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Fetal Blood Ferritin and Cobalamin in Normal Pregnancy

Abstract

In a cross-sectional study of 75 singleton pregnancies at 16–38 weeks gestation serum cobalamin and ferritin concentrations were measured in fetal and maternal blood samples. Fetal serum cobalamin concentration did not change significantly with gestation but ferritin concentration increased. The median fetal serum concentrations of both ferritin and cobalamin were significantly higher than the respective values in the mother. The median fetal-maternal ratio for ferritin was 3.2 and for cobalamin 1.2. These findings demonstrate that from at least 16 weeks gestation, there is efficient iron storage in the fetus and transfer of cobalamin from the mother to the fetus against a concentration gradient.

Key Words
Cobalamin
Folate
Ferritin
Cordocentesis
Fetal blood

Introduction

Iron and cobalamin play a vital role in growth and development; iron is essential for erythropoiesis while cobalamin is necessary for synthesis of nucleotides and therefore cell growth and division. Iron is stored mainly in the form of ferritin [1]. The measurement of ferritin reliably reflects the total body iron stores in both adults and newborns [2]. Previous studies of umbilical cord blood samples obtained after delivery have demonstrated higher concentrations of ferritin and cobalamin in the fetal than maternal circulation (table 1) [3–18]. Furthermore, studies involving the injection of radioactively lavelled iron and cobalamin to women undergoing termination of pregnancy or prior to delivery and subsequent measurement of radioactivity in the placenta and fetal tissues have suggested active transport across the placenta [19–21].

The aim of this study was to establish reference ranges for fetal serum ferritin and cobalamin concentrations with gestation and to investigate their relative fetal-maternal ratios.

Patients and Methods

Fetal blood was obtained by cordocentesis [22] (n = 63) or at elective cesarean section for breech presentation or previous cesarean section (n = 12). In all cases, maternal venous blood was collected from the antecubital fossa immediately before fetal blood sampling.

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Table 1. Literature review of previous studies examining fetal serum concentration, maternal serum concentration and fetal-maternal ratio (F/M) for cobalamin (ng/l) and ferritin (μg/l)

	n	Gestation	Maternal	Fetal	F/M
Cobalamin, ng/l					
Baker et al. [3]	104	38–42	190	390	2.0
Zachau-Christiansen et al. [4]	365	38–42	240	373	1.6
Loria et al. [5]	80	38–42	198	430	2.2
Vaz Pinto et al. [6]	30	38–42	236	375	1.6
Giugliani et al. [7]	51	38–42	340	799	2.3
Present study[1]	72	16–38	250	288	1.2
Ferritin, μg/l					
Rios et al. [8]	20	38–42	18.0	117.0	6.5
Fenton et al. [9]	33	38–42	12.0	174.0	14.5
Hussain et al. [10]	51	38–42	58.0	183.2	3.2
Kelly et al. [11]	115	38–42	30.3	169.0	5.6
Bartlid and Moe. [12]	54	38–42	29.1	144.4	5.0
MacPhail et al. [13	103	38–42	21.3	71.1	3.4
Puolakka et al. [14]	47	38–42	59.0	262.0	4.4
Celada et al. [15]	64	38–42	13.8	81.0	6.1
Okuyama et al. [16]	35	38–42	9.6	160.5	16.7
Milman et al. [17]	85	38–42	21.0	128.0	6.1
Wong and Saha [18]	72	38–42	17.4	142.0	8.2
Present study[2]	68	16–38	10.6	79.6	7.5

[1] Median values.
[2] Changes with gestation; the values given are those at term.

The indications for cordocentesis were (1) prenatal diagnosis of blood disorders such as haemophilia A (n = 15); (2) fetal karyotyping for women of advanced maternal age who booked late or in whom amniocyte culture had failed or a low maternal serum α-fetoprotein level had suggested a significant risk of chromosomal defect (n = 10); (3) karyotyping for fetal malformations such as mild hydronephrosis, unilateral multicystic kidney or congenital diaphragmatic hernia (n = 33), and (4) fetal blood grouping in red blood cell isoimmunised pregnancies in which the fetal blood was subsequently found to be Coomb's test negative (n = 2). In 3 cases at 16–17 weeks, fetal blood was obtained before elective termination of pregnancy for social indications. In all cases, the fetal abdominal circumference at the time of cordocentesis was within our reference range for gestation and the fetal karyotype was normal. Furthermore, the fetuses did not have the blood disorder for which they were investigated. Kleihauer-Betke testing confirmed that all cordocentesis samples contained only fetal blood. The project was approved by the hospital's ethical committee and informed consent was obtained from all the mothers.

Fetal (0.5–1.0 ml) and maternal (5 ml) blood samples were collected into plain tubes, centrifuged for 10 min at 2,000 rpm and the serum collected and stored at −20°C. Radioimmunoassay kits were used for measurement of cobalamin (Becton-Dickinson, Oxford, UK) and ferritin (Biorad Laboratories, Hamel Hamsted, UK). Because sample volumes were insufficient for all assays, ferritin was measured in 68 samples and cobalamin in 72 samples. The intra- and interassay coefficients of variation were 6.4 and 8.4% for cobalamin and 4.7 and 6.9% for ferritin, respectively.

Statistical Analysis

Regression analysis was used to examine any relationship between measured variables and gestational age, and to examine relationships between fetal and maternal levels. Additionally, paired t test was applied

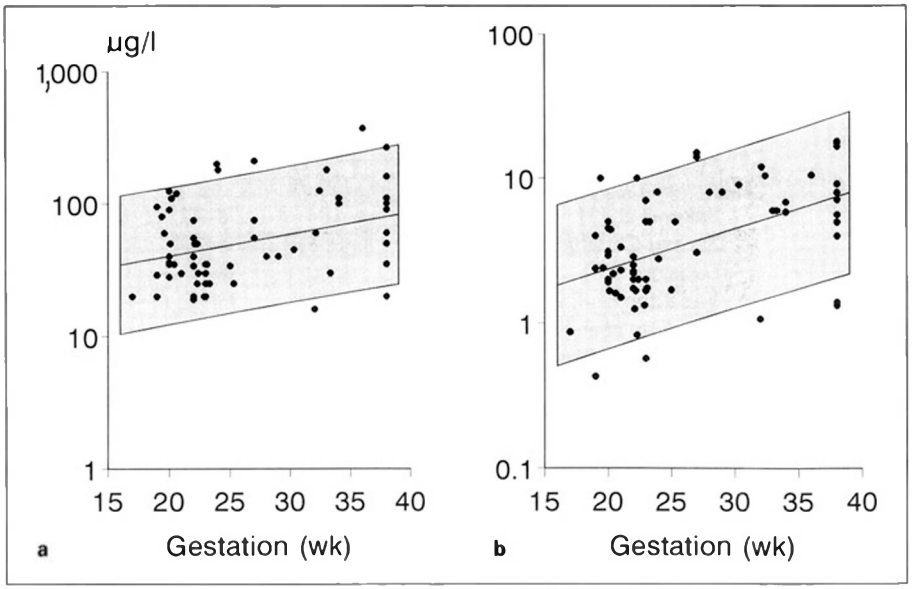

Fig. 1. Fetal and maternal serum ferritin concentration (**a**; µg/l), and fetal-maternal ferritin ratio (**b**) in 68 normal pregnancies plotted on the appropriate reference range with gestation (mean, 5th and 95th centile).

to examine significance of differences between fetal and maternal levels. For those measurements that were not normally distributed, the distribution was made Gaussian by logarithmic transformation. To produce the reference ranges with gestation in the original units the limits of the calculated reference range in logarithms were subjected to anti-logarithmic transformation.

Results

Fetal serum ferritin concentration increased significantly with gestation [fig. 1; $\log_{10}$ (ferritin) = 1.28 + 0.016 × gestation, SD = 0.305, r = 0.349, $p < 0.01$], maternal ferritin decreased [fig. 1; $\log_{10}$ (ferritin) = 1.46 – 0.011 × gestation, SD = 0.315, r = –0.245, $p < 0.05$], and fetal-maternal ferritin ratio increased [fig. 1; $\log_{10}$ (ratio) = –0.185 + 0.028 × gestation, SD = 0.326, r = 0.511, $p < 0.0001$]. In contrast, there were no significant changes with gestation in fetal serum cobalamin concentration (fig. 2; median 288 ng/l, r = 0.15), maternal serum cobalamin (fig. 2; median 250 ng/l, r = –0.16) or fetal-maternal cobalamin ratio (fig. 2, median 1.2, r = 0.21).

There were significant associations between fetal and maternal serum concentrations of both ferritin (r = 0.324, $p < 0.01$) and cobalamin (r = 0.522, $p < 0.0001$), and the fetal serum concentrations of both ferritin and cobalamin were significantly higher than respective values in maternal serum (ferritin: mean difference 50 µg/l, SEM 7.5, t = 6.78, $p < 0.0001$; cobalamin: mean difference 63 ng/l, SEM 17.3, t = 3.66, $p < 0.001$).

Discussion

The data of the present study demonstrate that in normal human pregnancy the fetal serum ferritin and cobalamin concentrations

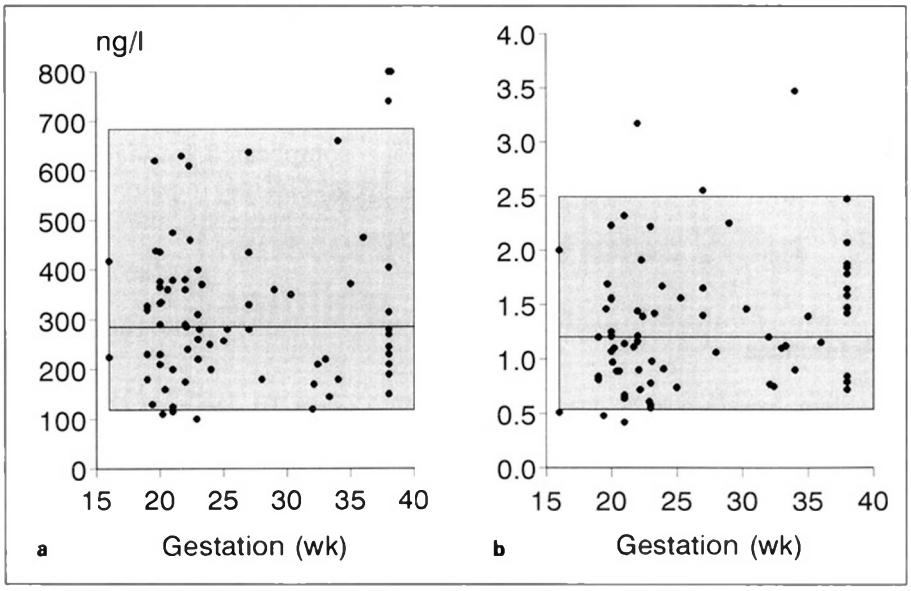

Fig. 2. Fetal and maternal serum cobalamin concentration (**a**; ng/l), and fetal-maternal cobalamin ratio (**b**) in 72 normal pregnancies. Neither fetal serum concentration nor maternal concentrations changed significantly with gestation.

are significantly associated with respective maternal serum concentrations and the levels in the fetal circulation are higher than the maternal. The fetal-maternal ratio of serum ferritin increases with gestation and is much higher than that of cobalamin which does not change significantly between 16 and 38 weeks. The fetal-maternal ratios throughout the gestational range examined were similar to those reported in studies of blood obtained after delivery at term and demonstrate effective placental transfer and efficient storage of iron in the fetus from at least 16 weeks gestation.

The mean fetal-maternal ratio for ferritin increased from 1.6 at 16 weeks gestation to 7.5 at 38 weeks. This increase in the mean fetal ferritin concentration with gestation could be explained by the increase in placental iron transfer. Indeed, Fletcher and Suter [19], examined the placental transfer of radiolabelled iron and reported that the average daily transfer increased from approximately 0.4 mg/day at 16 weeks to 4.7 mg/day at 30 weeks. Effective accumulation of iron in the fetus in the form of ferritin is presumably aimed at fulfilling increasing requirements for expansion of the fetal red cell mass [23]. Additionally, high fetal iron stores are necessary for the postnatal period, because iron concentration of breast milk is low [24]. The significant association between the fetal and maternal concentration of ferritin suggests lower fetal iron stores in anemic mothers.

The relatively low fetal-maternal ratio of cobalamin suggests that although there is some degree of active transport across the placenta it is not as efficient as the transport of iron. Moreover the association between the fetal and maternal concentration of cobalamin suggests that there is a preferential transport of cobalamin across the placenta that is

dependent on the levels in the mother. Indeed, in women with marginal deficiency in cobalamin, the newborns often have subnormal concentrations and may develop megaloblastic anemia, especially if breast fed [25, 26].

This study has established reference ranges for fetal serum concentrations of ferritin and cobalamin with gestation, and provides the background for the assessment of pregnancies complicated by maternal malnutrition/malabsorption, impaired placental perfusion and fetal hemolytic anemias.

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