On the role of Magnesium in fetal hypotrophy, pregnancy induced hypertension, and pre-eclampsia[++] [+++]

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Zusammenfassung

Von den 4905 Einlings-Schwangerschaften der 4 Jahre 1979 bis 1982 werden die 882 (18,0 %) mit Betamimetika und Magnesium tokolytisch behandelten Patientinnen im Vergleich zum übrigen Kollektiv (R) von 4023 (82,0 %) Patientinnen ohne derartige Behandlung retrospektiv betrachtet. Die tokolysierten Patientinnen (B/Mg) erhielten adjuvant zum Betamimetikum: seit 1979/1980 ein niedrig dosiert Mg enthaltendes Präparat zur „Kardioprotektion" (3—6 mval Mg^{++} pro die) und seit Beginn des Jahres 1981 zur „Unterstützung der Tokolyse" 30—40 mval Mg^{++}/die oral in Form von Magnesium-Aspartat.

Ermittelt werden in den Kollektiven B/Mg und R die Zahlen der aufgetretenen schwangerschaftsinduzierten Hypertonien und Prä-Eklampsien (PIH/PE). Aus dem Kollektiv R ergibt sich das Normal-Kollektiv (N) durch Abzug von PIH/PE. Erhoben und verglichen werden bei N, PIH/PE und B/Mg Durchschnittsalter und Parität der Patientinnen, Prozentsatz der adjuvanten Magnesium-Medikation (nur B/Mg-Kollektive); dazu die Schwangerschaftsausgänge anhand der Schwangerschaftsdauer und der Zahl der intrauterin retardierten Kinder (IUR: < 10. Perzentile BPE, < 25. Perzentile Hohenauer).

Die Zahl der PIH/PE ist bei den insgesamt 882 Betamimetika/Magnesiumbehandelten Patientinnen Null. Sie beläuft sich bei den übrigen Patientinnen auf 97 (2,0 %). Die IUR-Rate (< 10. Perz. BPE) beträgt: bei den 3926 N-Patientinnen 9,4 %, bei den 97 PIH/PE 45,4 %, bei den 398 B/Mg-Patientinnen der Jahrgänge 1979 + 1980 mit wenig Magnesium adjuvant (B/Mg (1)) 17,8 % und bei den 484 Patientinnen der Jahrgänge 1981 + 1982 mit viel Magnesium adjuvant (B/Mg (2)) 10,1 %. Die statistische Prüfung (explorativer Charakter) anhand der IUR (< 10. Perz. BPE) ergibt u. a. einen signifikanten Unterschied zwischen dem Betamimetikum/wenig Mg (1) und dem Betamimetikum/viel Mg (2)-Kollektiv; praktisch keinen Unterschied jedoch zwischen dem Normal-Kollektiv und B/Mg (2).

Das Verhältnis der Retardierungsgrade (< 25. Perz. Hohenauer: < 10. Perz. BPE) weist bei PIH/PE mit 1,3:1 die stärkste und bei B/Mg (1) mit 1,8:1 eine weniger starke „Verschiebung" zur schweren Hypotrophie auf; beim Kollektiv mit viel adjuvanter Mg-Gabe (B/Mg (2)) entspricht es dem Wert des Normal-Kollektives (2,4:1).

Die Ergebnisse zeigen, daß Patientinnen-Kollektive mit Betamimetika- und adjuvanter Magnesium-Therapie keine PIH und Prä-eklampsien aufweisen (nach den genannten Kriterien). In den beiden Jahrgängen mit 30—40 mval Mg-Zusatztherapie reduzierten sich die Häufigkeiten der IUR (auf die des Normal-Kollektivs). Danach würde Magnesium einen „beeinflussenden Faktor" der fetalen Hypotrophie darstellen. Vermutlich hat Magnesium in den vorliegenden Ergebnissen auch dazu beigetragen, daß keine PIH/PE auftraten. Umgekehrt könnte Magnesium-Mangel selbst eine Rolle bei der Entwicklung von schwangerschaftsinduzierten Hypertonien oder Prä-eklampsien spielen. Dadurch würde die bekannte, in den vorliegenden Kollektiven ebenfalls beobachtete, erfolgreiche Therapie von Prä-eklampsien mit Magnesium mehr kausal als empirisch sein.

Es wird ein Gestose-Modell aufgezeigt, in dem Magnesium-Mangel die Ursache der (essentiellen) Gestose darstellt.

Summary

Of 4905 single pregnancies between 1979 and 1982 the 882 (18.0 %) risk pregnancies managed tocolytically with Betamimetics and Magnesium were retrospectively compared with the remaining collective (R) of 4023 (82.0 %) patients without management. The tocolysed patients (B/Mg) received Magnesium in addition to Betamimetics: since 1979/1980 a low dose Mg containing drug aimed at "cardioprotection" (3—6 mval Mg^{++} daily), and since 1981 to "support tocolysis" 30—40 mval Mg^{++} daily per os in the form of Mg-aspartate.

All cases of pregnancy induced hypertension and preeclampsia (PIH/PE) in both collectives B/Mg and R were investigated. A normal collective (N) is obtained by subtracting PIH/PE from R. For all collectives N, PIH/PE, and B/Mg the following data were compared: mean age, parity, percentage with supplement Mg medication (only the B/Mg collective), the pregnancy outcome with respect to pregnancy duration and the number of intrauterine retarded infants (IUR: < 10th percentile of the BAVARIAN PERINATAL EVALUATION (BPE), < 25th percentile according to HOHENAUER).

The number of PIH/PE in the 882 B/Mg cases is zero. It is 97 (2.0 %) in the remaining 4023 patients. The IUR rate (< 10th perc. BPE) is 9.4 % in the 3926 N patients, and is 45.4 % in the 97 PIH/PE patients. The IUR rate is 17.8 % in the 398 B/Mg patients of 1979 + 1980 who had received less adjuvant Mg (B/Mg (1)), and it is 10.1 % in the 484 B/Mg patients of 1981 + 1982 who had received much higher Magnesium (B/Mg (2)). The tests of significance (carried out in an explorative sense) evaluated by means of the IUR (< 10th perc. BPE) show a significant difference between the Betamimetic/low dose Mg (1) and the Betamimetic/high dose Mg (2) collectives. However practically no difference is seen between the Normal Collective and B/Mg (2).

The ratio of the degrees of retardation (< 25th perc. HOHENAUER: < 10th perc. BPE) is 1.3:1 in PIH/PE and 1.8:1 in the B/Mg (1) group showing respectively the strongest tendency towards advanced hypotrophy in the former group. In the B/Mg (2) collective with high adjuvant Mg administration this value corresponds to that of the N group (2.4:1).

The results show that patients or collectives with Betamimetics and supplementary Magnesium therapy did not develop PIH and Pre-eclampsia (following the mentioned criteria). In the two years when a 30—40 mval daily Mg substitution therapy was practiced the IUR frequency dropped (to that of the Normal

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Collective). Thus Magnesium is an "influencing factor" of fetal hypotrophy. Also in the light of the present findings it seems plausible that Mg helped to prevent PIH/PE. Vice versa Mg deficiency could be possibly involved in the pathogenic pathway to pregnancy-induced hypertension or pre-eclampsia. It does appear that the rather antiquated and successful treatment of pre-eclampsia with Mg (also observed in our collectives) is more rational than empiric.

A gestosis model is shown in which Magnesium deficiency represents the cause of (essential) gestosis.

Résumé

De 4905 grossesses simples entre 1979 et 1982 882 (18,0 %) grossesses de risque, traitées avec des tocolytiques c-à-d les Bétamimétiques et du Magnésium, ont été comparées d'une façon rétrospective avec les 4023 (82,0 %) restants (R) sans traitement. Les malades tocolysées (B/Mg) avaient réçu du Mg supplémentaire aux Bétamimétiques: depuis 1979/1980 du Magnésium en dosage réduit et ceci pour assurer la «cardioprotection» (3—6 mval Mg^{++}/jour) et depuis 1981 pour «soutenir la tocolyse» 30—40 mval Mg^{++}/jour per os sous forme de Mg-aspartate.

Tous les cas de l'hypertension gravidiques et de prééclampsie (PIH/PE) dans les deux collectives B/Mg et R ont été étudiés. La collective normale (N) s'est obtenue par la soustraction PIH/PE de R. Pour tous les collectives N, PIH/PE et B/Mg les données suivantes ont été stratifiées et comparées: L'âge moyen, la parité, le pourcentage ayant reçu la médication magnésique supplémentaire (ici seulement la B/Mg collective), le sort de la grossesse considerant la durée de la grossesse et le nombre de rétardations intrautérines des enfants (IUR: $<10^e$ percentile de l'évaluation périnatale Bavaroise (BPE), $<25^e$ percentile de Hohenauer).

Le nombre de PIH/PE parmi les 882 B/Mg cas est zéro. Il est 97 (2,0 %) parmi les 4023 restants. Le taux de IUR ($<10^e$ perc. BPE) est de 9,4 % parmi les 3926 N femmes et de 45,4 % parmi les 97 PIH/PE malades. Il est de 17,8 % chez les 398 B/Mg malades qui en 1979+1980 ont réçues du Mg^{++} supplémentaire à dose réduite (B/Mg (1)), et de 10,1 % chez les 484 B/Mg malades qui en 1981+1982 ont réçues du Mg^{++} supplémentaire à dosage élevé (B/Mg (2)). Les tests de significance (d'une façon explorative) évaluées par moyen de la IUR ($<10^e$ perc. BPE) montrent une différence significative entre les B/Mg (1) et B/Mg (2) collectives. Toutefois il n'y a pratiquement pas de différence entre la collective normale et B/Mg (2).

Le rapport des degrés de rétardations ($<25^e$ perc. Hohenauer: $<10^e$ perc. BPE) est 1,3:1 parmi les PIH/PE et 1,8:1 dans le groupe B/Mg (1) montrant ainsi une tendance très importante vers l'hypotrophie avancée chez le premier groupe. Dans la collective B/Mg (2) avec un traitement magnésique à dosage élevé ce rapport coincide avec celui du groupe N (2,4:1).

Les résultats montrent que les malades ou collectives traitées avec les Bétamimétiques et du Magnésium supplémentaire n'ont pas developpés une PIH ou la Prééclampsie (d'après les critères déjà mentionnés). Dans les 2 années où une thérapie substitutive de Magnésium à 30—40 mval par jour a été practiquée la fréquence de IUR s'est tombée (au niveau des collectives normales). Ainsi le Magnésium est un facteur influent de l'hypotrophie fétale. En vue de ces résultats il parait plausible que le Magnésium a aidé de prévenir la PIH/PE. Vice versa la déficience magnésique pourra être engagée dans l'évolution pathogénique terminant en l'hypertension gravidique ou la pré-éclampsie. Il parait que le traitement de la pré-éclampsie avec du Magnésium si ancien et réussi (aussi observé dans nos collectives) soit plus rationnel qu'empirique.

Un modèle de préeclampsie est démontré dans lequel un manque du Magnésium représente la cause de la toxémie (essentielle).

Introduction

Gestosis (EPH-Gestosis, Preeclampsia, vasculorenal Syndrom, Toxemia) through hemorrhage and convulsion risks represents a potential danger for the mother. Also through placenta insufficiency and fetal hypotrophy it is seen as a handicap for the fetus or the infant. Cases of gestosis, mild or advanced, have reduced in the last years. This depends highly on the improved antenatal care with adequate management (*Friedberg* 1981 [38]). Today gestosis threatens almost 6 % of all pregnancies in our country (Bavarian Perinatal Evaluation 1979-1981 [102, 127]).

A relationship between gestosis, uteroplacental insufficiency and fetal intrauterine retardation has often been described [66, 71, 95]. In numerous experiments with animals attempts have been made to obtain a true "gestosis model" so as to study closely the etiology and physiopathologic evolution of the disease (Literature summarized in [11, 22]). It is still not completely clear today whether the disease stems from an uteroplacental ischemia or that the latter is a consequence of the disease (*Kyank* in: *Jaworski* et al. [58]). In the new reports of *Friedberg* [38] a disturbance in the uteroplacental blood flow being the cause of gestosis is more favoured.

By comparing the predisposing factors to gestosis [40, 57, 66, 69, 78, 91, 95], intrauterine retardation [6, 67, 82, 95] and to premature births [122] a close interrelationship could be noticed. *Robrecht* et al. [93, 94] found a low percentage of gestosis in their cerclage collective with 39 % tocolysis. *Salzer, Wagner* and *Reinold* [96, 116] observed an increased fetal dystrophy rate in their cerclage collectives with 83 % tocolysis (compared to the normal collectives) but likewise a low percentage of gestosis. This at first looks contradictory.

From the results of a 5 year gestosis-screening with MAP II values [84], Roll over Test [39], Gestosis Selection Test [16, 20, 21] and hematocrit values [46, 47] we have the impression that in patients who later needed tocolysis (for treatment of premature cervical ripeness or recorded premature labour pains) an even higher percentage of positive testing could be observed. One can for instance imagine that in some cases a premature birth precedes the development of gestosis and in some other cases the manifestation of the disease was prevented by the treatment with tocolytic drugs.

It is noticeable that methods effective in tocolysis like bed rest, the administration of Betamimetics [44, 59, 60, 61, 77, 119] and more recently Magnesium [106, 107, 109, 110, 114, 120] are also suitable for the treatment of gestosis (Betami-

metics [19, 56, 89, 90, 112], Magnesium since more than 50 years [12, 33, 64, 72, 73, 87, 99, 103, 128]). An evaluation of a 3 year tocolysis collective [22, 23] and of another 4 year collective with broader criteria [24, 25, 26, 27] showed a drop in the number of hypotrophic fetuses after the administration of Magnesium supplementary to Betamimetics.

This led us to examine the following questions retrospectively:

1. How frequent is gestosis in cases of premature cervical ripeness or threatening abortions/premature births after management with Betamimetics and Magnesium as compared with the remaining collective of patients in the same periods?

2. How frequent are births with poor intrauterine fetal growth (as a sign of uteroplacental insufficiency) after management with Betamimetics and Magnesium during pregnancy, after gestosis and after normal pregnancies?

3. Do the results following treatment with Magnesium, regarded as "a supplement tocolytic" [24, 26, 106] as well as "an influencing factor of fetal hypotrophy" [22, 25, 27] and also as a known "therapeutic drug of gestosis" (see above), give any hint at the possible pathogenic pathway to gestosis?

Material and methods

4905 single deliveries of the last 4 years (1979-1982) in the Womens Hospital Bayreuth were considered for study. Of these, 882 (18.0 %) patients all together (B/Mg) were managed with Betamimetics and low dose or highly dosed Magnesium. The remaining 4023 (82.0 %) patients (R) did not receive a similar treatment.

The B/Mg collectives comprise of the following: Patients who were tocolysed as outpatients against premature cervical ripeness and premature uterine contractions (supplement medication following instructions of house doctor); Patients who were tocolysed against threatening premature birth ≥29th week of gestation as in-patients (supplement medication being Magnesium; see below). In addition patients with premature cervical ripeness or premature labour before the 29th week of gest., negative medical history, and cases of 1st or 2nd trimester bleeding with an intact fetus were considered. These patients were primarily tocolysed as in-patients (supplement medication being Magnesium, see below) and received a cerclage of the cervix (detailed description see [24, 25]). Tocolysis was continued right up to the 38th week of gest. after which cerclage was removed or at least until the 36th/37th week (also in patients without cerclage). The Betamimetic mostly employed here was Clenbuterol (Spiropent®) orally.

Since 1979 tocolysis was carried out using additional Magnesium differently dosed: In the first two years Feto-Longoral®* (Magnesium-Potassium-Vitamin drug with 1 mval Mg/tablet) was applied to assure "cardioprotection". The patients took 3 × 2 tablets (≙6 mval Mg daily) during their stay in hospital and then 3 × 1 tablet throughout the tocolysis. Since the beginning of 1981 a second supplementary Magnesium therapy was administered aimed at "supporting tocolysis" and in the form of oral Magnesium-Aspartate, Mg5-Longoral®* (chewing tablet with 10 mval Mg/tablet). The patients received 3 × 1 to 4 × 1 tablet, corresponding to 30—40 mval Magnesium daily. This medication also was given throughout the described duration of the tocolytic management. The taking of drugs was controlled through specific questions to the patients on admission for delivery.

Only the complete "annual bloc" of deliveries was considered for evaluation due to the seasonal influences on deliveries observed each year. The deliveries taking place in the 4 year period between 1979 and 1982 were taken together and divided into a Betamimetic/Magnesium collective (B/Mg) and a Rest collective (R). All cases of gestosis (PIH/PE) were accordingly noted and separated from both collectives. In this way a Normal Collective (N) is obtained from the Rest Collective (R) after subtraction of PIH/PE. There after each of the three collectives (N, PIH/PE, B/Mg) was considered. Noted were: age and parity of the patients, the number managed with supplementary Magnesium medication (only B/Mg collective), pregnancy duration as well as the number of hypotrophic or intrauterine retarded infants. Finally, a comparison of the frequency of intrauterine retarded infants was made between the collectives N, PIH/PE and B/Mg. The B/Mg collective was subdivided into the group of patients with less adjuvant Magnesium therapy (1979 and 1980) and into the group with the higher dosed supplementary Mg medication (1981 and 1982).

The pregnancy duration was obtained on a gravidarium chart with the patient's LMP, and in cases of uncertainty this was estimated from the sonographic measurements in the I/II trimester. The number of short term pregnancies (≦36th week completed) was also noted.

We defined gestosis (using the criteria of the known proposals with a pathogenetic classification [11, 38, 50, 79] as follows:

1. Pregnancy induced Hypertension (PIH):
   (a) Diastolic pressure ≥90 mm Hg after the 24th week of gest., supported by repeated measurements.
   (b) A rise in the diastolic pressure ≥25 mmHg compared with the first known values measured during the first trimester.
2. Pregnancy Hypertension Gestosis or Pre/Eclampsia (PE):
   Diastolic pressure ≥90 mmHg, systolic pressure ≥140 mmHg and proteinuria (after elimination of urinary tract infection).

Both collectives (PIH and PE) were taken together in the evaluation. According to definition, cases of preexisting hypertension without aggravation of blood pressure in pregnancy are not included because in our collectives such cases mostly had to do with patients who started an antihypertensive therapy early in pregnancy (other standards appliable [51]) or with obese patients (BP determination problem).

All patients with blood pressure aggravation in pregnancy were considered including also those patients in whom seemingly no sufficient antihypertensive treatment was undertaken. Patients with superimposed preeclampsia from renal disease could not be observed in the collectives we evaluated. However this was not controlled by regular renal biopsy after preeclampsia.

The management of our cases of gestosis (PIH/PE) was carried out individually. In most patients hemodilution was performed with hyperoncotic solutions containing Dextran, Gelatin or Human Albumin. Betamimetics and antihypertensives were given, and since the beginning of 1981 we reestablished Magnesium therapy. Magnesium was given intravenously, individually 80—300 mval Mg^{++} daily ($MgSO_4$) depending on the severeness of pre-eclampsia. The indications for a premature termination of pregnancy were: Placenta insufficiency with an acute fetal jeopardy, uncontrollable hypertension of the mother, acute thrombocytopenia and hemorrhage.

To ascertain the number of hypotrophic or intrauterine retarded infants, two proceedings were undertaken. First the position of every single birth weight with respect to the 10th percentile on the gestation-weight-curve plotted from the data of the Bavarian Perinatal Evaluation (BPE) in 1979/1980 was studied (for fundamentals see [102, 127]). Cases clearly falling below the 10th percentile (mascu-

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line and feminine separately considered) were accordingly considered as "small for dates" (<10th percentile). To be able to realize a shift of birth weights in the above lying range the cases falling below the 25th percentile according to *Hohenauer* [52] were also studied.

Only single pregnancies were evaluated because for multiple pregnancies especially with respect to intrauterine growth and gestosis a comparison of unnecessary complicating factors would have been the case.

Table I: Frequency distribution of PIH + Preeclampsia in a total of 4905 single deliveries from 1979 to 1982 after classification of pregnancies into a tocolysed group (managed with Betamimetics + Magnesium) and those without this management.

years	total No. of single pregnancies	No. of patients treated with Betamimetics + Magnesium	No. of patients untreated	Development of PIH + Preeclampsia
1979 to 1982	4905	882 (18.0 %)	—	0
		—	4023 (82.0 %)	97 (2.0 %)

Results

From the 4905 single births of the four year period (1979—82) all together 882 (= 18.0 %) patients were treated with Betamimetics and low dose or high dose supplementary Magnesium (B/Mg) (Table I). There was no case of pregnancy-induced hypertension or Pre/Eclampsia (PIH/PE) in this collective. In the remaining 4023 (= 82.0 %) cases (R) where none of the above mentioned drugs was employed the number of PIH/PE was 97 (= 2.0 %).

The mean ages and percentages of primiparity in the three collectives of patients (Normal pregnancies, PIH + Preeclampsia, Betamimetic/Magnesium treated women) are shown in Table II.

The Normal collective of 3926 patients is obtained by subtracting PIH/PE from R (see above) (Table III). In this collective the percentage of pregnancies that terminated before the 36th week of gestation is about 2 %. The hypotrophic rate (< 10th percentile BPE) fluctuates with ± 1 % around 9.5 % and with respect to the 25th percentile with ± 3 % around 22.5 %.

In the 97 cases with gestosis (PIH/PE) an in-patient antenatal management of gestosis more than seven days long was received by the following (Table IV): 1979: 6 (30 %), 1980: 9 (37.5 %), 1981: 10 (40 %) and 1982: 14 (50 %). Magnesium was reestablished in the treatment of gestosis in 1981. The number of pregnancies which terminated before the 36th week of gest. came up to about 16 %, but in 1982 to 35.7 % (here there were more severe cases [see hypotrophy at this year] with an active premature termination of the pregnancy). The hypotrophic rate (< 10th perc. BPE) was 40.4 % in 1979, 37.5 % in 1980, 44.0 % in 1981 and 57.1 % in 1982. Below the 25th percentile (Hohenauer) fell 45.0/50.0/68.0/64.3 % of the fetuses respectively.

Among the 882 patients (B/Mg) treated with Betamimetics/Magnesium the supplementary Mg therapy with 3—6 mval

Table II: Mean ages and percentage of primiparity in the collectives of patients: Normal pregnancies, PIH + Preeclampsia, and Betamimetic/Magnesium treated pregnancies.

	mean ages (years)			
	1979	1980	1981	1982
Normal pregn.	25.5	25.6	25.6	25.7
PIH + Preecl	26.3	26.0	26.9	25.8
B/Mg collectives	25.6	26.1	26.2	25.9
	percentage of primiparity (%)			
	1979	1980	1981	1982
Normal pregn.	48.8	49.3	50.2	52.1
PIH + Preecl	70.0	70.8	60.0	50.0
B/Mg collectives	50.9	54.0	54.8	57.6

Table III: Frequency of intrauterine fetal retardation (IUR), and of a pregnancy duration ≤ 36 weeks (completed) in the 3926 Normal Pregnancies from 1979 to 1982 (also shown in the annual splitting).

years	No. of Normal Pregnancies	pregn. duration ≤ 36th wk (completed)	IUR < 25th perc. Hohenauer	IUR < 10th perc. BPE
1979—1982	3926	82 (2.1 %)	892 (22.7 %)	371 (9.4 %)
1979	953	20 (2.1 %)	248 (26.0 %)	108 (11.3 %)
1980	996	20 (2.0 %)	226 (22.7 %)	88 (8.8 %)
1981	988	17 (1.7 %)	225 (22.8 %)	79 (8.0 %)
1982	989	25 (2.5 %)	193 (19.5 %)	96 (9.7 %)

Mg daily (Feto-Longoral®) was received by: 31 (19.0 %) in 1979, 181 (77.0 %) in 1980, 223 (89.9 %) in 1981 and 225 (95.3 %) in 1982 (Table V). The higher dosed extra supplementary Mg therapy of 30—40 mval Mg daily (Mg5-Longoral®) was received by 113 (45.6 %) in 1981 and 151 (64.0 %) in 1982. The percentage of pregnancies terminating before the 36th week completed varied between 13.5 and 8.1 %. The hypotrophic rate (< 10th percentile BPE) is thus 20.9 % in 1979 and 15.7 % in 1980. It is reduced in 1981 and 1982 to 10.1 and 10.2 % respectively. The weight gain also exceeds the 25th percentile. Here the hypotrophic rate for 1979 and 1980 was 33.1 and 30.2 % respectively. It is reduced in 1981 and 1982 to 25.4 and 24.2 % respectively. Noteworthy here is that less supplementary Magnesium was administered in 1979 and 1980 whereas much more supplementary Magnesium was given in 1981 and 1982. To that extent in Table V above no summing up of the years 1979—1982 is presented; instead of this the years 1979 and 1980 with low dose supplementary Mg and the years 1981 and 1982 with high dose supplementary Mg are separately summarized. From the 398 patients of 1979 + 1980 a percentage of 53.3 % received 3—6 mval Mg daily. From the 484 patients of 1981 + 1982 92.6 % of the pat. received 3—6 mval Mg daily and additionally 54.5 % of the pat. received 30—40 mval Mg daily.

In the Normal-collective (N) with 3926 pregnancies 371 (9.4 %) infants below the 10th percentile (BPE) and 892 (22.7 %) below the 25th percentile *(Hohenauer)* were born (Table VI a). To the 97 gestosis patients (PIH/PE) 44 (45.4 %) infants below the 10th perc. and 56 (57.7 %) below the 25th perc. were born. Among the 882 B/Mg treated patients there are 398 pat. (B/Mg(1)) treated with less adjuvant Mg (1979 + 1980) and

Table IV: Frequency of intrauterine fetal retardation (IUR), pregnancy duration ≤ 36 weeks (completed), and of the inpatient antenatal treatment more than seven days among the 97 cases of PIH + Preeclampsia from 1979 to 1982 (also shown in the annual splitting).

years	No. of PIH + Preecl.	In-pat.treatm. antenatal > 7 days	pregn. duration ≤ 36th wk (completed)	IUR	
				< 25th perc. Hohenauer	< 10th perc. BPE
1979—1982	97	39 (40.2 %)	21 (21.6 %)	56 (57.7 %)	44 (45.4 %)
1979	20	6 (30.3 %)	3 (15.0 %)	9 (45.0 %)	8 (40.0 %)
1980	24	9 (37.5 %)	4 (16.7 %)	12 (50.0 %)	9 (37.5 %)
1981	25	10 (40.4 %)	4 (16.0 %)	17 (68.0 %)	11 (44.0 %)
1982	28	14 (50.0 %)	10 (35.7 %)	18 (64.3 %)	16 (57.1 %)

Table V: Frequency of intrauterine fetal retardation (IUR), and of a pregnancy duration ≤ 36 weeks (completed) among the annually splitted 882 Betamimetic treated patients from 1979 to 1982 with supplementary Magnesium therapy given at different doses.
Above the patients of 1979 and 1980 with a low dose supplementary Mg^{++} (B/Mg(1)), and those of 1981 and 1982 with a high dose supplementary Mg^{++} treatment (B/Mg(2)) are summarized.

years	No. of pat. Betamimetics	supplement Mg therapy		pregn. duration ≤ 36th wk (completed)	IUR	
		3—6 mval Mg/day (Feto-Longoral®)	30—40 mval Mg/day (Mg5-Longoral®)		< 25th perc. Hohenauer	< 10th perc. BPE
1979 + 1980	398	212 (53.3 %)	–	44 (11.1 %)	125 (31.4 %)	71 (17.8 %)
1981 + 1982	484	448 (92.6 %)	264 (54.5 %)	44 (9.1 %)	120 (24.8 %)	49 (10.1 %)
1979	163	31 (19.0 %)	–	22 (13.5 %)	54 (33.1 %)	34 (20.9 %)
1980	235	181 (77.0 %)	–	22 (9.4 %)	71 (30.2 %)	37 (15.7 %)
1981	248	223 (89.9 %)	113 (45.6 %)	20 (8.1 %)	63 (25.4 %)	25 (10.1 %)
1982	236	225 (95.3 %)	151 (64.0 %)	24 (10.2 %)	57 (24.2 %)	24 (10.2 %)

Table VI a: Frequency distribution of intrauterine fetal retardation (IUR) and the relationship of the degrees of retardation in a total of 4905 single deliveries from 1979 to 1982. The pregnancies are classified in Normals, PIH + Preeclampsia, and Tocolysed i. e. Betamimetics with low dose Magnesium (1) or high dose Magnesium (2) administered in supplement.

years	total No. of single pregnancies	No. of patients in the splitted collectives	IUR		Ratio of the degrees of I.U.R. (< 25th: < 10th perc.)
			< 25th perc. Hohenauer	< 10th perc. BPE	
1979 to 1982	4905	3926 Normals	892 (22.7 %)	371 (9.4 %)	2.4 : 1
		97 PIH + Preecl.	56 (57.7 %)	44 (45.4 %)	1.3 : 1
		398 Betamimetics + Mg (1)	125 (31.4 %)	71 (17.8 %)	1.8 : 1
		484 Betamimetics + Mg (2)	120 (24.8 %)	49 (10.1 %)	2.4: 1

(1): 3—6 mval Mg/day received by 53.3 % of the Betamimetic treated pat. in 1979 + 1980.
(2): 30—40 mval Mg/day received by 54.5 % of the Betamimetic treated pat. in 1981 + 1982.
3—6 mval Mg/day received by 38.1 %.

Table VI b: Results of the significance tests with respect to the frequency of IUR (< 10th percentile BPE).

Test	df	x^2	x^2 0.01/5; df	significance
global contingency	3	147.06	14.796	s.
N : B/Mg (1)	1	27.71	9.550	s.
N : B/Mg (2)	1	0.23	9.550	n. s.
N : PIH + Preecl.	1	131.95	9.550	s.
B/Mg (1) : B/Mg (2)	1	11.06	9.550	s.

484 pat. (B/Mg(2)) treated with much adjuvant Mg (1981 + 1982). To the B/Mg(1) collective 71 17.8 %) infants below the 10th percentile and 125 (31.4 %) below the 25th percentile were born. In the B/Mg(2) collective only 49 (10.1 %) infants fell below the 10th perc. and 120 (24.8 %) below the 25th percentile respectively. Considering the relationship of the retardation grades (< 25th: < 10th percentile) it is 2.4:1 in the N collective and 1.3:1 in the PIH/PE collective; i.e. in the Gestosis collective the percentage of severe hypotrophic fetuses is not only five fold as compared to the Normal collective, but also there is a tendency towards severe hypotrophy within this PIH/PE collective itself. The B/Mg(1) collective on the other hand with low dose Mg therapy has about twice the percentage of hypotrophic fetuses as the Normal collective. Within this collective itself the ratio of the degrees of retardation is 1.8:1. In the B/Mg(2) collective with high dose supplementary Mg therapy the number of intrauterine retardations and the corresponding ratio are almost the same as in the Normal collective.

The following statistical analysis has been done only in an explorative sense (notes about the explorative use of statistical tests can be found e.g. at *Victor* et al. [115]; Table VI b). Five x^2-tests have been put through simultaneously (level of significance: $\alpha = 0{,}01$) to compare the percentages of fetal hypotrophy (< 10th percentile BPE) of the following patients groups: N:B/Mg(1), N:B/Mg(2), N:PIH/PE, B/Mg(1):B/Mg(2). Differences of high significance are obtained between the group of normal patients (N) and the group of Gestosis patients (PIH/PE), likewise between the group of normal patients and the group of Betamimetics/low dose Mg treated patients (B/Mg(1)). Significant differences are obtained between the group of B/Mg(1) and the group of Betamimetics/high dose Mg treated patients (B/Mg(2)). No difference ($x^2 = 0{,}23$) has been found between N and B/Mg(2). In the sense of the explorative statistical analysis (see above), these results can be considered as "formally confirmed".

Discussion

The development of pregnancy-induced hypertension and pre-eclampsia in a large collective that has been treated for the described risks with Betamimetics and Magnesium is zero. To this result on the one hand the Betamimetic therapy and on the other hand the Magnesium therapy could have contributed.

Influence of Betamimetics

In the investigations mentioned in the introduction and carried out by other authors [93, 94, 96, 116] there was a low percentage of gestosis cases in the cerclage and tocolysis collectives as compared to the rest collective. In our results the number of gestosis was zero. The additional Magnesium administration could have contributed to this result. But there have also been some different criteria in the classification of gestosis to be taken into consideration.

For some time now we wanted to know if one has to expect a lower number of gestosis cases in tocolysed collectives of patients or if the development of gestosis was prevented through tocolytic treatment.

This led us to undertake a gestosis-screening among the above mentioned patients in whom tocolysis was already foreseen. The screening involved the calculation of the mean arterial pressure (MAP) in the 2nd trimester [84], the Roll over Test [39], the Gestosis Selection Test with Fenoterol [16, 20, 21] and the observation of hematocrit values [46, 47]. A first evaluation [21] and later comparable results showed that in almost 50 % of primiparas and about 30 % of multiparas, in whom tocolysis was necessary, one or more of these tests were striking. Noteworthy was the fact that those patients, who later had intrauterine retarded infants, fell into the group of patients with abnormal test results. Accordingly a certain number of placenta insufficiences and "potential" gestosis cases is presumed to be included in tocolysis collectives. Furthermore in tocolysis collectives a more frequent occurrence of intrauterine fetal retardation could be observed [22, 24, 26]. Hence it is supposed that tocolysis helped to prevent the development of gestosis symptoms but could not help to reduce in each case the outcome with fetal hypotrophy.

The following positive effects of Betastimulators on the maternal circulation and metabolic parameters, uteroplacental blood flow and fetal supply are either well known or in discussion (see also summaries [44, 59, 60, 61, 77, 119]):

1. The increase of the uterine blood flow through the betamimetic influenced rise in cardiac output and the drop in the peripheral resistance [34, 56, 68, 74, 125].
2. The additional drop in the uteroplacental flow resistance through the betamimetic relaxation of the uterus (in particular by labor activity) [59, 60, 68, 125].
3. The increase of the intravascular volume [29] after fluid retention [44, 65].
4. The improvement of hemorheology through the betamimetic mediated sinking of hematocrit [29] and their influence on erythrocyte deformability [46, 47].
5. The increased O_2-supply, on the one hand through the improvement of circulation and on the other hand through the betamimetic augmented arterialisation of blood (pO_2 increase) [17, 80, 111].
6. The increase of substrate supply to the fetus and placenta partly through the ameliorated blood circulation and partly through the metabolic effects produced by betamimetics [17, 29, 111].

Also possibly important is the known effect of betamimetics on lipid metabolism and fatty acids [17, 18], an effect which could influence the system of Prostaglandins and Thromboxane A_2/ Prostacyclin to the advantage of the vasodilatating and thrombocyte aggregation preventing products.

The effects of betamimetics investigated in many respects have led some authors [19, 56, 89, 90] to consider betamimetics for the causal (etiologic) treatment of gestosis [90].

Influence of Magnesium

In the present results it could be seen that the cases of gestosis (according to the described classification criteria about 2 % of the total collectives investigated) are found exclusively in the collective without tocolysis. A high percentage of fetal hypotrophy is also remarkable here (below the 10th percentile BPE 4 to 5 times the Normal collective). The theory of an insufficient uteroplacental blood flow being one causal factor in the pathogenesis of gestosis must be discussed here (detailed summary by *Friedberg* [38]). Considering the number of hypotrophic fetuses in the tocolysis collective one finds this almost twice as high as in the Normal collective. Similar observations have been reported by other authors whereby a beginning intrauterine retardation was held to be more frequently responsible for premature labor (for details see [24, 26]). It could give one the impression that fetal hypotrophy (utero-placental insufficiency) could play a role in threatening premature and growth retarded births respectively or in some cases later on in gestosis.

It is remarkable as already mentioned earlier that not only gestosis management but also tocolysis could be realized successfully with Magnesium. *Steer*

and *Petrie* 1977 [110], *Stallworth* et al. 1981 [109], *Spätling* 1981 [106], *Spisso* et al. 1982 [107] and *Valenzuela* et al. 1982 [114] have all reported about a successful arrest of premature labor with the help of Magnesium. The last two authors [107, 114] even regard Magnesium as a primary tocolytic agent. In the tocolysis collective we investigated we found out that after the introduction of Magnesium as a supplement to betamimetics there was a reduction in the cases of premature ruptured membranes and short term pregnancies [24, 26]. Furthermore in our earlier [22, 23, 25, 27] and current investigation we observed a reduction in the number of hypotrophic infants after the introduction of supplementary Magnesium to betamimetics (attaining the same frequency of IUR as in the Normal collectives). The number of gestosis occuring in our tocolysis collective as already mentioned was zero.

Magnesium is also considered by many as an essential cornerstone in the treatment of gestosis [12, 50, 64, 72, 87, 99, 103, 128]. In this respect we re-introduced it for the management of gestosis simultaneously with its use for tocolysis (in early 1981). In the cases of gestosis however a striking drop in the hypotrophic rate after the introduction of Magnesium could not be observed. Theoretically, this must not necessarily be expected because these cases of gestosis showed placenta changes with more or less important irreversible damages. There was indeed a difference in the cases of gestosis treated in 1981 and 1982 with Magnesium compared to those of 1979 and 1980 without Magnesium application: the duration of antenatal management. Although there were comparatively many advanced cases in the yearly collectives (see hypotrophic rates), in the last 2 years however an antenatal therapy duration of well over one week was evident. An explanation for this could be that following an exhaustion of placental functions an improvement was obtained with the help of Magnesium which made a prolongation possible.

In addition a reduced serum Magnesium level was often observed in women with gestosis [2, 5, 64, 117] and this even led some authors to suggest an etiologic relationship between Magnesium deficiency and gestosis (*Köberlin* and *Mischel* 1958 [64], *Weaver* 1980 [117], *Anastasiadis* et al. 1981 [2]). The determination of serum Magnesium gives only an indirect evidence of its metabolism at any time [85]. Meanwhile there are more hints not only from our results but also from literature that Magnesium deficiency could occur in pregnancy [35, 70, 92]; detailed summaries [22, 48, 53, 55, 100, 121].

The synopsis of the described results and reports gives the impression of an interrelation between fetal hypotrophy or uteroplacental insufficiency and Magnesium supply in one case or the other. Thereby following a deficient supply a tendency towards miscarriages, premature births or in the given case towards (essential) gestosis seems to be possible. The reason for this can be the role of Magnesium in metabolism and cell function, ranging from its electrolyte function to such important functions as an enzyme activator or as a physiologic Calcium antagonist (detailed descriptions [22, 45]). In the light of the present knowledge Magnesium deficiency seems in all probability to be causally involved in the pathomechanism of pregnancy-induced hypertension and preeclampsia [14, 15, 28]. A first model was shown in which Magnesium deficiency represents the cause of (essential) gestosis [22, 23]. The present concept is as follows.

Gestosis model based on Magnesium deficiency (Fig. 1)

A marginal Mg intake, a prompt consumption of Mg through the fast developing pregnancy, renal Mg loss (in diseases or as a result of some diuretics) or earlier disturbances of the Magnesium balance (i.e. during stress [13]), all lead to Magnesium deficiency with its resulting consequences for the organism (see [22]).

The Magnesium imbalance on the membranes and in the cells would among other things lead to an impairment of the Mg^{++}-dependant ATPases and their regulation ability for the Ca^{++}-flux in the vascular smooth muscles. A rise of the basal tone of these muscles and an increased reactivity towards endogenous pressor substances would be the consequences [1, 81, 83]. It would result in a generalised vasoconstriction or better in an insufficiently adaptive vasodilatation, whose impact on the evolution of gestosis is well accepted [4, 7, 11, 36, 38, 41, 62, 98].

From the metabolic effects of Magnesium deficiency another disturbance could develop (importance of Magnesium in the activation of about 300 enzymes and in protein as well as energy metabolism [45, 108]). Two effects would be given preference for discussion:

The deficient supply from a "Magnesium-poor" mother would endanger the fetus and placenta functions. It would cause a chronic (nutritive) placenta insufficiency, supported by the described preplacenta vasoconstriction (the higher number of growth retarded infants in the tocolysis collective, i.e. the risk collective for placenta insufficiency, and its "normalisation" after supplement Mg administration would support this fact).

On the other hand it could be assumed that the "Magnesium-impoverishment" of the mother

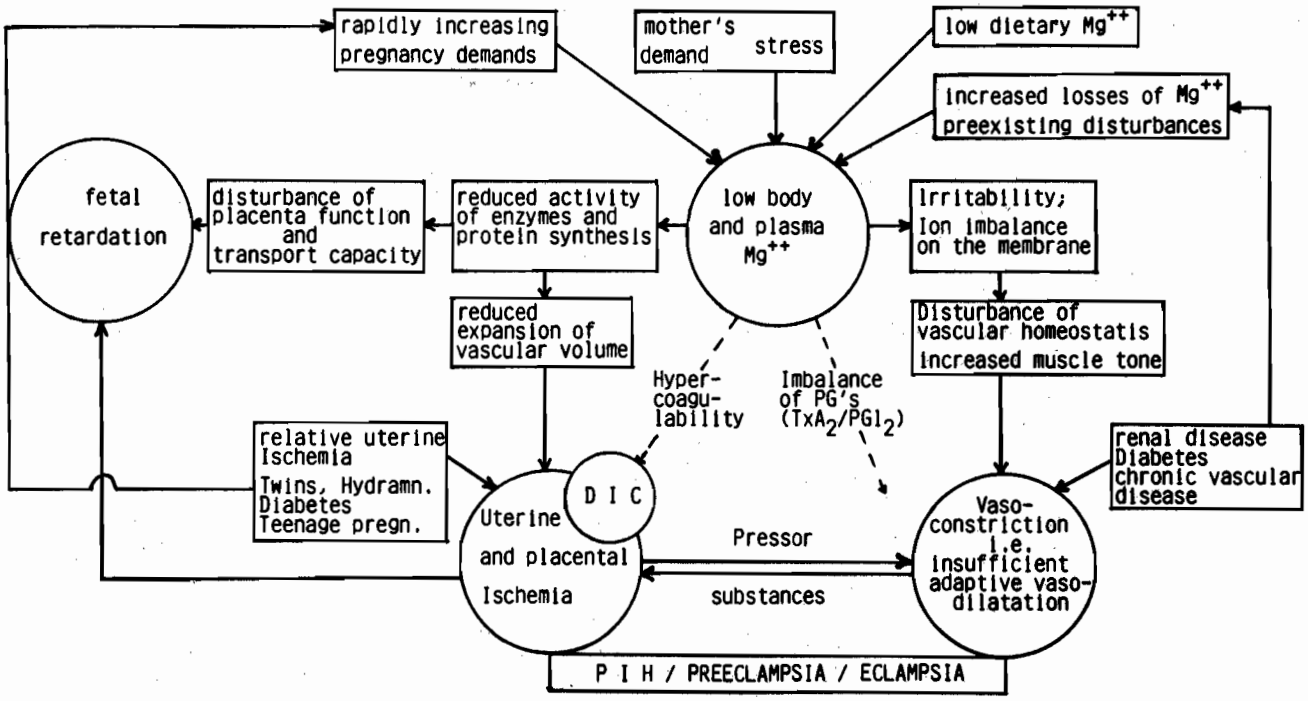

Fig. 1: Gestosis model based on Magnesium deficiency

would lead to the impairment of an increased production of proteins, which is necessary for the physiologic expansion of the circulating plasma volume in pregnancy [3, 37, 42, 97, 101, 105].

A direct effect of Mg deficiency on the processes of coagulation (Hypercoagulability) has also been suggested [53, 117]. In this way the local deposition of fibrin e.g. in the placenta could even be provoked prematurely. Hypercoagulability and microcirculatory disturbances (related through vasoconstriction, hypoproteinemia, dysproteinemia and hemoconcentration [10, 46, 49, 54]) could also finally lead to disseminated intravascular coagulation (DIC). As a result of DIC the outcome of some cases of gestosis is complicated [31, 63, 75, 76, 86, 123].

Mg deficiency could also influence, via lipid metabolism [88] or via catecholamines [45, 48] and c-AMP [118], the metabolism of essential fatty acids and the metabolism of Prostaglandins respectively. Changes in the concentrations of Prostaglandins especially of the Thromboxane A_2/Prostacyclin system are known to occur in pre-eclampsia [8, 9, 30, 32, 43, 104, 113, 126].

As a result of the disturbed competition of Mg^{++}/Ca^{++} provoked by Mg deficiency [45, 124] thereby favouring Ca^{++}-induced negative performances of cells and biochemical processes (i.e. vascular muscle cells contract, erythrocytes become more rigid) further tendencies towards gestosis would be expected to occur.

Conclusions

Individual investigations and hints from the literature led to suggest that Magnesium or rather its deficiency in pregnancy plays a remarkable role in fetal hypotrophy and in the development of pregnancy-induced hypertension as well as gestosis or pre-eclampsia.

Thus the prophylactic administration of Magnesium to a corresponding risk collective would be appropriate. The effective therapy of gestosis with Magnesium also seems to be more causal than empiric.

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