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(Anschrift der Verfasser: Dipl.-med. P. Brundig, Urologische Klinik und Poliklinik der Friedrich-Schiller-Universität, Lessingstraße 1, DDR-6980 Jena)

Effect of maternal Magnesium supply on spontaneous abortion and premature birth and on intrauterine foetal development: Experimental epidemiological study

By *V. Kuti, M. Balázs, F. Morvay, Zs. Varenka, A. Székely and M. Szücs*

Zusammenfassung

Im Rahmen einer experimentellen, epidemiologischen Studie wurde bei 1884 schwangeren Frauen der Einfluß einer unterschiedlich hohen Magnesium-Zufuhr untersucht. Wenn das über die Nahrung zugeführte Magnesium den Bedarf nicht abdeckte, konnte durch medikamentösen Ausgleich des Fehlbetrages die Häufigkeit von Spontanaborten und Frühgeburten signifikant gesenkt werden, und die intrauterine fötale Entwicklung wurde günstig beeinflußt.

Summary

In a series of 1884 pregnant women the effect of changes in Magnesium supplies has been examined within the framework of an experimental epidemiological study. It was found that if nutrition does not provide for the Magnesium requirement of pregnant women, artificial substitution of the difference between ingestion and requirement of Magnesium reduces the incidence of spontaneous abortion and praemature birth significantly from aspects of statistics and public health, while changing favourably intrauterine foetal development.

Résumé

Chez une série de 1884 femmes enceintes, nous avons examiné l'effet de modifications dans les apports en Mg dans le cadre d'une étude épidémiologique expérimentale. Il a été constaté que si la nutrition ne couvre pas le besoin en Mg des femmes enceintes, une substitution artificielle de la différence entre l'ingestion et le besoin en Mg réduit la fréquence de l'avortement spontané et de l'accouchement prématuré, de façon significative, tout en modifiant favorablement le développement foetal intrautérin.

* * *

Magnesium deficiency of alimentary origin is a part-phenomenon of a world-wide oecological problem. It affects wide circles of the population, its effect on health is manifold.

The magnesium requirement of pregnant women has been put by Seelig at daily 10—15 mg Mg^{++} per kg body-weight [14]. In the parts of Hungary where we performed our studies nutrition of pregnant women provided approximately half of the required amount: in their studies concerned with nutrition *Böjthe* et al. [2] found average daily Mg^{++} consumption to be 330 mg, *Molnár et al.* [11] to be 350 mg. In the same period in Hungary, according to statistical year-books, 12 per cent of the total number of pregnancies ended with spontaneous abortion [18] and in 11 per cent of the newborn birth weight was under 2500 g [8].

As a preliminary of our studies particular attention is to be paid to the report of *Hurley* [3] who found foetal oedema and anaemia in pregnant rats as a result of moderate withdrawal of magnesium, and the incidence of spontaneous abortion, premature birth, intrauterine foetal death and congenital malformations rose higher parallel with the increase of withdrawal. Light is thrown on the significance of adequate magnesium supplies by the work of *Ludmány* in connection with ontogenesis[7], by that of *Stolkowsky* [15] dealing with reproduction.

The effect of artificially improved magnesium supply has been studied in anaemia of pregnancy and infancy by *Melles, Kiss, Szakáll, Krekó* and *Balázs* [10, 16, 17], on the incidence of toxicosis of pregnancy by *Kovács, Rigó, Vajna, Kuti* [5, 6, 19], in connection with premature birth and abortion by *Balázs, Kiss, Szöke, Kuti, Morvay, Rusu* and by the Magnesium Team of the Scientific Society of Hungarian General Practitioners [1, 4, 6, 9, 12, 13], on intrauterine foetal development by *Balázs, Kuti* and the above mentioned Magnesium Team[1, 6, 9].

Material and Method

In agreement with the basic principles of experimental epidemiological studies, low magnesium level, held to be an essential factor in spontaneous abortion, premature birth and intrauterine atrophy, has been changed by the substitution of magnesium and the effect of this intervention has been studied by epidemiological methods.

Of the 1884 pregnant women of the series, 1181 were selected by a pseudorandom method and from their first appearance they were given every care required by their condition as well as magnesium substitution. In 457 cases magnesium substitution could be started in the 4th to 9th week of pregnancy, while in 724 cases, who appeared later, it was initiated only in the 10th to 27th week. The 703 pregnant women of the control group received similar care in every respect but no magnesium substitution. The forming of groups precluded preliminary selection. Upon analysis of the women's age, body-weight, obstetric history, births per seasons, the order of births and the sex of infants, there were differences between the groups, but they were not significant.

For the substitution of magnesium we used magnesium citrate, 1.0 g of which contained 116 mg Mg^{++}. The recommended daily dose was three times 1.0 g Mgcitrate. The regularity and continuousness of magnesium substitution depended on the readiness of the patient to cooperate. The total amount of magnesium supplemented in the course of a pregnancy depended on the point of time when supplementation began and on the regularity of ingestion. The real amount of incorporated magnesium was assesses by the district nurses who checked and recorded this very carefully. On the average 1.4—3.0 g Mgcitrate was consumed daily, which added on the average 170—340 mg Mg^{++} daily to the magnesium content of the food. In optimal cases this amount doubled the magnesium content of the food and satisfied modestly the daily Mg^{++} requirement of pregnant women, 10—15 mg daily per kg body weight.

Results

Three groups were formed to study the incidence of spontaneous abortion. The women of the first group were not given any magnesium substitution. The second group comprised the cases where magnesium substitution could be started in the 4th to 9th week, the most critical period from the aspect of spontaneous abortion. All those where magnesium substitution could be started later, in the 10th—27th week, belonged to the third group. The incidence of spontaneous abortion in these three groups is illustrated in Tab. 1.

Tab. 1: Incidence of spontaneous abortion in pregnant women given varying amounts of Magnesium.

Groups	Magnesium substitution	N° of pregnancies	Spontaneous abortion N°	Incidence
I	–	703	66	9,4 %
II	from 4.-9. weeks	457	7	1,5 %
III	from 10.-27. weeks	724	45	6,2 %

In those who were given magnesium substitution from the 4th to 9th week, the incidence of spontaneous abortion was 1.5 per cent, a sixth part of the incidence (9.4 per cent) found in the controls who received no magnesium substitution, and a quarter of the incidence (6.2 per cent) registered in those given substitution from the 10th—27th week. Hence the incidence of spontaneous abortion was so much lower than in both the other groups that the difference is convincing without any significance tests. The effect of magnesium substitution started late (6.2 per cent) is not so obvious compared to the control group (9.4 per cent), the incidence of spontaneous abortion was only reduced to two thirds, but the result of the χ^2 test ($\chi^2_{[1]}$ = 4.86) is still significant here ($P<5$ %). Markedly significant difference was found ($\chi^2_{[1]}$ = 13.29) upon comparison of groups II and III ($P<0.01$ %), and very strongly significant difference ($\chi^2_{[1]}$ = 26.40) upon comparison of groups I and III ($P<<0.001$ %). Our results are presented in Fig. 1.

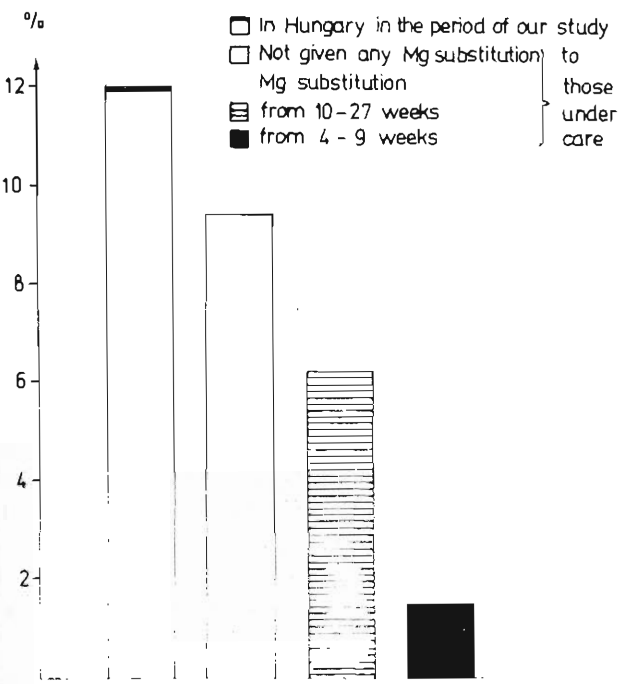

Fig. 1: Incidence of spontaneous abortion.

Statistical analysis of our studies calls for the description of cases where preceding spontaneous abortion, premature birth and stillbirth were followed on continuous substitution of magnesium, started in time, by keeping pregnancy until full term. In these patients no noteworthy disease was mentioned in the history, no induced abortion had been performed or any pathological change observed during pregnancies.

B. Gy., born in 1940. Menarche at 13 years. Pregnancies: 1: February, 1961, spontaneous abortion. 2: September 1961, spontaneous abortion. 3: May, 1964, premature birth of male infant weighing 1 010 g, lived for 2 days. 4: September 1966, male infant of 3 600 g anencephaly. After four failures, in the fifth pregnancy Gestanon was given from the 9th week, 1.2 g Mgcitrate daily from the 20th week. In May, 1969, the patient was delivered of a healthy daughter. In the 6th pregnancy 2.4 g Mgcitrate was given daily from the 10th week of pregnancy. In July, 1972, she was delivered of a healthy son of 3 100 g.

P. I., born in 1944. Menarche at the age of 12 years. Pregnancies: 1: October, 1966. A female infant of 2 050 g born in the 34th week. 2: June, 1967, spontaneous abortion. 3: July, 1968, spontaneous abortion. 4: October, 1970. With Gestanon pregnancy could be maintained for 30 weeks, when a male infant of 1 570 g was born who lived five days. 5: from the 9th week 2.4 g Mgcitrate was given daily. In November 1975, a viable healthy boy of 2 400 g was born.

P. N., born in 1950. Menarche at 15 years. Pregnancies: In November, 1972, ectopic pregnancy. 2: October, 1973, spontaneous abortion. 3: June, 1975, spontaneous abortion. 4: from the 10th week 2.6 g Mgcitrate was given daily. In June, 1976, the patient was delivered of a boy of 3 500 g. Mgcitrate was given daily. In March, 1978, she was delivered of a boy of 3 600 g. Both are healthy.

J. A., born in 1957. Menarche at 14 years. Pregnancies: 1: October, 1976, stillbirth. 2: May, 1977, spontaneous abortion. 3: November, 1977, spontaneous abortion. 4: from the 4th week of pregnancy 2.4 g Mgcitrate was given daily. In November, 1979, in the 36th week twins were born, a boy of 1 650 g and a girl of 2 400 g, both were healthy.

After 118 spontaneous abortions, the number of expectant mothers under observation was 1 766; of these 1 129 were given magnesium substitution, 637 were not. As regards magnesium substitution, the group of 1 129 women was not homogenous; from the start of substitution and depending on continuousness during the whole time of pregnancy the total amount of Mgcitrate consumed varied between 30 and 400 g, which made it necessary to divide the group. The controls were marked Group I, the women given 30—150 g Mgcitrate formed Group II, those given 151—250 g formed Group III, and those given 251—400 g Mgcitrate formed Group IV.

In the control group 2 pairs of twins were born, in the groups on magnesium substitution there were 9 pairs of twins and one case of quadruplets.

The distribution and number of groups are shown in Tab. 2. Further appraisal of our results has been performed without considering twin births.

Tab. 2: Grouping on the basis of the total amount of Mgcitrate substituted during pregnancy.

Groups	Mg citrate total amount (g.)	N° comprised by groups	Twin births N°	N° comprised by groups without twin births
I	-	637	2	635
II	30-150	592	4	588
III	151-250	424	4	420
IV	251-400	113	2	111
I-IV		1766	12	1754

Gestation time and birth weights have been registered per group (Tab. 3—6).

Tab. 3: Gestation time and birth weight without substitution of Magnesium during pregnancy.

Birth weight (g.)	Gestation time (weeks) 29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	unknown	Together (infants)	Percentual distribution of weight at birth
1000-1499			1														1	0,16
1500-1999	1	1	2	2							1						7	1,10
2000-2499				2	2	3	4	4	6	4	5	4	1			6	41	6,46
2500-2999					1	1	1	13	15	29	27	34	12	7	1	10	151	23,78
3000-3499						1	2	7	13	30	70	86	33	10	4	9	265	41,73
3500-3999							1	1	3	8	29	54	22	7		6	131	20,63
4000-4499									1	1	7	15	6	3	1	1	35	5,51
4500-4999												2	1	1			4	0,63
Together (infants)	1	1	3	4	3	5	8	25	38	72	139	195	75	28	6	32	635	100,00
Percentual distribution of gestation time	0,16	0,16	0,47	0,63	0,47	0,79	1,26	3,94	5,98	11,34	21,89	30,71	11,81	4,41	0,94	5,04	100,00	* 490 heads, 77,17 % of the cases

Tab. 4: Gestation time and birth weight when a total dose of 30—150 g Mgcitrate was given to the mother during pregnancy.

Birth weight (g)	Gestation time (weeks)															unknown	Together (infants)	Percentual distribution of weight at birth
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43			
1000–1499		1		1				1									3	0.51
1500–1999		1	1		2	1						1					6	1.02
2000–2499			1	1	3	6	6	7	5	5	6	3	1			1	45	7.65
2500–2999							5	12	16	21	23	25	13	2	2	5	124	21.09
3000–3499							1	5	8	23	57	70	30	11	2	15	222	37.56
3500–3999								1	2	20	28	56	20	11		6	144	24.49
4000–4499								1		2	7	18	6	5	1	2	42	7.14
4500–4999											1	1					2	0.34
Together (infants)	–	2	2	2	5	7	12	27	31	71	122	174	70	29	5	29	588	100.00
Percentual distribution of gestation time	,	0.34	0.34	0.34	0.85	1.19	2.04	4.59	5.27	12.08	20.75	29.58	11.91	4.93	0.85	4.93	100.00	• 448 heads. 76.19 % of the cases

Tab. 5: Gestation time and birth weight when a total dose of 151—250 g Mgcitrate was given to the mother during pregnancy.

Birth weight (g)	Gestation time (weeks)															unknown	Together (infants)	Percentual distribution of weight at birth
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43			
1000–1499																	–	–
1500–1999				1		1	1					1					4	0.95
2000–2499					1	1		2		3	1	5		2			15	3.57
2500–2999				1		2	2	6	5	20	17	23	5	1		2	84	20.00
3000–3499					1	1	1		5	20	36	83	18	5		4	174	41.43
3500–3999									1	4	21	62	11	11		1	111	26.43
4000–4499									1	2	3	15	1	2		2	26	6.19
4500–4999											1	3		2			6	1.43
Together (infants)	–	–	–	2	2	5	4	8	12	49	79	192	35	23	–	9	420	100.00
Percentual distribution of gestation time	,	,	,	0.48	0.48	1.19	0.95	1.90	2.86	11.67	18.81	45.71	8.33	5.48	,	2.14	100.00	• 360 heads 85.71 % of the cases

Tab. 6: Gestation time and birth weight when a total dose of 251—400 g Mgcitrate was given to the mother during pregnancy.

Birth weight (g)	Gestation time (weeks)															unknown	Together (infants)	Percentual distribution of weight at birth
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43			
1000–1499																	–	–
1500–1999									1								1	0.90
2000–2499								2									2	1.80
2500–2999										4	1	2		1			8	7.21
3000–3499										7	22	24	5	3			61	54.95
3500–3999									2	1	5	11	8	2		1	30	27.03
4000–4499										1	2	3	2				8	7.21
4500–4999												1					1	0.90
Together (infants)	–	–	–	–	–	–	–	2	3	13	30	41	15	6	–	1	111	100.00
Percentual distribution of gestation time	,	,	,	,	,	,	,	1.80	2.70	11.71	27.03	36.94	13.51	5.41	,	0.90	100.00	• 104 heads. 93.69 % of the cases

When Tab. 3—6 are examined in succession it is striking that parallel with the increase of magnesium substitution ever larger number of deliveries ensued in the 38th—42nd week and the weight of newborn infants was ever more rarely under 2 500 g. The number of infants born in the 38th—42nd week with 2 500—4 499 g weight and their percentual ratio to the numbers comprised by their groups have been summed up in Tab. 7, and we have examined whether or not there is a statistical difference between the four groups.

Tab. 7: Newborn infants of optimal gestation time and birth weight, grouped according to varying Magnesium substitution during pregnancy.

Groups	Total amount of Mg citrate given during pregnancy (g)	Newborn infants		
		total N°	born after 38-42 weeks of gestation with 2500-4499 g. birth weight	
			N°	%
I	–	635	490	77.17
II	30-150	588	448	76.19
III	151-250	420	360	85.71
IV	251-400	111	104	93.60

The χ^2 test has been used for comparison.

No difference has been found between groups I and II, hence 30—150 g Mgcitrate consumed during pregnancy was not effective from the aspect investigated.

Upon comparison of Groups I and III ($\chi^2_{[1]}$ = 11.80) the difference was very significant ($P < 0.1$ %);

Upon comparison of Groups II and IV ($\chi^2_{[1]}$ = 17.22) the difference was also very significant ($P < 0.1$ %).

The results of the χ^2 test showed significant difference ($\chi^2_{[1]}$ = 5.07) even upon the comparison of Groups III and IV ($P < 5$ %).

Thus magnesium substitution exented a favourable effect on gestation time and birth weight when the total dose of Mgcitrate during pregnancy exceeded 150 g and parallel with the increase of the dose this effect became always more marked. In Group IV 41 gravidas consumed 301—400 g Mgcitrate. Their number is too small to be studied as a statistically independent group, but it is worth while to examine gestation time and the birth weights of their newborn (Tab. 8) compared to Tab. 3—6.

Tab. 8: Gestation time and birth weight when a total dose of 301—400 g Mgcitrate was given to the mother during pregnancy.

Birth weight (g.)	Gestation time (weeks)															Unknown	Together (infants)	Percentual distribution of weight at birth
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43			
1000–1499																	–	–
1500–1999																	–	–
2000–2499																	–	–
2500–2999										1		1		1			3	7.32
3000–3499										2	7	11	4	2			26	63.41
3500–3999												4	4	1			9	21.95
4000–4499										1		1	1				3	7.32
4500–4999																	–	–
Together (infants)	–	–	–	–	–	–	–	–	–	4	7	17	9	4	–	–	41	100.00
Percentual distribution of gestation time	,	,	,	,	,	,	,	,	,	9.76	17.07	41.46	21.95	9.76	,	,	100.00	• 41 heads 100.00 % of the cases

The distribution of the neonates by gestation time and amount of supplemented Mg is shown in Fig. 2, that by birth weight — including national data — in Fig. 3.

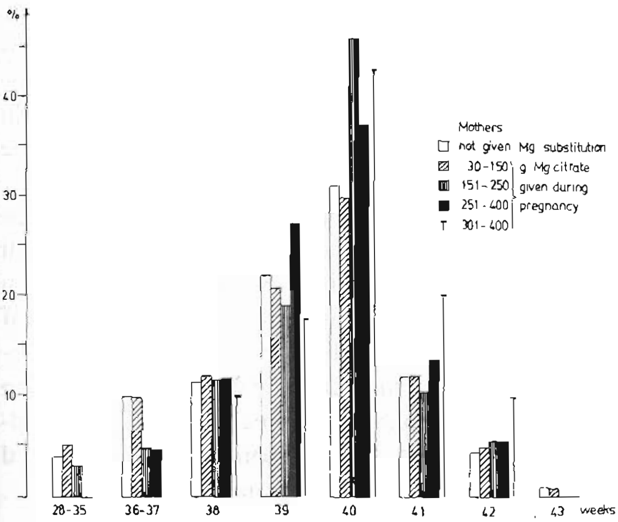

Fig. 2: Gestation time distribution of newborn infants.

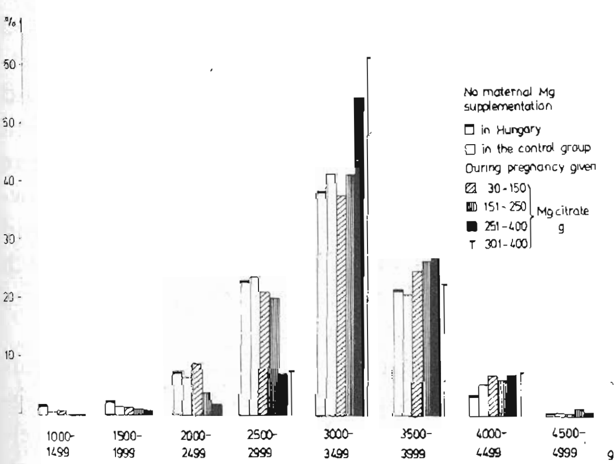

Fig. 3: Birth weight distribution of newborn infants.

We wished to find out whether foetal development is promoted by magnesium only through the improvement of gestation time or an additional favourable effect is exerted on intrauterine development. Therefore in the next step body-weight, body-length and head circumference distribution of babies born in the most favourable, 38th—42nd, weeks of gestation has been studied in groups given varying supplies of magnesium (Tab. 9—11 and Fig. 4—6).

Tab. 9: Percentual birth weight distribution of babies born in the 38th—42nd week of gestation in groups formed on the basis of total amounts of Magnesium supplemented during pregnancy.

Groups	Babies together		percentual distribution of weigt at birth (g)				
	N°	%	< 2500	2500-2999	3000-3499	3500-3999	3999<
I.	507	100,00	3,16	21,30	44,77	23,67	7,10
II	466	100,00	3,43	18,07	40,99	28,97	8,58
III.	378	100,00	3,17	17,46	42,85	28,87	7,65
IV	105	100,00	–	7,62	58,10	25,71	8,57
*	41	100,00	–	7,32	63,41	21,95	7,32

* Within group IV 41 gravidas supplemented 301-400g Mgcitrate

Tab. 10: Percentual body length distribution of babies born in the 38th—42nd week of gestation in groups formed on the basis of total amounts of Magnesium supplemented during pregnancy.

Groups	Babies together		percentual distribution of body length (cm)												
	N°	%	<46	46	47	48	49	50	51	52	53	54	55	56	56<
I.	510	100,00	0,59	2,35	3,33	7,84	9,02	17,25	14,71	14,12	9,02	9,21	5,88	4,51	2,17
II.	464	100,00	1,51	1,72	3,23	7,33	7,33	17,24	12,93	12,28	6,90	13,15	8,62	4,53	3,23
III.	376	100,00	1,06	2,39	4,52	11,44	12,50	24,47	14,89	11,97	5,85	5,59	1,86	1,86	1,60
IV	105	100,00	–	–	4,76	10,48	17,14	26,67	19,05	9,52	5,71	2,86	0,95	0,95	1,91
*	41	100,00	–	–	2,44	9,67	19,51	29,27	19,51	12,19	7,32	–	–	–	–

* Within group IV 41 gravidas supplemented 301-400g Mgcitrate

Tab. 11: Percentual head circumference distribution of babies born in the 38th—42nd week of gestation in groups formed on the basis of total amounts of Magnesium supplemented during pregnancy.

Groups	Babies together		percentual distribution of head circumference (cm)										
	N°	%	< 30	30	31	32	33	34	35	36	37	38	38 <
I	479	100,00	0,21	2,09	4,18	14,40	21,70	28,60	18,37	7,94	1,67	0,62	0,21
II	450	100,00	0,22	1,33	4,00	14,67	18,68	23,11	20,89	12,44	2,44	2,00	0,22
III.	372	100,00	–	0,27	1,34	7,53	13,98	23,39	27,68	17,74	7,53	0,54	–
IV.	104	100,00	–	0,96	–	11,54	22,12	23,08	20,19	16,35	2,88	1,92	0,96
*	41	100,00%)	–	–	–	9,75	26,83	26,83	21,95	7,32	7,32	–	–

* Within group IV 41 gravidas supplemented 301-400g. Mgcitrate

Parallel with the increase of the amount of supplemented magnesium the ratio of babies born with 3 000—3 499 g birth weight increased. This increase came about chiefly by considerably reduced ratio of infants born with weight under 3 000 g.

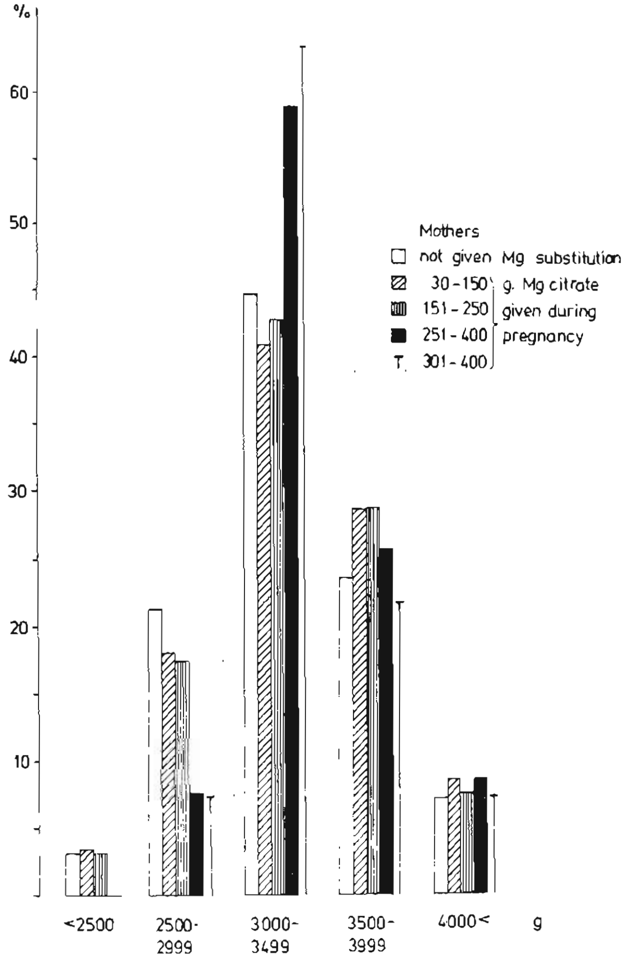

Fig. 4: Birth weight distribution of infants born in the 38th—42nd week of gestation.

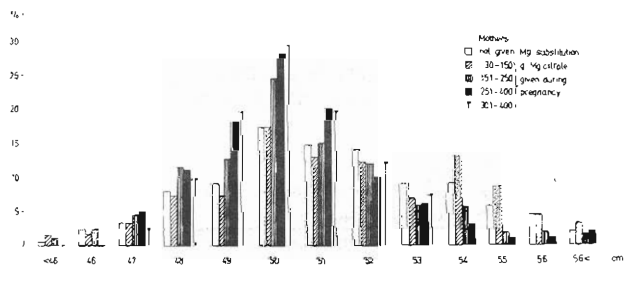

Fig. 5: Body-length distribution of infants born in the 38th—42nd week of gestation.

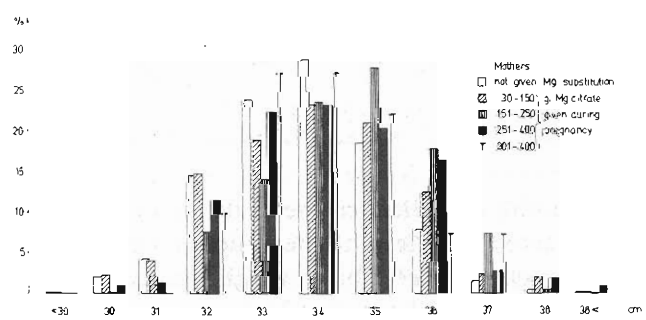

Fig. 6: Head circumference distribution of infants born in the 38th—42nd week of gestation.

Parallel with the increase of the amount of supplemented magnesium there was marked increase in the ratio of babies of 49—51 cm length, moderate increase in those born with 47—48 cm and decrease in those shorter than 47 cm and those longer than 52 cm.

The peak of the head circumference curve was 34 cm in the control group, parallel with the increase of the amount of substituted magnesium the two extreme values shifted towards mid value and the peak of 33—35 cm developed.

The favourable change observed in connection with improved maternal magnesium supplies in infants born after similar, 38—42 weeks gestation time shows that in addition to the existing level of magnesium supplies deriving from food, magnesium supplementation acts favourably on intrauterine foetal development through the advantages implied by providing for the desired time of gestation and also from other aspects.

Discussion

The maintenance of wanted pregnancy is promoted by numerous procedures which are used extensively in care of pregnancy and at departments of pathological pregnancy. By their aid spontaneous abortion, premature birth, and infant mortality connected with premature birth have been reduced to the present level, which is, however, still high. In addition to known causes and procedures, it is therefore still justified to search for causes and widen preventive procedures which are useful in practice.

On the basis of pertinent literature and our earlier studies we assume that maintenance of pregnancy to full term and intrauterine foetal development are treatened by magnesium deficiency and helped by adequate magnesium levels. Our assumption has been confirmed by experimental epidemiological studies.

Maintenance of pregnancy has been the most favourable when the substitution of magnesium was started in the early stage of pregnancy, at least in the 4th—9th week. Parallel with the increasing amount of substituted magnesium intrauterine foetal development improved. The most favourable effect was registered where maternal intake of magnesium amounted to 301—400 g Mgcitrate, which could be ensured with substitution from the 2nd or 3rd month with daily doses of 1.8—2.2 g Mgcitrate, containing

200—250 mg Mg^{++}. On the present supply of magnesium in food this quantity covered, the lower level of the daily requirement of 10—15 mg per kg body-weight of Mg^{++} in pregnancy. Notwithstanding the good intensions of the majority of gravidas, magnesium was taken irregularly, therefore it is worth while to prescribe a daily dose which on regular use provides for the upper limit of requirement, on irregular intake for the lower limit. The amount to be supplemented can be determined by studying nutrition in a group of the population, in the individual by calculation per kg body-weight.

Magnesium substitution does not replace or make unnecessary the supplementation of other substances of vital importance during pregnancy, it does not make the use of other pregnancy-guarding measures superfluous, but, adjuvating the latter, it promotes optimal development of the foetus.

The assortment of Mg compounds for magnesium substitution varies per country and production of the pharmaceutical industry. With due regard to the Mg^{++} content of these drugs, Mgcitrate can be replaced by other, adequate magnesium preparations.

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(Author's adress: Dr. Vilma Kuti, József Attila u. 84/b, H-1029 Budapest II)