Research Article

Analysis of causes, Maternal and Perinatal Outcomes in Third Trimester Pregnant Women with Normocytic Anemia

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Abstract

Objective: To analyze the causes and the maternal and perinatal outcomes of normocytic anemia in third-trimester pregnant women.

Methods: This study employed a descriptive-analytical, observational cross-sectional design to assess laboratory findings in anemic pregnant women, and a cohort design to evaluate maternal and perinatal outcomes in third-trimester pregnant women with normocytic anemia. The chi-square test was used to measure the strength of associations between variables. Laboratory tests included complete blood count, ferritin, TIBC, serum iron, reticulocyte count, and peripheral blood smear.

Results: Among the 50 pregnant women with normocytic anemia, 92.0% had mild anemia and 8.0% had moderate anemia; no cases of severe anemia were found. Maternal and perinatal outcomes showed significant associations ($p < 0.05$). Most third-trimester pregnant women had low serum iron levels <37 µg/dL (52.2%) in the mild-anemia group and normal serum iron levels of 37–148 µg/dL (75%) in the moderate-anemia group. Most participants also had low ferritin levels <13 ng/mL in both the mild-anemia (82.6%) and moderate-anemia (100%) groups. High TIBC levels ≥389 µg/dL were found in 87% of mild-anemia cases and in all moderate-anemia cases. Reticulocyte counts were elevated (>1.50%) in both mild and moderate anemia.

Conclusion: Chronic illness and infection were the most common causes of normocytic anemia in third-trimester pregnant women in this study. However, the normocytic anemia observed showed serum ferritin and iron profiles similar to microcytic anemia, suggesting that iron deficiency may be a contributing factor.

Keywords: ferritin, maternal and perinatal outcomes, normocytic anemia, pregnancy, reticulocytes, serum Fe, TIBC.

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INTRODUCTION

Anemia is a medical condition characterized by a reduction in the number of red blood cells or a decrease in oxygen-carrying capacity, resulting in diminished ability of the body to transport oxygen[1]. It is estimated that around two billion people worldwide suffer from anemia, with the highest prevalence observed in Asia and Africa[2]. The World Health Organization (WHO) reports that anemia affects approximately half a billion women aged 15–49 years and 269 million children aged 6–59 months globally. In 2019, 30% (539 million) of non-pregnant women and 37% (32 million) of pregnant women aged 15–49 experienced anemia[3]. Furthermore, data from the 2018 Basic Health Research (Riskesdas) in Indonesia indicates a concerning rise in the prevalence of anemia among pregnant women, increasing from 37.1% in 2013 to 48.9% in 2018. This upward trend underscores the urgency of addressing the issue, as maternal health continues to be a critical priority requiring immediate attention[4].

Anemia can be categorized based on its morphological characteristics into normocytic,

microcytic, and macrocytic anemia[5]. Normocytic anemia, primarily caused by chronic disease, is the second most prevalent type globally, following iron deficiency anemia[6]. The consequences of anemia significantly affect both maternal and fetal health by impairing the efficient transfer of oxygen from the placenta to the fetus, thereby inhibiting normal intrauterine growth and potentially leading to adverse outcomes, including fetal demise. Studies have shown that anemia is associated with increased risks of preterm birth (28.2%), preeclampsia (31.2%), and maternal sepsis. Numerous studies consistently demonstrate a strong correlation between anemia and heightened maternal morbidity and mortality[7].

Anemia is not a single disease but rather a manifestation of various underlying conditions. Therefore, diagnosing anemia requires more than simply identifying its presence; it is essential to determine the underlying cause[8]. This step is crucial, as the causative condition is often hidden. Identifying the underlying disease is also vital for effective management, since therapy cannot be optimally provided without understanding the root cause of the anemia[8]. Anemia may be suspected based on patient history and physical examination; however, laboratory evaluation particularly a complete blood count is the definitive method for confirming anemia. If anemia is suspected, laboratory assessment is necessary to validate the diagnosis, determine its severity, and identify its etiology[8].

One of the government programs in Indonesia to prevent anemia is the provision of 90 iron-folic acid tablets during pregnancy. However, the prevalence of anemia remains high. In 2018 *Riset Kesehatan Dasar (Riskesdas)*, the prevalence of anemia in Indonesia was 48.9%, exceeding the global average of 40%[3,9]. In response to this phenomenon, the present study was conducted with the aim of analyzing the causes and the maternal and perinatal outcomes in third-trimester pregnant women.

METHODS

Participants were third-trimester pregnant women with hemoglobin levels <11 g/dL and MCV values of 80–100 fL who attended prenatal visits and agreed to participate after providing informed consent. Third-trimester pregnant women from community health centers and mother-and-child hospitals in Makassar City were screened for hemoglobin levels using Sahli hemoglobin and digital hemoglobin test kits from October 2021 to June 2022. After hemoglobin levels <11 g/dL were confirmed, participants provided informed consent and completed a questionnaire through an interview.

A 9 mL blood sample was collected in an EDTA anticoagulant tube and sent to Dr. Wahidin Sudirohusodo Central General Hospital for complete laboratory testing, including serum iron (Fe), ferritin, TIBC, and reticulocyte count. Participants were subsequently monitored to assess maternal and perinatal outcomes. Laboratory tests included a complete blood count to determine anemia severity, MCV for anemia morphology classification, and measurements of serum Fe, ferritin, TIBC, and reticulocytes. Categories for serum Fe, ferritin, TIBC, and reticulocyte levels were predefined.

Maternal outcomes assessed included mode of delivery and complications such as preeclampsia, prolonged labor, premature rupture of membranes (PROM), hemorrhage, and placenta previa. Perinatal outcomes evaluated included birth weight and neonatal asphyxia (Apgar score 0–6).

This study employed a hybrid design combining descriptive analytical and observational methods, using a cross-sectional approach for laboratory examinations and a cohort approach for maternal and perinatal outcomes. Bivariate analysis was conducted using the chi-square test to evaluate the relationships between variables. The sample size was determined using the Slovin formula with a 99% confidence level. From a population of 160 third-trimester pregnant women with anemia, the final sample consisted of 50 pregnant women diagnosed with normocytic anemia.

RESULTS

Of the 162 pregnant women who underwent comprehensive blood tests, 120 (74.0%) were in their third trimester and had anemia, while 42 (26.0%) were in their third trimester without anemia. Among the 120 pregnant women in their third trimester with anemia, 50 (30.8%) showed normocytic anemia (MCV 80-100 fL), 70 (43.2%) had microcytic anemia (MCV < 80 fL), and none showed signs of macrocytic anemia (MCV > 100 fL). In the group of 50 pregnant women with normocytic anemia, 46 (92.0%) had mild anemia, 4 (8.0%) had moderate anemia, and there were no cases of severe anemia.

Table 1. Analysis of the Degree of Normocytic Anemia in Third Trimester Pregnant Women Using Laboratory Examination Results

Variable	Degree of Anemia		N (%)
	Mild (Hb 10-10.9 g/dL)	Moderate (Hb 7.0-9.9 g/dL)	
Serum Fe			
Low (< 37 µ/dL)	24 (52.2)	1 (25)	25 (50)
Normal (37-148 µ/dL)	22 (47.8)	3 (75)	25 (50)
Ferritin			
Low (< 13 ng/dL)	38 (82.6)	4 (100)	42 (84)
Normal (13-400 ng/dL)	8 (17.4)	0 (0)	8 (16)
Total Iron Binding Capacity (TIBC)			
Low (< 274 µ/dL)	1 (2.1)	0 (0)	1 (2)
Normal (274-389 µ/dL)	5 (10.6)	0 (0)	5 (10)
High (≥ 389 µ/dL)	40 (87)	4 (100)	44 (88)
Reticulocytes			
Normal (0.50-1.50%)	0 (0)	0 (0)	0 (0)
High (>1.50%)	46 (100)	4 (100)	50 (100)

Table 2. Analysis of the Relationship between the Degree of Normocytic Anemia in Third Trimester Pregnant Women and Maternal and Perinatal Outcomes

Variable	Degree of Anemia		*P-value*	RR (CI 95%)
	Mild (Hb 10-10.9 g/dL)	Moderate (Hb 7.0-9.9 g/dL)		
Types of childbirth			0.038	3.21 (0.58-17.67)
Normal	37 (80.4)	1 (25)		
Sectio Cesarea (SC)	9 (19.6)	3 (75)		
Childbirth problems			0.010	0.28 (0.17-0.44)
There is	13 (28.3)	4 (100)		
There isn't any	33 (71.7)	0 (0)		
Baby's birth weight			0.003	0.19 (0.10-0.35)
Normal (BB 2500-4000 gr)	37 (80.4)	0 (0)		
LBW (BB < 2500 gr)	9 (19.6)	4 (100)		
Newborn asphyxia			0.022	0.20 (0.08-0.49)
Yes	7 (15.2)	3 (75)		
No	39 (84.8)	1 (25		

Description: Chi Square test, $p < 0.05$

DISCUSSION

In this study, among mothers with serum iron levels < 37 µ/dL, 52.2% had mild anemia and 25% had moderate anemia. Among those with normal serum iron levels (37–148 µ/dL), 47.8% had mild anemia and 75% had moderate anemia. No participants showed elevated serum iron levels (>148 µ/dL). These findings differ from previous research, which reported that 100% of pregnant women with normochromic normocytic anemia had normal serum iron levels[10]. Only 7% of mothers in this study exhibited a normocytic pattern, all of whom consistently consumed iron supplements and vitamins. Despite all participants having kidney infections, their serum iron, vitamin B12, and folate levels remained normal. Anemia of chronic disease, also known as Anemia of Inflammation (AI), typically presents as mild to moderate normochromic normocytic anemia, caused by systemic inflammation that disrupts erythrocyte production and survival. In AI, hemoglobin levels rarely fall below 8 g/dL, and both AI and Iron Deficiency Anemia (IDA) may present with low serum iron[5].

Low ferritin levels (<13 ng/dL) were identified in 82.6% of mothers with mild anemia and 100% of mothers with moderate anemia. Among those with normal ferritin levels (13–400 ng/dL), 17.4% had mild anemia and none had moderate anemia. Most third-trimester pregnant women with normocytic anemia exhibited low ferritin levels, and no cases of elevated ferritin (≥400 ng/dL) were found. Low ferritin may indicate combined

AI and IDA or be influenced by comorbid health conditions. Ferritin typically remains normal or elevated in AI, whereas IDA is associated with low ferritin. The coexistence of AI and IDA can therefore result in decreased ferritin5. Low serum ferritin confirms iron deficiency regardless of hemoglobin status. During infection, ferritin may appear normal or elevated because apoferritin functions as an acute-phase protein similar to CRP. In pregnancy, ferritin decreases due to hemodilution, peaking at 12–16 weeks and declining thereafter[11]. In Indonesia, first-trimester serum ferritin ≤ 27.23 ng/mL was identified as a strong predictor of third-trimester anemia[12].

Low TIBC (<274 µ/dL) was observed in 2.1% of mothers with mild anemia and none with moderate anemia. For normal TIBC (274–389 µ/dL), 10.9% had mild anemia and none had moderate anemia. High TIBC (≥389 µ/dL) was present in 87.0% of mothers with mild anemia and 100% with moderate anemia. TIBC reflects serum transferrin concentration, which increases in iron deficiency. However, interpretation must consider inflammatory conditions, chronic infection, kidney disease, and malignancy. In IDA, serum iron decreases while TIBC increases, making transferrin saturation the most sensitive indicator. Conversely, untreated hemochromatosis is associated with low TIBC[13].

All participants had elevated reticulocyte levels (>1.50%); no normal or low values were observed. Normocytic anemia is characterized by low hemoglobin with normal MCV (80–100 fL). Clinical evaluation is essential to differentiate urgent causes such as active bleeding from non-emergent causes such as AI. The most common cause of normocytic anemia is chronic disease, including infections (18–95%), malignancies (30–77%), chronic kidney disease, and inflammatory disorders (23–50%)[14]. Chronic kidney disease reduces erythropoietin (EPO) production, impairing erythropoiesis. Elevated reticulocytes suggest bleeding or hemolysis, as the bone marrow increases red cell production to compensate[15].

A significant association was found between anemia severity and mode of delivery (normal vs. Cesarean section). Similar findings were reported in previous studies, where mild anemia predominated among women delivering by Cesarean section[16,17]. Other studies also reported that Cesarean delivery was more common among anemic mothers. Although vaginal delivery is possible, anemia may result in poor uterine contractions, prolonged labor, and delayed cervical dilation due to reduced oxygen delivery to the uterus[18]. However, some studies found no significant association between anemia and delivery mode[19].

Anemia severity was also associated with childbirth complications. In this study, complications included preeclampsia (17.6%), prolonged labor (29.5%), premature rupture of membranes (PROM) (17.6%), bleeding (23.5%), and placenta previa (11.8%). These findings align with previous studies reporting high rates of PROM, prolonged labor, and preeclampsia among anemic mothers [2,20-22]. Postpartum Hemorrhage (PPH) was a significant complication, occurring in 3.3% of women with anemia, with increasing risk at moderate to severe anemia ($p = 0.007$). Other studies similarly reported increased preeclampsia and placenta previa among anemic mothers,[23-28]. Anemia contributes to poor uterine contractions due to inadequate oxygen delivery, resulting in prolonged labor and increased risk of PPH. It also predisposes to PROM by weakening the amniotic membrane through impaired perfusion and collagen degradation[24]. Placental abnormalities may also arise due to reduced maternal oxygen reserves, resulting in altered vascular development and heightened susceptibility to hypoxic stress, including elevated CRH levels. Poor placentation and oxidative stress contribute to preeclampsia and fetal growth restriction[22].

Anemia severity was significantly associated with birth weight. Among mothers delivering low-birth-weight (LBW) infants (<2,500 g), 69.2% had mild anemia and 30.8% had moderate anemia. The higher the anemia severity, the greater the risk of LBW. This is consistent with cohort studies reporting increased LBW risk among mothers with moderate and severe anemia[21,23]. Anemia reduces oxygen and nutrient transfer to the fetus, impairing fetal growth. However, a large Californian cohort study found no increased LBW risk but instead reported reduced risk of small-for-gestational-age infants and increased risk of large-for-gestational-age infants[22].

Anemia severity was also associated with neonatal asphyxia. Among infants with asphyxia, 70% were born to mothers with mild anemia and 30% to those with moderate anemia. Severe maternal anemia reduces uteroplacental oxygen delivery, leading to fetal hypoxia, metabolic acidosis, and placental structural changes that impair gas exchange[23]. Previous research reported similar findings, with anemic mothers being 3.43

times more likely to deliver infants with asphyxia (p = 0.000, OR = 3.43)[25]. Although some studies found no statistically significant association, they still observed a higher tendency for asphyxia among newborns of anemic mothers[26].

CONCLUSION

Chronic diseases and infections were the biggest causes of normocytic anemia in third trimester pregnant women in this study, however in this study had a picture of serum ferritin and iron that almost resembled microcytic anemia, which was probably caused by iron deficiency, so it was necessary to examine CRP as a biomarker/ sign of infectious disease.The higher the degree of anemia, the greater the risk of birth problems, which will affect the birth process. Likewise, with perinatal outcomes, the higher the degree of anemia, the greater the incidence of LBW and asphyxia in babies.

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