Hepcidin Levels and Iron Homeostasis During Early Infancy

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ABSTRACT

Background: *Iron status is usually assessed in children and adults through the measurement of the concentrations of serum ferritin (SF) and serum soluble transferrin receptor (sTfR), which reflect storage iron and cellular iron needs, respectively. However SF and sTfR are difficult to interpret in infants. Hepcidin- liver hormone- is a negative regulator of iron absorption and mobilization.* ***Objective:*** *We aimed in this study to characterize changes in hepcidin levels in healthy breast fed infants in correlation to the dynamic change in iron status in this young age.* ***Patients and methods:*** *106 healthy breast fed infant were included in the study and followed from 4 to 9 mo. Iron supplementation was given to infants with iron deficiency (ID) at 6 mo till the age of 9 mo. Blood samples at 4, 6, and 9 months of age were analyzed for hemoglobin (Hb), mean cell volume (MCV), zinc protoporphyrin (ZPP), plasma ferritin, and transferrin receptors (TfR). Urinary hepcidin was measure at 4, 6 and 9 mo.* ***Results:*** *In unsupplemented infants, Hb, MCV and ferritin means decreased, whereas ZPP and sTfR means increased from 4 to 6 mo. Urinary hepcidin levels were decreasing with age between 4 and 6 months. We found significant urinary hepcidin deficiency in ID group at 6mo. Changes of Hb levels after iron supplementation were correlated significantly to urinary hepcidin at the age of 6 mo (r=-0.756), less significantly correlated to sTfR(r=394) and serum ferritin (r= 32).* ***Conclusions:*** *Iron deficiency in healthy full term infants is less common at 4 mo but iron deficiency increased after that. Not all ID infants will manifest by anemia and not all anemic infants are iron deficient. Urinary hepcidin could help to early diagnose infants with true iron deficiency.*

INTRODUCTION

Rapid growth and expansion of hemoglobin mass make infants particularly susceptible to iron deficiency.[(1)] The percentage of low birth weight infants is high in developing countries, and these infants have an even larger weight gain and lower iron stores. Both of these factors have a negative impact on their iron status, placing them at higher risk for iron deficiency at an early age[(2)]. Unlike adult and old children, the main food source for infants is breast milk, which does not contain heme iron. Instead nonheme iron, which is bound to other proteins or low molecular-weight ligands in breast milk, is the form of dietary iron

for infants. Moreover, iron supplementation, in the form of ferrous sulfate, is the common practice for infants. Hence, the form of dietary iron that infants are exposed to is mainly nonheme.

Studies of human infants indicate that iron deficiency may impair myelination in the central nervous system[3] and that the effects on transmission in the auditory and visual systems persist into childhood[4]. A sufficient iron supply in pregnancy and the prevention of iron deficiency in infancy may therefore be of profound importance to the health and development of children.

In the opposite side, However, the benefits and risks of iron supplementation in diverse populations have not been well documented. Iron is an essential nutrient required for infant growth and development, but it is also a potent prooxidant and its effects when given to iron-replete children have not been adequately studied. Iron supplements result in decreased growth[5] in iron-replete infants and may increase the incidence of certain types of infections, particularly gastrointestinal infections[6].

Iron status is usually assessed in children and adults through the measurement of the concentrations of serum ferritin (SF) and serum soluble transferrin receptor (sTfR), which reflect storage iron and cellular iron needs, respectively. Combined with hematologic measurements, these 2 iron indices are believed to provide a good picture of iron status[7].

Indicators of iron deficiency are difficult to interpret in infants, however, because of the effect of coincident changes in physiology and metabolism during growth and development and because of frequent infections[8]. The range of SF concentrations is quite wide[9], and normal reference limits are not available. The SF concentration changes markedly during the first year of life[10].

Studies of sTfR in the infants are sparse, but sTfR is believed to reflect erythropoietic activity[11]. The value of sTfR in the assessment of iron status in the infants has been questioned, however, sTfR are not perfect indicator of iron status because of the weak correlation to other iron indices[2].

Hepcidin, a 25-amino acid peptide produced by hepatocytes, in response to iron loading 12, is a key iron-regulatory hormone.[13] Hepcidin modulates iron availability by promoting the internalization and degradation of ferroportin[14], a key iron transporter and so far the only identified mammalian iron exporter, which is essential for both iron absorption in the duodenum and recycling of iron/iron efflux by macrophages. Hepcidin is a negative regulator of iron absorption and mobilization; high hepcidin levels turn off both duodenal iron absorption and release of iron from macrophages while low hepcidin levels promote iron absorption and heme iron recycling/iron mobilization from macrophages. Thus, hepcidin levels are expected to be high in iron overload states and diminished in iron deficient states.[15]

Our aim is to characterize changes in hepcidin levels in healthy breast fed infants in correlation to the

dynamic changes in iron status in this young age and its response to iron supplementation in comparison to other indices of iron status. We hypothesized that an abnormally low hepcidin levels could individualize infants in need for iron supplementation

SUBJECTS & METHODS

Participants

Healthy, full term infants 4 mo of age were recruited from the Batnan Medical Center, Tobruk, Lybia, after obtaining written informed consent from the parents. Infants were followed during the time interval from 4 to 9 month old. Selection criteria were as follows: *1*) gestational age >37 wk; *2*) birth weight >2500 g; *3*) no chronic illness; *4*) maternal age >16 y; *5*) infant exclusively breast-fed at 4 mo (and did not receive >90 mL/d of formula during any period since birth); *6*) mother intended to exclusively or nearly exclusively breast-feed until 6 mo (i.e., >1 tablespoon (15 mL)/d of foods or fluids other than breast milk, and no iron fortified foods); and *7*) mother intended to continue breast-feeding to at least 9 mo. Infants with Hb < 100 g/L at 4 mo were excluded.

Study Design

At 6 mo infants were assigned into 2 groups, group A consists of infants showed iron deficiency (ID) (diagnosed as Infants with combination of at least 2 of 3 of the following: MCV < 70 fL, ZPP > 80 µmol/mol heme, and ferritin <12 µg/L)[16] with or without anemia.
Group B, consists of infants without ID.

Group A were supplemented by iron as iron sulfate 1mg elemental iron/d, which is the recommended supplemental dose for prophylactic purposes, and the dose was adjusted monthly according to each infant's weight. The supplement was given by the mothers each morning, just before or after breastfeeding and at least 1 hour before or after any other food intake. Compliance with the intervention was monitored by asking the mothers to keep a daily checklist indicating whether the drops were given and by collecting the used iron bottles each month and measuring the amount of fluid remaining. Compliance was defined as taking the study drops for >75% of the time during the time intervals (6–9 months).

Biochemical assays.

Venous blood samples (5ml) were obtained by venipuncture at 4, 6 and 9 mo of age, (sampling was postponed for one week if the infant have acute illness) Part of the sample was collected in an EDTA. ZPP was analyzed (Protofluor Z, Helena Labs, Beaumont, TX).Hematological indices were analyzed by using of a Sysmex SE 9000 Autoanalyzer (Tillqvist). Hb was analyzed using Sysmex Sulfolyser automated hemoglobin reagent and MCV was automatically calculated from erythrocyte

Part of the sample was collected in a lithium heparin tube and, after centrifugation, plasma was stored frozen at <20°C until analyzed for ferritin, TfR and C-reactive protein. Serum ferritin was assessed using an automated chemiluminescence immunoassay analyzer (IMMULITE

2000®)[18] S-TfR was analyzed by ELISA (Ramco, Houston, TX).

Urinary hepcidin measurement at 4, 6 and 9 mo: Urinary creatinine concentrations were measured at first. Hepcidin was detected using rabbit anti–human hepcidin antibody[17] with goat anti–rabbit horseradish peroxidase as secondary antibody. Hepcidin quantity in each sample was then normalized using urinary creatinine concentrations and was expressed as nanogram hepcidin per milligram creatinine[19].

Statistical analysis

Data were collected and analyzed using SPSS for windows (version 10). All data were expressed in terms of mean value ± SD. Comparison of parameters among studied groups were made using student t test. Results were considered significant at P value <0.05. Correlation of variables were done using Pearson correlation test.

RESULTS

At 4 months old 130 infants were included in the study. Remaining in the study were 115 infants at 6 months and 106 at 9 months. Only infants remaining in the study at 9 months were included in the statistical analyses to allow direct comparison with the same infants.

Characteristics of the subjects at 4 and 6 months of age are shown in **Table 1**.

There were no significant differences between sexes at 4 months. Iron deficiencies (group A) at age of 6 months were more common among boys compared to girls (P<0.001). ID infants showed low weight at birth and rapid weight gain compared to infants without ID (group B) (Table I).

Table I: Participant characteristics

Patient information	At 4 months (n=106)	Infants at 6 months		P1
		Group A N=56	Group B N=50	
Boys n (%)	54 (51%)	34 (60.7%)	20(40%)	<0.001
Girls n (%)	52 (49%)	22 (39.3%)	30(60%)	<0.001
Birth weight(Kg)	3.4 ± 0.6	3.2 ± 0.5	3.5 ± 0.4	<0.001
Weight gain (0-9 months)		5.3 ± 0.9	4.8 ± 0.9	<0.001

P1: comparing group A Vs group B

Table I: shows that boys compared with girls had statistically significant incidence of ID (group A). Infants with ID at 6 month were of low birth weight and showed significant weight gain compared to infants without ID

In unsupplemented infants, Hb, MCV and ferritin means decreased, whereas ZPP and sTfR means increased from 4 to 6 months. This was paralleled by increasing SD, possibly suggesting an increasing proportion of iron-deficient infants. The only exception was Hb, for which the SD did not increase. This may suggest that the decrease in Hb from 4 to 6 months was physiologic and that the proportion of infants who developed anemia between 4 and 6 months of age was low despite the increasing ID with age.

Table II: Iron status in infants at 4 and 6 months of age.

	At 4 months N=106	At 6 months		P1	P2	P3
		Group A (n=56)	Group B (50)			
Hb (g/L)	119.2(9)	**103.6(8)**	**113.5(7)**	<0.001	**<0.001**	**<0.001**
MCV (fL)	**77.6(3.0)**	**72.8(3.8)**	**76(3.6)**	<0.005	**<0.005**	**<0.05**
ZPP(μmol/mol heme)	**47(1.3)**	**55(1.6)**	**50(1.5)**	<0.001	**<0.001**	**<0.05**
Ferritin (μg/L)	**85(2.5)**	**45 (2.8)**	**68(2.6)**	<0.001	**<0.001**	**<0.001**
sTfR (mg/L)	**7.6(1.6)**	**9.4(2.7)**	**7.8(2.5)**	<0.05	**<0.05**	**>0.05**

P1 Group A Vs Group B
P2 Infants at 4 month Vs group A
P3 Infants at 4 months Vs group B

Mean (standard deviation) for Hb, MCV, and TfR. Geometric mean (standard deviation) for ferritin and ZPP. Note that, whereas the arithmetic standard deviation is added (subtracted) to the mean, the geometric standard deviation is multiplied (divided) with the geometric mean.

Table II: shows that the mean Hb, MCV and Ferritin levels were significantly high in infants at 4 months compared to both groups of infants at 6 months with significant lower levels in group A compared to group B. ZPP and sTfR levels were significantly lower in infants at 4 month compared to both groups at 6 months and in group B compared to group A.

Iron deficiency and IDA at the age of 4 mo was absent in our healthy well selected breast fed infants. About 53 % of infants (n =56) at 6 months showed iron deficiency diagnosed by abnormal 2 of the 3 parameters (MCV, FT, and ZPP). Anemia was manifested in 40 (about 37.7%) of our infants population at the age of 6 mo. Anemia was diagnosed by Hb levels less than 105 g/L (20). Anemia without ID was detected in 5 infants and ID without anemia was diagnosed in 21 infants.

Urinary hepcidin levels were decreasing with age between 4 and 6 months (Tab III). With more significant decrease in ID group. Whether this decrease in Hepcidin is related to iron homeostasis or not was investigated by estimating the response of hepcidin to iron supplementation. "true" iron deficient infants will response to iron supplementation with elevation in Hb levels. So iron supplementation was given to the ID group from 6 to 9 months and the change in Hb levels was correlated to different parameters of iron status.

Table III: Comparison of urinary hepcidin levels in ng per mg creatinine between infants at 4 and 6 months.

Urinary hepcidin level	At 4 months (n=106)	At 6 months	
		Group A N =56	Group B n=50
Range	40–122	20–60	49 –90
Mean	80.1	38.5	67.85
SD ±	21.**2**	11.5	11.**4**
P1(A vs B)	**< 0.001**		
P2(at 4 mo Vs A)	**<0.001**		
P3(at 4 mo Vs B)	**<0,05**		

Table III shows that the mean urinary hepcidin levels were significantly lower in infants with ID (group A) at age of 6 months compared with infants without ID (group B) (P1<0.001) and infants at 4 months (P2<0.001). Mean urinary hepcidin levels in infants without ID at 6 mo were significantly lower compared to infants at 4 months (P3<0.05).

Hb response to iron supplementation of more than 5 g/L was found in 42 (75%) of ID infants. Mean Hb increased after iron supplementation by 9.6 g/L while mean Hb levels decreased in the unsuplemented group by 4.5g/L. MCV, ferritin and urinary hepcidin were significantly increased while sTfR and ZPP were significantly decreased after iron supplementation compared to unsupplemented group (Tab. IV).

Table IV: Iron status in infants at age of 9 months

	Group A (n=56)	Group B (n=50)	P value
Hb (g/L)	**113(8)**	**109(7)**	**<0.001**
MCV (fL)	**77.5(4.2)**	**72(2.7)**	**<0.001**
ZPP(μmol/mol heme)	**46(2)**	**58(1.6)**	**<0.001**
Ferritin (μg/L)	**67(2.7)**	**45(2.5)**	**<0.001**
sTfR (mg/L)	**6.1(2.1)**	**8.5(2.2)**	**<0.001**
hepcidin *	**102(15)**	**55(12)**	**<0.001**

** Urinary hepcidin levels in ng per mg creatinine*

Table IV: Shows significant elevation in Hb, MCV, ferritin and urinary hepcidin levels whereas STfR and ZPP were decreased in ID group (group A) after iron supplementation compared to non supplemented infants.

Mean (standard deviation) for Hb, MCV, and TfR. Geometric mean (standard deviation) for ferritin and ZPP. Note that, whereas the arithmetic standard deviation is added (subtracted) to the mean, the geometric standard deviation is multiplied (divided) with the geometric.

Changes of Hb levels after iron supplementation is considered the gold stander for the diagnosis of ID in infants, these changes were correlated

significantly to urinary hepcidin at the age of 6 mo (r=-0.876) (Fig 1), less significantly correlated to sTfR (r=476) (Fig 2) and serum ferritin (r= -354) (Fig 3).

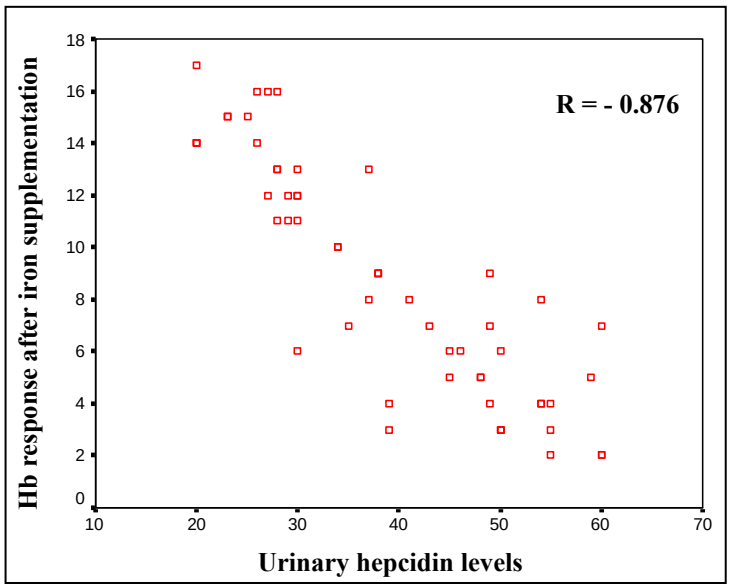

Fig.1: A significant negative correlations between urinary hepcidin levels in infants with ID at 6 mo and the increase in Hb levels after iron supplementation.

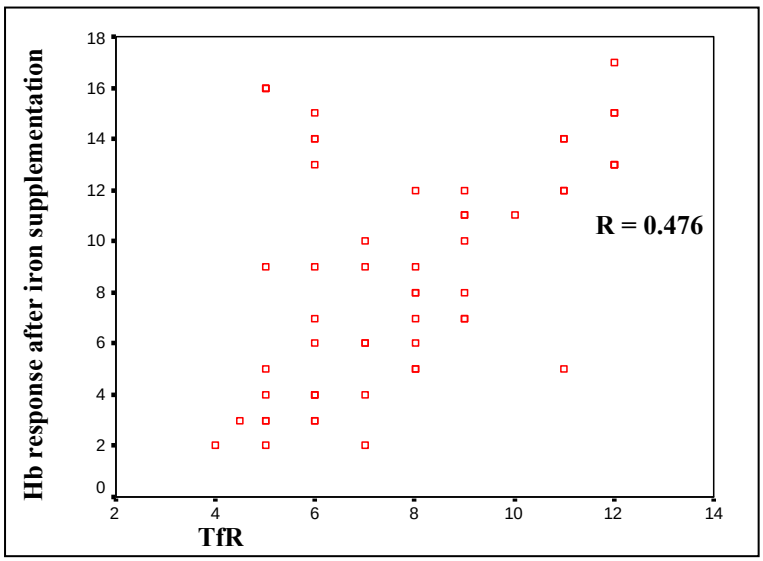

Fig.2 positive Correlation between sTfR levels in infants with ID at age of 6 mo and the increase in Hb levels after iron supplementation.

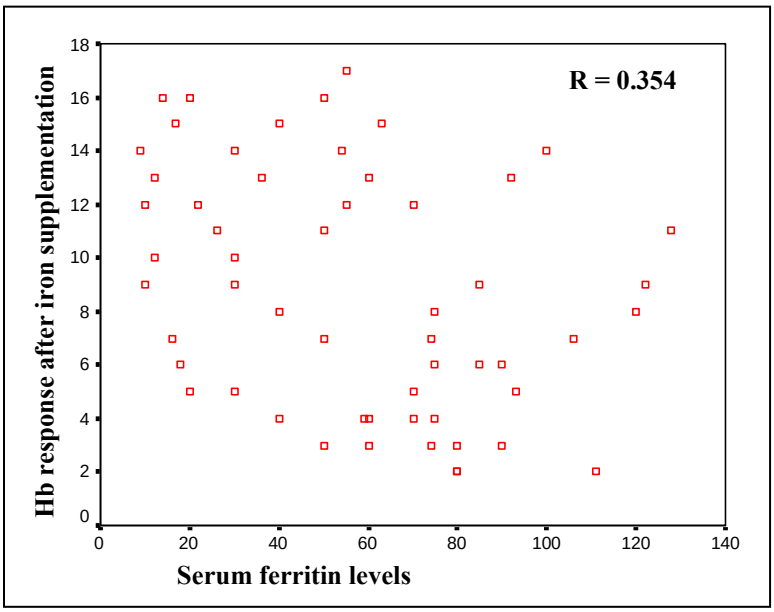

Fig.3: Correlations between serum ferritin levels in infants with ID at age of 6 months and the increase in Hb levels after iron supplementation.

DISCUSSION

Most health authorities recommend exclusive breastfeeding for 4–6 mo, a practice thought to prevent development of iron deficiency anemia in term, healthy infants[21]. However, if infants are exclusively breast-fed beyond that age, they are at increasing risk of developing iron deficiency anemia. To prevent this, iron supplements (in the form of liquid drops) are often recommended for breast-fed infants after 6 months of age if they do not consume adequate amounts of iron-rich complementary foods[22].

Our results confirmed this practice as iron deficiency anemia was not detected in infants at the age of 4 mo in our healthy term, breast fed infants. Anemia was found in 40 (37.7%) of unsupplemented infants at 6 mo. Criteria of IDA was met in 35 of them (87.5%). ID was more common in Lybian infants compared to Europeans and nearly the same incidence like in Chile. Only 24% of anemic infants met the criterion for iron deficiency in Europian study[23], whereas 85% of those infants in Chile did so[24]. This difference may be explained by the socioeconomic factors which would act through physiologic factors, such as a poorer diet for infant, mother, or both or more childbearing and hence poorer maternal nutrition.

Iron supplementation significantly increased Hb levels at 9

month while unsupplemented infants without ID (group B) showed a decrease in mean Hb levels of 4.5 g/L.

Estimates of iron requirements in infancy and recommendations regarding the quantity of iron to be used to fortify infant foods are often derived from absorption data[25]. In healthy adults, absorption of iron increases in states of iron depletion, but it is not known if the same regulating mechanism functions during infancy, a period characterized by dramatic changes in the size of iron stores and the rate of erythropoiesis. We found different hemoglobin responses to iron supplementation after 6 months of age – 25 % of infants showed Hb response less than 5g/L- suggesting other deficiencies rather than iron.

Girls have iron index values that are consistent with better iron status than those in boys. That finding was also reported previously[24,25]. This sex difference may be –in part- explained by more weight gain in the first year of life in boys compared to girls.

Hepcidin is a key regulator of iron homeostasis and is, now emerging as a fundamental diagnostic parameter of iron overload.

Hepcidin was significantly high in our infants at 4 months. And decreased significantly at the age of 6 months particularly in ID group. *Domellöf* et-al found insignificant difference in iron absorption between iron supplemented and unsupplemented infants at 4- 6 months.[27] Hepcidin may down-regulates intestinal iron absorption in these presumably iron-sufficient infants regardless of dietary iron intake. However, recent data from animal studies suggest that the expression of iron transporter -(divalent metal transporter1 (DMT1) and ferroportin1 (FPN1)- is not increased by Iron deficiency during early infancy but is increased in late infancy(28), which would support our findings.

Tiker et al revealed no significant correlations between serum pro-hepcidin level and serum iron, serum ferritin, or transferrin in the preterm or term newborns and that healthy preterm and term newborns have high pro-hepcidin levels.

On the other hand, Orhon et al.[29] indicated that serum pro-hepcidin levels in anaemic infants were similar to those of healthy ones. Regarding with this unexpected finding, we suggest that pro-hepcidin levels might not reflect the actual hepcidin levels, and this prohormone might not be a useful biomarker for clinical purposes[30].

Urinary hepcidin levels were significantly correlated with the change of Hb levels in response to iron supplementation. This correlation was less significant with ferritin and sTfR. Which may reflect that urinary hepcidin may be better predictor of "true iron deficiency" than other parameters.

Urinary hepcidin levels were well correlated to serum hepcidin levels. Ganz et-al[31] provided validation of a novel immunoassay for human serum hepcidin The availability of this assay opens the way to early diagnosis of infants with IDA.

In conclusion: Iron deficiency in healthy full term infants is less common at 4 mo but iron deficiency increased after that. Not all ID infants

will manifest anemia and not all anemic infants are iron deficient. Urinary hepcidin could help in early diagnosis of infants with true iron deficiency.

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مستوى الهبسيدين و الثبات الداخلى للحديد بالدم في الأطفال الرضع

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من قسم الأطفال. جامعة عمر المختار- ليبيا* قسم الفسيولوجي **و الأطفال ***
كلية طب طنطا – مصر

تقاس حالة الحديد في الدم في الأطفال و الكبار عن طريق قياس نسبة الفرتين و مستقبلات الترنسفرين الذائبة في الدم و اللذان يعبران عن مخزون الحديد و احتياجات الخلايا للحديد على الترتيب. و مع ذلك فان مستوى الفرتين في الدم و نسبة مستقبلات الترنسفيرين الذائبة تعتبر صعبة التحليل في الأطفال الرضع. هرمون الهبسيدين يفرز من الكبد و يقلل من امتصاص و حركة الحديد داخل الجسم

و الهدف من البحث هو دراسة التغيرات في مستوى الهيبسيدين في الأطفال الرضع الأصحاء المعتمدين في التغذية على الرضاعة الطبيعية و مقارنة ذلك بالتغيرات الديناميكية في حالة الحديد في هؤلاء الأطفال الرضع

أجريت الدراسة على ١٠٦ طفل رضيع رضاعة طبيعية و تم متابعتهم من عمر ٤ إلى ٩ شهور . تم إعطاء الحديد للأطفال الذين يعانون من نقص في الحديد عند عمر ٦ شهور و حتى عمر ٩ شهور . و قد أخذت عينات الدم عند عمر ٤ و ٦و٩ شهور لقياس نسبة الهيموجلوبين و حجم خلية الدم و نسبة برتوبورفرين الزنك و نسبة الفرتين في البلازما و مستقبلات الترنسفيرين الذائبة و تم قياس مستوى الهبسيدين في البول عند عمر ٤و٦و٩ شهور و كانت النتائج كالأتي :

- في الأطفال الذين لم يتم إعطائهم حديد كان متوسط نسبة الهيموجلوبين و حجم خلية الدم و مستوى الفرتين يقل في حين أن متوسط مستوى برتوبرفرين الزنك و مستقبلات الترنسفيرين الذائبة تزداد فى الفترة من ٤ إلى ٦ شهور
- مستوى الهبسيدين في البول كان يقل مع العمر من ٤ إلى ٦ شهور و قد وجد نقص ذو دلالة إحصائية فى مستوى الهبسيدين في البول في الأطفال الذين يعانون من نقص الحديد بالدم عند عمر ٦ شهور
- التغيرات في نسبة الهيموجلوبين بالدم بعد إعطاء الحديد كانت متوازية مع نسبة الهبسيدين فى البول عند عمر ٦ شهور و اقل توازيا مع مستقبلات الترنسفيرين الذائبة و الفريتين

و نخلص من هذه الدراسة أن نقص الحديد فى الأطفال الرضع اقل حدوثا قبل عمر ٤ شهور و لكنه يزداد بعد ذلك . و ليس كل الأطفال الذين يعانون من نقص الحديد مصابون بالأنيميا و ليس كل المصابون بالأنيميا عندهم نقص حديد و يعتبر قياس مستوى الهبسيدين في البول عاملا مساعدا فى الكشف المبكر عن الذين يعانون من نقص حقيقي فى نسبة الحديد