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FETAL AND NEONATAL MEDICINE

Serum ferritin and cobalamin in growth retarded fetuses

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ABSTRACT

Objective To examine fetal and maternal serum cobalamin and ferritin concentrations in pregnancies complicated by fetal growth retardation.

Setting Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London.

Design Cross sectional study.

Subjects Fetal blood samples obtained by cordocentesis from 20 growth retarded fetuses at 26 to 36 weeks of gestation. Maternal venous blood was also collected and serum ferritin and cobalamin concentrations were measured by radio-immunoassay in the fetal and maternal samples.

Results In the growth retarded group, the mean fetal serum concentration of cobalamin was higher than the normal mean for gestation ($t = 3{\cdot}27$, $P < 0{\cdot}01$), and this increase was significantly associated with fetal acidaemia ($r = -0{\cdot}686$, $P < 0{\cdot}001$) and erythroblastosis ($r = 0{\cdot}731$, $P < 0{\cdot}001$). In contrast, the fetal to maternal ferritin ratio was significantly reduced; there was a nonsignificant decrease in fetal serum and an increase in maternal serum ferritin concentration. There was an association between fetal serum ferritin concentration and erythrocyte count ($r = -0{\cdot}612$, $P < 0{\cdot}01$).

Conclusions In placental insufficiency, as in postnatal starvation and Kwashiorkor syndrome, uptake and storage of cobalamin by the fetal liver may be impaired. The decrease in fetal to maternal ratio of ferritin could be the consequence of impaired placental perfusion.

Intrauterine growth retardation (IUGR) is associated with fetal tissue hypoxia and a compensatory increase in erythropoiesis (Snijders *et al.* 1993). Consequently, the need for haematinics is increased and yet their availability may be restricted by the impaired placental perfusion and oxygenation. The aim of this study was to examine fetal and maternal serum cobalamin and ferritin concentrations in pregnancies complicated by fetal growth retardation.

Subjects and methods

Serum cobalamin and ferritin concentrations were measured in maternal and fetal blood obtained at 26 to 36 (mean = 31) weeks of gestation from 20 pregnancies complicated by IUGR, presumed to be due to uteroplacental insufficiency.

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Between 1988 and 1990, umbilical venous blood samples were obtained by cordocentesis (Nicolaides *et al.* 1986) from 256 women that were referred to our centre for further assessment of fetal growth retardation. A computer search of our data base was made to identify the cases fulfilling the following criteria: 1. fetal abdominal circumference and subsequently birthweight below the 5th centile of the appropriate reference range for gestation (Yudkin *et al.* 1987); 2. normal fetal anatomy and karyotype; 3. presence of an early diastolic notch in the waveform from at least one of the uterine arteries, and/or absence of end diastolic frequencies in the waveform from the umbilical arteries; 4. fetal blood pH, haemoglobin concentration, erythrocyte count and erythroblast count were measured; and 5. sufficient fetal and maternal serum for measurement of cobalamin and ferritin. The search identified 20 women who fulfilled these criteria. Cordocentesis for the assessment of IUGR was approved by the hospital ethical committee, and informed consent was obtained from all the mothers.

Maternal venous blood was collected from the antecubital fossa immediately before cordocentesis. The fetal and maternal blood samples were collected into plain tubes, centrifuged for 10 min at 2000 rpm, and the serum was collected and stored at −20 °C. Radio-immunoassay kits were used for measurement of cobalamin (Beckton-Dickinson, Oxford, UK) and ferritin (Biorad Laboratories, Hemel Hempstead, UK). The intra- and inter-assay coefficients of variation were 6·4% and 8·4% for cobalamin and 4·7% and 6·9% for ferritin, respectively.

Statistical analysis

In normal pregnancy, the various parameters that were measured change with gestation. Therefore, values obtained from the pregnancies with IUGR were expressed as the number of standard deviations by which the individual values differed from the appropriate normal mean for gestation (delta values and standard deviation) (Nicolaides *et al.* 1989a, b; Abbas *et al.* 1993). Student's *t* test was applied to determine if the mean values in the IUGR group were significantly different from the appropriate normal mean for gestation.

Results

The findings in the 20 IUGR pregnancies are compared with the appropriate normal mean for gestation in Table 1. The mean fetal serum cobalamin concentration was significantly increased, while the maternal was not significantly different from the appropriate normal mean for gestation; the mean fetal to maternal ratio of cobalamin was significantly increased (Table 1, Fig. 1). In contrast, the mean maternal serum ferritin was significantly increased, and there was a tendency for fetal serum concentration to be decreased; the mean fetal to maternal ratio of ferritin was significantly reduced (Table 1, Fig. 2).

The mean erythroblast count was significantly increased and the mean umbilical venous blood pH, erythrocyte count and haemoglobin concentration were significantly reduced in the IUGR group compared with normal pregnancy (Table 1, Fig. 3). Fetal serum cobalamin concentration was significantly related to fetal blood pH and erythroblast count but not gestational age or fetal erythrocyte count (Table 2, Fig. 4). In contrast, fetal serum ferritin concentration was significantly related to gestational age and fetal erythrocyte count but not to fetal blood pH or erythroblast count (Table 2, Fig. 5).

Table 1. Findings in 20 pregnancies with growth retard fetuses compared with the appropriate normal mean for gestation (MD = mean difference in SD; SEM = standard error of the mean).

	MD	SEM	*t*	*P*
Fetal serum cobalamin	0·9	0·28	3·27	< 0·01
Maternal serum cobalamin	0·1	0·21	0·25	NS
Fetal/maternal cobalamin	1·0	0·28	3·58	< 0·01
Fetal serum ferritin	−0·8	0·44	1·77	NS
Maternal serum ferritin	0·6	0·26	2·21	< 0·05
Fetal/maternal ferritin	−1·4	0·43	3·22	< 0·01
Umbilical venous blood pH	−1·9	0·41	4·77	< 0·0001
Fetal erythroblast count	3·4	0·38	8·79	< 0·0001
Fetal erythrocyte count	−0·8	0·35	2·21	< 0·05
Fetal haemoglobin	0·3	0·35	0·33	NS

Discussion

In normal pregnancy, cobalamin and ferritin are actively transported against a concentration gradient from the mother to the fetus; the median fetal to maternal ratio for cobalamin is 1.2 and for ferritin the ratio is 3.2 (Abbas *et al.* 1993). In growth retardation with evidence of uteroplacental insufficiency, the fetal to maternal ratio of cobalamin is increased and that of ferritin is decreased.

One possible explanation for the increased fetal serum cobalamin concentration is increased transport across

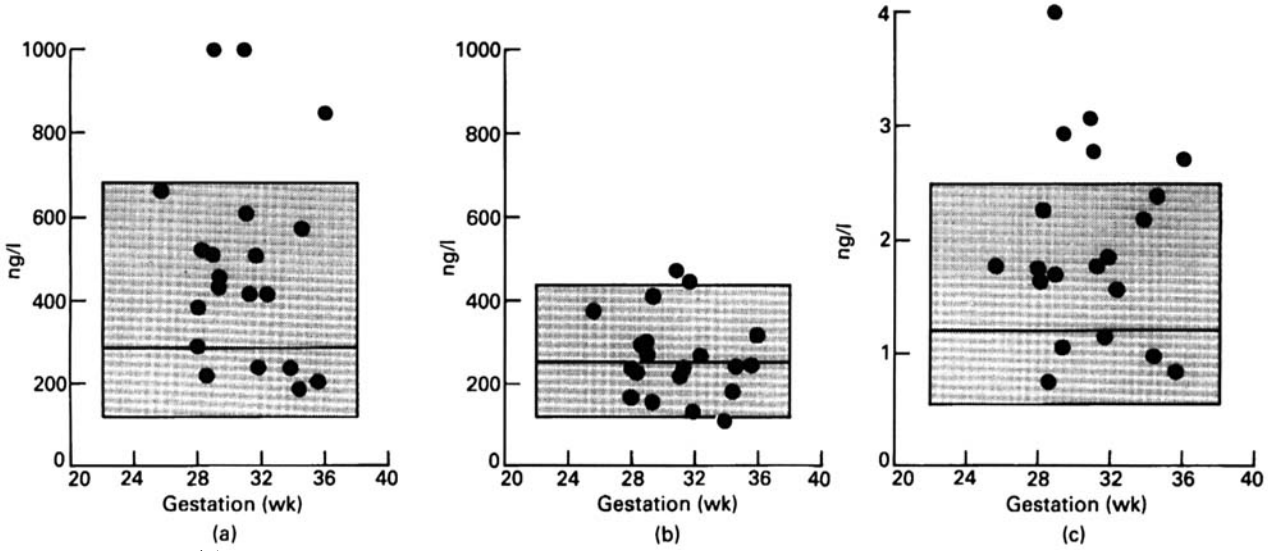

Fig. 1. Fetal (a) and maternal (b) serum cobalamin concentration and fetal to maternal ratio (c) in 20 growth retarded fetuses plotted on the appropriate reference range with gestation (mean, 5th and 95th centile).

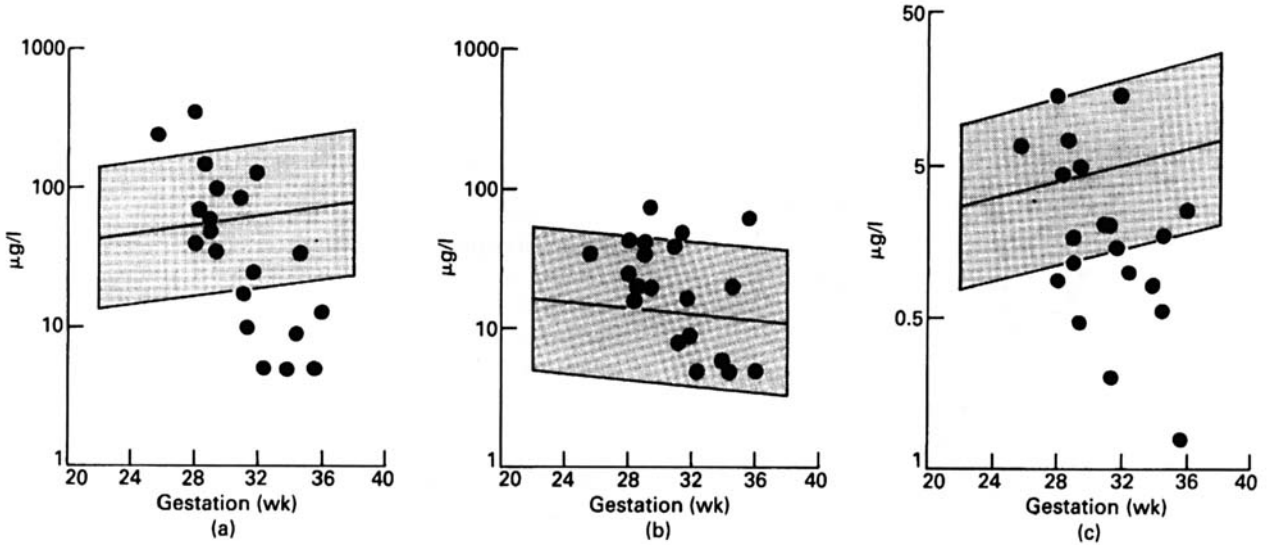

Fig. 2. Fetal (a) and maternal (b) serum ferritin concentration and fetal to maternal ratio (c) in 20 growth retarded fetuses plotted on the appropriate reference range with gestation (mean, 5th and 95th centile).

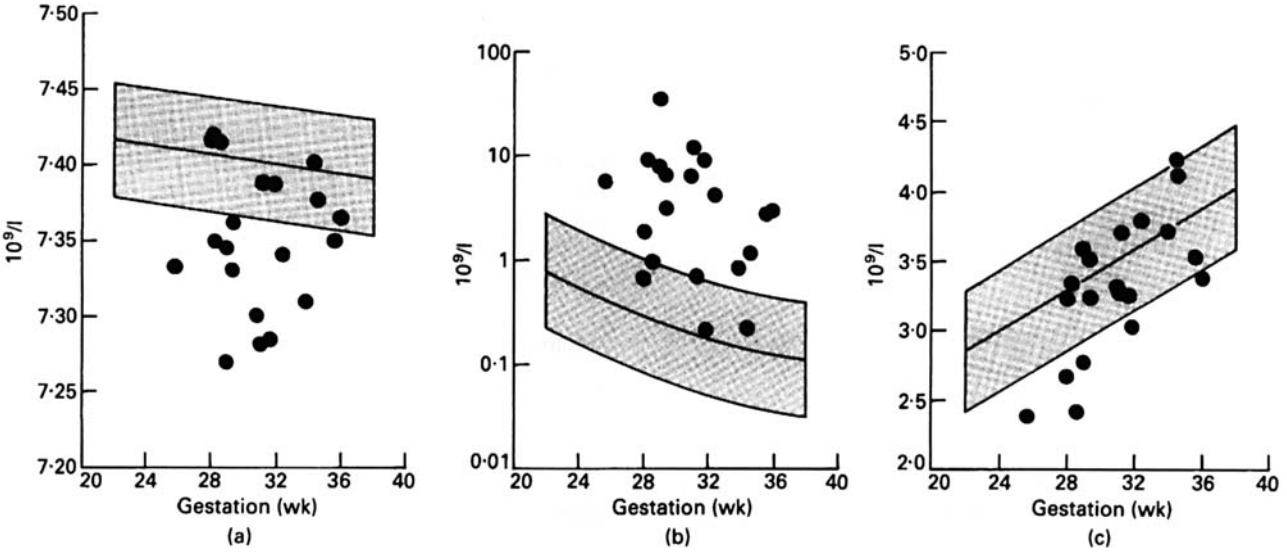

Fig. 3. Umbilical venous blood pH (a), erythroblast count (b) and erythrocyte count (c) in 20 growth retarded fetuses plotted on the appropriate reference range with gestation (mean, 5th and 95th centile).

Table 2. Correlation coefficients for the associations of fetal serum cobalamin and ferritin concentrations and fetal to maternal ratios with umbilical venous blood pH (UV pH), red blood cell (RBC) count, nucleated red blood cell (NRBC) count and gestational age (GA).

	UV pH	NRBC	RBC	GA
Fetal serum cobalamin	−0·69***	0·73***	0·09	−0·22
Fetal/maternal cobalamin	−0·55**	0·50*	0·27	−0·12
Fetal serum ferritin	0·04	−0·11	−0·61**	−0·79**
Fetal/maternal ferritin	0·06	−0·17	−0·60**	−0·57**
Gestational age	0·12	−0·09	0·47*	—
RBC count	−0·07	0·09	—	—
NRBC count	−0·86***	—	—	—

* $P < 0{\cdot}05$; ** $P < 0{\cdot}001$; *** $P < 0{\cdot}0001$.

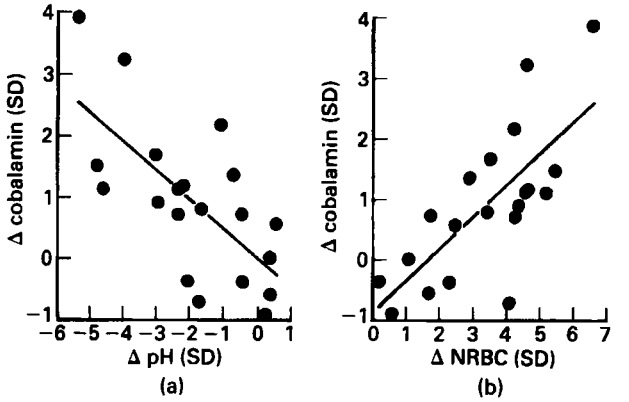

Fig. 4. Associations between fetal serum cobalamin concentration and umbilical venous blood pH (a) and erythroblast count (b). Delta values are the differences in SD from the appropriate normal mean for gestation.

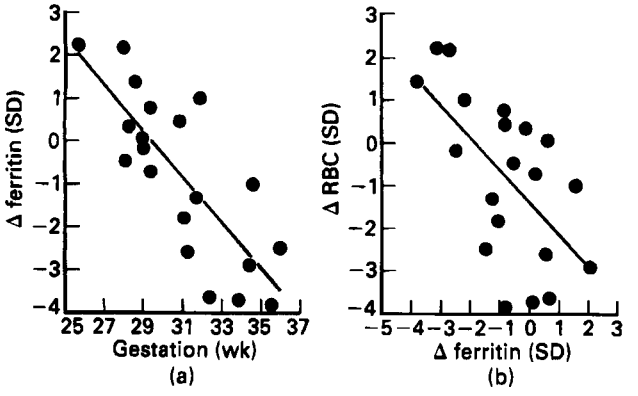

Fig. 5. Associations between fetal serum ferritin concentration and gestational age (a) and fetal erythrocyte count (b). Delta values are the differences in SD from the appropriate normal mean for gestation.

the placenta. However, since placental perfusion and oxygenation are impaired and maternal serum cobalamin concentration is not different from normal, it is unlikely that supply to the fetus is actually increased. An alternative and more likely explanation for increased fetal to maternal serum cobalamin ratio is decreased consumption by the fetus, presumably as a result of decreased metabolic rate in the face of reduced oxygenation and supply of essential nutrients (Economides *et al.* 1989a, b, c). Additionally, in IUGR, as in postnatal starvation and Kwashiorkor syndrome, uptake and storage of cobalamin by the liver may be impaired. Postnatally, high serum concentrations of cobalamin have been reported in various types of liver disease and have been related to the degree of hepatocellular damage (Macdougall & Ross 1960). In growth retarded fetuses there is serological evidence of liver dysfunction with increased concentrations of gamma-glutamyl transferase and lactic dehydrogenase (Cox *et al.* 1988).

The fetal serum cobalamin concentration was significantly associated with the degree of erythroblastosis and acidaemia. It has been suggested that erythroblastosis may be the consequence of erythropoietin-mediated stimulation of erythropoiesis (Snijders *et al.* 1993). However, the high cobalamin levels and the reduced erythrocyte count indicate that erythropoiesis is impaired. Rather than resulting from increased erythropoiesis, erythroblastosis may result from acidosis-mediated impairment of medullary erythropoiesis with premature or uncontrolled release of nucleated red cells.

Unlike cobalamin, the alterations in fetal and maternal serum ferritin concentrations in IUGR pregnancies were related to gestational age and fetal erythrocyte count rather than the degree of fetal acidaemia. Thus at early gestations fetal serum ferritin concentrations were normal and erythrocyte counts were reduced, whereas after 30 weeks ferritin was reduced and the erythrocyte count was normal. It could be postulated that in IUGR maturation of the mechanisms for compensatory increase in effective erythropoiesis occurs after 30 weeks. Although impaired placental perfusion and oxygenation presumably reduces active transport of ferritin to the fetus throughout pregnancy, reduced fetal serum levels are seen only when utilisation is increased.

In IUGR due to placental insufficiency and fetal acidaemia, there is fetal erythroblastosis and increased serum cobalamin concentration. These findings may be the consequence of acidosis-mediated impairment of medullary and hepatic function, respectively. There is an inverse correlation between fetal serum ferritin concentration and erythrocyte count so that in late pregnancy when the erythrocyte count was normal serum ferritin was reduced. This may indicate that in IUGR maturation of the mechanisms for compensatory increase in effective erythropoiesis occurs after 30 weeks.

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