11 Prenatal and Neonatal Mineral Deficiencies: Magnesium, Zinc, and Chromium

Mildred S. Seelig / Goldwater Memorial Hospital, New York
University Medical Center, New York, New York

I. Introduction

Until recently, there has been little cognizance taken of gestational and infantile deficiencies of minerals, additional to calcium and iron. This is particularly true for magnesium, about which a large body of knowledge of its metabolic importance and risks of deficiency has accumulated and about which exhaustive reviews have been written [1-10]. Its early recognition as a pharmacologically active substance [11], which has been applied to the treatment of eclampsia from the first third of this century [12,13], might be responsible for its general consideration as a drug instead of a nutrient. The trace minerals, such as zinc and chromium, have more recently been identified as nutrients, deficiencies of which cause specific clinical abnormalities. Not applicable to the dramatic relief of life-threatening clinical disorders, zinc and chromium retain their consideration as nutrients. Inadequacies of each of these essential minerals, from the time of conception throughout life, are associated with malfunctions, malformations, and acute and chronic diseases–the nature of which depends on the time, duration, and degree of the deficiencies. Difficulties in detecting these minerals in clinical material have hampered application of basic scientific and epidemiologic findings to patients. New and improved procedures now being available, obstetricians, neonatologists, and pediatricians should be alert to the possibility that inadequacies of magnesium, zinc, and chromium might all contribute to disorders of pregnancy and infancy. Maintenance of optimum intakes or repletion of deficiencies early in life can prevent some disorders and cure others. Therein may be the answer to many chronic diseases, even those of adult life.

II. Magnesium

First shown to be essential for growth in the mouse in 1926 [14], the acute magnesium deficiency syndrome was soon produced in rats [15]. It is characterized by hyperreactivity and nervousness, terminating in convulsions. Pathologic changes were early shown to involve especially the cardiovascular and renal tissues [1]. The type of damage is influenced by other nutritional factors. The lesions caused by moderately long intakes of diets that are low only in magnesium cause predominantly small artery disease and cardiac disorders [2]. Acute magnesium deficiency, which includes cardiac dysfunction as well as neuromuscular irritability, is now recognized in humans, but it was first identified as a clinical disorder (grass tetany) in ruminants during lactation [16]. It is caused by conditioned magnesium deficiency late in pregnancy and during lactation, and is treatable and preventable by magnesium [17–21]. Of interest is the observation that grass tetany of ewes occurs most frequently in flocks with a high incidence of toxemia before lambing [20]. Two years after magnesium deficiency was identified in cows, hypomagnesemia was reported in human eclampsia [22]. It has been reported many times since [1], but magnesium is traditionally considered the "drug of choice" in preeclampsia and eclampsia [23–26], not a nutrient, deficiency of which might have contributed to the maternal and infantile disorders in which it is efficacious.

Neonatal and infantile hypomagnesemia has been accepted as a serious metabolic problem that can cause refractory hypocalcemic convulsions, since the condition was reported in 1965 in a newborn infant of a mother with intestinal malabsorption [27]. The same year it was discovered in an infant with isolated malabsorption of magnesium [28]. Other maternal disturbances were soon thereafter found contributory to neonatal hypomagnesemia (Section II.E), including eclampsia, which is associated with a high incidence of low-birth-weight infants, many of whom have lower than normal magnesium serum levels [29].

A. Magnesium Deficiency and Gestational Disorders

Many gestational disorders have manifestations in common with changes that have been produced in experimental models of magnesium deficiency. Such alterations include:

1. Increased secretion of aldosterone and renin [30,31]
2. Sodium and water retention and potassium loss [5,8,9,32]
3. Increased arteriolar contractility (Section II.C.1)
4. Increased release of catecholamines, and hyperreactivity to vasopressors (Section II.C.1)
5. Coagulopathy (Section II.C.2)
6. Renal damage (Section II.C.3)

7. Neuromuscular irritability and convulsions (Section II.C.4)
8. Increased secretion of parathyroid hormone (PTH) (Section II.D.3)

Because magnesium deficiency causes so many aberrations that resemble those seen in complicated pregnancies, and because such complications are not rare (an estimate has been made that in the United States there are at least 100 deaths daily of fetuses whose mothers had toxemia of pregnancy [24], it is important to see whether the typical American diet provides sufficient magnesium for the pregnant woman. More than dietary factors must be considered, however. Hyperemesis can contribute; should not supplements include magnesium at such times? Immature mothers, who still require magnesium for their own growth and development, have little or no reserve. Frequent pregnancies and multiple births are contributory, as is diabetes mellitus, all of which cause depletion of maternal magnesium.

B. Evidence of Magnesium Deficiency During Pregnancy

1. Magnesium Balance During Pregnancy: Studies done in Europe and the United States in the first third of this century show that magnesium retention is reliably maintained during pregnancy when intakes are at least 450 mg per day [33], the basis of the current Recommended Dietary Allowance (RDA) during pregnancy [1]. Since those studies were done, the average daily intake of magnesium has fallen, and intakes of nutrients and supplements that increase magnesium needs have risen. Two studies of middle-class pregnant women (midwestern Americans), reported in 1976 [34] and 1979 [35], showed daily magnesium intakes of 103–333 mg, and an average net magnesium loss of 40 mg [35] (Fig. 1). Negative magnesium balance during active anabolism is clear evidence of deficiency.

2. Magnesium Serum Levels During Normal and Abnormal Pregnancies: Pregnant women tend to develop somewhat lower serum levels of magnesium than are seen in age-matched nonpregnant women [1]. This change is generally attributed to hemodilution, but even after correction for this factor, hypomagnesemia has been shown to be real during the first half of pregnancy and during the last month (Table 1). A preliminary study of the magnesium status of preeclamptic women, and of their response to moderate magnesium doses of 800–2000 mg Mg^{2+}, compared to the magnesium status of normal women near term, before and after 100 mg Mg^{2+} intramuscularly, demonstrated retention of almost all of the administered magnesium by both groups [37]. All pathologic manifestations of the preeclamptic patients showed improvement.

During preeclampsia and eclampsia, there are definite decreases in serum magnesium levels, often to below 1 mEq/liter [1], except at the end of the abnormal pregnancy, when the level often rises. This might reflect

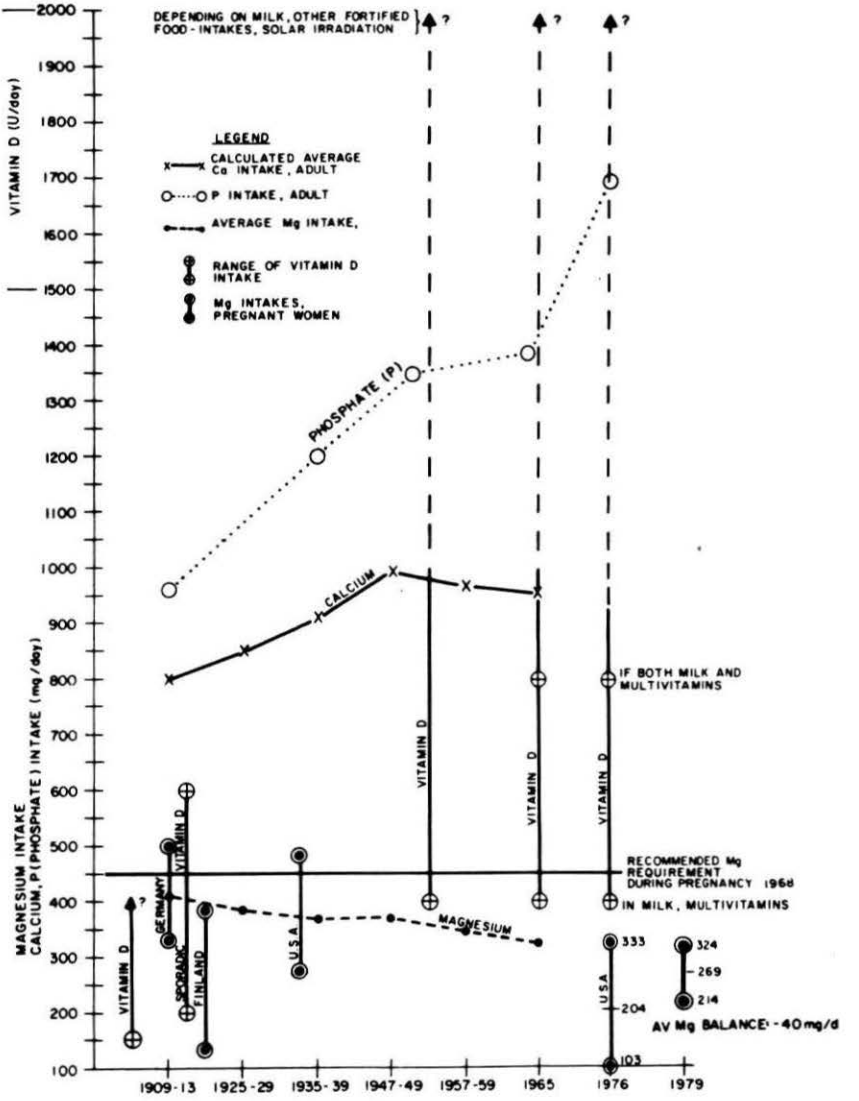

Figure 1 Intakes of magnesium, calcium, phosphorus, and vitamin D during pregnancy. (From Ref. 1.)

Table 1 Magnesium Serum Levels in Pregnant Women, as Measured and Corrected for Hemodilution

Gestation (days)	Magnesium levels in serum (mEq/liter ± S.D.)	Corrected for hemodilution
3	1.87 ± 0.10	1.83
31–60	1.83 ± 0.10	1.79
61–90	1.73 ± 0.09	1.77
91–120	1.69 ± 0.14	1.91
121–150	1.60 ± 0.18	1.96
151–180	1.56 ± 0.10	2.05
181–210	1.49 ± 0.10	2.08
211–240	1.53 ± 0.12	2.16
240–270	1.39 ± 0.17	1.88
Nonpregnant	2.09 ± 0.07	

Source: Reprinted with permission from The American College of Obstetricians and Gynecologists. *Obstetrics and Gynecology 25*, 253–254 (1964). (From Ref. 36.)

hemoconcentration at that time, or possibly renal damage. Eclamptic patients have tolerated as much as 150 g $MgSO_4$ (15 g Mg^{2+}) over a 5-day period without development of dangerous hypermagnesemia [38]. The necessity for repeated injections, or continuous magnesium solution infusions (Fig. 2) to sustain the anticonvulsant and antihypertensive effect, has suggested to several researchers that magnesium was being retained, and that this might indicate that magnesium deficiency might be contributory to development of the disease [1,37,40–42].

C. Correlation of Signs of Preeclampsia and Eclampsia with Those of Magnesium Deficiency

The possible contribution of magnesium deficiency to the pathogenesis of eclampsia is diagramatically shown in Figure 3 and described below.

1. Arteriolar Spasms: Toxemia of pregnancy is considered predominantly a vasospastic disease [23,24,26]. The arteriolar spasms can contribute to uterine and placental ischemia, and to the hypertension without which preeclampsia is not diagnosed [26]. Thus the demonstration that decreased ratios of Mg + K/Ca + Na in vivo [3,43] and in vitro [44,45] causes increased arterial resistance and increased arterial muscle contraction is germane to the arteriolar spasms of preeclampsia. Conversely, at such low rates of magnesium infusion to dogs as barely to affect arterial resistance, catecholamine-induced arterial contraction is substantially diminished [46,47]. This observation may contribute to the understanding of the efficacy of relatively low doses of magnesium in lowering the

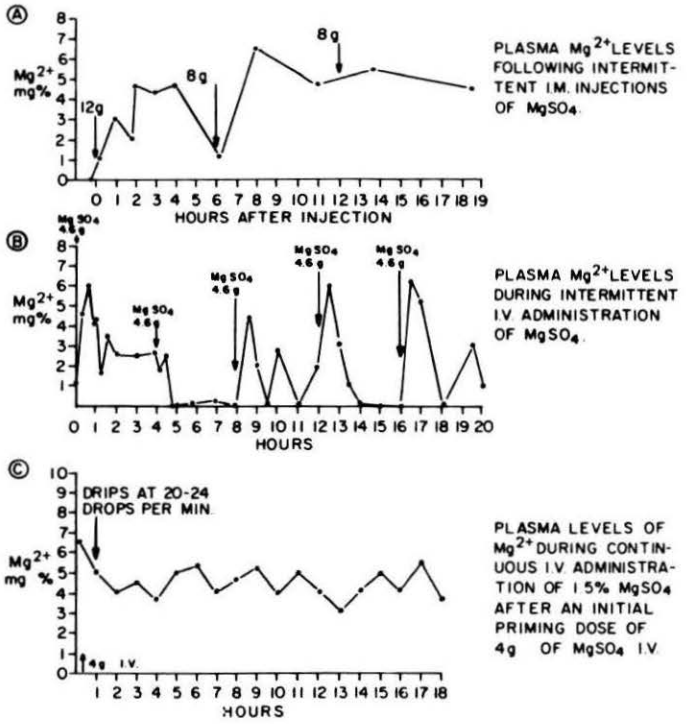

Figure 2 Plasma magnesium levels in eclamptic women treated with $MgSO_4$ intramuscularly and intravenously. (From Ref. 39.)

blood pressure of preeclamptic patients, since they exhibit increased reactivity to catecholamines, and increased epinephrine and norepinephrine excretion [48-50]. Possibly also pertinent to the toxemic patients' hypertension is the increase in catecholamine release from adrenergic granules that is caused by low magnesium levels [51].

When pharmacologic doses of magnesium are used to control hypertension, the vasodilatation seems to be mediated by magnesium's displacement of calcium that is bound to the cell surface, thereby uncoupling excitation from contraction [43,52-54].

2. Coagulopathy: Although not always found in eclamptic patients [26], when increased blood coagulability exists, it constitutes a risk of antenatal thrombo-

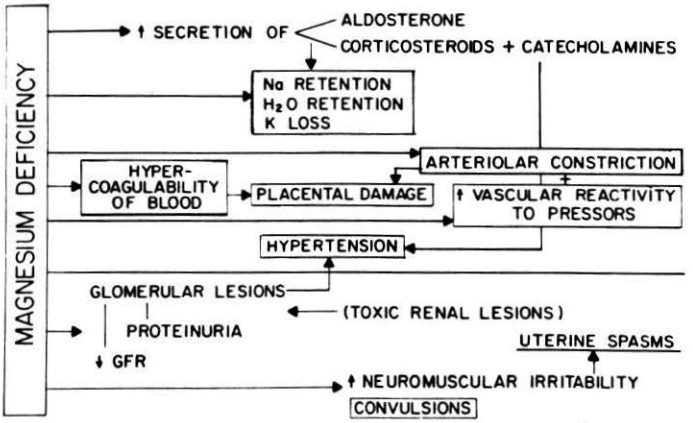

Figure 3 Possible contribution of magnesium deficiency to pathogenesis of eclampsia.

embolism [55,56]. Coagulopathy may also play a role in placental infarction and scarring, to which arteriolar spasm contributes [50,57], and to renal damage [56]. Preeclamptic women have shortened coagulation time and increased cohesiveness of platelets, both abnormalities of which are counteracted by administration of magnesium [42].

It is possible that magnesium deficiency is contributory to this abnormality as well. Thromboembolic disease with increased adenosine diphosphate (ADP)-induced platelet aggregation has been reported in patients with marginal magnesium deficiency associated with latent tetany [58,59]. Magnesium-deficient calves have exhibited shortened thrombin clotting time; magnesium-deficient rats have increased ADP-platelet aggregation [60]. Hypercoagulability, caused by feeding rats a thrombogenic diet, was counteracted by oral magnesium chloride, as was that of acutely butter-loaded dogs [61]. In vitro studies with high concentrations of magnesium show direct inhibition of several of the coagulation factors [6,62]. Conceivably, this effect might be helpful in the treatment of eclamptic patients of pharmacologic doses [42].

3. Renal Damage: The typical early renal lesion of the magnesium-deficient rat is formation of intraluminal microliths [63,64]. Proteinuria [65] and impaired glomerular filtration [64] have also been reported, as have glomerular degenerative changes [65,66]. Glomerular lesions are the predominant renal changes in eclampsia. Their etiology is uncertain. Coagulopathy has been

implicated [56], in which event magnesium anticoagulant activities might be protective.

4. Neuromuscular Hyperirritability: Restlessness, hyperexcitability, and finally sound-induced convulsions constitute the classic signs of magnesium depletion [8-10,15]. Comparable signs develop in conditions of acute clinical magnesium depletion and are seen in eclampsia. All are rapidly responsive to intravenous or intrathecal magnesium injections. It is noteworthy that susceptibility to convulsions of magnesium deficiency increases during periods of protein synthesis and new tissue formation [67]. This might contribute to our understanding of the convulsions of eclampsia that usually occur in the third trimester.

D. Gestational Hyperparathyroidism with Hypocalcemia

Gestational hyperparathyroidism is so common as to be considered physiologic [68,69]. It is associated with low normal or subnormal plasma phosphorus levels, as is to be expected, but hypocalcemia is also found, especially in the third trimester [70-72]. That the hyperparathyroidism is real is shown by increased levels of immunoparathyroid hormone during pregnancy [73]. Although hyperparathyroidism is generally considered a normal maternal response to fetal drains on calcium, there is a much greater likelihood of complications of pregnancy and fetal loss and morbidity among hyperparathyroid women than among normal women [74]. Asymptomatic hyperparathyroidism has been found in mothers of infants with neonatal and infantile convulsive hypomagnesemic hypocalcemia [27,75,76]. In view of the fact that this condition is associated with low magnesium levels in mothers and infants, the possibility that maternal magnesium deficiency is contributory should be considered, and the response to magnesium tested.

Magnesium deficiencies can cause parathyroid hyperplasia [77], and perfusion of goat and sheep parathyroids with hypomagnesemic, normocalcemic solutions increases parathyroid hormone (PTH) secretion [78-81]. Perfusion with solutions of higher magnesium concentration, and magnesium administration, have inhibited excess PTH secretion.

E. Magnesium Deficiency in Fetus and Neonate

1. Fetal Magnesium Requirements: Fetal requirements of magnesium increase with approach to term It has been estimated that in the ninth to tenth lunar month, the daily deposit of magnesium in fetal tissues doubles, with probable accumulation of about 9 mg per day during the last month [33]. Analysis of fat-free tissues from fetuses of different weights show that magnesium concentrations of 0.21-0.22 mg/kg are attained by the 200-g fetus and sustained as it

grows to about 2 kg [82,83]. From 3 to 4.5 kg, the magnesium concentration reaches 0.25–0.28 mg/kg. Thus the fetal magnesium requirement becomes substantial in the last trimester (Fig. 4). Note must be taken that these data were obtained from spontaneous fetal losses, and thus probably were products of gestational abnormalities. How much magnesium is accrued by normal fetuses is speculative. It is noteworthy that a woman who consumed a diet unusually rich

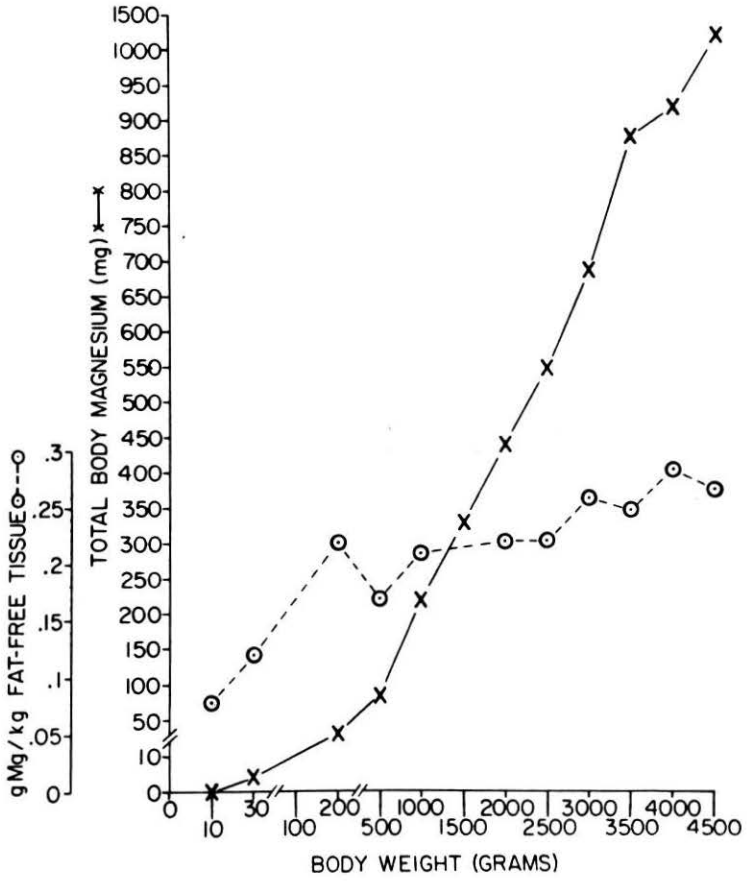

Figure 4 Fetal gains in magnesium by increasing weight (tissue from spontaneous abortions and stillbirths). (Adapted from Refs. 82 and 83.)

in magnesium (over 600 mg daily) retained over 9 g of magnesium in her last trimester. This was in contrast to the retention of less than half that amount of magnesium by a teen-aged primipara, who had had a poor nutritional history before her pregnancy [84,85].

2. Effect on Fetus of Experimental Magnesium Deficiency: Severe magnesium depletion (1/200 normal intake) during the entire gestation in rats caused 100% fetal loss [86,87]. The shorter the duration of the deficiency, the less severe the damage to the fetuses. Deficiency during the first half of gestation caused multiple anomalies, predominantly of skeleton, heart, and lungs. Lesser magnesium deficiency (1/130 normal intake) throughout pregnancy also caused almost complete fetal wastage. When the deficiency was maintained only during the second half of pregnancy, microcytic anemia and edema were present in all of the pups, even though the mothers appeared healthy [88]. Maternal tissue levels of magnesium were affected much less than were fetal tissue levels, but the serum magnesium levels were comparably low (0.3 mEq/liter) in dams and pups [88]. Less severe magnesium deficiency (1/10 normal intake) in pregnant rats resulted in prolonged labor; 36% of the pups were stillborn, and by the fifth day after birth only 7.5% were still living [89]. The deficient mothers looked normal but had subnormal serum magnesium levels. The pups in both studies were small for gestational age; in one [88], placental damage was noted.

3. Neonatal Hypomagnesemia Associated with Gestational Abnormalities: *Influence of Toxemias of Pregnancy*: There are insufficient data to conclude that the high incidence of placental and fetal abnormalities, of stillbirths and neonatal deaths, and of neonatal and infantile deaths among preeclamptic and eclamptic women are caused by gestational magnesium deficiency. Perinatal mortality has remained between 25 and 35% of all infants born to eclamptic women from the eighteenth century on, regardless of the combination of drugs used in treatment: anticonvulsants and other neurodepressants and tranquilizers; diuretics and other antihypertensives [26,49]. Only in the studies in which treatment was restricted to bed rest and magnesium sulfate alone has the mortality been reduced to about 10% [23-26,90,91]. Further supportive evidence that gestational magnesium deficiency might lead to fetal loss and abnormalities derives from the high rates of fetal complications among mothers with gestational abnormalities in which magnesium inadequacy seems likely to have played a role. Direct correlation of low magnesium maternal and cord blood levels with neonatal complications is difficult, since cord blood analyses reveal wide ranges: from 0.7 to 2.0 mEq/liter by atomic absorption spectroscopy [92,93]. Correlation of infantile with maternal status, and with maternal magnesium levels, has been infrequent [1]. Furthermore, serum or plasma magnesium levels taken at birth are often difficult to interpret. Intrauterine hypoxia, difficult labor, and

other causes of neonatal hypoxia–acidosis or hyperosmolarity–can all cause elevations in serum magnesium levels, as intracellular magnesium is lost to extracellular fluids and blood [1,94]. Infantile hypermagnesemia is a serious risk of magnesium treatment of eclamptic mothers shortly before delivery, since newborn infants (particularly prematures) have slow renal magnesium excretion [95,96].

Maternal Hyperparathyroidism, Neonatal Hypoparathyroidism, and Magnesium Deficiency: Maternal hyperparathyroidism has long been blamed for the transient neonatal hypoparathyroidism, to which convulsive hypocalcemia is attributed [97,98]. However, maternal PTH does not cross the placental barrier [99] and thus there cannot be direct inhibition of fetal PTH secretion by excess maternal PTH. Another cause must thus be sought for low neonatal PTH secretion [73,100,101], to which is attributed the low calcium/phosphorus ratio that is associated with irritability and seizures. There is evidence that neonatal magnesium deficiency can be responsible for impaired PTH release [102] and decreased target organ responsiveness to PTH [103] with resultant hyperphosphatemia and hypocalcemia [1].

Maternal Diabetes Mellitus; Malabsorption and Neonatal Hypomagnesemia: Diabetes mellitus is accepted as a disease that is associated with hypomagnesemia [104,105] as a result of the importance of insulin in cellular uptake of magnesium [106], and the renal magnesium wastage that is caused by hyperglycemia [107]. It is therefore not surprising that pregnant diabetic women, or those who develop gestational diabetes, have infants with neonatal hypomagnesemia [29,101,108–114]. They can be premature or large for gestational age, or both, often have respiratory distress and acidosis (which can mask neonatal magnesium inadequacy), and frequently exhibit rising serum phosphorus and falling calcium and magnesium by 24–48 hr after birth [111]. Subnormal neonatal serum magnesium levels are related to the severity of maternal diabetes, youth of the mothers, parity, and prematurity [29,109,114].

Maternal malabsorption was the predisposing factor in the neonate, whose refractory hypocalcemic convulsions were first found to be caused by hypomagnesemia [27].

4. Low-Birth-Weight Infants with Hypomagnesemia and Irritability: Low-birth-weight infants, whether born prematurely or suffering from intrauterine growth retardation (IUGR), generally have lower serum magnesium levels than do term infants of appropriate size [29,93]. When the low birth weight is due to prematurity, low blood magnesium levels reflect subnormal mineral accumulation in the final weeks of gestation. Those with IUGR are provided less via the damaged placenta. The magnesium content of 1.5-kg babies is only 42% that of normal-size term infants; that of 2.5-kg babies is 76% and that of a full-term baby [83]. IUGR infants often exhibit neonatal hyperirritability and jitteriness, as well as

being more subject to seizures than are term infants [110,113-116]. Neonatal magnesium deficiency in such infants might be masked by birth hypoxia or acidosis, which is common in such infants [116]. Determination of percentage retention of a parenteral loading dose of magnesium is a better means of detecting magnesium deficiency in neonatal infants with irritability or seizures than is reliance on serum levels [117-119]. It is now accepted that neonatal hypomagnesemia can be an important causative factor in neonatal "jitteriness" and metabolic seizures [1,120-122]. Where magnesium deficiency is the predisposing factor, its repletion is essential. Without it, convulsions can be refractory to calcemic or anticonvulsant therapy [122]. In fact, calcemic agents have intensified the seizures, and might even increase the risk of cardiovascular and renal damage, producing degenerative and calcific lesions such as those produced by diets low in magnesium and high in calcium, phosphate, and vitamin D in rats, dogs, and ruminants [1].

5. Neonatal Magnesium Deficiency Caused by Exchange Transfusion, Surgery, and Magnesium Malabsorption: Exchange transfusion with blood preserved with acid citrate dextrose (ACD) blood has caused severe infantile hypomagnesemia [123-129]. Citrate infusions cause hypomagnesemia [130]; ACD blood prime has lowered plasma magnesium levels profoundly [131]. Resultant arrhythmia (in heart surgery patients) has responded to magnesium [132]. The citrate-induced hypomagnesemia might be responsible for sudden infant death during exchange transfusions [133]. The customary procedure for infants receiving exchange transfusions who develop hyperirritability, seizures, or cardiac arrhythmias is to monitor serum calcium. Magnesium is generally investigated only on failure to improve with calcium treatment. Evidence has been presented that abnormal signs and symptoms develop almost exclusively in infants with both hypocalcemia and hypomagnesemia [126]. Thus magnesium, as well as calcium, should be routinely replaced in infants undergoing exchange transfusions. Neonatal infants who have undergone surgery to correct anomalies, and who have received ACD blood transfusions or infusions with magnesium-free fluids, are also at risk of hypomagnesemia [134,135].

6. Increased Susceptibility to Seizures in Bottle-Fed Versus Breast-Fed Infants: Bottle-fed infants are far more vulnerable to jitteriness and seizures caused by hypomagnesemic hypocalcemia than are breast-fed babies. Hypocalcemia is more common than is hypomagnesemia, but the latter has also been found associated with the disorder, in the absence of hypocalcemia [120,136]. Characteristic of breast-fed infants are higher serum magnesium and calcium levels than are seen in formula-fed infants [137]. Normal cow's milk-fed infants also exhibit the same pattern of magnesium, calcium, and phosphorus distribution [92]. Contributory to these differences is the difference in mineral ratios in cow's milk versus human milk. Cow's milk has three times as much magnesium and calcium,

and seven times as much phosphorus as does human milk [138], proportions more appropriate for calves than for human infants. No data have been found on the influence of the mother's magnesium status on her success of lactation, on the magnesium content of her milk, or on the magnesium status of her nursing infant. The woman who had retained 9 g of magnesium during her last trimester and who ingested over 600 mg of magnesium daily, remained in magnesium equilibrium during her successful lactation [85]. Another woman, who was lactating heavily, developed hypomagnesemic tetany on a diet delivering 500 mg of magnesium per day; she retained 78% of a loading test of magnesium [139]. The recent study of magnesium content of breast milk in the midwestern United States [140] shows that it remains stable throughout lactation. Almost identical values were obtained throughout lactation among the poor in India [141]. This probably explains the development of symptomatic hypomagnesemia in the heavily lactating woman, despite her seemingly adequate magnesium intake [139]. Applying to humans the data from a magnesium-deficiency rat study [89], in which a tenth of the normal magnesium was provided during gestation, failure of lactation would be expected in women with gestational magnesium inadequacy. Not only did the deficient rats have poor milk flow, but the magnesium content of the milk was little more than half that of controls.

III. Zinc

Identified as the cause of dwarfism, hypogonadism, and anemia of boys in the Middle East [142], zinc deficiency has attracted much attention in recent years. Very low plasma and hair levels of zinc have been found in American children [143], the complete significance of which is under active investigation.

A. Zinc Deficiency During Gestation

That decreasing levels of zinc have been found during advancing stages of pregnancy in low-income groups in the Middle East (Iran [144] and Turkey [145]) is not surprising in view of the identification there of zinc deficiency as a clinical disorder. However, even in well-nourished, affluent Turkish women, serum zinc levels are low early in pregnancy. In this group, which consumed diets rich in animal proteins, the plasma levels rose during pregnancy [145] to levels reported in American pregnant women at term [146]. This level, however, is only half that found in nonpregnant women. The low serum or plasma zinc levels during pregnancy, even among those assumed to be adequately nourished, might indicate either estrogen-induced lowered levels [147] or lowering of maternal zinc to meet fetal needs. That pregnancy diminishes zinc reserves is indicated by the lower maternal hair-zinc levels in high-parity mothers than in primiparas [148]. It has been proposed that zinc nutriture, which might be marginal in the United

States, can become a problem during pregnancy [149]. The intake of zinc required ranges from at least 8 to 12 mg per day, depending on the percentage of dietary zinc that is absorbed. It is estimated that the pregnant woman must retain 750 μg of zinc daily during the last two trimesters for optimal fetal growth and development [149], and suggested that zinc intake during pregnancy may be suboptimal in some [150].

1. Experimental Gestational Zinc Deficiency: Experimental studies suggest that the mother does not mobilize sufficient zinc from her own stores (e.g., from bone) to meet fetal requirements, even with zinc deficiency severe enough to cause teratology [151]. Marginal to low intake of zinc, even for short periods during gestation, has caused fetal abnormalities [152]. Different strains of rats have exhibited predilections for specific zinc-induced abnormalities, an observation which suggests that there might be genetic predisposition to manifestations of zinc deficiency [152]. Teratogenic effects predominantly involve the bones, brain, eyes, and lungs.

The high incidence of lung malformations in pups of zinc-deficient rats led to study of the effect of zinc deficiency on surfactants in the lungs. Surfactants, such as lecithin, are necessary for neonatal lung function, to keep the alveoli distended after the infant takes its first breath. Pulmonary lecithin levels were significantly lower in zinc-deficient fetuses than in controls [153]. The gross malformations of zinc-deficient fetuses have been attributed to diminished thymidine incorporation into fetal DNA [154]. Zinc is important, as well, in many enzyme systems and other aspects of protein synthesis [155,155a]. It is also required for cerebroside and lipid synthesis in the brain postnatally [156, 157]. It seems likely that gestational zinc deficiency during the time of most rapid growth of the brain would severely retard its development [158]. In fact, degrees of maternal zinc deficiency of a degree insufficient to cause congenital anomalies have caused early and late (even adult) behavioral disturbances in the progeny of rats [158,159] and monkeys [150], the nature and extent of which depends on the degree and duration of the deficiency.

2. Epidemiologic Clues: In Iran, where zinc deficiency is common in population groups consuming foods largely comprised of cereal products that contain phytates which interfere with zinc absorption [160], a high incidence of anencephaly has been reported [161]. Preliminary epidemiologic observations in the United States prompted the suggestion that there might be a connection between maternal zinc deficiency and fetal central nervous system malformations [162]. It was then observed that women who had complications of pregnancy and who delivered malformed infants had subnormal serum zinc levels, compared with levels in women who had normal pregnancies and infants [163]. Further supporting the premise that zinc deficiencies during pregnancy might be incompatible with normal gestation and fetal development are the gestational

outcomes of two women with the zinc-malabsorption disorder acrodermatitis enteropathica [164,165]. They had had a total of seven pregnancies before adequate treatment was instituted, among which there were one spontaneous abortion and two major congenital malformations. One was an infant with multiple skeletal abnormalities, who died in the neonatal period; the other was an anencephalic stillbirth. One of the women had three normal infants after institution of appropriate therapy.

B. Infantile Zinc Deficiency

Acrodermatitis enteropathica (AE) is a clinical disease of zinc deficiency that is clearly caused by malabsorption of zinc and that responds to zinc administration [165-167]. It provides an appropriate introduction to the problem of zinc deficiency in infancy.

1. Human Milk and Zinc Absorption: Even though breast milk contains no more zinc than does processed cow's milk, it has long been known to be an effective treatment for AE [168]. The greater bioavailability of zinc from human milk than from cow's milk [169] has recently been shown to be mediated by a zinc-binding ligand [170,171]. It has recently been identified as picolinic acid [172], which is present in high concentrations in human milk, is very low in cow's milk, and is undetectable in the infant formulas tested [172, 173].* It is a tryptophan metabolite that requires pyridoxine as a cofactor [155]. This observation explains the low tissue zinc levels of vitamin B_6-deficient rats [174] and the improved absorption of zinc as pyridoxine intakes are increased [175]. It also provides insight into the similarity between AE and pellagra. Both picolinic acid and nicotinic acid derive from tryptophan; pyridoxal phosphate is the coenzyme above the branch point in the pathway leading to formation of both picolinic acid and nicotinamide adenine denucleotide (NAD).

Marketed infant formulas that were low in zinc have had that deficiency corrected [176]. Now that picolinic acid has been identified, perhaps this defect, as well, will be able to be eliminated.

2. Neonatal Zinc Levels and Requirements: Normal newborn infants have higher zinc levels (in hair and cord blood) than do their mothers at time of delivery [148]. Despite this endowment at birth, the neonate does not have zinc reserves. That zinc requirements are high during the first year is indicated by:

1. Daily zinc retention of over 300 mg per day from birth to 5 months, and of about 200 mg per day from 6 months to 1 year [149]

*Similac, Isomil, SMA, and Enfamil.

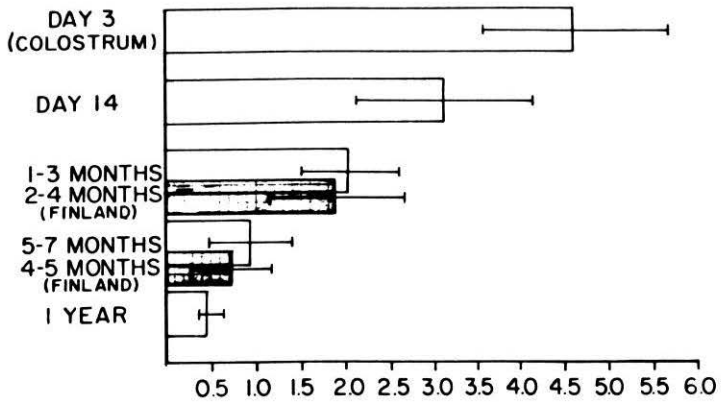

Figure 5 Mean concentration (ppm) of zinc in colostrum and human milk at different stages of lactation in the United States (Indiana) and Finland (middle class). (Adapted from Refs. 140 and 181.)

2. Increases in total body zinc [149]
3. Sharp drops in hair zinc levels of American children in the early months of life [143,177]

The fact that such a sharp decrease after birth was not seen in Thai infants [178] suggests that zinc deficiency during infancy and childhood might well be an American problem. It has been noted that hair and plasma zinc levels are exceptionally low in American infants from affluent families in several cities [143, 179,180]. Anorexia and poor growth were seen in those with hair zinc below 30 ppm [178].

A factor likely to contribute to American infantile zinc deficiency is the general reliance on formula feeding rather than on breast feeding from the time

of birth (a trend that may be in the process of reversal). Early breast feeding may be crucial in sustaining neonatal zinc nutriture, not only because of presence of picolinic acid, but because colostrum and milk during the early weeks of secretion are rich in zinc. It is provocative, however, that the zinc content of milk from American [140] and Finnish [181] middle-class women has been reported as lower (Fig. 5) than that from low-income Indian women [141]. That this might reflect inadequate maternal zinc is suggested by the much higher hair zinc levels in lactating Bushman mothers, compared with levels in milk from inner-city mothers in the United States [182].

It should be noted that the RDA of zinc for infants has been set at 3 mg [183]. This estimate was obtained by calculating the amount of zinc consumed by a totally breast-fed infant, assuming that the milk contained 3–5 μg/ml (an amount in excess of that provided after the first month of lactation). It is likely that the RDA of zinc for infants is too high [169].

IV. Chromium

Chromium was found to be the active component of glucose tolerance factor (GTF) in 1959 [184]. Its deficiency produced a syndrome in rats similar to diabetes mellitus: glycosuria and high fasting glucose levels [185]. Chromium deficiency in vivo causes decreased hypoglycemic response to insulin [186]; nanogram quantities of chromium are required for the optimal effect of insulin in every insulin-dependent system studied [187]. Patients with insulin-dependent diabetes have lower chromium levels than do normal subjects [188], and GTF-chromium increases glucose tolerance of diabetics [187]. In the normal subject, the serum chromium level rises after an oral glucose load. The rise is mediated by release of endogenous insulin, and coincides with a rise in the immunoinsulin level. Absence of the chromium rise suggests a depletion of body stores of chromium [187].

A. Chromium Deficiency During Gestation

These data suggest that gestational chromium deficiency might be contributory to gestational diabetes mellitus. Transfer of GTF-chromium across the placenta might lead to maternal chromium deficiency, prevent the normal maternal chromium response to a glucose load, and cause impaired glucose tolerance. Studies of fetal and maternal chromium levels show that fetal needs are built up at the cost of maternal supplies. Human fetal tissue chromium concentrations increase from the second through the seventh month of gestation, and fall after birth [189,190]. In rats, fetal chromium levels exceed those of the mother,

particularly in the liver [191]. Repeated pregnancies, as with breeder rats, cause progressive declines of tissue chromium levels [187,192]. Hair chromium levels of parous women are as much as a third lower than of nulliparous women [193, 194] and half as much as their infants [194].

Bone ash chromium concentrations of human fetuses increase with gestational age [190]. The tissue fetal levels are influenced not only by the mother's stores and intake, but also by the form of chromium in her diet, since inorganic chromium is poorly absorbed from the gut [187,195] and placental transport of chromium is much better with GTF than with chromium [187]. Adequate placental function is important in achieving transfer of maternal chromium to the fetus, as indicated by the very low hair-chromium levels of infants with intrauterine growth retardation, who are small for their gestational age [196].

B. Infantile Chromium

There is not a close correlation between the individual concentration of chromium of mothers at delivery with the hair-chromium of their newborn infants, but the mean value of maternal hair-chromium is less than half that of the newborn infants [194]. Analysis of tissues from necropsy studies shows that newborn infants have exceptionally high chromium levels [197].

Colostrum has a high content of chromium; mature milk has low concentrations [198]. The high fetal and early breast milk source of chromium contribute to the high hair chromium levels of infants in the first few months of life, compared with values at any later age [194,199].

V. Concluding Comments

Mineral deficiencies during gestation, infancy, and childhood can have serious consequences. Unlike calcium and iron, for which there has been generally accepted clinical concern for many years, deficiencies of magnesium, zinc, and chromium receive little attention by most obstetricians and pediatricians. Magnesium is used as a medication in eclampsia. In neonatology and during infancy, its plasma levels are generally investigated and hypomagnesemia corrected only when standard calcemic treatment fails to control convulsions. The significance of its deficiency goes far beyond correction of immediately life-threatening manifestations, both neuromuscular and cardiac (e.g., arrhythmias of exchange transfusion-induced acute magnesium depletion). Severe gestational depletions of this macromineral and of the micromineral, zinc, cause spontaneous abortions and gross congenital anomalies; less severe deficiencies cause lesser abnormalities and decrease the viability of the newborn. The importance of chromium in glucose metabolism suggests that its deficiency might contribute to gestational

diabetes. All of these mineral deficiencies are interrelated, zinc and magnesium participating in common enzymatic pathways, and diabetes mellitus causing magnesium loss. To what extent deficiencies of these minerals during pregnancy contribute to gestational failures and complications, and to neonatal and infantile morbidity and mortality, requires more study. Also needing further investigation is the prevalence of mineral deficiencies during infancy, as well as the immediate and longer-term sequellae.

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