Iron Supplementation in the NICU

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Disclosures

- No conflicts of interest to disclose
- Off label use of iron preparations will be discussed during this lecture
- Off label use of red cell growth factors erythropoietin and darbepoetin may be discussed during this lecture
- No other off label medications or devices will be discussed

Iron Supplementation in the NICU: Objectives

After participating in this presentation, you should have increased knowledge to:

- Summarize mechanisms of iron accretion in term and preterm neonates
- Review iron dosing in clinical studies of ESA-treated and non-treated neonates
- Discuss measures of iron sufficiency and guidelines for iron supplementation in neonates

Fetal iron accretion

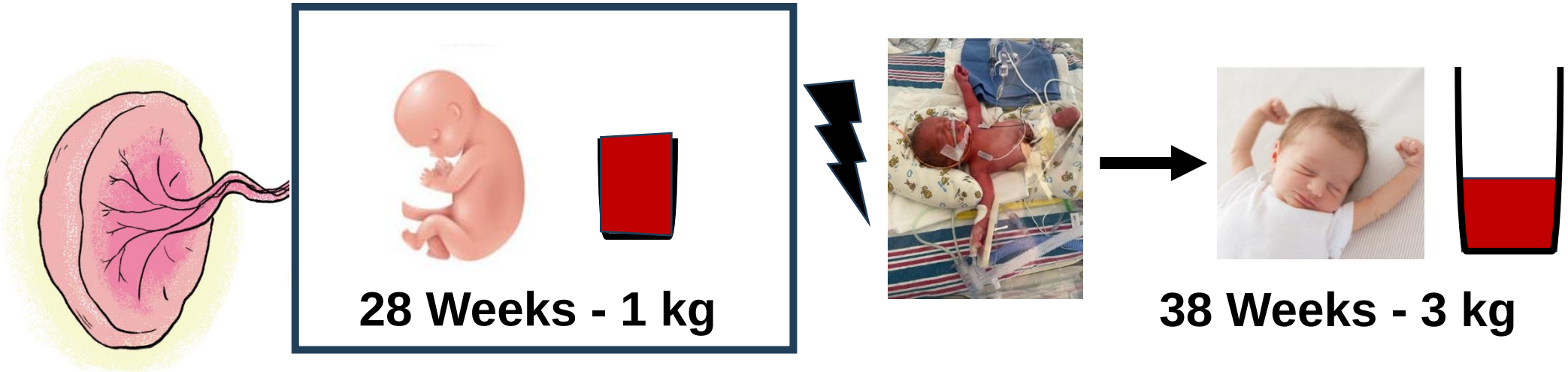
- Iron requirements increased during pregnancy
- Fetal iron status correlates poorly with maternal iron status (fetal iron stores are spared)
- Infants born to mothers with frank iron deficiency anemia have low umbilical cord blood ferritin and serum iron concentrations
- Normal 3rd trimester fetus has 70-75 mg/kg elemental iron
- Iron is stored in erythrocyte hemoglobin (~70%); liver; spleen; marrow; kidney (as ferritin and hemosiderin); hemoproteins
- Iron accretion in VLBW infants: 1 mg/kg/day

McArdle and Georgieff, Polin and Fox (5th ed)
Friel JK et al, JPEN 1995;19:114-8

Fetal/Neonatal Iron Sufficiency

28 Weeks - 1 kg

38 Weeks - 3 kg

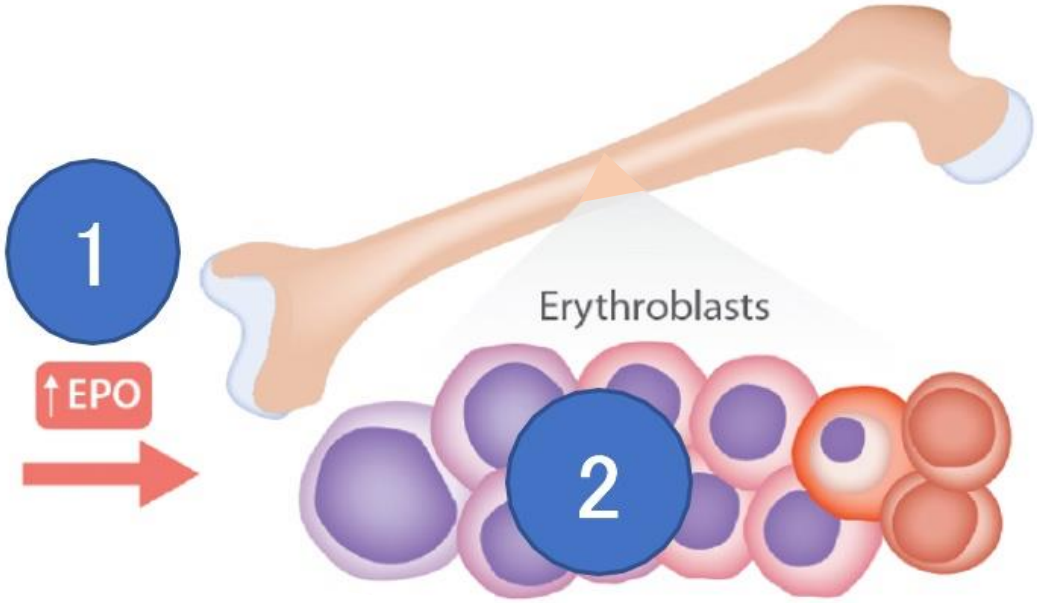


28 Weeks - 1 kg

38 Weeks - 3 kg

T Bahr

Iron homeostasis: The Epo Axis



ERFE: erythroferrone
EPO: erythropoietin
Fpn: Ferroportin
Hep: Hepcidin

Bahr TM et al, Blood Cells Mol Dis. 2021;88:102536

Iron Supplementation in Neonates

- Parenteral and enteral iron supplementation uncommon in preterm infants, despite nutritional recommendations
- Small studies of infants in New Zealand and Polynesia performed in the 1970s evaluated associations between parenteral iron (2 x 50 mg IM) and sepsis
- Later trials found no association between specific infections (such as Malaria) and iron supplementation
- Infant tolerance of enteral iron studied in the 1970s

Farmer K, Beecroft DM. Arch Dis Child 1976;51:486
Barry D, Reeve AW. New Zealand Med J 1973;78:376
Berman D. Arch Dis Child 1972;47:261-71
Oski F et al, Pediatrics 1980; 66:168-70

Multivitamin dosing

	1 mL	Recs (per kg/day)	500-2000 grams	0.5 mL/kg
Vitamin A (IU)	750	400-1000	750 to 188	375 IU/kg
Vitamin D (IU)	400	400-1000	400 to 100	200 IU/kg
Vitamin E (IU)	5	2.2-11	5 to 1.3	2.5 IU/kg
Vitamin C (mg)	35	20-55	35 to 9	17.5 mg/kg
Thiamin (mg)	0.5	0.14-0.3	0.5 to 0.13	0.25 mg/kg
Riboflavin (mg)	0.6	0.2-0.4	0.6 to 0.15	0.3 mg/kg
Niacin (mg)	8	1-5.5	8 to 2	4 mg/kg
Vitamin B_6 (mg)	0.4	0.1-0.8	0.4 to 0.1	0.2 mg/kg
Iron (mg)	10	2-3	10 to 2.5	5 mg/kg

Koletzko, Poindexter, Uauy, Eds: Nutritional Care of Preterm Infants, 2014

Question 1

True or false: Elevated hepcidin levels trigger degradation of ferroportin, the iron exporter, thereby inhibiting absorption of enteral iron

A. True
B. False

Iron supplementation and ESAs

- First randomized studies that included iron supplementation were ESA studies (Shannon et al, NICHD Epo trial)
- Preterm infants receiving ESAs received fewer transfusions, required increased iron
- Transfusions provide iron in the form of hemoglobin (1 gram hemoglobin contains 3.47 mg iron, or 5-8 mg iron/10 mL pRBC)
- Increased incidence of “iron deficiency” (ferritin <75 ng/mL) in preterm infants clinically receiving Epo—concerns regarding neuro-impairment

Shannon K et al, Pediatrics 1995;95:1-8
Siddappa AM et al, J Pediatr 2020;222: 98–105

Iron supplementation in ESA vs placebo study

Parenteral iron (iron dextran or iron sucrose): 3 mg/kg once a week (DOL 7) while on <60 mL/kg enteral feeds

- **added to TPN solution, run over 24 hours**
- **added to 2 mL normal saline, run over 4 hours**

Oral iron: multivitamin with iron or ferrous sulfate (5 mg/kg/d), starting when infants are receiving 80-120 mL/kg/day enteral feeds

Ohls RK et al, *Pediatrics* 2013;132:e119-127

Ferritin concentrations in ESA vs placebo study

	Darbe	Epo	Placebo	P=
Ferritin Day 14	121 [63, 184]	104 [58, 197]	204 [114, 348]	0.003
Ferritin Day 42	50 [27, 77]	61 [33, 99]	127 [67, 216]	0.002
Number of IV iron doses	1.7±1.3	1.6±1.5	1.9±2.3	0.317
oral iron started (days of age)	15.5±8.5	12.9±8.4	14.5±7.7	0.205
Ferritin <50 day 14	7	5	2	0.024
Ferritin <50 day 42	12	13	2	<0.001
Ferritin >400 day 14	1	1	5	0.118
Ferritin > 400 day 42	3	0	5	0.045

Dosing changes during the study:

- **12 infants in the ESA group and 2 in the placebo group had iron dose increased at 2 weeks (14%)**
- **25 infants in ESA group and 2 infants in the placebo group had iron dose increased at 6 weeks (25%)**

Ohls RK et al, *Pediatrics* 2013;132:e119-127

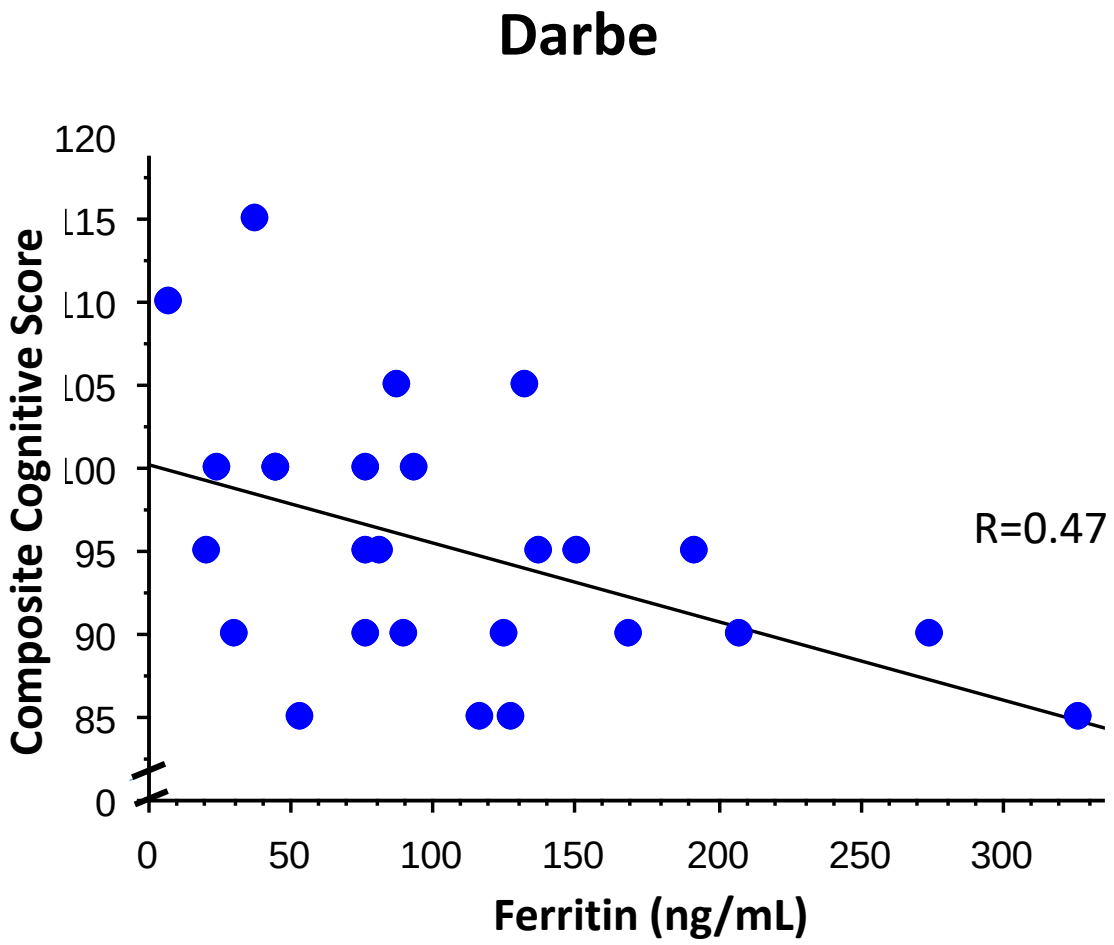
Cognitive Outcomes at 2 years

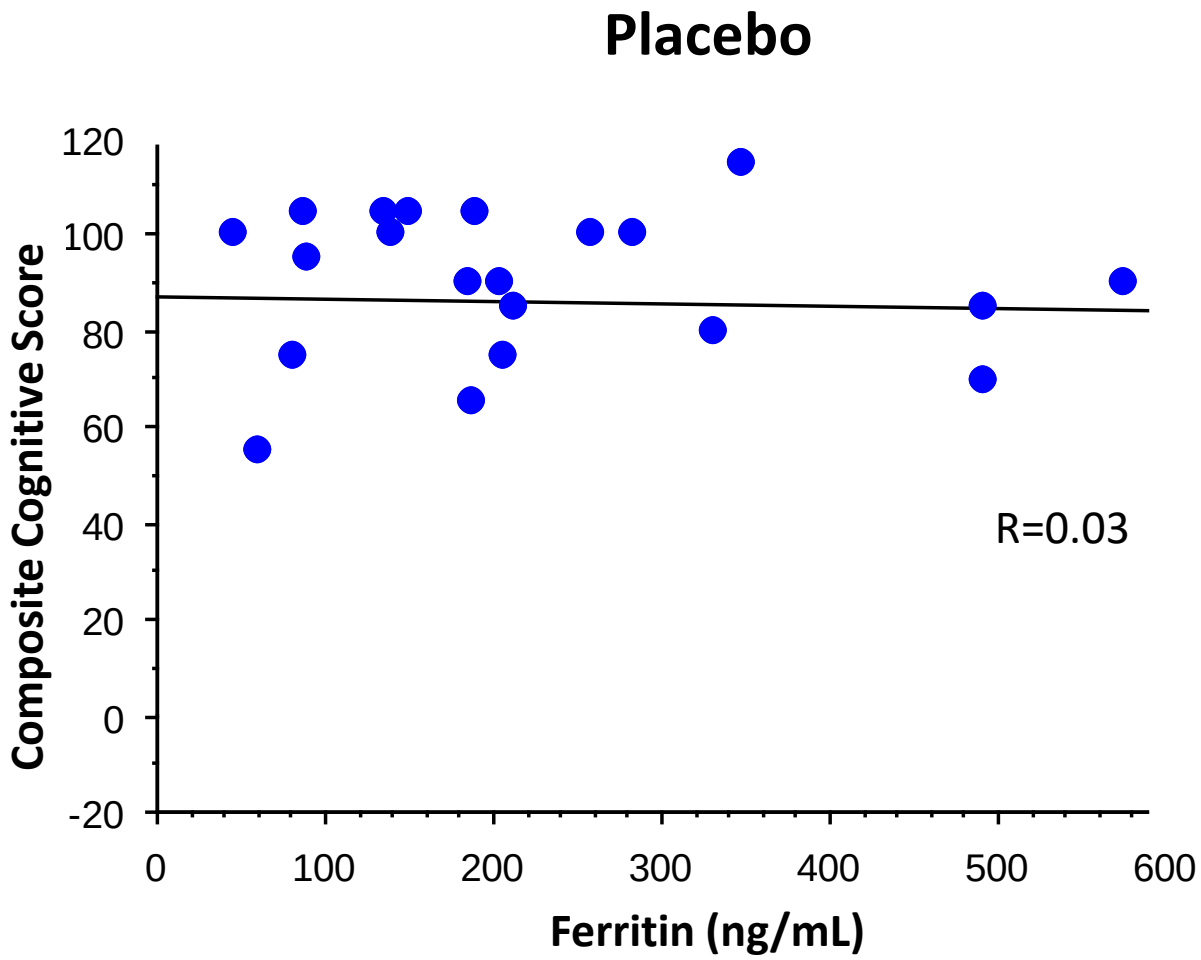
BSID III	Darbe (n=27)	Epo (n=29)	Placebo (n=24)	p
Cognitive	96.2±7.5	97.9±14.0	88.7±13.3	0.01
Language	92.4±12.8	89.9±17.4	83.6±13.9	0.06
Executive Function (EF)	2.8±0.4*	2.4±0.8	2.2±1.0	0.05
Neurodevelopmental Impairment	3 (11%)	2 (7%)	9 (38%)	0.01

*p<0.05, Darbe vs Epo

Ohls RK et al, *Pediatrics* 2014;133:1023-30

Ferritin concentrations versus cognitive score





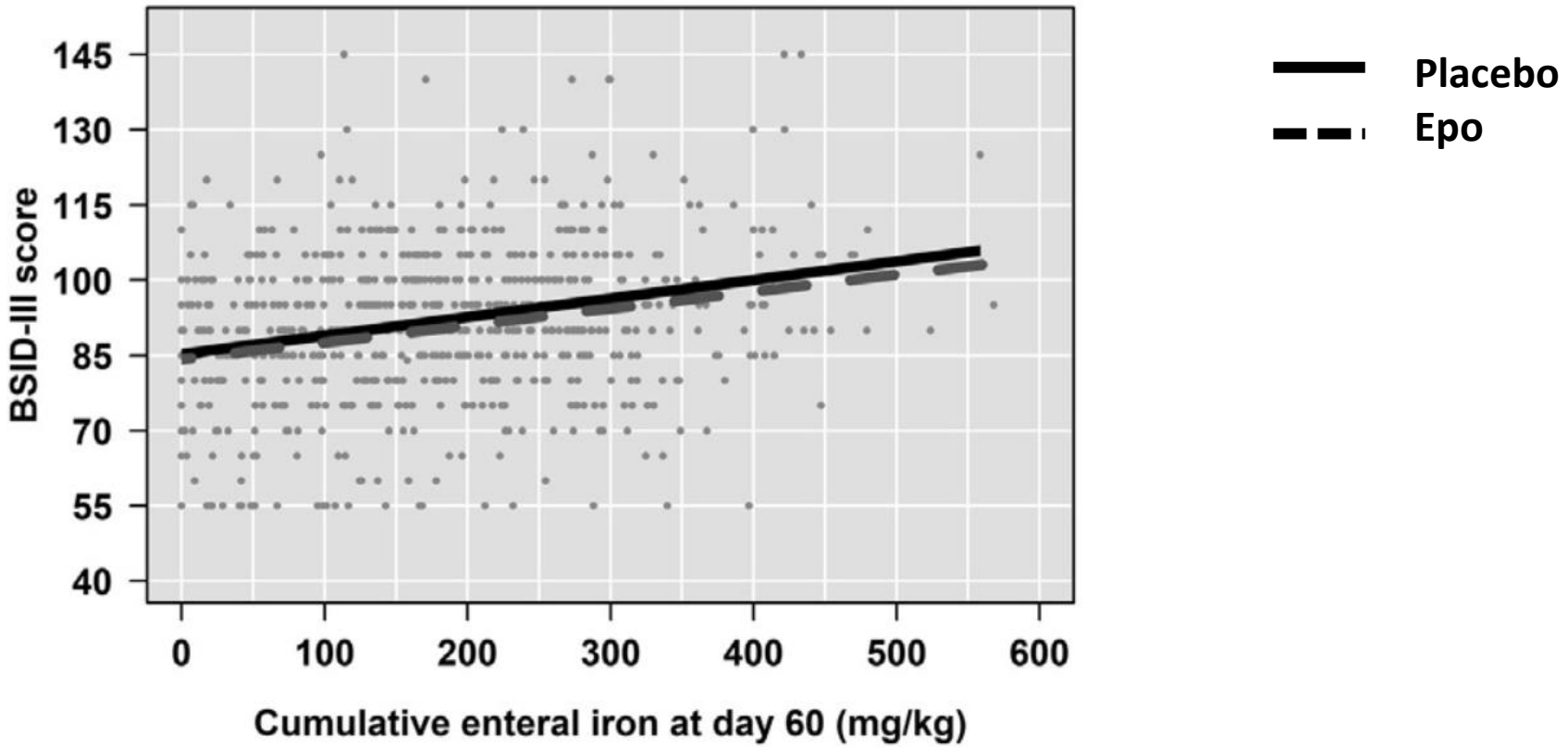
2 year BSID Composite cognitive score was not correlated with serum ferritin measured at 6 weeks

PENUT: iron dosing and outcomes

- PENUT enrolled 940 infants 24-28 weeks gestation; 1000 units/kg IV x 6 doses, then 400 units/kg TIW through 32 corrected weeks
- 692 analyzed for iron and outcomes (355 placebo, 337 Epo)
- Parenteral iron (iron dextran or iron sucrose): 1.5 mg/kg twice a week (DOL 8) while on <60 mL/kg enteral feeds
- Oral iron: multivitamin with iron or ferrous sulfate (3 mg/kg/d), starting when infants were receiving 60 mL/kg/day enteral feeds, increasing to 6 mg/kg/day when infants were on 100 mL/kg/day enteral feeds
- Oral iron dosing adjusted based on serum ferritin or zinc protoporphyrin-to-heme ratio

German K et al, J Pediatr 2021; Jul 27

PENUT: iron dosing and Bayley III cognitive outcome



Similar relationship seen between cumulative iron at day 60 and BSID Motor and Language Scores

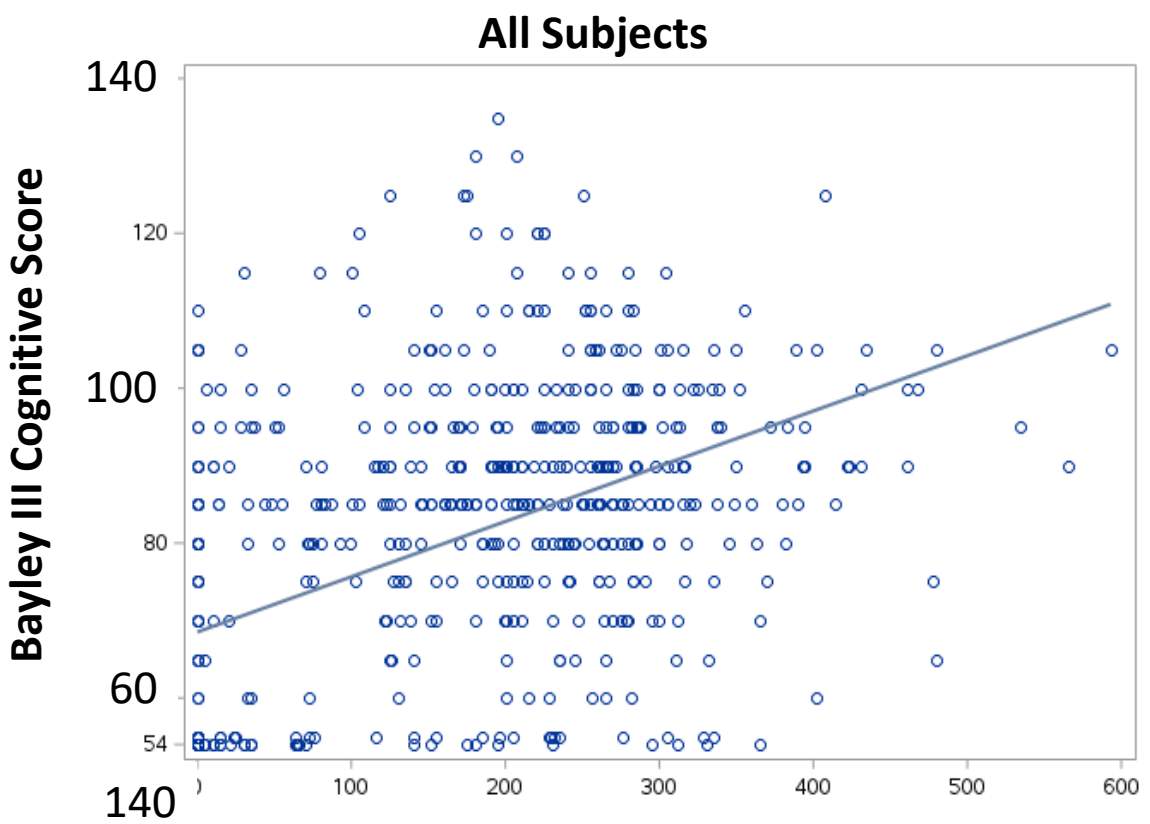
German K et al, J Pediatr 2021; Jul 27

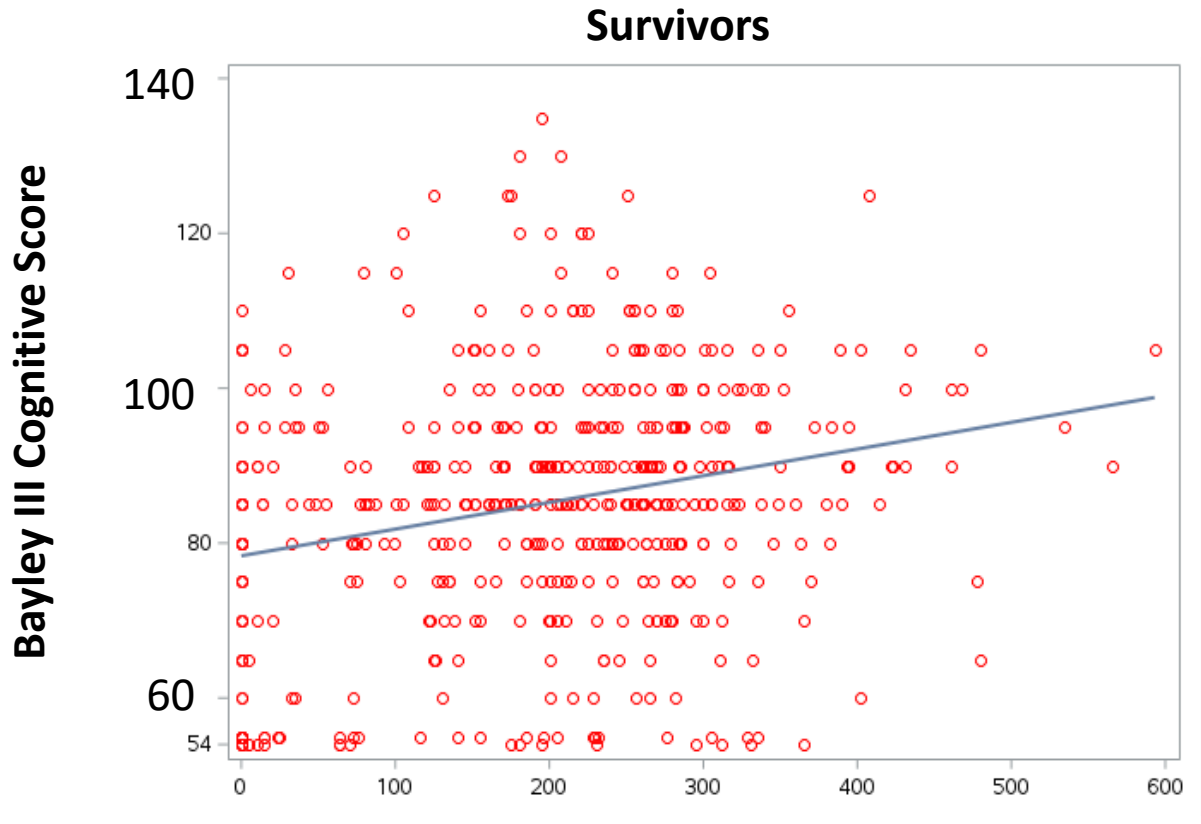
PENUT: iron dosing and outcomes

- Significant positive association was seen between Bayley-III cognitive scores and iron dose at 60 days
- 0.77 cognitive score points per 50 mg/kg increase in cumulative iron dose (*P* = .03)
- The effect size in the infants treated with Epo was consistently greater compared with placebo
- Conclusion: increased iron supplementation in infants born preterm, at the doses administered in the PENUT Trial, may have positive neurodevelopmental effects

German K et al, J Pediatr 2021; Jul 27

Darbe Study: oral iron and cognitive outcome





Significant positive association was seen between Bayley-III cognitive scores and cumulative oral iron at 60 days

Question 2

Which of these is true?

A. Infants receiving red cell growth factors require additional iron

B. The greater the amount of iron administered, the lower the cognitive score

C. Red cell transfusions provide an immediate increase in available iron

D. Parenteral iron has been a common supplement in preterm infants for the past 30 years

What is the best way to evaluate iron status in preterm neonates?

- **MCV/MCH/Iron/IBC/ferritin panel (adults)**
- **Ferritin (Lozoff et al; Georgieff et al)**
- **Reticulocyte hemoglobin content (RET-He, a new marker)**

Is the RET-He as valid as serum ferritin for evaluating iron status?

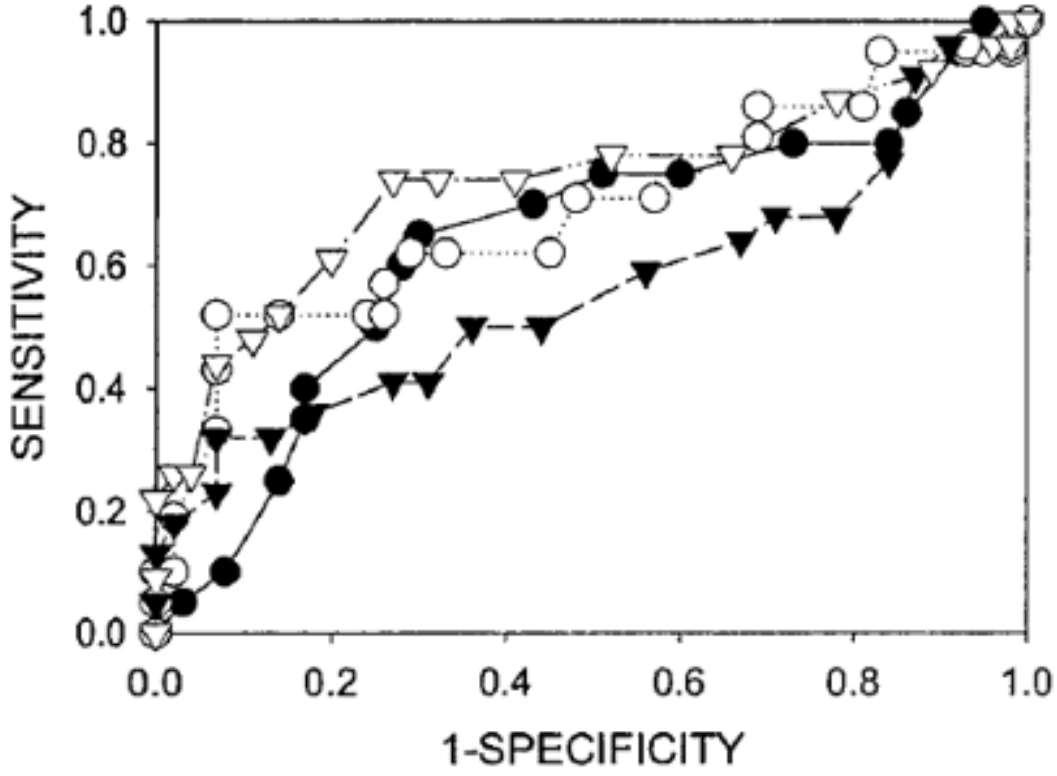
Reticulocyte Hemoglobin Content (RET-He)

Measurement of iron available for erythropoiesis 3-4 days prior to specimen collection

Benefits:

- Not affected by inflammation
- Part of CBC measured by Sysmex or Bayer machines
- Requires 88 µL blood (NO additional phlebotomy)
- Measured in picograms (pg), similar to MCH

RET-He



Ret-He
Transferrin
MCV
Ferritin

Compared to bone marrow analysis of iron stores, RET-He had higher sensitivity and specificity for iron deficiency than ferritin, transferrin saturation, or MCV in adults

Mast et al. *Blood* 2002, 99(4): 1489-1491.

RET-He

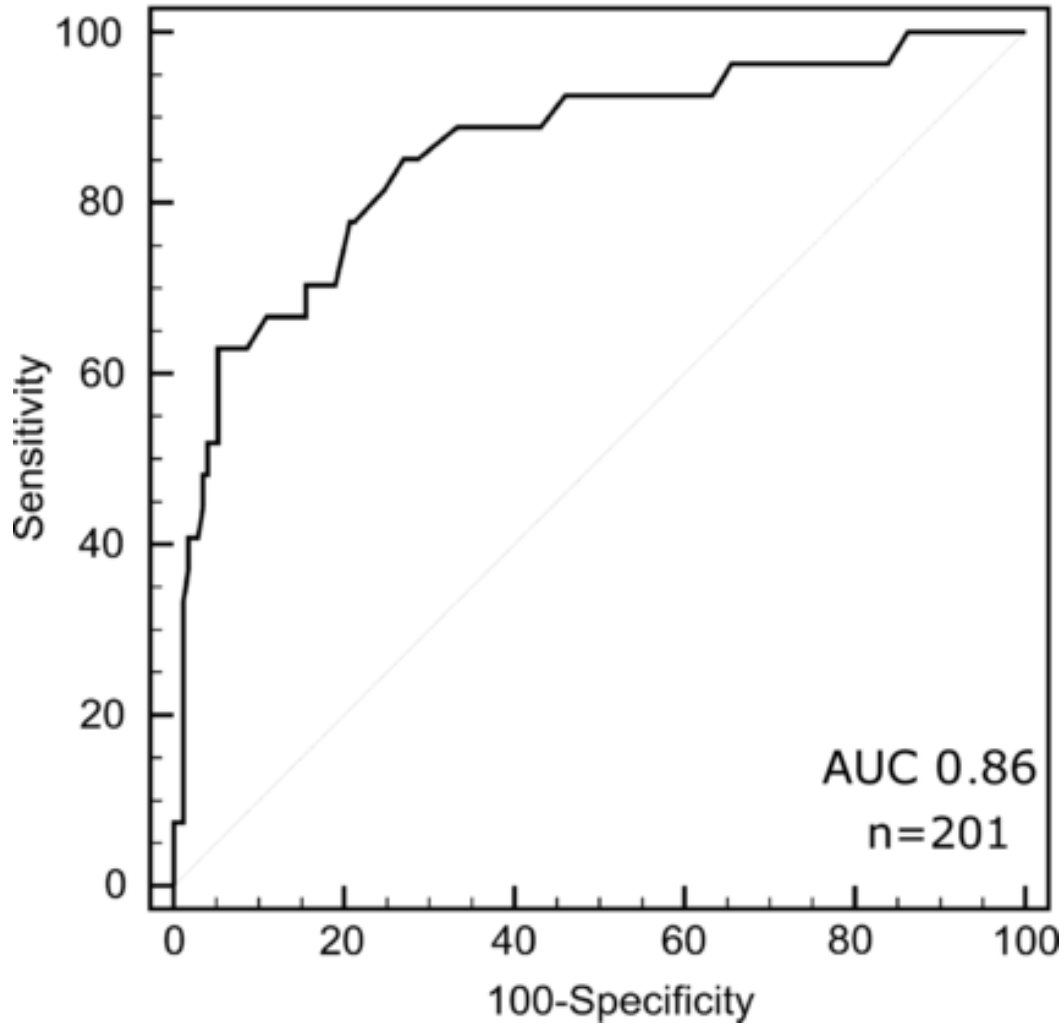
In young children, using transferrin saturation <20% as definition of iron deficiency, RET-He was the strongest predictor of iron deficiency and iron deficiency anemia compared to serum iron, transferrin, ferritin, and circulating transferrin receptor

- **Area under ROC curve: 0.913 for RET-He cutoff of 27.2 pg**
- **Sensitivity: 93.3%**
- **Specificity: 83.2%**

Brugnara et al. *JAMA* 1999, **281**(23)**:** 2225-2230.

RET-He

- RET-He evaluating iron status in preterm infants at 3-4 months corrected age
- At cut off of 29 pg:
  - Sensitivity 85%
  - Specificity 73%



Lorenz et al. *Arch Dis Child Fetal Neonatal Ed*. 2015, **100**(3)**:** 198-202.

RET-He versus Ferritin Study

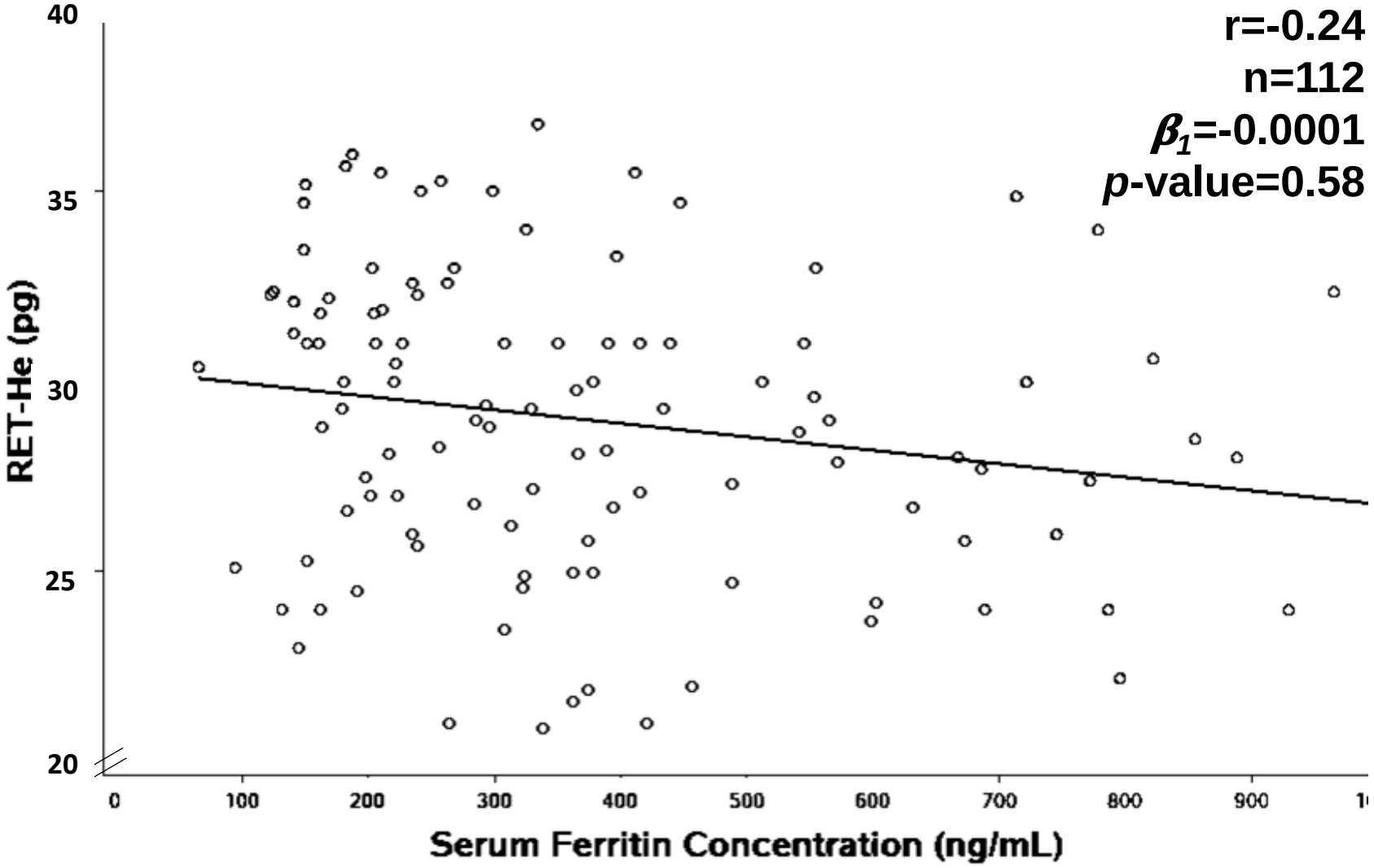
- No “gold standard” for iron status in preterm neonates
- Limited data on how RET-He values compare to ferritin levels in preterm neonates (<29 weeks)
- Comparing large number of RET-He values to ferritin levels in a randomized trial of Darbe versus placebo will provide important information about use of RET-He in preterm neonates as a test for iron status

Methods

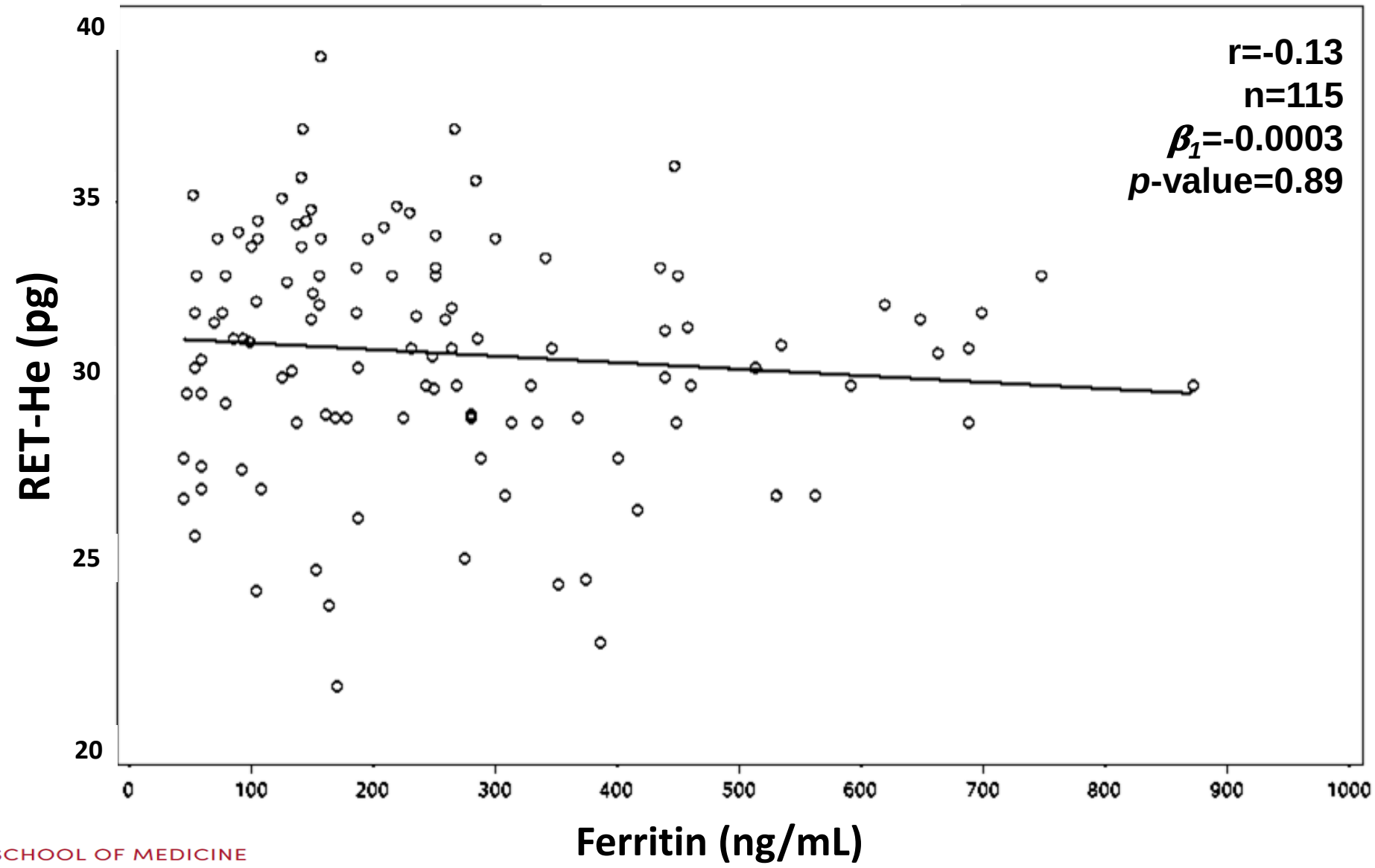
- All infants entering main study at sites that have a Sysmex or Bayer hematology analyzers were included
- No additional phlebotomy for infants enrolled in study (ferritins measured at weeks 2 and 6 as part of the main trial)
- RET-He obtained part of retic parameters at baseline, week 2 and 6
- For initial analysis, only placebo/control infants were included (more transfused, 1-2 doses of parenteral iron; iron held for ferritin>400, iron increased for ferritin <50)

RET-He and Ferritin Correlations at 2 weeks

Early: DOL 11-17

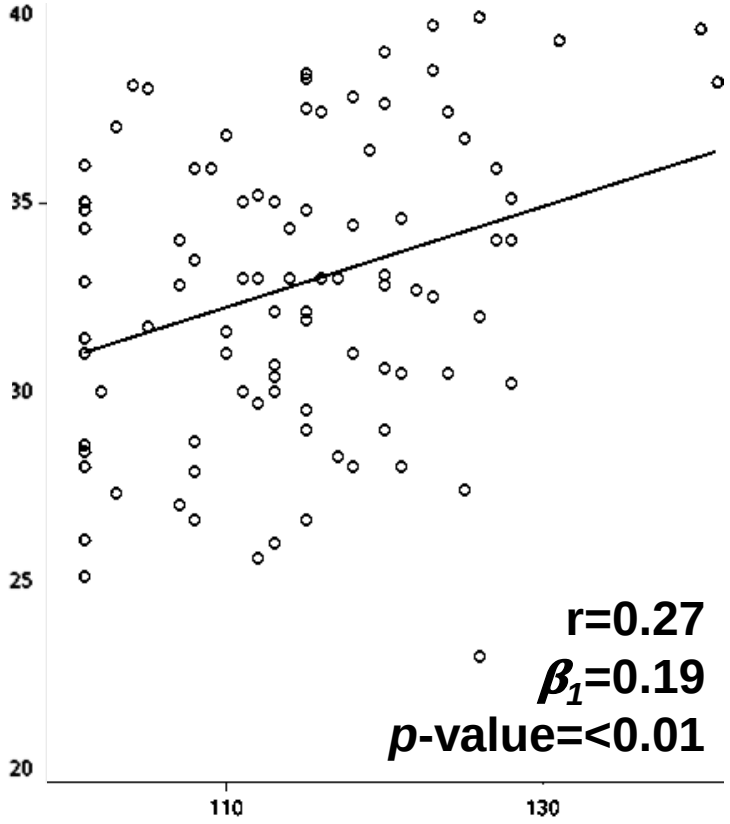


RET-He and Ferritin Correlations at 6 weeks

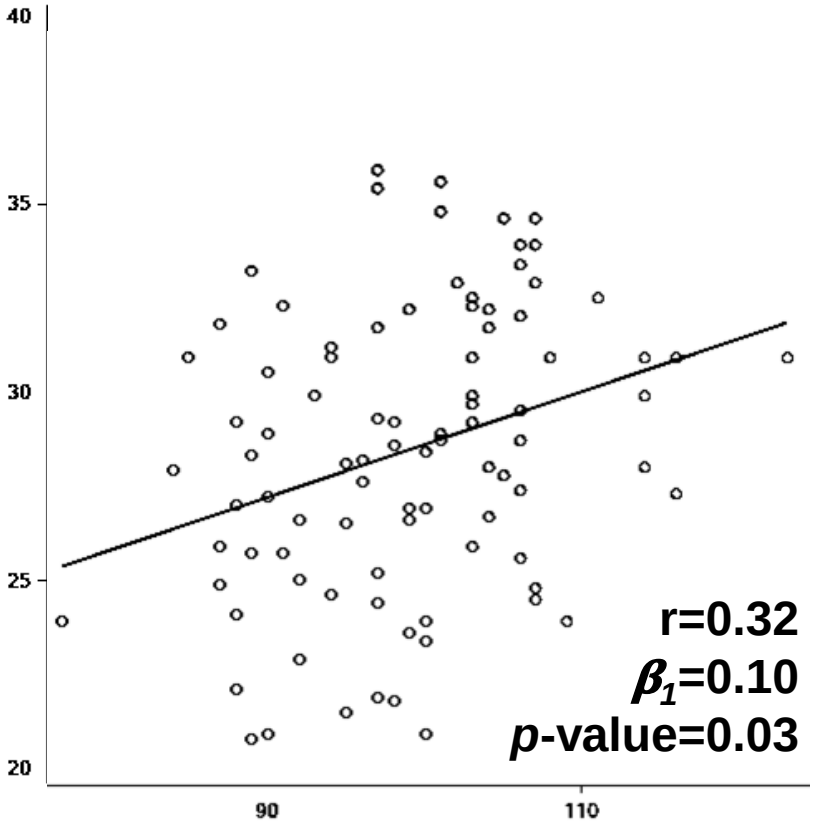


RET-He and MCV correlations

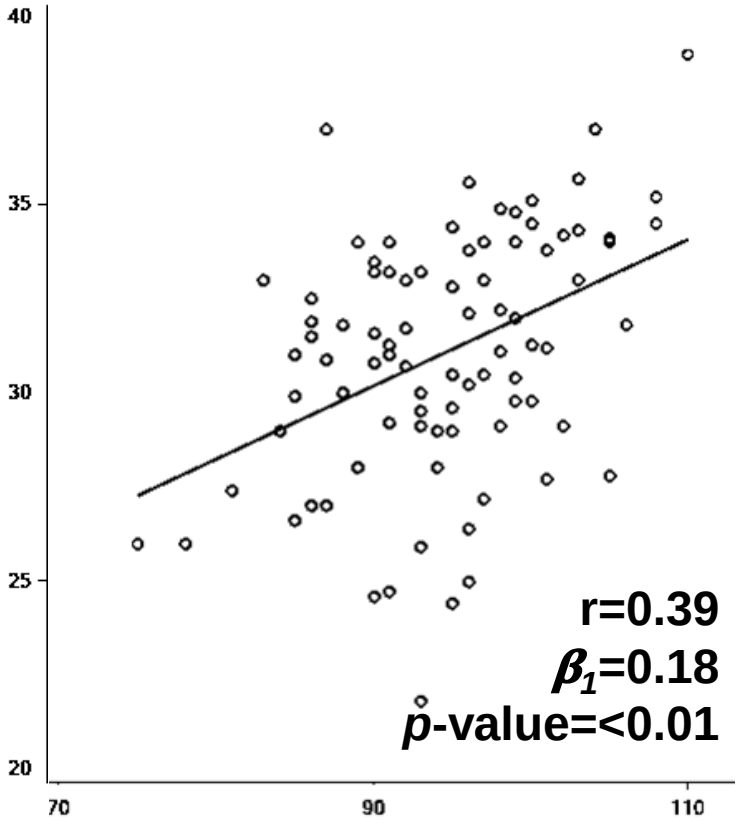
Baseline: DOL 0-1



Early: 2 weeks

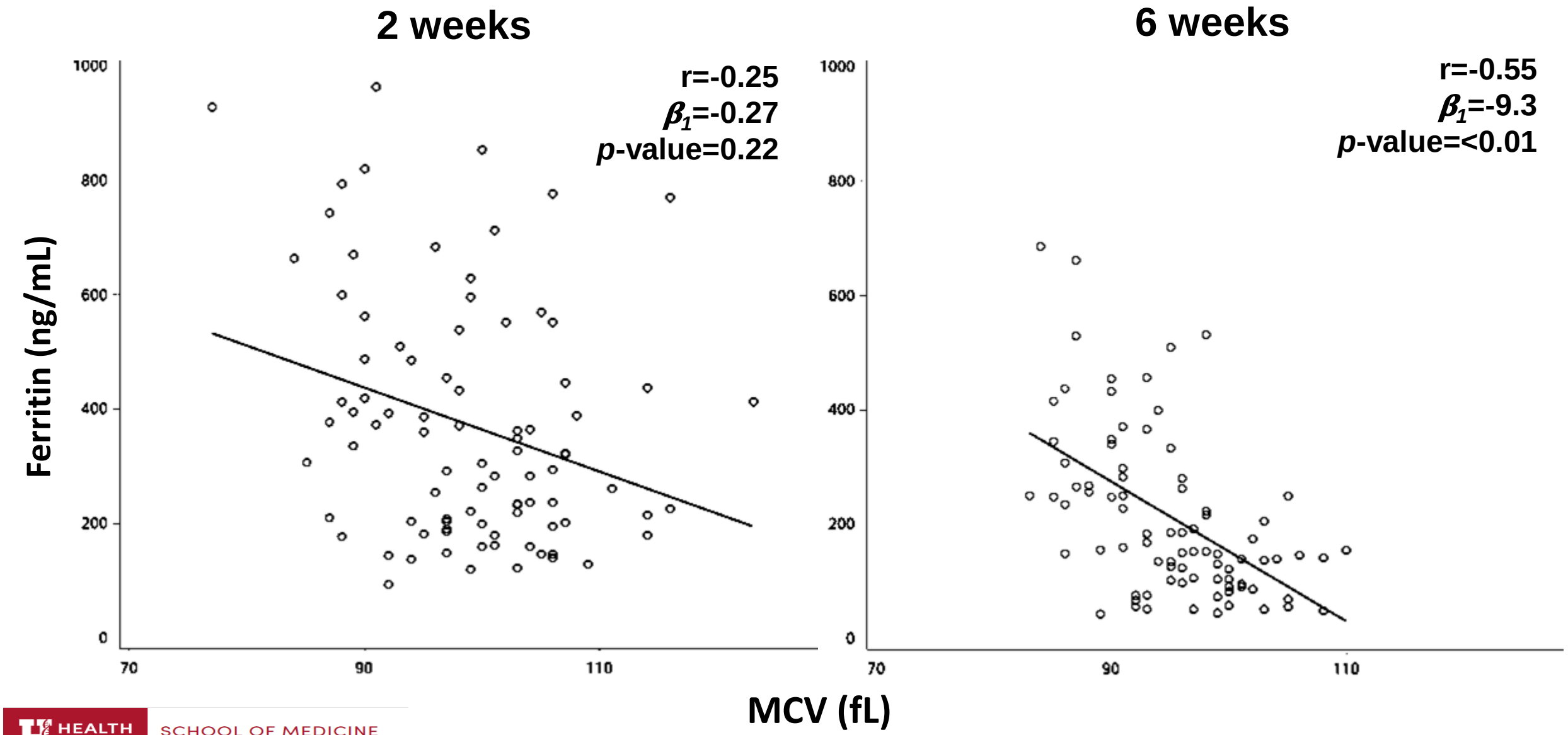


Late: 6 weeks



MCV (fL)

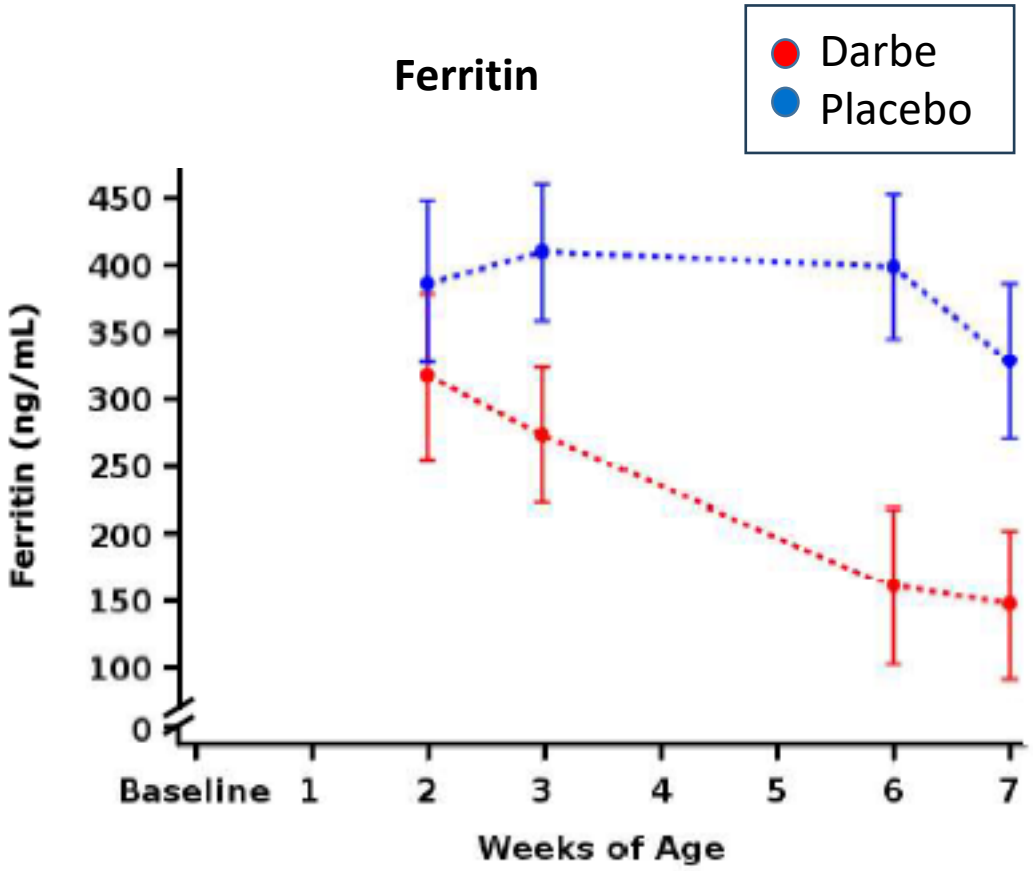
Ferritin and MCV correlations



Summary of RET-He analyses

- Ferritin and RET-He were not correlated
- Ferritin is an acute phase reactant; in this population (GA <29 weeks) may be increased due to inflammation
- RET-He correlation with MCV suggests RET-He might reflect RBC changes associated with iron deficiency better than ferritin
- Analyses are ongoing; final correlations to be evaluated in Darbe/placebo groups between RET-He, ferritin and developmental outcomes

Darbe Trial iron dosing and outcomes



- Lower ferritin in Darbe group
- Significantly greater iron supplementation in Darbe group (247±113 vs 185±92 mg/kg)

Question 4

Which measure of iron sufficiency do you use?

A. ferritin
B. RetHe
C. We don’t routinely check for iron sufficiency

Early iron treatment for ELBW infants (especially infants receiving ESAs):

Iron sucrose, 3 mg/kg IV once a week over 30-60 minutes (can add iron dextran in TPN, 3 mg/kg once a week)

Start oral iron at 6 mg/kg/day when on adequate volume feeds

Monitor iron sufficiency at 2 weeks (reticulocyte hemoglobin >28 pg; ferritin >50 ng/mL)

Adjust iron dosing to maintain iron sufficiency

Continue treatment through discharge

Thank you for your attention!

Special thanks to the Division of Neonatology and our Neo-Heme group:

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Cognitive Composite Score versus Serum Ferritin