Title
Hepcidin, serum iron and transferrin saturation in full term and premature infants
during the first month of life: A state-of-the-art review of existing evidence in humans

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Short running head
Hepcidin, iron and TSAT in the neonatal period

Abbreviations
AGA  Appropriate for gestational age
CI    Confidence Interval
CRP   C-reactive protein
DFID  Department for International Development
DMT-1 Divalent metal transporter 1
EIA   Enzyme immunoassay
ELISA Enzyme-linked immunosorbent assays
EPO   Erythropoietin
3.1 ABSTRACT

Neonates regulate iron at birth and in early postnatal life. We reviewed literature from PubMed and Ovid Medline containing data on umbilical cord and venous blood concentrations of hepcidin, iron and transferrin saturation (TSAT) in human neonates from 0-1 month of age. Data from 59 studies were used to create reference ranges for hepcidin, iron and TSAT for full-term neonates over the first month of life. In full-term neonates,
venous hepcidin increases 2-3-fold over the first month of life (to reach 61.1 ng/mL; CI: 20.1-102.0 ng/mL) compared to umbilical cord blood (29.7 ng/mL; CI: 21.1-38.3 ng/mL). Cord blood has high levels of serum iron (28.5 μmol/L; CI: 26.0-31.1 μmol/L) and TSAT (51.7%; CI: 46.5-56.9%). Following a short-lived immediate postnatal hypoferremia, iron and TSAT rebounded to approximately half the levels in the cord by the end of the first month. There was insufficient data to formulate reference ranges for preterm neonates.

**KEYWORDS:** Nutritional immunity, host-pathogen interaction, hepcidin, neonates, hypoferremia, transferrin, serum iron

### 3.2 INTRODUCTION

**Iron homeostasis during pregnancy**

Three important mediators of hepcidin synthesis: iron status, inflammation, and erythropoiesis, are all altered during pregnancy.(1–4) Iron demand on the mother increases significantly to support expanded maternal erythropoiesis and iron requirements of the growing fetus.(5–9) During pregnancy, the placenta transfers ~270mg of iron from the mother to the fetus via the placenta.(10,11) Syncytiotrophoblasts in the placental villi take up transferrin-bound iron from the maternal circulation by endocytosis via transferrin receptor 1 (TFR1) (Figure 1).(12,13) As reviewed in Cao et al.(14) and Fisher et al.,(15) iron is released from TFR1 and transferred from the acidified endosome into the syncytiotrophoblast cytoplasm by DMT-1,(13) ZIP8,(16) and ZIP14,(17). Ferroportin transports iron out of placental syncytiotrophoblasts, and then ceruloplasmin, hephaestin, and zyklopen assist in the oxidization of Fe^{2+} to Fe^{3+} helping it pass through the endothelium to reach the fetal circulation.(18–20)
Maternal control of fetal and early neonatal iron metabolism

Increases in maternal dietary iron uptake and placental iron transfer occur in the second and third trimester,(21,22) when maternal hepcidin decreases to trigger increased duodenal iron absorption,(23) splenic macrophage iron recycling, and the release of maternal hepatic iron stores.(24–26) The resulting increased circulating maternal iron is then freely available for transfer to the fetus. Factors that are thought to contribute to maternal hepcidin suppression in the second and third trimester include maternal iron deficiency, erythropoiesis in the mother or fetus,(26) oestrogen,(27) and progesterone receptor membrane component-1.(28) Conflicting evidence now exists as to whether pregnancy-induced plasma dilution may also play a role.(15,29)

Fetal control of fetal and early neonatal iron metabolism

Eighty percent of all the iron transferred from the mother to the fetus occurs in the last trimester.(30) An illustration of the fetal demand for iron (amounting to 1.6-2.0 mg/kg per day(31)) is that umbilical cord blood contains a higher serum iron concentration than in the maternal circulation and at delivery babies have higher total body iron per kilo than that measured in their mothers or in healthy adults.(32–43) This pattern is seen even in anemic mothers and their babies.(31,42,44,45) The relative roles of maternal and fetal hepcidin levels in controlling placental iron transport are unclear and may change during the course of gestation.(24,25,29,41,43,44,46–53) As iron becomes more available in the last months of pregnancy, the fetus synthesizes hepcidin probably to control the rate of placental iron transfer and thereby to protect itself from iron-overload.(15,29,54) Evidence showing the importance of fetal hepcidin includes: 1) umbilical cord hepcidin concentrations at birth are higher than maternal levels before and during delivery(24,25,43,52,55,56) and 2) in pregnancies with multiple gestations, differences in cord hepcidin between siblings
explained a greater fraction of variability in cord hemoglobin, serum ferritin, sTfR, and EPO than maternal hepcidin levels. (48)

**Placental control of fetal and early neonatal iron metabolism**

The placenta may also independently regulate iron transfer to the fetus in some scenarios. (57) A reduction of ferroportin expression on the apical fetal-facing membrane of placental syncytiotrophoblasts during maternal iron deficiency, in addition to increased expression of TFR1 on the maternal-facing side supports this hypothesis. (29) Sangkhae et al. propose that during maternal iron deficiency, iron is held in the placenta to ensure that its metabolic homeostasis is maintained. Placental protein synthesis and critical transfer mechanisms can then continue, ensuring the more detrimental condition of placental dysfunction does not occur. These findings were observed in murine and *in vivo* human trophoblast models, but not in respect to the human pregnancies analysed. (29)

**Impact of labor and delivery on hepcidin**

Childbirth is an intensely stressful event. Inflammatory pathways (including IL-6 mediated pathways) are induced at the onset of human labor, even in the absence of intrauterine infection. (58–65) Initiating stimuli for IL-6 production and release could involve the endocrine events of labor, (64–66) mechanical distension of the membranes and cervix (smooth muscle), (58,66–69) placental hypoxia and/or hypo-perfusion, (66,70) fetal hypoxia-acidemia, (71) pain (72) or exposure to infective agents. (63,65,66,73) The production of IL-6 leads to an increase in hepcidin levels along with a massive influx of immune cells (predominantly neutrophils) into the cervix, decidua, myometrium, chorioamnionic membranes and amniotic fluid. (64,74) This further exacerbates the rise in IL-6 and other cytokines. (72,75) The increase in post-delivery maternal hepcidin concentrations is larger with caesarean section deliveries (5.5-fold increase) as compared to standard vaginal deliveries (3-fold increase). (76) This is most likely due to the surgical procedure and the subsequent inflammation. Similar increases in serum hepcidin are seen postoperatively
during other abdominal surgeries. The effect of this maternal rise in hepcidin before, during and immediately after childbirth on the late fetal/early neonatal iron status is unknown, although like IL-6, hepcidin is not thought to cross the placenta.

Effects of infection on neonatal serum hepcidin levels

Intra-amniotic infections can cause an increase in fetal hepcidin. Multiple studies have documented an association between chorioamnionitis, perinatal acidosis and neonatal sepsis with high umbilical cord hepcidin concentrations. For example, an extremely high cord concentration (437.6 ng/mL) was found in a neonate with confirmed *Enterococcus faecalis* early-onset sepsis. Similarly, very-low birth weight, premature neonates with late-onset culture-confirmed sepsis, exhibit elevated levels of hepcidin. Nevertheless, despite the well-documented regulatory pathways of infection and inflammation on iron regulation, it is important to note that multiple publications have shown a lack of correlation between hepcidin, IL-6 and CRP in sick neonates. This is likely due to differences in the biochemical kinetics of these molecules. IL-6 concentrations spike very early in the course of perinatal infection, whereas the rise of CRP is delayed.

Standardizing hepcidin measurements

Multiple assays, including mass spectrometry (MS) and immunochemistry ELISA methods, are available to quantify hepcidin in various body fluids (urine, serum and plasma). However, in the studies included in this state-of-the-art review, none of these methods are calibrated using the same standards and, as a result, there are significant differences in hepcidin values between studies.

In 2016, Van der Vorm *et al.* harmonized many of the available hepcidin ELISA assays using native, lyophilized plasma with cyrolyoprotectant as a commutable candidate reference material. Linear equations were formulated to standardize the hepcidin assays. These equations can now be used to conduct post-hoc standardization of non-calibrated test
results, aiding the retrospective comparison of data from previous publications. We have used these equations in this state-of-the-art review to generate standardized hepcidin values (Supplementary Table 1). The production of standardized reference material, which was refined in 2019, is available for purchase allowing hepcidin measurements to be standardized in all laboratories (89).

To our knowledge, this is the first time that retrospective comparisons have been made between serum hepcidin concentrations in different studies, using post-hoc standardized values to produce calculated weighted mean averages in umbilical cord and venous blood. This state-of-the-art review contributes this comparative analysis and also offers an example for how other authors could approach retrospective comparisons of hepcidin levels from different studies.

### 3.3 METHODS

In March 2019, we reviewed the literature searching two databases: PubMed and Ovid Medline with no restrictions on language. The original search was for human studies only published between the date range of 1st January 1975 to 1st December 2019. Corresponding authors of extracted publications were not contacted. One individual carried out the inclusion/exclusion process of the retrieved studies, and there was no assessment of bias or the quality of studies as seen in a systematic review process. Table 1 displays the search strategy used. Figure 2 shows the flow diagram of the literature search. The search generated publications containing data on cord and venous concentrations of hepcidin, serum iron and transferrin saturation in the neonatal period. Studies that analyzed healthy neonates were included. Mean, median or range of the gestational age of the study population was a requirement for inclusion. Neonates >37 weeks at delivery were regarded as full-term neonates (FTB). Studies or study groups with a gestational <37 weeks were
classed as premature (PTB) neonates. Retrieved publications had to report a mean time of bleed 0-720 hours post-delivery to be analyzed. Mean (SD or 95% CI), or median (range, IQR, or 95% CI) data were extracted from the included publications. Studies reporting mean (95% CI) were included in the calculation of weighted means (95% CI) and the associated Figures 3-5. Reference ranges for adults and children were presented for comparison. Many retrieved publications did not stratify results by birthweight; as a result, this variable was not recorded in Tables 2-7. Publications were not stratified by sample type (serum or plasma) due to the overall lack of studies. If multiple publications on the same study population were retrieved, only one was included in the analysis.

The standardization of hepcidin values using different ELISA assays was performed using the slopes and intercepts from Van der Vorm et al. This was performed for studies that used ELISA test kits from DRG (hepcidin-25 (human) EIA Kit, DRG, USA), Bachem (hepcidin-25 EIA Kit, Bachem, USA) and Intrinsic Lifesciences (Intrinsic Hepcidin ELISA Kit, Intrinsic Lifesciences, USA). It was not possible to standardize hepcidin values acquired using the ELISA from Hangzhou Eastbiopharm (Hangzhou Eastbiopharm Co. Ltd., Hangzhou, Zhejiang, China) and mass spectroscopy (MCProt Biotechnology, Kanazawa, Japan), used in Basu et al. and Ichinomiya et al., respectively. Prohepcidin was not included in the analysis as it is a poor proxy for biochemically active hepcidin-25.

The software Stata IC version 15 (StataCorp LP, College Station, Texas, USA) and R (R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, 2020, https://www.R-project.org) were used to analyze data. To calculate the confidence interval (CI) around the weighted mean, the weighted variance was calculated using the wtd.var function from the R package Hmisc. The standard error derived from this weighted variance was then used to calculate the t-statistic (i.e. weighted mean divided by weighted standard error), from which the 95% CI was derived. GraphPad Prism version 8
3.4 RESULTS

The initial search of two electronic databases for three different iron markers yielded 13,931 publications. After the exclusion of duplicated studies and selection criteria filtering, 20 publications were included in the analysis for hepcidin, 23 publications for TSAT and 51 publications for serum iron. Many of these studies were found to contain information on multiple parameters of interest. Overall, we identified 59 publications containing data on hepcidin, serum iron or TSAT in FTB neonates. Sixteen publications were found to contain data on PTB neonates.

In publications detailing the effects of cord clamping interventions, all retrieved cord blood values were from groups that underwent 60 seconds of delayed cord clamping. This is consistent with current WHO policy. Cord blood weighted mean values are generated in Tables 2-7, and are represented by a dashed line in Supplementary Figures 1-3 and α (95% CI) in Figures 3-5.

Hepcidin

Standardized weighted mean umbilical cord blood hepcidin levels were higher in FTB neonates (29.7 ng/mL; CI: 21.1-38.3 ng/mL) vs PTB neonates (8.4 ng/mL; CI: 2.0-14.7 ng/mL) (Supplementary Figure 1A and 1B and Tables 2 and 3). Full-term cord blood hepcidin levels were 2-fold higher than in adult male (13.1 ng/mL; CI: 1.4-43.2 ng/mL) and female (10.6 ng/mL; CI: 1.4-43 ng/mL) references ranges (Table 2). FTB standardized venous hepcidin levels increased (61.1 ng/mL; CI: 20.1-102.0 ng/mL) over the first four days of life (Figure 3A). This trend is unclear for PTB neonates due to the lack of studies. (Table
3 and Figure 3B). No studies were retrieved that assessed post-delivery venous blood samples >77 hours in FTB or >168 hours in PTB.

**TSAT**

The weighted mean TSAT in cord blood was higher in FTB neonates (51.7%; CI: 46.5-56.9%) compared to PTB neonates (36.5%; CI: 0.8-72.1%) (Tables 4 and 5 and Supplementary Figure 2). Cord blood TSAT in FTB neonates was double the reference levels found in adults (23.5%; CI: 12-38.8%) and children aged 1-5 years (19.4%; CI: 8.2-32.9%) (Table 4). The weighted mean average of TSAT decreased 2-fold from cord blood to venous blood in FTB neonates (down to 25.2%; CI: 20.1-30.3%) (Figure 4A). This hypoferremic response in FTB neonates was followed by a steady increase from 21.8% (CI: 18.8-24.7%) to 44.2% (CI: 32.1-57.8%). No trend was identifiable in PTB neonates due to the lack of data (Table 5 and Figure 4B).

**Serum Iron**

Unlike TSAT values, serum iron levels in cord blood were higher in PTB (46.8 μmol/L; CI: 29.7-63.8 μmol/L) neonates compared to FTB neonates (28.5 μmol/L; CI: 26.0-31.1 μmol/L) (Supplementary Figure 3). Like TSAT, a similar 2-fold decrease in the weighted mean average of venous blood compared to cord blood is seen in FTB (13.8 μmol/L; CI: 10.8-16.9 μmol/L) (Table 6), and PTB neonates (16.2 μmol/L; CI: 15.3-17.0 μmol/L) (Table 7). Figure 5 suggests that after the initial reduction (in the first 48 hours of life), levels of serum iron remain consistent over the first month of life in FTB (A) and PTB neonates (B). Serum iron was lowest between 0-48 hours post-delivery (Table 6 and Table 7).
3.5 DISCUSSION

Hypoferremia in FTB neonates

The weighted mean average for cord blood hepcidin was calculated using data from 11 studies. Almost all included studies reported a mean value between 11-41ng/mL, apart from Kulik-Rechberger et al. This study reported a much higher cord blood hepcidin value (67.9ng/mL; CI: 59.3-76.5ng/mL) as seen in Supplementary Figure 1A. In addition, this study also recorded higher hepcidin levels in venous samples collected at 72 hours (92.9ng/mL; CI: 83.3-102.3ng/mL), compared to those collected by Prentice et al. at 77 hours (55.6ng/mL; CI: 47.1-65.5ng/mL).

When all the data are reviewed together (Figure 3A), hepcidin increases from within the first 2-11 hours of life and then continues to increase up to 82 hours post-delivery. At all times the hepcidin levels are much higher than those recorded in adults. This excess hepcidin production may provide a quick, comprehensive and relatively long-lasting (0-3 days) hypoferremic response to aid protection during this vulnerable period. After the first few days, TSAT gradually increases as do serum iron levels, eventually reaching a plateau at approximately 1 month of age.

Iron metabolism biomarker data gaps in first month of life in full-term babies

Gaps in the time course of the concentration of hepcidin, TSAT and serum iron in the first month of life in full-term neonates still exist. This hinders our understanding of neonatal iron metabolism, particularly because hepcidin, TSAT and serum iron are transient and dynamic iron parameters. At the point in which hypoferremia is believed to be maximal, publications detailing the concentration in early (<12 hours) venous samples are lacking in both groups.
(FTB n=2, PTB n=1). Further research at this time point is required to fully elicit the strength and consistency of this response, as well as understanding the process in greater detail.

**Lack of data on preterm neonates during the first 24 hours**

After analysis of the current literature, the extent of the role that hypoferremia plays in neonates with a gestational age less than 37 weeks is still unclear. This is primarily due to the limited number of publications documenting hepcidin (n=5), TSAT (n=6) and serum iron (n=13) in the first month of life in preterm neonates. The variability between the studies is vast and further complicated by the complex, intensive and inconsistent care of premature neonates worldwide.

Data analysis of the retrieved publications suggests that preterm neonates have lower cord hepcidin than in full-term neonates, infants and healthy adults. Weighted cord mean values are 3-fold higher in full-term (29.7ng/mL; CI: 21.1-38.3ng/mL) neonates compared to preterm (8.4ng/mL; CI: 2.0-14.7ng/mL) neonates. We speculate that this could be due to very early preterm neonates (<30 weeks’ gestation) possessing circulatory monocytes with decreased surface expression of TLR4, lower mRNA expression of TLR4 and reduced cytokine production.(100) An effect on the production of IL-6 at delivery, might then lead to a reduced ability to stimulate hepcidin expression as suggested in full-term babies.

Our analysis proposes that peripheral venous hepcidin values in preterm neonates increase to 44ng/mL at 168 hours. However, decreases in TSAT between the cord and venous samples are not observed (36.5% to 45.6%). We propose that this is due to a lack of data on TSAT levels in preterm neonates over the first hours of life, potentially due to the complex ethical questions around bleeding preterm neonates so early in postnatal life. This results in the collection of skewed data, focusing only on later time points in the first month of life.
Limitations

The aim of this state-of-the-art review was to evaluate our current knowledge on neonatal iron homeostasis in preterm and full-term neonates. As a result of the dearth of publications detailing the parameters of interest during this period, our review has several limitations discussed below. First, we were unable to stratify by geographical location. Many studies do not stratify their study groups by gestational age (preterm: <37 weeks, full term: >37 weeks). Subsequently, we have had to assign each study group or population by the mean gestational age. This will result in a reduction of any natural variation potentially caused by gestational age between the reviewed populations. This is also the case with respect to birth weight and hemoglobin concentration.

Similarly, the studies on preterm neonates are made up of multiple small sample size subgroups with different gestational ages. Due to the lack of preterm studies, we have had to combine these study groups to formulate weighted means and figures. This in itself, could distort the impact of gestational age on our results, since data from the very early preterm newborns is combined with that from the late preterm neonates.

The retrieval of gestational age was a crucial aspect of the search strategy; however, few studies document the method used. There are large differences in the accuracy of different techniques.(101)

Post-hoc standardization of different hepcidin ELISA kits has, to our knowledge, never been completed before with retrospective data. However, care should be given to the accuracy of the standardized values, as standardization was only possible for DRG, Bachem and Intrinsic Lifesciences ELISA test kits. Studies that used alternative methods(102) were not included in summary statistics.
An essential criterion of inclusion in this publication was that all neonatal data came from healthy newborns. However, documentation of labor practices (including mode of delivery) and postnatal care, along with postnatal medication lack detail in the publications retrieved. Vaginal delivery is occasionally referred to as the method of delivery; however, the use of inflammation-inducing forceps, cesarean section or vacuum delivery is not consistently reported in each publication.

**Conclusion**

Currently available data suggests that hepcidin, serum iron and TSAT levels for adults and infants are much lower than those found in cord blood and venous blood from neonates during the first month of life. We have strengthened the evidence that full-term neonates possess the ability to produce a hepcidin-mediated hypoferremic response post-delivery. Whether this mechanism is found in PTB neonates is still unclear. This is predominately due to the lack of studies on healthy preterm neonates during the first hours of life. If premature or low birthweight neonates are unable to mount a hypoferremic response, this could enhance their risk of early neonatal infections. Conversely, if the hypoferremic response is seen in both preterm and full-term neonates, it will further support the hypothesis that regulation of iron distribution plays a fundamental role as an innate mechanism of protection against infection.

In summary, serum hepcidin is likely triggered by the inflammatory effect of labor and delivery. We suggest that this intrinsic mechanism of protection protects newborns with immature immune systems to transition from a semi-allogeneic, protected fetal setting to a microbe-rich extrauterine environment. (103,104) Hepcidin-induced hypoferremia then potentially provides a broad action innate bacteriostatic action to invading micro-organisms, when physiological adaption to postnatal life is so critical for survival.
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J.H.C., A.M.P. and C.C. designed the research; J.H.C. conducted the search strategy and analyzed data; J.H.C., A.M.P. and C.C. wrote the paper. All authors reviewed the final manuscript prior to submission.

Consent for Publication:
Not applicable.
| Parameter   | Database  | Search Strategy                                                                                                                                 |
|-------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Hepcidin    | Ovid Medline | (Human) AND (neonate OR neonates OR infant OR infants OR baby OR babies OR cord OR "umbilical cord".mp.) AND (hepcidin OR prohepcidin.mp.) |
|             | PubMed    | (Human) AND (neonate OR neonates OR infant OR infants OR baby OR babies OR cord OR "umbilical cord") AND (hepcidin OR prohepcidin)            |
| TSAT        | Ovid Medline | (Human) AND (neonate OR neonates OR infant OR infants OR baby OR babies OR cord OR "umbilical cord".mp.) AND ("transferrin saturation" OR TSAT.mp.) |
|             | PubMed    | (Human) AND (neonate OR neonates OR infant OR infants OR baby OR babies OR cord OR "umbilical cord") AND ("transferrin saturation" OR TSAT)     |
| Serum Iron  | Ovid Medline | (Human) AND (neonate OR neonates OR infant OR infants OR baby OR babies OR cord OR "umbilical cord".mp.) AND ("serum iron" OR iron.mp.) |
|             | PubMed    | (Human) AND (neonate OR neonates OR infant OR infants OR baby OR babies OR cord OR "umbilical cord") AND ("serum iron" OR iron)                |

Searches conducted via PubMed and Ovid Medline.
Table 2: Hepcidin concentration (ng/mL) in full-term newborns over the neonatal period.

| Publication                      | Refere ence | Ye ar | Locatio n | n  | Test Type                   | Hemoglobin (g/dL)* | Hepcidin (ng/mL) | Standardized Hepcidin (ng/mL)* |
|----------------------------------|-------------|-------|------------|----|-----------------------------|-------------------|-----------------|-------------------------------|
|                                  |             |       |            |    |                             | Mean (SD or 95% CI) | Median (IQR) | Mean (SD 95% CI) | Mean (SD or 95% CI) |
| Ambrus et al. (106)              | (106)       | 2016  | Greece     | 10 | ELISA (DRG)                 | 17.6 (±2.0)        | 17.65 (4.75- 69.2) | 24.1 (3.1-48.2) |
| Ambrus et al. (54)               | (107)       | 2016  | Poland     | 98 | ELISA (Intrinsic)           | 14.8 (±2.8)        | 18.5 (7.0-36.8)  | 38.3 (8.9-103.2) |
| Dehaye et al. (106)              | (108)       | 2016  | USA        | 7  | ELISA (Bachem)              | 15.3 (±1.3)        | 14.6 (4.1-41.6)  | 29.2 (7.6-95.2)  |
| Doshi et al. (106)               | (109)       | 2016  | USA        | 47 | ELISA (DRG)                 | 14.6 (±1.8)        | 18.5 (5.4-36.9)  | 21.8 (5.4-92.2)  |
| Garcia-Valdez et al.             | (110)       | 2016  | Spain      | 52 | ELISA (DRG)                 | 15.9 (±2.1)        | 16.0 (4.1-69.5)  | 21.8 (5.4-92.2)  |
| Hepper et al. (111)              | (111)       | 2016  | Sweden     | 15 | ELISA (Bachem)              | 38.5 (±19.8)       | 38.5 (±19.8)     | 38.5 (±19.8)     |
| Kato-Reichberger et al.          | (112)       | 2016  | Poland     | 44 | ELISA (DRG)                 | 46.6 (±8.3)        | 47.2 (18.3-101.7)| 67.9 (28.3-140.5) |
| Lee et al.                       | (113)       | 2016  | USA        | 10 | ELISA (Intrinsic)           | 14.9 (±2.8)        | 14.9 (±2.8)      | 31.2 (±9.0)      |
| Lorenz et al. (114)              | (114)       | 2016  | Germany    | 10 | ELISA (Bachem)              | 15.9 (±2.0)        | 15.9 (±2.0)      | 38.3 (±9.0)      |
| Prudent et al. (115)             | (115)       | 2016  | Sweden     | 81 | ELISA (Bachem)              | 32.9 (±4.7)        | 32.9 (±4.7)      | 32.9 (±4.7)      |
| Rentu et al. (116)               | (116)       | 2016  | Finland    | 11 | ELISA (Intrinsic)           | 33.0 (8.8- 52.2)   | 33.0 (8.8- 52.2) | 33.0 (8.8- 52.2) |
| Ru et al.                        | (117)       | 2016  | Poland     | 50 | ELISA (Bachem)              | 17.8 (±1.7)        | 17.8 (±1.7)      | 17.8 (±1.7)      |
| Sironius et al. (118)            | (118)       | 2016  | Poland     | 54 | ELISA (DRG)                 | 16.6 (±3.1)        | 16.6 (±3.1)      | 16.6 (±3.1)      |
| Young et al. (119)               | (119)       | 2016  | USA        | 19 | ELISA (Intrinsic)           | 13.4 (±2.0)        | 13.4 (±2.0)      | 13.4 (±2.0)      |

ELISA, enzyme-linked immunosorbent assay; CI, confidence interval; IQR, interquartile range.

- Not determined as not applicable to the calculation of weighted mean hepcidin or standardized hepcidin values.

1Values from Basu et al (102) were not standardized because the study used the Hangzhou Eastbiopharm ELISA, which was not part of the Van der Vorm et al. analysis. (88)

2Extracted standard deviations were converted to 95% confidence intervals.
3Median (IQR or 95% CI) were not included in weighted means.

4Reference ranges for adults (male and female) and infants are displayed for comparison. (91)

5Hepcidin standardization was conducted using the linear equations documented in Supplementary Table 1.

6Hemoglobin concentrations are provided to aid interpretation of neonatal iron status.

Table 3: Hepcidin concentration (ng/mL) in preterm newborns over the neonatal period.

| Publication | Reference | Year | Location | n | Test Type | Type of Sample | Study Group | Mean (SD or 95% CI) | Median (IQR or 95% CI) | Weighted Mean (Cord) | Weighted Mean (Venous) |
|-------------|-----------|------|----------|---|-----------|---------------|-------------|---------------------|------------------------|-----------------------|-----------------------|
| Delaney et al. | (114) | 2019 | USA       | 6 | ELISA     | Cord (Serum)  | 1           | 15.3 (±2.3)         | 15.78 (13.6-14)        | 13.1                   | 13.1                  |
| Ichinomiya et al. | (81) | 2017 | Japan     | 9 | Mass Spec | Cord (Serum)  | 1           | 7.3 (2.85-16.36)    | 26.9 (13.5-63.1)       | -                     | -                     |
| Lorenz et al. | (87) | 2014 | Germany   | 4 | ELISA     | Cord (Plasma) | 24-29 wks   | 16.8 (15.1-18.0)    | 26.9 (13.5-63.1)       | 14.7 (8.0-23.7)        | 14.7 (8.0-23.7)        |
|         |           |     |           | 1 | ELISA     | Cord (Plasma) | 30-36 wks   | 16.1 (±2.2)         | 48.5 (24.7-74.5)       | -                     | -                     |
| Ru et al. | (110) | 2018 | USA       | 9 | ELISA     | Cord (Serum)  | 1           | 15.1 (±0.3)         | 12.1 (3.5-15.7)        | 7.8 (5.9-10.1)         | 114.8                 |
| Uijtersout et al. | (112) | 2016 | Netherlands | 16 | ELISA     | Venous - 168 hours (Serum) | 1           | 16.5 (12.0-21.3)    | 69.6 (14.6-180.1)      | 114.8                 | -                     |
| Male Adults$^a$ | (91) |      |           |    |           |               |             | 14.4 (2.9)          | 44.4                   | 114.8                 | -                     |
| Female Adults$^a$ | (91) |      |           |    |           |               |             | 10.6 (1.4-40)       | 44.4                   | 114.8                 | -                     |
| Infants$^a$ | (91) |      |           |    |           |               |             | 11.9 (3.3-37.7)     | 44.4                   | 114.8                 | -                     |

ELISA, enzyme-linked immunosorbert assay; CI, confidence interval; IQR, interquartile range; Mass Spec, mass spectrometry.

- Not determined as not applicable to the calculation of weighted mean hepcidin or standardized hepcidin values.

* Ichinomiya et al.(81) was not standardized because the study used a mass spectrometry...
based method that was not part of the van der Vorm et al. analysis.\(^{(88)}\)

\(^1\)Extracted standard deviations were converted to 95% confidence intervals.

\(^2\)Median (IQR or 95% CI) were not included in weighted means.

\(^3\)Reference ranges for adults (male and female) and infants are displayed for comparison.\(^{(91)}\)

\(^4\)Hepcidin standardization was conducted using the linear equations documented in Supplementary Table 1.

\(^5\)Hemoglobin concentrations are provided to aid interpretation of neonatal iron status.

Table 4: Transferrin saturation (%) in full-term newborns over the neonatal period.

| Publication          | Reference | Year | Location  | n   | Type of Sample | Mean (SD or 95% CI) | Median (IQR or 95% CI or Range) | Mean (95% CI)\(^1\) | Median (IQR or 95% CI or Range)\(^2\) |
|----------------------|-----------|------|-----------|-----|----------------|---------------------|----------------------------------|-----------------|-----------------------------------|
| Al-Tawil et al.      | (113)     | 2012 | Egypt     | 9   | Venous - 24 hours | 19.6 (±3.8)         | 19.6 (±3.8)                      | 25 (24.6-25.4)  | 19.5 (18.9-20.1)                  |
| Ali et al.           | (114)     | 2016 | USA       | 6   | Cord            | 15.95 (13.4-20.7)   | 15.95 (13.4-20.7)              | 55.5 (52.4-57.6)| 15.95 (13.4-20.7)                |
| Anderson et al.      | (115)     | 2007 | Sweden    | 10  | Venous - 48 hours | 18.9 (±1.7)         | 18.9 (±1.7)                     | 23 (21.9-24.1)  | 18.9 (±1.7)                       |
| Balogh et al.        | (92)      | 2007 | Hungary   | 9   | Cord            | 15.95 (13.4-20.7)   | 15.95 (13.4-20.7)              | 60.5 (14-90)    | 15.95 (13.4-20.7)                |
| Basu et al.          | (102)     | 2016 | India     | 15  | Cord            | 16.3 (±1.6)         | 16.3 (±1.6)                     | 61.6 (54.7-68.9)| 16.3 (±1.6)                      |
| El-Farrash et al.    | (116)     | 2012 | Egypt     | 3   | Cord            | 17.7 (±1.4)         | 17.7 (±1.4)                     | 49.5 (42.4-56.5)| 17.7 (±1.4)                      |
| Ervasti et al.       | (117)     | 2007 | Finland   | 9   | Cord            | 15.9 (±1.5)         | 15.9 (±1.5)                     | 55 (52.4-57.6) | 15.9 (±1.5)                      |
| Haga et al.          | (118)     | 2007 | Norway    | 9   | Cord            | 15.9 (±1.5)         | 15.9 (±1.5)                     | 55 (52.4-57.6) | 15.9 (±1.5)                      |
| Kalem et al.         | (119)     | 2019 | Turkey    | 8   | Cord            | 15.9 (±1.5)         | 15.9 (±1.5)                     | 55.8 (54.8-56.9)| 15.9 (±1.5)                      |
| Kelly et al.         | (41)      | 1978 | Scotland  | 1   | Cord            | 15.9 (±1.5)         | 15.9 (±1.5)                     | 58.8 (55.6-62) | 15.9 (±1.5)                      |
| Kitajima et al.      | (120)     | 2011 | Japan     | 8   | Venous - 720 hours | 15.1 (8.3-27.5)     | 15.1 (8.3-27.5)                | 44.2 (32.1-57.8)| 15.1 (8.3-27.5)                 |
| Kleven et al.        | (121)     | 2007 | USA       | 2   | Cord            | 15.7 (±1.0)         | 15.7 (±1.0)                     | 42 (32.4-51.6) | 15.7 (±1.0)                      |
| Mashako et al.       | (122)     | 1919 | DRC       | 1   | Cord            | 15.7 (±1.0)         | 15.7 (±1.0)                     | 42 (32.4-51.6) | 15.7 (±1.0)                      |
| Milman et al.        | (39)      | 1987 | Denmark   | 7   | Cord            | 16.1 (14.3-18.2)    | 16.1 (14.3-18.2)               | 48 (32-71)      | 16.1 (14.3-18.2)                |
| Study                  | Year | Country | Area     | Age   | Sample Size | Cord (Mean ± SD) | Venous (Mean ± SD) | Reference Ranges |
|------------------------|------|---------|----------|-------|-------------|------------------|-------------------|------------------|
| Prentice et al.        | 1999 | The Gambia |         |       |             | 17.6 (17.1-18.2) | 19.2 (18.3-20.0) | 21.8-23.2        |
|                        |      |          |          |       |             |                  |                   |                  |
| Puolakka et al.        | 1980 | Finland |          |       |             | 15.1 (±1.2)     | 16.1 (±1.5)       | 15.1-16.1        |
| Rehu et al.            | 2010 | Finland |          |       |             | 16.1 (±1.5)     | 16.0 (±1.8)       | 15.5-16.5        |
| Rois et al.            | 1975 | USA     |          |       |             | 16.1 (±1.5)     | 16.0 (±1.8)       | 15.5-16.5        |
| Slomka et al.          | 2013 | Poland  |          |       |             | 16.1 (±1.5)     | 16.0 (±1.8)       | 15.5-16.5        |
| Yamada et al.          | 2014 | Brazil  |          |       |             | 16.0 (±1.8)     | 16.0 (±1.8)       | 15.5-16.5        |

**Weighted Mean (Cord):**

- Adults: 23.5 (12-38.8)
- Infants: 39.8 (44.9) (19.4-32.9)

TSAT; transferrin saturation; CI, confidence interval; IQR, interquartile range.

- Not determined as not applicable to the calculation of weighted mean hepcidin or standardized hepcidin values.

1. Extracted standard deviations were converted to 95% confidence intervals.

2. Median (IQR or 95% CI) were not included in weighted means.

3. Reference ranges for adults and infants are taken from the National Health and Nutrition Examination Survey, 1999–2000.(125)

4. Hemoglobin concentrations are provided to aid interpretation of neonatal iron status.
Table 5: Transferrin saturation (%) in preterm newborns over the neonatal period.

| Publication      | Reference | Ye | Location | n | Type of Sample | Study Group | Mean (SD or 95% CI) | Median (IQR or 95% CI or Range) | Weighted Mean (Cord) | Weighted Mean (Venous) |
|------------------|-----------|----|----------|---|----------------|-------------|--------------------|------------------------------|------------------------|------------------------|
| Celik et al.     | (126)     | 20 | Turkey   | 4 | Venous - 648 hours | AGA Group   | 13.4 (±4.0)        | 46.5 (41.2-51.8)             | 36.5 (8.2-32.9)         | 23.5 (12.6-36.8)       |
| Haga et al.      | (118)     | 19 | Norway   | 2 | Cord            | SGA Group   | 48 (39.8-56.2)     | 41 (23.4-58.6)              |                           |                        |
| Ichinomiya et al.| (81)      | 20 | Japan    | 3 | Cord            |             | 87.2 (68.3-100)    |                             |                           |                        |
| Kitajima et al.  | (120)     | 20 | Japan    | 1 | Cord            |             | 64.3 (15.8-88.9)   |                             |                           |                        |
| Lackmann et al.  | (127)     | 19 | Germany  | 1 | Venous - <1 hour | <32 wks     | 39 (5-83)          |                             |                           |                        |
|                  |           |    |          | 2 | Venous - <1 hour | 33-34 wks   | 36 (7-87)          |                             |                           |                        |
|                  |           |    |          | 4 | Venous - <1 hour | 35-36 wks   | 31 (13-68)         |                             |                           |                        |
| Yamaeda et al.   | (124)     | 20 | Brazil   | 1 | Cord            | 15.7 (±1.8) | 24.8 (18.5-31.1)   |                             |                           |                        |
|                  |           |    |          | 2 | Venous - 720 hours | 10.8 (±1.3) | 44.1 (37.3-50.9)   |                             |                           |                        |

| Mean (95% CI)   | Median (IQR or 95% CI or Range) |
|-----------------|----------------------------------|
|                 | 36.5 (8.2-32.9)                  |

| Reference ranges for adults and infants are taken from the National Health and Nutrition Examination Survey, 1999–2000. (125) |

- Not determined as not applicable to the calculation of weighted mean hepcidin or standardized hepcidin values.

1 Extracted standard deviations were converted to 95% confidence intervals.

2 Medians (IQR or 95% CI) were not included in weighted means.

3 Reference ranges for adults and infants are taken from the National Health and Nutrition Examination Survey, 1999–2000. (125)

4 Hemoglobin concentrations are provided to aid interpretation of neonatal iron status.

a AGA group of Haga et al. (1980) can be identified in Supplementary Figure 2B.

b SGA group of Haga et al. (1980) can be identified in Supplementary Figure 2B.
Table 6: Serum iron concentration (μmol/L) in full-term newborns over the neonatal period.

| Publication            | Reference Year | Country | Sample Type | Mean (95% CI) | Median (IQR or Range) |
|------------------------|----------------|---------|-------------|---------------|-----------------------|
| Ahlsen et al.          | (128) 1989     | Sweden  | Cord        | 38 (34.9-41.1) |                       |
| Ali et al.             | (114) 2016     | USA     | Cord        | 26.8 (24.4-29.2) |                       |
| Amarnath et al.        | (129) 1989     | USA     | Cord        | 24.1 (21-27.2)  |                       |
| Anderson et al.        | (115) 2011     | Sweden  | Venous - 48 hours | 18.9 (18.7)   |                       |
| Armitage et al. (VA)   | (105)          | The Gambia | Cord    | 13.7 (12.4-14.6) | 18.8 (15.4-22.3)      |
| Armitage et al. (VPM)  | (105)          | The Gambia | Cord    | 16.0 (12.7-18.7) |                       |
| Awadallah et al.       | (32) 2004      | Jordan  | Cord        | 20.7 (20.1-21.3) |                       |
| Balogh et al.          | (92) 2007      | Hungary | Cord        | 15.95 (13.4-20.7) | 25.5 (8-43)           |
| Bastida et al.         | (130) 2000     | Spain   | Cord        | 41.5 (38.3-44.7) |                       |
| Basu et al.            | (50) 2016      | India   | Cord        | 23.8 (22.2-25.4) |                       |
| Basu et al.            | (102) 2015     | India   | Cord        | 26.5 (25.3-27.5) |                       |
| Bermudez et al.        | (131) 2015     | Spain   | Cord        | 6.26 (5.37-7.15) |                       |
| Briana et al.          | (49) 2013      | Greece  | Cord        | 24.14 (22.4-25.9) |                       |
| Busariri et al.        | (132) 2009     | Libya   | Cord        | 23.69 (23.5-23.9) |                       |
| Cao et al.             | (107) 2016     | USA     | Cord        | 39.73 (35-44.4)  |                       |
| Chong et al.           | (133) 1984     | UK      | Cord        | 41.1 (29.6-52.6)  |                       |
| Delaney et al.         | (114) 2019     | USA     | Cord        | 40.8 (37.3-44.3)  |                       |
| El-Farrash et al.      | (116) 2012     | Egypt   | Cord        | 26.29 (25.6-31)   |                       |
| Ertikin et al.         | (134) 2015     | Turkey  | Cord        | 26.1 (24.1-28.1)  |                       |
| Ervasli et al.         | (117) 2007     | Finland | Cord        | 27.4 (26.9-28.5)  |                       |
| Giucio et al.          | (135) 2014     | Argentina | Cord    | 27.03 (25.7-28.4) |                       |
| Haga et al.            | (118) 1980     | Norway  | Cord        | 27.1 (24.2-30.0)  |                       |
| Kelly et al.           | (41) 1978      | Scotland | Cord       | 27.0 (25.8-28.4)  |                       |
| Kleven et al.          | (121) 2007     | USA     | Cord        | 44.1 (32.2-56)    |                       |
| Korylowski et al.      | (38) 2018      | Poland  | Cord        | 35.1 (33.2-37)    |                       |
| Lao et al.             | (40) 1991      | Hong Kong | Cord   | 35.8 (32-38.9)    |                       |
| Lee et al.             | (34) 2006      | South Korea | Cord | 31.3 (28.4-34.2) |                       |
| Lee et al.             | (43) 2016      | USA     | Cord        | 35.4 (32.9-32)    |                       |
| Meddoud et al.         | (136) 2017     | Algeria | Cord        | 20.1 (19.1-21.3)  |                       |
| Milman et al.          | (39) 1987      | Denmark | Cord        | 16.1 (14.3-18.2)  | 28 (19-39)            |
| Muhopadhyay et al.     | (137) 2011     | India   | Cord        | 29 (25.8-32.2)    |                       |
| Murata et al.          | (138) 1989     | Japan   | Cord        | 28.5 (26.7-30.3)  |                       |
| Oliveria et al.        | (139) 2014     | Brazil  | Cord        | 24.6 (23.5-25.7)  |                       |
| Ozkiran et al.         | (140) 2011     | Turkey  | Venous - 216 hours (96-336) | 14.0 (±1.3) | 16.4 (13.8-19) |

Type of Sample: Venous - 39 hours (18-114), Venous - 120 hours (19-31), Cord.
Patidar et al. (141) 2013 India 50 Venous - 8 hours (1-23) 15.0 (±2.0) 19.4 (17.2-21.6)
Prentice et al. (99) 2019 The Gambia 81 Cord 14.4 (13.8-14.9) 24.7 (22.5-26.9)
Venous - 6 hours (2-11) 17.6 (17.1-18.2) 13.6 (12.0-15.2)
Venous - 29 hours (26-34) 19.2 (18.3-20.0) 11.6 (10.1-13.1)
Venous - 77 hours (74-80) 17.9 (17.0-18.7) 14.5 (13.1-16.0)
Puolakka et al. (53) 1980 Finland 47 Cord 15.1 (±1.2) 28.8 (26.2-31.4)
Rois et al. (123) 1975 USA 26 Cord 16.1 (±1.5) 6.19 (6.18-6.20)
Venous - 6 hours (2-11) 17.6 (17.1-18.2) 13.6 (12.0-15.2)
Venous - 29 hours (26-34) 19.2 (18.3-20.0) 11.6 (10.1-13.1)
Venous - 77 hours (74-80) 17.9 (17.0-18.7) 14.5 (13.1-16.0)
Ruos et al. (110) 2018 USA 49 Cord 15.3 (±0.4) 48.3 (39.3-59.1)
Sormina et al. (94) 2013 Poland 49 Cord 16.1 (±1.7) 22.4 (20.5-24.3)
Sweat et al. (142) 2001 UK 68 Cord 16.1 (±1.7) 26 (24.2-27.8)
Szabó et al. (143) 2009 Hungary 10 Cord 23.2 (16.3-30.1)
Venous - 47 hours 7.2 (6.15-8.25)
Tiker et al. (144) 2006 Turkey 16 Venous - 209 hours (96-288) 13.9 (±22.1-17.1) 19.9 (12.7-28.4)
Tsuzuki et al. (145) 2013 Japan 30 Cord 31.1 (±27.3-34.9)
Venous - 120 hours 19.5 (16.4-22.6)
Yamada et al. (124) 2014 Brazil 21 Cord 16.0 (±1.8) 23.9 (19.4-28.4)
Venous - 720 hours 12.0 (±2.0) 16.7 (14.8-18.5)
Venous - 211 hours (±46) 14.0 (±1.4) 19.9 (17.9-21.9)
Yapakci et al. (146) 2009 Turkey 16 Venous - 211 hours (±46) 14.0 (±1.4) 19.9 (17.9-21.9)

| Weighted Mean (Cord) | - | - | 28.5 (26.0-31.1) | - |
| Weighted Mean (Venous) | - | - | 13.8 (10.8-16.9) | - |

**Adults** (125)

**Infants** (125)

CI, confidence interval; IQR, interquartile range.

- Not determined as not applicable to the calculation of weighted mean hepcidin or standardized hepcidin values.

1 Extracted standard deviations were converted to 95% confidence intervals.

2 Median (IQR or 95% CI) were not included in weighted means.

3 Reference ranges for adults and infants are taken from the National Health and Nutrition Examination Survey, 1999–2000.(125)

4 Hemoglobin concentrations are provided to aid interpretation of neonatal iron status.
Table 7: Serum iron concentration (μmol/L) in preterm newborns over the neonatal period.

| Publication | Reference | Year | Location | Type of Sample | Study Group | Mean (SD or 95% CI) | Median (IQR or 95% CI or Range) |
|-------------|-----------|------|----------|----------------|-------------|---------------------|----------------------------------|
| Celik et al.| (126)     | 2015 | Turkey   | Venous - 648 hours (288-1872) | AGA Group^a| 13.4 (±4.0)         | 15.6 (13.3-17.9)                  |
| Delaney et al.| (114)    | 2019 | USA      | Cord           | AGA Group^a| 15.3 (±2.3)        | 53.1 (49.8-56.4)                 |
| Haga et al.| (118)     | 2019 | Norway   | Cord           | AGA Group^a| 16.8 (13.2-20.4)   |                                  |
| Ichinomiya et al.| (81)    | 2019 | Japan    | Cord           | AGA Group^a| 17.8 (11.2-25.4)   |                                  |
| Lackmann et al.| (127)    | 1988 | Germany  | Venous - <1 hour | AGA Group^a| 23.27 (15.2-32.4)  |                                  |
| Ru et al.| (110)     | 2018 | USA      | Cord           | AGA Group^a| 15.1 (±0.3)         | 73.4 (57.3-93.1)                |
| Ru et al.| (48)      | 2018 | USA      | Cord           | AGA Group^a| 15.3 (±2.1)         | 53.7 (50.1-60.8)                |
| Schiza et al.| (147)    | 2007 | Greece   | Venous - 336 hours | AGA Group^a| 30.36 (24.9-39.2)  |                                  |
| Sweet et al.| (142)    | 2005 | UK       | Cord           | AGA Group^a| 15.8 (±2.1)         | 20.8 (18.4-23.2)                |
| Tikier et al.| (144)    | 2006 | Turkey   | Venous - 67 hours (24-144) | AGA Group^a| 14.9 (10.5-18.5)   | 15.81 (4.83-33.48)              |
| Tsuchi et al.| (145)    | 2013 | Japan    | Cord           | AGA Group^a| 24.9 (16.3)         | 17.4 (13.3-21.5)                |
| Yamada et al.| (124)    | 2014 | Brazil   | Cord           | AGA Group^a| 15.7 (13.3-21.5)   | 19.26 (6.8-39.2)                |
| Yapalci et al.| (146)    | 2009 | Turkey   | Venous - 336 hours (36-720) | AGA Group^a| 12.7 (±2.2)         | 17.63 (11.2-20.3)               |

**Weighted Mean (Cord)**

- **Mean (95% CI or Range)**
  - Adults: 15.2 (8.1-24.5)
  - Infants: 12.5 (5.5-20.6)

**CI, confidence interval; IQR, interquartile range; AGA, appropriate for gestational age; SGA, small for gestational age.**

- Not determined as not applicable to the calculation of weighted mean hepcidin or standardized hepcidin values.

^Extracted standard deviations were converted to 95% confidence intervals.
Median (IQR or 95% CI) were not included in weighted means.

Reference ranges for adults and infants are taken from the National Health and Nutrition Examination Survey, 1999–2000. (125)

Hemoglobin concentrations are provided to aid interpretation of neonatal iron status.

AGA group of Haga et al. (1980) can be identified in Supplementary Figure 3B.

SGA group of Haga et al. (1980) can be identified in Supplementary Figure 3B.

Ru et al. (2018) can be identified in Supplementary Figure 3B. (110)

Ru et al. (2018) can be identified in Supplementary Figure 3B. (48)

30–36 wks group of Sweet et al. (2001) can be identified in Supplementary Figure 3B.

24–29 wks group of Sweet et al. (2001) can be identified in Supplementary Figure 3B.
Figure 1: Placental iron transfer between mother and fetus. Fe^{2+} = ferrous iron, Fe^{3+} = ferric iron, Tf = transferrin, Apo-Tf = unsaturated transferrin, Fetal Tf = fetal-derived transferrin, NTBI = non-transferrin bound iron. Syncytiotrophoblasts in the placental villi take up transferrin-bound iron from the maternal circulation by endocytosis via transferrin receptor 1 (TFR1). Iron is released from TFR1 in acidified endosomes and transferred into the syncytiotrophoblast cytoplasm. Ferroportin transports iron out of placental syncytiotrophoblasts, and then ceruloplasmin, hephaestin, and zyklopen oxidize Fe^{2+} to Fe^{3+} helping it pass through the endothelium to reach the fetal circulation. It is still unclear as to whether newly transported iron enters the fetal circulation as NTBI or bound to fetal transferrin. Fetal-derived hepcidin is believed to regulate ferroportin expression on the fetal basal-side of placental syncytiotrophoblasts. (12,26) Maternal-derived hepcidin is believed to play a role in regulating TFR1 expression on the maternal-side of the placental syncytiotrophoblasts (148).
Figure 2: Flow diagram of the literature search and selection criteria. Retrieving publications on hepcidin, TSAT or serum iron in neonates over the first month of life.
Figure 3: Standardized hepcidin (ng/mL) over the neonatal period: (A) full term neonates, $\alpha$ shows the weighted mean (95%CI) for all studies seen in Supplementary Figure 1A. $\beta$, $\chi$ and $\varepsilon$ shows Prentice et al.(99) $\delta$ shows Kulik-Rechberger et al.(25). (B) preterm neonates, $\alpha$ shows the weighted mean (95%CI) for all studies seen in Supplementary Figure 1B. $\beta$ shows Uijterschout et al.(112)
Figure 4: Transferrin saturation (%) over the neonatal period: (A) full term neonates, α shows the weighted mean (95%CI) for all studies seen in Supplementary Figure 2A. β shows Prentice et al.(99) χ shows Al-Tawil et al.(113) δ shows Prentice et al.(99) ε shows Balogh et al.(92) Φ shows Anderson et al.(115) γ shows Prentice et al.(99) η shows Milman et al.(39) τ shows Kitajima et al.(120) φ shows Yamada et al.(124). (B) preterm neonates, α...
shows the weighted mean (95%CI) for all studies seen in Supplementary Figure 2B. β shows Lackmann et al. (127) χ shows Celik et al. (126) δ shows Yamada et al. (124) ε shows Kitajima et al. (120) All values are mean (95%CI), unless marked with ◊ median (range) and • median (95%CI). Lackmann et al, 1998 (β) data from the three study groups (<32 wks, 33-34 wks and 35-36 wks) was averaged as all groups are classed as PTB neonates and are bled at the same time of life. (127)
Figure 5: Serum iron (μmol/L) over the neonatal period: (A) full term neonates, α shows the weighted mean (95%CI) for all studies seen in Supplementary Figure 3A. β shows Prentice et al.(99) χ shows Patidar et al.(141) δ shows Prentice et al.(99) ε shows Balogh et al.(92) ϕ shows Szabo et al.(143) γ shows Anderson et al.(115) η shows Prentice et al.(99) τ shows Milman et al.(39) ψ shows Tsuzuki et al.(145) κ shows Tiker et al.(144) λ shows
Yapakci et al. (146) μ shows Ozkiraz et al. (140) ν shows Yamada et al. (124). (B) preterm neonates, α shows the weighted mean (95%CI) for all studies seen in Supplementary Figure 3B. β shows Lackmann et al. (127) χ shows Tiker et al. (144) δ shows Tiker et al. (144) ε shows Tsuzuki et al. (145) φ shows Schiza et al. (147) γ shows Yapakci et al. (146) η shows Celik et al. (126) ι shows Yamada et al. (124) All values are mean (95%CI), unless marked with * mean (range), ° median (range) and • median (95%CI). Lackmann et al, 1998 (β) data from the three study groups (<32 wks, 33-34 wks and 35-36 wks) was averaged as all groups are classed as PTB neonates and are bled at the same time of life. (127)