Magnesium in pregnancy

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Magnesium deficiency is prevalent in women of childbearing age in both developing and developed countries. The need for magnesium increases during pregnancy, and the majority of pregnant women likely do not meet this increased need. Magnesium deficiency or insufficiency during pregnancy may pose a health risk for both the mother and the newborn, with implications that may extend into adulthood of the offspring. The measurement of serum magnesium is the most widely used method for determining magnesium levels, but it has significant limitations that have both hindered the assessment of deficiency and affected the reliability of studies in pregnant women. Thus far, limited studies have suggested links between magnesium inadequacy and certain conditions in pregnancy associated with high mortality and morbidity, such as gestational diabetes, preterm labor, preeclampsia, and small for gestational age or intrauterine growth restriction. This review provides recommendations for further study and improved testing using measurement of red cell magnesium. Pregnant women should be counseled to increase their intake of magnesium-rich foods such as nuts, seeds, beans, and leafy greens and/or to supplement with magnesium at a safe level.

INTRODUCTION

Magnesium is the most common metal ion involved in the function of enzymes and acts as a cofactor in over 600 enzymatic reactions and as an activator for an additional 200 enzymes. It is essential for the synthesis of nucleic acids and proteins, for glucose utilization and the production of adenosine triphosphate, and for bone formation, cardiac excitability, neurological function, muscular contraction, and regulation of vascular tone.

The World Health Organization states that subclinical deficiencies of magnesium prevail in both developed and developing countries. Studies of the prevalence of hypomagnesemia in the general population are both scarce and problematic. Although a range between 2.5% and 15% in otherwise healthy individuals has been reported, these studies measured serum magnesium levels, which may in fact underestimate the prevalence of magnesium deficiency. Serum magnesium as a marker of deficiency is unreliable, as most magnesium exists intracellularly: 1% or less is present in the circulation, with 0.3% present in serum. Furthermore, the release of magnesium from bone (≈60% of body stores) can compensate for a decrease in serum magnesium, acting as a buffer and regulating extracellular concentrations. The measurement of red cell magnesium more accurately reflects intracellular magnesium status, and numerous studies have detected changes in red cell magnesium in healthy subjects and in individuals with diabetes, migraine, and asthma that were not demonstrable by serum measurement. Red cell magnesium is most commonly measured using atomic absorption spectrophotometry, which is available commercially.
This is reported to be a highly sensitive, accurate, and precise method that is amenable to automation, but there have been no large population studies to determine a standard reference range, and it is possible that such a range would differ in pregnancy. The determination of normal reference ranges for the general population and for pregnant women would provide guidance for diagnosing magnesium deficiency. The gold standard of magnesium measurement involves magnesium loading and subsequent measurement of urinary excretion, but this is rarely done in the clinical setting.13

Magnesium intakes are estimated to have decreased as a result of overprocessing of foods. For example, the refinement of carbohydrates removes a high proportion of magnesium.14,15 Changes in cultivation practices have also decreased the mineral content of foodstuffs. Modern wheat is most commonly the semidwarf variety, which produces higher yields but is lower in magnesium by 20%–27% than long-straw wheat cultivated prior to 1968.16 Cultivation of fruits and vegetables has also changed; analysis of the US Department of Agriculture databases showed marked decreases in the mineral content of common vegetables from 1950 to 1999.17

The European Union Recommended Daily Amount (EU RDA) for magnesium was raised in 2008 from 300 mg/d to 375 mg/d.18 The US Recommended Dietary Allowance (RDA) is 310 mg/d and 320 mg/d for females aged 19–30 years and 31–50 years, respectively.19 Analysis of the National Health and Nutrition Examination Survey (NHANES) 2005–2006 showed, alarmingly, that 65% of females aged 19–30 years consumed less than the Estimated Average Requirement of 255 mg/d, and 48% of females aged 31–50 years consumed less than the Estimated Average Requirement of 265 mg/d.20 NHANES data from 2009 to 2010 show an increase in magnesium intake, but the average intake – 301 mg/d – is still short of the US RDA.21 Similarly, the average intake in the United Kingdom in 2012 was 240 mg/d for adults, with 8% of women consuming less than 190 mg/d (ie, the Lower Reference Nutrient Intake).22 These UK figures exclude magnesium intake from water, however. Since the mean intake from food alone is 240 mg/d for women, it is possible that women in areas with hard water who drink 2 L of water per day would obtain 100 mg of extra magnesium, although total intake would still be below the EU RDA. The magnesium content of water varies considerably, however, depending on geographic location, as does that of bottled water (1–120 mg/d).6

The absorption of magnesium in the gastrointestinal tract is approximated to be 30%–40% of intake.23 Magnesium absorption is affected by calcium and vitamin D intake and status and is decreased in certain gastrointestinal conditions such as celiac disease, Crohn’s disease, and ulcerative colitis; in addition, excretion is increased under conditions of renal insufficiency or excess alcohol intake.24,25 Absorption is also inhibited by certain drugs such as proton pump inhibitors and diuretics.26,27

Serum magnesium concentrations can become slowly depleted over periods of up to 4 months before symptoms of deficiency become evident.28 By the time latent magnesium deficiency is clinically recognized on the basis of serum concentrations, the deficiency may already be moderate to severe.11 Even in persons with severe hypomagnesemia, clinical signs associated with magnesium deficiency may be absent.29 Early signs of deficiency can include loss of appetite, nausea, vomiting, fatigue, and weakness.30 Severe hypomagnesemia is usually accompanied by imbalances of other electrolytes such as calcium or potassium.31 Profound magnesium deficiency causes tetany (usually due to low blood calcium), cardiac arrhythmia, and bone instability and promotes renal stone formation.32

**MAGNESIUM IN PREGNANCY**

The requirements of magnesium in pregnancy are not well understood. Serum magnesium has been shown to decrease in pregnancy, but this may be due in part to hemodilution. Since accurate data are lacking, the US RDA increase of 40 mg/d during pregnancy is based solely on the relative increase in body mass.19 In lactation, breast milk provides approximately 42 mg/d (in 750 mL of breast milk).34 Given that the majority of women of childbearing age do not meet the US RDA for magnesium, it is unlikely that the increased demand for magnesium during pregnancy or lactation is being met. Evidence from the literature suggests that optimum magnesium levels are essential for the health of the mother and the fetus during pregnancy and for the health of the child post partum. However, some studies have significant limitations, and well-designed trials are needed to fully elucidate the role of magnesium and to establish optimum levels of intake and/or supplementation.

**PRETERM LABOR/BIRTH**

Preterm birth is the leading cause of perinatal mortality and morbidity, and incidence is increasing in some developed countries.35 Magnesium may inhibit preterm uterine contractions via calcium antagonism, and magnesium sulfate has been used as a tocolytic agent for over 50 years.36 Magnesium supplementation during pregnancy, however, represents a simple nontoxic prophylactic measure that could decrease the risk of preterm labor/delivery.37
Several studies have demonstrated significantly lower serum magnesium levels in women with either preterm labor or preterm delivery (<37 wk) compared with women who delivered at term.\(^3\)\(^8\)\(^-\)\(^4\) Converesly, a recent prospective study of Taiwanese women showed no difference in magnesium intakes or serum magnesium levels between women who delivered at term and those who delivered preterm.\(^3\)\(^3\) An increase in serum magnesium at preterm delivery was actually reported, but notably, the study did not distinguish between women who received magnesium sulfate as a tocolytic agent prior to this measurement and those who did not, which would be a major confounding factor. However, all of these studies measured serum magnesium, which, as noted above, is inaccurate and therefore represents a major limitation. Just one study examined red cell magnesium in relation to preterm delivery (Table 1).\(^4\)\(^2\) The case group (n = 105 cases, n = 36 controls) comprised women who delivered prematurely between 28 and 36 weeks, with unknown etiology. Red cell magnesium analysis showed marked hypomagnesemia in the case group compared with controls (0.86 mmol/L vs 2.96 mmol/L, P < 0.01). While a decrease in serum magnesium was also evident, it is notable that the average serum magnesium level in the study group still fell within normal limits (0.93 mmol/L vs 1.12 mmol/L, P < 0.01).

Magnesium sulfate is no longer recommended as a first-line tocolytic agent. Recent high-quality meta-analyses disagree about whether magnesium sulfate is more efficacious in preventing preterm birth than no treatment or placebo.\(^4\)\(^3\)\(^4\)\(^4\) The incidence of adverse events is also high. Interestingly, though, one study has demonstrated that basal magnesium levels may have good predictive power in evaluating the response of tocolysis to magnesium sulfate (positive predictive value = 64.5% and negative predictive value = 92.5% when cutoff was set at a serum magnesium concentration of <1.75 mg/dl or 0.72 mmol/L).\(^4\)\(^0\) This suggests that magnesium sulfate may be efficacious when preterm labor is related to maternal magnesium deficiency.

Further study is required to define the role of magnesium in preterm labor. Accurate assessment of deficiency as well as individually tailored therapy would help determine the efficacy of magnesium sulfate treatment, prophylactic magnesium supplementation, or increased dietary intakes of magnesium during pregnancy.

**PREECLAMPSIA**

Preeclampsia is a multifactorial condition that affects between 2% and 8% of pregnancies and represents a major cause of fetal and maternal morbidity and mortality.\(^4\)\(^5\) Preeclampsia is defined by the National Institute of Health and Care Excellence as hypertension after 20 weeks’ gestation combined with proteinuria.\(^4\)\(^6\) The pathogenesis is not fully understood but is thought to include an initial trigger that results in abnormal vasculization of the placenta followed by a systemic maternal inflammatory response.\(^4\)\(^7\) Preeclampsia can progress and cause eclampsia, placental abruption, injury, and high-risk perinatal outcomes.\(^4\)\(^8\)

<table>
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<th>Table 1 Relevant trials investigating magnesium in pregnancy-related conditions</th>
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<td><strong>Condition</strong></td>
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*Abbreviations: IUGR, intrauterine growth restriction; Mg, magnesium; RCT, randomized controlled trial; SGA, small for gestational age.*
hemolysis, elevated liver enzymes, low platelet count syndrome, and fetal growth restriction.48 The only definitive treatment for preeclampsia is to deliver the placenta and, thus, the fetus, and there are strict guidelines to consider when weighing the potential outcomes of preterm delivery vs the risk of continued pregnancy to the mother and fetus.

Magnesium may play a role in the pathology of preeclampsia, and magnesium sulfate is recommended for treatment.49 Magnesium sulfate has been shown to have vasodilatory effects via inhibition of angiotensin II and endothelin I and may have an immunomodulatory role as well.50,51 Administration of magnesium sulfate decreases the risk of eclampsia and maternal death by 50%52 and is recommended by the American College of Obstetricians for severe preeclampsia.53

As stated above, magnesium is an important regulator of vascular tone. In nonpregnant individuals, magnesium levels are negatively correlated with cardiovascular risk factors, including hypertension.54 A 2006 Cochrane review concluded that magnesium supplementation may lower blood pressure in nonpregnant individuals, although higher-quality studies are needed.55 A recent meta-analysis identified a nonsignificant correlation between reduced magnesium intakes and hypertensive disorders of pregnancy,56 although the difference in magnesium intake between normal women and those with hypertensive disorders was just 8 mg.

A number of studies have compared magnesium levels in preeclamptic women with those in controls. Multiple studies of women of diverse ethnicities have detected significantly lower serum magnesium levels in women with preeclampsia than in women without preeclampsia.57–63 Unfortunately, as with other conditions examined in this review, the analysis of serum is a major limitation of these studies, and only a few studies using analysis of red cell magnesium were found. In a small cohort (n = 20 cases, n = 20 controls), a significant decrease in red cell magnesium was observed in women with preeclampsia compared with controls (0.98 ± 0.15 mmol/L vs 1.35 ± 0.30 mmol/L, P < 0.001), which was notably not evident in the analysis of serum in the same group.64 An earlier study measured magnesium within erythrocyte membranes and, similarly, reported decreased levels in women with preeclampsia.65

A small number of intervention studies on magnesium supplementation have been performed. A 2014 Cochrane review only included studies from 1988 to 1992, and almost all were considered to be of low quality, resulting in the conclusion that the evidence was too weak to support a recommendation for magnesium supplementation in women with preeclampsia.66 In a recent double-blind randomized controlled trial, however, 300 mg of magnesium citrate was found to prevent an increase in diastolic blood pressure during the last weeks of pregnancy, with the average diastolic reading being significantly lower in the magnesium-supplemented group at week 37 (72 mmHg vs 77 mmHg, P = 0.031) (Table 1).67 This study also reported an inverse relation between urinary magnesium levels and diastolic blood pressure (P = 0.005), with urine levels considered to be a good marker of dietary intake, intestinal absorption, and renal wasting.4 The authors identify some limitations of their trial, including a small number of subjects (treatment group n = 29, placebo group n = 30), a lack of nutritional data, and a possible selection bias. This study used magnesium supplementation as a prophylactic agent, which may be useful if baseline magnesium levels are measured routinely in pregnant women. This may also be useful in women with a history of hypertension or with other risk factors for preeclampsia, such as obesity or insulin resistance.45,68 Given the potential for preeclampsia to progress rapidly, leading to significant mortality and morbidity, the use of magnesium supplements as treatment is not proposed. However, prophylactic supplementation as outlined above may be beneficial.

**GESTATIONAL DIABETES**

Gestational diabetes mellitus (GDM) is reported in 1%–14% of pregnant women, depending on the screening method employed, the population screened, and the diagnostic criteria used.69 As the rates of obesity continue to rise, the prevalence of GDM is likely to increase, since obesity is a significant risk factor for GDM.70 Although predictive of type II diabetes, GDM usually resolves after pregnancy. However, women who maintain a higher body mass index postpartum are at an increased risk of developing type II diabetes.71 Gestational diabetes mellitus has also been significantly associated with an increased risk of preeclampsia and delivery by cesarean section.72,73 A large study of 23 316 women also found positive associations between increasing plasma glucose levels and preterm delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, preeclampsia, and newborn adiposity.74 For the progeny, insulin resistance and elevated glucose levels in utero can increase the risk of obesity and insulin resistance in later years.75,76

Magnesium is involved in multiple steps of the insulin-signaling pathways such as secretion, binding, and receptor activity.77 A large meta-analysis concluded that magnesium intakes are negatively correlated with risk for type II diabetes,78 while another study found magnesium depletion to be inversely correlated with progression of glucose intolerance and hyperinsulinemia.79 Supplementation or administration of
magnesium has been shown to significantly improve insulin sensitivity in both hypo- and normomagnesemic states and to improve glucose status in prediabetic patients with hypomagnesemia. The analysis of serum magnesium has given mixed results in limited observational studies of GDM, showing increased, decreased, or unchanged magnesium levels in women with GDM compared with pregnant women without GDM. A 1995 study measured both serum magnesium and red cell magnesium and demonstrated a significant decrease in both analytes in women with GDM compared with pregnant and nonpregnant women without GDM. However, the study size was very small, with only 13 cases in the GDM group. A 2014 study demonstrated no significant difference between measurements of either red cell magnesium or serum magnesium in pregnant women with GDM compared with pregnant women with normal glucose control (n = 40 in each group). In cases in which a diagnosis of GDM has already been given, it is possible, or indeed likely, that patients would have altered their dietary or supplemental intake of magnesium, and this was not assessed by the authors.

A recent convincing intervention study has clearly shown benefit of magnesium supplementation in women with GDM (Table 1). In a carefully controlled double-blind randomized controlled trial, women with GDM were given 250 mg of magnesium oxide or placebo for 6 weeks. According to serum measurements, all women were deficient in magnesium at the beginning of the study period. Diet, magnesium intakes, and additional supplementation were carefully monitored and recorded. Compliance was also strictly monitored. After 6 weeks, women in the treatment group showed significantly and markedly improved glucose control and insulin secretion, whereas values for women in the placebo group worsened over time (fasting plasma glucose, −9.7 vs +1.8 mg/dL, P < 0.001; serum insulin concentration, −2.1 vs +5.7 mIU/mL, P = 0.001; homeostasis model of assessment-estimated insulin resistance, −0.5 vs +1.4, P < 0.001; homeostasis model of assessment-estimated beta cell function, −4.0 vs +22.0, P = 0.006). In addition, newborns of supplemented mothers experienced a significant reduction in hyperbilirubinemia and hospitalization (8.8% vs 29.4%, P = 0.03, and 5.9% vs 26.5%, P = 0.02, respectively). It is clear from this study that magnesium supplementation had a marked effect on the health of both mothers and newborns. It is notable that serum magnesium levels in the groups did not change over the study period when the baseline concentration was taken into account, providing further evidence that serum magnesium does not accurately reflect magnesium levels. The authors echoed this finding in their comments and expressed regret that red cell magnesium could not be measured. On the basis of this trial, it could be proposed that magnesium supplementation in cases of deficiency may have a significant impact on the progression of GDM. While evidence from this study is strong, further trials are needed to add weight to a recommendation. Thus far, there has been no evidence that supplementation has any effect in the absence of magnesium deficiency, although additional well-designed studies are warranted.

**SMALL FOR GESTATIONAL AGE AND INTRAUTERINE GROWTH RESTRICTION**

The terms intrauterine growth restriction (IUGR) and small for gestational age (SGA) are often used interchangeably, although they are not always synonymous. Growth restriction in IUGR will always be a consequence of abnormal genetic changes or epigenetic alterations in response to environment, whereas SGA does not always have a pathological origin. Moderate to severe SGA is associated with maternal age, maternal weight, maternal nutrition, maternal smoking habits, and maternal alcohol consumption, as well as with preeclampsia and preterm labor. Symmetric IUGR can result from fetal chromosomal abnormalities and other defects such as placental or umbilical cord insufficiency. It is associated with maternal size, nutrition, multiparity, uterine size, uterine shape, certain maternal diseases, and first-trimester insults that affect blood vessels or blood cells. Symmetric IUGR growth abnormalities begin in the first or second trimester. Infants with symmetric IUGR are characterized by low weight, small head, and small abdominal circumference. Asymmetric IUGR is often a consequence of adaptation to environmental factors such as living in an area of high altitude or maternal use of medication, alcohol, cigarettes, or recreational drugs.

The influence of maternal diet and supplementation on infant birth weight was investigated in a prospective cohort study (n = 504 subjects). Magnesium was significantly and markedly correlated with birth weight in this cohort, along with other nutrients such as pantethenic acid, biotin, and vitamin D. In a separate study, an analysis of serum magnesium showed magnesium to be lowest in preterm low-birth-weight newborns, then term low-birth-weight (including IUGR) infants, and then term normal controls. Another prospective study of serum magnesium in newborns examined samples taken at birth (from umbilical cord) and...
at days 3 and 7. Despite arguments by the authors that ionized magnesium should be more useful as a measurement because it is the more active constituent, serum levels are still carefully maintained homeostatically, and thus this study has the same limitations as the other studies described above. Levels of ionized magnesium and total magnesium followed the same pattern, ie, they were increased in newborns with IUGR over the first week of life compared with infants without IUGR. The authors suggest this could be an adaptation to the adverse environment, representing an effort to maintain serum levels of magnesium. Just one study was found that assessed the correlation of infant birth size with intracellular magnesium, which was measured in platelets from umbilical cord blood (Table 1). Magnesium levels were significantly lower in SGA newborns (n = 20) than in appropriate-for-gestational-age infants (n = 45) (284 μmol/L vs 468 μmol/L, P < 0.0001) and correlated significantly with gestational age, birth weight, and length.

There is limited data thus far to elucidate the role of magnesium in the prevention of IUGR or SGA. The pathologies of IUGR and SGA overlap with those of other conditions that can be influenced by nutrition, which complicates the issue. For example, the study of intracellular magnesium also investigated markers of insulin resistance in newborns with SGA. The quantitative insulin sensitivity check index (QUICKI) was lower in the SGA group than in the control group, and magnesium levels correlated with the QUICKI score in all subjects. In both this study and a later review, the author suggests that magnesium may be a good marker of fetal growth and future health of the progeny in terms of metabolic disorders or insulin resistance. Therefore, in cases of insulin resistance or GDM, IUGR or SGA may represent an indirect result of magnesium deficiency, though further research is required.

OTHER PREGNANCY-RELATED CONDITIONS

Up to 30% of women are affected by leg cramps during pregnancy. In light of the role of magnesium in muscle relaxation, magnesium supplementation has been investigated as a safe and simple treatment of leg cramps in both pregnant and nonpregnant individuals. A recent systematic review agrees with earlier conclusions that magnesium appears to be efficacious in treating leg cramps in pregnant women, reducing severity and frequency, but perhaps not in the normal population. This might be explained by mixed etiologies of leg cramps in the normal population and a higher prevalence of magnesium deficiency in pregnant women as a result of fetal demands. The reviewers also echo previous statements that further research is required. Small sample size, insufficient treatment periods (eg, 2–3 weeks), inaccurate reporting of blinding methods, and high attrition rates confound the evidence in some studies. A more recent intervention study showed a reduction in the frequency and severity of pregnancy-induced leg cramps when treatment with a highly absorbable form of magnesium (magnesium bisglycinate chelate) was used over 4 weeks (Table 1). However, while there was a significant reduction in the frequency and severity of cramps, there was also a notable reduction in the placebo group. A 50% reduction of cramp frequency was seen in 86% of the treatment group vs 60.5% of the placebo group (P = 0.007), with similar pattern observed for reduction of cramp intensity (69.8% vs. 48.8%, P = 0.048). Despite current weak evidence, magnesium supplementation, particularly in cases of deficiency, could be safely recommended for the treatment of pregnancy-related leg cramps.

Migraine is another condition that can have a marked impact on quality of life in pregnancy, particularly since pharmacological treatment is avoided during this time. Women with a history of migraine who become pregnant often experience an increase in attacks in the first trimester, followed by a marked decrease as the pregnancy progresses, often to a lower frequency than when nonpregnant. A minority will experience migraine for the first time in pregnancy. Magnesium depletion may be related to the incidence of migraine, and supplementation may represent a simple and safe prophylaxis or treatment for pregnant women. A recent systematic review also linked incidence of migraine in pregnancy with increased risk for gestational hypertension, preeclampsia, and cardiovascular disease. It could be hypothesized that restoring any magnesium deficiencies may also reduce the risk of these related conditions. In nonpregnant migraineurs, 500 mg of magnesium oxide per day was shown to significantly reduce the symptoms and frequency of migraine in a clinical trial. Although a systematic review found the evidence to support magnesium as a treatment for migraine to be weak, and opinions about the efficacy of magnesium for treatment of migraine are divided, the prophylactic effect of magnesium supplementation will most likely be greatest when deficiency or depletion is identified initially and treatment is tailored to the individual.

CONCLUSION

It is clear that further study in this field is required, since only a handful of recent trials are of a standard sufficient to use as a basis for recommendations.
(Table 1). However, despite the lack of robust data, it is also evident that the majority of pregnant women are unlikely to meet the recommended intakes of magnesium. Pregnant women should be counseled to include good sources of magnesium in their diets, such as nuts, seeds, green leafy vegetables, and fish (Table 2). Ideally, magnesium status based on measurement of red cell magnesium should be determined in all pregnant women, and reliable reference ranges should be developed for this cohort. At the very least, red cell magnesium should be measured in women at higher risk for the above-named conditions, eg, those with risk factors such as obesity, hypertension, poor glycemic control, a previous or family history of these conditions, or other conditions with similar pathologies. Identifying deficiency is the safest and most effective way to determine supplement requirements. In the absence of this, a low-dose magnesium supplement could be safely recommended to pregnant women in general, eg, 100–200 mg/d. A safe upper limit is 350 mg/d. Any digestive disturbances should be minimal at this dosage, and dividing the dose into 2 or 3 over the course of the day could further minimize risk. It is notable that magnesium salts/compounds are large in size and tend to be included in very low amounts in multinutrient supplements, such as those commonly taken as a prenatal supplement. Thus, higher levels of supplementary magnesium may be required, and these are likely to be of greatest benefit in women in whom need has been accurately assessed.

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**Table 2: Dietary sources of magnesium**

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<th>Whole grains</th>
<th>Fish</th>
<th>Leafy greens</th>
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