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Screening umbilical cord blood for congenital Iron deficiency

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ABSTRACT

Objectives: Small for gestational age infants (SGA), infants of diabetic mothers (IDM), and very low birth weight infants (VLBW) are at risk for congenital iron deficiency. We evaluated the iron status of SGA, IDM, and VLBW neonates at birth and sought mechanistic explanations in those with iron deficiency.
Methods: This was a prospective study. If congenital iron deficiency was present, maternal iron studies were obtained. When neonates were two weeks old, their iron status was reevaluated.
Results: Sixteen of 180 neonates screened were iron deficient at birth. The Body Mass Index of the 16 mothers was high. These mothers often had mild iron deficiency and measurable hepcidin levels. Two weeks after birth, neonates had improved iron measurements.
Conclusions: Among SGA, IDM, and VLBW neonates, maternal obesity is a risk factor for congenital iron deficiency. We speculate that elevated hepcidin levels in obese pregnant women impede iron absorption and interfere with transplacental iron transfer.

1. Introduction

Biochemical iron deficiency, an early stage of iron deficiency, is defined as abnormally low serum and storage iron but without erythropoietic impairment or anemia [1]. Thus, biochemical iron deficiency precedes the more severe stages of iron deficiency; iron-limited erythropoiesis and iron deficiency anemia. Recognizing and treating biochemical iron deficiency in neonates might avoid progression to iron-deficient neurological impairments, including reduced cognitive performance, which can be permanent even after the iron deficiency is treated [1,2].

Certain risk factors for the development of iron deficiency in early infancy have been identified. These include small for gestational age neonates (SGA, < 10th percentile weight for gestation), infants of diabetic mothers (IDM), and very-low-birth-weight preterm neonates (VLBW, < 1500 g at birth) [1]. Chronic fetal hypoxia and impaired maternal-to-fetal iron transport can contribute to iron deficiency in SGA or IDM neonates. Infants born preterm do not have the advantage of the large accretion of iron that normally occurs in the third trimester of gestation, leading to an increased risk of iron deficiency at birth [1,2].

We recently reported a pilot study designed to assess the iron status of neonates at birth [3]. We found that six of 50 who were screened had congenital biochemical iron deficiency. None of the six had iron deficiency anemia. Thirty of the 50 who were screened were SGA, IDM or VLBW infants and five of these (17%) were iron deficient.

We conducted the present multicenter hypothesis-generating pilot study to provide a more accurate estimate of the incidence of biochemical iron deficiency of SGA, IDM, and VLBW neonates at birth in our population, and to assess the iron status of the mothers of those neonates we found to be iron deficient. We also sought to assess the risk factors and iron status of iron deficient neonates at two weeks of age before beginning oral iron supplements, since it is our usual practice not to administer medicinal iron during the first 14 days [4].

2. Materials and methods

This was a prospective, multicenter trial conducted in three Intermountain Healthcare NICUs; McKay-Dee Hospital, Ogden, UT,

Abbreviations: SGA, small for gestational age; IDM, Infant of diabetic mother; VLBW, very low birth weight; BMI, body mass index

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Table 1
Results of screening umbilical cord blood for biochemical iron deficiency, at the birth of SGA, IDM, and VLBW neonates.

"AT RISK" GROUP	Number Screened	Gest age (w)	Birth Weight (g)	Serum Fe (μg/dL)	TIBC (μg/dL)	Transferrin Saturation (%)	Ferritin (ng/mL)	Number with Biochemical Iron Deficiency*
SGA	17	35 ± 1	1882 ± 225	181 ± 51	224 ± 81	83 ± 24	232 ± 219** 161;97,321	0
IDM	15	34 ± 2	2482 ± 771	129 ± 90	262 ± 95	55 ± 38	69 ± 75** 44;17,105	4
Both SGA and IDM	2	36 ± 3	1840 ± 170	180 ± 155	320 ± 54	60 ± 57	39 ± 43*** 8;8–69	1
VLBW	64	28 ± 2	1179 ± 260	116 ± 68	180 ± 54	62 ± 32	127 ± 152** 83;45,157	5
Both SGA and VLBW	27	32 ± 3	1127 ± 316	158 ± 84	250 ± 49	63 ± 32	159 ± 376** 68;23,145	5
Both VLBW and IDM	1	28	1420	163	109	100	126	0
SGA, VLBW and IDM	1	34	1430	71	440	16	11	1
None of the above	53	32 ± 2	2028 ± 488	168 ± 62	189 ± 45	85 ± 20	125 ± 91	0
Total	**180**	**31 ± 3**	**1606 ± 620**	**146 ± 74**	**207 ± 68**	**70 ± 31**	**134 ± 191** 82;54,162**	**16**

None of the above = umbilical cord blood screening was sent, but the neonate was found not to be SGA, IDM, or VLBW.
SGA, small for gestational age; IDM, infant of diabetic mother; VLBW, very-low-birth-weight; Fe, iron; TIBC, total iron binding capacity; w, weeks; g, grams.
* Statistical definition of Biochemical Iron Deficiency at birth = Iron < 100 μg/dL and Transferrin saturation < 30% and Ferritin < 50 ng/mL [3].
** Median; 1st and 3rd Interquartile range.
*** Median, Range.

Utah Valley Regional Medical Center, Provo, UT, and Intermountain Medical Center, Murray, UT. The protocol was approved by the Intermountain Healthcare Institutional Review board and an informed consent document was signed by the parents of participating neonates when enrolling in the study. Intermountain Healthcare is a not-for-profit system that owns and operates 22 hospitals in Utah and Idaho.

IDM, SGA, and VLBW neonates admitted to NICUs at the participating hospitals were screened using umbilical cord blood levels of ferritin, serum iron, and transferrin saturation. Umbilical cord blood was drawn after placental delivery, as described [5]. Infants were eligible for the study if all three values from cord blood were indicative of iron deficiency, as defined in our previous study [3] as < 5th percentile reference interval for serum ferritin < 50 mg/dL, serum iron < 100 μg/dL, and transferrin saturation < 30%. Parents of eligible infants were contacted and informed that their neonate qualifies for participation in a research study of iron deficiency at birth.

Following consent, a battery of iron studies were drawn on the mothers. These included serum iron (μg/dL), total iron binding capacity (TIBC, μg/dL), transferrin saturation (%), ferritin (ng/mL), soluble transferrin receptor (mg/L), zinc protoporphyrin (ZPP) to heme ratio (μmol ZPP/mol heme), reticulocyte hemoglobin content (pg), plasma hepcidin (ng/mL), and complete blood count (CBC) parameters. These laboratory tests were also obtained from neonates found iron deficient at birth, when they were between 12 and 16 days of life, and prior to any introduction of supplementary medicinal iron. Body mass index (BMI) was recorded for all mothers of screened infants. BMI was calculated as weight (kg)/height^2 (m^2).

The plasma levels of hepcidin-25, were measured by mass spectrometry (University of Utah Research Core Facilities), using methods we previously detailed [6]. Samples were stored at −80 °C then thawed and kept on ice prior to assay. A calibration curve of, 0.5 nM, 2 nM, 10 nM, 50 nM of human hepcidin ($C_{113}H_{170}N_{34}O_{31}S_9$, Peptide Institute Inc.) were spiked into 100 μL of FBS and treated along with patient samples in an identical manner. Chromatographic separation was carried out using an Infinity 1290 LC system (Agilent). The MS/MS detection was performed using an Agilent 6490 Triple Quad LC/MS system. The obtained data were analyzed using MassHunter Quantitative Analysis program (Agilent). The ratios between peak areas of human hepcidin and [$^{13}C_{18}$, $^{15}N_3$]-hepcidin in the calibration standard were plotted against the concentration to construct the calibration curve. The ratios found in the samples were used to calculate the hepcidin concentrations.

Study data were collected and managed using REDCap electronic data capture tools hosted at Intermountain Healthcare [7]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data were managed and accessed by authorized data analysts. Means, standard deviations, and 95% Confidence Intervals were used to express values in groups that were normally distributed, and medians and interquartile ranges to express values in groups that were not. Differences in categorical variables were assessed using the Fisher exact test or χ^2 for normally distributed data and Tukey's bi-weight estimator for groups that were not. Statistical analysis used Statit (Midas, Tucson, AZ, USA). Comparisons were exploratory, and p values were not adjusted. Statistical significance was set as $p < 0.05$.

3. Results

Study enrollment began in June 2017 and concluded in March 2018. One hundred eighty neonates were screened, of which 16 were found to have biochemical iron deficiency. All 16 of these neonates had delayed cord clamping or cord milking performed at birth. Eight of

Table 2
Neonates who were identified at birth as having biochemical iron deficiency. Shaded cells show values below the lower reference interval for gestational age [3].

Patient	Group	Gestational Age (w)	Birth Weight (g)	Serum Iron (μg/dL)	Transferrin Saturation (%)	Ferritin (ng/mL)	Hgb (g/dL)	MCV (fL)	Mother's BMI
1	SGA & VLBW	33	1380	63	20	18	21.8	107.1	46.4
2	IDM	37	3350	27	6	9	18.1	97.1	43.4
3	VLBW	28	900	27	13	21	16.5	118.9	39.0
4	VLBW	29	1090	60	25	9	16.6	116.1	28.1
5	SGA & VLBW	32	1290	50	20	22	21.5	112	39.9
6	SGA & VLBW	28	900	54	16	13	14.4	107.2	46.4
7	IDM	31	1985	5	2	6	13.7	95.7	36.6
8	SGA & IDM	38	1960	71	20	8	19.4	108	32.4
9	VLBW & IDM	30	1320	66	24	40	17.2	110.6	36.7
10	VLBW	28	1010	67	27	27	16.3	111.6	27.9
11	IDM	34	1430	71	16	11	15.1	110.5	45.9
12	SGA & VLBW	34	1500	63	23	21	16.8	111.4	31.3
13	SGA & VLBW	29	750	74	27	23	14.1	124.8	34.6
14	VLBW	29	1070	89	30	29	14.3	115.2	33.3
15	IDM	38	4384	76	24	11	15	110	41.6
16	IDM	33	2390	55	24	25	20.1	114.4	32.4

SGA, small for gestational age; IDM, infant of diabetic mother; VLBW, very-low-birth-weight; Fe, iron; TIBC, total iron binding capacity; w, weeks; g, grams; Hgb, hemoglobin; MCV, mean corpuscular volume; BMI, body mass index.

these 16 were enrolled in the study to measure a battery of iron parameters in mothers, and also in neonates when they were about two-weeks old.

Screening results are shown in Table 1. As seen in the first column, 96 of the 180 neonates were in only one of the three "at risk" categories, while 31 were in more than one category; for instance, they were both SGA and VLBW. Fifty-three of the 180 screened neonates were in none of the three "at risk" categories. These 53 were screened because before birth it was thought that they were likely to be SGA or VLBW, thus their umbilical cord blood samples were drawn and submitted for testing. However, once the neonates were weighed and examined, they were found not to be SGA or VLBW.

Data from the 16 with fetal iron deficiency are shown in Table 2. All 16 had low serum iron, low transferrin saturation, and low serum ferritin levels. Two had microcytosis, defined as a MCV below the 5th percentile lowest reference interval for age [8]. None were anemic, although one of those with microcytosis (patient #7) had a borderline low hemoglobin, 13.7 g/dL, for gestational age [9].

Laboratory studies evaluating the iron status of mothers of the iron deficient neonates are shown in Table 3. One had a low serum iron, four had low transferrin saturations, one had an elevated soluble transferrin receptor level, and one had an elevated zinc protoporphyrin to heme ratio. Hepcidin levels in mothers were all higher than expected for adults with biochemical iron deficiency. In iron deficiency hepcidin values < 2.0 ng/mL are typical [6], apparently as a mechanism for increasing dietary iron absorption and release of iron from stores into the circulation [7]. We commonly find that hepcidin levels of iron deficient individuals are below the lower limit of detectability [6]. However, all hepcidin values from these women were measurable.

Table 4 shows the iron studies drawn two weeks after birth from neonates who were iron deficient at birth. Serum iron levels had risen in six of eight, but were still below the lower reference interval in all but one. Similarly, transferrin saturation and ferritin typically increased from the values at birth, but were still below the lower reference interval in most. The zinc protoporphyrin to heme ratio was elevated in all (this parameter typically takes several weeks to normalize after iron treatment). Microcytosis was present in three. None were anemic. Hepcidin levels in the iron-deficient neonates, when two weeks old, varied from not detectable to 21.1 ng/mL.

The influence of the mother's BMI on fetal iron deficiency is illustrated in Table 5. In this analysis we compared the three "at risk" groups with the 53 neonates who had none of the three "at risk" diagnoses. In that group of 53, none were iron deficient. If the neonate was in any of the three "at risk" groups, the maternal BMI had a significant association with fetal iron deficiency. Specifically, when the mother's BMI was < 30, iron deficiency was present in 4% of neonates, but when the mother's BMI was ≥30, 20% of the neonates were iron deficient ($p = 0.03$). Examined another way, mother's BMI was higher (95% CI; 33.9 to 40.5) when "at risk" neonates had iron deficiency than when "at risk" neonates did not have iron deficiency (95% CI, 31.4 to 34.2; $p = 0.019$).

4. Discussion/Conclusion

SGA, IDM, and VLBW neonates are reported to be at risk for iron deficiency in the perinatal period [9]. We found congenital biochemical iron deficiency in 13% (16/127) of neonates who were SGA, IDM or VLBW. One neonate in our study (patient #7) had evidence of iron-

Table 3
Iron status of mothers whose neonates had biochemical iron deficiency at birth. Shaded cells show values below the lower reference interval for women, or abnormally elevated hepcidin levels.

	Group	Serum Fe (μg/dL)	TIBC (μg/dL)	Trans sat (%)	Ferritin (ng/mL)	Soluble trans recept or (mg/L)	ZPP/Heme Ratio (μmol ZPP/mol Hem)	Hgb (g/dL)	MCV (fL)	Retic He (pg)	Plasma Hepcidin (ng/mL)
Reference Intervals for Women ‡		30–160	240–450	20–50	18–340	1.9–4.4	0–69	12–16	80–96	27.9–37.0	*
1	SGA & VLBW	59	336	18	76	1.9	48	9.4	90.0	36.2	0.9
2	IDM	40	236	17	115	3	36	12.5	90.2	29.5	7.8
3	VLBW	88	353	25	110	3.4	43	14.4	87.5	36.3	2.0
4	VLBW	72	338	21	205	2	40	11.8	94.0	36.4	3.8
5	SGA & VLBW	***	***	***	***	***	***	***	***	***	***
7	IDM	84	345	24	20	2.9	55	9.1	85.2	30.2	1.4
8	SGA & IDM	37	376	10	114	2.4	76	10.5	88.1	33.7	3.8
10	VLBW	30	414	7	249	4.8	66	11.3	87.0	33.5	12.0

*In iron deficiency hepcidin levels are typically unmeasurably low [6].
***Data not available.
‡Reference intervals from ARUP laboratories, Salt Lake City, UT.
SGA, small for gestational age; IDM, infant of diabetic mother; VLBW, very-low-birth-weight; Fe, iron; TIBC, total iron binding capacity; trans, transferrin; sat, saturation; ZPP, zinc protoporphyrin; Hgb, hemoglobin; MCV, mean corpuscular volume; Ret He, reticulocyte hemoglobin content.

limited erythropoiesis at birth, with a low MCV for age of 95.7 fL and a borderline low hemoglobin for age of 13.7 g/dL [3,8,10].

We observed that the mother's BMI had a significant effect on whether neonates were congenitally iron deficient. Specifically, if the SGA, IDM, or VLBW neonate's mother had a BMI < 30, iron deficiency was rare (4%). However, if the mother's BMI was ≥30, thereby categorizing them as obese according to the World Health Organization definition [11], iron deficiency was present in 20%. The association between a high BMI and iron deficiency was recently reviewed by Aigner *et al*, who proposed obesity-associated inflammation causing high hepcidin levels would impair duodenal iron absorption [12,13]. Previous publications suggest that maternal obesity is a risk factor for perinatal iron deficiency [14–16]. We previously found that adults with iron deficiency have very low hepcidin levels; < 2.0 ng/mL, and typically undetectably low levels [6]. However, in the present study the obese mothers carrying fetuses with biochemical iron deficiency had measurable hepcidin levels, and therefore abnormally high. A possible explanation for what appears to be an inappropriately elevated hepcidin level might be obesity-associated inflammation leading to decreased dietary absorption of iron in these mothers, and also perhaps to

Table 4
Iron status of neonates at 2 weeks of age, who were identified at birth as iron deficient. Shaded cells show values below the lower reference interval for gestational age [3].

Patient	Group	Serum Fe (μg/dL)	TIBC (μg/dL)	Trans Sat (%)	Ferritin (ng/mL)	Soluble trans recept or (mg/L)	ZPP /Heme ratio	Hgb (g/dL)	MCV (fL)	Ret He (pg)	Plasma Hepcidin (ng/mL)
Reference Intervals for Preterm Neonates		130–190	100–250 ‡	61–100	81–200	3.6–5.0	70–95	*	*	*	**
1	SGA & VLBW	100	194	52	88	3.5	134	16.4	99.1	34.1	1.3
2	IDM	142	291	49	91	18.6	263	18.3	91	32.9	0.9
3	VLBW	54	304	18	258	6.4	183	17.3	104.7	32.8	21.1
4	VLBW	40	369	11	55	8.4	212	13.4	94.6	30	2.9
5	SGA & VLBW	112	248	45	79	4.2	211	15	102.4	36.7	1.0
7	IDM	55	320	17	23	7	272	***	***	***	Not detectable
8	SGA & IDM	111	210	53	97	***	187	18.9	94.7	33	***
10	VLBW	60	245	24	168	4.6	193	12.7	100.6	30.4	Not detectable

*Lower reference interval is dependent on gestational age [8,10,20].
**Reference intervals for plasma hepcidin at 2 weeks of age in this population has not been established.
*** Data not available.
‡Reference interval from ARUP Laboratories, Salt Lake City, UT, for neonates 0–6 weeks old.
SGA, small for gestational age; IDM, infant of diabetic mother; VLBW, very-low-birth-weight; Fe, iron; TIBC, total iron binding capacity; trans, transferrin; sat, saturation; ZPP, zinc protoporphyrin; Hgb, hemoglobin; MCV, mean corpuscular volume; Ret He, reticulocyte hemoglobin content.

Table 5
Biochemical iron deficiency according to; 1) high risk group (SGA, IDM, VLBW) and 2) mother's BMI (< 30 *vs.* ≥30**).** (Note: Some neonates were in more than one group, *i.e.* they were both SGA and IDM). Fifty-three neonates were screened for iron deficiency but turned out not to be in any of the three high risk categories (not SGA, nor IDM, nor VLBW) and no cases of iron deficiency were identified among these 53.

High Risk Group	N	Biochemical Iron Deficiency n (%)	Mother's BMI <30 Fraction with fetal iron deficiency	Mother's BMI ≥ 30 Fraction with fetal iron deficiency	Relative risk (RR) of fetal iron deficiency if mother had a BMI ≥ 30 (RR, 95% CI; p value *vs.* those with mother's BMI <30)
SGA	47	7/47 (15%)*	0/17 (0%)	7/30 (23%)	8.7; 0.5 to 143.7; p=0.13
IDM	20	8/20 (40%)	0/1 (0%)	6/19 (42%)	1.3; 0.1 to 15.6; p=0.83
VLBW	93	11/93 (12%)**	2/31 (6%)	9/62 (15%)	2.3; 0.5 to 9.7; p=0.28
Total of the three groups	160	26/160 (16%)	2/49 (4%)	22/111 (20%)	**4.9; 1.2 to 19.8; p=0.03**
In none of the three group	53	0/53 (0%)***	0/25 (0%)	0/28 (0%)	**0.90; 0.01 to 43.6; p=0.96**

*$p = 0.024$ *vs* IDM.
**$p = 0.022$ *vs* IDM.
***$p < 0.001$ *vs* total of the 3 groups.

reduced placental transport of iron to the fetus [17].

Our present findings support that some neonates are indeed iron deficient at birth. This study is the first to reassess the iron status of neonates born iron deficient two weeks after birth. Most of the infants with iron deficiency at birth had a slight improvement in some of their iron parameters at two weeks. This could be due to the umbilical cord stripping or delayed cord clamping at birth, which significantly increases the hemoglobin-iron they received at delivery.

Four of the mothers of iron deficient newborns in our study had low biochemical iron markers, but none had iron deficiency anemia. It is unlikely that their neonates were born iron deficient on the basis of maternal iron deficiency alone. It is possible that iron transport across the placenta in these pregnancies was impaired, perhaps by hepcidin or another iron transport inhibitor. Iron is transported from maternal transferrin-bound iron by transferrin receptors on the placental microvillar membrane surface and subsequently to the fetal circulation by ferroportin [18,19]. Further investigation of transplacental iron transport in such pregnancies is needed.

Our study has several limitations. First, we followed the iron status of infants born with iron deficiency but did not compare these with a control group without iron deficiency. We also do not have the type of feeding that the neonates were on to compare breast milk *versus* formula fed infants. Second, our number of neonates born iron deficient was small, thus larger studies are needed to confirm or refute our findings. Third, the population of mothers and infants in this study are medically complicated and likely has cofounders that could affect the iron status and iron transfer including maternal medications, maternal or neonatal infection, and complicated deliveries. Fourth, though we investigated the iron status of the mothers we did not study the placentas, which could potentially be a location of abnormal iron transfer. Also, the association between maternal obesity and fetal iron deficiency requires further validation and precise mechanistic explanation. Future studies would need to compare the iron status of neonates born to obese women *versus* non-obese women, both in the term and the preterm populations.

Among SGA, IDM, and VLBW neonates, maternal obesity may be an additional risk factor for congenital biochemical iron deficiency. The iron status of the neonates was invariably improved two weeks later, even without medicinal iron, possibly from hemoglobin-iron received from delayed cord clamping. A prospective study that includes non-iron deficient controls would be useful to further delineate maternal risk factors for neonatal iron deficiency. Additional studies are also needed to define which neonates should be screened at birth for iron deficiency, and once iron deficiency at birth is identified, studies must determine how supplemental iron should be dosed and monitored. Furthermore, large randomized trials will be needed to assess whether an individual precision-medicine approach to diagnosing and treating neonatal iron deficiency has beneficial effects on neurodevelopmental outcomes.

Disclosure statement

The authors have no conflicts of interest to declare.

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