

Review

New Data on the Importance of Gestational Mg Deficiency

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Chronic primary Mg deficiency is frequent. About 20% of the population consumes less than two-thirds of the RDA for Mg. Women, particularly, have low intakes. For example, in France, 23% of women and 18% of men have inadequate intakes. Mg deficiency during pregnancy can induce maternal, fetal, and pediatric consequences that might last throughout life. Studies of gestational Mg deficiency in animals show that Mg deficiency may have marked effects on parturition and postuterine involution. It has interfered with fetal growth and development, and caused morbidity from hematological effects and disturbances in temperature regulation, to teratogenic effects. Emphasis, here, is on effects of chronic clinical gestational Mg deficiency as it affects the infant. Premature labor, contributed to by uterine hyperexcitability caused by chronic maternal Mg deficiency, that can be intensified by stress, gives rise to preterm birth. If the only cause of uterine overactivity is Mg deficiency, its supplementation constitutes nontoxic tocolytic treatment, as an adjuvant treatment, that is devoid of toxicity and enhances efficacy and safety of tocolytic drugs such as beta-2 mimetics. Evidence is considered that Mg deficiency or Mg depletion can contribute to the Sudden Infant Death Syndrome (SIDS). SIDS may be a fetal consequence of maternal Mg deficiency through impaired control of Brown Adipose Tissue (BAT) thermoregulation mechanisms leading to a modified temperature set point. SIDS can result from dysthermias: hypo- or hyperthermic forms. Possibly, simple nutritional Mg supplements might be preventive. Various stresses in an infant can transform simple Mg deficiency into Mg depletion. For example, lying prone can be stressful for the baby, as can parental smoking. The role of chronopathological stress appears to be often neglected, as it constitutes a clinical form of primary hypofunction of the biological clock [with its anatomical and clinical stigma such as reduced production of melatonin (MT) and of its urinary metabolite: 6 Sulfatoxy-Melatonin (6 SMT)]. SIDS might be linked to impaired maturation of both the photoneuroendocrine system and BAT. Prophylaxis of this form of SIDS should include atoxic nutritional Mg therapy for pregnant women with total light deprivation at night for the infant. Consequences of maternal primary Mg deficiency have been inadequately studied. To determine ultimate outcomes of gestational Mg deficiency in infants, a long-term multicenter placebo-controlled prospective study should undertaken on effects of maternal nutritional Mg supplementation on lethality/morbidity in fetus, neonates, infants, children and adults, not only during pregnancy and the baby's first year, but throughout life.

Key teaching points:

- Gestational Mg deficiency contributes uterine hyperactivity that can cause preterm birth.
- It can cause fetal abnormalities that can result in infantile complications that can cause morbidity that persists throughout life or death in infancy.
- One of the calamities to which Mg deficiencies can contribute is SIDS—in which gestational Mg deficiency is a factor.
- Intensifying risk of SIDS is infantile Mg deficiency that is worsened by environmental stresses, such as being placed in a prone position, and exposure to parental smoking.
- Subnormal function of the biological clock with resultant reduced melatonin production has been linked to impaired maturation of the photendocrine system and of brown adipose tissue (BAT).
- There is need for a multi-center long-term study to determine the effect of gestational Mg inadequacy on fetal, infant, childhood and adult health of those born to mothers whose intake of Mg is not optimal during pregnancy.

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INTRODUCTION

Chronic magnesium (Mg) deficiency in human beings is common. Dietary Mg intakes lower than the recommended dietary allowances (RDAs) is prevalent in a large proportion of the population in all the continents. Nutritional adequacy of Mg is based on major traditional indicators, mainly balance studies. American RDAs are 420 mg/day for adult men and 320 mg/day for adult women [2]. The expression of RDAs for Mg in terms of the daily Mg intake for each age and sex group correspond to 22 items [2]. Whereas calcium (Ca) kinetics essentially depend on age, the best expression of RDA for Ca is related to various life stage groups [1,2], but Mg kinetics rely on body weight independently of age and sex [1,2]. [1] For example 23% of women of the SUVIMAX cohort consumed less than two thirds of the RDA for Mg [2]. The best expression of RDA for Mg is the daily value per kg body weight [1,3–7]. Marginal or moderate chronic primary Mg deficiency frequently occurs in fertile women.

EXPERIMENTAL AND CLINICAL CONSEQUENCES OF GESTATIONAL MAGNESIUM DEFICIENCY

Well-documented experimental rat studies, of gestational Mg deficiency during pregnancy, show that Mg deficiency has marked effects on the processes of parturition and post-uterine involution and on fetal growth and development, including teratogenic effects or morbidity (i.e. hematological disorders and disturbances in thermoregulation) [8–14]. The consequences of clinical maternal primary Mg deficiency have been insufficiently investigated. Gestational Mg deficiency can induce maternal, fetal, neonatal and pediatric consequences that can be life-long. To determine the importance of maternal primary chronic Mg deficiency, a long term multicenter placebo controlled study on effects of maternal oral Mg supplementation on morbidity and lethality in fetus, neonates, infants, children and adults should be carried out, not only during pregnancy and during the first year, but throughout life. Such an intervention trial may be the only means to assess the clinical consequences of gestational chronic Mg deficiency [1,5,7,15].

Stressed here are two sequelae of chronic gestational Mg deficiency:

- Premature labor or spontaneous abortion when chronic maternal Mg deficiency is involved in uterine hyperexcitability [16], and
- Sudden Infant Death Syndrome (SIDS), caused either by simple Mg deficiency or by degrees of Mg depletion.

PRETERM BIRTH AND MAGNESIUM

Premature delivery is the major cause of perinatal morbidity and mortality in the developed world. The aim of tocolysis is to prolong pregnancy. Long-term tocolysis (over 48 hours) is no longer common, since it has not proven to improve perinatal or neonatal outcomes, and can increase maternal and fetal adverse effects. Short-term tocolysis enables the obstetrician and neonatologist to optimize management of prematurity, by administration of antepartum corticoids, which reduces hyaline membrane disease and permits timely transfer to a center with neonatal intensive care facilities [16–24].

Beta-2 mimetics are the principal agents used for myometrial relaxation [17]; they are the reference tocolytic drugs in most countries [20]. There is good evidence that beta-2 mimetics prolong pregnancy, but there is no proof of their beneficial effects on perinatal or neonatal outcomes, and they are associated with a high level of maternal, fetal and neonatal side-effects which may be more or less severe [16–23,25–35]. Besides rare sudden maternal death and pulmonary edema, other side-effects are frequent. They involve the cardiovascular apparatus: chest pain, dyspnea, cardiac arrhythmias, palpitations, tachycardia, hypotension, as well as headache, nasal stuffiness, nausea, vomiting, tremor, dizziness, hyperglycemia, hypokalemia and hypomagnesemia, and metabolic imbalance—side-effects that may necessitate discontinuation of treatment. Two mechanisms may be involved in these side-effects: beta-1 receptor stimulation and excessive doses of beta-2 mimetics (for example lipolytic effects causing hypomagnesemia) [16]. Because of high incidence of their side-effects, use of high dosage beta-2 mimetics for suppression of premature labor has been either stopped or limited to short therapy (48 hours) with the lowest possible doses (inducing heart rate <120) [16].

TOCOLYTIC MAGNESIUM THERAPY, BY NUTRITIONAL MEANS AND PHARMACOLOGICALLY [16]

Nutritional Magnesium Therapy for Tocolysis

Premature births and repeated miscarriages have been observed during experimental Mg deficiency. Chronic primary Mg deficiency is very frequent, particularly during gestation because of sub-optimal dietary Mg intake [1,16]. When gestational Mg deficiency is involved in uterine overactivity, nutritional Mg supplementation constitutes atoxic tocolytic treatment: it is devoid of toxicity since it restores a physiological Mg balance [16]. It significantly reduces spontaneous abortion incidence, prolongs gestation and favors a better outcome for the newborn (weight, height, head circumference). Adequate maternal Mg intake improves neonatal development [16,36]. Mg supplements are intended to correct Mg deficiency.

To identify pregnant women with gestational Mg deficiency, the most appropriate way is to evaluate their Mg intake. If the dietary history is not easily available, existence of other clinical manifestations of Mg deficiency, such as neuromuscular hyperexcitability, should be investigated, Chvostek sign, particularly (which correlates with magnesium intake, but not with serum Mg), click, iterative EMG tracings, and/or <<idiopathic>> mitral valve prolapse. But the dynamic oral physiological Mg load test (5 mg/kg/day) constitutes the best evidence of Mg deficiency [1,15,16].

Nutritional Mg therapy is useful for tocolysis; it is devoid of toxicity, and increases efficacy and safety of tocolytic drugs such as beta-2 mimetics. Their efficiency and tolerance are considerably improved by physiological oral Mg supplementation both for the mother (neural, pulmonary and cardiovascular protection) and for the fetus (normal birthweight instead of underdevelopment). The dose of the beta-2 adrenergic receptor agonists used for tocolysis may be reduced by the synergic myorelaxant effects of beta-2 mimetics and of Mg on the myometrium [16,25,36,38–40].

L. Spätling recommends oral atoxic Mg supplementation with 2 or 3 single doses of 5 mMol Mg per day, for all pregnancies. A randomized placebo-controlled double-blind crossover study has indicated that this Mg supplementation is efficient and well tolerated [36,37].

Pharmacological Magnesium Therapy for Tocolysis

Pharmacologic tocolytic Mg therapy (most often high dosage intravenous infusions of MgSO₄) are useful, regardless of the Mg status. The usual route is parenteral [28–33], but large doses have occasionally been given orally [41,42]. High dosage intravenous MgSO₄ is the most commonly used first line tocolytic agent among obstetricians in the United States [20,43]. Despite lack of clear tocolytic effects, high dose intravenous MgSO₄ therapy is one of the most popular tocolytics in North America [18,21], but they may induce side effects. The mechanism by which pharmacological Mg therapy achieves tocolysis is inhibition of myometrial activity due to modulation of Ca uptake, binding and distribution in smooth muscle cells. But intravenous MgSO₄ lacks specificity with regard to its relaxing action on uterine muscle. For example, it is able to induce not only myometrial relaxation but also vasodilator effects [15,16,23,25,44,45]. Furthermore, intravenous MgSO₄ for tocolysis has not been evaluated rigorously, and because several randomized trials did not produce evidence of tocolytic efficacy, intravenous MgSO₄ tocolysis has been considered of dubious value and safety, and not recommended as a tocolytic agent for women in preterm labor [16,18–20,45,66].

Maternal Side-Effects

Several maternal side-effects are frequent and most often of mild importance. Flushing, sweating, a sensation of warmth, weakness, headache, palpitations, chest pain, shortness of breath, and nausea and vomiting may be related to dosage and

speed of infusion. Risk of pulmonary edema is rare, and is increased by concomitant corticotherapy. Administration of very high dosage Mg can lead to depression, hypothermia, respiratory and cardiac arrest. Long term MgSO₄ tocolysis may induce local adverse events (such as injection site pain, itching, erythema, swelling, induration and palpable venous cord), deficits in information processing ability, increased rate of chorioamnionitis and osteoporosis [5,15,16,23,25,44–51].

Fetal and Pediatric Side-Effects

Mg crosses the placental barrier. Since the fetal kidney does not excrete Mg as efficiently as does the mature kidney, maternal treatment with high intravenous doses of MgSO₄ (for tocolysis) exposes the newborn to hypermagnesemia that is correlated with the amount and duration of the pharmacologic amounts of Mg. Neonatal hypermagnesemia can lead to hyporeflexia, poor suckling and, rarely, respiratory depression. Neonatal Mg overload can affect intracardial and peripheral circulation, the APGAR score, Ca metabolism and induce meconial discharge. Other forms of neonatal Mg overload with normal magnesemia may be demonstrable by myoelectric tracings that reveal inhibition of neuromuscular transmissions, which rule out use of medication that may enhance such latent curariform effects [5,15,16,45,52–54]. However, several retrospective observational studies associate maternal tocolytic high intravenous MgSO₄ treatment and a reduction in cerebral palsy in low birthweight infants. In order to ascertain whether antenatal exposure to maternal pharmacological magnesium supplementation has neuroprotective effects on premature infants, several prospective trials were conducted [55–58]. There was profound disappointment when a scheduled interim data safety analysis of the American trial MAGNET disclosed a strong association between maternal MgSO₄ treatment and total (fetal + neonatal + post neonatal) pediatric mortalities. Contrary to the original hypotheses, the data have shown that maternal pharmacological Mg exposure was not associated with a lower risk of cerebral palsy but a statistically significant increase in the risk of neonatal intraventricular hemorrhage as well as total adverse pediatric outcomes [19,59,60]. But other research has shown that prenatal exposure to intravenous MgSO₄ was not associated with increased neonatal morbidity or mortality [51].

Differences between the effects of antenatal pharmacological maternal therapy might be due to the dosage of MgSO₄ since in an animal model fetal mortality was dose related [61]. However, the nature of the anion should be considered. Pharmacologic doses of Mg salts may induce toxicity which differs according to the anion of the salt. MgSO₄ seems to be the worst Mg salt toxicologically and pharmacologically. Strangely enough, in all these important trials it was the only salt that was routinely used, although nowhere can be found justification for that choice. It seems, therefore, necessary to determine the therapeutic ratio (LD50/ED50) of the various available Mg

salts before pharmacological use. The higher its value, the greater the safety margin [16,44,59,62–65].

In summary, high dosage intravenous MgSO_4 for tocolysis is inefficient and unsafe. Because of its maternal and pediatric side-effects, pharmacological maternal magnesium therapy should be forsaken for tocolysis. Anions other than sulfate might have a better effect on health outcome in the neonate. The therapeutic ratio of Mg salts should be determined before high dose clinical use.

SUDDEN INFANT DEATH SYNDROME (SIDS) AND MAGNESIUM

1. SIDS and Magnesium Deficiency

That Mg deficiency might participate in the pathogenesis of SIDS was hypothesized for the first time in the seminal paper published in 1972 by Caddell [66]. She highlighted the analogy between anaphylactic shock from histamine release induced by mild stress in a Mg deficient weanling rat and the final SIDS event, concluding that SIDS could be due to Mg deficiency shock [66]. In 1988, she reported the results of a retrospective study in 200 premature neonates with apnea neonatorum. Of these infants, no SIDS was observed in the Mg treated group [67]. However, this hypothesis raises several methodological problems:

- analogy does not mean causality;
- young infants do not present a pattern of Mg deficiency before SIDS;
- no allergen was detected before the anaphylactoid shock of SIDS;
- the study of 200 premature neonates was retrospective, not blinded, and the criteria applied to the infants treated with Mg are not known.

A superacute lethal anaphylactoid Mg deficiency shock is inexplicable as a mechanism of SIDS [68–70]. Although Caddell did not refute these various criticisms, she maintains that SIDS is caused by Mg deficiency shock [71] and describes a corresponding experimental risk model [72]. Instead of superacute severe infant Mg deficiency being a cause for SIDS, our theory [69] stresses the possible link between gestational chronic Mg deficiency and some forms of SIDS, and is consistent with all the epidemiological and pathological prerequisites characterizing SIDS, the curve of age at death, the stigmata of early maternal intrauterine injury, the seasonal predominance in winter, the absence of an adequate cause of death at autopsy, the risk factors subgroups (low socioeconomic level, environmental factors and mistakes in baby care) and the importance of dysthermic forms.

SIDS may result from impaired control of brown adipose

tissue (BAT) thermoregulatory mechanisms, leading to a modified temperature set point. Hypothermic forms may be induced by functional failure of BAT and hyperthermic forms by inappropriate functional excess of chemical thermogenesis. Among the morphological features of SIDS, BAT alterations have been described [60], but nevertheless omitted in recent reviews [71,73].

Some SIDS may result from chronic maternal Mg deficiency, causing chronic Mg deficiency in the infant, giving rise to dysthermia resulting from a Mg dependent disorder—a modified temperature set point—of the transition from chemical to physical infant thermoregulation [69,70]. Prevention of SIDS due to the fetal consequence of maternal Mg deficiency could be achieved by simple maternal nutritional Mg supplementation [69,70]. The levels of Mg in the traditional diets of selected ethnic groups with either the highest or the lowest rates of SIDS appear to confirm the importance of maternal Mg intake in protecting the offspring from SIDS [74].

2. SIDS and Magnesium Depletion

It is always important to discriminate between the two types of Mg deficit: Mg deficiency due to insufficient intake, which merely requires oral physiological nutritional Mg supplementation, and Mg depletion, that is related to dysregulation of Mg status that is not controlled by oral nutritional Mg intake, but requires more or less specific correction of its pathogenesis [15,70,75]. Among the various forms of Mg depletion, experimental and clinical data highlight the importance of the forms caused by the association of a low Mg intake with various types of stress.

For example, several stresses may be associated with gestational Mg deficiency which may induce SIDS due to various subgroups of Mg depletion. These stresses concern baby care and environment [70]. Stress in baby care may involve sleeping position, bedding, wrapping, ambient temperature and feeding. A recent decline in the rate of SIDS is attributed to putting the infant to bed in a nonprone sleeping position [69,70,73], providing adequate bed clothes, without eiderdown and soft cot mattress (and particularly without a mattress containing phosphorus and antimony as fire retardant [70], wrapping and room temperature, neither excessive nor insufficient, to avoid thermal stress [69–70]. Breast feeding is less common than bottle feeding among cases of SIDS than among controls [70]. Besides the environmental factors involved in baby care, such as thermal stress by ambient temperature, high altitude and exposure to various toxic substances may constitute diverse noxious environmental stressors. High altitude exposure may increase the risk of SIDS but is not commonly found in SIDS cases [69,70]. Parental smoking and maternal alcoholism are associated with an increased risk of dying from SIDS [69,70].

Drugs such as phenobarbital and phenothiazines, pesticides (lindane particularly), ambient pollutants (either contributing factors to hypoxia such as carbon monoxide, sulphur dioxide

and hydrocarbons or metal pollutants, mainly cadmium (Cd) and lead (Pb) [69,70,73] may constitute risk factors for SIDS.

The role of chronopathological stress [76] is most often neglected. SIDS may be induced by the primary chronopathological form of Mg depletion with hypofunction of the biological clock, the main marker for which is a decrease in melatonin production [75,76]. The pineal gland of SIDS infants is smaller and less responsive to photoperiod stimulatory effects than the pineal gland of normal infants. The epochal papers from the lab of Wurtman [78,79] stress directly the links between SIDS and pineal dysfunction.

Samples of whole blood, ventricular cerebrospinal fluid (CSF) and/or vitreous humor were obtained at autopsy from 68 infants whose deaths were attributed to SIDS or other causes. Melatonin (MT) concentrations were measured by radio-immunoassay. There was significant correlation for MT levels in different body fluids from the same individual. After adjusting for age difference, CSF melatonin levels were significantly lower among the SIDS infants than among those dying of other causes [78]. Post mortem blood levels of MT were lower by about 50% in infants who died from SIDS [79].

The following SIDS research has focused on infants who have experienced an Apparent Life Threatening Event (ALTE). Sivan et al [80] compared the urinary excretion of the main MT metabolite: 6 sulfatoxy-melatonin (6 SMT) in 80 infants who had (and had not) experienced an ALTE. On a double blind basis, the total of 6 SMT excreted over 24 hours and the diurnal rhythm in the rate of 6 SMT excretion were assessed, using urine samples taken from disposable diapers. The mean daily excretion of 6 SMT was significantly lower in the group having experienced ALTE [80]. The deleterious effects of this pineal deficit in SIDS may be due to the decrease of the direct stimulating action of MT on BAT [69,70,81] and to the effects of the multiple other mechanisms of action of the hypofunction of the biological clock [2,70,77]. In the cases of SIDS due to Mg depletion with hypofunction of the biological clock, this dysfunction of the timing oscillator appears as a primary disorder without the stigmata of the secondary forms of hypofunction of the biological clock, light hypersensitivity, reactive photophobia, diurnal, spring and summer prevalence [70]. The mechanism of the primary hypofunction of the biological clock in SIDS seems to imply that ontogenic SIDS might be linked to impaired maturation of the photoneuroendocrine system [70,80–82] and of BAT [69]. For example, the follow-up of the ALTE infants, performed 6 to 8 weeks later (59 to 66 weeks of post conceptional age) revealed that urinary 6 SMT excretion increased in all of them, suggesting a delayed ontogeny rather than a permanent deficit of MT production [80].

It is necessary to ensure Mg intake corresponding to the RDA for Mg (6 mg/kg/day) in each maternal diet [1,15,16,69,70]. Practically, Mg supplementation lower or equal to 300 mg per day provides a Mg supplement below the tolerable upper level (UL) intake for Mg, that is unlikely to pose risks of adverse health effects, that is to say an atoxic nutritional supplement [1,2]. The palliative correction of

chronic gestational Mg deficiency may constitute the only preventive treatment of SIDS due to maternal Mg deficiency [69,70]. When to fetal Mg insufficiency is added infantile Mg depletion, caused by association of a low Mg intake with diverse types of stress, either in baby care or the environment, it is necessary to correct them. Avoidance of prone sleeping position for the baby, discontinuation of parental smoking particularly [70] and chronopathological treatments, darkness therapy *per se*: total light deprivation at night for the infant, possibly with an eye mask [70,76,83] might reduce SIDS risk. Whether prevention of SIDS can further be achieved by Mg treatment of the infant, by what form of the Mg salt and its dosage or administration: (oral or parenteral route) is as yet uncertain, as is use of darkness-mimicking agents such as L-tryptophan and taurine [70,76].

CONCLUSION

Nutritional Mg therapy is efficient and non-toxic in preventing consequences of chronic gestational Mg deficiency in women, such as premature labor and SIDS. However, pharmacological Mg therapy, that causes a therapeutic Mg overload, may induce Mg toxicity, especially through high doses and the nature of the anion. It seems necessary to determine the therapeutic ratio (LD50/ED50) of the various available Mg salts before their pharmacological use [5,15,44,62,70].

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