Serum Ferritin Values do not Correlate with Reticulocyte Hemoglobin Content (RET-He) in Extremely Low Gestational Age Neonates

NICHD
NEONATAL RESEARCH NETWORK

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Introduction

Iron Insufficiency in Neonates

- Iron insufficiency in neonates period can cause cognitive problems even after the iron deficiency is treated.
- Iron transfer from mother predominately occurs late in pregnancy.
- Premature neonates are at particularly high risk.

Measuring Iron Stores in Preterm Neonates

- Serum ferritin is commonly used but not well-validated as a measurement of iron sufficiency in extremely low gestational age neonates (ELGANs, <29 weeks). It is also an acute phase reactant
- Ferritin, ZnPP/H ratio, serum iron, iron binding capacity, etc., require large phlebotomy.

Reticulocyte Hemoglobin Content (RET-He)

- RET- He is a new metric of the iron available for hemoglobin production during the previous several days.
- RET- He has been studied and validated in pediatric and adult populations but not well-studied in neonates.
- It can be obtained with any CBC (as little as 40 µL).
- **We hypothesized that RET-He would correlate well with Serum Ferritin in ELGANs.**

Methods

NICHD NRN Darbe Study (NCT03169881)

- Randomized, masked, placebo controlled clinical study
- Neonates receive weekly darbepoetin or placebo (sham).
- The parent study (Darbe) enrolled **650 subjects, $23^{0/7}$ to $28^{6/7}$** weeks gestation.

Secondary Study to NRN Darbe Study

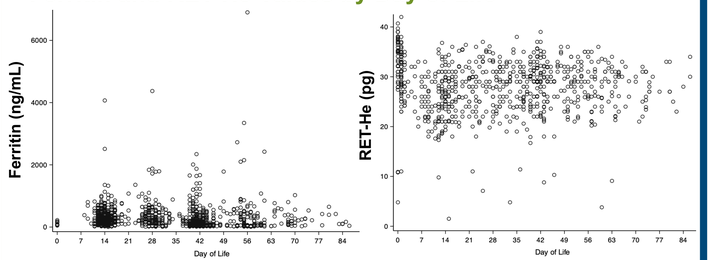
- Only the placebo group was included in this study.
- Ferritin was collected as part of study protocol..
- RET-He was collected at 9 sites that used Sysmex hematology analyzers in clinical laboratories.
- We analyzed paired RET-He and Ferritin values (collected within 24 hours of one another)

Results

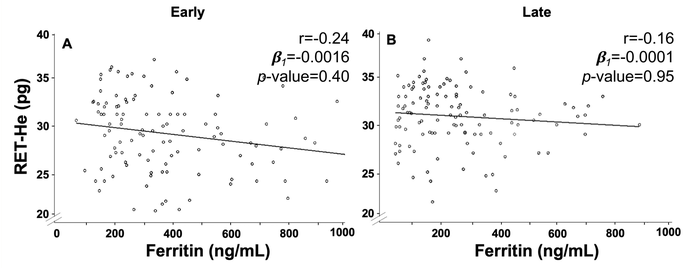
Baseline Cohort Characteristics

Characteristics	Mean or Count (n, SD or %)
Gestational age (weeks)	26.7 (102, 1.5)
Female	61 (59.8)
RET-He - baseline (pg)	32.7 (87, 4.1)
RET-He - early (pg)	28.9 (96, 3.8)
RET-He - late (pg)	31.0 (88, 3.2)
Ferritin - early (ng/mL)	372.3 (96, 215.3)
Ferritin - late (ng/mL)	219.8 (86, 151.6)
Total Oral Iron (mg/kg)	11.0 (102, 10.5)
Total Parenteral Iron (mg/kg)	3.6 (102, 2.0)
Total Iron (mg/kg)	14.6 (102, 10.6)
Hemoglobin - baseline (g/dL)	14.6 (102, 2.5)
Hemoglobin - early (g/dL)	11.8 (93, 1.9)
Hemoglobin - late (g/dL)	10.2 (96, 2.1)

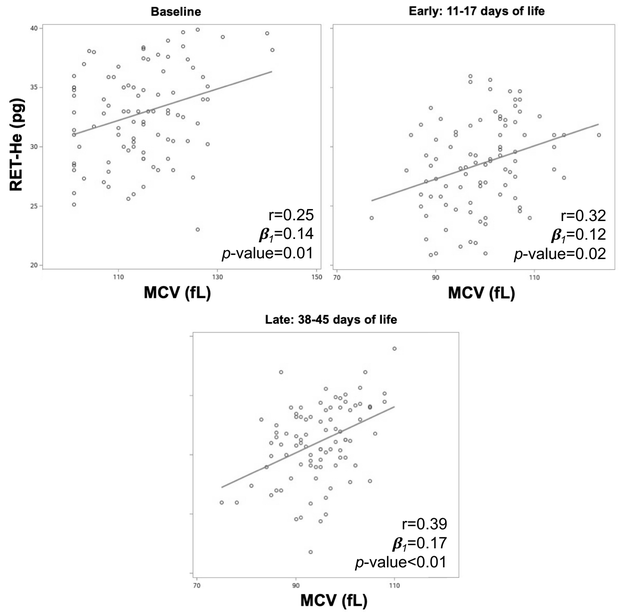
Ferritin and RET-He Values by Day of Life



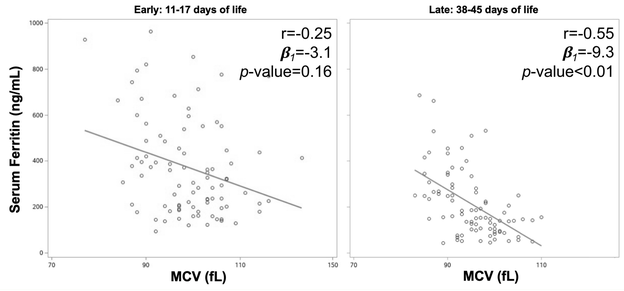
Paired Ferritin and RET-He Values do not Correlate



RET-He Correlates with MCV



Ferritin *Does Not* Correlate with MCV



Discussion

Unexpected Results

- In the present study we evaluated the correlation between serum ferritin and RET-He in extremely preterm neonates.
- We hypothesized that although the two tests measure different biological variables, they should be correlated.
- However, that was not the case in this population of ELGANs infants.

Ferritin may be Affected by Other Factors

- Very few early and late serum ferritin concentrations were below 100 ng/mL.
- Adult studies have shown that high concentrations of ferritin can be found in cases of liver disease, alcoholism, inflammatory syndrome and metabolic syndrome, even with iron deficiency.
- A number of studies in neonates have shown similar findings. (Koren 2022, Haga 1980, Griffin 2002, Kumar 2021, Cooke 2021)

Conclusions

- We showed that the reliability of ferritin as a marker of iron sufficiency in ELGANs was poor as it did not correlate with MCV.
- In contrast, we demonstrated that RET-He correlated with MCV, a marker of microcytic iron-limited erythropoiesis.
- We therefore suggest that RET-He is a more accurate measure of iron insufficiency in ELGANs.

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