

EFFECTIVENESS OF THE MAGNESIUM APPLICATION IN OBSTETRICAL PRACTICE

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ABSTRACT

The aim: Conducting an evaluation of the effectiveness and safety of the use of magnesium in pregnant women.

Materials and methods: A comprehensive examination of 60 pregnant women was conducted, of which 30 were taking a magnesium preparation in a daily dose of 2473.72 mg of magnesium citrate and 40 mg of pyridoxine hydrochloride (the main group) and 30 pregnant women who were not taking a magnesium preparation (comparison group). The analysis of the clinical course of the first half of the pregnancy with the determination the frequency and structure of complications, blood pressure levels, indicators of ultrasound, general and biochemical blood tests, urinalysis, lipid status and carbohydrate metabolism.

Results: The main complications of the first half of pregnancy were: threatening miscarriage, abortion in progress, early gestosis, anemia, respiratory viral infection, exacerbation of extragenital pathology, hypertension. During the analysis of carbohydrate and lipid metabolism increased atherogenic potential. Analyzing the results of ultrasound studies reliably earlier comes down the local hypertonus.

Conclusions: The correction of chronic magnesium deficiency, performed by the drug magnesium has allowed to reduce cases of threat of abortion, the abortion that was started, the symptoms of early preeclampsia, anemia of pregnant women, symptoms of respiratory viral infection, reduces the number of bed-days in the case of hospitalization. The use of magnesium helped to normalize blood pressure, carbohydrate and lipid metabolism, reduces hypertonus of the myometrium.

KEY WORDS: magnesium deficiency, pregnancy complication, magnesium

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INTRODUCTION

The problem of maintaining reproductive health, reducing obstetric and perinatal complications, taking into account the complex demographic situation that has developed in Ukraine over the last 10-15 years, goes beyond the medical sector and is of national importance [2,4,5]. Among the many factors that support the life of the body of the pregnant and the fetus, micronutrients that are necessary for the normal growth and functioning of cells, tissues, organs and systems, prevention of infections, metabolism of the main classes of nutrients, hormones, mediators and other biologists are of great importance [6,12]. In the structure of the pathology of the elemental status of women, magnesium deficiency occupies a leading position, the individual prevalence of magnesium deficiency in the female population is 1.3 times higher than in the male population. Magnesium functions as a cofactor in more than 300 known enzymatic reactions, which can explain its effect on carbohydrate and lipid metabolism, myometrial function, and nerve tissue. The daily requirement for magnesium for women is 280-300 mg, and during pregnancy and lactation increases by

20-30% - up to 340-355 mg. Although magnesium is quite common in nature, its deficiency is observed in the population of 16-42%, clinical manifestations are much more frequent [3, 9, 15].

Magnesium deficiency is of particular importance in obstetric and gynecological practice. Hypomagnesemia during pregnancy is caused by a significant need for this element, as well as increased renal excretion. An important role belongs to the state of magnesium deficiency in the genesis of pregnancy miscarriage. In conditions of low magnesium concentration, pathological activation of calcium-dependent contractile reactions in the myometrium occurs and the risk of pregnancy termination increases, especially in the II-III trimester. In addition, hypomagnesemia promotes the development of increased excitability of the CNS, which provokes the central mechanisms of spastic reaction of the uterus.

In addition, concomitant hypertension disrupts the blood supply to the fetoplacental complex, increases the blood content of vaso-constrictor factors (renin, angiotensin II, prostaglandin F, serotonin), which increases the risk of miscarriage [7,8].

Antiplatelet effect of magnesium on platelets and directly on the vascular wall has been established as it reduces the imbalance between the synthesis of the prostacyclin of the vascular wall and thromboxane. There was also a decrease in the synthesis and release of catecholamines from the depot. All this improves perfusion in tissues, in particular in the chorion [1, 4, 11, 13].

A fundamental mechanism of the physiological effects of magnesium is its role as a natural calcium antagonist. At the same time magnesium competes with calcium not only in the structure of membrane channels but also at all levels of the cellular system, suppressing various reactions initiated by calcium. This mechanism provides anti-angina, anti-arrhythmic and antihypertensive effects of magnesium. Due to its antagonism with calcium, magnesium is able to influence the processes of oxidative phosphorylation in the mitochondria, resulting in increased ATP synthesis and reduced cellular oxygen demand (Table I) [1-4].

During pregnancy, due to hormonal changes occurring in the body of a woman, there is a tendency to the formation of hypomagnesemia. This is also due to the increase in 2-3 times the consumption of magnesium, which in turn is due to the growth and development of the fetus.

High micronutrient activity is determined by their mutual influence on each other's metabolism, as well as synergism and potentiation of biological effects. An example of this interaction is the tandem of magnesium and vitamin B6. Pyridoxine is involved in the synthesis of neurotransmitters and many enzymes, has neuro-, cardio-, hepatotropic, as well as hematopoietic effects, promotes energy reserves, maintains skin health, digestive tract, immune system. Vitamin B6 improves the absorption of magnesium in the digestive tract, serves as a conductor for it inside the cell, increases the permeability of cell membranes for magnesium and potassium ions, transfers them as an endogenous substance.

Magnesium drug therapy plays a significant role during pregnancy, childbirth, postpartum rehabilitation, and for the prevention of gestational diabetes and obesity. When carrying out magnesium therapy, it should be borne in mind that the endothelial and antiplatelet effect of magnesium preparations is short-lived and ends after their excretion. Therefore, long-term maintenance of oral forms of magnesium preparations during pregnancy is required [1,4-6].

THE AIM

Conducting an evaluation of the effectiveness and safety of the use of magnesium in pregnant women.

MATERIALS AND METHODS

In the first half of pregnancy, 60 pregnant women aged 29-38 years (mean age 28 ± 1.9 years) were observed in the Department of Gynecology KNP "Maternity Clinical House №1" in Lviv for six months of 2021 during the first half of pregnancy in the period from 13 weeks to 21 weeks+6 days. All patients were referred to a hospital or treated independently with lower abdominal pain (22 women) and a combination of pain with blood flow (8 women).

The patients were divided into two groups according to the features of treatment. The main group of observation included 30 pregnant women who, in order to prevent obstetric and perinatal complications, used a pharmaceutical preparation, which is an organic combination of magnesium citrate 618.43 mg and pyridoxine hydrochloride 10 mg. The drug was used at a daily dose of 2473.72 mg of magnesium citrate and 40 mg of pyridoxine hydrochloride. The daily dose was divided into 2 doses. Shelf life – during the first half of pregnancy. In addition, patients in the main group received micronized progesterone, vitamin E.

Patients of the comparison group (30 women) received in the complex treatment preparations of micronized progesterone, vitamin E, multivitamin complex for pregnant women.

The distribution of pregnant women into groups was carried out in accordance with the principle of randomization. Before forming observation groups, all pregnant women were asked to sign informed consent to participate in a clinical trial.

Diagnosis of magnesium deficiency was performed by the method of colorimetric result from venous blood at Synevo Medical Laboratory. Considering the speed of execution within 2 days and the relative inexpensiveness of the method, all women were determined to determine magnesium levels.

During the analysis of anamnestic data, the age categories of pregnant women, extragenital and ingenious pathology, reproductive function, clinical course of the first half of pregnancy were systematized determination of frequency and structure of complications. Blood pressure, ultrasound, general blood and urine tests, lipid (total cholesterol, B-lipoproteins, triglycerides, low-density lipoproteins, high density lipoproteins) metabolism were performed. The studies were performed by standart methods. The ultrasound examination focused on the presence of local myometrium hypertension in combination with subjective pain, the study was performed with an abdominal ultrasound sensor. Cervicometry, performed by a vaginal sensor (after 18 weeks of pregnancy), aimed to detect structural changes in the cervix, such as shortening of less than 30 mm, opening the inner eye.

Table I. Clinical manifestations of magnesium deficiency

Violation	Clinical manifestations
Increase of nervous excitability of a muscle cell	The redundancy of reduction processes in relation to the processes of relaxation (convulsions of extremities)
Increase of cardiomyocyte excitability	Disorders of the heart rhythm (tachycardia, extrasystole, heartache during physical activity)
Increasing the excitability of vascular smooth muscle cells	Sudden changes in blood pressure, headache, fatigue, apathy, increased risk of bronchospastic conditions
Imbalance in neuropeptides	Irritability, anxiety, bouts of fear, tearfulness, sometimes depression
Disorders of blood supply in the vessels of the brain	Frequent headaches, dizziness
Damage to neurons	Memory impairment, ability and concentration
Disorders of circadian melatonin synthesis processes and processes of excitation and inhibition in the nervous system	Insomnia, daytime sleepiness, night terrors, "broken" in the morning
Disruption of energy production and use processes	Muscle weakness, nervous exhaustion, general fatigue, chronic fatigue syndrome

The average length of stay in the gynecological hospital is $14 \pm 5,3$ days.

Statistical data processing was performed using Statistica 6.0 for WINDOWS v8.0.550 (StatSoft, USA). The comparison group and the main group were evaluated for subordination to the normal law of distribution according to the Pearson test. The significance of the difference of the mean values was determined by calculating the Student's t-test. The difference between the values compared was considered significant at $p < 0,05$ [7].

RESULTS

In the study, we did not find any significant differences between the pregnant women in the compared age groups (the mean age in the main group was $28 \pm 1,9$; in the comparison group $29 \pm 2,2$; $p = 0,08$). In the structure of somatic pathology of the examined pregnant women, diseases of the cardiovascular system (19.2%), digestive tract (15.7%), respiratory organs (14.3%), kidneys (10.7%), endocrinopathy took the main place (11.2%), varicose veins of the lower extremities (7.5%). Analyzing the history of patients from both the main and the comparison group with approximately the same frequency ($p < 0,05$) were noted: pathology of the cervix (17.3%), adenomyosis (21.2%), miscarriage (27.3%), intrauterine infection (19.3%), preterm birth (34.2%).

This allowed us to consider the groups representative and to exclude the possible effects of pregnancy factors other than our therapy. During the evaluation of the clinical effectiveness of treatment and prevention measures, the absence of allergic reactions and the individual intolerance of the drug magnesium were ascertained.

The concentration of magnesium in serum from 12 to 17 mg/l (1-1.4 mEq/l, or 0.5-0.7 mmol/l) indicates a deficiency of magnesium; below 12 mg/l (1 mEq/l, or 0.5 mmol/l) for severe magnesium deficiency.

Analysis of the course of the first half of pregnancy in the surveyed women is presented in table II.

To accept the distribution between the specified checks as conforming to one law, according to the χ^2 -Pearson criterion, it was determined that the practical value of the level $\chi^2_{pr} = 1,327$, and the tabular value at the selection volumes $n = 30$ and the number of degrees of freedom equal to 6, the value of $\chi^2 = 14,1$, at levels significance $p < 0,05$.

Since $\chi^2_{pr} < \chi^2$, the sample data obey one distribution law at a given level of significance. According to Student's t-test, the difference in mean values between the comparison group and the main group is probably not reliable ($t_{pr} = 1,943$, $p > 0,05$).

The criteria for diagnosing the threat of termination of pregnancy were: complaints about the pulling nature of the pain in the abdomen; ultrasound signs of local uterine hypertension, and in the case of abortion, the presence of a retrochoric hematoma, sometimes the attachment of minor blood flow from the genital tract. Hypomagnesemia is an independent and proven risk factor for early preeclampsia. According to our data, early preeclampsia developed in 3 (10.0%) women of the comparison group. A similar pattern was characteristic of other complications of the first half of pregnancy. Thus, anemia (13.3%), respiratory viral infection (10.0%), exacerbation of extragenital pathology (3.3%) were diagnosed in pregnant women more often than in the main group.

The regularities established by us testify to the negative impact of hypomagnesemia on the clinical course

of the first half of gestation, especially regarding the high incidence of non-pregnancy and reproductive losses (Table 2).

While evaluating the course of the first half of pregnancy in women in the main group, there was a tendency to reduce the incidence of complications in pregnant women compared. Thus, the number of cases of threat of abortion was 1.5 times lower; started abortion - 1.5 times and symptoms of early preeclampsia - 1.5 times; anemia of pregnant women – 2 times; adherence of symptoms of respiratory viral infection – 3 times. Important is the fact that there were no reproductive losses in this contingent of women during the first half of pregnancy. The use of therapeutic and prophylactic measures with the use of the drug magnesium reduced the number of bed-days in pregnant women during hospitalization with the threat of abortion to 9.4 ± 1.1 days, and in the manifestations of early preeclampsia – to 7.8 ± 1.2 days. Therefore, in our opinion, reducing the incidence of complications during the first half of pregnancy will contribute to its physiological course in the future and will have a positive effect on the condition of the pregnant, fetus and newborn.

Indicators of blood pressure in the examined pregnant women are presented in table III. Analysis of the level of blood pressure showed that in 12 (40.0%) pregnant women with hypomagnesemia revealed the 1st degree of hypertension. Assessment of the level of blood pressure on the background of therapy with the drug magnesium revealed normalization of indicators, while in pregnant women who did not use there indicators remained significantly higher (table III).

Indicators of carbohydrate and lipid metabolism in the examined pregnant women are presented in table IV.

During the analysis of carbohydrate and lipid metabolism in pregnant women prior to therapy, the level of total cholesterol, β -lipoproteins, triglycerides and LDL was at the upper limit of the reference values. Changes in the lipid spectrum of the blood toward increasing the concentration of total cholesterol in LDL and triglycerides is physiological for pregnancy. However, in the case of pronounced increase in lipids in the blood, the processes of atherogenesis are accelerated, and lipolytic action on insulin receptors increases the insulin resistance that already exists with magnesium deficiency [9,10]. As a result of therapy with magnesium, positive changes in blood lipid spectrum were recorded in pregnant women of the main group, as evidenced a decrease in the level of total cholesterol, β -lipoproteins – by 1.2 times, LDL – by 1.1 times ($p < 0.05$) (table IV).

During an ultrasound examination on the day of hospitalization, it was revealed that fetal OPS (occipital-parietal size) corresponded to the pregnancy period in both study groups.

The main sonographic sign of the threat of pregnancy termination was thickening of the myometrium, which was more often located at the place of attachment of the chorion to the wall of the uterus. Ultrasound in the dynamics was performed in both study groups after 1 week of treatment and before discharge (preferably on day 14). The results obtained are shown in table V.

Table V shows that in the main group significantly earlier there is a decrease in local hypertension, and since the first control ultrasound (a week from the start of treatment). This clinical effect is achieved due to the synergistic effect of the drug magnesium and micronized progesterone on myometrium.

Thus, the use of magnesium in the first half of pregnancy helped reduce the incidence of hypomagnesemia, reduce the number of complications of pregnancy, normalization of carbohydrate and lipid metabolism. The conducted clinical studies revealed no organic and systemic disorders in women.

DISCUSSION

The current situation in Ukraine (martial law, environmental problems, violations of living conditions and food quality) has led to significant changes in the course of pregnancy. Irrational and poor-quality nutrition of a pregnant woman can harm both herself during the period of greatest stress on the body and the fetus. In the future, the refusal of breastfeeding or its impossibility for any reason further increases the negative metabolic changes in the body of a newborn child, which lay the already disturbed foundation of health for the next life.

Nutritional deficiencies do not depend on the season and place of residence, and 70-80% of pregnant women have polyhypovitaminosis [11]. Such a situation should be prevented by determining a woman's micronutrient status even before pregnancy, during the period of pre-gravid preparation, and by correcting it. According to current WHO recommendations, it is mandatory for women to receive iron and folic acid, starting from the stage of preparation for pregnancy and during its entire course. As for other trace elements and vitamins, their use in this contingent of women should be justified by evidence of their deficiency [12].

Calcium (Ca) and vitamin D, as well as iodine, are often lacking today, especially in endemic regions, which requires their appointment in the form of mineral-vitamin complexes or individual trace elements [13].

At the same time, another one of the most important macronutrients — the fourth cation in quantity and the second most physiologically important trace element in the human body after potassium — remains overlooked, namely magnesium (Mg). It acts as a cofactor

Table II. Complications of the first half of pregnancy in the surveyed women

Complication	Comparison group, n=30		Main group, n=30		Statistical analysis	
	abs	%	abs	%	Pearson's Chi2	Significance level
The threat of termination of pregnancy	9	30,0	6	23,3	1,92	0,04
Abortion started	6	20,0	5	16,7	1,95	0,04
Unintended termination of pregnancy	3	10,0	5	16,7	1,96	0,03
Early preeclampsia	3	10,0	3	10,0	1,96	0,03
Anemia of pregnant women	4	13,3	3	10,0	1,97	0,02
Respiratory viral infection	3	10,0	4	13,3	1,97	0,02
Exacerbation of extragenital pathology	2	6,7	3	10,0	1,98	0,01

Note: *-Difference is significant in comparison group ($p < 0,05$).

Table III. Indicators of blood pressure in the examined pregnant women

Indicator	Comparison group, n =30		Main group, n=30		Statistical analysis	
	Before treatment	After treatment	Before treatment	After treatment	Pear-son's Chi ²	Significance level p
Systolic blood pressure, mm Hg.Art.	150,2±1,2	135,5±0,7	145,7±1,8	124,8±0,8	2,83	0,03
Diastolic blood pressure, mm Hg. Art	98,7±0,8	85,7±0,7	91,3±0,4	91,3±0,4	2,69	0,04

Table IV. Indicators of carbohydrate and lipid metabolism in the examined pregnant women

Indicator	Comparison group, n =30		Main group, n=30		Statistical analysis	
	Before treatment	After treatment	Before treatment	After treatment	Pear-son's Chi ²	Significance level p
Glucose, mmol/l	4,3±0,25	4,2±0,24	4,2±0,06	4,1±0,07	1,94	0,03
Total cholest-erol, mmol/l	6,02±0,1	5,97±0,09	6,08±0,09	5,02±0,07	1,94	0,03
β-lipopro-teins, units/l	63,15±0,92*	54,21±0,88	63,13±0,82	50,44±0,62	1,34	0,02
Triglycerides, mmol/l	2,78± 0,02	2,61± 0,03	2,77±0,03	2,26± 0,22	1,97	0,02
LDL, mmol/l	64,81±0,96	60,35±0,72	64,75±0,82	58,10±0,7	1,30	0,04
HDL, mmol/l	1,26±0,05	1,31±0,08	1,25±0,07	1,32±0,05	1,98	0,01

Table V. Ultrasonographic characteristics in the dynamics of treatment

Ultrasonographic characteristics	Comparison group, n =30		Main group, n=30		Statistical analysis	
	One week later	Two weeks later	One week later	Two weeks later	Pear-son's Chi ²	Significance level p
Local hypertonic of the myometri-um	22 (73,3)	7 (23,3)	12 (40,0)	5 (16,7)	1,51	0,03
Structural changes of the cervix uterus	4 (13,3)	1(3,3)	3 (10,0)	1 (3,3)	1,50	0,03

in more than 600 enzymatic reactions and is necessary for the synthesis of nucleic acids and proteins. Magnesium contributes to the formation and hydrolysis of ATP, plays an important role in the processes of glycolysis, in the citrate cycle. With the participation of Mg,

cholinesterase is activated, cholesterol synthesis and esterification takes place, it regulates the secretion of parathyroid hormone and neuromuscular conduction, participates in the functioning of muscle tissue and osteogenesis. At the same time, extracellular Mg affects

the heart rhythm, its deficiency can lead to ventricular tachycardia and sudden death. Hypomagnesemia is often accompanied by increased excitability of the central nervous system, and hypermagnesemia by its depression [14].

The physiological daily need for Mg for adults is 280-300 mg, and during pregnancy and lactation it increases by 20-30% to 340-355 mg.

The main sources of dietary Mg are legumes and cereals, spinach, as well as nuts and chocolate. However, these products also contain a large amount of such elements as Ca, sodium and phosphorus (P), which prevent sufficient absorption of Mg. According to various researchers, Mg deficiency in the population reaches 14.5%, among pregnant women this figure is 16-43% [15].

There are primary and secondary Mg deficiency. Primary, or latent, Mg deficiency is associated with gene mutations that lead to disturbances in its transmembrane exchange. Secondary deficiency of Mg in the body can be caused by various diseases (gastroenteritis, nephrotic syndrome, hypercorticism, etc.), taking drugs (diuretics, cytostatics, estrogen-containing drugs), as well as living conditions (chronic stress, physical overload, hypodynamia, pregnancy and lactation) [16].

It should be noted that many women at the onset of pregnancy already have a certain deficiency of Mg, which is confirmed by research conducted in Germany. Thus, in 56.4% of people aged 14-18 years, in 38.3% - 19-24 years, and in 26.5% - 25-34 years, the level of serum Mg did not meet the recommendations of the German Nutrition Society [17].

Thus, the periods of pregnancy and lactation are recognized as risk factors for the development of hypomagnesemia, since it is at this time that the mother's and the fetus's bodies consume most of the micro- and macroelements, including and Mg. During pregnancy, the need for Mg increases 1.5-2 times, which is largely due to the formation and functioning of the placenta, intrauterine growth and development of the fetus, as well as an increase in estrogen and aldosterone levels [4, 10].

In addition to the needs of the mother and fetus in Mg and its insufficient intake with food, pregnant women have increased excretion of the mineral with urine; according to L. Spätling et al. (2017) — by 20% [11]. This can be explained by a 40% increase in cardiac stroke volume due to pregnancy, which leads to increased renal filtration and inadequate Mg reabsorption [17].

Thus, Mg deficiency in pregnant women can lead to the development of placental dysfunction, pre-eclampsia due to uterine artery spasm, fetal growth retardation syndrome; the relative deficiency of Mg²⁺ ions causes the threat of termination of pregnancy,

the development of a pathological preliminary period, uncoordinated labor activity, a violation of the state of the connective tissue, and the development of isthmic-cervical insufficiency (ICI) [16].

Placental cells contain the maximum number of mitochondria, the deficiency of Mg in which negatively affects their functioning [4, 12]. Thus, it has been proven that hypomagnesemia in the mother leads to impaired placental function and, as a result, fetal growth retardation and fetal distress [13, 14]. Mg deficiency in pregnant women can lead to an increase in intrauterine death of the fetus, a decrease in its body weight and size. Magnesium has an antioxidant effect, activates the production of nitric oxide and prostacyclin, thus preventing the development of vascular endothelium pathology. It is a disaggregant and moderate anticoagulant [17, 18]. Increased urinary Mg excretion during pregnancy can also cause an increase in blood pressure [18].

Modern views on the use of Mg in obstetrics and gynecology practice are based on the need to determine its deficiency at the stage of pre-gravid preparation, correct this deficiency with the help of adequate therapy and continue taking Mg drugs throughout pregnancy, taking into account the multitude of its effects in the body of the woman and the fetus, and as well as its insufficient entry into the body with food products.

Specialists of the German Society for Magnesium Research (Society for Magnesium Research e.V.) recommend the use of Mg preparations throughout pregnancy, as they have a good safety profile, a low frequency of side effects and are economically available [18]. According to them, a pregnant woman should receive Mg in a dose of 240-480 mg (10-20 mmol) daily. Reception should be started as early as possible, continue throughout the entire period of gestation and during lactation. Treatment should not be stopped even before childbirth, since the inhibitory effect of these drugs on the onset of labor is unproven. The only contraindication for taking Mg drugs is severe renal failure [18].

CONCLUSIONS

1. The correction of chronic magnesium deficiency, performed by the drug magnesium has allowed to reduce by 1.5 times the number of cases of threat of abortion, by 1.2 times – the abortion that was started, by 1.5 times – by the symptoms of early preeclampsia, by 2 times – anemia of pregnant women, 3 times – symptoms of respiratory viral infection, 1.5 times to reduce the number of bed-days in the case of hospitalization ($p < 0.05$).

2. The use of magnesium helped to normalize blood pressure, carbohydrate and lipid metabolism.
3. Correction of magnesium deficiency with the drug magnesium antistress in the complex treatment of patients with the risk of pregnancy termination (in combination with the preparations of micronized progesterone) leads to a reliable ($p < 0.05$) faster reduction of local hypertonic of the myometrium.
4. Effective correction of magnesium deficiency during pregnancy is provided by the modern oral magnesium drug, which combines a combination of magnesium citrate with pyridoxine, which has high bioavailability, maximum absorption in the intestines and the passage of magnesium into cells, sufficient efficiency, low reactogenicity, and is completely safe for application in midwifery practice.

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The Authors declare no conflict of interest.

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