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Magnesium supplementation in pregnancy. A double-blind study

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Summary. The effect of magnesium supplementation in pregnancy was studied in 568 women who were treated with 15 mmol magnesium-aspartate-hydrochloride per day or aspartic acid as placebo given orally during pregnancy from ≤16 weeks. Allocation to the two groups was performed according to the women's birthdates. Magnesium supplementation during pregnancy was associated with significantly fewer maternal hospitalizations, a reduction in preterm delivery, and less frequent referral of the newborn to the neonatal intensive care unit. The results suggest that magnesium supplementation during pregnancy has a significant influence on fetal and maternal morbidity both before and after delivery.

In recent years, although intensive care has resulted in an important increase in neonatal survival rates, preterm delivery remains responsible for most neonatal morbidity. Even though magnesium has had its place in obstetrics for the management of eclampsia since the beginning of the century, a connection with preterm labour was only recognized in the 1960s (Dumont 1965). Wider interest in the role of magnesium in obstetrics was reactivated by our observations that supplemental magnesium medication allowed a considerable reduction in the dose of beta adrenergic agents used for tocolysis of preterm labour (Spätling 1981). Based on these findings, Conradt *et al.* (1984) showed in a retrospective study that the frequency of fetal growth retardation and pre-eclampsia was reduced in association with magnesium supplementation. In the light of these findings, we conducted a double-blind study to clarify whether magnesium supplementation has an influence on these variables. The following null hypotheses were stated: magnesium supplementation has no effect on: (i) pre-eclampsia; (ii) preterm labour (and consequently gestational age at delivery) and (iii) fetal growth.

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Subjects and methods

Between March 1983 and March 1985 all patients who attended the outpatient clinic at the department of obstetrics, University of Zürich, were asked to participate in the study. All normal- and high-risk patients were included. A total of 568 women gave their general agreement and they were included in the trial as early as possible in pregnancy, but not later than 16 weeks gestation which was estimated from the first day of the last menstrual period. This sample size was determined by the limitation of the recruitment period which, for practical reasons, could not exceed 2 years.

The method of allocation was based on the subjects' date of birth. Women with an even birthdate were given 15 mmol of magnesium-aspartate-hydrochloride; women with an odd birthdate were given a placebo containing 13·5 mmol of aspartic acid per day. These doses were divided into six tablets to be taken daily. At

each visit patients were questioned on regular intake, number of tablets and side-effects of medication.

Classification of diagnoses and therapies used the coding system of the Munich Perinatal Study (Selbmann *et al.* 1980).

Statistical analysis

The Wilcoxon and Mann–Whitney *U*-tests were used to compare the central trends. Categorical variables were analysed by the χ^2 test. The results were considered significant at the 5% level. Assessment always used two-tailed tests. Values are given as medians and the 5th and 95th centiles. For various reasons, such as refusal to take further tablets, delivery in other hospitals or abortion, some data were not available for analysis. Reference values for the 10th centile of birthweight were taken from Largo *et al.* (1980).

Results

Of the 568 women entered into the study, 278 were treated with magnesium and 290 received the placebo. Age, parity and gravidity were similar in the two groups. There was no difference with regard to the birthweight of children born before the start of this study or the duration of previous pregnancies (Table 1). Based on the clinical history of the patients, the risk of abnormal pregnancy was comparable in the two groups.

The daily rate of tablet consumption was comparable in the two groups. However, the total number of tablets ingested was much higher in the group receiving magnesium, because of the longer length of gestation in that group (Table 2).

The frequency of complaints attributed to the tablets was low and comparable in the two groups. In the magnesium group one woman complained of diarrhoea, four of nausea, six of vomiting and six of heartburn; in the placebo group two complained of diarrhoea, one of nausea, 10 of vomiting, six of heartburn and one of fullness.

Five women in the magnesium group and three women in the control group had a miscarriage.

Median maternal weight increase was 11 kg in both groups and there were no statistically significant differences in maximum systolic and diastolic blood pressures or in oedema between the two groups (Table 2).

In the magnesium group 44 women were hospitalized for 533 days. In the placebo group 65 women spent 887 days in hospital. Of the indications for admission to hospital, haemorrhage during pregnancy, incompetent cervix and preterm labour were more frequent in the placebo group, the difference was statistically significant. The average duration of each admission to hospital was similar in the two groups and so were the number of miscarriages (Table 3).

The median gestation was significantly longer in the women treated with magnesium, although the difference between the medians was not more than 1 day. This difference was particularly notable when the preterm deliveries (< 37 weeks) are compared (Table 4). There were no differences between the groups in the duration of the first stage of labour. Although the second stage of labour was longer and operative delivery more frequent in the magnesium-treated group than in the placebo group, these differences were not statistically significant (Table 4).

Differences between the two groups in respect of placental weight, infant weight and length, frequency of low Apgar scores (≤ 7) and low birthweight are shown in Table 5. These differences reflect the decreased frequency of preterm delivery associated with magnesium supplementation but they do not reach statistical significance. There were no differences between the groups in infant head circumference or in neonatal acid base values. Significantly fewer infants in the group receiving magnesium were admitted to the neonatal intensive care unit. The biggest differences were found in the admission rates for preterm birth and asphyxia (Table 5).

There was one perinatal death in the magnesium group. The mother was a 40-year-old diabetic in her first pregnancy. She was hospitalized twice, in early pregnancy because of haemorrhage and hyperemesis gravidarum and again in later pregnancy because of the diabetes and preterm labour. A growth-retarded fetus was born at 33 weeks gestation by forceps after severe fetal bradycardia and died immediately after delivery because it proved impossible to oxygenate the infant sufficiently.

In the subsidiary analysis we excluded all those women who did not fulfil the protocol of medication as prescribed. After these exclusions, 217 women remained in the magnesium

Table 1. Characteristics of the two groups of women recruited to the study

	Magnesium group (n=278) Centile			Placebo group (n=290) Centile		
Variable	5th	50th	95th	5th	50th	95th
Age (years)	20·3	28·2	37·9	19·5	28·0	34·6
Parity	1	2	3	1	2	3
Gravidity*	1	2	5	1	2	5
Birthweight of 1st child (g)	2500	3250	3915	2200	3280	4020
Duration of 1st pregnancy (weeks)	37	40	42	36	40	42

* The present pregnancy is included. There were no significant differences between the two groups.

Table 2. Clinical details of women treated with magnesium or placebo during pregnancy

	Magnesium group Centile			Placebo group Centile			
Variable	5th	50th	95th	5th	50th	95th	Significance
Number of tablets/day	3	6	6	3	6	6	NS
Duration of medication (days)	53	182	217	32	168	224	<0·01
Total number of tablets	266	1050	1302	189	966	1344	<0·01
Weight gain (kg)	5	11	18	4	11	19	NS
Maximum blood pressure (mmHg)							
Systolic	107	125	135	108	124	136	NS
Diastolic	61	73	85	61	73	87	NS
No. with oedema (subjective)							
+		59			79		NS
++		15			15		NS
+++		3			1		NS
Total (n)		77			95		NS

NS, Not significant.

Table 3. Indications for hospitalization during pregnancy in women treated with magnesium or placebo

Variable	Magnesium group	Placebo group	Significance
Number of admissions to hospital (n)	48	80	—
Number of women hospitalized (n)	44	65	<0·05
Time spent in hospital (days)			
Total length	533	887	—
Median length/patient	7·5	7·0	NS
Indications coded (n)			
Haemorrhage	4	17	<0·01
Threatened miscarriage	3	2	NS
Incompetent cervix	8	17	<0·05
Preterm labour	12	26	<0·05
Premature membrane rupture	1	1	NS
Urinary tract infection	4	2	NS
Diabetes	1	0	NS
Pre-eclampsia	2	2	NS
Twin pregnancy	1	2	NS
Fetal growth retardation	0	3	NS
Not encoded	12	8	—
Miscarriage	5	3	NS

NS, Not significant.

Table 4. Mode of delivery in the study groups

Variable	Magnesium group Centile			Placebo group Centile			Significance
	5th	50th	95th	5th	50th	95th	
Gestational age at delivery (weeks/days)	37/3	40/0	41/6	35/1	39/6	41/6	<0·05
Delivery before 37 weeks (*n*)		7			14		NS
Length of 1st stage (h)	2	6	13	2	6	15	NS
Length of 2nd stage (min)	5	19	100	5	18	90	NS
Operative delivery (*n*)		70			55		NS

NS, Not significant.

Table 5. Fetal outcome in women treated with magnesium or placebo during pregnancy

Variable	Magnesium group Centile			Placebo group Centile		
	5th	50th	95th	5th	50th	95th
Placental weight (g)	400	580	800	390	570	800
Birthweight (g)	2530	3325	4270	2280	3300	4120
No. < 2500g		12			19	
No. < 1500g		3			6	
No. < 10th centile		30			33	
Infant length (cm)	46	50	53	45	49	53
Head circumference (cm)	32	34	37	32	34	37
Umbilical blood pH						
Artery	7·17	7·28	7·37	7·17	7·28	7·36
Vein	7·23	7·33	7·44	7·24	7·35	7·44
No. with Apgar score ≤7						
at 1 min		42			47	
at 5 min		3			8	
at 10 min		1			5	
Admitted to intensive care (*n*)		20			36*	
Indications coded (*n*)						
Preterm birth		4			8	
Growth retardation		5			6	
Prolonged asphyxia		2			5	
Observation		3			3	
Respiratory insufficiency		2			2	
Rh-incompatibility		0			2	
Jaundice		2			4	
Malformation						
face		0			1	
abdomen		0			1	
multiple		1			1	
Metabolic disease		0			1	
Fits after delivery		1			0	
Not encoded		0			2	
Perinatal death		1			0	

* Significantly different between the two groups $P<0·01$.

Table 6. Comparison between magnesium and placebo groups after exclusion of patients who did not take their tablets regularly*

	Magnesium group (n=217) Centile			Placebo group (n=220) Centile			
Variable*	5th	50th	95th	5th	50th	95th	Significance
Birthweight (g)	2610	3340	4285	2245	3300	4110	<0·05
No. <2500g		6			18		<0·05
No. <1500g		0			6		<0·05
Infant length (cm)	46	50	53	44·5	49	53	<0·05
Head circumference (cm)	33	35	37	31	34	36·5	<0·05
No. with 10-min Apgar score ≤7		0			5		<0·05
No. of women hospitalized		26			48		<0·01
No. with oedema grade+		42			63		<0·05

* Only the variables with better significance than in the main analysis are listed.

group and 220 in the placebo group. Some of the differences that only reflected a trend in the main study became statistically significant and some of the differences that were already significant in the main study were confirmed at a higher level of significance (Table 6).

Discussion

We found no evidence of a protective effect of magnesium supplementation on the frequency of pre-eclampsia and to be able to address this question the study groups would have had to have been considerably bigger. Similarly, the observation that a very early start of magensium supplementation is associated with a decreased rate of early miscarriage (Kiss *et al.* 1981) could not be assessed because insufficient numbers of women joined the study early enough and there were no statistically significant differences in the frequency of miscarriage between the groups.

In spite of a relatively small difference of only 1 day between the median lengths of gestation, this difference is significant at the 5% level. This is due to fewer preterm deliveries in the magnesium group, an observation which confirms our second hypothesis. Although this difference was reflected in a reduction in the frequency of low birthweight, there was no evidence that magnesium supplementation had any effect on fetal growth as such.

Nevertheless magnesium supplementation was associated with a significant reduction in maternal and fetal morbidity both before and after delivery. It seems reasonable to suppose that the specific magnesium depletion in pregnant women may be compensated by magnesium replacement. More than 300 enzymatic reactions depend on magnesium (Günther 1981). The results of this study suggest that magnesium supplementation during pregnancy may have important benefits.

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