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LATE **PROF. B O VAHLQUIST,**
UPPSALA

IRON & BRAIN

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Prevalence of nutritional anemia in 'Brain Growth Period'

As many as 4–5 billion people, 66–80% of the world's population, may suffer from reduced learning ability and work capacity due to iron deficiency. "*Battling iron deficiency anemia* WHO 2002*

Iron deficiency, and specifically iron deficiency anemia, is one of the most severe and important nutritional deficiencies in the world. **Preschool children and women of reproductive age** are at highest risk. More than 2 billion people, > 30% of the world's population, are anemic. It is estimated that **more than half of the pregnant women in developing countries are anemic.**

As early as in 1967, Routh&Agarwal Indian J Med Res(IJMR); studied iron content in liver, spleen and muscle of healthy rich who died in personal car accidents on the streets of Delhi. It was found that >65% healthy had no or very low iron content in hepatic tissue indicating severe degree of iron deficiency in our well to do population.

Later Agarwal, et al studied in Uttar Pradesh and Bihar;(national studies by Indian Council Medical Research(ICMR)- covering 11 states; reported in 1989), prevalence of anemia by estimating hemoglobin using cyanmethemoglobin method in pregnant rural women was 87.6% , hemoglobin being <10.9g/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; 1992 (62% inspite of iron-folate therapy continued to be anemic). 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, reducing low birth weight deliveries significantly (Agarwal et al IJMR; 1991).

- Nutrition Foundation of India in 2002-2003-studied prevalence of anemia in pregnancy and lactation in 7 states (Assam, Himachal Pradesh, Haryana, Kerala, Madhya Pradesh, Orissa, Tamil Nadu). The anemia prevalence was- Pregnancy 86.1%(Hb<7.0g/dl- in 9.5%); Lactation 81.7 %(Hb<7.0g/dl in 7.3%) Agarwal et al 2006;IJMR 124: 173-184.

- ICMR_–1999-2000- 11 states 19 districts in the District Nutrition Survey found pregnancy anemia prevalence of 84.6% (Hb<7.0 g/dl-in 9.9%). These workers also found 90% adolescent girls with anemia Teoteja et al 2001.

- >87% < 3 yr children were iron deficient (Kapur, Agarwal et al 1999, Indian Pediatr).

The above studies clearly showed that prevalence as well as severity of anemia during pregnancy and lactation is grave. This is the period when brain receives iron for brain.

Maternal Death risk in child birth due to anemia-

- African countries- 4.6/1000 births
- Asian countries- India, P R Korea, Maldives, Myanmar and Nepal- 2.6/1000 births.
- European countries- 1 in 1400 births.

Effects of maternal iron deficiency on feto placental unit (Agarwal et al):

- NormallyPlacental Iron transfer to fetus becomes 3 to 4 times during 20-37 wk of gestation.

a) Cord serum iron and hemoglobin were reduced in preterm as well as full term. 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 hypoferriemia.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 have no controls, as placenta continues to trap iron even when fetus is removed in animals (Fletcher &SuteClinSci 1969). In spite of this efficient protective mechanism the placental iron content reduces significantly in maternal hypoferriemia (Agarwal et al .Am J ClinNutr 1979, ActaPaediatr 1978 & 1984). This was a very important finding as earlier studies by Vahlquist 1941; ActaPaediatr, on Swedish women had shown that cord iron does not change in iron deficient pregnant women. This was also observed by Rios et al Pediatrics 1975.

The placenta of anemic women showed qualitative decrease in villous surface area, volume of villi and length of blood vessel, while surface area and volume of intervillous space was increased. These placental changes in anemia did not normalise on rehabilitation- suggesting "Maturational arrest"(Agarwal et al; Indian J Path Micro 1979; J Trop Paediatr 1981; ProcNutrSoc of India 1991).

b) Fetal Liver iron stores are reduced significantly in maternal hypoferremia. 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 last 8 weeks of gestation. Infant born before 36 weeks of gestation, had half the iron content in hepatic reserve (Agarwal et al; Acta Pediatr1985).

Placenta in iron transport to fetus-

- *Placenta formation needs iron in first 2 wk*; continues to trap iron at a gradient even when fetus is removed in animals (Fletcher & Sute Clin Sci 1969).
- In spite of this efficient protective mechanism the placental iron content reduces significantly in maternal hypoferriemia (Agarwal et al .Am J Clin Nutr 1979, Acta Paediatr 1978 & 1984).

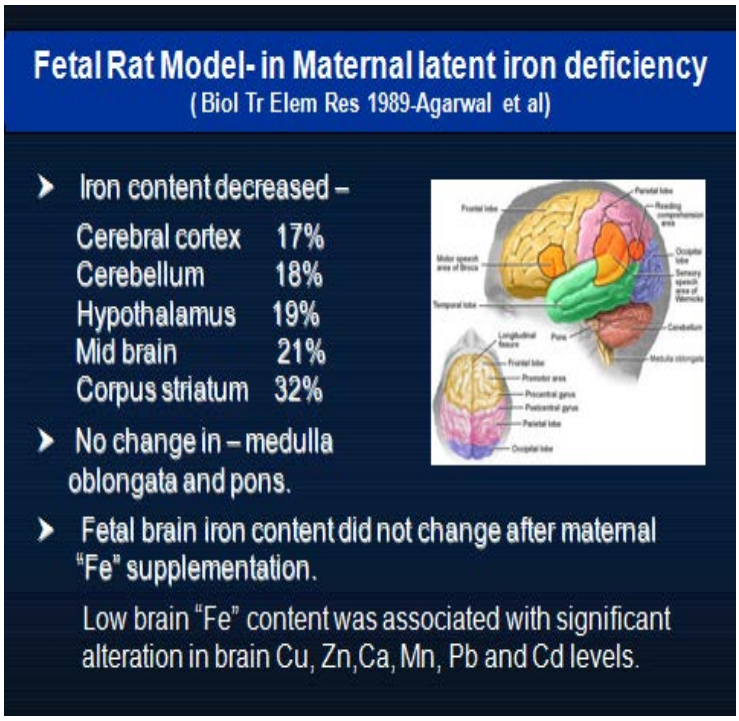

Placenta in cross-section at umbilical cord

- In Contrast, Vahlquist ACTA Paediatr 1941; Rios et al Pediatrics 1975, had shown that cord iron does not change in iron deficient pregnant women (in Sweden and USA)

- Fetal brain iron content and neurotransmitters are reduced and their receptors are altered (Agarwal et al; Brit J Nutr 2001;J Neurochem&Tr El Res 1989).
- Breast milk -Physiological Trapping- iron content is increased in hypoferriemic mothers (Agarwal et al. Indian Pediatr 1970; ActaPaediatr 1985).

Rat Fetal Brain Iron Content in Maternal Latent Iron Deficiency (BiolTr Elem Res 1989-Agarwal et al)

- Iron decreased 'IRREVERSIBLY' in all brain parts except medulla oblongata and pons.
- Susceptibility to Iron deficiency showed 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 Cu, Zn, Ca, Mn, Pb and Cd.



Fetal Latent Iron Deficiency- brain neurotransmitters- showed irreversible reduction in- (Agarwal et al; Indian J ExptlBiol 1986; J Neurochem 1986, 1989; Experentia 1989, Nutr Res 1989; Brit J Nutr 1991).

Brain 'Glutamate metabolism'-(GAD, GDH, and GABA-T)

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 were also reduced.

,b)Binding of GABA receptor increased by 143% , but glutamate receptor binding decreased by 63% .

- Brain 'TCA-cycle' enzymes- mitochondrial NAD+ linked dehydrogenase significantly reduced

- Brain 'Catecholamine metabolism'- Whole brain- dopamine, neonephrine, tyrosine and TAT significantly reduced; Corpus striatum – same as in whole brain, except TAT increased.
- Brain '5-HT metabolism'- Tryptophan, 5-HT, 5-HIAA significantly reduced.

The whole brain and corpus striatum showed reduction in catecholamine,

Dopamine nor-epinepherine, tyrosine and monoamino oxidase, while tyrosine amino transferase increased in corpus striatum, inspite of reduction in whole brain

Suggesting that latent iron deficiency induced irreversible neurotransmitter alterations (Agarwal et al . cited above) .

These changes were specific to iron deficiency as neurotransmitter alterations in fetal brain due to malnutrition get normalised partially or completely on rehabilitation (Agarwal et al; J Neurochem 1979 & 80).

The significant effects on neurotransmitterreceptors (glutamate mediators) during early stages of iron deficiency clearly indicate the deficits in both excitatory and inhibitory pathways of the central nervous system (Agarwal Brit J Nutr 2001).

Anemia and Brain -MRI studies- iron deficiency and thalassemia; both are clinical conditions with anemia but former has no or low iron content and the later excess of iron in body tissues.

- The iron content on globuspallidus, caudate and dentate nuclei was similar in both the clinical conditions.
- There was an increase in creatinine and aspartate and reduction in choline concentration. These are very significant findings as choline is synthesized in the brain in very small amounts; its uptake is Na+ dependent, which requires oxygen (Agarwal;BJN 2001). Such changes are also observed in Hutington's chorea and Alzeimher's disease.
- In contrast in anemia the changes are due to anoxia, irrespective of body iron status.

Under nutrition (UN) and or anemia- effects on brain-

- Prenatal UN induces permanent deviations in the normal age related sequence of Brain maturation-particularly the coordinated development of various cell groups– affecting the formation of neural circuits & neurotransmission (Morgane et al N Y AcadSci 1993).
- Malnutrition - Wheat and/ or legume diets (form common staple diet in rural/poor India) in rat, affect fetal brain growth without altering body size (DISSOCIATION); brain proteins and partially reversible changes in neurotransmitters. (Agarwal et al J Neurochem 1979 & 1980).

- In contrast, Latent Iron Deficiency did not affect Brain Structure but reduction in neurotransmission was irreversible (Agarwal et al- cited above).

Impact of Iron Deficiency-

Anemia (nutrition controlled) and Mental Functions in RuralPrimary School Children.

- Mental functions in nutrition controlled 388(6-8 yr of age), matched for social and educational status were studied by WISC and arithmetic test to assess "Intelligence, Attention and Concentration". Anemia does not affect intelligence, except subtest- digit span. In Arithmetic test Attention and Concentration was poor in anemia children (Agarwal DK et al 1989; Ann Trop Paeditr.)

- Grantham McGregor 2001, J Nutr showed improvement after iron supplementation. Improvement in- Concentration, Discriminate learning and Short-term memory were significant.
- Lozoff et al 2001- a) long lasting developmental disadvantages with iron def in Infancy. b) those treated with Iron; later at 3-4 yr of age showed slow transmission of nerve impulses thru out the brain in auditory and visual systems. This is due to defective myelination in iron deficiency.
- Pugh- 2005, this defective development appears prior to development of anemia (Latent Iron deficiency).

These studies supported our 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 e.g. poor cognition and learning disabilities.

The above researches by our group are mainly on affects of Latent Iron Deficiency on irreversible brain function alterations in 'Brain Growth Period'. Our nation is faced with the problem of anemia- a clinical condition due to deficiency of many nutrients- mainly iron, folic acid and vitamin B12. Folic acid is essential from prenatal period its deficiency causes neural tube defects. Once anemia sets in additional affects are due to anoxia.
In INDIA-*Our population lives in life cycle with anemia endangering child growth and development*.

Nutritional Anemia is treatable as well as preventable and the available control measures are affordable. Lets do it now. K N Agarwal

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