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Hepcidin and iron status in pregnant women and full-term newborns in first days of life

Hepcydyna a wybrane wskaźniki gospodarki żelazem u ciężarnych kobiet i donoszonych noworodków w pierwszych dniach życia

Beata Kulik-Rechberger[1], Artur Kościesza[1], Elżbieta Szponar[1], Justyna Domosud[2]

[1] Zakład Propedeutyki Pediatrii, Uniwersytet Medyczny w Lublinie, Polska
[2] Samodzielny Publiczny Szpital Wojewódzki im. Jana Bożego w Lublinie – Oddział Neonatologii z Patologią i Intensywną Terapią, Polska

Abstract

Objectives: *The amount of iron is regulated by hepcidin. The aim of the study was to assess hepcidin concentrations in healthy pregnant women before delivery, in cord blood, and in 3-day-old newborns in relation to maternal and neonatal iron status.*

Material and methods: *The study group consisted of 44 mother-newborn pairs. Serum concentrations of hepcidin, ferritin, and transferrin receptor (sTfR) were assessed.*

Results: *Maternal hepcidin was significantly lower than cord blood (p<0.001), and full-term newborn values (p<0.001). Mothers also had the lowest ferritin and sTfR concentrations. The highest concentration of hepcidin was observed in the newborns. They had lower sTfR and higher ferritin concentrations than in cord blood (p<0.001). Maternal ferritin correlated negatively with sTfR (R=-0.50 p=0.005), and positively with hepcidin (R=0.41; p=0.005). There were no correlations between hepcidin and ferritin or sTfR concentrations in cord blood, nor between hepcidin and ferritin or sTfR concentrations in the newborns. Moreover, there were no correlations between maternal and cord blood or neonatal blood hepcidin, nor between maternal hepcidin and infant iron status. There were also no correlations between hepcidin in cord blood and hepcidin or parameters of the iron status in the children.*

Conclusions: *It may be assumed that a relatively low concentration of hepcidin in women in late pregnancy facilitates their iron accumulation. Higher levels of hepcidin in full-term newborns than in their mothers may be the result of a relatively high level of iron from the stored supplies. Neonatal iron status was independently associated with either maternal or cord blood hepcidin.*

Key words: **pregnancy** / **newborn** / **hepcidin** /

Adres do korespondencji:
Beata Kulik-Rechberger
Zakład Propedeutyki Pediatrii
ul. A. Gębali 6, 20-093 Lublin, Polska
tel. 81 7185371
e-mail: brechberger@interia.pl

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Streszczenie

Cel pracy: *Niedobór żelaza lub jego nadmiar ma niekorzystny wpływ na rozwój dziecka. Ilość żelaza regulowana jest przez hepcydynę. Celem pracy było określenie stężenia hepcydyny u zdrowych ciężarnych i u donoszonych noworodków, w zależności od stanu ich zaopatrzenia w żelazo.*

Materiał i metody: *Badaniem objęto 44 pary matka-dziecko. Pobrano próbki krwi od ciężarnych przed porodem, z pępowiny i od noworodków w trzeciej dobie życia. W surowicy oznaczano stężenie hepcydyny, ferrytyny i rozpuszczalnego receptora transferyny (sTfR).*

Wyniki: *Stężenie hepcydyny u matek było istotnie statystycznie niższe niż w krwi pępowinowej (p<0,001) i u noworodków (p<0,001). Matki miały najniższe stężenia ferrytyny i sTfR. Najwyższe stężenie hepcydyny stwierdzono u noworodków (p<0,001). Noworodki miały też najwyższe stężenie ferrytyny (p<0,001) i niższe niż w krwi pępowinowej stężenie sTfR (p<0,001). U matek, stężenie ferrytyny korelowało negatywnie ze stężeniem sTfR (R=-0,50; p=0,005) i pozytywnie ze stężeniem hepcydyny (R=0,41; p=0,005). Nie wykazano korelacji między stężeniem hepcydyny a ferrytyny czy sTfR w krwi pępowinowej oraz między stężeniem hepcydyny a stężeniem ferrytyny, sTfR czy poziomem Hb u noworodków. Nie było również korelacji między stężeniami hepcydyny u matki, w krwi pępowinowej czy w krwi noworodka, jak też między stężeniem hepcydyny u matki i parametrami gospodarki żelazem u noworodka.*

Wnioski: *Na podstawie przeprowadzonych badań można przypuszczać, że niskie stężenie hepcydyny u ciężarnych pozwala na zwiększenie zasobów żelaza do poziomu pokrywającego zapotrzebowanie płodu. Wysokie jej stężenie w krwi pępowinowej i u noworodków wynika ze stosunkowo dobrego zaopatrzenia w żelazo dzieci urodzonych o czasie. Gospodarka żelazem u noworodków nie zależy bezpośrednio od hepcydyny w krwi matki czy w krwi pępowinowej.*

Słowa kluczowe: **ciąża** / **noworodek** / **hepcydyna** /

Introduction

The regulation of iron availability is particularly critical during periods of rapid growth and development, such as fetal and neonatal life. Iron deficiency or excess during these periods can have disadvantageous effects on the development and cellular function of many organs. Iron is particularly important for brain growth, structure, and function. It supports neuronal energy metabolism, myelination, and neurotransmitter synthesis. The consequences of iron deficiency may not be corrected by restoration of normal iron levels. Poor iron status in the fetus, assessed by low cord ferritin concentrations, appears to be associated with impaired mental and psychomotor function of children in later life [1].

In maternal blood, iron is transported by transferrin. This complex is bound to transferrin receptor (sTfR) on the placental cells and endocytosed into the cells. Iron is transported to the fetal circulation via ferroportin. The amount of this protein is regulated by hepcidin, a small 25-amino acid peptide, operating as a negative feedback regulator of iron homeostasis. Hepcidin decreases the expression of iron transport molecules and regulates iron transport. It binds to ferroportin in enterocytes, macrophages, and placental cells, inhibits its activity, and limits iron entry into the extracellular spaces. Iron requirements increase during pregnancy, reaching a maximum in the third trimester [2, 3]. By contrast, hepcidin concentration decreases gradually from the first to the third trimester of pregnancy [4]. It enables increased iron absorption from dietary sources and its mobilization from hepatocytes and macrophages [5, 6]. Iron is transferred across the placenta and accumulated by the developing fetus, mostly in the last 10 weeks of gestation [7]. At this time, iron availability is elevated [8]. On the other hand, hepcidin can protect the feto-placental unit from iron toxicity, and avoid excess iron transfer to the fetus. The fetus produces hepcidin independently. In rats, the production begins in the first trimester of gestation [9]. Thus, fetal hepcidin also regulates placental iron trafficking proteins in response to fetal iron needs. The production of hepcidin is highly up-regulated, not only in iron overload, but also in inflammation. It is increased in neonatal sepsis and decreased in hypoxia or anemia [10]. Active erythropoiesis also has a strong effect on hepcidin concentration. In this condition, despite iron overload, the level of hepcidin is decreased [11]. At present, the extent to which hepcidin regulates iron homeostasis in the feto-maternal unit and the influence of maternal hepcidin on neonatal iron status remain to be fully elucidated.

Few researchers have investigated serum hepcidin concentrations in healthy mother-newborn pairs [12, 13, 14]. To the best of our knowledge, there have been no studies regarding maternal, cord, and neonatal blood concentrations of hepcidin in their first days of life. The aim of our study was to determine the association between hepcidin level in the maternal, umbilical cord, and peripheral blood of full-term neonates on the third day of life, with reference to maternal and infant iron status.

Material and methods

A total of 44 mother-newborn pairs were studied in the maternity wards of 2 hospitals in Lublin. The women gave informed consent before delivery. Twenty-eight out of 44 women (63.6%) declared systematic use of dietary supplements with iron and vitamins during pregnancy for about 3 months (this information is not well-documented), while the remaining subjects reported non-systematic use of such preparations. All of the investigated mothers denied smoking tobacco. All newborns were full-term, from singleton and uncomplicated pregnancies, without intrapartum hypoxia. They remained with their mothers

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Table I. Description of the study population.

Mothers	Mean	St. Dev.	Min.	Max.
Age (year)	27.8	5.5	18	42
Weight (kg)	70.4	13.1	47	96
Height (cm)	167.2	5.9	157	183
Pregnancy	1.6	0.7	1	4
Labor	1.6	0.7	1	4
Newborns				
Gestational age (weeks)	39.5	1.2	38	42
Birth weight (g)	3487.1	549.5	2550	4850
Birth length (cm)	54.7	2.6	48	60
Head circ. (cm)	34.9	1.6	32	38
Chest circ. (cm)	34.0	2.0	30	38
CRP (mg/L)	1.4	1.8	0.0	4.6
Bilirubin (mg/dL)	8.7	3.5	1.0	12.3

Table II. Maternal and neonatal hemoglobin (Hb) levels as well as serum concentrations of hepcidin, soluble transferrin receptor (sTfR), and ferritin in maternal (M), cord (C), and neonatal blood (N).

	Mothers (M) (n=44) Mean±SD	Cord blood (C) (n=44) Mean±SD	Newborns (N) (n=44) Mean±SD	M vs C	C vs N	M vs N
Hb (g/dL)	12.19±0.76	–	16.79±2.07	–	–	p<0.001
Ht (%)	36.22±2.92	–	48.0±5.93	–	–	p<0.001
RBC (10^6/mm^3)	3.95±0.30	–	5.52±0.52	–	–	p<0.001
Ferritin (µg/L)	21.97±14.94	94.48±44.72	216.23±96.19	p<0.001	p<0.001	p<0.001
sTfR (µg/mL)	1.22±0.38	3.34±1.16	2.63±0.95	p<0.001	p<0.001	p<0.001
Hepcidin (ng/mL)	17.12±9.23	48.98±20.70	66.79±22.85	p<0.001	p<0.001	p<0.001

Table III. Correlations between serum concentration of ferritin, soluble transferrin receptor (sTfR), and hepcidin in maternal, cord, and neonatal blood.

		Mothers (M)				Cord blood (C)			Newborns (N)			
		Ferritin	sTfR	Hepcidin	Hb	Ferritin	sTfR	Hepcidin	Ferritin	sTfR	Hepcidin	Hb
Mothers (M)	Ferritin	–	R=-0.50 p=0.005	R=0.41 p=0.005	ns	ns	ns	ns	ns	ns	ns	ns
	sTfR		–	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Hepcidin			–	ns	ns	ns	ns	ns	ns	ns	ns
	Hb				–	ns	R=-0.36 p=0.016	ns	ns	ns	ns	ns
Cord blood (C)	Ferritin					–	ns	ns	R=0.56 p=0.0001	R=-0.33 p=0.028	ns	ns
	sTfR						–	ns	ns	ns	ns	ns
	Hepcidin							–	ns	ns	ns	ns
Newborns (N)	Ferritin								–	ns	ns	ns
	sTfR									–	ns	R=0.39 p=0.01
	Hepcidin										–	ns
	Hb											–

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(rooming-in system) and were breastfed. Twenty-two of them were boys, 15 were born by cesarean section. None of the investigated children had symptoms of an infection. A detailed description of the study population is shown in Table I.

Blood for the examinations was drawn from the umbilical cord (mixed venous and arterial blood), from maternal peripheral vein (within 24h before delivery), and from neonatal peripheral vein on the third day of their life. The sera were stored at -20°C until assayed. Ferritin, sTfR, and hepcidin concentrations were assessed in maternal, cord and neonatal serum. Ferritin concentration was measured by a commercially available latex-enhanced immunoturbidimetric test. Concentrations of sTfR and hepcidin were measured using commercial ELISA kits (DRG Instruments, Marburg, Germany). The level of hemoglobin, hematocrit, and red blood cell count were determined in the mothers and the newborns using a full-automated hematology analyzer (Pentra 60, Horiba ABX, France). In further analysis, only the level of hemoglobin in the mothers and the children was taken into consideration.

The differences between the two independent groups were assessed with the Mann-Whitney U test. Dependent groups were compared by means of Wilcoxon ascending order pair test. Correlations between the two measurable parameters were examined by Spearman's rank correlation coefficient R test. A 5% deduction error and a significance level of $p < 0.05$ showing existence of statistically important differences or correlations were adopted. Statistical analyses were performed by STATISTICA v.8.0 (StatSoft, Poland) computer software. Local Ethics Committee approved of the study.

Results

As no significant differences between concentrations of hemoglobin or ferritin in blood of the mothers reporting systematic as well as non-systematic use of iron dietary supplements for 3 gestational months were detected, all of the investigated women were categorized into one group.

There were differences between concentrations of ferritin, sTfR, and hepcidin in maternal, cord, and neonatal blood on their third day of life (Table II). Ferritin concentrations in maternal blood were lower than in cord blood ($p<0.001$), which in turn were lower than in neonatal blood ($p<0.001$). Three women had hemoglobin concentration of <11.0g/dL, but none of <10.0g/dL. Sixteen (36.4%) mothers had serum ferritin concentration below <15µg/L, which is consistent with depleted iron reserves [8]. The mothers also had the lowest sTfR concentration. However, the concentration of sTfR in cord blood was higher than in neonatal blood ($p<0.001$). The highest level of hepcidin was noticed in 3-day-old newborns. Hepcidin levels in maternal blood were significantly lower than in cord ($p<0.001$) and in neonatal blood ($p<0.001$).

There were no differences in ferritin, sTfR, and hepcidin levels in cord or neonatal blood with regard to delivery type and neonatal gender. No correlations were found between ferritin concentrations in maternal and cord or neonatal blood, but there was a positive correlation between ferritin concentrations in cord and neonatal blood ($R=0.56$; $p=0.0001$) (Table III). We found a negative correlation between ferritin and sTfR concentrations in the mothers ($R=-0.50$; $p=0.005$), as well as a weak negative correlation between ferritin concentration in cord blood and sTfR concentration in neonatal blood ($R=-0.33$; $p=0.028$). There was a negative correlation between maternal hemoglobin level and sTfR concentration in cord blood ($R=-0.36$; $p=0.016$). Maternal hepcidin correlated positively with their ferritin levels ($R=0.41$; $p=0.005$). There were no correlations between hepcidin and ferritin or sTfR concentrations in cord blood, nor between the concentration of hepcidin and ferritin, sTfR, or Hb levels in the newborns (Table III). There were no correlations between maternal hepcidin and hepcidin in cord or neonatal blood, nor between maternal hepcidin and iron status of 3-day-old newborns.

Discussion

Hepcidin is regarded as the systemic regulator of iron metabolism and is responsible for its availability for adults and children. It also plays a role in the regulation of transplacental iron transport [15]. Serum ferritin concentration has been used as a standard measurement of iron stores. Low ferritin concentration is seen only in iron deficiency. Elevated ferritin can be a consequence of hemochromatosis, excessive iron administration, red blood cell transfusions, and infection. During infection, serum ferritin behaves as an acute-phase reactant which can mask iron deficiency [16, 17]. The transferrin receptor (TfR) is responsible for the incorporation of iron into the intracellular spaces. It is present in almost all body cells, but mostly in the placenta [18]. Cell iron deficiency increases, while iron overload decreases, TfR synthesis [19]. In our research, neither the mothers nor the newborns had symptoms of an infection. Ferritin concentration was nearly four times higher in cord blood than in maternal blood. Moreover, almost one-third of the mothers had serum ferritin concentration of <15µg/L, indicating fetal iron accretion against a concentration gradient. High level of sTfR in cord blood appears to be influenced by the high rate of erythropoiesis in the fetus. Increased numbers of erythroid progenitor cells express a high amount of transferrin receptors [20], which also suggests that iron accumulation in the placenta is intensive. Higher cord blood ferritin and sTfR concentrations than maternal values have also been reported by other authors [21]. We observed a high negative correlation between ferritin and sTfR concentrations in the mothers, but no correlation between ferritin and sTfR in cord blood, which can be explained by the contribution of both, the placenta and the fetus in its synthesis. There were also no correlations between ferritin concentrations in maternal and cord blood. In agreement with other studies, the concentration of hepcidin in the mothers was also lower than in cord blood [12, 13, 14]. As mentioned above, hepcidin concentration decreases gradually from the first to the second and third trimester of pregnancy [22]. On the basis of these observations, it can be speculated that lower hepcidin concentration in the mothers increases duodenal iron absorption, allows the release of iron from macrophages and hepatic stores to maternal circulation, and increases iron availability for the fetus. On the other hand, higher hepcidin concentration in the placenta than in the mother avoids iron overload, which can be harmful for the child. Distinct from the mother, the concentration of hepcidin in the fetus increases with gestational age, and is higher in term as compared to preterm infants [23]. Similarly to other authors [23, 24, 25, 26], we also found a positive correlation between serum ferritin and hepcidin in the mothers, and no correlation between maternal ferritin and hepcidin, ferritin, and sTfR in cord or peripheral

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blood of the newborns. In a study by Young et al., serum hepcidin concentrations were associated with multiple indicators of iron status in the mother at delivery, but were not significantly correlated to hepcidin or other markers of iron status in cord blood [14]. This suggests that neonatal hepcidin is probably regulated independently of maternal hepcidin concentrations. A lower level of hepcidin in maternal blood than in cord blood was also found by Rehu et al. [12], who demonstrated that maternal and cord blood hepcidin were independently associated with iron status in pregnant women and in newborns at birth.

To the best of our knowledge, this study has been the first to assess the relationships between serum concentration of hepcidin in maternal, cord, and in 3-day-old newborn blood, in relation to maternal and neonatal iron status. We found a strong positive correlation between ferritin concentrations in cord blood and neonatal peripheral blood. There was no correlation between cord blood hepcidin concentrations and iron status indices, which is consistent with reports of other authors [27]. High level of ferritin in full-term healthy newborns on the third day of life can be the result of sufficient transplacental transmission of iron, as well as lysis of senescent RBCs. The decrease of sTfR concentration during the first days of neonatal life was due to sufficiency of iron and reduction of erythropoiesis, but its level was higher than in the mothers. We revealed that concentration of hepcidin in 3-day-old newborns was higher than in cord and maternal blood, indicating an active synthesis of this protein, which is probably due to the comparatively high level of ferritin in children at that age.

Conclusions

It may be assumed that relatively low concentrations of maternal hepcidin in late pregnancy facilitate their iron accumulation to a level which protects fetal demand. Higher level of hepcidin in cord blood and in full-term newborns on the third day of life than in the mothers can be due to relatively high level of iron from the stored supplies. The iron status of newborns on the third day of life was independently associated with either maternal or cord blood hepcidin levels.

Oświadczenie autorów:

1. Beata Kulik-Rechberger – autor koncepcji i założeń pracy, analiza statystyczna wyników, przygotowanie manuskryptu i piśmiennictwa – autor zgłaszający i odpowiedzialny za manuskrypt.
2. Artur Kościesza – współautor tekstu pracy i protokołu, zebranie materiału, opracowanie wyników badań, przechowywanie dokumentacji, przygotowanie manuskryptu.
3. Elżbieta Szponar – ostateczna weryfikacja i akceptacja ostatecznego kształtu manuskryptu.
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