Review

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*Review*

# The Yin and Yang of Maternal Calcium & Magnesium: How Chronic Magnesium Insufficiency and an Unbalanced Calcium to Magnesium Ratio Impact Fetal Development and Maternal Health

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**Abstract:** During pregnancy a mother experiences increased metabolic demands to meet the needs of the fetus. A mismatch between these demands and nutrient intake can result in a host of developmental abnormalities to the fetus and health risks to the mother. Several studies have reported strong correlations between deficiency of the essential mineral, magnesium ($Mg^{2+}$), and many pregnancy complications, including intrauterine growth restriction, preeclampsia, gestational diabetes, and preterm delivery. $Mg^{2+}$ also impacts fetal programming and disease presentation in childhood and adulthood, showing that aberrant $Mg^{2+}$ levels *in utero* have far reaching consequences. Unfortunately, there is no established clinical range of normal serum $Mg^{2+}$ levels, which makes it challenging to identify mothers and/or fetuses at risk of adverse effects. In this review, we evaluated recently published data to establish a range of serum $Mg^{2+}$ concentrations that may reflect chronic $Mg^{2+}$ insufficiency (0.7- 0.85 mmol/L). We then evaluated independent studies that reported on the relationship between $Mg^{2+}$ levels and pregnancy outcomes to assess whether this cutoff may help identify patients at risk for adverse events and inform therapeutic strategies. Our literature review showed that chronic $Mg^{2+}$ insufficiency coupled with a molar ratio of calcium ($Ca^{2+}$) to $Mg^{2+}$ greater than 3 may indicate increased risk to mother or fetus. Given the high social and economic burdens of pregnancy complications, nutritional supplementation that includes $Mg^{2+}$ at all stages of pregnancy may be a safe and cost-effective way to mitigate the risk of adverse outcomes for mother and child.

**Keywords:** magnesium; calcium; pregnancy; lactation; fetus; supplement; birth defects

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## 1. Introduction

**Calcium & Magnesium – Two Major Mineral Nutrients**

Calcium ($Ca^{2+}$) and magnesium ($Mg^{2+}$) are both essential minerals that play vital roles in many physiologic processes. $Mg^{2+}$ and $Ca^{2+}$ work together to support each other's absorption and utilization. Maintaining a proper ratio (i.e., balance) between these minerals is necessary for each of them to carry out their individual roles, which are discussed below.

Ca is the most abundant mineral in the human body with nearly all (99%) of it contained as insoluble calcium phosphates within the skeleton and teeth. The remainder, which is found as ionized calcium in the circulatory system, intra- and extracellular fluids, and various tissues, is vital to maintaining the skeleton, transmitting nerve impulses, and regulating hormone secretion, vascular tone, cellular signaling, blood clotting, and cardiac and skeletal muscle function [1]. Ca participates in the structural stabilization of biomolecules and membranes and controls the catalytic activity of hundreds of enzymes [2,3]. With respect to pregnancy and lactation, Ca triggers new life at fertilization, controls several developmental processes, and may also regulate diverse cellular

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processes during differentiation including metabolism, proliferation, secretion, contraction, synaptic transmission, learning and memory [4].

$Mg^{2+}$ is the fourth most abundant mineral in the human body, behind Ca, sodium (Na), and potassium (K), and the second most abundant intracellular cation following K [5–8]. Like Ca, most of the body's $Mg^{2+}$ is found in the skeleton (50-60%) with the remainder contained in the muscles and tissues (40-50%). Less than 1% is found in the circulatory system, with the largest fraction of this 1% contained in erythrocytes. $Mg^{2+}$ plays crucial roles in many diverse physiological processes [5–8]. It is critical to the stability of all polyphosphate compounds and their roles in many enzymatic reactions. These reactions facilitate the hydrolysis of phosphate esters (ATPases), and the transfer phosphoryl groups (kinases and phosphatases) in virtually every metabolic pathway [7]. $Mg^{2+}$ serves as a cofactor in over 600 enzyme systems that govern a variety of physiological activities, including glucose metabolism, protein synthesis, muscle and nerve transmission, neuromuscular conduction, blood glucose management, and blood pressure regulation [5–8]. It also plays an important role in signal transduction, most likely as a second messenger [11], and is required for the active transport of Ca and K ions across cell membranes, making it essential for proper immune responses, antioxidant synthesis, vitamin D activation, nerve impulse transmission, muscular contraction, vasomotor tone, and proper heart rhythm [7,9,10].

In this review we evaluated how maternal levels of Ca and $Mg^{2+}$ during pregnancy affect health outcomes of the fetus. We focused on these two minerals because they are critical for proper fetal growth and development, and disruptions to their maternal levels are strongly associated with poor outcomes. The goal of this literature analysis was to determine if a cutoff concentration of $Mg^{2+}$, which may reflect chronic $Mg^{2+}$ insufficiency, could potentially inform on adverse health risks to mother and/or baby.

## 2. Materials and Methods

We performed a literature review using terms such as "pregnancy," "lactation," "calcium," "magnesium," "fetus," "maternal," "serum," and related search terms. We screened over 1,500 results and selected 107 core articles after removing duplicates, as well as secondary, non-English, and irrelevant studies.

## 3. Results

**Reported levels of serum Ca and $Mg^{2+}$ during pregnancy and lactation**

Pregnancy and lactation are times of high Ca and $Mg^{2+}$ demand [12,13]. Approximately 25-30 g of Ca and 0.8 to 1 g of $Mg^{2+}$ are transferred from mother to the fetal skeleton by the end of a normal pregnancy. Typically, the fetus accumulates 2-3 mg Ca/day during the first trimester [12]. During the second and third trimesters the rate of accumulation increases to 250 mg Ca/day and over 300 mg Ca/day, respectively.

Less is known about the rates of $Mg^{2+}$ accumulation by the fetus. Historical data suggest that about 80% of fetal mineral content is accumulated during the third trimester, as Ziegler's 1976 study reported that the rate of $Mg^{2+}$ transfer increases from 1.8 mg/day to 5-7.5 mg/day over the last five weeks of pregnancy [13]. However, more recent clinical data from Larsson *et al*. clearly show that maternal $Mg^{2+}$ transfer to the placenta and fetus takes place in parallel with Ca transfer and begins early in the first trimester (**Table 1**) [14]. It is our stance that Larson's tabulated data is particularly important because they were gathered from a defined population in a single laboratory over time, and thus less susceptible to the variability introduced by inter-laboratory analyses of diverse populations [15]. The question then, of whether these data could be applicable to the population at large, can be answered by other reports by Cai *et al*. (China) and Hansu and Cikim (Turkey), which suggest the trends summarized in **Table 1** are characteristic of pregnancy in women around the world [16,17].

**Table 1.** Changes in average serum concentrations of key minerals during pregnancy (Larsson [14]).

| **Period** | **Calcium (mmol/L)** | | **Magnesium (mmol/L)** | | **Phosphate (mmol/L)**[1] | |
|---|---|---|---|---|---|---|
| | Lower Limit | Upper Limit | Lower Limit | Upper Limit | Lower Limit | Upper Limit |
| Week 7–17 | 2.18 (2.12–2.23) | 2.53 (2.50–2.57) | 0.70 (0.69–0.71) | 0.96 (0.88–1.059) | 0.85 (0.80–0.90) | 1.65 (1.43–1.86) |
| Week 17–24 | 2.08 (2.04–2.11) | 2.45 (2.41–2.50) | 0.66 (0.65–0.66) | 0.87 (0.84–0.90) | 0.84 (0.74–0.95) | 1.45 (1.41–1.48) |
| Week 24–28 | 2.04 (1.99–2.08) | 2.40 (2.36–2.43) | 0.63 (0.63–0.63) | 0.91 (0.86–0.97) | 0.81 (0.67–0.95) | 1.47 (1.43–1.51) |
| Week 28–31 | 2.07 (2.03–2.11) | 2.41 (2.33–2.49) | 0.63 (0.63–0.64) | 0.91 (0.88–0.94) | 0.77 (0.70–0.85) | 1.44 (1.38–1.49) |
| Week 31–34 | 2.05 (1.99–2.10) | 2.38 (2.37–2.40) | 0.64 (0.64–0.64) | 0.90 (0.84–0.97) | 0.84 (0.72–0.95) | 1.42 (1.35–1.49) |
| Week 34–38 | 2.04 (1.96–2.11) | 2.41 (2.39–2.43) | 0.57 (0.50–0.65) | 0.87 (0.84–0.90) | 0.85 (0.80–0.90) | 1.50 (1.43–1.57) |
| Predelivery | 1.98 (1.91–2.05) | 2.46 (2.42–2.50) | 0.64 (0.63–0.65) | 0.94 (0.91–0.96) | 0.89 (0.86–0.92) | 1.50 (1.43–1.57) |
| Postpartum | 2.06 (1.90–2.22) | 2.57 (2.51–2.63) | 0.68 (0.66–0.71) | 0.99 (0.92–1.06) | 1.00 (0.89–1.12) | 1.80 (1.62–1.99) |

90% Confidence Intervals are bracketed.

Some have asserted that the changes in $Mg^{2+}$ levels reported by Larsson *et.al.* reflect its dilution caused by increases in plasma volume during pregnancy. This idea is not supported by data published by De Jorge *et al*., which shows $Mg^{2+}$ concentrations are not significantly altered by plasma dilution associated with pregnancy (**Table 2**) [19].

**Table 2.** Effects of plasma volume on serum magnesium concentrations (De Jorge [19]).

| **Gestation (Days)** | **Gestation (Weeks)** | **No. of Women** | **Mean [Mg], mEq/L** | **SD** | **Plasma Volume (mL)** | **Corrected Conc. Mg (mEq/L)** | **Conc. Mg (mmol/L)** |
|---|---|---|---|---|---|---|---|
| ~30 | ~4 | 5 | 1.873 | 0.104 | 2644 | 1.834 | 0.92 |
| 31-60 | 4-9 | 12 | 1.826 | 0.103 | 2643 | 1.787 | 0.89 |
| 61-90 | 9-13 | 28 | 1.728 | 0.091 | 2770 | 1.773 | 0.89 |
| 91-120 | 13-17 | 29 | 1.694 | 0.139 | 3047 | 1.912 | 0.96 |
| 121-150 | 17-21 | 23 | 1.599 | 0.177 | 3305 | 1.957 | 0.98 |
| 151-180 | 21-26 | 23 | 1.558 | 0.104 | 3550 | 2.048 | 1.02 |
| 180-210 | 26-30 | 17 | 1.488 | 0.101 | 3769 | 2.077 | 1.04 |
| 211-240 | 30-34 | 9 | 1.526 | 0.121 | 3820 | 2.159 | 1.08 |

[1] Phosphorus data are included for reference. Phosphorus and calcium are interrelated because hormones, such as vitamin D and parathyroid hormone (PTH), regulate the metabolism of both minerals. In addition, phosphorus and calcium make up hydroxyapatite, the main structural component in bones and tooth enamel. In adults, normal phosphate concentration in serum or plasma is 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L) [18].

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 240-270 | 34-39 | 5 | 1.392 | 0.173 | 3658 | 1.882 | 0.94 |
| Normal Value | | | 2.087 | 0.067 | | 2.087 | 1.04 |

In another study, Rigo *et al*. confirm that Larsson's findings on the mineral levels in the mother also inform $Mg^{2+}$ levels in the fetus [20]. Here, a systematic literature review and meta-analysis of serum $Mg^{2+}$ levels in newborns was conducted with the goal of quantifying normal and tolerable concentration ranges during the neonatal period. In this review they also highlighted factors that influence $Mg^{2+}$ levels and how maternal $Mg^{2+}$ levels during pregnancy relate to serum $Mg^{2+}$ in the neonate at birth. Their literature review showed that mothers who did not receive dietary $Mg^{2+}$ supplementation during pregnancy gave birth to neonates with $Mg^{2+}$ levels (0.76 (95% CI: 0.52, 0.99) mmol/L) similar to those of their mother during pregnancy (0.74 (95% CI: 0.43, 1.04) mmol/L). However, neonate levels increased during the first week of life (0.91 (95% CI: 0.55, 1.26) mmol/L) before returning to their baseline levels (0.74 (95% CI: 0.43, 1.04) mmoL/L). This pattern was also seen in mothers who received dietary $Mg^{2+}$ supplementation during pregnancy. In this group the average neonatal serum $Mg^{2+}$ concentration was higher at 1.29 mmol/L (95% CI: 0.50, 2.08), which rose to 1.44 mmol/L (95% CI: 0.61, 2.27) during the first week of life. It should be noted that despite the low average $Mg^{2+}$ levels in mothers who did not receive dietary supplements, some individuals in this group gave birth to newborns with $Mg^{2+}$ levels as high as 2.0 mmol/L. Serum $Mg^{2+}$ levels > 2.5 mmol/L have been linked to an increased risk of mortality, admission into intensive care, hypotonia, hypotension, and respiratory depression [21–23]. However, in Rigo's study, serum $Mg^{2+}$ levels of 2.0 mmol/L were shown to be well tolerated by neonates.

Maternal transfer of minerals continues during lactation [24]. Breastmilk contains higher levels of Ca and $Mg^{2+}$ at the start of lactation, which start to decline after approximately 6 months (**Table 3**) [25–27]. Assuming a daily neonatal intake of about 800 mL of breast milk, this fluid provides 225-240 mg Ca/day early in lactation and 200-210 mg Ca/day later in lactation to support continuing neonatal growth and development. Likewise, $Mg^{2+}$ content in this volume of breast milk is 27 mg/day early in lactation and decreases to 18 mg/day later in lactation.

**Table 3.** Mineral content of whole milk.

| Category | Mineral content, mmol/L | | | Source |
|---|---|---|---|---|
| | Ca | P | Mg | |
| Human (Early lactation) | 7.4 | 3.9 | 1.4 | Sánchez [25] |
| Human (Late lactation) | 6.3 | 3.9 | 1.4 | |
| Human (Early lactation) | 6.9 | - | 1.0 | Li [26] |
| Human (Late lactation) | 6.6 | - | 0.9 | |
| Human (Established feeding) | 6.7 | - | 1.5 | |
| Human | 7 | 4.7 | 1.3 | Sanchez [26] |
| Human (Day 7 post-partum) | 6.1 | 4.7 | 1.3 | Gates [27] |
| Human (Day 14 post-partum) | 5.6 | 4.6 | 1.2 | |
| Human (Day 21 post-partum) | 5.5 | 4.4 | 1.2 | |
| Human (Day 28 post-partum) | 5.3 | 4.1 | 1.4 | |
| The values in this table are means and do not reflect the reported standard deviations, confidence intervals, or the ranges of concentrations found. | | | | |

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The data generated by Gates *et. al*. (**Table 3**) also reveal insight into how mineral deficiencies in mothers of preterm infants are reflected in the quality of their breastmilk [27]. Their preterm children had an average gestational age of 28.2 ± 2.8 weeks and average birth weight of 1,098 g (vs. normal term birth weight of about 3,200 g). The volumes of breast milk each day increased from an average of 171.8 mL (day 7) to 224.2 mL (day 21) and then decreased slightly to 210.3 mL. In addition to the shortfall in milk supply by these mothers as compared to mothers who carry to term, the Ca content in their breastmilk was initially low and decreased during lactation. In contrast, both the $Mg^{2+}$ and phosphorus content of their breastmilk paralleled the contents of breastmilk provided by mothers of full term babies.

**Another Perspective: The Molar Ratio of Serum Ca to Serum $Mg^{2+}$ and Impacts on Fetal and Maternal Outcomes**

Larsson's data on Ca and $Mg^{2+}$ levels from pregnancy to postpartum (**Table 1**) may also be considered from another perspective: the molar ratio of serum Ca to serum $Mg^{2+}$ (**Table 4**).

**Table 4. Molar ratios of Ca:Mg during pregnancy**. The ratios are calcluated as ratios of the means cited by Larsson [14].

| Period | Molar Ratio Ca:Mg | | | |
|---|---|---|---|---|
| | LoCa:LoMg | HiCa:LoMg | HiCa:HiMg | LoCa:HiMg |
| Week 7–17 | 3.11 | 3.61 | 2.64 | 2.27 |
| Week 17–24 | 3.15 | 3.71 | 2.82 | 2.39 |
| Week 24–28 | 3.24 | 3.81 | 2.64 | 2.24 |
| Week 28–31 | 3.29 | 3.83 | 2.65 | 2.27 |
| Week 31–34 | 3.20 | 3.72 | 2.64 | 2.28 |
| Week 34–38 | 3.58 | 4.23 | 2.77 | 2.34 |
| Predelivery | 3.09 | 3.84 | 2.62 | 2.11 |
| Postpartum | 3.03 | 3.78 | 2.60 | 2.08 |

Both clinical guidelines and published data show that the risk of adverse effects on mother and/or fetus is minimal when both serum Ca and serum $Mg^{2+}$ are high in the reference ranges (**Table 4**, HiCa:HiMg column).[2] In contrast, these same documents raise minor concerns when serum Ca is low in the reference ranges. For example, Tsakiridis *et al*. reviewed the most recently published guidelines for antenatal nutrition issued by the Australian Government Department of Health (2018), the Canadian Nutrition Working Group and Society of Obstetricians and Gynaecologists of Canada (2016), the World Health Organization (2016), the Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland (2016), the International Federation of Gynecology and Obstetrics (2015), the Academy of Nutrition and Dietetics (2014), and the National Institute for Health and Care Excellence (2008) [28]. They found that most of these authorities recommended Ca supplementation in populations with low dietary Ca intake. Clinical data suggested that supplementation benefitted women at risk for preeclampsia and reduced the risk of gestational hypertension, neonatal mortality, and preterm birth in women with low dietary Ca intake. The data were sufficient to prompt the recommendation that Ca consumption be highly encouraged during pregnancy, especially during the second and third trimester.

Likewise, Adams *et al*. summarized evidence for the benefits associated with supplementation of Ca and $Mg^{2+}$ [29]. They identified clear associations between low serum Ca and risk of preeclampsia, eclampsia, and pregnancy-induced hypertension, supporting the benefits of

[2] The reference ranges for serum calcium and serum magnesium vary but generally range from 2.2-2.7 mmol/L and 0.7-1.0 mmol/L, respectively.

supplementation. Less definitive correlations between the effects of supplementation and preterm birth or maternal mortality were identified. Maternal Ca supplementation was also related to reductions in neonatal hypertension, low birth weight, and neonatal intensive care unit admission. The authors concluded that Ca supplementation of 550 mg of elemental Ca daily should be recommended for U.S. women, with a need for higher levels of supplementation if the woman had a low intake of milk, vegetables, or milk-based foods or had higher risk of preeclampsia, preterm birth, and/or gestational hypertension. It was speculated that supplementation could help reduce the risk of other conditions associated with low Ca intake including preterm birth, low birth weight, neonatal mortality, and autism.

Despite the value of Ca in maintaining skeletal integrity [30,31], neither Adams nor other recent reviewers identified a relationship between low serum Ca and maternal bone health. For example, Tihtonen *et al*. screened 3,555 records in 11 databases and analyzed data from seven randomized controlled trials (RCTs) including 1,566 pregnant women [32]. No advantage of Ca supplementation was found on maternal bone mineral density after delivery or during breast-feeding, even when dietary Ca intake was low. Further, the conclusion was not modified even when the dose of Ca or concomitant vitamin D administration was considered. Similarly, Cai et al. screened supplementation reports in multiple databases and analyzed five randomized controlled trials including 567 lactating women [33]. Their meta-analysis indicated that Ca supplementation does not provide clinically important benefits for bone mineral density in lactating women. However, both groups of investigators noted confounding elements, in that there was adequate dietary intake before supplementation in some studies, and others did not measure baseline Ca intake. These findings suggested that advising lactating women to meet the current recommended Ca intakes (with supplementation if dietary intake is low) is warranted unless new high-certainty evidence to the contrary from robust clinical trials becomes available.

Conversely, when the serum $Mg^{2+}$ concentration is low (**Table 4**, LoCa:LoMg and HiCa:LoMg columns), the published literature is rife with adverse consequences.

**Adverse Effects Associated with Maternal Chronic $Mg^{2+}$ Insufficiency Early in Pregnancy**

Instead of describing reduced $Mg^{2+}$ as a "deficiency," we will use the term "chronic insufficiency" to define a metabolic state where the serum mineral concentration is in the lowest quartile of its normal range for a period of months to years. Recent reports suggest that chronic $Mg^{2+}$ insufficiency enhances the risks of adverse events for mother and child (**Table 5**). We will focus our attention on examples of adverse events that occur early in pregnancy (**Table 6**), because adverse effects that occur late in pregnancy are widely recognized.

**Table 5. Increased risks associated with low maternal serum $Mg^{2+}$.** Conditions that occur late in pregnancy (third trimester) will not be the focus of this review.

| For mother with chronic $Mg^{2+}$ insufficiency | For child |
|---|---|
| Mental health during pregnancy<br>Pre-eclampsia and related side effects<br>Placental abruption<br>Immune health<br>Gestational diabetes<br>Time of delivery (pre-term delivery)<br>Post-partum depression<br>Post-partum recovery of bone mineral density | Intrauterine growth and development (Fetal Growth Restriction)<br>Spontaneous pre-term birth |
| **Late pregnancy complications** | |
| Embryonic development | Organ development/fetal programming |

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| | |
|---|---|
| Placental development<br>Spontaneous abortion<br>Renal health<br>Hypertension | Congenital abnormalities<br>Skeletal development |

**Table 6.** Examples of Increased Risks Potentially Associated with Low Maternal Serum $Mg^{2+}$ Early in Pregnancy.

| |
|---|
| **Risk: Failure to appropriately glycosylate lipid intermediates and proteins** |
| • **Significance:** Over 500 human glycoenzymes regulate the expression of transcription factors, epigenetic regulators, and miRNAs [34–36].<br>• **Importance of $Mg^{2+}$:** Regulation of glycogene expression involves a spectrum of non-coding and silenced RNAs that are biosynthesized via $Mg^{2+}$ and/or manganese-dependent mechanisms. For example, $Mg^{2+}$ catalyzes the phosphorylation of sugars, which are the building blocks of many glycosyltransferases. $Mg^{2+}$ is also a critical component of *N*-glycosylation reactions in the endoplasmic reticulum (ER).<br>• **Importance of Ca:** Concurrently, Ca plays a key role in the "quality control" of N-glycoproteins modified in the ER. As Durin *et al*. acknowledge, "The reticular control mechanism, therefore, "decides" in a way, on the utilization or deliberate destruction of the glycoprotein that has been produced. The major chaperones and enzymes involved in the ER, including calnexin, calreticulin, BiP, glucosidases, mannosidases and protein disulfide isomerases (PDIs), **require $Ca^{2+}$** for their functions [35]." (Emphasis added.) Moreover, once the oligosaccharide precursor has been transferred from its lipid carrier to the polypeptide, a series of mandatory trimming steps and lectin chaperone associations occur, most of which are Ca-dependent.<br>• **Potential Impact:** We theorize that disrupting the homeostatic balance between these two metals will have particular impact during embryogenesis, placental development, and cell and tissue structuring during the first trimester. In addition, we theorize the maternal ratio of Ca to $Mg^{2+}$ may affect the composition and concentrations of human milk oligosaccharides in breast milk and the infant's response to maternal milk [37,38]. |
| **Risk: Inability to meet nutrient demands retards embryonic development [39]** |
| • **Significance:** Neural tube closure requires two types of cell movements: 1) mediolateral intercalation or convergent extension (i.e., the migration of cells toward the midline of the embryo) and 2) radial intercalation (the movement of cells from inside the embryo to the outside of the lateral side of the neural plate). Failure of either type of cell movement will prevent neural tube closure, which can produce a range of neural tube defects.<br>• **Importance of $Mg^{2+}$:** Two transient receptor potential (TRP) channels, TRPM6 and TRPM7, and the $Mg^{2+}$ ions that are conducted through these channels are novel and key factors that regulate both mediolateral and radial intercalation during neural tube closure, a key step in organogenesis [40,41].<br>• **Potential Impact:** Studies on *Xenopus laevis* have shown that $Mg^{2+}$ deficiency during embryogenesis inhibits the growth and development of the head and heart [40,41]. Rodent studies have provided evidence of low nephron numbers and decreased tolerance for hypoxia, suggesting that the kidneys and lungs are also affected by low serum $Mg^{2+}$ [42]. |
| **Risk: Aberrations in placental development** |

| |
|---|
| • **Significance:** The placenta is the first and the largest fetal organ to develop. During early pregnancy it performs the functions of diverse organ systems while it and the fetus differentiate and mature, which makes appropriate placental development critical to normal fetal development [42]. Placental dysfunction may affect as many as one in three pregnancies as compromised placental structure and function is thought to contribute significantly to perinatal and maternal morbidity and mortality [43]. <br>• **Importance of $Mg^{2+}$:** Inadequate nutrition among females of reproductive age may be a significant cause of placental dysfunction [44–46], and the amount of $Mg^{2+}$ brought to the placenta and developing fetus depends on $Mg^{2+}$ levels in the mother. Kocylowski *et al*. tested for an association between neonatal abnormalities and levels of both folate and essential and toxic elements in maternal serum and amniotic fluid [46]. 258 pregnant Polish women aged 17-42 years participated. During vaginal delivery or cesarean section, amniotic fluid and maternal serum samples were collected from study participants and profiled for folate and elements. Compared to the rest of the cohort, a significantly lower amount of $Mg^{2+}$ was found in serum of mothers who gave birth to a child with a birth defect. Follow-up analysis showed that a low concentration of $Mg^{2+}$ in maternal serum was related to an increased risk of birth defects (β coefficient = 0.31; $p = 0.007$) <br>• **Potential Impact:** Overall, these findings support $Mg^{2+}$ as an important factor in proper development of the placenta and subsequent mitigator of birth defects associated with abnormal placental development. |
| **Risk: Spontaneous abortion** |
| • **Significance:** Repeated pregnancy loss, also known as recurrent spontaneous abortion and habitual abortion, can be defined as three more successive miscarriages, which the World Health Organization defines as the loss of a fetus that weighs ≤ 500 g generally around 20–22 weeks' gestation [47]. <br>• **Importance of $Mg^{2+}$:** Sami *et al*. completed a study which compared nutrient levels in 30-year-old women with habitual abortus (HA) to nutrient levels in an age-matched healthy control group (n = 39 each group) [48]. Zinc (Zn), copper (Cu), manganese (Mn), selenium (Se), iron (Fe), cobalt (Co), chromium (Cr), nickel (Ni), lead (Pb), magnesium (Mg), calcium (Ca), sodium (Na), potassium (K), retinol, cholecalciferol, a-tocopherol, phylloquinone, total antioxidant (TAS), oxidative stress index (OSI), and total oxidation status (TOS) levels were measured, and the relationships between these variables and spontaneous abortion were determined. Statistical analysis revealed that serum concentrations of cholecalciferol, phylloquinone, TAS, Se, Zn, Cu, Mg, K and Na in the HA group were significantly lower than those in the control group (all $p \leq 0.05$). However, the TOS, OSI, and Ca to $Mg^{2+}$ ratio in the HA group were significantly higher than those in the control group (all $p \leq 0.05$). <br>• **Potential Impact:** While further study will be needed to characterize the individual contribution of $Mg^{2+}$ to spontaneous abortion, lower $Mg^{2+}$ levels relative to Ca levels in HA subjects, as reflected by a higher Ca to $Mg^{2+}$ ratio, suggests a protective role for $Mg^{2+}$ against this pregnancy complication. |
| **Risk: Declines in renal health** |
| • **Significance:** Pregnancy marks a time of substantial change in kidney physiology and function. <br>• **Importance of $Mg^{2+}$:** Lin *et al*. analyzed blood samples from over 1,000 participants in Project Viva during their first trimester of pregnancy (mean timepoint: 9.7 weeks' gestation) [49]. Samples were assessed for erythrocyte non-essential minerals and essential elements [magnesium ($Mg^{2+}$), manganese (Mn), selenium (Se), and zinc (Zn)]. Plasma creatinine was measured to assess kidney function. After adjusting for covariates, study participants who demonstrated higher $Mg^{2+}$ (β 10.53 mL/min/1.73 $m^2$; 95% CI 5.35, 15.71), Se (β 5.56 ml/min/1.73 $m^2$; 95% CI 0.82, 10.31), and Zn (β 5.88 ml/min/1.73 $m^2$; 95% CI 0.51, 11.26) concentrations relative to the rest of the cohort were associated with higher $eGFR_{CKD-EPI}$, indicating more robust kidney function than those with lower levels of these elements. In mixture analyses, higher essential trace elements mixture concentration was also associated with higher eGFR (Ψ 1.42; 95% CI: 0.48, 2.37). <br>• **Potential Impact:** Adequate $Mg^{2+}$ is associated with maintenance of kidney function during pregnancy. |

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| Risk: Inadequate biosynthesis of active Vitamin $D_3$ |
|---|
| • **Significance:** During normal kidney function 25(OH) vitamin D (25D) is hydroxylated to 1,25(OH) vitamin D (1,25D) and catabolized by further hydroxylation. Vitamin D acts with other major minerals to regulate placental and fetal development [50] <br>• **Importance of $Mg^{2+}$:** Rothen *et al*. carried out a retrospective observational study of the effects of renal insufficiency and $Mg^{2+}$ deficiency on the formation of biologically active cholecalciferol, the molecule that becomes 25(OH) vitamin D after being hydroxylated in the liver [51]. Although neither renal function or $Mg^{2+}$ level affected 25D levels (r = - 0.144 pmol/L and 0.030 pmol/L, respectively), a weak positive correlation was observed between 1,25D and estimated glomerular filtration rate (eGFR) (r = 0.317), and between 1,25D and serum $Mg^{2+}$ (r = 0.217), indicating that low $Mg^{2+}$ could exacerbate existing kidney disease. From these findings they concluded, "In patients with renal insufficiency adequate magnesium supply should be ensured." <br>• **Potential Impact:** $Mg^{2+}$ is a cofactor of all hydroxylase enzymes involved in these steps of vitamin D metabolism and $Mg^{2+}$ deficiency increases the risk of inadequate synthesis of active Vitamin D. |
| **Risk: Essential Hypertension** |
| • **Significance:** "Essential hypertension" refers to the elevation in blood pressure that is observed early in pregnancy as opposed to hypertensive complications that are observed and treated during the second half of pregnancy [52,53]. <br>• **Importance of Mg:** As Rosanoff notes: "Magnesium has both direct and indirect impacts on the regulation of blood pressure and therefore on the occurrence of hypertension. In most humans, healthy blood pressure depends upon a balance of both Na:K and $Mg^{2+}$:Ca ratios at both cellular and whole body levels which, in turn, require adequate, long-term intakes of nutritional magnesium [54]." <br>• **Potential Impact:** Based on this report and a wealth of related studies, the U.S. Food and Drug Administration has concluded that "there is some credible evidence suggesting that combined intake of elemental magnesium from conventional foods and dietary supplements may reduce the risk of hypertension by lowering blood pressure [55]." FDA officials cautioned, however, that this evidence is inconclusive and inconsistent. |

**Interim Summary & Action Steps**

Pregnancy and lactation are periods of increased metabolic demands associated with changes in the mother's physiology and social environment and developmental requirements of the child. Clinicians recognize that many women fail to consume adequate vitamins and minerals necessary to support a healthy pregnancy. When this is the case, supplementation of key vitamins and minerals may be required. Optimizing endometrial wellbeing may also help to prevent common pregnancy complications, including adverse effects on both early and late fetal development, as well as compromised mineral and complex oligosaccharide levels in breast milk.

For a mineral such as iron, the U.S. Food and Drug Administration has provided specific recommendations for provision with folate. In contrast, no specific recommendations for prenatal Ca or $Mg^{2+}$ supplementation have been established. This is a significant shortcoming, since inadequate stores or intake of these two essential mineral nutrients can have adverse effects on the mother, such as hypertension, complications of labor, and extended disability and recovery time after delivery. Furthermore, the fetus can be affected, resulting in abnormal organ and tissue development, intrauterine growth retardation, congenital malformations, reduced immunocompetence, preterm delivery, and lifelong, increased risk of metabolic disturbances such as type 2 diabetes, metabolic syndrome/obesity, hypertension, and chronic kidney disease.

**What constitutes the Reference Range for these minerals?**

Serum Ca is routinely monitored, and the reference range for Ca (2.2-2.7 mmol/L) is relatively consistent around the world [1]. Consequently, Ca levels are readily available to clinicians, providing guidance in patient care. In contrast, $Mg^{2+}$ is often viewed as a micromineral that has little significance until serious adverse events (e.g., preeclampsia, eclampsia, high risk of premature birth) prompt administration of tocolytics such as intravenous magnesium sulfate. Also, the interpretation of serum $Mg^{2+}$ levels presents a number of practical problems. First, serum $Mg^{2+}$ may not be routinely monitored, although clinical instruments for such monitoring are readily available [56]. Interlaboratory variability further complicates interpretation of existing data [57,58]. Equally problematic is the observation that there is little consensus on reference values and the units in which they are reported. Serum $Mg^{2+}$ values are reported in mg/dL, mmol/L, or mEq/L. In addition, serum $Mg^{2+}$ values may be determined as total $Mg^{2+}$ or ionized $Mg^{2+}$. As a result of these differences, no standardized reference range for serum $Mg^{2+}$ has been established, which has led to a wide variety of reference ranges being reported (**Table 7**).

**Table 7.** Reference values for serum magnesium concentration in adults.

| |
|---|
| 0.68-0.88 mmol/L [Martin 59] |
| 0.70 – 0.96 mmol/L [Lowenstein and Stanton 60] |
| 0.70 – 0.95 mmol/L [Mejía-Rodriguez 61] |
| 0.7 – 1.0 mmol/L [a U.S. standard; Misra 62] |
| 0.85 – 0.96 mmol/L [Costello 63; Rosanoff 64] |
| 0.5 – 1.05 mmol/L [a Japanese standard; Yamanaka 65] |
| 0.7 – 1.0 mmol/L [Workinger 66] |
| 0.7 – 1.05 mmol/L [a European standard; Leenders 67] |
| 0.84 – 1.05 mmol/L [Zhan 68] |
| 0.7 – 1.1 mmol/L [Van de Wal-Visscher 69; Glasdam 70] |
| 0.54 – 1.19 mmol/L [Akizawa 71] |
| 0.76 – 1.15 mmol/L [a European standard; Severino 72] |

Serum $Mg^{2+}$ concentration shows little variation as a consequence of tight physiological regulation, and clinicians have concluded that its serum concentration may not provide the most informative picture of $Mg^{2+}$ status in an individual [73,74]. Nonetheless, if chronically low serum $Mg^{2+}$ is a concern, defining ranges of serum $Mg^{2+}$ concentrations that will support the health of both normal subjects and patients remains a challenge that merits attention [75,76]. Indeed, the German Society for Magnesium Research e.V. recently proposed a value of 0.85 mmol/L to define the lower limit of serum $Mg^{2+}$ concentration associated with lower risks to good health [77,78].

**Are the dietary requirements for calcium and magnesium adequately met?**

The recommended daily Ca intake in the general adult population ranges between 500 and 1,300 mg daily [1,79]. Surprisingly, the Recommended Daily Allowances (RDAs) for pregnant and lactating women (1,000-1,300 mg Ca daily) fall within the same range. Maternal sources of both Ca and $Mg^{2+}$ include increased uptake from the diet, increased renal uptake and recirculation, and bone resorption. In fact, bone resorption is so extensive that the loss of Ca during pregnancy and 6 months of lactation is equivalent to 4-5% of the mother's total skeletal calcium content (about 1,200 g Ca) [1]. (Bone loss is expected to be more extensive if a mother bears twins or triplets.)

As Weaver, Heaney and others have noted, most of the Ca in the American diet comes from dairy products [80]. (N.B. Dairy products do not include oat, soy or other plant-derived "milk.") Changes in the Western diet indicate that diet alone may not be sufficient to meet maternal needs for Ca during pregnancy and lactation. As a result, in 2020, the World Health Organization issued an updated guideline for Ca supplementation before and during pregnancy [81]. The committee concluded that low-certainty evidence suggests that starting Ca supplementation before and/or early in pregnancy (compared to placebo or no treatment) may include the possibility of a risk reduction for preeclampsia and eclampsia, particularly for those women with greater than 80% compliance with calcium supplementation. They also noted "that the acceptability of Ca supplementation by women

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may vary – while women may value nutritional interventions that can lead to a healthy baby and a positive pregnancy experience, Ca tablets can be large, have a powdery texture and be unpalatable to consume. Feasibility may also be limited in settings where Ca is not always available due to logistical or staff constraints or cost. In addition, limited access to pre-conception healthcare services may be a barrier to the provision of calcium supplements prior to pregnancy."

The recommended daily $Mg^{2+}$ intake in the general adult population ranges between 310 and 420 mg, whereas pregnant women have a recommended daily $Mg^{2+}$ intake of 350–400 mg [82]. Maternal sources of $Mg^{2+}$ include uptake from the diet, renal uptake and recirculation, and bone resorption. In addition, some evidence suggests altered tissue distribution and an increased renal output of $Mg^{2+}$ during pregnancy [83]. Unlike Ca, $Mg^{2+}$ uptake is not significantly affected by vitamin D. Dietary surveys confirm that dietary $Mg^{2+}$ remains below recommended levels in Europe and the United States. According to several recent reports, these diets include between 30% and 50% less $Mg^{2+}$ than the daily recommended dosage [84,85]. Many authorities state, however, "magnesium deficiency is extremely rare [87]."

Likewise, both the Australian Government Department of Health and World Health Organization guidelines state that there is insufficient evidence to conclude whether dietary $Mg^{2+}$ supplementation during pregnancy is beneficial, even for leg cramps [28]. Other government authorities are silent about $Mg^{2+}$. Adams *et al*. and other investigators provide weak recommendations for $Mg^{2+}$ supplementation [29]. "Overall, because U.S. women have average magnesium intake that is 22% less than the RDA, and because levels decrease during pregnancy, we recommend supplementing with 350 mg because 345 mg was found be sufficient to keep magnesium levels stable, and supplementation studies with doses of 345–500 mg were found to be beneficial. This recommendation appears likely to reduce the rate of pregnancy-induced hypertension, maternal hospitalization, preterm birth, low birth weight, and low Apgar scores, and could possibly help with other conditions as well [29]."

**Defining an Action Range for $Mg^{2+}$**

By considering all this information together with recent reports by Čabarkapa *et al*., Escobedo-Monge *et al*., and Rosanoff *et al*. an action range for $Mg^{2+}$ (i.e., a concentration range that would prompt clinical intervention) can be reasonably defined as 0.7 to 0.85 mmol serum Mg/L [87–89].

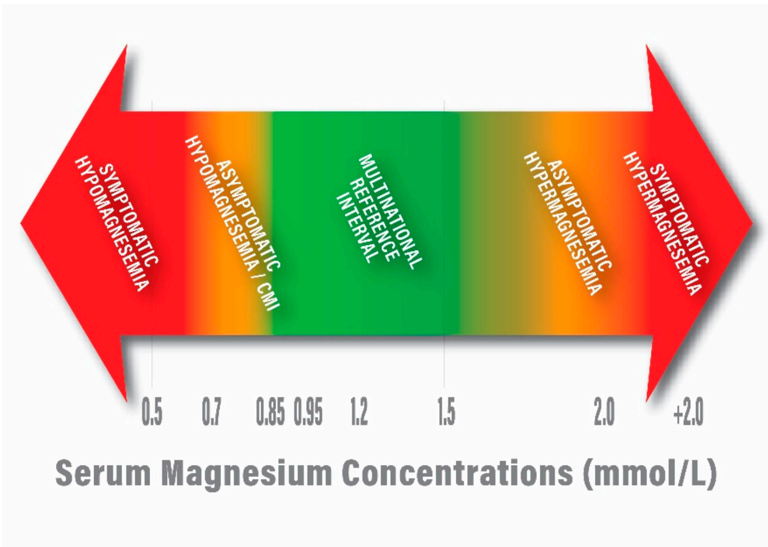


**Figure 1.** Thermograph of relationships between serum $Mg^{2+}$ and health.

For example, Čabarkapa's prospective study included 403 pregnant women > 18 years old, with singleton pregnancies [87]. Between 11- and 14-weeks' gestation a single blood sample was collected from every study participant and concentrations of urea, creatinine, uric acid, $Mg^{2+}$, free beta subunit of human chorionic gonadotrophin, plasma protein A related to pregnancy, and C-reactive protein

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were measured. All subjects were followed through the rest of pregnancy. 61 of the study participants developed pre-eclampsia and were retrospectively compared to a group of 342 participants who experienced uncomplicated pregnancies and normal outcomes. Serum $Mg^{2+}$ levels were significantly lower in PEKT mothers compared to the TNT group (0.69 ± 0.18 vs. 0.85 ± 0.08 mmol/L; $p < 0.001$). The level of serum $Mg^{2+}$ had the strongest significant positive correlation ($p < 0.05$) with the week of gestational outcomes ($R = 0.442$), weight ($R = 0.416$), and Apgar score ($R = 0.343$) of the newborns, and the strongest significant negative correlation with the number of miscarriages ($R = -0.413$), serum creatinine levels ($R = -0.471$), and the number of pregnancies ($R = -0.326$). The week of gestational outcome was predicted with the greatest reliability by the serum $Mg^{2+}$. A serum $Mg^{2+}$ level ≤ 0.81 mmol/L in the first trimester predicted preeclampsia with a sensitivity of 77.0% and specificity of 71.6%. When serum creatinine levels were considered in conjunction with serum $Mg^{2+}$ it was found that creatinine levels > 53 µmol/L detected preeclampsia with a sensitivity of 93%. (preeclampsia 62.3 µmol/L vs. normal 49.2 µmol/L; $p < 0.001$).

**Together with the other reports cited above, this information suggests that a serum magnesium concentration in the range from 0.7 to 0.85 mmol/L or a molar ratio of serum calcium:serum magnesium of > 3 constitutes a marker of increased risks for adverse events to mother and child during pregnancy, less than optimal mineral concentrations in breastmilk during lactation, and prolonged recovery of maternal bone density and strength post-partum.**

**Moving the Needle on Risks**

If our working hypothesis has validity, high Ca: $Mg^{2+}$ molar ratios (i.e., values in the range > 3) and serum $Mg^{2+}$ concentration in the lowest quartile of the reference range (0.7 - 0.85 mmol/L) present increased risk for complications during pregnancy and lactation. "Moving the needle" by increasing maternal serum $Mg^{2+}$ concentration to ≥ 0.85 mmol/L is a potential action step. How can this be accomplished? Actions such as the following may reduce the risks associated with chronic $Mg^{2+}$ insufficiency.

***Diet and education***

As a first action step, let us echo the words of Murphy *et al.* [90]. "Adequate consumption of nutrients that support infant neurodevelopment is critical among pregnant women and women of childbearing age." Their review of the potential effects of socioeconomic inequalities on nutrient gaps in these life stages is particularly informative. They analyzed data from 2007–2018 NHANES related to usual intake (foods and dietary supplements) of neurodevelopment-related nutrients among women of childbearing age and pregnant women (20–44 years). Usual intake was compared across household food security, poverty-to-income ratio (PIR), and household participation in federal food and nutrition assistance programs. Women in households that participated in the Supplemental Nutrition Assistance Program had a significantly lower intake of multiple nutrients relative to those who did not participate. For example, 50% had intakes below the estimated average requirement (EAR) for vitamin A (versus 32%), 42% were below the EAR for calcium (versus 33%) and 65% were below the EAR for magnesium (versus 42%). Similar gradients were observed by PIR and household food security, and among pregnant women wherein gaps were more evident in those experiencing socioeconomic inequalities. The use of dietary supplements attenuated shortfalls for most nutrients. *These findings highlight a critical need to support the nutritional requirements for women of childbearing age and pregnant women.*

As Henriksen and others have pointed out, a mixed diet including whole grain cereals, milk and dairy products, vegetables, starchy roots, berries, meat and fish constitutes the best sources of $Mg^{2+}$ [80,91]. Magnesium concentrations are especially high in dark chocolate, nuts, and coffee. "Hard" water contains more $Mg^{2+}$ than "soft" water and drinking either "hard" or mineral water can contribute 10–20 mg/day to the total $Mg^{2+}$ intake.

***Supplementation***

Numerous clinical trials have tested whether the risk the pregnancy complications mentioned herein can be mitigated by supplementing the diet with $Mg^{2+}$ alone or with a combination of $Mg^{2+}$ and Ca. Unfortunately, the results are conflicting and have often been judged to be of low evidentiary

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value [92–99]. When statistical analyses fail to establish causal relationships, authors may conclude that serum mineral levels were "adequate" [99].

On the other hand, since $Mg^{2+}$ is involved in roughly 80% of physiological processes, establishing causal relationships between serum $Mg^{2+}$ and risks associated with chronic $Mg^{2+}$ insufficiency through statistical analyses of data from large clinical trials may be an unrealistic expectation. For example, well-designed trials typically include large cohorts of women having a wide range of serum $Mg^{2+}$ levels. Mechanistically, those with sufficient $Mg^{2+}$ will not benefit from supplementation, since absorption will be limited naturally; their lack of responsiveness will skew subsequent statistical analyses. Some of the trial designs include supplementation that is started during pregnancy and is of short duration. This may be "too little and too late," since some studies suggest twelve weeks or more of supplementation may be needed to restore intracellular $Mg^{2+}$. Moreover, Larsson's data (**Table 1**) show that $Mg^{2+}$ is utilized from start to finish of pregnancy [14]. Finally, the course of supplementation may be inadequate.

This last comment is illustrated by comparison of the outcomes of two randomized clinical trials in which nominal supplemental doses of 300 mg of magnesium citrate were administered daily to pregnant women at risk for adverse events (**Table 8A**) [100,101]. The BRAMAG study (**Table 8A**) was carried out at three centers in Brazil [100]. Over 800 women were enrolled, each with a singleton pregnancy and at least one risk factor for adverse events. The 407 women in the treatment group received a tablet containing 300 mg of magnesium citrate daily from the 12$^{th}$ to the 20$^{th}$ week of gestation.[3] Preeclampsia or eclampsia, severe hypertension, placental abruption, and stroke or death were monitored in the mothers. Preterm birth, stillbirth, neonatal death or NICU admission after birth, and small for gestational age birthweights were monitored in the offspring. Data from the 407 study participants who received magnesium citrate compared to data from 422 participants who were given placebo. 75 neonates (18.4%) in the magnesium supplement arm and 76 neonates (18.0%) in the placebo arm developed at least one of the adverse effects listed above – an adjusted odds ratio (aOR) of 1.10 (95% CI 0.72–1.68). The most common outcome among neonates was preterm birth (9.3%). 49 (12.0%) women in the magnesium arm and 41 women (9.7%) in the placebo arm developed at least one of the pregnancy complications listed above – an aOR of 1.29 (95% CI 0.83–2.00). The most common complication was pre-eclampsia prior to 37 weeks' gestation (9.3%) and severe gestational hypertension prior to 37 weeks' gestation (4.9%). Of note, the risk of placental abruption was lower in the magnesium group (9 events [2.2%]) compared to the placebo arm (21 events [5.0%]), equivalent to an adjusted OR of 0.43 (95% CI 0.20 to 0.95). The authors concluded, "Oral magnesium citrate supplementation ***did not appear to reduce adverse perinatal or maternal outcomes in high-risk singleton pregnancies***."

Conversely, in a separate study that was carried out in Turkey (**Table 8B**), the effects of $Mg^{2+}$ supplementation in women with serum $Mg^{2+}$ concentrations in the lowest quartile of the normal range were evaluated [101]. The study included 120 pregnant women at 12-14 weeks' gestation. Participants had an average age of 29 and normal weight. Most study participants had a history of gestational diabetes mellitus, preeclampsia, preterm birth, and stillbirth. Participants with $Mg^{2+}$ serum levels higher than 1.9 mg/dl were considered a control group (Group A, n = 60). Participants with $Mg^{2+}$ levels lower than this were considered to have hypomagnesemia and were divided into Groups B and C (n = 60 for both). Each participant received a daily multimineral tablet containing 100 mg $Mg^{2+}$ until delivery. Group A had an average serum $Mg^{2+}$ level of 0.86 mmol/L. Groups B and C had an average serum $Mg^{2+}$ level of 0.71 mmol/L. Group C received an additional tablet daily for one month during pregnancy that contained 200 mg $Mg^{2+}$ as magnesium citrate in an effervescent formulation. The data showed that supplemental $Mg^{2+}$ significantly reduced maternal preeclampsia ($P = 0.018$), preterm birth ($P = 0.044$), gestational diabetes ($P = 0.003$), and leg cramps ($P < 0.001$) for the mother, as well as a reduced risk of IUGR ($P < 0.001$), low birth weight ($P = 0.002$), and Apgar

[3] Magnesium citrate contains 11% magnesium by weight. If 300 mg of magnesium citrate was administered, the magnesium content was 34 mg.

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score under 7 ($P = 0.006$) for the child. The investigators concluded, "***Mg supplement during pregnancy likely decreases the probability of occurrence of many complications of pregnancy***."

**Table 8.** Comparison of two RCTs in which supplemental magnesium citrate was administered.

| | |
|---|---|
| **8A. BRAMAG Trial** – a Multicenter, double-masked, placebo controlled, randomized, superiority trial carried out at 3 centers in Brazil; ClinicalTrials.gov NCT02032186, registered January 9, 2014 | |
| Source | de Araújo CAL, Ray JG, Figueiroa JN, Alves JG. BRAzil magnesium (BRAMAG) trial: a double-masked randomized clinical trial of oral magnesium supplementation in pregnancy. BMC Pregnancy Childbirth. 2020 Apr 21;20(1):234. doi: 10.1186/s12884-020-02935-7. PMID: 32316938; PMCID: PMC7175576. |
| Eligible participants | Women with singleton pregnancy and ≥1 risk factor, age > 35 years or elevated body mass, mean serum Mg 1.8 mg/dL (0.74 mmol/L); 159 women in each arm |
| Treatment | 300 mg magnesium citrate, oral, daily, given at 12-20 weeks gestation |
| Primary perinatal composite outcome | Preterm birth < 37 weeks' gestation, stillbirth > 20 weeks, neonatal death or NICU admission < 28 days after birth, or small for gestational age birthweight < 3rd percentile |
| Co-primary maternal composite outcome | Preeclampsia or eclampsia < 37 weeks, severe gestational hypertension < 37 weeks, placental abruption, or maternal stroke or death during pregnancy or ≤ 7 days after delivery |
| Results | Analyses comprised 407 women who received magnesium citrate and 422 who received placebo. The perinatal composite outcome occurred among 75 (18.4%) in the magnesium arm and 76 (18.0%) in the placebo group – an adjusted odds ratio (aOR) of 1.10 (95% CI 0.72–1.68). The most common outcome among this arm was preterm birth (9.3%). The maternal composite outcome occurred among 49 (12.0%) women in the magnesium arm and 41 women (9.7%) in the placebo group – an aOR of 1.29 (95% CI 0.83–2.00). The most common outcome among this arm was pre-eclampsia < 37 weeks gestation (9.3%) and severe gestational hypertension < 37 weeks' gestation (4.9%). Of note, the risk of placental abruption was lower in the magnesium group (9 events [2.2%]) compared to the placebo arm (21 events [5.0%]), equivalent to an adjusted OR of 0.43 (95% CI 0.20 to 0.95). |
| Conclusion | Oral magnesium citrate supplementation did not appear to reduce adverse perinatal or maternal outcomes in high-risk singleton pregnancies. |
| | |
| **8B. Turkish Trial.** A randomized controlled trial with three sixty populated groups of pregnant women carried out at a single center in Iran; registered under trial registry code IRCT2015121925611N1 at the National Registry for Clinical Trials | |
| Source | Zarean E, Tarjan A. Effect of magnesium supplement on pregnancy outcomes: a randomized control trial. Adv Biomed Res. 2017;6:109–14. |

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| | |
|---|---|
| Eligible participants | Women having an age of 29-36 years with gestational age of 12-14 weeks, singleton pregnancy; 80-90% with history of GDM, pre-eclampsia, preterm birth, and/or stillbirth; lack of acute renal disease; lack of history chronic HTN; lack of history of overt diabetes; lack of history of severe anemia; lack of history of diagnostic heart disease; lack of anomaly in this pregnancy and previous ones; lack of use cigarette and alcohol; lack of molar pregnancy; lack of acute pancreatitis; lack of multiparity<br>Women in Group A (n=30): Mg serum levels more than 1.9 mg/dL<br>Women in Group B and C (n=30, each group): serum Mg levels < 1.9 mg/dL |
| Treatment | Group A: One multimineral tablet (100 mg Mg) once a day until the end of pregnancy<br>Group B: One multimineral tablet (100 mg Mg) daily until the end of pregnancy<br>Group C: One multimineral tablet (100 mg Mg) daily until the end of pregnancy and 200 mg Mg in an effervescent tablet once daily for 1 month |
| Primary composite outcome | Intrauterine growth retardation, preterm labor, maternal body mass index, neonatal weight, pregnancy-induced hypertension, preeclampsia, gestational diabetes mellitus, cramps of the leg, Apgar score |
| Results | All pregnancy outcomes such as preeclampsia ($P = 0.018$), IUGR ($P < 0.001$), preterm birth ($P = 0.044$), LBW ($P = 0.002$), GDM ($P = 0.003$), cramps of leg ($P < 0.001$), Apgar score (under 7) ($P = 0.006$), birth weight (continuous) ($P = 0.002$), and Apgar (continuous) ($P = 0.01$) were significantly better in the group who received supplemental magnesium than in the control group and the group receiving only the multimineral tablet. |
| Conclusion | Mg supplement during pregnancy likely decreases the probability of occurrence of many complications of pregnancy. |

## 4. Discussion

In summary, available data affirm the importance of maintaining adequate maternal mineral nutrition before and during pregnancy and during lactation. Adequate Ca and $Mg^{2+}$ may be particularly important to both mother and child, given the broad spectrum of physiological roles of these two key minerals.

Taken together, a growing body of data suggests that a woman who presents with serum $Mg^{2+}$ of 0.70 to 0.85 mmol/L and serum Ca in the reference range should be counseled about increased risks associated with pregnancy. Actions as straightforward as counseling to improve a mother's diet, adding necessary supplements both before, during and after pregnancy, have proven valuable and cost-effective [102–104].

Given the high burden of pregnancy complications, nutritional supplementation at all stages of pregnancy may well be a safe and cost-effective way to reduce risk of adverse outcomes for mother and child [105–107].

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**Conflicts of Interest:** All authors are either employees or consultants of BioLink Life Sciences, Inc. Combinations of soluble calcium and magnesium salts are a patented product of BioLink.

## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| Ca | Calcium |
| CI | Confidence Interval |
| Co | Cobalt |
| Cr | Chromium |
| Cu | Copper |
| EAR | Estimated Average Requirement |
| Fe | Iron |
| K | Potassium |
| Mg | Magnesium |
| Mn | Manganese |
| Ni | Nickel |
| NHANES | National Health and Nutrition Examination Survey |
| NICU | Neonatal Intensive Care Unit |
| OR | Odds Ratio |
| OSI | Oxidative Stress Index |
| P | Phosphate |
| Pb | Lead |
| PTH | Parathyroid Hormone |
| RDA | Recommended Daily Allowance |
| Se | Selenium |
| TAS | Total Antioxidant |
| TOS | Total Oxidation Status |
| TRPM6 | Transient Receptor Potential Channel 6 |
| TRPM7 | Transient Receptor Potential Channel 7 |
| Zn | Zinc |

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