Manganese is an essential mineral nutrient needed for proper fetal development and other important aspects of metabolism. However, manganese excess can have a potent neurotoxicity effect, especially in infants. Little is known about the effects of manganese deficiency or excess on the developing human fetus. The findings of two recent studies indicate that lower maternal blood manganese is associated with fetal intrauterine growth retardation (IUGR) and lower birth weight. In light of the importance of IUGR and birth weight on neonatal morbidity and mortality, additional basic studies of maternal and fetal manganese physiology are needed, as well as more epidemiologic studies in different populations of the association of manganese exposure and birth outcome.

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INTRODUCTION

Manganese is an essential mineral nutrient in humans and other animals and is required for normal amino acid, lipid, protein, and carbohydrate metabolism. Functionally, manganese can act by activating certain enzymes (many hydrolyses, kinases, decarboxylases, and transferases) or through manganese-dependent metalloenzymes (Table 1) that are needed for proper immune function, regulation of blood sugars and cellular energy, reproduction, digestion, bone growth, and the body’s defense against free radicals. On the other hand, excess manganese is a potent neurotoxin. Although environmental toxicity studies have described some of the adverse effects of high manganese exposure in humans, little is known about the effects of manganese deficiency or manganese toxicity on fetal development and pregnancy outcome. In experimental animals, manganese deficiency is associated with impaired growth, skeletal defects, reduced reproductive function, abnormal glucose metabolism, and altered lipid and carbohydrate metabolism, while excess manganese can induce adverse neurological, reproductive, and respiratory effects.1

REFERENCES


SOURCES OF MANGANESE EXPOSURE

Atmospheric contamination can be an important exposure route for manganese under certain circumstances.2-4 Water can also be a significant source of manganese under some conditions,5-11 but typically most water sources provide from 1 to 100 μg/L with most supplying less than 10 μg/L. Dietary manganese is the main route of exposure under normal circumstances for most people. Manganese is fairly widespread in the diet and manganese deficiency has not been recognized as a significant problem in human nutrition. Recommended adequate dietary manganese intakes are ~2 mg/day. Upper limits of manganese ingestion are 11 mg/day.12

The body is protected from accumulating excess dietary manganese because only a small fraction of dietary manganese is absorbed from the intestine. Manganese absorption can also be inhibited by some common dietary constituents (fiber, phytate, ascorbic acid, iron, phosphorous, and calcium). Phytate is found in whole grains. In adults, manganese absorption from extrinsically labeled soy milk-based formula containing usual amounts of endogenous phytate was only 0.7%. The important role of phytate as an inhibitor of manganese absorption is not determined.

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absorption was evident when the absorption efficiency more than doubled to 1.7% when the soy formula was treated with the enzyme phytase to lower phytate levels. Measurement of manganese absorption in young women from a normal diet indicated an important effect of iron status. Women with low iron stores absorbed ~5% of dietary manganese, while women with normal iron stores absorbed only ~1% on a low-manganese diet supplying 0.7 mg manganese per day. Magnesium deficiency in animals increases manganese absorption, while iron deficiency is known to increase manganese absorption in both animals and humans. The effect of iron deficiency on manganese absorption is apparently due to the ability of the divalent metal transporter 1 (DMT1), the primary non-heme iron transporter in the intestine, to transport not only iron, but also manganese, as well as some other trace elements. Thus, iron deficiency, a global nutritional problem, particularly among women of reproductive age, is a potential risk factor for manganese toxicity when intestinal manganese exposure is high.

Developmental stage is also important in determining the availability of manganese. A much higher efficiency of manganese absorption and retention has been reported during the neonatal period in infants. For example, 20% of ingested manganese has been reported during the neonatal period in infants. For ciency of manganese absorption and retention has been ciency in both animals and humans. The effect of iron deficiency on manganese absorption is apparently due to the ability of the divalent metal transporter 1 (DMT1), the primary non-heme iron transporter in the intestine, to transport not only iron, but also manganese, as well as some other trace elements. Thus, iron deficiency, a global nutritional problem, particularly among women of reproductive age, is a potential risk factor for manganese toxicity when intestinal manganese exposure is high.

Developmental stage is also important in determining the availability of manganese. A much higher efficiency of manganese absorption and retention has been reported during the neonatal period in infants. For example, 20% of ingested manganese has been reported to be retained in term infants who are fed with formula. An additional factor that makes the neonate vulnerable to manganese excess is that the uptake of manganese in the developing brain during this developmental period is relatively high.

However, some factors contribute to protection against manganese accumulation in vulnerable tissues like the brain. For example, absorbed manganese is first delivered to the liver and considerable manganese is found in the bone. In addition, the blood-brain barrier reduces the uptake of manganese into the brain from the blood. Moreover, excess manganese can be reduced by secretion into the bile and pancreatic fluid. Thus, under normal circumstances, manganese homeostasis mecha-

**Table 1 Manganese-dependent metalloenzymes.**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>Arginase</td>
<td>Final step in the urea cycle</td>
</tr>
<tr>
<td>Glutamine synthetase</td>
<td>Controls body pH and ammonia removal from body</td>
</tr>
<tr>
<td>Manganese superoxide dismutase</td>
<td>Mitochondrial enzyme that catalyzes the dismutation of superoxide radical. Acts as primary defense against free radicals produced in the mitochondria</td>
</tr>
<tr>
<td>Pyruvate carboxylase</td>
<td>Carries out the conversion of pyruvate to oxaloacetate in the mitochondria</td>
</tr>
</tbody>
</table>

**BIOMARKERS OF MANGANESE EXPOSURE**

Sensitive biomarkers of manganese exposure and nutritional status are not available. However, some estimate of manganese status can be based on blood concentrations, activity of manganese-dependent enzymes, and tissue manganese concentration, especially in experimental animal studies. The ready availability of blood makes it the tissue of choice in human biomarker studies, especially in large-scale epidemiologic studies. However, there are some important caveats to consider in the use of blood-based measures of manganese exposure. For example, red blood cell manganese concentrations are considerably higher (10–15-fold) than those found in plasma (~1 to 2 μg/L). Thus, slight hemolysis, a not uncommon occurrence in phlebotomy, can result in arti-
ficially raised plasma or serum manganese, and provides an advantage to using whole-blood manganese concentration instead, if available. However, blood manganese levels are also affected by developmental life stage; they tend to be high in neonates and drop to adult levels by 1 year of age. Pregnant women also have elevated blood manganese. Although some studies have found that plasma or blood manganese reflected manganese intake/exposure, overall, these measures are not a sensitive or reliable indicator. There has been some research interest in using lymphocyte manganese superoxide dismutase (MnSOD) as a biomarker of manganese exposure. However, again, the reliability of this measure is questionable because it is not specific and MnSOD activity is influenced by other common exposures, such as alcohol, non-heme iron, strenuous exercise, and diets rich in polyunsaturated fatty acids. Little research has been done on manganese-containing enzymes as biomarkers of manganese exposure. Measuring manganese in other tissues, besides blood, such as liver or bone, is of limited utility due to the need for invasive tissue biopsy.

MANGANESE AND BIRTH OUTCOME

The effects of manganese intake and status on fetal development and birth outcome have been an area of interest in animal studies by nutritional toxicologists, but the literature on the relationship between manganese status and pregnancy outcomes in humans is very sparse. However, this is an area of potential public health interest because high manganese exposure during pregnancy may have toxic effects on the developing fetus. Women who are particularly vulnerable to high levels of manganese exposure are those whose place of work or residence brings them into contact with manganese-contaminated dust, which may be produced as a byproduct of the steelmaking industry, or who consume well water with a very high manganese content. On the other hand, manganese is an essential mineral nutrient and is needed for proper fetal development. However, optimal manganese levels have not been defined. Two recent studies have provided some intriguing new findings concerning the relationship between manganese and birth outcomes.

Intrauterine growth retardation

Fetal growth restriction is an important cause of perinatal morbidity and mortality. For example, neonatal mortality is 5-fold higher in small-for-gestational age infants born at 38 weeks compared to infants with a normal birth weight. There are several known risk factors for neonatal growth restriction including smoking, low prepregnancy weight, constitutionally small mother, poor maternal weight gain and nutrition, hypertension, infections, severe anemia, vascular disease, congenital malformations, and chromosomal abnormalities. Vigeh et al. have now reported on the relationship between whole-blood manganese concentration and intrauterine growth restriction. In this study, 401 paired mothers (age 18–35 years) and neonates in Tehran, Iran, were initially identified as potential study candidate dyads. After excluding some participants with chronic conditions such as heart disease, chronic hypertension, diabetes, cancer, renal failure, positive test for hepatitis B virus antigen or human immunodeficiency virus (HIV), and another group of subjects due to delivery of more than one infant, obese mothers (BMI > 30), and mothers with preeclampsia, placental previa or congenital malformation, or unreliable samples, there were 271 eligible pairs for study.

Vigeh et al. found that 40 (15%) of infants from the study cohort of 271 infants were diagnosed with intrauterine growth retardation (IUGR). IUGR was defined as a newborn’s weight lower than the tenth percentile for its gestational age, based on growth curves from the United States. Among the mothers, 38 (14%) were anemic. Anemic mothers had a 15% higher blood manganese concentration than their non-anemic counterparts (21.1 vs. 18.4 μg/L) and it was significantly and negatively correlated with hemoglobin and hematocrit. On the other hand, maternal blood manganese concentration of infants with IUGR was 13% lower than that of mothers who had normal infants (16.7 vs. 19.1 μg/L). In contrast, manganese concentration of umbilical cord blood from IUGR infants was 17% higher (44.7 versus 38.2 μg/L) than that of their normal counterparts. Vigeh et al. also reported that the weight of the mother just before delivery was lower in mothers who gave birth to infants with IUGR, and these mothers were more likely to be nulliparous women. Correlation analysis of maternal blood manganese concentration and birth weight of the neonate tended (P = 0.12) to be positive, while a significant, but modest (r = 0.14), negative correlation was evident between birth weight and umbilical cord blood manganese. Multiple logistic regression analysis was also used to ascertain whether blood manganese was an independent risk factor for IUGR. In this analysis, it was found that blood manganese was a significant explanatory variable for IUGR risk when controlled for other independent variables, such as nulliparity, blood pressure, pregnancy weight gain, maternal BMI, height, end pregnancy weight, hematocrit, age, gestational age, and sex of the newborn.

Overall, these findings in the study by Vigeh et al. are consistent with the notion that blood manganese is associated with the risk of IUGR. However, as the authors point out, there are some important limitations to this study, such as the fact that IUGR develops at various
times during gestation and diagnosis of the condition usually occurs around week 32 as the fetus begins a rapid growth period. In the current study, blood was collected only at the time of delivery, limiting a potential causative interpretation of the association between maternal blood manganese and fetal development.

The directionality of the observed differences in blood manganese and fetal growth are difficult to interpret at our current state of knowledge about manganese and birth outcome. It is also still unclear why IUGR is associated with lower maternal blood manganese, but higher umbilical cord blood manganese.

**Birth weight**

Some additional light has been shed on the relationship between blood manganese and birth outcome in a recent report by Zota et al. These researchers investigated the association of blood manganese and infant birth weight in a cohort of 470 mother-infant pairs from Oklahoma. The study infants were born at term (>37 weeks’ gestation). These investigators found no association between umbilical cord blood manganese and infant birth weight. However, they did find a non-linear relationship between mother’s blood manganese and infant birth weight. At the fifth percentile of mother’s blood manganese, birth weight was 169 g lower than at an optimal empirically determined higher manganese concentration, while maternal blood manganese at the 95th percentile was associated with a slight reduction (46 g lower) in birth weight, which suggests a possible inverted U-shaped relationship between these two variables. The authors of this American study suggested that more studies are needed in populations with higher blood manganese concentrations to better define the apparent negative effect of high blood manganese on birth weight.

**CONCLUSION**

The findings of these recent studies are noteworthy because in both studies, low maternal blood manganese concentration was associated with poorer birth outcomes (increased risk of IUGR and lower birth weight). However, many questions remain to be answered before we have a sufficiently clear picture of the role of manganese in various birth outcomes. For example: 1) Are the lower blood manganese concentrations found at the time of delivery in mothers that gave birth to IUGR infants a reflection of “manganese deficiency” or are they a proxy for other unmeasured critical factor(s) associated with lower blood manganese concentrations? 2) What is the meaning of higher cord blood manganese in IUGR infants? Is the modestly higher (17%) manganese in cord blood indicative of “manganese toxicity”, or do they reflect different distribution patterns of manganese in the IUGR infant-mother dyad? 3) Is the lower blood manganese in mothers who gave birth to IUGR neonates caused by a greater sequestering of manganese in the cord blood?

Unfortunately, our ability to answer these questions, given our current state of knowledge of maternal and fetal manganese handling, is limited. Additional research in this area of trace mineral physiology and nutrition, as well as additional epidemiologic research related to the role of manganese exposure in birth outcome, appear to be warranted and, hopefully, will be encouraged by these new studies.

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