Iron Status of Newborns in Maternal Inflammation Status Differences

Qodri Santosa [1][a], Alfi Muntafiah[2][b], and Lantip Rujito[3][c]
[1] *Department of Child Health, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Indonesia*
[2] *Department of Biochemistry, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Indonesia*
[3] *Department of Molecular Biology, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Indonesia*

Keywords: inflammation, pregnancy, IL-6, CRP, iron status, ferritin, newborn

Abstract: The human nervous system develops rapidly during the last pregnancy period and the beginning of human life, requiring much iron. Inflammation during pregnancy may interfere with materno-fetal iron transfer. The study aimed to compare the newborn iron status levels in maternal inflammation status differences. A cross-sectional study was conducted with subjects of 84 clinically healthy newborns. We used C-reactive protein (CRP) and interleukin-6 (IL-6) as parameters of maternal inflammation. Maternal IL-6 was classified into two test groups based on quartile 1 (Q1) and quartile 2-4 (Q2-4), while CRP in the positive and negative groups. Statistical analysis used a t-test independent or Mann-Whitney test, with 95% confidence intervals and a significance limit at $p < 0.05$. All newborns and their mothers were in healthy condition. Ferritin newborns' levels were higher in the positive than negative CRP group (450.6 ± 194.86 vs. 365.1 ± 212.91, with $p = 0.02$). Ferritin newborns were also higher in the maternal IL-6 Q2-4 group than in Q1, at levels 299.03 ± 154.98 vs. 492.35 ± 276.25, with $p = 0.003$. The study concluded that newborns' serum ferritin levels are higher in the maternal with CRP-positive and higher IL-6 groups. We should be careful in interpreting the elevated serum ferritin because it is also an acute-phase reactant.

1 INTRODUCTION

Iron sufficiency during late pregnancy and early human life is essential for the nervous system's rapid growth (Collard, 2009). Cellular respiration in the hippocampus and frontal cortex, neurotransmitter concentrations, fatty acid profiles, and myelination will be disrupted if an iron deficiency occurs during this period, potentially disrupting growth and development (Georgieff, 2007).

An iron status assessment is essential, but no single laboratory examination can determine the diagnosis in all compartments, among red blood cells, transport, functional, and storage (Wu, 2002). Human iron stores in the body exist primarily in the form of ferritin. Declining (low) serum ferritin levels reflect depleted iron stores. However, ferritin is an acute-phase reactant whereby concentrations increase during inflammation and no longer reflect the iron store's size. Interpretation of average or high serum ferritin values is difficult in areas of widespread infection or inflammation. Without inflammation or liver disease, increased serum ferritin concentrations indicate iron overload (WHO, 2011).

The inflammatory process is generally characterized by an increase in pro-inflammatory cytokines and acute-phase reactants levels. Interleukin-6 (IL-6), a pro-inflammatory cytokine, and C-reactive protein (CRP) are the primary mediators of the host response to inflammation, and both are also early markers of the acute-phase response (Sorokin et al., 2010). High levels of IL-6 in pregnancy can induce hepcidin transcription. Interleukin-6 - hepcidin axis is responsible for hypoferremia in pregnant women with excessive inflammation (Zhang & Enns, 2009; Wrighting & Andrews, 2006), then interferes with a materno-fetal

[a] https://orcid.org/0000-0001-7712-2549
[b] https://orcid.org/0000-0002-1424-6111
[c] https://orcid.org/0000-0001-6595-3265

Santosa, Q., Muntafiah, A. and Rujito, L.
Iron Status of Newborns in Maternal Inflammation Status Differences.
DOI: 10.5220/0010490001940201
In *Proceedings of the 1st Jenderal Soedirman International Medical Conference in conjunction with the 5th Annual Scientific Meeting (Temilnas) Consortium of Biomedical Science Indonesia (JIMC 2020)*, pages 194-201
ISBN: 978-989-758-499-2

iron transfer (Nemeth et al., 2004), and may affect neonatal iron status (Yanoff et al., 2007).

Mild acute inflammation did not increase serum hepcidin in pregnant women with iron deficiency anemia. Even Abioye et al. confirmed that anemia of inflammation during human pregnancy did not affect newborn iron endowment (Abioye et al., 2018). The underlying mechanisms are still being debated so that during pregnancy, it seems unclear how the difference in newborn iron status between maternal inflammation status differences.

This study aimed to compare the newborn iron status in maternal inflammation status differences, using maternal IL-6 and CRP inflammation parameters.

2 MATERIAL AND METHODS

Our study was part of comprehensive research that assessed various factors associated with neonates' iron status. A cross-sectional study was conducted in Purbalingga Regency, Central Java, Indonesia, in three hospitals, with 84 newborns, from September to November 2015. The inclusion criteria for newborns were born spontaneously, from single and term pregnancy, normal birth weight (≥2.500 to <4.000 grams), with an Apgar score ≥of 7 in the first minute, and not suffer from significant congenital abnormalities. We excluded newborns subjects if they were suffering from severe illness and hematologic-oncological disease, and the mother had a postpartum hemorrhage. The Health and Medical Research Ethics Commission of the Faculty of Medicine, Diponegoro University/Dr. Kariadi Hospital Semarang provided ethical approval with No.48/EC/FKRSDK/2015. The father or mother of the newborn subject signed the written informed consent before joining the research.

We used CRP and IL-6 as parameters of maternal inflammation, using maternal venous blood samples. Maternal IL-6 was classified into two test groups based on quartile 1 (Q1) and quartile 2-4 (Q2-4), while CRP in the positive and negative groups. Newborn iron status parameters included red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Ht), and hepcidin using blood samples taken from umbilical cord blood. In contrast, serum iron (SI) and serum ferritin (SF) were taken from newborns' venous blood.

Maternal venous blood samples were taken when the mother was admitted to the hospital for delivery. The blood samplings from the umbilical cord blood were collected immediately after the placenta was born, whereas the newborn's vein was performed directly after the baby was born. Parameters of RBC count, Hb, and Ht of newborns were checked using Sysmex XN-1000, while hepcidin using the ELISA method. SI was tested using the IRON Flex® reagent cartridge, Cat. No. DF85, while SF and maternal IL-6 using the chemiluminescence immunoassay (ECLIA) method. Maternal CRP was performed using the C-Reactive Protein Extended Range (RCRP) method used on the Dimension® clinical chemistry.

The statistical analysis to compare newborn iron status between maternal inflammation status differences was tested with the independent t-test or Mann-Whitney test. In groups (positive and negative), maternal CRP, hepcidin variables were analyzed using the Mann-Whitney test, while other variables used the independent t-test. In the two maternal IL-6 quartile groups (Q1 and Q2-4), variable RBC, hematocrit, and hepcidin variables were analyzed using the Mann-Whitney test, while other variables were tested using an independent t-test. The statistical test used 95% confidence intervals, with a limit of significance at $p < 0.05$.

3 RESULTS

A total of 84 newborns participated in our cross-sectional study. We interviewed as many as 108 pregnant women/parents of prospective subjects in the initial process. Seven pregnant women refused because they were afraid or worried about the blood collection process. Two babies with clinical features of Down's syndrome, four babies born with respiratory problems, and 11 babies failed blood sampling or laboratory techniques, so they could not continue the study process.

All newborn subjects were at term babies, born spontaneously, from singleton pregnancies, Apgar scores ≥ seven at the first minute, average birth weight (≥ 2,500 to <4,000 grams), and not suffering from significant congenital abnormalities. The CRP of all newborn subjects was negative. (Table 1). Table 2 shows that all maternal subjects were pregnant at term, did not suffer from diabetes mellitus, pre-eclampsia/eclampsia, and antepartum hemorrhage, came from Javanese, and with Hb >8 g/dL.

The results showed that hematocrit levels, SF, and hepcidin newborns in the maternal CRP group had abnormal data distribution. The hepcidin variable was still not standard after being transformed, so it was analyzed using the Mann-Whitney test, while other variables used the independent t-test. (Table 3)

Table 1. Characteristics of newborn

Characteristics of newborn	Value
Sex (gender): - Male, n (%) - Female, n (%)	 38 (45.2) 46 (54.8)
Gestation, week [median (range)	39.22 (37 – 41)
Apgar score (AS) - 1 min, [median (range) - 5 min, [median (range)	 8.04 (7 – 9) 9 (8 – 10)
Heart rate, beats/min [median (range)	129.88 (110 – 148)
Birth weight, gram [median (range)	3190.06 (2600 – 3900)
CRP: - Positive, n (%) - Negative, n (%)	84 (100) 0 (0)

Table 2. Characteristics of the mother

Characteristics of mother	Value
Age of mother, year ($\overline{x}$ ± SD)	27.43 ± 5.38
Gravida: - Gravida ≤ 2, n (%) - Gravida ≥ 3, n (%)	 68 (81.0) 16 (19.0)
Education levels: - > Senior High School, (%) - ≤ Senior High School, (%)	20 (23.8) 64 (76.2)
Systolic, mmHg ($\overline{x}$±SD)	119.85 ± 9.19
Diastolic, mmHg ($\overline{x}$±SD)	73.33 ± 6.47
Fe tablet, n (%)	84 (100)
Ante-natal care ≥ four times	84 (100)
Smoking during pregnancy: - Yes, (%) - No, (%)	 1 (1.2) 83 (98.8)

Table 3. Iron Status Parameters based on Maternal CRP Groups

Iron Status Newborns Parameters	Maternal CRP Groups		p
	CRP positive (n=48)*)	CRP negative (n=36)	
RBC (umbilical cord), 10^6/mm^3 ($\overline{x}$±SD)	4.2±0.44	4.3±0.46	0.209[a]
Hb (umbilical cord), g/dL ($\overline{x}$±SD)	15.2±1.47	15.2±1.49	0.857[a]
Ht (umbilical cord), % ($\overline{x}$±SD)	45.0±5.12	44.9±4.98	0.986[a]
Serum Iron, µg/dL ($\overline{x}$±SB)	114.3±51.30	111.3±54.96	0.799[a]
Serum Ferritin ng/mL ($\overline{x}$±SD)	450.6±194.86	365.1±212.91	0.023[a]
Hepcidin (umbilical cord), ng/mL ($\overline{x}$±SD) [median (min-max)]	4.2±1.62 4.8(1.66-6.90)	3.8±1.73 3.3(1.58-6.85)	0.426[b]

Remarks: a t-test independent; b, Mann-Whitney; *, ferritin, n=45

The results showed that SF newborn levels were higher in the CRP positive mothers group than the opposing group, with a mean of 450.6 ± 194.86 vs. 365.1 ± 212.91 ng/mL with p = 0.023. Other parameters of iron status for newborns were not significantly different in these maternal CRP groups. We divided newborns subjects into the two quartile groups of maternal IL-6 (Q1 and Q2-4). Parameters RBC, hematocrit, and hepcidin levels have abnormal data distribution. After transforming the data, the data distribution of hematocrit and hepcidin were not expected, so they were analyzed using the Mann-Whitney test. Meanwhile, other variables were tested using an independent t-test. Table 4 shows that the mean SF newborns in the quartile group (Q1 vs. Q2-4) were higher in the maternal IL-6 group Q2-4, with a mean of 299.03 ± 154.98 v.s 492.35 ± 276.25 ng/mL and statistically significant with p = 0.003. In Table 5, we divided newborn hepcidin and SF into maternal IL-6 gradations Q1, Q2-3, and Q4. Among the maternal IL-6 quartile group, we found that the median hepcidin cord blood was not different (p: 0,610), while the mean of newborn SF was significantly different (p: 0.006). However, by post hoc of LSD analysis, we only found differences in SF newborns' standard in the IL-6 Q1 vs. Q2-3 (p: 0.002). Meanwhile, the newborn SF levels in the IL-6 maternal Q1 group were not different from the Q4 group (p: 0.068). Likewise, the mean SF newborns at Q2-3 and Q4 did not differ (p: 0.267).

Table 4. Iron status parameters based on maternal IL-6 quartile (Q1 and Q2-4) groups

Iron Status Newborns Parameters	Maternal IL-6 Quartile Groups		p
	Q1 (n=21)	Q2-4 (n=63)*)	
RBC (umbilical cord), $10^6/mm^3$ ($\overline{x}$±SD)	4.3±0.47	4.2±0.45	0.432[a]
Hb (umbilical cord), g/dL ($\overline{x}$±SD)	15.4±1.80	15.1±1.35	0.358[a]
Ht (umbilical cord), % ($\overline{x}$±SD) [median (min-max)]	45.7±5.88 44.5(38.10-59.70)	44.7±4.74 44.3(34.80-56.90)	0.877[b]
Serum Iron, µg/dL ($\overline{x}$±SB)	121.7±50.34	110.1±53.40	0.386[a]
Serum Ferritin ng/mL ($\overline{x}$±SD)	299.03±154.98	492.35±276.25	0.003[a]
Hepcidin (umbilical cord), ng/mL ($\overline{x}$±SD) [median (min-max)]	4.2±1.75 3.6(1.58-6.85)	4.0±1.65 3.9(1.66-6.90)	0.345[b]

Remarks: a t-test independent; b, Mann-Whitney test; *, ferritin neonatal (n=61)

Table 5. Serum ferritin and hepcidin of newborn based on maternal IL-6 quartile (Q1, Q2-3, and Q4) groups

Newborns Parameters	Maternal IL-6 Quartile Groups			*p*
	Quartile 1 (n=21)	*Quartile* 2-3 (n=42)	*Quartile* 4 (n=21)	
Hepsidin cord blood, [median (min-max)]	3.6 (1.58-6.85)	4.4 (1.66-6.90)	3.9 (1.83-5.89)	0.610[b]
Serum ferritin, ng/mL, ($\overline{x}$±SB)	299.0 ± 154.98	472.3 ± 206.75	412.3 ± 210.61	0.006[a]

Remarks:

Statistical tests used 95% confidence intervals ($\overline{x}$±SB), mean ± standard deviations; a one-way Anova test; Post hoc analysis of LSD: IL-6 Mother quartile I vs. II-III p = 0.002; I vs. IV p = 0.068; II-III and IV p = 0.267

4 DISCUSSION

The study aimed to compare the newborn iron status levels in maternal inflammation status differences. The newborns' iron status using the RBC count, Hb, Ht, SI, and hepcidin did not differ between the maternal CRP group (positive vs. negative) and the IL-6 maternal quartile group (Q1 vs. Q2-4). In contrast above, the mean SF newborn was significantly higher in the CRP positive group. Likewise, the mean SF newborn was higher in the maternal IL-6 Q2-4 group (inflammatory mothers), p <0.05. However, after dividing the maternal IL-6 into Q1, Q2-3, and Q4, the newborn SF levels in the IL-6 Q4 group tended to decrease compared to Q2-3, although the two groups did not differ significantly.

These results indicate that iron status was generally unaffected. Still, SF newborns as a parameter of iron storage will increase or be higher in newborns born to mothers with positive CRP and more elevated IL-6 (inflammatory mothers). We assume that maternal inflammatory status in the last trimester of pregnancy tends to increase the iron stores (SF) of babies born under normal pregnancy conditions. We considered that the maternal inflammatory disease is a "physiological strategy" to increase iron storage (SF levels) of the fetus for the third trimesters' rapid growth.

Research on inflammation in pregnancy (such as pregnancy with obesity) has different effects. Dao et al. found no statistically significant differences in CRP, IL-6, or hepcidin levels in cord blood between the obese and non-obese maternal groups (Dao et al., 2013). Still, serum iron and transferrin saturation in cord blood were lower in neonates born to obese women than those of average weight. Furthermore, Cao et al. also concluded that the prepregnancy body mass index (BMI) has no negative impact on maternal or neonatal iron status (Cao et al., 2016). Jones et al. (2016) reported that maternal obesity during pregnancy is negatively associated with maternal and neonatal iron status (Jones et al., 2016). Research in 316 newborns said that compared to non-obese pregnant women (BMI <30 kg/m2), obese women

delivered offspring with lower iron status, as assessed using SF and zinc protoporphyrin/heme (Phillips et al., 2014).

Inflammation is the necessary process as a response to injury and also central to reproductive success. Such as ovulation, menstruation, implantation, and parturition are all inflammatory processes. A physiologic systemic inflammatory response also characterizes pregnancy (Romero et al., 2007). Concentrations of CRP and IL-6 in obese women compared to normal-weight women indicated an inflammatory response (Buss et al., 2012). CRP level has been reported to be elevated in pregnant women without pregnancy complications than in non-pregnant women (Fink et al., 2019; Watts et al., 1991). Reproductive success appears to be influenced by cytokine activity's strict regulation (Austgulen et al., 1994). So, if not exaggerated/not excessive, inflammation has essential roles in reproductive physiology.

Another review of the inflammatory process, in which chronic and excessive inflammation of pregnancy can lead to poor pregnancy outcomes. Generally, research on IL-6 in pregnancy has been associated with poor outcomes in mothers and their babies. IL-6 has been implicated as a mediating factor in maternal inflammation processes to alterations in fetal brain development (Buss et al., 2012; Rudolph et al., 2018; Estes and McAllister, 2016).

The main factor responsible for altered iron metabolism in inflammatory conditions is hepcidin (Wessling-Resnick, 2010). Hepcidin regulated iron homeostasis by controls iron absorption and recycling (Ganz, 2013). Transcription of hepcidin is induced when systemic iron levels are high and down-regulates its receptor, ferroportin (FPN), preventing iron export to blood plasma (Ganz, 2013). The abnormality of raised hepcidin causes intracellular sequestration and decreased intestinal iron absorption due to the downregulation of FPN expression in macrophages and enterocytes (Cherayil, 2015). Furthermore, changes in hepcidin levels can rapidly modulate and control plasma iron concentrations.

Commonly, in non-pregnant obese women, hepcidin is up-regulated (Tussing-Humphreys et al., 2012), otherwise during a healthy pregnancy, hepcidin is reduced and enabling increased materno-fetal iron transfer (Fisher & Nemeth, 2017). Maternal hepcidin is suppressed during the second and third trimesters, which increases iron availability for materno-fetal transfer (Fisher & Nemeth, 2017). The mechanism of maternal hepcidin suppression is unclear (Sangkhae et al., 2020). The interpretation of hepcidin levels, such as ferritin, should also be considered concurrently with inflammation markers (Sanni et al., 2020).

The inflammatory markers of CRP and IL-6 have long been known. As a pro-inflammatory cytokine, IL-6 is frequently elevated in obese pregnant women. It has been shown to induce hepcidin expression, a negative regulator of intestinal iron absorption, macrophage iron efflux, and hepatic iron stores (Ganz & Nemeth, 2006). Inflammation, such as obesity in pregnant women, may lead to hepcidin excess and decreased iron transfer to the fetus (Flynn et al., 2018), affecting newborn iron status.

In low-grade inflammation in non-pregnant women, obesity is associated with increased hepcidin, induced iron sequestration, and decreased circulating iron (Tussing-Humphreys et al., 2012). The CRP and IL-6 were more remarkable in obese than normal-weight pregnant women (Fisher & Nemeth, 2017), and inflammatory conditions in pregnancy are lower and more visualized in obese pregnancies (Dosch et al., 2016). However, Flynn et al. found no relationship between CRP or IL-6 and hepcidin in obese or normal-weight women. It might indicate that the association between inflammatory mediators and hepcidin is not extant in pregnancy (Fisher and Nemeth, 2017). Other pathways may play an essential iron regulatory role in pregnancy.

Why does maternal inflammatory condition increase in SF newborns (iron stores) while all newborn subjects with CRP are negative? A recent study confirmed that mild acute inflammation did not increase serum hepcidin in women with IDA, suggesting that low iron status and erythropoiesis drive offset the inflammatory stimulus on hepcidin expression. In non-anemic women, inflammation increased serum hepcidin and produced mild hypoferremia. However, it did not reduce dietary iron absorption, suggesting that iron-recycling macrophages are more sensitive than the enterocyte high serum hepcidin during inflammation (Stoffel et al., 2019). Abioye et al. confirmed that anemia of inflammation during human pregnancy did not affect newborn iron endowment (Abioye et al., 2018).

Previous concepts still understand that cytokines (e.g., IL-6) can cross the placenta when the placental barrier was damaged. An animal experiment by Dahlgren J et al. proved that maternal IL-6 could cross the placental border to the fetus, both in a condition where the placental barrier is impaired or normal (Dahlgren et al., 2006). In previous research, Zaretsky et al. confirmed that fetal IL-6 could also penetrate the placenta into the maternal circulation (Zaretsky et al., 2004). So, IL-6 can pass bidirectional transfer from maternal to fetus and vice versa.

Maternal IL-6 passes to the fetus, and subsequently, IL-6 in the fetus can affect iron status.

Our data (Table 5) showed, in maternal IL-6 gradations Q1, Q2-3, and Q4, we found that the mean of newborn SF was significantly different among those groups. The Post Hoc of LSD analysis stated that SF newborns' standard was higher in the IL-6 maternal Q2-3 (middle quartile) group than in the Q1 (lowest quartile) group with p: 0.002. We also noted that the newborn SF levels in the IL-6 Q4 (highest quartile) group were not different from the Q1 and Q2-3 groups. The hepcidin and SF newborn values increased IL-6 maternal Q1 to Q2-3, then decreased in the IL-6 Q4 group. These results may indicate an inverted U-shaped association between IL-6 maternal and neonatal iron status (SF and hepcidin).

Maternal iron status (including serum ferritin) has a U-shaped association with adverse pregnancy outcomes (Dewey & Oaks, 2017). We must be careful because SF is also an acute-phase reactant. However, elevated ferritin is a marker of increased iron stores and inflammation, and the specific contribution of excess iron has not been resolved. It is poorly understood how to regulate iron homeostasis between maternal and fetal during pregnancy, including maternal, placental, and fetal signals (Sangkhae et al., 2020). Like ferritin, IL-6 maternal, as an acute-phase response, so we must be careful to interpret the meaning of increased SF in newborns.

The implication of this study, because there is an indication of an inverted U-shaped association between maternal inflammation (levels of maternal IL-6) and neonatal iron status. Hence less or excessive inflammation may decrease the iron status of newborns. We must be careful to interpret the newborn SF level because it is also an acute reaction protein.

5 CONCLUSION

Our study compared neonate iron status levels in maternal inflammation status differences. Our findings indicated that inflammation is the necessary process for reproductive success. We conclude that (not excessive) inflammation in pregnancy does not affect iron status (based on RBC count, Hb, Ht, SI, hepcidin parameters) but increases the SF (iron storage) of the newborns. The SF levels of newborns are higher in the maternal with CRP-positive and higher IL-6 groups. There is an indication of an inverted U-shaped association between maternal inflammation and neonatal iron status. Hence less or excessive inflammation during pregnancy may decrease the iron status of newborns. We must be careful to interpret the newborn SF level because it is also an acute reaction protein. This study's limitation could not conclude a cause and effect between maternal inflammation and the iron status of newborns because it is only an observational study. Future studies need to involve broader factors, especially IL-6, hepcidin, and other variables affecting neonate iron status in maternal, placenta, and cord blood. It is necessary to carry out research that can describe how orchestral iron metabolism in the fetus.

ACKNOWLEDGMENTS

Our gratitude goes to all parties involved in the research, from Ummu Hani Hospital, Harapan Ibu Hospital, and Panti Nugroho Hospital, Purbalingga.

REFERENCES

Abioye AI, Park S, Ripp K, McDonald E A, Kurtis J D, Wu H, Pond-Tor S, Sharma S, Ernerudh J, Baltazar P, Olveda RM, Tallo V, Friedman JF. (2018) 'Anemia of inflammation during human pregnancy does not affect newborn iron endowment.' *J Nutr.,* 148 (3), pp. 427–436. DOI: 10.1093/jn/nxx052.

Austgulen R, Lien E, Liabakk N-B, Jacobsen G, and Arntzen KJ. (1994) 'Increased levels of cytokines and cytokine activity modifiers in normal pregnancy.' *Eur J Obstet. Gynecol. Reprod. Biol*., 57(3), pp. 149-155. DOI: 10.1016/0028-2243(94)90291-7.

Buss C, Entringer S, and Wadhwa PD. (2012) 'Fetal programming of brain development: intrauterine stress and susceptibility to psychopathology.' *Sci Signal*., 5(245):pt7. DOI: 10.1126/signal.2003406.

Cao C, Pressman EK, Cooper EM, Guillet R, Westerman M, and O'Brien KO. (2016) 'Prepregnancy body mass index and gestational weight gain have no negative impact on maternal or neonatal iron status.' *Reprod Sci.,* 23(5), pp. 613–622. DOI: 10.1177/1933719115607976.

Cherayil BI. (2015) 'Pathophysiology of iron homeostasis during inflammatory states.' *J Pediatr*., 167(0): S15–S19. DOI: 10.1016/j.jpeds.2015.07.015.

Collard KJ. (2009) 'Iron homeostasis in the neonate.' *Pediatrics.* 123(4), pp.1208-1216. DOI: 10.1542/peds.2008-1047.

Dao MC, Sen S, Iyer C, Klebenov D, and Meydani SN. (2013) 'Obesity during pregnancy and fetal iron status: is hepcidin the link?' *J Perinatol.,* 33(3), pp.177–181. DOI: 10.1038/jp.2012.81.

Dahlgren J, Samuelsson A, Jansson T, and Holmäng AA. (2006) 'Interleukin-6 in the maternal circulation reaches the rat fetus in mid-gestation'. *Pediatr Res.,* 60 (2), pp. 147–151. DOI: 10.1203/01.pdr.0000230026.74139.18.

Dewey KG and Oaks BM. (2017) 'U-shaped curve for risk associated with maternal hemoglobin, iron status, or iron supplementation.' *Am J Clin Nutr.,* 106(Suppl 6):1694S–1702S. DOI: 10.3945/ajcn.117.156075.

Dosch NC, Guslits EF, Weber MB, Murray SE, Ha B, and Coe CL. (2016) 'Maternal obesity affects inflammatory and iron indices in umbilical cord blood.' *J Pediatr.,* 172: 20–28. DOI: 10.1016/j.jpeds.2016.02.023.

Estes ML & McAllister AK. (2016) 'Maternal immune activation: implications for neuropsychiatric disorders'. *Science*. 353(6301), pp.772–777. DOI: 10.1126/science.aag3194.

Fink NR, Chawes B, Bønnelykke K, Thorsen J, Stokholm J, Rasmussen MA. (2019) 'Levels of low-grade systemic inflammation in pregnant mothers and their offspring are correlated.' *Scientific Reports.* 9:3043. Doi: 10.1038/s41598-019-39620-5.

Fisher AL and Nemeth E. (2017) 'Iron homeostasis during pregnancy.' *Am. J. Clin. Nutr*., 106(Suppl 6): 1567s–1574s. DOI: 10.3945/ajcn.117.155812.

Flynn AC, Begum S, White SL, Dalrymple K, Gill C, and Alwan NA. (2018) 'Relationships between maternal obesity and maternal and neonatal iron status.' *Nutrients.* 10(8):1000. DOI: 10.3390/nu10081000.

Ganz T and Nemeth E. (2006) 'Iron imports IV Hepcidin and regulation of body iron metabolism.' *Am J Physiol Gastrointest Liver Physiol*., 290(2): G199-203. DOI: 10.1152/ajpgi.00412.2005.

Ganz T. (2013) 'Systemic iron homeostasis.' *Physiol Rev.,* 93(4), pp.1721–1741. DOI: 10.1152/physrev.00008.2013.

Georgieff MK. (2007) 'Nutrition and the developing brain: nutrient priorities and measurement.' *Am J Clin Nutr*., 85(2):614S–620S. DOI: 10.1093/ajcn/85.2.614S.

Jones AD, Zhao G, Jiang YP, Zhou M, Xu G, and Kaciroti N. (2016) 'Maternal obesity during pregnancy is negatively associated with maternal and neonatal iron status.' *Eur. J. Clin. Nutr*., 70(8), pp. 918-924. DOI: 10.1038/ejcn.2015.229.

Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz T. (2004) 'IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin'. *J Clin Invest*., 113(9), pp. 1271–1276. DOI: 10.1172/JCI20945.

Phillips AK, Roy SC, Lundberg R, Guilbert TW, Auger AP, Blohowiak SE, Coe CL, Kling PJ. (2014) 'Neonatal iron status is impaired by maternal obesity and excessive weight gain during pregnancy.' *J Perinatol*., 34(7), pp.513–518. DOI: 10.1038/jp.2014.42.

Rudolph MD, Graham AM, Feczko E, Miranda-Dominguez O, Rasmussen JM, Nardos R, Wadhwa PD, Buss C, Fair DA. (2018) 'Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring'. *Nature Neuroscience*. 21(5), pp.765-772. DOI: 10.1038/s41593-018-0128-y.

Romero R, Gotsch F, Pineles B, and Kusanovic JP. (2007) 'Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury.' *Nutrition Reviews*. 65(12 Pt 2): S194–S202. DOI: 10.1111/j.1753-4887.2007.tb00362.x.

Sangkhae V, Fisher AL, Wong S, Koenig MD, Tussing-Humphreys L, Chu A, Lelić M, Ganz T, Nemeth E. (2020) 'Effects of maternal iron status on placental and fetal iron homeostasis.' *J Clin Invest*., 130(2):625-640. DOI: 10.1172/JCI127341.

Sanni OB, Chambers T, Li JH, Rowe S, Woodman AG, Ospina MB, and Bourque SL. (2020) 'A systematic review and meta-analysis of the correlation between maternal and neonatal iron status and haematologic indices.' *clinical medicine*. 27:100555. DOI: 10.1016/j.eclinm.2020.100555.

Sorokin Y, Romero R, Mele L, Wapner RJ, Iams JD, Dudley DJ, Spong CY, Peaceman AM, Leveno KJ, Harper M, Caritis SN, Miodovnik M, Mercer BM, Thorp JM, O'Sullivan MJ, Ramin SM, Carpenter MW, Rouse DJ, Sibai B. (2010) 'Maternal serum interleukin-6, c-reactive protein, and matrix metalloproteinase-9 concentrations as risk factors for preterm birth < 32 weeks and adverse neonatal outcomes'. *Am J Perinatol*., 27(8):631–640. DOI: 10.1055/s-0030-1249366.

Stoffel NU, Lazrak M, Bellitir S, Mir NE, Hamdouchi AE, Barkat A, Zeder C, Moretti D, Aguenaou H, Zimmermann MB. (2019) 'The opposing effects of acute inflammation and iron deficiency anemia on serum hepcidin and iron absorption in young women.' *Haematologica*. 104(6):1143-1149. DOI: 10.3324/Haematol.2018.208645.

Tussing-Humphreys L, Pusatcioglu C, Nemeth E, and Braunschweig C. (2012) 'Rethinking iron regulation and assessment in iron deficiency, anemia of chronic disease, and obesity: Introducing hepcidin.' *J Acad Nutr Diet*., 112(3), pp.391–400. DOI: 10.1016/j.jada.2011.08.038.

Watts DG, Krohn MA, Wener MH, and Eschenbach DA. (1991) 'C-reactive protein in normal pregnancy.' *Obstet. Gynecol*., 77(2), pp.176–180. DOI: 10.1097/00006250-199102000-00002.

Wessling-Resnick M. (2010) 'Iron homeostasis and the inflammatory response.' *Annu Rev Nutr*., 30:105-122. DOI: 10.1146/annurev.nutr.012809.104804.

Wrighting DM and Andrews NC. (2006) 'Interleukin-6 induces hepcidin expression through STAT3'. *Blood*. 108(9), pp.3204-3209. DOI: 10.1182/blood-2006-06-027631.

Wu AC, Lesperance L, Bernstein H. (2002) 'Screening for iron deficiency.' *Pediatrics in Review*. 23(5), pp. 171-178. DOI: 10.1542/pir.23-5-171.

WHO. (2011) 'Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations.' Available at: https://www.who.int/vmnis/indicators/serum_ferritin.pdf

Yanoff LB, Menzie CM, Denkinger B, Sebring NG, McHugh T, Remaley AT, Yanovski JA. (2007) 'Inflammation and iron deficiency in the hypoferremia of obesity.' *Int J Obes*., 31(9), pp.1412–1419. DOI: 10.1038/sj.ijo.0803625.

Zhang A and Enns CA. (2009) 'Molecular mechanisms of normal iron homeostasis.' *Hematology Am Soc Hematol Educ Program*., 207-214. DOI: 10.1182/asheducation-2009.1.207.

Zaretsky MV, Alexander JM, Byrd W, and Bawdon RE. (2004) 'Transfer of inflammatory cytokines across the placenta.' *Obstet Gynecol.,* 103(3),pp. 546-550. DOI: 10.1097/01.AOG.0000114980.40445.83.