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Can iron be teratogenic?

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Abstract Several kinds of evidence indicate that elevated iron during the 3–8 week embryonic (organogenesis) period of human gestation may be teratogenic. (1) In the embryonic period, the natural maternal absorption of food iron is 30% below the estimated daily iron loss. (2) As compared with maternal serum, embryonic fetal coelomic fluid contains only one-fourth as much iron but nearly six times the quantity of the iron withholding protein, ferritin. (3) In the embryonic period, intraplacental oxygen pressure is 2–3 times lower than in the subsequent fetal growth period. (4) Iron is a strong inducer of emesis which peaks in the embryonic period. (5) In a murine gestation model, iron was neurotoxic at a sharp peak of 8–9 days. Thus it would be prudent, in human pregnancy, to delay any needed iron supplementation until the embryonic period has been completed.

Keywords Embryonic period · Iron · Pregnancy · Teratogen

Introduction

Normal fetal development can be disrupted not only by genetic mutations but also by the presence of specific teratogens at unique times of gestation (Gilbert 2008). Among the scores of known inanimate teratogens are such agents as radiation, various drugs and other organic compounds, alcohol, lead, methylmercury and zinc.

In human pregnancy, the period of maximal susceptibility to many inanimate teratogens is between 3 and 8 weeks; that is, during the embryonic period (Larson 2001; Jones and Lopez 2006; Gilbert 2008). Organogenesis occurs mainly during this 6 week span (Moore and Persaud 1993). If indeed iron is teratogenic, natural maintenance of a very low concentration in the fetal milieu might permit normal differentiation.

The fetal growth period (weeks nine to thirty-eight) involves mainly cell multiplication rather than differentiation (Gilbert 2008). Thus non-living teratogens are less hazardous. During this time, the fetal requirement for growth essential iron is markedly elevated. Moreover at delivery, additional maternal erythrocytes are needed to compensate for bleeding. Accordingly, as compared with the normal amount in non-pregnancy, maternal absorption of dietary iron is enhanced fivefold in the second trimester and ninefold in the third trimester (Barrett et al. 1994).

Cytotoxicity of iron

In low concentrations, iron serves as an essential nutrient for nearly all forms of life. The cytotoxicity

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of moderate to high concentrations is becoming well recognized (Connor and Ghio 2009). Although mildly mutagenic (Dunkel et al. 1999), iron is toxic primarily by virtue of its strong induction of oxidative stress. Iron-catalyzed formation of hydroxyl (free) radicals can destroy proximate cells by initiating lipid peroxidation, denaturation of enzymes, depolymerization of polysaccarides and rupture of DNA strands (McCord 1996).

Inasmuch as cell types differ in antioxidant potential, the minimal cytotoxic iron concentration is variable. For instance, in the pancreas, insulin producing cells are far more sensitive than those that form digestive enzymes. Thus diabetes mellitus 1 and 2 are frequent complications of persons who load iron (Forhoui et al. 2007). Osteoblasts (fibroblast lineage) that build bone are much more sensitive to iron than are osteoclasts (macrophage lineage) that destroy bone (Weinberg 2008). Accordingly, up to 50% of persons who for any reason load iron, suffer from osteoporosis.

Anterior pituitary cells in culture are killed by as little as 1.0 μM iron whereas hepatocytes survive in concentrations of 10–100 μM (Eby et al. 1993). Not surprisingly, young children who begin to load iron early (e.g., thalassemics) are deprived of growth hormone and are short in stature. Persons who begin iron loading in adolescence or early adulthood (e.g., some hemochromatotics) beome deprived of gonadal hormones. Thus amennorhea and infertility can occur in female patients, impotence in males.

Within the past half century, excessive/misplaced iron has been found to be a serious risk factor for a great variety of acute and chronic diseases (Weinberg 2009a) as well as for reduced longevity (Mainous et al. 2004). Unfortunately, iron supplements are sometimes recommended for pregnant women without ascertainment of the patients' iron status. Although this practice usually is considered harmless, the association of gestational diabetes and preeclampsia with elevated iron is well documented (Weinberg 2009b).

Iron requirement/withholding in embryonic period

In early pregnancy, the physiological demand for iron is considerably reduced as compared with that of non-pregnant, menstruating women. The iron requirement of the fetus is minimal and the increase in red cell mass has not yet begun (Svanberg 1975). The total maternal plus fetal daily iron demand is assumed to be similar to the basal daily loss; that is about 0.8 mg. However, in a well constructed study of 17 pregnant women during the embryonic period (Svanberg 1975), only 3.2% of 3.0 mg labelled iron in a test meal and 12% of 3.0 mg labelled ferrous iron was absorbed. In contrast, the same women, when not pregnant, absorbed 12.6 and 50.2% of the respective samples. The author noted that absorption of dietary iron in early pregnancy is about 0.5 mg/d. Thus a negative balance of approximately 30% occurs during the embryonic period. No hypotheses were proposed for this unexpected observation.

In a different laboratory, early fetal iron and ferritin values were compared with those of maternal serum. Coelomic and amniotic fluids were collected from 36 apparently normal, legally aborted, 7–13 week fetuses (Gulbis et al. 1994). Also, iron concentrations in two of the embryos were assayed in placental villi and fetal liver. Significantly lower median iron values were found in coelomic fluid (4.8 μmol/l) than in maternal serum (21 μmol/l). In contrast, the former contained much higher ferritin values than the latter (287 vs. 49 μg/l; $P < 0.001$). Amniotic fluid had less than 1.8 μmol/l iron and 2.0 μg/l ferritin.

The concentration of iron in coelomic fluid increased significantly when gestation advanced from the close of the embryonic period (7–9 weeks) to the start of the fetal growth period (9–11 weeks). The respective amounts of iron were 3.8 and 5.9 μmol/l ($P < 0001$). Fetal liver iron likewise increased between 8 and 10 weeks: from 15 to 52 μmol/kg dry wt. Placental villi iron changed from 7.5 to 8.7 mmol/kg dry wt.

Thus at the end of the embryonic period, the content of fetal iron was only 23% of maternal iron whereas ferritin content was 5.8 fold higher than that in maternal serum. Inasmuch as the main function of ferritin in the non-inflammed host is that of safe sequestration of iron (Arosio et al. 2009), the early fetus is able to maintain some protection from the possible teratogenicity of elevated iron.

Several investigators (Casenueva and Viteri 2003; Agarwal et al. 2006; Jauniaux et al. 2006) have emphasized the danger of oxidative stress throughout

pregnancy. Special concern has been noted about conditions that can induce formation of hydroxyl (free) radicals during the organogenesis period (Casenueva and Viteri 2003). Fortunately, normal intraplacental oxygen pressure is maintained at a level of two to three times lower at 8–10 weeks than after 12 weeks (Jauniaux et al. 2006).

Maternal emesis helps to minimize teratogenic damage during organogenesis. In a group of 363 pregnant women who kept daily symptom diaries, 28% had nausea and 52% nausea plus vomiting. The mean number of weeks from their last menstrual period to the onset of emesis was 5.6. Cessation of symptoms occurred at a mean of 12 weeks. Peak symptoms were reported in the ninth week (Gadsby et al. 1993).

In a study of 96 pregnant women given a multivitamin supplement with high iron and 96 given the supplement with low iron, emesis was significantly higher in the high iron group ($P = 0.006$; Gill et al. 2009).

It will be of considerable interest to compare formation of hepcidin (which controls dietary iron absorption by binding to ferroportin) during the embryonic period with that of the fetal growth period. In a study of 149 pregnant women, urines were sampled for hepcidin at the start of fetal growth (Schulz et al. 2008). Hepcidin level was directly correlated with maternal serum ferritin. However, hepcidin values were not compared with those of the same women when they were not pregnant, nor were samples obtained during the embryonic period.

Iron teratogenicity in an animal model

In a study of 500 pregnant mice (Kuchta 1982), batches of 100 animals were intraperitoneally injected with ferric gluconate on day six, seven, eight and nine. A batch of 100 served as uninoculated controls. In the control group as well as in the batch injected on day six, no malformations occurred. In the seventh day batch, the malformation rate was 1%. The eighth day batch contained 33% malformed pups and the ninth day 17%. The most prominent histological defects were encephalic. Also, malformations of the spine and ribs occurred in 11% of the eighth day batch and in 3% among the ninth day group.

Perspectives

Although the available evidence strongly suggests that elevated iron should be avoided during the human embryonic period, additional animal research is needed to confirm the time of onset and duration of maximal susceptibility to iron as well as the upper level of the metal that is compatible with safe organogenesis. With present knowledge, it would be prudent to advise avoidance of supplemental iron during the initial 10–12 weeks of pregnancy. Thereafter, supplemental iron is best reserved for those women who truly are iron deficient. Accordingly, a serum ferritin test (a useful marker for body iron) should routinely be administered prior to or at the start of the second trimester.

Pregnant women have a 2–3 times higher risk of restless legs syndrome (RLS) than the general population (Dickanovic et al. 2008). In some clinics, RLS has been associated with low iron. If a low serum ferritin value is detected early in pregnancy, iron supplementation should be delayed until the completion of the embryonic period.

In addition to withholding iron supplements during the embryonic period, anti-emetic drugs should be used with caution. Cryptic teratogens other than iron may be present in the diet.

Between 2 and 5% of human infants are born with a readily observed anatomic abnormality (Gilbert 2008) In a preliminary report on the possible teratogenicity of iron (Weinberg 2009c), it was urged that women who have miscarried or delivered an anatomically abnormal infant be asked to recall how much supplemental iron, if any, was taken and how early in the pregnancy supplementation was initiated. Similar data should be obtained from women who have birthed normal infants. In addition to iron, recall information should be requested for other possible teratogens.

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