance with several previous research. There is 4 times chance of premature delivery with anemia in pregnancy.[21] Sixty one percent anemic mother had adverse perinatal outcome which one of them is preterm delivery (22.2%).[22]

There is significant relation between anemia in pregnancy and low birth weight. Anemia in pregnancy increase the incidence of low birth weight about 1.6 times then non anemic mother (Univariate OR 1.01%, 95% CI 0.80 – 1.27, P 0.953 vs multivariate OR 1.6, 95% CI 1.12 – 2.27, P 0.009). This research is in accordance with several research where anemia in pregnancy causing low birth weight (birth weight <2500 g). The risk of low birth weight in mother with anemia increase 1.9 times compared to non anemic mother.[21] Anemia in pregnancy causing changes in hemoglobin concentration level which related to birth weight.[23]

Anemia in pregnancy tend to lower APGAR score (Univariate OR -0.28%, 95% CI -0.47 – (-0.09), P 0.003 vs multivariate OR -0.65, 95% CI -0.96 – (-0.34), P < 0.001). The risk of APGAR score within 1 minute is < 5 and within 5 minutes is < 7 and tend to be lowered in anemic mother.[21] Fourty out of 405 pregnant women had APGAR score < 7 in the first 1 minute and 5 minutes.[23]

In this research there is no significant relation between anemia in pregnancy and IUGR (Univariate OR 1.15%, 95% CI 0.84 – 1.56, P 0.384 vs multivariate OR 1.1, 95% CI 0.80– 1.50, P 0.557). Even though there was a tendency for the probability of IUGR to increase in more severe anemia. To explain the mechanism of anemia in pregnancy for causing adverse perinatal outcome, several aspect can be seen like uteroplacental circulation. In anemia in pregnancy the amount of oxygenated blood towards uteroplacental circulation is low and lowered nutrient distribution, thus causing fetal growth restriction.

There was a significant relation between fetal mortality and anemia in pregnancy. Anemia in pregnancy increases fetal mortality rate as high as 1.62 times compared to nonanemic mother (Univariate OR 1.59%, 95% CI 1.04 – 2.43, P 0.032 vs multivariate OR 1.62, 95% CI 1.06 – 2.48, P 0.026). Severe anemia further worsens the fetal mortality. Studies showed that 61.9% of anemia in pregnancy causes adverse perinatal outcomes like IUFD or stillbirth as high as 1.5%.24 While research from Rahman et al showed perinatal mortality (OR, 2.90; 1.97-3,78, p < 0,05) in anemic mothers during pregnancy[23] Disease or inadequate nutrition during pregnancy further disrupts fetal growth. Thus causing low birth weight, premature delivery, and stillbirth. These factors are the primary contributors to neonatal mortality.[24]

## CONCLUSION

There is no significant relation between mothers with anemia in pregnancy with preeclampsia, prolonged labor, IUGR, and maternal mortality. There was a significant relation between anemia in pregnancy with an increased rate of cesarean section, premature delivery, low birth weight, low APGAR score, and fetal mortality.

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