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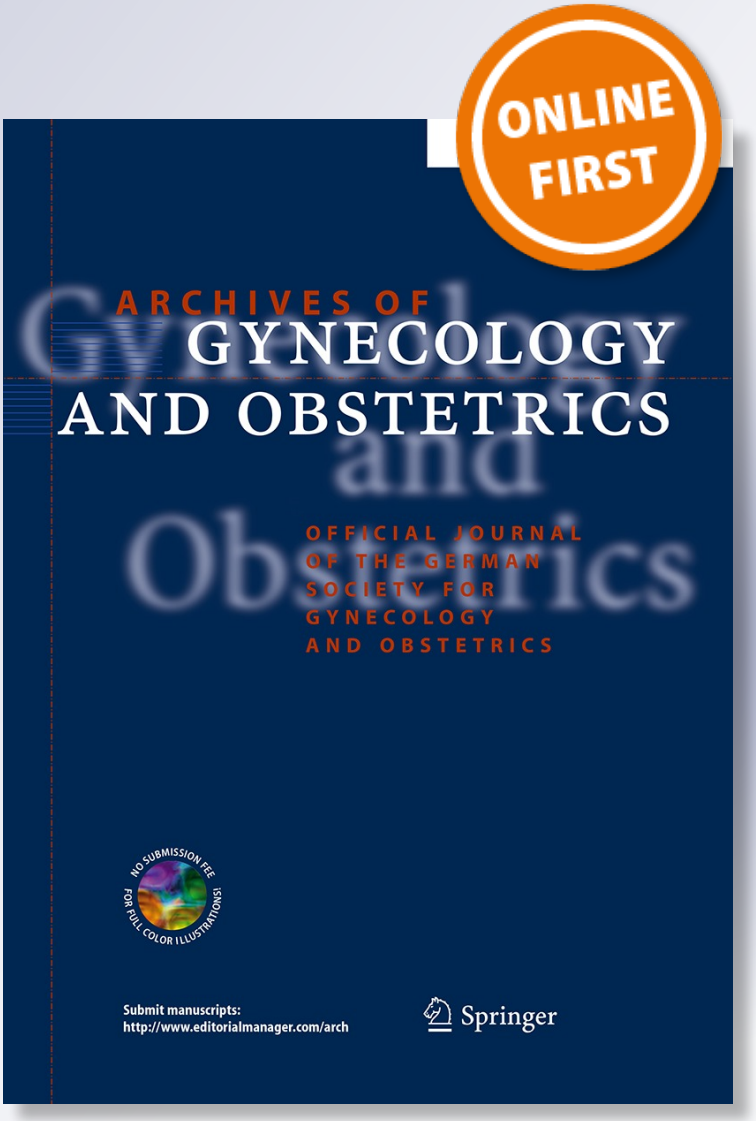

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MATERNAL-FETAL MEDICINE

Magnesium supplementation to prevent high blood pressure in pregnancy: a randomised placebo control trial

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Abstract
Purpose To assess if hypertension during the last part of pregnancy could be prevented by magnesium supplementation.
Methods Pregnant primagravida women from a local antenatal care unit were given an oral supply of 300 mg magnesium as citrate or placebo from pregnancy week 25 in a randomised double-blind setup. Blood pressure was recorded during pregnancy as well as pregnancy outcome.
Results In the magnesium-supplemented group, the average diastolic blood pressure at week 37 was significantly lower than in the placebo group (72/1.4 mean/SEM vs 77/1.4, $p = 0.031$). The number of women with an increase in diastolic blood pressure of $\geq$15 mmHg was significantly lower in the magnesium group compared with the women who received placebo ($p = 0.011$). There was an inverse relation between the urinary excretion of magnesium during pregnancy and the diastolic blood pressure ($p = 0.005$).
Conclusions Magnesium supplementation prevented an increase in diastolic blood pressure during the last weeks of pregnancy. The relation between diastolic blood pressure and urinary excretion of magnesium suggests that magnesium is involved in the regulation of blood pressure and that the increase in diastolic blood pressure in pregnancy could be due to a lack of magnesium.

Keywords Pregnancy-induced hypertension · Magnesium · Prevention

Introduction

Hypertension is a common disorder during pregnancy and may be present in up to 10 % of all pregnancies [1]. Increased cardiac output and blood volume are normal vascular changes that occur during pregnancy. Typically, blood pressure decreases during the first trimester. It reaches its lowest point by mid-pregnancy and then usually returns to pre-pregnancy levels during the third trimester. In some cases, however, blood pressure gradually increases from around gestational week 30. If the systolic/diastolic blood pressure reaches 140/90, it is defined as pregnancy-induced hypertension. If this is accompanied by proteinuria, the condition is diagnosed as pre-eclampsia (PE) which involves an increased risk of eclampsia (E). Both conditions are associated with a major increase in maternal and foetal morbidity and mortality [2]. In developing countries, maternal mortality due to E has been estimated to be around 50,000 deaths/year [3].

Trial registration number: ISRCTN 98365455.
www.controlled-trials.com.

M. Bullarbo · N. Ödman · T. Nielsen
Department of Obstetrics and Gynaecology, at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
e-mail: maria.bullarbo@vgregion.se

M. Bullarbo · N. Ödman · T. Nielsen
Department of Obstetrics and Gynaecology, Södra Älvsborgs Hospital, 501 82 Boras, Sweden

A. Nestler · M. Kolisek
Institute of Veterinary-Physiology, Freies Universität, Berlin, Germany

J. Vormann
Institute for Prevention and Nutrition, Ismaning, Germany

R. Rylander (✉)
BioFact Environmental Health Research Center, Bjorkasv 21, 44391 Lerum, Sweden
e-mail: envhealth@biofact.se

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PE and E have been related to defective placentation and proinflammatory cytokines. Another risk factor is lack of nutrients, such as vitamins C and D. Several studies suggest that the risk of hypertension and PE is related to changes in mineral homoeostasis. An increased risk has been found in populations with a low intake of calcium and a low urinary excretion of calcium [4–6]. Some studies have reported a beneficial effect of calcium supplementation on the risk of PE. However, the Food and Drug Administration (FDA) in the USA concluded that there was insufficient evidence for such an effect [7].

Another mineral related to the risk of hypertension is magnesium. An epidemiological study reported that the incidence of PE was higher in developing countries where nutritional insufficiencies including a low magnesium intake are prevalent [8]. In a clinical study on food constituents, low dietary intake of magnesium was highly associated with the risk of PE [9]. Some studies have reported significantly lower amounts of plasma magnesium in women with PE [10, 11] and with pregnancy-induced hypertension [12]. Other studies have not found such a relationship [13, 14].

On the cellular level, the membrane magnesium content in erythrocytes from subjects with PE was found to be reduced [15]. Intracellular free magnesium concentration in brain and muscle from patients with PE was significantly lower than in non-pregnant women and pregnant women without PE [16]. Likewise, magnesium concentration in cerebrospinal fluid was lower in patients with PE [17].

Intravenous magnesium sulphate has long been used in the treatment of PE and E [18]. A recent review analysed data from cohort, before–after and serial cross-sectional studies from five different countries [19]. It was concluded that improvements in maternal outcome after treatment with magnesium sulphate were also present in real-world use and not only in research centres. The underlying mechanism is probably a reduction of inflammatory cytokines by magnesium sulphate [20]. Addition of magnesium to pre-eclampsia placentas was found to reduce the amount of tumour necrosis factor α (TNFα) [20] and interleukin-6 (IL-6) [21].

Magnesium supplementation to decrease the risk of PE and hypertension has been assessed in previous studies. In an in vivo study on neonatal monocytes, addition of $MgSO_4$ decreased the production of TNFα and IL-6 and decreased cytokine gene and protein expressions [22]. One clinical, randomised, double-blind study of 58 women found a lower blood pressure and a higher birth weight in the treated group (360 mg Mg orally) [23]. However, a similar study of 185 women could not detect such effects of magnesium treatment (360 mg Mg/day orally) [24]. In that study, all participants received vitamins containing 100 mg of elemental magnesium/day. A large study investigated the effect of oral supplementation with 15 mmol magnesium (=369 mg Mg) against placebo in 985 pregnant women (500 women receiving placebo, 485 magnesium) [25]. The incidence of PE in the magnesium-treated group was significantly lower than in the placebo group (3.7 vs. 5.6 %). In a meta-analysis of magnesium supplementation, it was concluded that there was an effect on both systolic and diastolic blood pressure [26].

A possible explanation for the divergent results regarding the effect of magnesium supplementation on pregnancy-induced hypertension could be heterogeneity in the studied populations with regard to magnesium deficiency in different populations. Support for this concept is found in a study where urinary excretion of magnesium and calcium was determined around the 12th week of pregnancy and compared with blood pressure during the last part of pregnancy [27]. The increase in diastolic blood pressure was related to urinary excretion of calcium ($p = 0.001$) and less to magnesium ($p = 0.018$) at gestational week 12.

The present study was performed to assess the effect of supplementation with magnesium on blood pressure among pregnant women with a high urinary excretion of calcium around pregnancy week 12. They were given either oral magnesium or placebo from around pregnancy week 25 throughout pregnancy and blood pressure was recorded at regular intervals.

Methods

Participants

In Sweden, practically all pregnant women attend an antenatal care unit (ACU). Participants included in the study were voluntarily recruited among primagravida visiting the ACU at Boras municipality in Sweden for their first checkup (around week 12 of pregnancy). They were invited to collect a 24 h urine sample, which was analysed for the contents of calcium and magnesium, using standard techniques at an accredited hospital laboratory.

A total number of 61 women with a urinary calcium excretion of ≥7.5 mmol/L were invited to participate. All agreed and all were healthy with no history of cardiovascular or hypertensive disorders. In addition, those with a urinary excretion of calcium <7.5 mmol/L were also followed up. Thus, the study had three groups—placebo, magnesium intervention and not treated. All participants had their blood pressure measured at the ACU at intervals of 2–3 weeks throughout pregnancy. Another urine sample was taken at gestational week 37. In addition, data regarding gestational length, duration of labour, pH in umbilical cord blood and birth weight were registered.

Intervention

Following computerised, double-blind randomisation, the participants were allocated to either a daily, oral dose of 300 mg magnesium given as citrate (Magnesium Diasporal, Protina GmbH, Ismaning, Germany) or placebo of identical design from pregnancy week 25 until delivery. Compliance with medication was controlled through regular contacts with the physician in charge and finally after delivery. The intake of supplements containing magnesium was recorded in postpartum interviews. The code was not broken till the end of the study when all participants had terminated their pregnancy.

Statistical treatment

Differences between groups were evaluated using the Mann–Whitney test or Fisher's exact test. Relationships between different variables were evaluated using Spearman's test. A p value of <0.05 was interpreted as statistically significant.

Results

Baseline characteristics

The demographic characteristics of the participants in the placebo, magnesium- and not-treated groups at enrolment are shown in Table 1.

There were only minor differences between the groups except in the excretion of calcium (which reflects the inclusion criterion) and magnesium.

Changes during pregnancy

At week 39, the number of participants had decreased considerably due to deliveries (placebo $n = 24$, magnesium $n = 17$). In view of this, the continued evaluation focused on week 37. The diastolic blood pressure at week 37 was 77/1.2 (M/SEM) in the placebo group and 76/1.1 in the not-treated group, and 72/1.4 in the magnesium-treated group ($p = 0.031$). Regarding systolic blood pressure, the tendency was the same as for diastolic blood pressure, but there were no significant differences between the groups at week 37.

Figure 1 shows the changes in diastolic blood pressure at different times during pregnancy in relation to the value at 12 weeks in the placebo and magnesium groups.

The difference at week 37 was statistically significant ($p = 0.022$), while those at 32 and 35 weeks were on the borderline of significance ($p = 0.072$ and 0.093, respectively).

Table 1 Baseline characteristics in different groups

Group	Placebo	Magnesium	Not treated
n	30	29	78
Age, M/SEM	28.3/1.0	28.8/0.7	27.5/0.5
Smokers, *n*	9	3	8
Mg 24 h urine, mmol/L M/SEM	4.2/0.3	4.2/0.2	3.7/0.1
Ca 24 h urine, mmol/L M/SEM	9.7/0.3	10.0/0.3	5.5/0.2
Systolic, bp mmHg M/SEM	114/2	113/2	115/1.3
Diastolic, bp mmHg M/SEM	66/1	68/1	66/0.9

M/SEM mean/standard error of mean

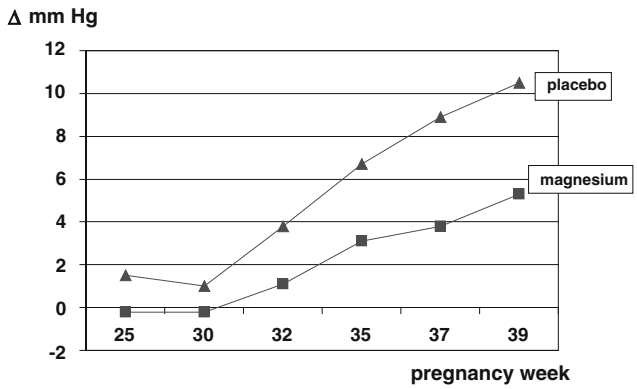

Fig. 1 Changes in diastolic blood pressure (mmHg) during pregnancy in relation to the value at 12 weeks in placebo and magnesium-supplemented groups

Some women in the placebo group had taken vitamin and mineral supplements during pregnancy. This did not influence the difference in diastolic blood pressure at week 37 (no supplement $n = 23$, change 9.9/2.1 mm, supplement $n = 6$, change 11.7/3.1, NS). Also, there was no difference between those who reported that they had forgotten to take the intervention preparation more than ten times and those who had taken magnesium or placebo regularly until delivery (data not shown).

Figure 2 shows the proportion of participants in each group with an increase in diastolic blood pressure of at least 15 mmHg at different pregnancy weeks. The numbers in the different groups deviate slightly from those in Table 1 due to no-shows or deliveries.

There were no differences between the groups at weeks 32 and 35. At week 37, the proportion of women with an increase of $\geq$15 mm was higher in the placebo and the not-treated groups as compared to the magnesium-supplemented group. The difference between the placebo and magnesium groups at week 37 was significant ($p = 0.012$), between magnesium- and not-treated group almost significant ($p = 0.087$), and between magnesium and both groups combined significant ($p = 0.037$).

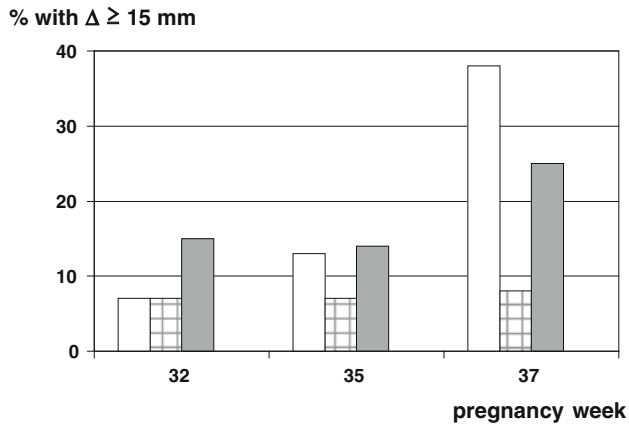

Fig. 2 Percent of women with an increase in diastolic blood pressure of ≥15 mmHg at different pregnancy weeks. *White bars* placebo ($n = 29$), *squares* magnesium ($n = 28$), *grey bars* not treated ($n = 71$)

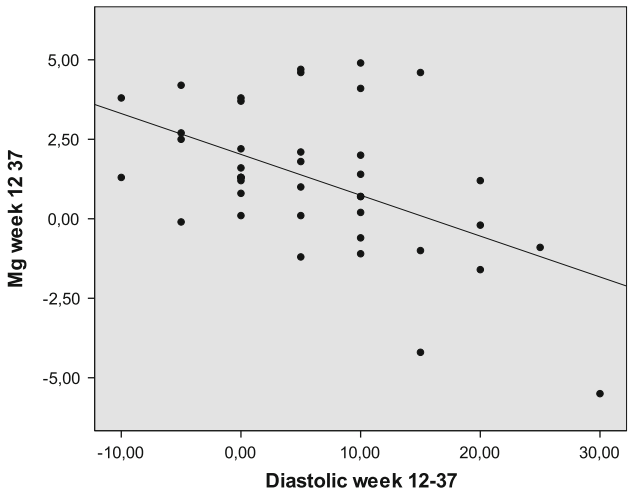

Fig. 3 Relation between changes in magnesium excretion (mmol/L) and diastolic blood pressure (mmHg) between weeks 12 and 37 in the placebo and not-treated groups (corr coeff. 0.438, $p = 0.005$)

In the placebo and not-treated groups, there was an inverse relation between the change in magnesium urinary excretion between pregnancy week 12 and 37 and the change in diastolic blood pressure during the same period as illustrated in Fig. 3.

A decrease in magnesium excretion from week 12 to 37, suggesting a deficiency, was accompanied by an increase in the diastolic blood pressure.

Labour and infant characteristics

The urinary excretion of magnesium was higher in the magnesium-supplemented group than in the placebo group at week 37 (8.6 vs. 4.7, $p = 0.002$). There were no differences between the magnesium and placebo groups regarding gestational length, duration of labour, birth weight or umbilical cord blood pH.

A comparison was made between women in the placebo group with or without an increase in diastolic blood pressure of ≥15 mm at week 37 in relation to the findings at week 12. Those with an increase of ≥15 mm at week 37 had a higher excretion of magnesium (5.0/0.6 mm vs. 3.8/0.2, $p = 0.021$) and a lower diastolic blood pressure (61/0.6 mm vs. 69/1.4, $p < 0.001$) at week 12.

Discussion

This study demonstrates that intervention with magnesium decreased the risk of high diastolic blood pressure during the late phase of pregnancy. In addition, an inverse relation between the changes during pregnancy in excretion of magnesium and the diastolic blood pressure was found.

The study has some shortcomings. The number of subjects is rather small and it is thus of a pilot nature. No information on dietary intake of magnesium was obtained. In a certain sense, it is incomplete as subjects with a urinary calcium excretion <7.5 mmol/L could also have been randomised for magnesium supplementation.

Contrary to the hypothesis and to a previous study [27], the group with a high excretion of calcium was not particularly at risk of developing high blood pressure during pregnancy. On the other hand, those with a higher excretion of magnesium were at risk. This is in agreement with the previous study where subjects with an increase in blood pressure had a higher urinary excretion of both calcium and magnesium [27]. Calcium was chosen as the selection criterion for this study because of a stronger significance, which retrospectively was not optimal. Both studies comprised relatively few subjects with a substantial increase in blood pressure, and variations in the distribution of subjects at risk could be one explanation for the differences in calcium and magnesium excretion correlations.

In the present study, the main effect of the supplementation was found on diastolic blood pressure and when this was evaluated as changes over time. The risk group could be identified as those with an increase of ≥15 mmHg in diastolic blood pressure. This could explain why no effect of magnesium supplementation had been found in some previous studies where only average changes in systolic blood pressure in the whole group were evaluated. Regarding the systolic blood pressure, it increased in several women, but the difference between placebo and magnesium-supplemented groups was not statistically significant. Systolic blood pressure is generally more fluctuating than diastolic pressure as illustrated by the higher variation of values in this study (systolic SEM 2.2 vs. diastolic SEM 1.8 in the placebo group) and smaller differences among certain individuals would thus not be detected.

Magnesium homoeostasis is determined by intake of food and water. The absence of data on the nutritional status of the participants is thus a drawback. On the other hand, the randomised selection of treatment in a homogenous group of pregnant women would prevent a skewed distribution of nutritional deficiencies in the material studied.

Taken together, the results suggest that women with a magnesium deficiency are a risk group for the development of pregnancy-induced hypertension and hence PE. The proportion of such subjects will vary between and within different populations. The supply of magnesium to the body is by intake through food and water. An increased urinary acidity related to the acid–base homoeostasis will prevent the reabsorption of magnesium in the renal tubuli and lead to an increased loss of magnesium [28–30]. A common reason for high acidity and an increased excretion of magnesium is a large intake of protein and/or a lack of vegetables in the daily diet. Such dietary factors will vary between individuals and between different study groups, and also over time as illustrated by the changes in magnesium excretion between weeks 12 and 37. The relation between magnesium and high blood pressure in this study is in agreement with several previous studies where magnesium deficiency has been related to a high blood pressure [31, 32].

The results from this study suggest that oral intervention with magnesium citrate from gestational week 25 reduces the risk of a high increase in diastolic blood pressure during the last weeks of pregnancy, hence PE and probably also E. A high urinary excretion of magnesium during the early part of the pregnancy could be diagnostically used as a risk indicator for an increase in diastolic blood pressure. Further studies are required to verify the effect of the supplementation of magnesium during pregnancy and the possibility of identifying groups at risk.

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Ethical Standard Ethical committee approval was obtained (ECG T 515-10, 098-09, Ethical Committee, Gothenburg University 8 April 2009) as well as permission to register according to Swedish law on personal information. Informed consent was obtained from all participants. Registration at ISRCTN98365455.

Conflict of interest The authors report no conflict of interest. Dr Vormann is a scientific consultant to Protina GmbH.

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