Thai Journal of Obstetrics and Gynaecology
September 2024, Vol. 32, No. 5, pp. 391-399.

GYNAECOLOGY

Prevalence and Associated Factors of Iron- Deficient Erythropoiesis in Thai Pregnant Women

Palinlat Wittayatanaseth, M.D.*,
Chonlada Laoruangroj, M.D.**,
Sakchai Panitwong, M.D.*

** Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand*
*** Department of Hematology, Phramongkutklao Hospital, Bangkok, Thailand*

ABSTRACT

Objectives: The primary objective was the prevalence of iron-deficient erythropoiesis (IDE) in Thai pregnant women during early pregnancy, with the identification of associated factors as the secondary goal.

Materials and Methods: A cross-sectional survey was conducted on pregnant women aged ≥ 20 years, who visited the antenatal clinic during the first 14 weeks of gestation without anemia. IDE was defined as hemoglobin level ≥ 11 g/dL and serum ferritin < 30 ng/mL.

Results: A total of 130 pregnant women were enrolled. IDE was detected in 10.77% (95% confidence interval 6.26 - 16.83). In univariate analysis, various factors with p value of ≤ 0.2 were identified. From multivariate analysis of these factors, the number of pregnancies (parity ≥ 2) was significantly associated with IDE (adjusted odds ratio 5.728, 95% confidence interval 1.019 - 32.210, p = 0.048).

Conclusion: Out of every 100 pregnant women without anemia, 10 had IDE in early pregnancy. Multiparity emerged as the most significant factor for IDE.

Keywords: Iron-deficient erythropoiesis, iron deficiency anemia, serum ferritin, pregnant women.

Correspondence to: *Palinlat Wittayatanaseth, M.D., Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand. E-mail: Palinlat.wit@gmail.com*

Received: 31 August 2023, **Revised:** 13 May 2024, **Accepted:** 13 June 2024

ความชุกและปัจจัยที่เกี่ยวข้องของการมีธาตุเหล็กสะสมในร่างกายต่ำแต่ยังไม่มีภาวะโลหิตจางในหญิงตั้งครรภ์ชาวไทย

ภาลินรัตน์ วิทยธนเศรษฐ์, ชลลดา เหล่าเรืองโรจน์, ศักดิ์ชัย พานิชวงษ์

บทคัดย่อ

วัตถุประสงค์*: วัตถุประสงค์หลักเพื่อหาความชุกของการมีธาตุเหล็กสะสมในร่างกายต่ำแต่ยังไม่มีภาวะโลหิตจางในช่วงแรกของการตั้งครรภ์ของหญิงตั้งครรภ์ชาวไทย และปัจจัยที่เกี่ยวข้องเป็นวัตถุประสงค์รอง*

วัสดุและวิธีการ*: การศึกษาภาคตัดขวางในหญิงตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 20 ปี ที่มาเข้ารับการฝากครรภ์ในช่วงอายุครรภ์ 14 สัปดาห์แรกที่ไม่มีภาวะซีด โดยนิยามของการมีธาตุเหล็กสะสมในร่างกายต่ำแต่ยังไม่มีภาวะโลหิตจางคือระดับฮีโมโกลบินในเลือดมากกว่าหรือเท่ากับ 11 กรัม/ดล. และค่าซีรัมเฟอริตินน้อยกว่า 30 นาโนกรัม/มล.*

ผลการศึกษา*: ผู้เข้าร่วมการวิจัยทั้งสิ้น 130 ราย พบภาวะธาตุเหล็กสะสมในร่างกายต่ำแต่ไม่มีภาวะโลหิตจางคิดเป็นร้อยละ 10.77 (95% confidence interval 6.26 - 16.83) จากการวิเคราะห์ข้อมูลแบบตัวแปรเดียวพบปัจจัยที่มีค่า $p < 0.2$ จำนวนหลายปัจจัย และเมื่อนำปัจจัย เหล่านั้น มาวิเคราะห์ข้อมูลแบบหลายตัวแปร พบว่าการมีบุตรมากกว่าหรือเท่ากับสองคน มีความสัมพันธ์ต่อการเกิดธาตุเหล็กสะสมในร่างกายต่ำอย่างมีนัยสำคัญทางสถิติ (adjusted odds ratio 5.728, 95% CI 1.019 -32.210, $p = 0.048$)*

สรุป*: ในหญิงตั้งครรภ์จำนวน 100 รายที่ไม่มีภาวะซีด มีโอกาสพบธาตุเหล็กสะสมในร่างกายต่ำแต่ยังไม่มีภาวะโลหิตจางประมาณ 10 ราย ในช่วงแรกของการตั้งครรภ์ ซึ่งปัจจัยเสี่ยงที่สำคัญคือ การตั้งครรภ์มากกว่าหรือเท่ากับ 2 ครั้ง*

คำสำคัญ*: ธาตุเหล็กสะสมในร่างกายต่ำแต่ยังไม่มีภาวะโลหิตจาง, โลหิตจางจากการขาดธาตุเหล็ก, ค่าซีรัมเฟอริติน, หญิงตั้งครรภ์*

Introduction

Iron deficiency is the most global nutritional deficiency disorder, impacting more than 2 billion individuals[1]. Although pregnant women and infants in developing countries are at heightened risk, comparable vulnerabilities are evident in developed nations as well. The World Health Organization (WHO) defines anemia in pregnant women as hemoglobin levels < 11 g/dL during the first trimester[2]. Adverse pregnancy outcomes, such as preeclampsia, preterm birth, and neurocognitive developmental issues are associated with iron deficiency anemia (IDA)[1]. Furthermore, infants born to mothers with IDA often have low birth weight[3]. Beyond its impact on pregnancy, IDA can lead to symptoms like fatigue, and impaired cognitive function in the women.

Iron-deficient erythropoiesis (IDE), also known as latent iron deficiency (LID) is a medical condition characterized by the presence of iron deficiency without concurrent anemia, as evidenced by normal hemoglobin level. Maintaining a balanced iron status is a crucial protective measure against IDA during pregnancy[4]. Individuals with negative iron status may progress to IDA due to an inability to support red blood cell synthesis during menstruation, pregnancy, and lactation(5). Without inflammation, serum ferritin can be a key indicator for assessing iron status and IDE can be diagnosed when the ferritin level is below 30 ng/mL without anemia. It is also important to note that serum iron levels fluctuate throughout the day and should not be solely relied upon for diagnosis[6].

A study conducted at Maharaj Nakorn Chiangmai Hospital in 648 pregnant women across all gestational age revealed a significant prevalence of IDA of 51.8%, with 43.8% of cases exhibiting serum ferritin levels of < 30 ng/mL[3]. Unfortunately, specific data on IDE was not provided. Another study from Naresuan University focusing on the prevalence and risk factors of IDA, which included 401 pregnant women, with and without anemia in all gestational age, revealed 15.2% of IDE and serum ferritin levels < 15 ng/mL[7]. Additionally, a study from China with 4,000 participants included across all gestational ages reported a prevalence of 42.6% for IDE[8]. Notably, none of these studies identified the associated factors of IDE. Conversely, a study conducted in European Mediterranean countries focusing on 791 pregnant women before 12 weeks gestation with a hemoglobin level ≥ 11 g/dL reported a prevalence of 13.9% for iron deficiency with serum ferritin < 15 ng/mL. The associated factors included being underweight, multiparous, or a vegetarian diet[9].

Despite its high prevalence, IDE is often unrecognized by clinicians due to suboptimal screening recommendations[6]. This research emphasizes the important aspect of detecting IDE before it progresses to IDA. Effective prevention of IDA can be achieved through iron supplementation. While many studies primarily focus on populations with established IDA, there is limited attention given to individuals at risk of developing IDA.

This research aimed to identify the prevalence and risk factors of IDE in early pregnancy. The results could be used to guide and generate a strategy for primary prevention of IDA in order to alleviate its consequences during the pregnancy period. Insights from this study can also suggest future investigations into appropriate iron therapy and its impact on newborn iron storage, promoting optimal care throughout pregnancy, post-gestation, and the postnatal periods.

Materials and Methods

A cross-sectional study conducted at Phramongkutklao Hospital, approved by the Institutional Review Board of the Royal Thai Army Medical Department (R171h/65), enrolled 130 pregnant women aged ≥ 20 years in the first 14 weeks of gestation without anemia, no prior iron supplements, and without active systemic diseases. Anemia was defined as hemoglobin level < 11 g/

dL during the first trimester according to WHO criteria[2]. The sample size was calculated based on 42.6% prevalence of IDE in pregnant women from The Chinese Children, Pregnant Women & Premenopausal Women Iron Deficiency Epidemiological Survey Group (November 2004) [8] with tolerance of 20% of the prevalence. In this study, we utilized a serum ferritin threshold of < 30 ng/mL, based on a sensitivity of 92% and specificity of 98% for detecting iron deficiency[10]. Blood samples (7 ml from each woman) were collected for iron studies, accompanied by a questionnaire covering demographic data, menstruation details, dietary habits, and lifestyle factors. Menstruation regularity was categorized as monthly, tri-monthly and once in 5-6 months. Menstruation amount was evaluated by average number of menstrual pads used per day; unfortunately, menstrual duration data was not collected. The primary outcome was the prevalence of IDE, and the secondary outcome was the associated risk factors. Descriptive statistics included age, body mass index (BMI), education, residency, career, marital status, parity and income. Continuous data was categorized in mean ± standard deviation (SD). A chi square was used to find associated factors. Statistical significance was set at p values < 0.05. The related factors and factors with p value < 0.2 were selected to analyze in multiple logistic regression with a confidence interval (CI) of 95%. All statistical analyses were performed using SPSS version 26.

Results

Between February 2023 and May 2023, a total of 130 eligible pregnant women were enrolled and analyzed. The mean age was 29.89 ± 5.73 years, and the mean gestational age was 9 ± 2.23 weeks. The majority held a bachelor's degree (56.92%). Most women resided in Bangkok (96.15%), and most worked as company employees (72.31%). Over half were primiparous (56.92%), and about half had an average monthly income ranging from 15,000 to 29,999 baht. The mean age of menarche of the women was 13.08 ± 1.55 years with most having regular monthly menstruation, and over half using on average of ≥ 3 menstrual pads per day. Fourteen participants (10.77%) had a history of gastrointestinal tract bleeding and 10% of the women had a history of regular, monthly non-steroidal anti-inflammatory drugs (NSAIDs) use. Among the participants, one woman was a vegetarian (0.77%) and eight were weekly alcohol drinkers prior to pregnancy. Seventy percent had never donated blood, while 6.92% were regular blood donors, contributing up to four times a year (Table 1).

The mean hemoglobin level was 12.40 ± 0.79 g/dL, The prevalence of IDE in the study population was 10.77% (95%CI 6.26 - 16.83). Potential associated factors were systematically organized in the questionnaire, as outlined in Table 2.

Univariate logistic regression analysis showed potential associated factors with p value of < 0.2 as follows: number of parities, income, average menstrual pad usage of ≥ 3, and blood donation. Following the adjustment of odds ratios through multiple logistic regression, having had ≥ 2 deliveries emerged as a significant predictor (adjusted odds ratios (OR) 5.728, 95%CI 1.019 - 32.210, p = 0.048) (Table 3).

Table 1. Baseline Characteristics (n = 130).

	n	%
Age (years)		
Mean ± SD	29.89 ± 5.73	
Education		
Below Bachelor's degree	56	43.08
Bachelor's degree	74	56.92
Residence		
Bangkok	125	96.15
Other Provinces	5	3.85
Career		
Government officer	20	15.38
Employee	94	72.31
Others	16	12.31
Marital status		
Single	36	27.69
Married	93	71.54
Divorced	1	0.77
Number of parities		
0	74	56.92
1	46	35.38
≥ 2	10	7.69
Income (Baht per month)		
< 15,000	19	14.62
15,000 – 29,999	64	49.23
30,000 – 39,999	25	19.23
40,000 – 49,999	7	5.38
≥ 50,000	15	11.54
BMI (kg/m^2)		
mean ± SD	22.77 ± 4.76	

	n	%
Menarche (years)		
mean ± SD	13.08 ± 1.55	
Menstrual regularity		
Every month	113	86.92
Every 3-4 months	16	12.31
Every 5-6 months	1	0.77
Average menstrual pads per day (pads)		
1-2	53	40.77
≥ 3	77	59.23
History of gastrointestinal bleeding		
Yes	14	10.77
No	116	89.23
Frequency of NSAIDs use/**		
Once a month	13	10.08
More than a month	51	39.53
More than a year	65	50.39
Dietary style		
Normal diet	129	99.23
Vegetarian	1	0.77
Alcohol consumption		
Weekly	8	6.15
Monthly	25	19.23
> Monthly	21	16.15
Never	76	58.46
History of blood donation		
Every 3 months	9	6.92
Yearly	29	22.31
Never	92	70.77

** n = 129
SD: standard deviation, BMI: body mass index, NSAIDs: non-steroidal anti-inflammatory drugs

Table 2. Univariable Analysis for Iron Deficiency (n = 130).

	No iron-deficient erythropoiesis (n = 116)	Iron-deficient erythropoiesis (n = 14)	p value
	n (%)	n (%)	
Age (years)			0.499
< 35	92 (90.20)	10 (9.80)	
≥ 35	24 (85.71)	4 (14.29)	
Education			0.986
Below bachelor's degree	50 (89.29)	6 (10.71)	
Bachelor's degree	66 (89.19)	8 (10.81)	
Number of parities			0.108
0	68 (91.89)	6 (8.11)	
1	41 (89.13)	5 (10.87)	
≥ 2	7 (70.00)	3 (30.00)	
Income (Baht per month)			0.003
< 15,000	15 (78.95)	4 (21.05)	
15,000 – 29,999	60 (93.75)	4 (6.25)	
30,000 – 39,999	24 (96)	1 (4)	
40,000 – 49,999	3 (42.86)	4 (57.14)	
≥ 50,000	14 (93.33)	1 (6.67)	
BMI (kg/m2)			0.722
≤ 18.5	21 (87.5)	3 (12.5)	
> 18.5	95 (89.62)	11 (10.38)	
Menstrual regularity			0.719
Every month	101 (89.38)	12 (10.62)	
Every 3-4 months	14 (87.5)	2 (12.5)	
Every 5-6 months	1 (100.00)	-	
Average menstrual pads per day (pads)			0.038*
1-2	50 (96.15)	2 (3.85)	
≥ 3	66 (84.62)	12 (15.38)	
History of gastrointestinal bleeding			0.648
Yes	12 (85.71)	2 (14.29)	
No	104 (89.66)	12 (10.34)	
Frequency of NSAIDs use**			0.245
Multiple times per year	55 (85.94)	9 (14.06)	
Less than once a year	60 (92.31)	5 (7.69)	
Blood donation			0.115
Yes	31 (81.58)	7 (18.42)	
No	85 (92.39)	7 (7.61)	

BMI: body mass index, NSAIDs: non-steroidal anti-inflammatory drugs
**n = 129

Table 3. Multivariable analysis for iron deficiency (n = 130).

	Crude odds ratio (95%CI)	p value	Adjusted odds ratio (95%CI)	p value
Number of parities				
1	1.382 (0.397 - 4.817)	0.611	1.279 (0.348 - 4.701)	0.711
≥ 2	4.857 (0.991 - 23.802)	0.051	5.728 (1.019 - 32.210)	0.048
Income < 15,000 Baht/month	2.693 (0.749 - 9.688)	0.129	2.792 (0.712 - 10.954)	0.141
Average menstrual pads/day ≥ 3	4.545 (0.973 - 21.232)	0.054	3.358 (0.684 - 16.478)	0.136
History of blood donation	2.742 (0.890 - 8.450)	0.079	2.626 (0.780 - 8.838)	0.119

CI: confidence interval

Discussion

This study aimed to identify the prevalence and associated factors of IDE in early pregnancy. The findings revealed a prevalence of 10.77%, aligning with similar studies reporting 15.2% in northern regions of Thailand[7] and 13.9% in Europe[9].

In contrast, a study from China reported a notably higher prevalence of IDE at 42.6%. However, their extensive sample size of nearly 4,000 participants included pregnant women across all gestational ages[8]. It is noteworthy that half of the IDE cases in their study were observed in late pregnancy. Presumably, as pregnancy progresses, a growing number of women may become iron-deficient if not adequately supplemented. Further studies should dive into the incidence of IDA in pregnant women with IDE, exploring the efficacy of routine iron supplementation as a preventive measure for IDA in this population. These data could significantly contribute to refining guidelines for iron supplementation during pregnancy, particularly as a primary prevention strategy for IDA. Additionally, investigating children born to mothers with IDE/IDA could unveil potential long-term effects, including physical and cognitive developmental delays.

Among the analyzed maternal biomarkers, baseline demographics, and lifestyle conditions, multiparity (≥ 2 pregnancies) emerged as the most significant factor for IDE in early pregnancy, illustrating almost six times higher odds compared to women without or with only one prior delivery. However, it is worth recognizing that the 95%CI almost crosses 1, indicating potential imprecision in the analysis. This finding aligned with a prior study conducted in Singapore, which examined the iron status of 985 Asian pregnant women during the first 14 weeks of gestation (cut-off ferritin level of < 30 ng/mL). Multiparity was linked to an increased risk of iron depletion (OR 1.73, 95%CI 1.23–2.44)[11]. A similar result was also observed in The United States National Health and Nutrition Examination Survey which involved 6,463 pregnant women of unknown gestational age, with a cut-off ferritin level of < 15 ng/mL (OR 7.39, 95%CI 3.10-17.59)[12]. It is explained by the high iron requirement of pregnancy, putting multiparous women at risk of not recovering iron stores between pregnancies[10,12,13]. Another statistically relevant factor was income, but the trend of association could not be demonstrated due to the uneven number of women in each income level. In contrast to other studies[9] where being underweight was a related factor, we found no association with IDE, likely due to the majority of participants being within the normal weight range. Vegetarian diet has been shown to play a significant role in recent studies affecting IDE[6, 9] by stating that iron absorption from meat diet is higher than from vegetarian diet[14,15] However, as there was only one vegetarian in the current study, this issue could not be analyzed.

A significant proportion of women with IDE in early pregnancy are underdiagnosed, allowing their low iron stores to go undetected and untreated, given that IDE is asymptomatic. This is primarily because hemoglobin, often the sole biomarker assessed for iron status in routine practice, is altered only in the late stages of iron deficiency when stores are further depleted[5,16]. Consequently, hemoglobin proves to be an ineffective biomarker for preventing iron deficiency in pregnancy. Although, serum ferritin is not commonly measured in clinical practice due to cost considerations, it is internationally recognized as a robust marker for assessing iron storage[6]. From this study, we propose adding a test for serum ferritin level in women without anemia in early pregnancy who had ≥ 2 prior deliveries.

The strength of this study lays in its contribution to bridging a gap in the limited available data by revealing the prevalence of IDE in early pregnancy in Thailand. This study emphasizes the need for assessment of iron reserves and proactive prevention especially in multiparous women to alleviate the consequences of IDE during pregnancy. Certain limitations should be considered, primarily the small sample size due to financial constraints, potentially limiting the generalizability of our findings. Future research should examine the long-term outcomes of IDE and appropriate iron supplement therapies.

Conclusion

This research sheded light on the prevalence and risk factors of IDE in early stages of pregnancy, revealing a rate of 10.77% and multiparity was the significantly associated factor for IDE.

Acknowledgments

The authors express their grateful thanks to The Department of Obstetrics and Gynecology, Phramongkutklao College of Medicine, for the support in completing this study. Most appreciation to Dr. Chonlada Laoruangroj, and Dr. Sakchai Panitwong for your guidance. The authors declare no conflict of interest.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Friedrisch JR, Friedrisch BK. Prophylactic iron supplementation in pregnancy: A controversial issue. Biochem Insights 2017;10:1178626417737738.
2. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Loano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood 2014;123: 615-24.
3. Sukrat B, Sirichotiyakul S. The prevalence and causes of anemia during pregnancy in Maharaj Nakorn Chiang Mai Hospital. J Med Assoc Thai 2006;89 Suppl 4: S142-6.
4. Milman N. Prepartum anaemia: prevention and treatment. Ann Hematol 2008 ;87:949-59.
5. Teichman J, Nisenbaum R, Lausman A, Sholzberg M. Suboptimal iron deficiency screening in pregnancy and the impact of socioeconomic status in a high-resource setting. Blood Adv 2021;5:4666–73.
6. Al-Naseem A, Sallam A, Choudhury S, Thachil J. Iron deficiency without anaemia: a diagnosis that matters. Clin Med (Lond) 2021;21:107-13.
7. Sritippayawong S, Wong P, Chattrapiban T. Iron deficiency anemia during pregnancy in the lower north of Thailand-prevalence and associated factors. MJPHM 2012;12:1-5.
8. Liao QK; Chinese Children, Pregnant Women & Premenopausal Women Iron Deficiency Epidemiological Survey Group. Prevalence of iron deficiency in pregnant and premenopausal women in China: a nationwide epidemiological survey. Zhonghua Xue Ye Xue Za Zhi 2004;25:653-7.
9. Iglesias-Vázquez L, Gimeno M, Coronel P, Caspersen IH, Basora J, Arija V. Maternal factors associated with iron deficiency without anaemia in early pregnancy: ECLIPSES study. Ann Hematol 2023;102:741-8.
10. Siu AL; U.S. Preventive Services Task Force. Screening for iron deficiency anemia and iron supplementation in pregnant women to improve maternal health and birth outcomes: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2015;163:529-36.
11. Loy SL, Lim LM, Chan SY, Tan PT, Chee YL, Quah PL, et al. Iron status and risk factors of iron deficiency among pregnant women in Singapore: a cross-sectional study. BMC Public Health 2019;19:397.
12. Miller EM. Iron status and reproduction in US women: National Health and Nutrition Examination Survey, 1999-2006. PLoS One 2014;9:e112216.
13. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser 1968;405:5-37.

14. Bothwell TH. Iron requirements in pregnancy and strategies to meet them. Am J Clin Nutr 2000;72(1 Suppl):257S-264S.
15. Caspersen IH, Iglesias-Vázquez L, Abel MH, Brantsæter AL, Arija V, Erlund I, et al. Iron status in mid-pregnancy and associations with interpregnancy interval, hormonal contraceptives, dietary factors and supplement use. Br J Nutr 2021;126:1270-80.
16. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet 2007;370:511-20.