

Supplementation of Magnesium in Pregnancy

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Abstract

Although the relevance of magnesium in obstetrics has been known for a long time and its effect in many diseases is well documented, oral magnesium supplementation during pregnancy is a subject of discussion. The evaluation of the variety of studies regarding magnesium supplementation in pregnancy clearly shows positive effects of oral substitution, in contrast to the Cochrane analysis. In addition to the needs of the growth of the fetus and the maternal tissue, elevated renal magnesium excretion is a reason for an increased magnesium requirement during pregnancy. This enhanced renal loss leads to a decreased serum magnesium concentration, which can also be recognized in the myometrium.

Keywords: Magnesium; Preeclampsia; Pregnancy

Introduction

The importance of magnesium in obstetrics has been appreciated for decades. Magnesium infusion in cases of preeclampsia/eclampsia is standard therapy, but general oral magnesium supplementation during pregnancy remains controversial. In disease such as diabetes mellitus, heart arrhythmias, hypertension, or disturbances of the nervous system, the effect of magnesium has been extensively recorded [1-3]. Moreover, in pregnancy, various studies have shown a positive effect of magnesium supplementation [4,5]. Pregnancy represents a physiological situation with increased magnesium requirement. Symptoms of magnesium deficiency such as calf muscle cramps can be easily treated with oral magnesium supplementation [6], as can neuromuscular disorders or enhanced uterus contractions. Magnesium supplementation can prevent pregnancy-induced hypertension [4] and has a positive effect on the height and maturity of fetuses [7]. In the

following, we will outline the effect of oral magnesium supplementation on the course of pregnancy.

Does pregnancy lead to magnesium deficiency?

Symptoms of magnesium deficiency are common in pregnant women (Table 1). However, various reviews contain claims that magnesium status is not affected by pregnancy. This misinterpretation is based on the only criterion for magnesium deficiency being hypomagnesemia, which has partly been defined with incorrectly low limits (0.63-0.75 mmol/l). However, the reference interval for serum magnesium concentration is 0.76-1.10 mmol/l [1]. In addition, normomagnesemia does not exclude magnesium deficiency [8] and further tests have revealed that this lower limit of the reference interval is not optimal [9]. If an optimal serum magnesium concentration of >0.80 mmol/l is taken as a basis, then the majority of pregnant women can be said to suffer from magnesium deficiency when the serum concentration only is considered.

Neurovegetative-functional disorders
Cramps of skeletal muscles (e.g., calf muscle cramps)
Spasms of the smooth muscles (gastrointestinal spasms, dysmenorrhea, uterine contractions, premature labor)
Extrasystoles, tachycardia, angina pectoris symptoms

Table 1: Symptoms of magnesium deficiency.

What is the Cause for Increased Magnesium Requirement during Pregnancy?

Undoubtedly, pregnancy leads to increased magnesium requirements [10,11]. On the one hand, the fetus requires magnesium. Furthermore, increased requirements because of maternal tissue changes and renal magnesium loss have to be balanced. Various studies of animal models have revealed that, for normal pregnancy/gestation with an optimal outcome, a markedly higher magnesium intake is necessary than the minimum as assessed by balance studies [12]. In addition, the National Study of Nutrition in Germany has shown that 56.4% of women aged 14-18 years, 38.3% of women aged 19-24 years, and 26.5% of women aged 25-34 years do not have, even before pregnancy, magnesium values that meet the recommendations of the DGE (German society for nutrition) [13].

In addition to the requirement of the fetus and maternal tissue for magnesium and the low dietary intake of this mineral, renal loss is a major cause for increased magnesium requirements during pregnancy. Studies by Spätling et al. have demonstrated that renal magnesium excretion is enhanced by about 20% in pregnant women [14]. This can be explained by the pregnancy-induced increase of the heart rate volume of about 40% followed by an increase of primary urine production and the non-adequate reabsorption of magnesium.

Hypomagnesemia during pregnancy should not falsely be interpreted as a diluting effect ("Pseudo-Hypomagnesemia") because of a decrease in total and ionized magnesium, as this magnesium deficiency can also be verified in the tissue [15]. The myometrial magnesium concentration declines during pregnancy and is significantly correlated with the plasma magnesium concentration [16].

Does the Magnesium Status Influence Pregnancy?

Evidence is growing that magnesium status is associated with pathological incidents in pregnancy. Based on retrospective data Schimatschek and Classen [17] have described a significant increase of preterm birth, spontaneous abortions, calf muscle cramps, and dysmenorrhea in cases of mothers suffering from hypomagnesemia. A case control study has revealed that a higher magnesium intake is

associated with a decreased risk of preeclampsia, although broad confidence intervals [18] exist. The association of a low dietary magnesium intake and an increased risk for preeclampsia has been confirmed in a meta-analysis regarding the effects of various dietary factors on the risk of pregnancy-induced high blood pressure [19].

Studies with vastly different approaches have followed up the possible link between magnesium status and risk for preeclampsia. Kisters et al [20] have shown that the plasma magnesium concentration in healthy pregnant women and pregnant women with preeclampsia is lower than that in healthy non-pregnant women. The magnesium concentration in the erythrocyte membrane of pregnant women with preeclampsia is also lower than that in healthy non-pregnant women. A decreased plasma magnesium concentration in pregnant women with preeclampsia in contrast to pregnant women without preeclampsia has been confirmed by numerous current investigations in diverse countries [21-25].

Trials carried out by Resnick et al [26] have revealed a reduced ionized magnesium concentration in the brain of pregnant women with preeclampsia. Moreover, molecular biological examinations indicate alterations in the magnesium concentration in preeclampsia. Kolisek et al. [27] and Yang et al. [28] have characterized significant differences in placental gene expression for several magnesium transporter systems from pregnant women with and without preeclampsia. An adequate magnesium intake also seems to be important for further healthy development in pregnancy: A low post-partum magnesium status is a significant predictor for the development of later diabetes type 2 in pregnant women with gestational diabetes [29].

What are the Results of Magnesium Supplemental Studies?

Since the 1980s, several studies have dealt with magnesium supplementation in pregnancy (Table 2). Despite different designs, dosages, study targets, and duration of treatment, many of the results of oral magnesium supplementation are positive. In none of the studies have any serious side effects been described.

Author	Number of patients	Study design	Mg-dosage/day	Duration	Study target/results
Kuti V, et al. 1981 [30]	1884	open control group without Mg-supplementation	348 mg	Group 1: from 4th-9th week of pregnancy Group 2: from 10th-24th week of pregnancy	Higher reduction in frequency of spontaneous abortion and preterm birth in group 1 with earlier start of Mg-supplementation
Kovacs L et al. 1988 [31]	985	prospective randomized double-blind placebo-controlled	365 mg	from 9th week of pregnancy	Prevention of pregnancy-associated complications; verum compared to placebo: fewer preterm births, fewer newborns < 2500 g, fewer intrauterine retarded newborns, rarer EPH-gestosis
Spätling L, Spätling G 1988 [5]	568	prospective randomized double-blind placebo-controlled	365 mg	from 16th week of pregnancy	Improvement in the course of pregnancy and of outcomes; verum compared to placebo: fewer hospitalizations (p<0.05); lower numbers of preterm labour (p<0.05), bleeding (p<0.01), cervix insufficiency (p< 0.05), preterm births < 2500 g (p<0.05), newborns in intensive care unit (p<0.01)

Sibai BM et al. 1989 [32]	374	prospective randomized double-blind placebo-controlled	365 mg plus verum and placebo group 100 mg magnesium	begin within 13th and 24th week of pregnancy	Prophylaxis of preeclampsia: no significant differences in course of pregnancy and outcomes
D'Almeida A et al. 1992 [33]	150	prospective, randomized, partly double-blind, placebo-controlled	3 groups: placebo, primula and fish oil, magnesium 300 mg	begin <16th week of pregnancy	Prophylaxis of preeclampsia: fewer pregnant women in the magnesium group developed hypertension
Zarcone R et al. 1994 [34]	100	prospective randomized double-blind placebo-controlled	365 mg	begin <12th week of pregnancy	Improvement in the course of pregnancy; verum compared to placebo: fewer hospitalizations, fewer preterm births, no child with 5-min-Apgar < 7, fewer newborn < 2500 g
Dahle LO et al. 1995 [35]	73	prospective randomized double-blind placebo-controlled	365 mg	3 weeks	Treatment of leg cramps during pregnancy: fewer leg cramps (p<0.05 comparing verum/placebo; p<0.01 comparing before/after)
Arikan G et al. 1997 [7]	530	prospective randomized control group without magnesium supplementation	365 mg	begin < 18th week of pregnancy	Improvement in the course of pregnancy; Magnesium group compared with control group: fewer hospitalizations because of preterm birth (p<0.05), lower rate of preterm births (n.s.), fewer newborns < 2500 g (n.s.)
Li S, Tian H 1997 [36]	51	prospective randomized double-blind control group without magnesium supplementation	175 mg	from 28th week of pregnancy	Influence of magnesium supplementation on pregnancy-induced hypertension; Magnesium-group compared with control group: reduced appearance of hypertension (p<0.05)
Meier B et al 2005 [37]	80	case-control-study, 40 magnesium supplementation, 40 controls without magnesium supplementation	365-730 mg	at least 4 weeks	Treatment with Mg because of leg cramps, constipation or preterm labour; Magnesium group compared with control: fewer pregnant women needed spasmolysis, mothers could fully breastfeed their children
Harrison V et al. 2007 [38]	4494	prospective randomized double-blind placebo-controlled	128 mg	mostly started after 20th week of pregnancy	Primary study aim: hypotoxic-ischemic encephalopathy; Magnesium group compared with placebo: fewer children (15 vs 22; n.s.) secondary study aim: rarer fetal bradycardia (p=0.002) and death birth at due date (p=0.016)
Bullarbo M et al. 2013 [4]	61	prospective randomized double-blind placebo-controlled	300 mg	from 25th week of pregnancy	Influence of Mg-supplementation on prevention of hypertension in the last weeks of pregnancy; Magnesium group compared with control group: reduced average diastolic blood pressure in the 37th week of pregnancy (p<0.031), fewer pregnant women with increase in diastolic blood pressure >15 mm Hg (p=0.011)

Table 2: Description of studies with oral magnesium supplementation.

Kuti V et al [30]

1884 pregnant women were treated with 348 mg magnesium daily from 4th to 9th week of pregnancy (group 1) or from 10th to 24th week of pregnancy (group 2) or did not receive any magnesium substitution (control group). The influence of magnesium supplementation on the frequency of spontaneous abortion and preterm birth and on intrauterine fetal development was investigated. The reduction of spontaneous abortion and preterm birth were higher, the earlier that magnesium substitution was started. No side effects were noted.

Kovacs L et al [31]

In this prospective randomized double-blind placebo-controlled study with the aim of preventing pregnancy complications, 985 pregnant women received 365 mg magnesium or placebo daily, most of them starting at 9th week of pregnancy, but nearly all of them in the first trimester. The results of the study showed a statistically significant more favourable course of pregnancy in the magnesium group compared with placebo: fewer premature births, fewer underweight newborns (<2500 g), fewer intrauterine retarded new-borns, and rarer EPH gestosis. The registered side effects of vomiting, nausea and others

(heartburn and constipation) were almost equally frequent in the verum and placebo group.

Spätling L and Spätling G [5]

568 pregnant women were treated with 365 mg magnesium or placebo, starting before the 16th week of pregnancy in a prospective, randomized, double-blinded and placebo-controlled study. The targets of the study were an improvement in the course of pregnancy and outcome. In the magnesium group, significantly fewer hospitalizations occurred because of preterm labour, bleeding and insufficiency of the cervix; fewer preterm births of <2500 g and fewer newborns who had to be transferred to intensive care unit were recorded. Diarrhea, nausea, vomiting, heartburn, and abdominal fullness were occasionally reported as side effects at same frequency in the verum and placebo group.

Sibai BM et al [32]

374 pregnant women received 365 mg magnesium or placebo starting between 13th and 24th week of pregnancy in this prospective randomized placebo-controlled double-blind study aimed at the prevention of preeclampsia. No significant differences were noted between the two groups concerning the course of pregnancy and outcome. However, notably, this study was inconclusive as both the verum and the placebo groups took 100 mg magnesium in addition to the study medication. Furthermore, these pregnant women were a high risk group for preeclampsia prevention (very young, black pregnant women, average age: placebo: 18.5 years, verum: 17.8 years). In drop outs (6% in the magnesium group and 7% in the placebo group), only gastro-intestinal symptoms (nausea, vomiting, diarrhea) were mentioned as side effects.

D´Almeida et al [33]

In a randomized, prospective, partly double-blinded, placebo controlled study with the target of preventing preeclampsia, 150 pregnant women were treated in 3 groups with either placebo (olive oil), primula and fish oil, or 300 mg magnesium. In the magnesium group, statistically significantly fewer pregnant women developed hypertension. Diarrhea was mentioned as a side effect in the magnesium group without any details of frequency.

Zarcone R et al [34]

In this prospective randomized double-blinded placebo-controlled study, 100 pregnant women received 15 mmol magnesium or placebo daily, starting at 12th week of pregnancy. In the magnesium group, significantly fewer pregnant women hospitalized, fewer preterm births, no child with a 5-min-Apgar <7, and fewer underweight newborns were noted compared with the placebo group. Undesirable side effects such as diarrhea, nausea, and vomiting were only reported in dropouts (3 in the verum group, 4 in the placebo group).

Dahle LO et al [35]

73 pregnant women with calf muscle cramps received 15 mmol magnesium for 3 weeks in this prospective randomized placebo controlled study. Oral magnesium supplementation was successful in the treatment of pregnancy-induced leg cramps. Rare side effects such as mild and early nausea were reported; one patient in the placebo group had to quit because of serious permanent nausea.

Arikan et al [7]

In this prospective randomized study, 530 pregnant women were divided into 2 groups either receiving 15 mmol magnesium beginning at 18th week of pregnancy or no supplementation (control group). Magnesium supplementation led to significantly fewer hospitalizations attributable to preterm birth. Frequency of preterm birth (4.6% vs. 8.0%) and birth weight <2500 g (2.9% vs. 4.8%) were lower but not significant. Side effects were reported in 5 pregnant women who were excluded from the study.

Li S and Tian H [36]

51 pregnant women were treated with 175 mg magnesium daily starting at 28th week of pregnancy, and 51 pregnant women served as control group (randomized double-blind prospective study). An influence of magnesium supplementation on pregnancy-induced hypertension was observed. Magnesium reduced, statistically significantly, the occurrence of hypertension (4% in the magnesium group, 16% in the placebo control group). No side effects were listed in the abstract of this Chinese study.

Meier et al [37]

This retrospective case-control-study compared 40 pairs of pregnant women: one half received 15-30 mmol magnesium daily for at least 4 weeks because of constipation, calf muscle cramps, or premature labor, whereas the other half was not supplemented [38]. The authors concluded that significantly fewer of the magnesium-supplemented pregnant women needed spasmolysis (3 vs. 14) and could fully breastfeed their children at discharge (24 vs. 34). No side effects were reported.

Harrison V et al [38]

In this prospective randomized double-blind study, 4494 pregnant women received 128 mg magnesium or placebo mostly starting after 20th week of pregnancy. The incidence of the primary study parameter frequency of hypoxic-ischemic encephalopathy was 22 children in the placebo group and 15 children in the magnesium group; the aimed significance was not reached. However, secondary study aims were significantly improved; in the magnesium group, significantly lower fetal bradycardia and stillbirths at term were registered. Side effects such as nausea, vomiting, and abdominal pain were observed with equal frequency in the verum and placebo groups.

Bullarbo M et al [4]

In a prospective placebo-controlled double-blind study, 61 pregnant women were supplemented with 300 mg magnesium or placebo daily from 25th week of pregnancy. The influence of magnesium supplementation on the prevention of preeclampsia during the last few weeks of pregnancy was examined. Pregnant women in the magnesium group had significantly reduced average diastolic blood pressure at 37th week of pregnancy, significantly fewer pregnant women of the magnesium group had an increase in diastolic blood pressure ≥ 15 mm Hg, and an inverse correlation between urine magnesium excretion and diastolic blood pressure during pregnancy was observed. No side effects were reported.

What is the clinical relevance of the Cochrane review from 2014?

A prospective placebo-controlled randomized double-blind study represents the gold standard for the assessment of pharmaceutical efficacy. In Cochrane reviews, the main focus for the assessment of studies is the compliance to formal biometric criteria without evaluation of dosages. Clinical aspects are often not considered. This is especially a problem in the Cochrane analysis of Makrides et al [39]. In this analysis, a prospective placebo-controlled randomized double-blind study was considered as “high quality”, although magnesium was supplemented in the placebo group [32]: an incorrect study design that was not taken into account in the Cochrane analysis. In a further positively evaluated study, no differentiation was made between oral and parental magnesium treatment [40]. A third “high quality” rated study involved women who were treated with only 128 mg magnesium daily with critical compliance [38].

On the other hand, the prospective placebo-controlled double-blind study of Spätling and Spätling [5] of 568 pregnant women was rated as “low quality” because randomization was carried out based on birth date, which did not represent the optimal method for randomization. This criticism is formalistic as a randomization on the date of birth is acceptable from the clinical point of view. Nevertheless, the Society for Magnesium Research e.V. (Gesellschaft für Magnesiumforschung e.V.) relies on this study, which was performed before the introduction of “good clinical practice” because study results show a successful randomization by an equal distribution of pregnancy risks being reached in both groups. A recent study has not been included in the Cochrane review and yet has confirmed the positive effect of magnesium supplementation [4].

Conclusion and Recommendation

When magnesium deficiency is anamnestically assumed, or when magnesium deficiency exists with corresponding symptoms (e.g., calf muscle cramps, inadequate uterus contraction, (Table 1), magnesium supplementation is essential. Notably, women in risk groups (e.g., patients with sprue, diabetics, metabolic syndrome, and multiple birth) have a higher magnesium requirement. Currently, those women that are at risk of having decreasing magnesium levels with a negative effect on the course of pregnancy are clinically not predictable. The performance of a placebo-controlled study is hard to justify from an ethical point of view and is moreover impracticable in Germany, because, after being informed about the study, an unknown number of participations would take prescription free magnesium as they would be fearful of being part of the placebo group. For these reasons, the Society for Magnesium Research e.V. recommends general magnesium supplementation during pregnancy as magnesium supplementation is safe, low in side effects, and cost efficient.

Recommendation of the Society

Every pregnant woman should be supplemented with 240-480 mg (10-20 mmol) magnesium daily. Magnesium supplementation should start as soon as possible, continue until birth, and be continued postnatally, since the magnesium requirement of the body also increases during breast-feeding. Magnesium supplementation should not be discontinued some weeks before birth, since an effect on the beginning of spontaneous labour pain has not been proved. Side effects of a magnesium supplementation might be soft stools (a welcome effect in cases of constipation), which can be easily avoided by the intake of

equal doses during the day. Oral magnesium supplementation is contraindicated in severe renal impairment.

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