

# Erythrocyte transfusions increased the risk of elevated serum ferritin in very low birthweight infants and were associated with altered longitudinal growth

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## Abstract

**Aim:** There has been a lack of population-based longitudinal data on serum ferritin in very low birthweight (VLBW) infants during hospitalisation. Our aim was to fill this gap in the knowledge and investigate risk factors for elevated serum ferritin and associations between erythrocyte transfusions and longitudinal growth.

**Methods:** We retrospectively reviewed longitudinal data on 126 VLBW infants treated at Umeå University Hospital, Sweden, between 2010 and 2013.

**Results:** The infants' mean gestational age and birthweight were 26.9 weeks and 899 g. Most (91%) received erythrocyte transfusions, and the majority had multiple erythrocyte transfusions. There was a significant correlation between serum ferritin and the volume of transfusions. Almost two-thirds had at least one serum ferritin measurement of more than 350 µg/L, indicating iron overload. In those with complete anthropometric data (n = 78), there was no significant effect of serum ferritin concentrations in relation to longitudinal growth, but there was a positive association between the erythrocyte transfusion dose and longitudinal growth in VLBW infants born before 25 weeks.

**Conclusion:** This is the first population-based study to investigate longitudinal data on serum ferritin in VLBW infants during hospitalisation. The unexpected positive finding in the subgroup born at less than 25 weeks needs further research with a larger cohort.

## KEYWORDS

blood transfusion, growth, premature infants, serum ferritin, very low birthweight

## 1 | INTRODUCTION

Very low birthweight (VLBW) infants, who weigh less than 1500 g, are born with lower iron stores, and they deplete their iron stores

earlier than the full-term infants due to rapid growth.<sup>1</sup> In addition, iron losses occur through repeated blood sampling during neonatal intensive care unit (NICU) admission. Thus, VLBW infants have a high risk of iron deficiency, which has been associated with impaired

**Abbreviations:** CI, confidence intervals; CRP, C-reactive protein; NICU, neonatal intensive care unit; VLBW, very low birthweight.

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neurological development.<sup>2</sup> Iron is essential for normal brain development, and studies have shown that iron deficiency anaemia was associated with impaired cognitive, behavioural and motor achievements.<sup>1-4</sup> Iron supplements of 2-3 mg/kg/d are generally recommended for VLBW infants.<sup>1</sup>

However, unlike most other nutrients, there is no mechanism for iron to be excreted from the human body. Because iron is a highly reactive pro-oxidant, as well as an important substrate for pathogens, excessive iron supplements may have adverse effects on infants.<sup>5</sup> Administering iron to infants without an iron deficiency has been associated with an increased risk of infections, as well as impaired growth.<sup>1,6-8</sup>

While they are being treated in a NICU, VLBW infants undergo frequent blood sampling and frequently receive erythrocyte transfusions, even though transfusion policies vary considerably between countries and institutions.<sup>9,10</sup> This poses a challenge in clinical care, because excessive blood sampling may lead to iron deficiency, while unwarranted erythrocyte transfusions may lead to iron overload. Sources of iron intakes during NICU care are primarily erythrocyte transfusions, human milk fortifiers, preterm formulas and iron supplements.<sup>8</sup>

Serum ferritin is commonly used to monitor iron stores in children and has recently been suggested to be useful in VLBW infants.<sup>11</sup> Serum ferritin concentrations can be used to diagnose both iron deficiency and iron overload. Since serum ferritin is a positive acute-phase reactant, an elevated level must be interpreted with caution in the presence of possible inflammation.<sup>12</sup> To exclude the presence of inflammation, clinicians are often recommended to carry out a simultaneous analysis of C-reactive protein (CRP) or other biomarkers of inflammation. Given that foetal iron stores accumulate most rapidly during the third trimester, preterm infants are born with lower iron stores per kilogram of body weight.<sup>13</sup> The reference range for serum ferritin in preterm newborn infants is 35-300 µg/L.<sup>1</sup> Even though it is important to identify both iron deficiency and iron overload in this high-risk patient group, there has been a lack of population-based studies of serum ferritin in VLBW infants.

The objectives of this study of the first 28 days of life were to investigate the serum ferritin concentrations of VLBW infants and their relation to the accumulated erythrocyte transfusion dose. We also examined other factors that influenced the risk of developing iron overload and analysed the correlation between iron and longitudinal growth. To our knowledge, this was the first population-based study to obtain longitudinal data on serum ferritin in this particular patient group.

## 2 | PATIENTS AND METHODS

This study was a single-centre retrospective observational study that included VLBW infants born at Umeå University Hospital, Sweden, or transferred to the Hospital during the first 24 hours of life. The inclusion criteria were being treated by the Hospital's

### Key notes

- This study addressed the lack of population-based longitudinal data on serum ferritin in very low birthweight infants.
- Overall, there was no significant effect of serum ferritin concentrations in relation to longitudinal growth during the first 28 postnatal days in 78 infants treated at Umeå University Hospital.
- However, there was an unexpected positive association between the erythrocyte transfusion dose and longitudinal growth in those born before 25 weeks.

NICU between 1 February 2010 and 30 September 2013 and having a birthweight of less than 1500 g. Infants who were treated at the Hospital for less than 7 days, or died during this period, were excluded from the study. During the study period, VLBW infants treated at the Hospital underwent routine weekly screening for serum ferritin. In total, 126 infants fulfilled the inclusion criteria and had at least one serum ferritin measurement during their first 28 postnatal days.

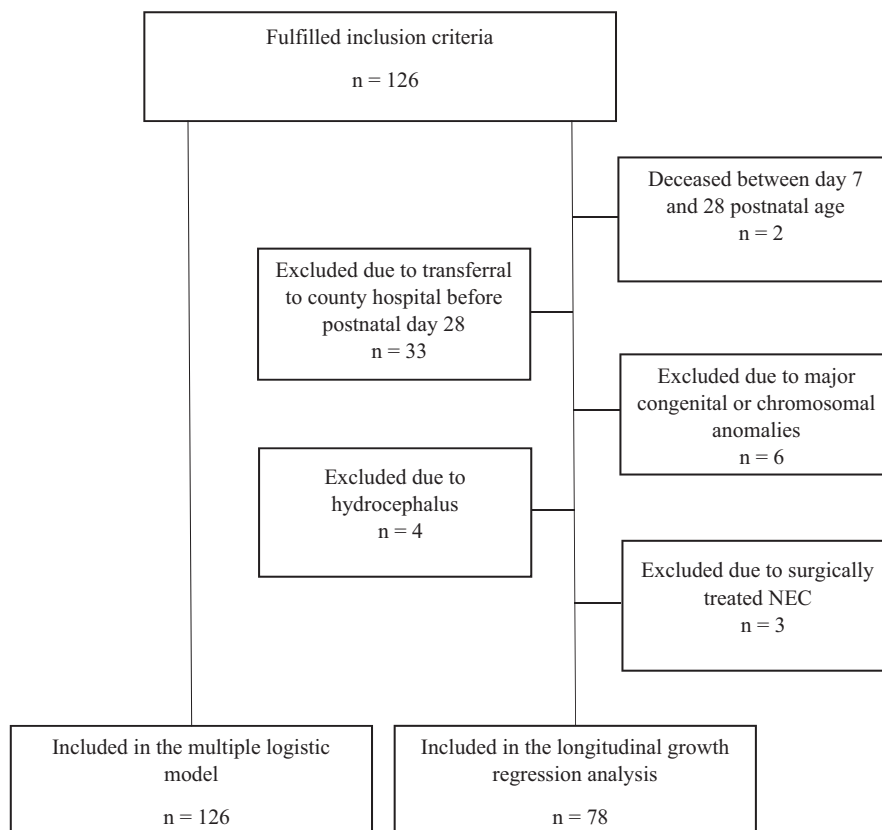
The erythrocyte transfusion policy in place at the Hospital during the study period is presented in Table S1.

We were unable to include all 126 infants in the analyses of the associations between serum ferritin, the accumulated erythrocyte transfusion dose during the first 28 postnatal days and growth. This was because 33 infants were transferred to county hospitals before postnatal day 28 and two infants died between seven and 28 days of postnatal age. Furthermore, four infants with hydrocephalus were excluded due to the expected influence on anthropometry and eight infants surgically treated for necrotising enterocolitis were excluded due to the expected impact on enteral iron absorption. We also excluded six infants with major congenital or chromosomal anomalies known to affect growth. Of the eight infants with necrotising enterocolitis, only three were excluded solely on that basis: one died and one was discharged before postnatal day 28. The other three were among the six with major congenital or chromosomal anomalies. This meant that 78 infants were included in the regression analysis. The numbers of included and excluded infants are shown in Figure 1.

### 2.1 | Data collection

All available laboratory results on biomarkers of iron status, serum ferritin and haemoglobin were collected. Data on biomarkers of iron status, inflammatory status, anthropometry and nutrition were collected from birth until discharge or transfer to other hospitals. The threshold for an elevated serum ferritin concentration was set at 350 µg/L, based on published results that compared liver iron content in relation to serum ferritin in VLBW infants.<sup>14</sup> Given that

**FIGURE 1** Inclusion flowchart for analyses of correlation between length gain and erythrocyte transfusion dose and serum ferritin. <sup>a</sup>NEC, necrotising enterocolitis



ferritin is a positive acute-phase protein, we used CRP, when available, to determine whether inflammation could have affected the serum ferritin concentration. CRP analyses were carried out based on clinical indications and CRP values within 2 days of a serum ferritin analysis were considered. The method of analysing CRP changed at the Hospital during the study period. During 2010 and some of 2011, the Hospital laboratory analysed CRP with a lower detection limit of 5 µg/L. In May 2011, the method changed to high sensitivity CRP, with a lower detection limit of <0.6 µg/L. Perinatal and morbidity data were collected from the Swedish Neonatal Quality Register and included gestational age at birth, sex, duration of mechanical ventilation treatment and necrotising enterocolitis.

All available postnatal anthropometric measurements, including weight, length and head circumference, were obtained from hospital charts. We used a Swedish longitudinal sex-specific growth chart<sup>15</sup> to calculate standard deviation scores of anthropometric values. If infants were not weighed daily or measured at even 7-day intervals, linear interpolation was used to generate daily weights and weekly lengths and head circumferences.

Lastly, daily enteral and parenteral nutritional intakes were retrospectively collected from Hospital records and nutrient intakes were calculated using software. The nutrition data collection included all transfusions of blood products during the first 28 postnatal days. Transfused blood products, such as erythrocytes and plasma, were included in calculations of nutrient intakes, and the nutrient contents of blood products were based on published values.<sup>16,17</sup> Nutrient intakes included all parenteral and enteral nutrition and were calculated using data from the manufacturers, as described previously.<sup>18</sup>

## 2.2 | Statistical analyses

In addition to the cumulated erythrocyte transfusion dose, other predictor variables that were candidates for an elevated serum ferritin concentration were included in the models: elevated CRP, postnatal age and standardised birthweight scores. Elevated CRP and highly sensitivity CRP were defined as a value above the respective reference limit. The odds of elevated serum ferritin were first estimated using univariate analysis in relation to each of the predictor variables using logistic regression estimated by generalised estimating equations. Thereafter, a multiple logistic model was built by using a backward stepwise procedure, where candidate predictor variables were excluded at each step using .25 as the limit for the *P* value.

To estimate the association between serum ferritin and growth, the highest serum ferritin concentration during days 21 to 28 was used and was assessed in relation to the change in standardised length scores between the day of birth and postnatal day 28. First, the association was estimated using univariate linear regression. Then, the multiple linear regression model was used to adjust for possible confounding by gestational age at birth and the total days that infants needed mechanical ventilation during the first 28 postnatal days.

The statistical analyses were performed using version 25.0 of the SPSS Statistical software (IBM Corp, New York, USA). A *P* value of less than .05 was considered statistically significant.

The Regional Ethical Review Board in Umeå, Sweden, approved the study (Dnr 2011-417-31M, 2012-458-31M and 2017-35-32M).

**TABLE 1** Characteristics of the 126 infants included in the study

	Unit	Mean	25th–75th percentiles	Min-max
Gestational age, n = 126	Weeks	26.9	25.0–29.1	22.4–33.3
Birthweight, n = 126	Grams	899	669–1149	396–1490
	SDS	–1.4	–2.2 to –0.5	–5.9 to 0.7
Birth length, n = 123	Centimetres	34.3	31.0–38.0	26.0–43.0
	SDS	–1.7	–2.7 to –0.5	–6.4 to 2.3
MV, n = 126	Days	10	0–18.5	0–29
		n	%	
Sex, female		54	42.9	
Sepsis		29	23	
CRP above threshold day 0–28, n = 125		57	45.2	
NEC surgery <28 d		8	6.3	

Abbreviations: MV, mechanical ventilation between day of birth and postnatal day 28; NEC, necrotising enterocolitis; SDS, standard deviation scores.

### 3 | RESULTS

Characteristics of the study population are presented in Table 1. During hospitalisation, 115/126 (91%) of the studied infants received at least one erythrocyte transfusion, with a mean total dose of 115 mL/kg. In the first postnatal week, the mean transfusion dose was 27.5 mL/kg, which was also the highest average weekly dose during the study period. The mean total erythrocyte transfusion dose was equivalent to 77.8 mg iron. During the study period, the median dose given at the Hospital was 10 mL/kg. Weekly transfusion data are presented in Table 2. Of the 831 samples collected from the 126 infants, 293 samples (35%) had elevated serum ferritin concentrations (>350 µg/L). Most of the

**TABLE 2** Data on weekly erythrocyte transfusions

Postnatal age, weeks	n	Weekly mean erythrocyte transfusion dose, mL/kg, (SD)	Iron, mg, (SD)
1	126	27.5 (±28.5)	18.6 (±19.3)
2	126	18.8 (±18.3)	12.7 (±12.4)
3	108	18.2 (±15.6)	12.3 (±10.6)
4	100	14.4 (±12.3)	9.7 (±8.3)
5	91	11.0 (±11.2)	7.4 (±7.6)
6	85	9.0 (±8.8)	6.1 (±6.0)
7	78	7.7 (±7.7)	5.2 (±5.2)
8	60	7.4 (±9.7)	5.0 (±6.6)
9	54	6.6 (±8.9)	4.4 (±6.0)

Abbreviation: SD; standard deviation.

infants (60%) had at least one serum ferritin concentration above 350 µg/L, indicating iron overload. The concentration of serum ferritin plotted against the accumulated erythrocyte transfusion dose is shown in Figure 2. The odds of presenting an elevated serum ferritin increased by 14% with a 95% confidence interval (95% CI) of 7.2%–22% per 10 mL/kg of accumulated erythrocyte transfusion and by 77% (95% CI 23%–156%) for elevated CRP. However, it decreased by 38% (95% CI 24%–49%) per week of postnatal age. There was no association between elevated serum ferritin and birthweight in the standard deviation score.

To evaluate the effect of iron on longitudinal growth, two linear regression models were used, with the change in standard deviation score between birth and postnatal day 28 as the dependent variable. Due to missing anthropometric data, discharges to county hospitals and other reasons already mentioned, 78 (62%) of the 126 infants were included in these analyses. To account for possible confounding by disease severity, the analyses were stratified by gestational age at birth: 22–24 weeks, 25–27 weeks and 28–32 weeks (Table 3). Both of the linear regression models were also adjusted for disease severity using a variable that was stratified by quartiles for the accumulated number of days during the first 28 postnatal days that the infant needed assisted mechanical ventilation.

A statistically significant correlation between accumulated erythrocyte transfusion dose and longitudinal growth was found among the infants born before 25 weeks of gestation (0.10, 95% CI 0.004–0.016). However, a negative correlation was found among infants born at 28 weeks of gestation or more (–0.06, 95% CI –0.011 to 0.001).

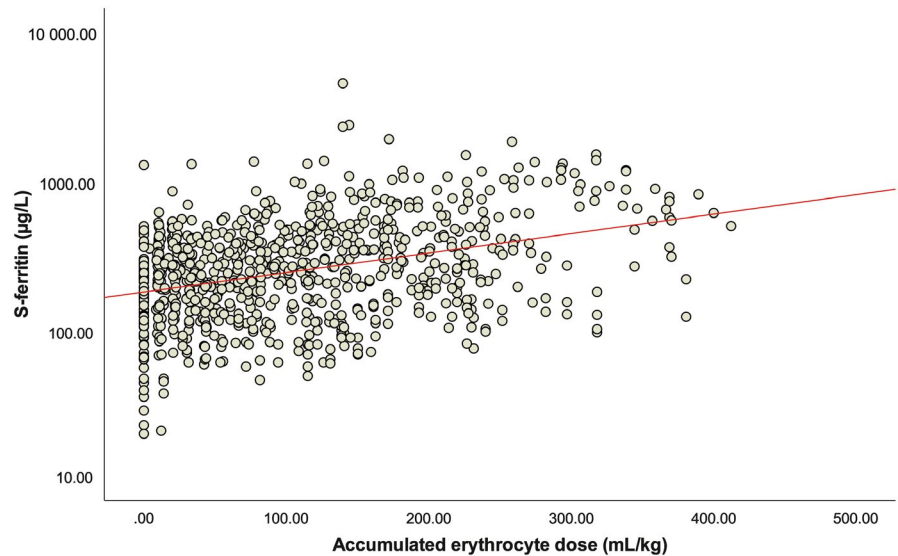
When we assessed the effect of serum ferritin on longitudinal growth, no significant correlation was shown during the first 28 postnatal days.

### 4 | DISCUSSION

This study was based on VLBW infants who were treated in a Swedish NICU with a relatively liberal erythrocyte transfusion policy. We found that there was a high incidence of elevated serum ferritin concentrations and that 60% of the infants had levels above 350 µg/L, indicating iron overload.<sup>19</sup> Our results identified that the independent determinants of elevated serum ferritin concentrations were accumulated erythrocyte transfusion dose, concurrent elevated CRP and lower postnatal age. Regression analysis showed no significant association between serum ferritin and longitudinal growth when gestational age and disease severity were taken into account.

We had previously found a negative correlation between iron intake, mainly from erythrocyte transfusions, and longitudinal growth in a cohort of extremely preterm infants,<sup>8,20</sup> but we could not confirm those results in the current study. In fact, we found a positive correlation in a subgroup of infants born before 25 weeks gestational age. The possible reasons for these conflicting results may include a wider range of gestational age in our latest study and

**FIGURE 2** Accumulated erythrocyte transfusion dose vs serum ferritin. Log scale on y-axis



**TABLE 3** Linear regression slope estimates for the association between longitudinal growth and erythrocyte transfusion dose and serum ferritin, stratified by gestational age in 78 infants

Gestational age	Association with longitudinal growth postnatal days 0-28 (SDS)		
	n	Unadjusted (95% CI)	Adjusted (95% CI)
22-24 wk	21 <sup>b</sup>	0.08 (0.003 to 0.013)	0.10 (0.004 to 0.016)
25-27 wk	30	0.05 (-0.003 to 0.012)	0.05 (-0.003 to 0.012)
28-32 wk	25	-0.05 (-0.010 to 0.001)	-0.06 (-0.011 to 0.001)
Gestational age	Serum ferritin postnatal day 21-27 <sup>c</sup> (per 50 µg/L)		
	n	Unadjusted (95% CI)	Adjusted (95% CI)
22-24 wk	16 <sup>d</sup>	0.00 (-0.001 to 0.002)	0.00 (-0.001 to 0.002)
25-27 wk	24 <sup>e</sup>	0.00 (-0.002 to 0.002)	0.00 (-0.002 to 0.002)
28-32 wk	19 <sup>f</sup>	0.20 (-0.005 to 0.013)	0.20 (-0.005 to 0.014)

Note: Estimates are presented with, and without, adjustment for disease severity.

Abbreviation: SDS; standard deviation score.

<sup>a</sup>Accumulated transfusion dose postnatal days 0-28.

<sup>b</sup>Two missing anthropometric data.

<sup>c</sup>Highest serum ferritin during the fourth postnatal week.

<sup>d</sup>Five missing serum ferritin days 21-27.

<sup>e</sup>Six missing serum ferritin days 21-27.

<sup>f</sup>Six missing serum ferritin days 21-27.

the number of erythrocyte transfusions. The extremely preterm infant study<sup>8,20,21</sup> only included infants born below 27 weeks of gestation, but about half of the infants in the current study were at least 27 weeks at birth. The earlier and current studies also differed in other ways: the median birthweight (standard deviation score) was 755 (-0.6) g vs 829 g (-1.0)<sup>8</sup> and the infants received a median (25th-75th percentile) of 75 (44-120) mL/kg of erythrocyte concentrate<sup>21</sup> vs 75 (22-122) mL/kg during the first 28 postnatal

days. However, when we just considered the infants born before 27 gestational weeks in the current study, the median (25th-75th percentile) dose of 105 (64-133) mL/kg was strikingly higher than the earlier cohort. Lastly, the findings of the previous study might have been confounded by morbidity, even though the data were adjusted for gestational age, the birthweight standard deviation score and the duration of mechanical ventilation. Unfortunately, serum ferritin was not routinely analysed in the extremely preterm study, which is why a comparison was not possible. We have not identified any published studies that have assessed longitudinal growth in relation to serum ferritin concentrations in VLBW infants.

Ng et al<sup>14</sup> showed that serum ferritin was associated with iron stores. In our study population, erythrocyte transfusions and iron overload were common. Avoiding iron overload in iron-replete VLBW infants has been reported to be beneficial for avoiding increased oxidative stress, increased risk of bacterial infections and a negative influence on growth.<sup>5,22</sup> The finding that longitudinal growth during the first 28 postnatal days was negatively affected by higher accumulated erythrocyte transfusion doses in VLBW infants born at 28 weeks of gestational age or more was not significant. However, it does support the benefit of avoiding iron overload.

The unexpected finding of a positive correlation between erythrocyte transfusion doses and longitudinal growth during the first 28 postnatal days for VLBW infants born before 25 weeks gestational age is difficult to explain. We can speculate that it was mediated by an increase in oxygen transport capacity that promoted growth or perhaps it was a chance finding due to a small sample size of 21 infants. The negative trend regarding the correlation between erythrocyte transfusion dose and longitudinal growth for the subgroup born between 28 and 33 weeks of gestation was in line with some previous studies that described a negative effect on longitudinal growth.<sup>20,23</sup>

A 2018 review by Howarth et al<sup>24</sup> concluded that, in addition to the complications of oxidative diseases, erythrocyte transfusions can overload the livers of VLBW infants with iron. However, the authors



pointed out that the clinical implications of this were unknown. There are two ongoing randomised controlled trials that are investigating the effect of different transfusion thresholds for preterm infants, the Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants study in Germany and the Transfusion of Premature study in the USA.<sup>24,25</sup> The German study includes infants with a birthweight of 400-999 g, whereas the American study includes infants with a birthweight of  $\leq 1000$  g and a gestational age of less than 29 weeks.<sup>26</sup> The primary outcomes are focused on death or neurodevelopmental impairment. It is unclear whether serum ferritin is included in the data collection for these studies.

A strength of our study was the number of serum ferritin samples that were analysed for each infant and the fact that we were able to adjust for the presence of inflammation by using CRP and high sensitivity CRP.

The limitations of this study included its retrospective design, a relatively low sample size and a high heterogeneity with regard to gestational age at birth and neonatal morbidity.

## 5 | CONCLUSION

To our knowledge, this was the first population-based study to investigate longitudinal data on serum ferritin in VLBW infants while they were treated in the NICU. Erythrocyte transfusions were administered to 91% of the infants, and transfused volume was strongly associated with serum ferritin. Most of the infants received multiple erythrocyte transfusions during the first 28 days of life and almost two-thirds had at least one serum ferritin measurement of more than 350  $\mu\text{g/L}$ , indicating iron overload. Regression analysis of 78 infants with complete anthropometric data showed no significant association between serum ferritin and longitudinal growth during the first 28 postnatal days. However, we did find a positive association between erythrocyte transfusion doses and longitudinal growth among the subgroup of VLBW infants born before 25 weeks of gestation and this unexpected finding requires further research in a larger cohort of premature infants.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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