



Review

Effect of maternal iron status on placenta, fetus and newborn

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Maternal anemia (hypoferriemia) results in increased pre-term and low birth weight deliveries and higher rate of stillbirths. There are irreversible structural alterations in placenta. The transfer of iron to fetus is reduced in spite of gradient in relation to severity of maternal hypoferriemia. The fetal hepatic and brain iron contents were reduced. The brain iron reduction was irreversible on rehabilitation and was associated with irreversible neurotransmitter and their receptor alterations.

Key words: Maternal anemia, stillbirths, placenta.

INTRODUCTION

The outcome of severe pregnancy anemia has been associated with increased incidence of premature births, fetal distress, increased perinatal mortality, and a higher frequency of maternal deaths Nair et al., (1970). In the case of moderate to severe anemia, breathlessness, edema, congestive heart failure and even cerebral anoxia have been observed. 200 anemic pregnant women observed in the University Hospital, Institute of Medical Sciences, Varanasi, showed: reduced gestation; higher incidence of premature labor, preterm, low birth weight and still birth deliveries. These newborns had low apgar score and there were increased number of neonatal deaths. Maternal mortality was 13 out of 200 anemic as compared to 1 in 50 controls. The anemic mothers do not tolerate blood loss during childbirth; as little as 150 ml can be fatal. Normally, a healthy mother during childbirth may tolerate a blood loss of up to 1,000 ml Agarwal (1984).

Current knowledge in the development of iron deficiency

Iron deficiency is an end result of a long period of negative iron balance mainly due to poor dietary availability, rapid growth and blood loss. The pathological stages are:

- a) Pre-latent deficiency: hepatic (Hepatocytes and macrophages), spleen and bone marrow show reduced iron stores (reduced bone marrow iron and serum ferritin).
- b) Latent deficiency: as the bone marrow iron stores become absent, plasma iron decreases and bone marrow receives little iron for hemoglobin regeneration (bone marrow iron absent, serum ferritin < 12ug/L, transferrin saturation < 16% and free erythrocyte protoporphyrin is increased), however, hemoglobin concentration remains

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normal.

c) Iron deficiency anemia: this is a very late stage of iron deficiency with progressive fall in hemoglobin and mean corpuscular volume.

Prevalence of nutritional anemia in pregnant women (India)

National studies by the Indian Council of Medical Research (ICMR) Indian Council Medical Research (1989), covering 11 states, reported in 1989, prevalence of anemia by estimating hemoglobin using cyanmethemoglobin method in pregnant rural women as 87.6%, hemoglobin being < 10.9 g/dl. These anemic women were given different doses of iron 60, 120 and 180 mg with 500 ug folic acid daily for 90 days in 6 states; 62% in spite of iron-folate therapy for 3 months, continued to remain anemic Indian Council Medical Research (1992). Thus indicating that short-term treatment as recommended in the National anemia control programme may not be sufficient to control anemia in pregnancy. However, it was observed that birth weight improved and low birth weight deliveries were significantly reduced Agarwal et al., (1991). The administration of higher dose 335 mg of ferrous sulphate and 500 ug of folic acid for 14 weeks as daily dose was found to be effective in control of pregnancy anemia Gomber et al., (2002).

National family Health Survey 1998-99 (NFHS-2) using hemocue method reported prevalence of anemia as 49.7% in pregnant women; 56.4% in breastfeeding non-pregnant women and 50.4% among non-pregnant non-breastfeeding women. Hemocue method estimates higher levels of hemoglobin thus difficult to compare with the other National studies. In 2005, NFHS-3 demonstrated increase in prevalence of anemia, suggesting marginal rise in anemia nation wide NFHS-2 &- 3 India 1998-99-& 2005 (2000).

Nutrition Foundation of India in 2002 to 2003 studied prevalence of anemia in pregnancy and lactation in 7 states (Assam, Himachal Pradesh, Haryana, Kerala, Madhya Pradesh, Orissa, Tamil Nadu). The prevalence of pregnancy anemia was 86.1% (Hb < 7.0 g/dl in 9.5%), and in lactation up to 3 months was 81.7% (Hb < 7.0 g/dl in 7.3%). The interstate differences responsible for differences in prevalence of anemia were particularly related to fertility, women education, nutrition status and occupation, availability of antenatal services and iron folate tablets as possible factors (Agarwal et al., 2006; Sharma and Agarwal 2007).

The Indian Council of Medical Research (ICMR) in 1999 to 2000 conducted District Nutrition Survey in 11 states covering 19 districts pregnancy anemia prevalence was 84.6% (Hb < 7.0 g/dl in 9.9%). The study also found 90% adolescent girls with anemia in these districts Teoteja and Singh (2001). The prevalence as well as severity of anemia during pregnancy and lactation is grave. This is the period when brain cells grow and

neurotransmitters develop, iron is essential for it.

Iron status in pregnancy

This includes:

1. Fetal growth depends, to a large extent, on the availability of iron from the mother.
2. Normal non-pregnant woman needs iron 1.3 mg/day.
3. Total pregnancy need of iron is 1000 mg or more. Absorption rate of 6 mg/day in the last 2 trimesters.
4. 350 mg of iron is lost to the fetus and placenta.
5. 250 mg is lost in blood at delivery. 450 mg is needed to increase the RBC mass. Lastly around 240 mg is lost as basal losses.
6. In cesarean delivery blood loss is almost twice (500 ml). In moderate and severe anemia mother will die if blood loss is >150 ml.
7. During lactation, iron loss is 0.3 mg/day.

Placenta in iron deficiency

Iron transport

Normally 'placental iron transfer' to fetus becomes 3 to 4 times during 20 to 37 weeks of gestation. The placenta traps maternal transferrin removes iron and actively transports it across to the fetus where it becomes bound to fetal transferrin and is distributed to the liver, spleen and other fetal hemopoietic tissues, maintaining higher levels of fetal iron as compared to the mother. Placenta plays an important role in maintaining iron transport to fetus. This process of iron transport is purely a placental function over which mother and fetus has no control, as placenta continues to trap iron even when fetus is removed in animals Fletcher and Suter (1969). The placental trophoblastic membrane appears to act as an effective barrier against the further transport of iron to the fetus. In spite of this efficient protective mechanism, the placental iron content reduces significantly in maternal hypoferriemia (Agarwal 1984; Singla et al., 1978; Singla et al., 1979; Agarwal et al., 1983). This was an important finding as earlier studies on Swedish and American women had shown that cord iron does not change in iron deficient pregnant women (Vahlquist, 1941; Rios et al., 1975). However, recent studies have confirmed that the maternal anemia affects the placento-fetal unit (Emamghorashi and Heidari 2004; Paiva et al., 2007; Kumar et al., 2008; Lee et al., 2006).

Morphometry and biochemical alterations

Beischer et al (1970) analysed data (from Australia, India, NewGuinea, Singaore and Thailand) and demonstrated that in all the studies, placental weight in maternal

anemia was higher than the control. This increase in placental weight was higher with increasing parity. The placental hypertrophy did not correspond to fetal size and had no correlation with maternal serum protein. Ratten and Beischer (1972) confirmed that the placental weight exceeds the 90th centile in 20% of patients with hemoglobin < 8.2 g/dl and in 13.2% of those with hemoglobin 8.2 to 9.1 g/dl. The placental hypertrophy is postulated to be due to hypoxia, which is supported by evidence of similar phenomenon at higher altitudes. In our studies, maternal anemia was associated with low maternal serum albumin. Both deficiencies were associated with reduced weight and volume of placenta. Placentae in maternal anemia showed reduced number of cotyledons and increase in incidence of ill-defined cotyledons and eccentric attachment of cord. There was increased shrinkage in formalin in pregnancy anemia (Sen and Agarwal 1976; Khanna et al., 1979; Agarwal et al., 1981; Marwah et al., 1979). This reduction in placental weight was due to reduced DNA (cell number), however cell size was increased (weight/DNA). In maternal hemoglobin RNA, content per cell remained constant (Agarwal (1991)). Placental succinic dehydrogenase activity was decreased, total nicotinamide adenine dinucleotide phosphate (NADP) - dependent isocitrate dehydrogenase (ICDH) was more than NAD + dependant ICDH in severe maternal hypoferricemia; suggesting impaired citric acid cycle (Agarwal (1984)).

Histology

There was decreased villous vascularity leading to fibrosis with increased endarteritis obliterans reflecting response to hypoxia. There was progressive decrease of surface area and volume of villi per unit volume of blood vessel in relation to degree of anemia; suggesting maturational arrest (Agarwal 1984; Marwah et al., 1979; Agboola 1975; Fox 1967). On treatment with iron, there was increase in hemoglobin, cord iron and placental (non-hem iron) and placental shrinkage in formalin reduced. However, the reduced villus vascularity, increased villus fibrosis and endarteritis obliterans in placenta of anemic mother did not reverse. It was postulated that moderate-severe anemia present from the early days of pregnancy induces irreversible structural alteration, as iron is needed in 2nd week of pregnancy for placenta formation (Agarwal (1984)).

Fetus-newborn

Cord serum iron and hemoglobin were reduced in preterm as well as full term infants of hypoferric mothers. There is an increased gradient in presence of maternal iron deficiency for transport of iron from mother to fetus but the transport remains proportionate to the degree of maternal hypoferricemia. The weight of full term singleton babies born of anemic mothers was reduced in

direct relation to hemoglobin level. Similarly, these babies showed a progressive decrease in Apgar scores also (Agarwal (1984)). Fetal liver iron stores are reduced significantly in maternal hypoferricemia. Normally bigger, the infant, and more advanced the gestational age higher, was the amount of iron in fetal liver, spleen and kidney. The tissue iron content increases steeply in the last 8 weeks of gestation. Infant born before 36 weeks of gestation had half the iron content in hepatic reserve (Singla et al., (1985)). Breast milk iron content is increased in hypoferric mothers, a phenomenon of "Physiological trapping" (Khurana et al., 1970; Franson et al., 1985).

To understand more, a rat model was created with latent iron deficiency (low hepatic iron without change in hematocrit) in pregnancy (Agarwal 2001; Shukla et al., 1989; Taneja et al., 1986; Taneja et al., 1986; Shukla et al., 1989; Mittal et al., 2002).

Fetal brain iron content and neurotransmitters in maternal (rat) latent iron deficiency

Iron as a micronutrient is required for regulation of brain neurotransmitters by altering the pathway enzymatic system. To study iron deficiency, a rat model was developed to create iron deficiency (low hepatic iron) without change in hematocrit (Agarwal (2001)). In post-weaning rats, iron decreased irreversibly in all brain parts except medulla oblongata and pons. Susceptibility to iron deficiency showed variable reduction in different parts of the brain: corpus striatum, 32%; midbrain, 21%; hypothalamus, 19%; cerebellum, 18%; cerebral cortex, 17%; and hippocampus, 15%. Alterations in brain iron content also induced significant alterations in copper (Cu), zinc (Zn), calcium (Ca), manganese (Mn), lead (Pb) and cadmium (Cd) (Shukla et al., (1989)).

Fetal latent iron deficiency (Rat) and- brain neurotransmitters

In latent iron deficiency there was irreversible reduction in neurotransmitters: Brain 'glutamate metabolism'-[glutamic acid decarboxylase (GAD), glutamate dehydrogenase (GDH), gamma amino butyric acid (GABA-T)] (Taneja et al., 1986; Shukla et al., 1989):

a) Marked reduction in levels of brain GABA, L glutamic acid and enzymes for biosynthesis of GABA and L- glutamate like glutamate decarboxylase and glutamate transaminase.

b) Binding of H3 muscimol at pH 7.5 and 1 mg protein/assay (GABA receptor) increased by 143%, but glutamate receptor binding decreased in the vesicular membranes of latent iron deficient rats by 63% (Agarwal 2001; Mittal et al., 2002).

c) Brain 'TCA-cycle' enzymes-mitochondrial NAD+ linked

dehydrogenase significantly reduced

d) Brain '5-HT metabolism'- Tryptophan, 5-HT, 5-HIAA significantly reduced.

e) The whole brain and corpus striatum showed reduction in catecholamine, dopamine nor-epinephrine, tyrosine and monoamine oxidase, while tyrosine amino transferase increased in corpus striatum, in spite of reduction in whole brain suggesting that latent iron deficiency induced irreversible neurotransmitter alterations Shukla et al., (1989).

f) Brain 'catecholamine metabolism'- Whole brain-dopamine, neonephrine, tyrosine and TAT significantly reduced in 'corpus striatum', same as in whole brain, except TAT was increased Shukla et al., (1989).

These changes specific to iron deficiency as neurotransmitter alterations in fetal brain due to malnutrition (undernutrition or on diets with limiting amino acids) get normalized partially or completely on rehabilitation (Prasad et al., 1979; Prasad and Agarwal, 1980). The significant effects on neurotransmitter receptors (glutamate mediators) during early stages of iron deficiency clearly indicate the deficits in both excitatory and inhibitory pathways of the central nervous system, showing an important role of iron in brain (Agarwal, 2001).

To test the above findings in humans, babies born of moderate to severely anemic mothers were examined for "impact of iron deficiency on mental functions". The intrauterine growth retarded offspring's of anemic as well as undernourished mothers showed hypotonia in 72% and hypoexcitability in 56% (Bhatia et al., 1979; Bhatia et al., 1980; Agarwal et al., 2002). There was modification of responses in several neonatal reflexes for example, limp posture, poor recoil of limbs, incomplete moro's and crossed extensor responses. Their electroencephalogram (EEG) had shortening of sleep cycle [rapid eye movement (REM) and non-rapid eye movement (NREM)], the reduction was more marked for REM sleep. There was some inter and intra hemispheric asymmetry and abnormal paroxysmal discharges; suggesting dysmaturity of brain (Bhatia et al., 1979; Bhatia et al., 1980).

The above findings were not specific to effects of anemia on mental functions. Therefore effects of anemia (nutrition controlled) on mental functions were then studied in rural children during a period of three years.

Mental functions in nutrition controlled 388 rural primary school (6 to 8 year of age), matched for social and educational status were studied by WISC and arithmetic test to assess "Intelligence, attention and concentration".

Anemia did not affect intelligence - except subtest-digit span, but in arithmetic test, attention and concentration was poor in anemic children Agarwal et al., (1989).

Effects of iron deficiency and/or anemia on brain

Iron deficiency anemia in infancy has been consistently shown to negatively influence performance in psycho-

motor development. Short-term iron therapy did not improve the lower scores, despite complete hematological replenishment. Neurological maturation was studied in infants 6 months old, including auditory brain stem responses and naptime 18 lead sleep studies. The central conduction time of the auditory brain stem responses was slower at 6, 12 and 18 months and at 4 years, despite iron therapy beginning at 6 months. During sleep-wakefulness cycle, heart rate variability- a developmental expression of the autonomic nervous system, was less mature in anemic infants. This is possibly due to altered myelination of auditory nerves Walter (2003). It has been observed that these changes are resistant to iron therapy in children < 2 years of age with iron deficiency with anemia, but not in older children McCann and Ames (2007). These studies supported earlier findings that brain functions are significantly affected in latent iron deficiency in the brain growth period, and such changes are irreversible. These have serious consequences for example, poor cognition and learning disabilities.

CONCLUSION

The above researches review mainly affects of maternal hypoferrremia on iron status of placenta, cord blood (hemoglobin and ferritin), and fetus (brain and hepatic iron content). The rat model of "latent iron deficiency" showed irreversible brain iron reduction and irreversible neurotransmitter alterations in 'brain growth period'. Once anemia sets in, the additional effects are due to anoxia. Our nation is faced with the problem of iron deficiency that leads to anemia- a clinical condition due to deficiency of many nutrients, mainly iron, folic acid and vitamin B12. Folic acid is essential from prenatal period and its deficiency causes neural tube defects.

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