

# Prevalence of Iron Deficiency in Infants of Diabetic Mothers at the Age of 6 to 12 Months

Pontipa Engkakul, MD<sup>1</sup>, Sudatip Kositamongkol, MD<sup>1</sup>

<sup>1</sup> Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand

**Background:** Iron deficiency (ID) and iron deficiency anemia (IDA) are worldwide problems in infants. The infants of diabetic mothers (IDMs) usually have low iron storage at birth. Therefore, they are at risk for developing ID and IDA during late infancy.

**Objective:** To determine the prevalence of ID and IDA in IDMs aged 6 to 12 months and to identify the risk factors associated with abnormal iron status.

**Materials and Methods:** The present study was a prospective descriptive study conducted in healthy, full-term, IDMs between the ages of 6 to 12 months. Growth and dietary history of IDMs as well as maternal history of diabetes were evaluated. Anemia and iron status were determined by hemoglobin, serum ferritin, and transferrin saturation.

**Results:** Of the 50 IDMs, the prevalence of ID was 46%, and iron depletion was 14%. IDA was found in 11 IDMs. Although the gender, gestational age, birthweight, and the age of complementary food introduction were not found to be associated with abnormal iron status, infants with ID and iron depletion were more likely to be breastfed, or breastfed longer than six months, when compared to iron sufficient infants ( $p < 0.001$ ). No exclusively breastfed infants had iron sufficiency in the study.

**Conclusion:** There was a high prevalence of ID and IDA in IDMs. Therefore, screening for iron status along with anemia is crucial in IDMs at an earlier age. Moreover, iron supplementation starting at four months should be considered in IDMs who were exclusively or mainly breastfed.

**Keywords:** Anemia, Iron deficiency, Iron deficiency anemia, Infants of diabetes mothers

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Iron is an essential micronutrient that plays a crucial role in cellular functions and is necessary for normal brain development<sup>(1)</sup>. Iron deficiency (ID) is a common micronutrient deficiency among infants and children under five years due to the high requirements during their rapid growth and development. Iron deficiency anemia (IDA) is also the major cause of anemia in young children. It is well known that ID, even with or without anemia, in infancy and early

childhood periods can adversely affect long-term neurodevelopment and behavior, some of these effects are not likely to be corrected by subsequent iron treatment<sup>(2,3)</sup>.

Full-term infants are born with enough iron storage that it is sufficient for their growth and development during the first four to six months of life<sup>(1,4)</sup>. Thereafter, additional dietary iron is critical. Thus, infants at the age of 6 to 12 months are at risk for developing ID if complementary foods did not provide sufficient iron intake.

Diabetes mellitus is a global concern. The prevalence of pregnancy complicated with diabetes increased. Most of diabetes during pregnancy is gestational diabetes mellitus (GDM), followed by preexisting type 2 and type 1 diabetes. Diabetes during pregnancy has been associated with a higher rate of maternal and fetal complications<sup>(5)</sup>. Infants of diabetic mothers (IDMs) also have a greater risk of perinatal complications, such as macrosomia, shoulder dystocia, neonatal hypoglycemia, polycythemia, and neonatal hyperbilirubinemia. Moreover, long-term

## Correspondence to:

Engkakul P.

Department of Pediatrics, Faculty of Medicine, Thammasat University, 95 Paholyothin Road, Klong-luang, Pathum Thani 12120, Thailand.

**Phone:** +66-2-9269514, +66-89-1393382, **Fax:** +66-2-9269513

**Email:** [eporntip@staff.tu.ac.th](mailto:eporntip@staff.tu.ac.th)

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adverse effects such as lower general intelligence, language impairment, impulsivity, attention and behavioral problems, and increased risk of obesity and type 2 diabetes later in life, have been documented in the offspring<sup>(6,7)</sup>.

It is clear that diabetes during pregnancy has been linked to abnormally low body iron stores in the fetus<sup>(8-11)</sup>. The mechanisms most likely have two factors. The first is an increase of fetal iron utilization resulting from fetal erythropoiesis augmentation, caused by chronic intrauterine hypoxemia<sup>(11)</sup>. The second is a decrease of maternal fetal iron transfer across the placenta<sup>(8,10)</sup>. Theoretically, IDMs are born with low iron endowment, therefore, these infants are at risk of developing ID during infancy.

To the authors' knowledge, there is no previous study of the prevalence of ID and IDA in IDMs during late infancy. The authors aimed to determine the prevalence and risk factors of ID and IDA in infants at the age of 6 to 12 months born to mothers with diabetes during pregnancy.

## Materials and Methods

The present study was conducted between April 2016 and April 2017. The authors enrolled 50 term healthy IDMs, aged 6 to 12 months, who were born at the authors' hospital and had attended the Well Child Care Clinic at Thammasat University Hospital, Pathumthani, Thailand. Infants who were twins, had history of significant birth complications, chronic disease, previous blood transfusions, or previously received iron supplementation were excluded. Informed consents were obtained from all the infants' legal guardians. Complete physical examinations were performed, and dietary histories were obtained from caregivers. Birth history along with maternal history of diabetes and treatment were reviewed in the medical records. Venous blood was collected for hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), ferritin, serum iron, total iron-binding capacity (TIBC), and C-reactive protein. Percent transferrin saturation (TST) was calculated from serum iron and TIBC.

Diabetes during pregnancy included GDM and pre-existing type 1 or type 2 diabetes. GDM was determined by 100 g oral glucose tolerance test at the first antenatal care and repeated at 28 to 32 weeks of gestation using the cut-off by Carpenter and Coustan<sup>(12)</sup>. The mother's diabetes was treated by diet control, with or without insulin, under the guidance of an obstetrician and endocrinologist.

Anemia was defined using the World Health Organization (WHO) criteria of Hb less than 11 g/dL<sup>(13)</sup>. ID was diagnosed if the serum ferritin was less than 12 ng/mL or the TST was less than 16%. Iron depletion was defined by serum ferritin between 12 and 30 ng/mL with TST at 16% or more<sup>(14,15)</sup>. IDA was diagnosed in infants who had anemia with ID or anemia with iron depletion who had an increase in Hb concentration of at least 1 g/dL after one month of iron treatment. Iron sufficiency was defined as serum ferritin of more than 30 ng/mL with TST of 16% or more. Iron insufficiency was defined by either ID or iron depletion.

All analyses were performed at the Thammasat University Hospital Central Laboratory. Red blood cell indices and Hb were measured using the DxH800 Hematology Analyzer. Ferritin was analyzed by an enzyme immunoassay using Dimension RxL Max, serum iron and TIBC were determined by Ferene method from Dimension RxL Max. C-reactive protein was measured by turbidimetric (IFCC Cal.) by UniCel® DxC 800. This laboratory was regularly audited for international standard quality controls.

All analyses were conducted using Stata, version 14.2 (StataCorp LP, College Station, TX, USA). Descriptive statistics were used for demographics. Fisher exact test and two sample t-test compared the iron deficient and iron sufficient groups. A p-value of less than 0.05 was considered to be statistically significant.

The present study was approved by the Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine), Project code MTU-EC-PE-1-174/58.

## Results

There were 23 males in the 50 IDMs enrolled. The characteristics are shown in Table 1. Mean age was 7.8±0.9 months (ranged 6.2 to 10.3 months), and mean weight was 8.3±0.9 kg (ranged 5.8 to 10.2 kg). The majority (94%) were born to GDM mothers, and three infants were born to pre-gestational type 2 diabetic mothers. Thirty infants were born by C-section. Mean birthweight was 3,242 g with mean length being 51 cm. Ninety percent were average for gestational age, 4% were large, and 6% were small. Twenty-two infants had perinatal complications, including hypoglycemia (9), neonatal jaundice receiving phototherapy (15), transient tachypnea of newborn (2), neonatal sepsis (2), and polycythemia (1).

The mean maternal age was 33.9 years. For the 47 GDM mothers, the mean gestational age of

**Table 1.** Baseline characteristics of the participants (n=50)

Characteristics	Mean±SD
Mothers' characteristics	
Maternal age (years)	33.9±4.6
Maternal Hct during pregnancy (%)	36.9±3.2
Characteristics at birth	
Gestational age (weeks)	38.4±0.8
Mode of delivery; n (%)	
• Normal labor	19 (38)
• Cesarean section	30 (60)
• Vacuum extraction	1 (2)
Birthweight (grams)	3,242±454
Hct at 1 hour (%)	52.0±5.3
Nutritional history	
Age of complementary food introduction (months)	5.7±0.9
Age of iron rich food introduction (months)	6.1±0.8
Number of meals of complementary food	1.5±0.7
Type of current milk intake; n (%)	
• Breast milk only	12 (24)
• Breast milk + infant formula	6 (12)
• Infant formula only	32 (64)

SD=standard deviation; Hct=hematocrit

diagnosis was 22.9 weeks. All mothers were treated with diet control, with only nine mothers needing insulin therapy.

At the time of study, most infants were formula-fed, and most of them had eaten at least one meal of complementary food. The mean Hb, ferritin, and TST were 11.5±1.0 g/dL, 44±33 ng/mL, and 18.0±7.4%, respectively. All participants had C-reactive protein of less than 5 mg/dL.

ID was found in 23 infants and iron depletion in seven. For infant groups with ID or iron depletion to iron sufficiency, there were no differences in gender, gestational age, birthweight, hematocrit (Hct) at birth, maternal age, maternal Hct, and maternal type of diabetes. In addition, the age of complementary food introduction, the volume of red meat, and the Hb level did not vary among the two groups. Infants with ID or iron depletion tended to have lower birthweight (3,105±373 versus 3,350±510 g,  $p=0.08$ ) than the iron sufficient infants. Infants with either ID or iron depletion were more likely to currently be breastfed, or breastfed longer than six months, compared to the iron sufficient infants ( $p<0.01$ ). None of the iron sufficient infants was exclusively breastfed at the time of the study. Table 2 demonstrates the comparison

between ID and iron depletion with iron sufficient groups.

Eleven infants had IDA, seven of which were male. Iron insufficient infants with or without anemia had no differences in birthweight, gestational age, Hct at birth, maternal age, maternal Hct, maternal type of diabetes, or age of introduction of complementary food (Table 3). However, IDA infants had lower bodyweight and weight gain per month as compared to iron insufficient infants without anemia. All IDA infants were treated with oral iron, and their Hb normalized after treatment.

## Discussion

ID and IDA remain major health challenges worldwide. The prevalence of ID and IDA in infants 0.5 to 2 years old were 14% to 34.9% and 4.3% to 9.5%<sup>(16-18)</sup>. To the authors' knowledge, no previous study has reported the prevalence of ID or IDA in IDMs. The present study highlighted the high prevalence of abnormal iron status IDMs (22% IDA, 24% ID without anemia, and 14% iron depletion).

IDMs are often polycythemic at birth because chronic intrauterine hypoxia leads to increased erythropoiesis<sup>(19)</sup>. However, several studies demonstrated defective iron transport in GDM<sup>(20,21)</sup>. Therefore, most IDMs are born with low iron endowment that predispose them to ID during infancy period<sup>(8-11)</sup>. A previous study showed that infants born with low iron storage, identified by low ferritin at birth continued to have low iron storage in later infancy periods<sup>(22)</sup>. Additionally, a study in healthy breastfed infants showed that plasma ferritin declined after the first month and flattened out at 5.5 months and infants with ID at 5.5 months had lower plasma ferritin at the age of one month in comparison to non-ID infants<sup>(23)</sup>. Therefore, low iron endowment at birth is one of the major risk factors of ID during late infancy period. In addition, the risk of ID may be increased if they were exclusively breastfed or delayed introduction of iron rich food.

The risk factor associated with iron insufficiency in the present study was breastfeeding longer than six months. This had been noted elsewhere<sup>(24,25)</sup>. Other research has shown higher rates of anemia and IDA in breastfed versus formula-fed infants<sup>(26,27)</sup>. Furthermore, several papers demonstrate an inverse correlation between duration of breastfeeding and iron status<sup>(28,29)</sup>.

Although breast milk is considered the best food for infants, its iron content is quite low. During the first four to six months of life, infants use iron from the

**Table 2.** Comparison between iron deficiency and iron depletion with iron sufficient groups

Characteristics	Iron deficiency and iron depletion (n=30)	Iron sufficient (n=20)	p-value
	Mean±SD	Mean±SD	
Male; n (%)	13 (43)	10 (50)	0.64
Gestational age (months)	38.3±0.9	38.5±0.8	0.40
Birthweight (grams)	3,170±406	3,350±510	0.17
Growth at birth; n (%)			0.10
Large for gestational age (LGA)	0 (0)	2 (10)	
Average for gestational age (AGA)	27 (90)	18 (90)	
Small for gestational age (SGA)	3 (10)	0 (0)	
Hct at 1 hour (%)	51.6±5.1	52.5±5.7	0.59
Maternal age (years)	33.3±5.2	33.3±3.7	0.46
Maternal Hct during pregnancy (%)	36.7±3.3	37.2±3.1	0.60
Maternal type of DM; n (%)			0.33
Pre-gestational DM	1 (3)	2 (10)	
GDM	29 (97)	18 (90)	
Mode of delivery; n (%)			0.38
Cesarean section	16 (53)	14 (70)	
Vaginal delivery or vacuum extraction	14 (47)	6 (30)	
Age of complementary food introduction (months)	5.6±0.7	5.7±1.0	0.79
Age of iron fortified food introduction (months)	6.2±0.7	6.1±0.9	0.64
Number of meals of complementary food	1.6±0.8	1.5±0.6	0.76
Red meat (tablespoons/day)	0.8±0.9	0.7±1.1	0.86
Breastfeeding at least 6 months; n (%)	17 (57)	1 (5)	<0.001
Current milk; n (%)			<0.001
Breast milk only	12 (40)	0 (0)	
Breast milk + infant formula	5 (17)	1 (5)	
Infant formula only	13 (43)	19 (95)	
Age (months)	7.9±0.8	7.8±1.0	0.59
Bodyweight (kg)	8.2±1.0	8.3±0.8	0.89
Weight gain per month (g)	647±118	643±95	0.92
Hemoglobin (g/dL)	11.5±0.8	11.6±1.2	0.64
Hct (%)	35.5±2.2	35.7±3.8	0.82

SD=standard deviation; Hct=hematocrit; DM=diabetes mellitus; GDM=gestational diabetes mellitus

iron endowment at birth. Thereafter, infants increase their daily iron requirement, which is not sufficient only by breast milk. Therefore, breastfed IDMs will have a higher risk for developing ID and IDA especially if they did not have enough iron-containing complementary food. The currently breastfed infants in the present study were iron deficient.

The iron in complementary food is essential for all infants' requirements at this age group. The WHO recommends the introduction of complementary foods after the age of six months. However, several studies have confirmed that the earlier introduction of

complementary food was associated with iron status improvement<sup>(30,31)</sup>. The mean age of the introduction for iron-containing complementary food in the present study was 6.1 months. This is not a delay according to WHO recommendations. However, most Thai families use low iron containing complementary food, such as bananas and rice soup without or with a small amount of meat or liver as the first choice of complementary food. Therefore, these IDMs may easily develop ID.

Male infants are at risk of ID more than female infants, due to their higher pre- and post-natal growth

**Table 3.** Comparison between iron deficiency anemia and iron deficiency and iron depletion without anemia groups

Characteristics	Iron deficiency anemia (n=11)	Iron deficiency & iron depletion without anemia (n=19)	p-value
	Mean±SD	Mean±SD	
Male; n (%)	7 (63)	6 (32)	0.13
Gestational age (months)	38.5±1.0	38.2±0.8	0.28
Birthweight (grams)	3,052±308	3,238±447	0.23
Hct at 1 hour (%)	50±6	53±5	0.10
Maternal age (years)	34.5±5.4	34.3±5.2	0.92
Maternal Hct during pregnancy (%)	36.9±2.7	36.5±3.6	0.75
Age of complementary food introduction (months)	5.7±0.6	5.5±0.8	0.48
Red meat (tablespoons/day)	0.7±1.2	0.9±0.7	0.61
Breastfeeding at least 6 months; n (%)	7 (64)	4 (36)	0.71
Current milk; n (%)			0.21
Breast milk only	6 (55)	6 (32)	
Breast milk + infant formula	0 (0)	5 (26)	
Infant formula only	5 (45)	8 (42)	
Age (months)	7.9±0.9	7.9±0.8	0.92
Bodyweight (kg)	7.6±0.8	8.5±1.0	0.03
Weight gain per month (g)	581±95	685±124	0.03
Hemoglobin (g/dL)	10.7±0.2	11.9±0.7	<0.01
Ferritin (ng/mL)	25.1±25.7	34.0±17.2	0.33
Transferrin saturation (%)	11.2±3.2	12.9±2.4	0.16

SD=standard deviation; Hct=hematocrit

rates, lower iron absorption, larger intestinal iron loss, and more frequent infections<sup>(32,33)</sup>. In the present study, male infants did not increase the risk of ID and iron depletion, but IDA was relatively more prevalent in males versus females (1.75:1) without statistical significance.

Prevalence of ID in pregnancy is constantly high all over the world even in highly developed countries. There are increasing evidence that suboptimal maternal iron storage might negatively affect fetal iron storage<sup>(34-36)</sup>. In the present study, mean Hct of mothers in both iron sufficient and iron deficient were not different. To the authors' knowledge, there were no report of higher prevalence of IDA in GDM mothers compare to non-GDM. In contrast, there are concern that iron might plays a role in the pathogenesis of developing GDM<sup>(37)</sup>, as evidence in recent meta-analysis where women with GDM had higher serum iron than those without<sup>(38)</sup>.

The prevalence of ID and IDA depends on the definition and cut-off values used for the different iron tests. Currently, there is no gold standard for the diagnosis of ID and IDA in the late infancy period. The authors used ferritin below 12 ng/mL for the diagnosis of ID according to WHO criteria, and below 30 ng/

mL for the diagnosis of iron depletion according to Camaschella<sup>(15)</sup>. The authors wanted to detect the early stage of iron depletion in IDMs, as early treatment would provide long-term benefits to IDMs. Low fetal iron is associated with suboptimal language ability, fine-motor skills, and tractability at the age of five years<sup>(39)</sup>. Moreover, the IDMs with perinatal brain ID had impaired auditory recognition memory processing at birth and low psychomotor developmental scores at one year, compared to the iron-sufficient IDMs<sup>(40)</sup>. The early detection and treatment of post-natal ID is crucial for any long-term development.

The American Academy of Pediatrics (AAP) recommends screening for anemia in infants aged 12 months, with infants at risk for developing ID, including IDMs, to be screened earlier<sup>(4)</sup>. For the present study, the mean age of IDMs was 7.8 months. Moreover, the youngest IDMs with ID were only 6.5 months, and only 36% of iron insufficient infants had anemia. It would be prudent to screen iron status, as well as anemia, at an earlier age. In addition, the IDMs who were breastfed or partially breastfed more than half of their daily intake should receive iron supplementation of 1 mg/kg/day starting at four months to prevent ID, as recommended by the AAP.

As of now, more research is needed to evaluate the optimal age and dose for iron supplement and potential benefits to IDMs. It would be of great use to see if the age-matched normal infants have similar or varying levels of ID and IDA. In Thailand, universal screening for anemia is not mandatory. The present study draws attention to the necessity of iron status and anemic screening, at the very least, for high-risk groups such as IDMs.

## Conclusion

High prevalence of ID and IDA in IDMs is demonstrated in the present study. Thus, screening for iron insufficiency in addition to anemia is important in IDMs. Factors associated with abnormal iron status is breastfed duration longer than six months. Therefore, iron supplementation starting at four months should be considered at least in exclusively or mainly breastfed IDMs.

## What is already known on this topic?

Normal infants have a possibility of developing ID at the age of 6 to 12 months. Infants born to diabetic mothers have low iron storage since birth, therefore, they have greater risk for developing ID during the infancy period.

## What this study adds?

This study showed a high prevalence of ID and IDA in a certain group of infants, IDMs at late infancy period. Screening for anemia with iron status is important in IDMs. Factor associated with abnormal iron status is breastfed.

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## Conflicts of interest

The authors declare no conflict of interest.

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