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Canada Beef releases a bi-monthly Nutrition Journal Tracker as a summary report of health/nutrition research published that is of significance for beef.

TOPIC	Iron
ARTICLE	Iron deficiency in pregnancy – Expert Review
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CITATION	Georgieff MK. Iron deficiency in pregnancy. Am J Obstet Gynecol. 2020;S0002-9378(20)30328-8. doi:10.1016/j.ajog.2020.03.006
SIGNIFICANCE	Highlights the consequences of fetal iron deficiency on brain development and function that lasts a lifetime. Iron is critical for healthy infants even prior to birth.

SUMMARY

Importance of Iron

- Since iron is so fundamental to cellular functions through its roles in oxygen delivery, electron transport, and enzymatic activity that its uptake by cells is a highly prioritized process.
- Iron deficiency is associated with adverse pregnancy outcomes, including increased maternal illness, low birthweight, prematurity, and intrauterine growth restriction.
- The rapidly developing fetal brain is at particular risk of iron deficiency, which can occur because of maternal iron deficiency, hypertension, smoking, or glucose intolerance.
- Low maternal gestational iron intake is associated with autism, schizophrenia, and abnormal brain structure in the offspring.
- Newborns with iron deficiency have compromised recognition memory, slower speed of processing, and poorer bonding that persist despite postnatal iron repletion.
- Iron sufficiency is essential for oxygen delivery to the maternal-placental-fetal unit to support the increased oxygen consumption demand of pregnancy.
- Beyond oxygen delivery, iron in cytochromes catalyzes the generation of ATP at a time when the fetal oxygen consumption rate is very high, driven largely by the structural development of fetal organs. Of these, the brain is particularly "greedy," accounting for an astounding 60% of the total fetal oxygen consumption rate.
- Nearly 2 billion of the 7.5 billion people on the planet are iron deficient, making it the most common micronutrient deficiency in the world.

Iron Needs Increased During Pregnancy

- Pregnancy increases maternal iron demand for 3 reasons:
  - Increased maternal plasma and blood volumes.
  - Fetus requires iron for its metabolic and oxygen delivery needs as well as loading its iron stores that will be used in the first 6 months of life.
  - The placenta is a highly metabolically active organ with large iron requirements. It has the capacity to store iron to provide a buffer against periods of low maternal iron supply.
- Women with marginal or even adequate iron status pre-pregnancy are prone to iron deficiency when they become pregnant. Their nutritional status influences the brain development of the offspring.

Fetal Iron

- Fetal iron can be divided into 3 compartments:
  - Red cells (largest compartment) - iron is prioritized to red cells over all other compartments, including the brain.
  - Storage iron - proper fetal iron loading is important since breast milk is very low in iron. Breast milk may be the only dietary source for the infant in the first 6 months, therefore the infant relies on the iron stores to support hemoglobin synthesis and organ development.
  - Non-storage tissue iron (smallest compartment which includes the brain and heart) is at risk once fetal iron stores have been exhausted. Iron deficiency symptoms, fatigue and altered brain function, stem from iron deficiency at the tissue level. The hippocampus - which plays a role in learning and memory - is rapidly developing in the last trimester. Iron deficiency that is not corrected results in long-term neurocognitive abnormalities.
- Children born with lower fetal iron loading have lower iron stores at 9 months of age and a greater risk of iron deficiency. Proper fetal iron loading has taken on greater importance in public health strategies to combat postnatal iron deficiency and its long-term neurodevelopmental risks.
- Postnatal iron deficiency is extremely common in infants and toddlers, with rates approaching 80% in low- and middle-income countries and 9% to 45% in North America and Europe.

Diagnosis of Iron Deficiency in Pregnant Women

- Hemoglobin concentration is used to screen for iron status since it's widely available, easy to measure and low cost. However, there are significant concerns with relying solely on hemoglobin screening. Because iron incorporation into hemoglobin is a highly prioritized process, anemia is the end-stage result of negative iron balance. Thus, hemoglobin concentration lacks the sensitivity to detect early stages of iron deficiency, when there are already physiologic effects at the tissue level. In addition, conditions other than iron deficiency cause anemia, including hemoglobinopathies, hemolysis, and inflammation/chronic disease. Reliance on hemoglobin alone lacks sufficient sensitivity and specificity to diagnose iron deficiency in pregnancy.
- Iron-specific biomarkers that can be used guage iron status:
  - Serum ferritin: measures body's iron storage capacity. Ferritin is stored in reticuloendothelial cells and released to the red cells for hemoglobin synthesis and to the tissues for iron-dependent enzymes and hemoproteins. Both the liver and the placenta have remarkable ability to store iron as ferritin to buffer the mother and the fetus from wide swings in iron availability. Clinically, the finding of low serum ferritin concentration is highly diagnostic for iron deficiency. However, because ferritin is an acute phase reactant, rising when inflammation is present, high ferritin may represent a response to inflammation. A normal ferritin concentration may mask an iron-deficient state if inflammation is present. Serum ferritin should be used in conjunction with hemoglobin concentration to more precisely define iron status in pregnancy.
  - Percent total iron binding capacity saturation (%TSAT): a calculation derived by dividing the serum iron level by the total iron-binding capacity and multiplying times 100. It reflects the percentage of iron binding sites on serum iron transport proteins that are occupied by iron molecules. Serum iron concentrations decrease early during negative iron balance, thereby decreasing the %TSAT. In stage 2 iron deficiency, transferrin concentrations increase to optimize iron binding capacity for transport, which drives the %TSAT even lower. All of these changes occur before anemia making it an early biomarker of iron deficiency.
  - Hepcidin: a measurement of serum hepcidin concentrations may be the best biomarker of iron deficiency. Hepcidin is the master regulator of intestinal iron absorption and iron distribution from the reticuloendothelial cells. Hepcidin is synthesized by the liver in response to iron status and inflammation. Hepcidin is a negative regulator, which means that high concentrations reduce intestinal iron absorption and promote iron sequestration, whereas low levels increase intestinal iron absorption and iron release from reticuloendothelial cells. Patients with low hepcidin levels likely require iron.

Iron Deficiency and Iron Deficiency Anemia

- Iron deficiency and iron deficiency anemia are not synonymous:
  - Iron deficiency - state of negative iron balance where iron supply does not meet iron demand.
  - Iron deficiency anemia - defines the condition when hemoglobin synthesis has been limited by the lack of iron and the person is anemic as a consequence.
- Because iron is prioritized to red blood cells for hemoglobin synthesis, iron deficiency proceeds through multiple non-anemic stages before anemia ensues. Iron deficiency anemia can be thought of as the end stage of the iron deficiency process and is not a sensitive marker of tissue level iron deficiency including brain iron deficiency.
- Iron stores are mobilized during the first stage of iron deficiency, resulting in reduced %TSAT and ferritin concentrations. This process reflects the body's attempt to maintain iron delivery to the red cells and non-heme tissues including the brain. However, when placed in direct competition for iron, the red cells will be prioritized over the brain.
- Children with pre-anemic iron deficiency demonstrate abnormal brain and behavioral function, indicating the likely presence of brain tissue-level iron deficiency before the appearance of anemia.

Iron Supplementation During Pregnancy

- Iron supplements protect the health of the mother, improve pregnancy outcomes, and foster fetal development.
- Emerging research suggests an increased risk of glucose intolerance in iron-sufficient pregnant women treated with iron.

Effects of Gestational Iron Deficiency on the Fetus

- During mild maternal iron deficiency, iron is prioritized to the fetus.
- However, during moderate and severe iron deficiency, the entire maternal-placental-fetal unit becomes iron deficient, with significant short and long-term consequences to the fetus. These consequences also occur in fetuses of iron-sufficient mothers who have conditions that compromise fetal iron delivery: hypertension, smoking, diabetes mellitus, and carrying twins.
- Insufficient fetal iron results in 3 risks to the fetus:
  - Altered brain development.
  - Long-term brain dysfunction despite replenished iron stores by 9 months of age.
  - Greater risk of becoming iron deficient resulting in long-term effects such as anxiety and depression in adulthood.

Link Between Fetal/Postnatal Iron Status and Long-Term Neurocognitive and Mental Health

- Maternal-fetal iron status has been linked to a number of neurocognitive and mental health disorders in the offspring, driven in part by the timing of iron deficiency during pregnancy:
  - Low maternal iron intake at the time of conception and first trimester is associated with a greater risk of autism in the offspring.
  - Low maternal iron intake during the second trimester is associated with a 30% increased risk of schizophrenia.
- Risk for several adult mental health conditions are driven in part by fetal conditions.
  - Infants born with low serum ferritin concentrations, reflecting reduced fetal iron loading, have:
    - Poorer recognition memory at 3½ to four years of age.
    - Poorer school performance at 5-6 years of age.
    - Difficulty with planning and attention at 10 years of age.
- Infants with onset of iron deficiency in early postnatal life, likely driven by inadequate fetal iron loading, have:
  - Slower speed of neural processing that persists beyond the period of iron deficiency and despite treatment.
  - Greater risk of cognitive and socioemotional problems including anxiety and depression in their second decade of life and into young adulthood.

- The resulting loss of education and job potential can be considerable. Thus, ensuring fetal nutritional and in particular iron health can be seen as an investment in the mental health of the next generation and an investment in society.
- Need to expand the role of nutrition in ensuring childhood brain health from solely focusing on postnatal nutrition to focusing on prenatal and even preconceptional nutrition. Require policies that promote maternal nutritional health heading into pregnancy, followed by close attention to iron during pregnancy.

COMMENTS

The increased risk of offspring having poor cognitive development, autism and schizophrenia provides compelling reasons for women to ensure healthy iron status preconception and throughout pregnancy. As one of the best dietary sources of bioavailable heme iron, including beef regularly in the diets of these women makes nutritional sense. Including beef as a first introductory food around 6 months of age can also help restore iron stores in infants.

Of Note: Iron fortified foods and supplements are used to top up dietary shortfalls.