SUGGESTION OF AN ACTIVE TRANSPORT OF IRON TO THE FETUS IN HUMAN PREGNANCY AND ITS DEPENDENCE ON MATERNAL SERUM IRON LEVELS

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SUMMARY

The present findings suggest the possible involvement of an active mechanism for transport of iron to the fetus. In all the 19 subjects studied, the cord serum iron levels tended to be higher (129.2 ± 56.8 ug/100ml) than the maternal serum iron levels (74.0 ± 35.9 ug/100ml) at parturition even in maternal iron deficiency. The significant difference ($P < 0.001$) between cord serum iron levels and the maternal iron levels shows that an active transport mechanism working against a gradient in favour of the fetus exists. The availability of iron to the fetus appears to be dependent on maternal serum iron levels but not on maternal iron stores. This finding serves to stress the importance of iron supplements in pregnancy. A hypothetical model for iron transfer from maternal circulation to fetal circulation is described.

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INTRODUCTION

Iron requirements increase progressively during pregnancy. Studies (Arey, 1946 and Osgood, 1955) have shown that at various stages of pregnancy both the iron content and weight of the fetus increase proportionately with age. The total amount of iron assimilated by the fetus is approximately 300 mg in human pregnancy, by a process of placental transfer thought to involve active transport (Pribilla *et al.*, 1958). The rate of transfer of iron across the thin walled fetal villi from maternal circulation is rapid (Pommerenke *et al.*, 1942). The exact biochemical processes involved in the transfer are yet to be determined. We report our random observation on pregnant mothers at the end of pregnancy. Our findings that the transport of iron

across the placenta occurs against a gradient suggest that it is probably an active process. Further it appears that the amount of iron transported is dependent on the maternal serum iron levels. A hypothetical model for the active transport of iron from the maternal to fetal circulation via the placenta is proposed.

MATERIALS AND METHODS

Using disposable syringes 20 ml blood was collected from pregnant subjects at the onset of labour. Subjects were mothers admitted to the labour wards at the Maternity Hospital, Kuala Lumpur, during the month of May - June 1980. 15.0 ml was drained into a clean iron-free sterile bottle and allowed to clot at room temperature for about an hour, after which serum was separated and stored frozen. 5.0 ml was transferred into disposable EDTA bottles and mixed gently for about two minutes to prevent clotting. Haemoglobin (Hb) and other blood parameters including blood urea were done on the same day. 20 ml cord blood was collected soon after delivery, of which about 15.0 ml was allowed to clot in iron free sterile universal bottle and 5.0 ml was treated similarly as in the case of the maternal blood.

The parameters studied for the maternal serum include folate, B_{12}, serum iron (SI), total iron binding capacity (TIBC) and serum ferritin, while for the EDTA blood the tests include urea, full blood counts, red cell folate and haemoglobin analysis.

For cord serum all the parameters mentioned under maternal serum was studied along with serum bilirubin. For the EDTA cord blood all the parameters mentioned under EDTA maternal blood were studied except that urea was not done.

SI and TIBC were measured using the method of Jung and Parikh (1970), serum ferritin (SF) estimation was performed using Radioimmuno-assay kits obtained from Diagnostic Products Corporation, Los Angeles, California, U.S.A. Haemoglobin (Hb) and other blood parameters were performed using standard methods.

RESULTS

The results of Hb, reticulocyte counts, SI and TIBC and SF are presented. The results of all other parameters (viz Folate, B_{12}, Urea, bilirubin, Hb analysis, etc) will be published elsewhere.

TABLE I
VALUES FOR SERUM IRON, TOTAL IRON BINDING CAPACITY, PERCENT SERUM IRON SATURATION, HAEMOGLOBIN AND RETICULOCYTE COUNTS IN BLOOD AT LABOUR AND CORD BLOOD AT PARTURITION

GROUP		Sr. Iron -ug/100 ml	Sr. TIBC -ug/100 ml	$\frac{\text{Sr. Iron}}{\text{TIBC}} \times 100$	HAEMOGLOBIN g%	RETIC COUNT
MATERNAL BLOOD	Range	15.4 to 142.8	107.7 to 571.4	5.0 to 60.0	6.5 to 13.6	0.2 to 4.0
	Mean	74.0	310.6	26.4	11.6	2.1
	SD(σ_{n-1})	35.9	108.6	14.5	1.3	0.91
	n	19	19	19	30	30
CORD BLOOD	Range	61.5 to 285.7	92.3 to 485.7	20.8 to 90.9	11.7 to 16.4	2.0 to 10.0
	Mean	129.2	282.0	48.3	14.3	5.4
	SD(σ_{n-1})	56.8	98.8	19.2	1.24	2.11
	n	19	19	19	30	30
	P	(P < 0.001)	(P < 0.5)	(P < 0.001)	(P < 0.001)	(P < 0.001)

The maternal SI values ranged between 15.4 to 142.8 ug/100 ml with a mean of 74.0 ± 35.9 while the cord SI levels ranged between 61.5 to 285.7 ug/100 ml with a mean of 129.2 ± 56.8 (Table I). The difference between the maternal and cord SI levels was highly significant ($P < 0.001$).

The values obtained for percent saturation of transferrin for maternal serum ranged between 5.6 to 60.0% with a mean of 26.4 ± 14.5. The corresponding values obtained for cord serum level were much higher ranging between 20.8 to 90.9% with a mean of 48.3 ± 19.2%. The difference between the maternal and cord serum values was highly significant ($P < 0.001$). The maternal SF level was 51.6 ± 44.4 ng/ml which was significantly different ($P < 0.025$) from the cord SF levels, which is 166.0 ± 91.8 ng/ml. (Table II).

The cord SI tends to be much higher than maternal SI even when the maternal blood is iron deficient as suggested by low transferrin saturation. Fig. I shows the maternal and cord SI and TIBC levels in 19 subjects studied. In one subject the maternal SI level was as low as 15.4 ug/100 ml whereas the corresponding cord SI level was 76.9 ug/100ml. Similarly in another subject the maternal SI was 30.8 ug/100 ml while the corresponding cord SI level was 123.0 ug/100 ml. Normal valves for SI is 95 to 115 ug/100 ml and for TIBC 290-330 ug/100 ml by the present method (Jung and Parikh, 1970).

The Hb content of the cord blood was significantly higher (14.3 ± 1.2 g/dl) than that of

TABLE II
SERUM FERRITIN LEVELS IN HEALTHY, NON-PREGNANT WOMEN, AT PARTURITION AND IN CORD BLOOD — NG/ML.

	NORMAL	MB	CB
Range	17 - 425	16 - 170	64 - 320
Mean	71·1	51·6	166·0
σ_{n-1}	80·5	44·4	91·8
n	26	10	10
	(P<0·5)	(P<0·025)	

NORMAL : Non-pregnant healthy women.
MB : Maternal blood collected at parturition.
CB : Cord blood collected soon after delivery.

maternal blood (11.6 ± 1.3 g/dl) and none of the babies borne by iron deficient mothers had any haemotological changes of iron deficiency.

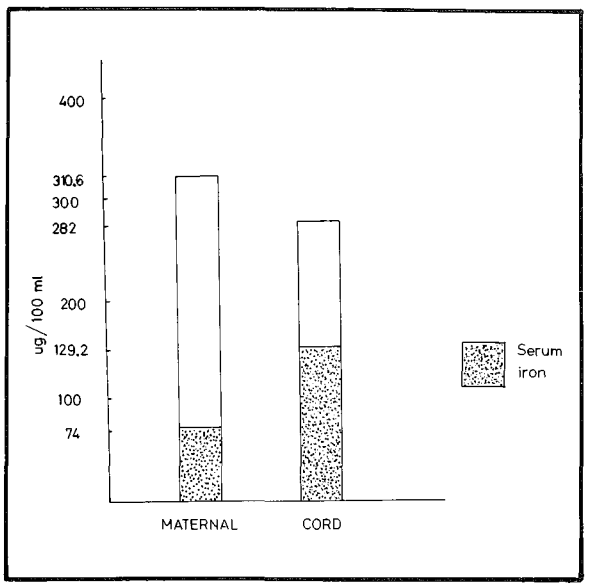

Fig. 1 Maternal and cord serum iron and total iron binding capacity.

DISCUSSION

Morgan (1974) suggested that the major source of iron for the fetus is that bound to maternal transferrin. It was earlier suggested that human trophoblast expressed specific receptor sites that bind maternal transferrin (Fletcher and Suter, 1969). Galbraith *et al.* (1980) have shown in immunohistologic studies of the human placenta that abundant quantities of transferrin are indeed present on the apical aspect of trophoblast in both mature and immature placentae (Faulk and Johnson, 1977 and Johnson and Faulk, 1978). Employing immunoelectron-microscopic techniques King (1976) found transferrin localized on the microvilli of the trophoblast. But the origin of such trophoblast transferrin whether maternal or fetal is yet to be established. In vitro studies of Galbraith *et al* (1980) demonstrated the presence of specific binding sites for maternal transferrin on the syncytiotrophoblastic cell membrane. Galbraith *et al* . (1980) have suggested that since maternal serum iron required by the fetus for growth and development must be obtained in competition with maternal erythropoietic centres, placental transferrin receptors would thus provide a mechanism whereby iron could be diverted to the trophoblast. It is widely accepted that maternal transferrin delivers iron to the placental villi and fetal Transferrin conveys iron from placenta to fetal tissues. Transferrin itself has not been observed to traverse the placenta in significant amounts (Gitlin *et al* 1964).

The mechanism of this active transport of iron can only be speculated upon at the present moment. A possible transport mechanism may be based on the findings of Galbraith *et al.* (1980). An iron-transferrin complex on having been first bound to transferrin receptor sites on the placental trophoblast get internalised, followed by dissociation of the iron intracellularly possibly due to a change in pH. On dissociation from transferrin the irons ions then may traverse the villus membrane coupled to a carrier protein (Fig. 2). At the fetal end of the membrane the iron-carrier complex would dissociate. This mechanism presumably requires energy which is made available by the enzymatic systems in the villus membrane. The released iron ions could then bind to the fetal transferrin and finally enter the fetal circulation. The carrier molecule on having been released may then bind more iron ions and repeat the process. The possible involvement of placental hormones in the iron transfer mechanism cannot be excluded.

It is reasonable to speculate an energy requiring process here since transport of iron occurs against a gradient. But the implication that the placental iron transport mechanism ensures adequate iron supply to meet fetal requirements even in the presence of maternal iron deficiency is of clinical

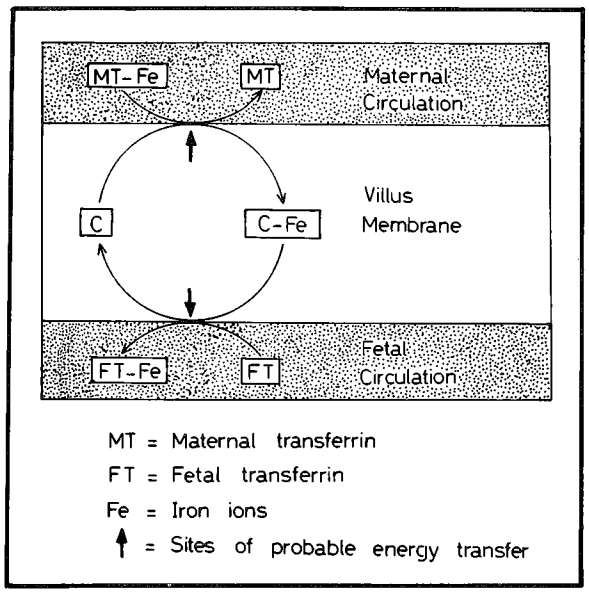

Fig. 2 Proposed model for the active transport of iron across the placental villus membrane.

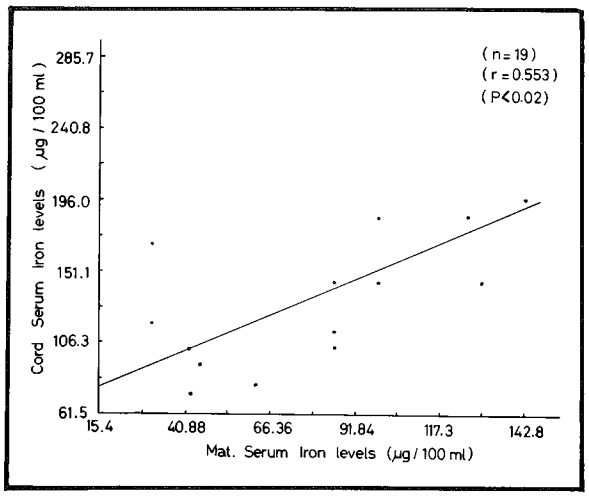

Fig. 3 Correlation between maternal and cord serum iron levels.

importance. It underscores the need to ensure that pregnant mothers are given iron supplements throughout pregnancy.

Fig. 3 shows that a positive correlation exists between the maternal and cord serum iron levels. The correlation ($r = 0.553$) is significant ($P < 0.02$) suggesting that the fetus takes iron from the mother in amounts proportional to the iron available in the maternal circulation. In other words if the mother is iron deficient, the fetal level even though higher than the mother's will however be still lower than in the case of a fetus whose mother has a higher level of serum iron. Thus the availability of iron to the fetus is dependant on maternal iron in the circulation.

There is no significant correlation ($r = 0.0333$) between the maternal and cord serum ferritin levels. This goes to show that the availability of iron to the fetus is not directly dependant on the maternal stores.

In conclusion we have verified what others have shown before (Rios *et al.*, 1975 and Singla *et al.* 1978) that the transport of iron across the placenta occurs against a gradient in favour of the fetus suggesting that it is an active mechanism. This is of clinical significance because it means that this mechanism ensures adequate supply of iron for the normal development of the fetus except probably in rare cases of severe maternal iron deficiency when the fetus may receive subnormal amounts of iron. Mothers must be protected from developing iron deficiency by iron supplements given throughout pregnancy.

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