

NUTRITION IN PREGHANCY

**Selected Papers
from a Seminar
Designed for
Practicing Nutritionists**

**March 9-11, 1981
Louisville, Kentucky**

Edited by

J. Patrick Lavery, M.D.

Printed by

**University Graphics
University of Louisville
Louisville, Kentucky**

Chapter Thirteen

Magnesium Deficiency in Gestational and Infantile Disorders

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Introduction

Magnesium is an essential mineral that plays numerous intracellular and extracellular roles (1). Those experiencing rapid growth and development (as during gestation and infancy) are particularly vulnerable to nutritional deficiencies. It is therefore noteworthy that experimental magnesium deficiency causes changes that resemble abnormalities of gestation and infancy, and that magnesium administration is therapeutic in those conditions (2-4).

Magnesium has long been accepted as an effective treatment of eclampsia (5-8). It is thus considered a drug rather than a nutrient. However, some investigators have noted the similarity of some of the signs of eclampsia to those produced in experimental animals deprived of magnesium (2-8), as well as the tolerance of high parenteral doses of magnesium by the eclamptic patient (5-8). The possibility that a deficiency of this mineral might contribute to abnormalities of pregnancy is rarely considered, largely because low serum magnesium levels are seen in normal, as well as in abnormal pregnancy.

Metabolic studies of pregnant women have demonstrated that positive balance (that should be maintained during this period of new tissue formation) is not reliably achieved on intake below 450 mg/day (10). Those studies, done early in the 20th century, provide justification of the 450 mg RDA for pregnant and lactating women (11). Recent studies have shown that middle class pregnant women commonly eat diets that provide less than half that amount (12,13). Their low intake of magnesium reflects the generally suboptimal intake of this essential nutrient by Americans and Canadians (14-17).

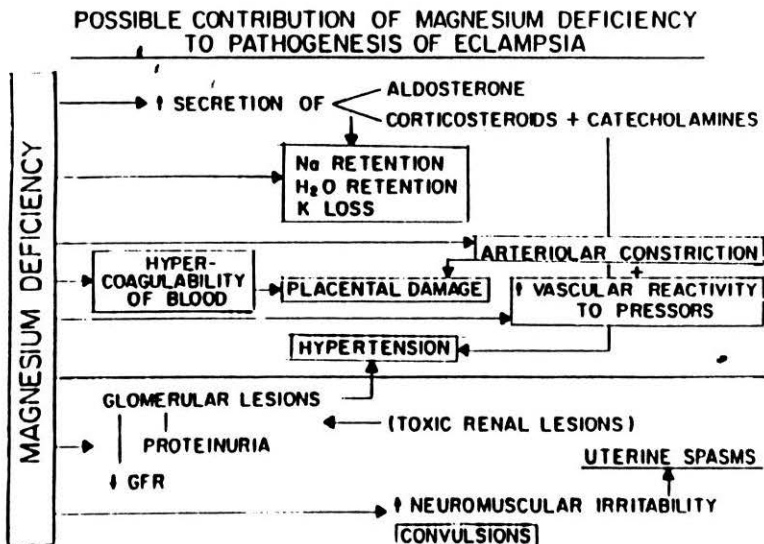
It seems plausible that infants born of mothers with inadequate supplies of this essential mineral might suffer some adverse consequences. Neonatal hypomagnesemic convulsions are a problem in low birth weight infants (18), and in infants with a number of disorders (19), that predispose to low magnesium levels (2-4). Older infants that are bottle-fed are more prone to such convulsions than are breast-fed infants (2-4,20).

These observations provide clues to the need for evaluation of magnesium in dietetic and metabolic surveys during pregnancy and infancy. It is safe to say that diets should include foods rich in magnesium.

Magnesium Deficiency and Gestational Disorders

Manifestations of Magnesium Deficiency that Resemble Those in Abnormalities of Pregnancy

Figure 1



Convulsions of eclampsia, the severe late disease of pregnancy, are associated with hypomagnesemia (2-8, 21,22). It is thus interesting that hyperexcitability and convulsions were the first recognized signs of experimental dietary magnesium deficiency in rats (23). The same year (1932), magnesium deficiency was correlated with neuromuscular irritability and convulsions in lactating cows soon after delivery (24). The risk of magnesium deficiency during pregnancy and lactation is recognized in grazing animals (25).

Eclampsia is a disease in which constriction of the arteries and arterioles causes hypertension and tissue damage (26). There have been studies done that show that low levels of magnesium cause arterial constriction in dogs (27,28) and in isolated tissue *in vitro* (29). Hormones that increase blood pressure are the mineralocorticoid (aldosterone), the catecholamine (adrenalin), and renin. Magnesium deficient rats develop renal and adrenal changes associated with increased secretion of renin and aldosterone (30). The release of catecholamine from adrenal granules is increased when the magnesium concentration is low (2,31). Aldosterone also increases sodium and water retention, which favors edema-formation, so common in preclampsia. There is another way in which magnesium deficiency can intensify this problem. The

enzymes that control sodium, potassium, and water distribution are magnesium-dependent (1). With insufficient magnesium, sodium and water is retained and potassium is lost.

Another abnormality that can develop during pregnancy, and that might contribute to eclampsia, is hypercoagulability of blood (32,33). Mg deficiency also increases blood coagulability (34-27). Mg administration to preeclamptic women has corrected their short coagulation time and increased platelet adhesiveness (33).

Damage to the kidneys, with resultant proteinuria, is seen in eclampsia. Glomerular and tubular renal lesions are also characteristic of experimental magnesium deficiency (2,4,30,38-41).

Hyperparathyroidism

Gestational hyperparathyroidism is so common as to have been termed "physiologic" (42). Pregnant women with high parathyroid hormone levels have subnormal plasma phosphorus levels, which is expected. But instead of hypercalcemia, which is usually seen with hyperparathyroidism, they have low serum calcium levels, additional to low magnesium levels, especially in the third trimester (2-4, 21, 22,42). Low serum Mg (during pregnancy) can contribute to increased parathyroid hormone secretion (43,44) and to low serum calcium levels, as a result of impaired response of bone to the hormone when there is Mg deficiency (45). Gestational hyperparathyroidism is associated with a much greater likelihood of complications of pregnancy and of fetal loss and infantile morbidity than is seen among pregnant women with normally functioning parathyroids (46). A particularly interesting observation is that neonatal tetany caused by hypomagnesemic hypocalcemia can be a clue to maternal hyperparathyroidism (47).

Evidence That Dietary Magnesium Deficiency Can Be A Problem During Pregnancy

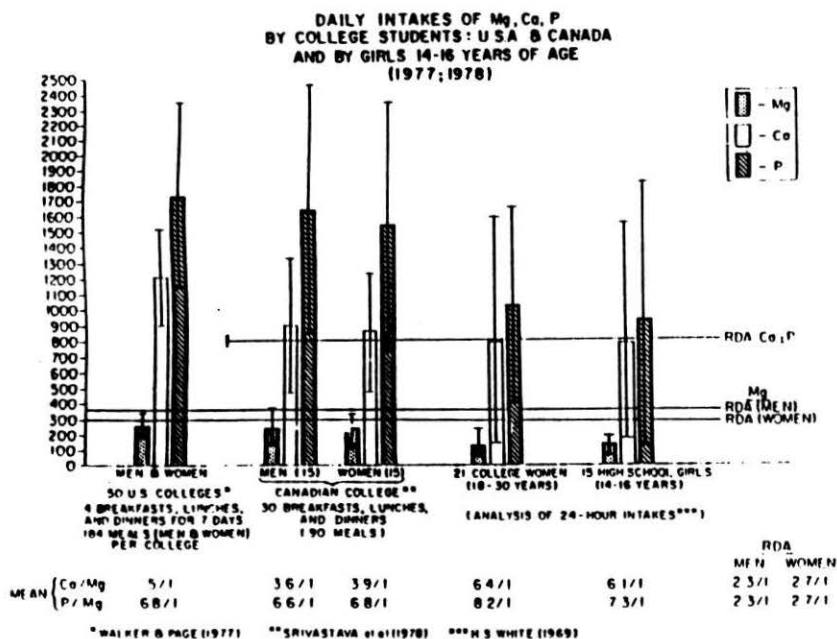
Magnesium Intakes and Needs of College Students and Adolescent Girls

Analysis of many typical sample meals of Americans has shown that magnesium intakes are below the RDA for adult women of 300 mg/day (11,14). Most of randomly selected students in American and Canadian Colleges chose meals that provide much less than the RDA for Mg, and twice as much or more calcium and phosphorus (15-17). In 1964, the author published an analysis of metabolic balance data, obtained from studies throughout the world, that showed that magnesium intake of less than 5 mg/kg/day is unlikely to maintain equilibrium (48). An updated evaluation of metabolic studies led to reiteration of a statement of probable magnesium needs of 6-10 mg/kg/day with higher needs of pregnant and lactating women, and of infants and children (49). A metabolic balance study of young women, given controlled diets that provided 265-305 mg/day or 4 to 5 mg/kg/day, showed that they remained in mean strongly negative magnesium balance over three consecutive 20-day balance periods (50).

Random meal analyses of college students show mean magnesium intakes that fall far below the RDA of 300 mg (Figure 2) (11,15-17, 49). The mean calcium and phosphorus intakes far exceed the

RDA. These nutrients, and vitamin D (the intake of which also exceeds the amount required to prevent rickets) increase the need for magnesium (2).

Figure 2

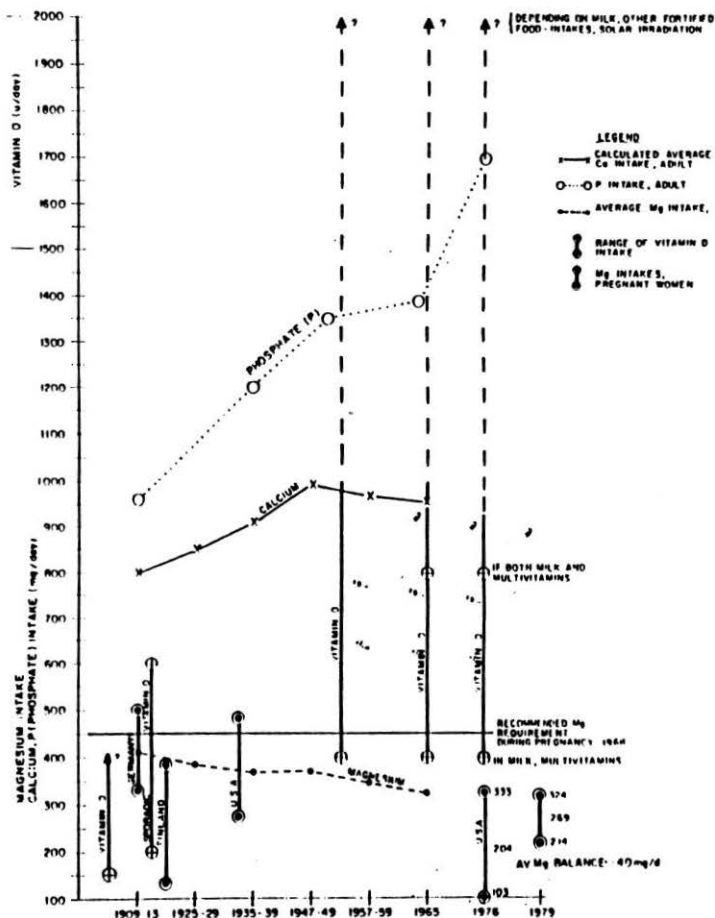


Adolescent girls have higher requirements, to meet their needs for growth and development. Metabolic balance studies have shown positive balances on Mg intakes of 6-10 mg/kg/day (51), and negative balances on lower intakes (52). Girls 17-18 years of age apparently have the higher requirements of younger adolescents, rather than the maintenance needs of adults (53). Should they become pregnant, their customary Mg- intakes are insufficient to meet their own requirements, let alone the greater needs during gestation.

Most of the Mg balance studies with pregnant women were done in Europe and the United States during the first third of this century. They showed that Mg retention was reliably achieved with intakes of at least 450 mg/day (2,9).

Since then, the average daily intake of Mg has fallen slightly, and the daily intakes of vitamin D and phosphate have risen substantially (Figure 3).

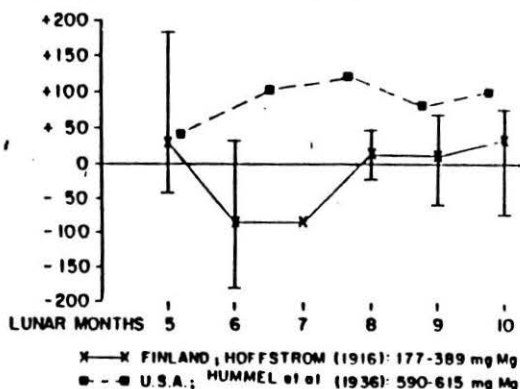
Figure 3



The range of daily magnesium intakes depicted by the two vertical lines on the lower right of Figure 3 show how low the intakes are likely to be, (12,13), to the extent that the pregnant women were in negative magnesium balance (13). Long-term balance studies, of pregnant women in the last half of pregnancy, on diets that provided 177 to 389 mg of magnesium daily, show that positive balances were not maintained at those intakes (4,54). (Figure 4).

Figure 4

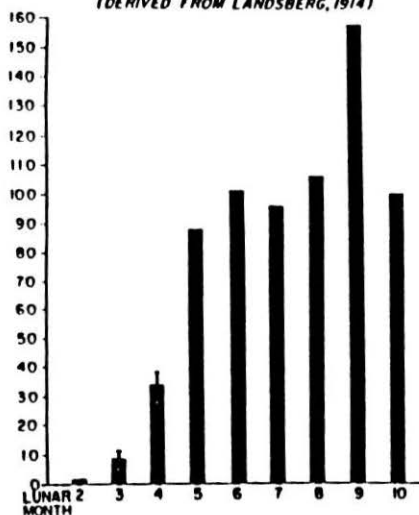
LONG-TERM MAGNESIUM BALANCES IN PREGNANCY



The line depicting strong magnesium balances throughout the last half of pregnancy depicts a continuous study of a woman during her fourth pregnancy, with a history of having had three "remarkably healthy" babies. Whether as much magnesium as she had consumed (about 600 mg daily) is actually desirable, remains to be determined. It is intriguing, however, that in the earliest metabolic balance studies of pregnant women (done in Germany in 1914) the range of magnesium intakes was 338 to 510 mg/day (56), strongly positive balances were found (Figure 5).

Figure 5

MAGNESIUM BALANCE DURING PREGNANCY
ON INTAKES OF 338-510 mg / DAY
(DERIVED FROM LANDSBERG, 1914)



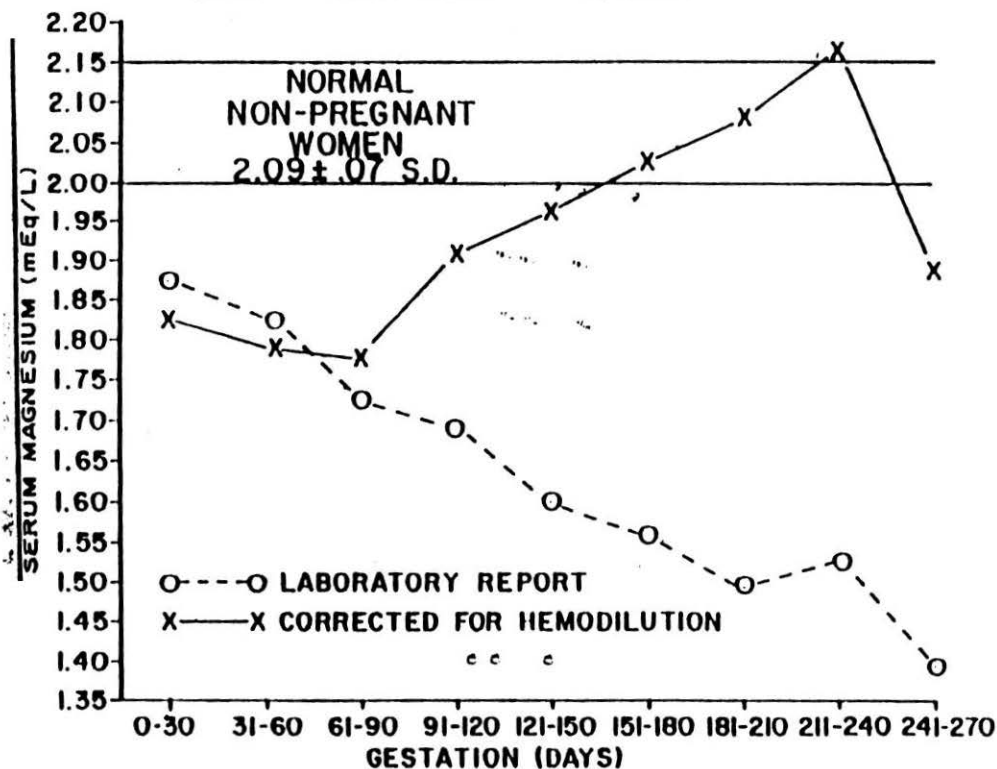
Low Serum Magnesium During Pregnancy

Magnesium Level and Retention during Normal Pregnancy

Pregnant women tend to have somewhat lower serum Mg levels than do age-matched non-pregnant women (2-4,9,21). This change is generally attributed to hemodilution, but even after correction, there is hypomagnesemia during the first half of pregnancy and during the last month (57, Figure 6). Studies have not been reported on serum magnesium levels of normal pregnant women on the customary low magnesium intakes, as compared with levels of women consuming diets that provide at least the RDA.

Figure 6

MAGNESIUM SERUM LEVELS IN PREGNANT WOMEN (DERIVED FROM DE JORGE et al, 1965)



Measurement of magnesium retention after a parenteral injection is a more valuable index of adequacy of magnesium in the body, than is the serum level. Retention of more than 20 percent of a test dose is indicative of a deficit (2, 58). A preliminary study of normal pregnant women near term, all of whom were hypomagnesemic (1.0-1.5 mEq/L), showed that a small intramuscular dose of Mg (100 mg) as the sulfate was largely retained (59). A study of 198 moderate-income American mothers showed retention of half of an intravenous magnesium-load injection in the post-partum period (60). Biologically immature mothers (under 17 years of age), multiparas, and young mothers of twins retained over 90 percent. In Thailand, where the magnesium intake of well-fed women is greater than it is in the United States, postpartum women retained only 15 percent of the parenteral magnesium-load (61).

Causes of Low Magnesium Levels During Pregnancy

Several situations can cause even lower magnesium levels than are seen in the normal pregnant woman (Table 1). Dietary imbalances, such as have been mentioned above, can intensify the inadequacy of a marginal magnesium intake. High sugar, fat, and protein intakes, and drinking alcoholic beverages also increase magnesium requirements (1,2). Vomiting during pregnancy can intensify the problem of inadequate intake. A mother who is immature or who has had frequent or multiple pregnancies might well have inadequate intake of magnesium to meet her needs, as well as that of the developing fetus. The low magnesium levels of eclampsia and of hyperparathyroidism might reflect consequences of low intakes but can also increase magnesium loss.

Table 1

CAUSES OF LOW GESTATIONAL MAGNESIUM LEVELS

- DIETARY INSUFFICIENCY; IMBALANCE -
 le. HIGH Ca/Mg; P/Mg
 - HYPEREMESIS -
 - IMMATURE MOTHER -
 - FREQUENT PREGNANCIES -
 - MULTIPLE PREGNANCY -
 - DIABETES MELLITUS -
- PRE - ECLAMPSIA; ECLAMPSIA | HYPERPARATHYROIDISM
 ? OR DOES ?
 LOW MAGNESIUM
-

Magnesium Levels During Preeclampsia and Eclampsia

Serum magnesium levels are lower in preeclamptic and eclamptic women than they are in normal pregnant women (2-4, 8-18, 21, 22, 57, 59). They tolerate very high doses of magnesium, given intravenously or intramuscularly, without developing dangerous

hypermagnesemia (6-8). The necessity for repeated or continuous treatment with magnesium to sustain the antihypertensive and anti-convulsant effect has suggested that this might indicate suboptimal magnesium levels (2-4,9,33,59). Treatment of preeclamptic women with intramuscular injections of magnesium showed both clinical improvement and retention of most of that administered (59).

Influence of Magnesium Deficiency on the Fetus

Experimental Gestational Magnesium Deficiency

Severe magnesium depletion (1/200 normal intake) from the time of conception is incompatible with fetal survival; less profound deficiency (1/130 normal intake) results in a variety of fetal abnormalities (62). Microcytic anemia and edema were found in the young of rats fed magnesium poor-rations for the last half of pregnancy (63). On magnesium intakes 1/10 normal, a third of each litter was stillborn; most of the remainder died during the week after birth (64). It is important to note that the young of magnesium deficient mothers are more deficient than are the mothers (63,64) (Table 2).

Table 2

MAGNESIUM LEVELS IN MATERNAL AND FETAL TISSUES (FROM MAGNESIUM DEFICIENT AND CONTROL RATS) (FROM DANCIS ET AL, 1971)

	MAGNESIUM DEFICIENT (mEq/L OR kg ± SE)	CONTROL
MATERNAL PLASMA	0.33 ± 0.03	1.6 ± 0.04
MATERNAL BONE	176.0 ± 12.1	213 ± 0.8
MATERNAL MUSCLE	24 ± 0.5	23 ± 0.8
FETAL PLASMA	0.31 ± 0.02	2.4 ± 0.07
FETUS	8.9 ± 0.22	142 ± 0.39

Fetal Losses With Gestational Abnormalities: Role of Magnesium?

Eclampsia and Hyperparathyroidism^c

Conditions that cause low levels of magnesium during pregnancy are associated with high incidences of fetal and infantile losses. In the case of eclampsia, to which immature mothers and multiparas are a particular risk, there is placental

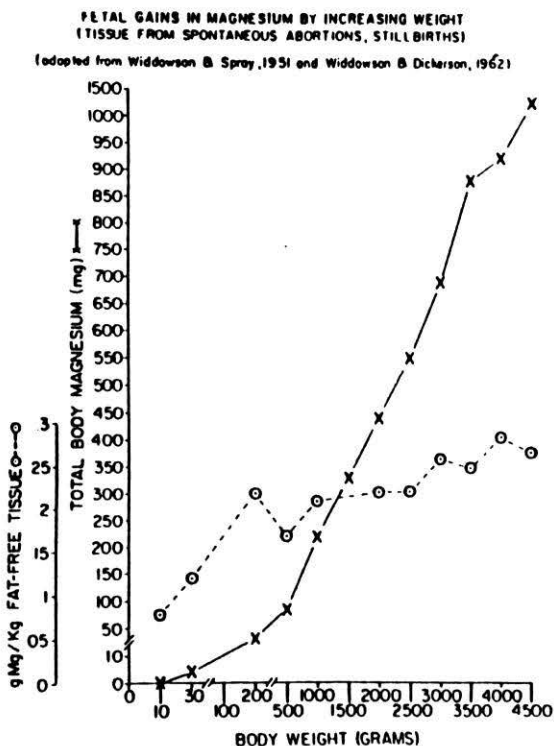
damage, with resultant intrauterine growth retardation and fetal damage (65). Mothers with gestational hyperparathyroidism have an almost 50 percent chance of complications involving their infants - including spontaneous abortion, stillbirth, low birth weight infants, neonatal deaths, or neonatal or subsequent tetany (46).

There are insufficient data to conclude that it is the low magnesium that is responsible for the gestational problems or for the fetal complications. It is suggestive, however, that perinatal mortality has remained between 25 and 35 percent of all infants born to eclamptic women, regardless of the combination of drugs used in treatment: anticonvulsants and other tranquilizers; diuretics and antihypertensives (66). Only among women whose treatment was restricted to bedrest and magnesium sulfate has the infantile mortality been reduced to 10 percent or less (8,26,66,67).

Fetal Magnesium Accumulation

As the fetus increases in size, its requirements of nutrients, including magnesium, increase. Although the magnesium concentration in the tissues remains fairly constant, there is a sharp rise in the amount of magnesium accumulated by the fetus during the last two lunar months of gestation (10,68,69) (Figure 7).

Figure 7



Magnesium Deficiency and the Infant

Neonatal Magnesium Levels

Serum magnesium levels taken at birth are difficult to interpret because low tissue levels can be masked by two major factors: hypoxia and renal immaturity. Hypoxia, whether caused by poor intrauterine blood supply (when the placenta is damaged) or by difficult delivery (2-4,68), causes a rise in serum magnesium as the magnesium is lost from cells. Furthermore, the infant's immature kidneys cannot excrete the magnesium (19,69) whether it is drawn from his own tissues or comes from the maternal circulation. This can be a problem in infants born to eclamptic mothers given large amounts of magnesium shortly before delivery (2,69). Such infants can exhibit hypermagnesemia even though their tissue levels are low. Their magnesium deficit may not be expressed by hypomagnesemia until late in the first week of life.

The infants who are at greatest risk of hypomagnesemia are low birth weight infants, those recovering from respiratory distress, and those born to very young primiparas, to young mothers who have had frequent and/or multiple pregnancies, to those who had preeclampsia, eclampsia or hyperparathyroidism and to diabetic mothers (2,18,19).

Infantile Hypomagnesemic Hypocalcemia and Hypoparathyroidism

Neonatal magnesium deficiency can be responsible for neonatal hypoparathyroidism and hypocalcemia. Although moderate magnesium deficiency has been shown to increase parathyroid hormone secretion (as is postulated to be the case in gestational hyperparathyroidism, *supra vide*), severe magnesium deficiency can suppress the release of the hormone from the glands (70). This explains the combination of low magnesium and calcium with high phosphate levels of infancy. Babies fed the high phosphate-containing cow's milk formulas have this neonatal imbalance perpetuated and intensified with the result that they are more prone to jitteriness and convulsions than are breast-fed infants (2-4,20). Direct evidence of the importance of magnesium deficiency in this syndrome is the markedly better response of the convulsing infants to magnesium injections than to calcium or barbiturates (72) (Table 3 [72]).

Actually, using calcemic agents to treat a condition in which the hypocalcemia is secondary to magnesium deficiency has risks (2, 72) (Figure 8). Both high calcium and high phosphate loads increase the risk of formation of microscopic-size kidney stones (microliths), thereby damaging renal tubules. The area of the tubules most damaged is where magnesium is reabsorbed (2), so the basis for renal magnesium loss might be established.

Infantile Hypomagnesemia, Cardiac Arrhythmia, and Sudden Death

When newborn infants are given exchange transfusions, there is a risk of cardiac arrhythmia and sudden death. This has been attributed to the use of acid-citrate-dextrose (ACD) blood (73,74) which removes magnesium as well as calcium - although it is often only the calcium loss that is corrected. Such arrhythmias, similarly produced in cardiac surgery patients, are promptly responsive to magnesium therapy (75).

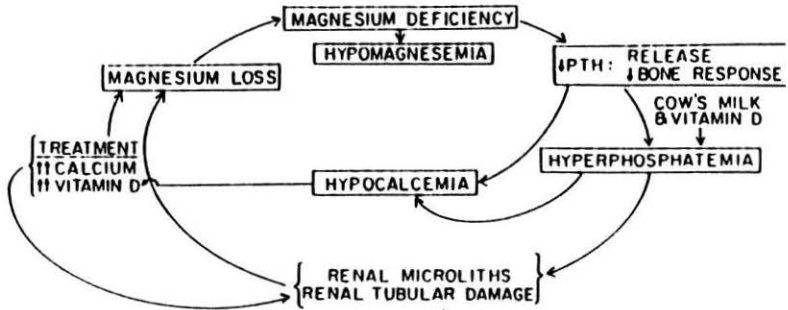
Table 3

PRE- AND POST-TREATMENT PLASMA MAGNESIUM, CALCIUM AND PHOSPHORUS
IN RESPONSE TO TREATMENT OF NEONATAL TETANY
(Adapted from Turner, Cockburn and Forfar, 1977)

Results of Treatment with Magnesium, Calcium, or Phenobarbitone (Mean \pm SD)

	MAGNESIUM THERAPY (37)		CALCIUM THERAPY (34)		BARBITURATE THERAPY (33)	
	PRE - R _x	POST - R _x	PRE - R _x	POST - R _x	PRE - R _x	POST - R _x
PLASMA MAGNESIUM (mEq/L)	1.18 \pm 0.34	1.75 \pm 0.41	1.21 \pm 0.18	1.27 \pm 0.22	1.17 \pm 0.22	1.28 \pm 0.21
PLASMA CALCIUM (mg/100 ml)	6.16 \pm 0.64	8.19 \pm 0.97	5.80 \pm 0.72	7.24 \pm 1.12	6.11 \pm 0.66	7.05 \pm 1.06
PLASMA PHOSPHORUS (mg/100 ml)	9.7 \pm 1.05	9.02 \pm 1.42	9.94 \pm 1.04	8.94 \pm 1.26	9.71 \pm 1.32	8.53 \pm 1.13
NUMBER OF SEIZURES	1.96 \pm 0.9	(AFTER R _x STARTED) 3.24 \pm 4.23	1.72 \pm 0.9	(AFTER R _x STARTED) 8.36 \pm 10.2	1.67 \pm 0.8	(AFTER R _x STARTED) 8.93 \pm 9.4
NUMBER OF DOSES REQUIRED FOR CURE	2.31 \pm 0.5		15.63 \pm 5.9		12.48 \pm 5.3	

Figure 8



Magnesium deficiency is also suspected in the sudden infant death syndrome (SIDS) which generally occurs in older bottle-fed, often overweight infants (76). It also occurs in low birth weight breast-fed infants of poor multiparous women. Many theories have been proposed to explain the tragic unexpected death of apparently healthy babies. Release of histamine has been proposed as a triggering mechanism (76). Magnesium deficiency causes histamine release (77). Deranged thiamine biochemistry has been suggested as a factor in the apnea of SIDS (78). Magnesium deficiency causes abnormalities in thiamine metabolism (79). Infantile hypoparathyroidism, a condition that is clearly associated with hypomagnesemia, is also associated with SIDS (80). And finally, there might be changes in the conducting system of the heart (81,82). Possibly narrowing of the small arteries supplying those tissues might be contributory (2,83). This point is raised because experimental magnesium deficiency causes damage to the small coronary arteries with thickening of the walls that is similar to that seen in infants dying in the first year of life (2,84).

Concluding Comments

There is suggestive evidence that dietary magnesium deficiency can contribute to a number of disorders of pregnancy, fetal development, and infancy. The definitive studies remain to be done to determine whether correcting dietary inadequacy and imbalances that interfere with magnesium utilization will lessen or prevent disorders that are associated with low magnesium levels and that respond favorably to magnesium administration.

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