Importance and safety of magnesium supplementation in pregnancy. To supplement or not?

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Magnesium (Mg^{2+}) is an essential mineral that participates in different and important biochemical reactions in the maternal body and in the foetus. Magnesium deficiency during pregnancy should not be underestimated. Requirements for magnesium are increased during pregnancy. The hypomagnesaemia observed in animal models provides the ability to evaluate to what extent the deficiency can influence human offspring later in life. This article summarizes the importance of magnesium in pregnancy, changes in magnesium pharmacokinetics, and consequences of maternal and foetal magnesium deficiency. The article aims to answer whether it is necessary to supplement with magnesium during pregnancy and, if so, to what extent.

Key words: magnesium, pregnancy, hypomagnesaemia, maternal magnesium deficiency, foetal hypomagnesaemia.

Význam a bezpečnosť suplementácie magnéziom v období tehotenstva. Suplementovať alebo nie?

Magnézium (Mg^{2+}) je esenciálny minerál, ktorý sa podieľa na rôznych dôležitých biochemických reakciách v tele matky a plodu. Magnéziová deficiencia v tehotenstve by nemala byť podceňovaná. Počas tehotenstva sú zvýšené požiadavky na príjem magnézia. Hypomagneziémia pozorovaná na zvieracích modeloch umožňuje vyhodnotiť, do akej miery môže nedostatok magnézia ovplyvniť zdravie plodu u ľudí neskoršie v živote. Tento článok sumarizuje dôležitosť magnézia v tehotenstve, zmeny vo farmakokinetike magnézia a dôsledky magnéziovej deficiencie u matky a plodu. Cieľom článku je zodpovedať otázku, či je v tehotenstve potrebná suplementácia magnéziom a ak áno, v akom rozsahu.

Kľúčové slová: magnézium, tehotenstvo, hypomagneziémia, deficiencia magnézia u matky, fetálna hypomagneziémia.

Introduction

Magnesium is an essential mineral and, during pregnancy, there is an increased need for magnesium; however, the intake tends to be lower than the recommended daily dose (1, 2). The maternal serum magnesium values during trimesters may fluctuate slightly, with a slightly more significant change observed when approaching the third trimester (3). Serum magnesium levels in the sequence of trimesters slowly decrease, but increase after labour (4). Generally, in most of the population, magnesium is stored in the bones, muscles, and non-muscular soft tissue (5), and the same can be applied to the maternal pregnant body. According to animal data, the foetus is fully dependent on the provision of minerals (6). In human observations, foetal magnesium is received from maternal source by placental transport (7). Some magnesium-rich foods can be beneficial for providing a higher supply of magnesium (8). Moreover, magnesium supplementation during pregnancy may have perinatal benefits (9). A study conducted between

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Ethical principles compliance:
The authors attest that their study was approved by the local Ethical Committee and is in compliance with human studies and animal welfare regulations of the authors' institutions as well as with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly in Helsinki, Finland, in June 1964, with subsequent amendments, as well as with the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, updated in December 2018, including patient consent where appropriate.

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the years 2017 and 2018 found that US women had approximately 22% less dietary intake of magnesium than is the Recommended Dietary Allowance in relation to magnesium intake in pregnancy (10). The concentration of magnesium present in the umbilical cord blood is higher than maternal magnesium levels, the placenta is involved in the active transport of magnesium, and according to Jouanne et al. (2021), 50% of the dietary magnesium is absorbed (4).

Recommended daily dietary allowance for pregnant women

Magnesium is an important cation (11). Magnesium is also available as a supplement (12), while having significant importance as an electrolyte (13, 14) and also being an essential biogenic element (15). *The recommended dietary allowance in pregnancy is* 350 to 400 mg/day (2). It has been estimated that approximately 10% higher supply of magnesium is needed during pregnancy compared to non-pregnant women (2). Pregnant women can find magnesium-rich food in certain vegetables, fruits, (16) and in dairy or some fish products (17). Low levels of magnesium have been linked to various negative health consequences in the general population (18).

Magnesium formulations, types of salts, and their absorption

Magnesium can be present in different pharmaceutical dosage forms (19). There are different organic and inorganic forms of magnesium and their properties (15). **Table 1** shows magnesium forms (20), their bioavailability, and absorption. Bioavailability is influenced by solubility. Convenient solubility at the point of absorption is crucial for good bioavailability (21).

Magnesium as an electrolyte, mechanism and cellular physiology

Electrolyte and fluid balance are of significant importance in preserving homeostasis (23). Electrolytes are necessary for keeping electrical neutrality in the cells (24). Magnesium is part of neurotransmitter activity and provides muscle and neurological functioning (24). Mg^{2+} is a versatile ion present in the main metabolic and biochemical pathways of the cell (25). Magnesium maintains normal cellular and organ functions (8).

Tab. 1. *Overview of organic and inorganic magnesium salts with a focus on their solubility, bioavailability, and other-related information*

Magnesium salts	Type of magnesium salt	Absorption and bioavailability of magnesium salts
magnesium citrate	OS	■ according to a small study, it is among the most bioavailable forms[20] ■ it is well soluble[21] ■ it is absorbed more completely, more bioavailable[22]
magnesium oxide	IS	■ it has lower solubility in GIT and lower bioavailability[21] ■ it is absorbed less completely and less bioavailable[22]
magnesium chloride	IS	■ well absorbed in GIT[20] ■ lower solubility in GIT[21] ■ absorbed more completely, more bioavailable[22]
magnesium lactate	OS	■ easily absorbed in GIT[20] ■ absorbed more completely, more bioavailable[22]
magnesium malate	OS	■ very well absorbed in GIT[20]
magnesium taurate	OS	■ insufficient data
magnesium L-threonate	OS	■ easily absorbed[20]
magnesium sulfate	IS	■ absorbed less completely, less bioavailable[22]
magnesium glycinate	OS	■ easily absorbed[20] ■ good solubility and good bioavailability[21]
magnesium orotate	OS	■ easily absorbed[20] good solubility and bioavailability[21] ■ dihydrate magnesium orotate showed the highest absorption in an *in vitro* simulated small intestinal environment and excellent *in vitro* dissolution parameters[21]
magnesium carbonate	IS	■ lower solubility in GIT and lower bioavailability[21]
magnesium aspartate	OS	■ good solubility and better bioavailability[21]

Note: Insufficient data: more detailed information that could provide a closer explanation in terms of solubility and bioavailability is not available.
IS – inorganic salt, OS – organic salt, GIT – the gastrointestinal tract

Magnesium pharmacokinetics in pregnancy

Magnesium is primarily absorbed in the small intestine (14) and preserved as a bone mineral (5). Absorption can be decreased by nausea and vomiting (26, 27). During pregnancy, gastric pH is increased (26), intestinal motility is lowered, and blood flow in the intestinal area is increased (26). In terms of magnesium distribution, one-third of serum magnesium is bound to albumin in the general population (28), and it can be influenced by other distribution factors (29). Magnesium distribution is available and described in the case of parenterally administered magnesium sulphate in pregnancy (30). However, sufficient information about magnesium pharmacokinetics after oral administration has been available mainly in healthy male adults (31). Magnesium metabolism and balance are dependent on intestinal absorption, bone turnover, and renal excretion (5, 32); intestinal absorption is not dose-dependent, but it is dependent on magnesium status (5). Serum magnesium concentration is affected by renal magnesium reabsorption (32). Pregnancy leads to changes in the hepatic enzyme activities (33). Maternal endocrinological and nutritional status influence changes in bone mineral content (34). For magnesium elimination, the kidneys are the principal organ that influences magnesium homeostasis (35). Progesterone can produce an increase in renal plasma flow and glomerular filtration rate (36). In pregnancy, there is increased renal output of magnesium (37).

Magnesium pharmacodynamics

Magnesium plays a role in hundreds of reactions within the metabolism, as well as in the excitability of cardiac cells, neural activity, neurotransmitter release, muscle contractions, receptor binding, and others; furthermore, it has a role in bone mineralization, in mitochondrial function, and in ATP (adenosine triphosphate) creation (11, 38, 39).

Aetiology of magnesium deficiency in pregnant women

Various factors can contribute to the aetiology of magnesium deficiency besides pregnancy itself. For this purpose, **Table 2** was created. The table does not summarise all possible aetiologies, and the information was derived from magnesium deficiency in the general population or from sources relevant to pregnancy data.

Tab. 2. *Overview of the aetiology of magnesium deficiency in pregnancy or in the preconception period*

Aetiology	General population and pregnant women	Detailed information
genetic aetiology	G	hypercalciuric hypomagnesaemias[40]
	G	Gitelman-like hypomagnesaemias[40]
	G	mitochondrial hypomagneasemias[40]
	G	other genetic hypomagnesaemias[40]
aetiology of use of addictive substances	G	addictive substance use (heroin, morphine, cocaine, nicotine, alcohol, caffeine, or other addictive substances)[41]
nutritional deficiency or overnutrition	G	unmet nutritional or dietary requirements[14]
	G	parenteral nutrition[14, 42]
	P	malnutrition[3]
	G	starvation[42]
	G	diet high in fat or sugar[43]
gastrointestinal aetiology	G	fistulas[14], vomiting[14]
	G, P	diarrhoea[3, 14, 42]
	G, P	malabsorption[3, 14]
	G	acute pancreatitis[14, 42] (Note: can also be classified into section- transfer from the extracellular to the intracellular compartment)
	G	
	G	gastric bypass surgery[42]
	G	liver disorders[43]
renal losses	G	■ familial: genetic aetiology[14]
	G	■ acquired: from therapeutic agents[14]
	G	■ other acquired tubular dysfunctions and diseases[42, 44]
endocrine aetiology	G, P	hypercalcaemia[3, 14, 44] (reduced NaCl reabsorption)
	G	■ primary hyperparathyroidism[44]
	G	■ malignant hypercalcaemia[44]
	G	hyperthyroidism[44]
	G, P	hyperaldosteronism (reduced NaCl reabsorption)[3, 44]
	G, P	osmotic polyuria – poorly controlled diabetes mellitus[3, 44]
transfer from the extracellular to the intracellular compartment	G	treatment of diabetic ketoacidosis with insulin[42]
	G	refeeding syndrome[14, 42, 44]
	G	correction of metabolic acidosis[42, 44]
	G	ethanol withdrawal syndrome[42]
	G	hungry bone syndrome[42] – a state of profound hypocalcaemia[14]
	G	catecholamine excess[44]
	G	significant blood transfusion[44]
use of therapeutic agents	G	proton pump inhibitors[14, 42]
	G	aminoglycoside antibiotics[14, 42, 44]
	G, P	loop and thiazide diuretics[3, 14, 42 ,44]
	G	monoclonal antibodies – cetuximab and others[42]
	G	amphotericin B[14, 42]
	G, P	cytotoxic drugs: cisplatin[3, 14, 42, 44]
	G	certain antitubercular drugs[44]
	G	beta-adrenergic agonists: theophylline, salbutamol[44]
	G	digitalis[42]
	G	antacids[43]
	G	laxatives[43]
pregnancy and puerperal aetiology	P	excessive lactation[3]
other factors	G	stress[45]
	G	sweating[43], exercise[43]
	G	oestrogen therapy[43]
	G	low salt intake[43]
	G	low selenium intake[43]
	G	vitamin B6 deficiency[43]
	G	vitamin D hypervitaminosis or hypovitaminosis[43]

Note: endocrine aetiology can overlap with renal aetiology.
Sign: G indicates that information was mainly retrieved from available information from the general population.
Sign: P indicates causes of hypomagnesaemia relevant to pregnancy data.

Assessment of magnesium status in pregnancy

To evaluate magnesium status, serum magnesium concentration (5) can be used, or other methods such as measuring magnesium concentration in erythrocytes, saliva, and urine. Laboratory tests and clinical assessment are recommended for overall evaluation (22). According to Morton, A., (2018), serum magnesium concentrations in the preconception time range from 0.62 to 0.95 (mmol/l), and in the first, second, and third trimesters, their values are 0.65–0.9 (mmol/l), 0.62–0.9 (mmol/l), and 0.45–0.9 (mmol/l), respectively (3).

Maternal hypomagnesaemia and clinical manifestations

The deficiency, depending on the rate and factors contributing to magnesium loss (11), can manifest as nonspecific (11) and can be similar to other electrolyte imbalances (11), but can also manifest specifically.

Tab. 3. *List of possible consequences of lowered maternal magnesium levels manifested in maternal body systems*

Anatomical maternal body systems	Clinical manifestation	Frequency of clinical manifestations
exocrine or integumentary systems	skin aging[46]	
skeletal system	risk for osteoporosis[14]	
muscular system	muscle spasms and cramps, tingling, numbness[11], tetany[14]	frequently mentioned
nervous system	agitation, change in behaviour, tremor[11], headache[14], depression[5], anxiety[43], vertigo[32, 43], fatigue[14]	frequently mentioned
respiratory system	worsened lung functions in respiratory diseases[11] asthma[32]	
gastrointestinal and excretory systems	change in appetite, nausea[11]	
endocrine system (metabolic)	hypokalaemia[5, 11] and hypocalcaemia[5, 11] altered glucose homeostasis[14]	frequently mentioned (more prevalent in inpatient care)
circulatory and cardiovascular systems	different types of cardiac arrhythmia[11] hypertension[14] ECG changes[5, 11] atherosclerotic vascular disease[32] myocardial infarction[32]	frequently mentioned
immune and lymphatic systems	depressed activity of innate and adaptive immune system[47]	
renal and urinary systems	nephrolithiasis[14]	
reproductive system	narrowing of human uterine arteries[48] may worsen uteroplacental perfusion[48]	

Note: In the case of muscular and nervous systems, the clinical manifestation may overlap between these two anatomical systems.
Frequency was derived from data of non-pregnant patients and can vary from asymptomatic to life-threatening[5, 11, 14, 32].

For this purpose, **Table 3** was developed. The table does not represent all possible clinical manifestations. The frequency of clinical manifestations was derived from the general population of adult patients (5, 11, 14, 32).

Hypermagnesaemia in pregnancy

Hypermagnesaemia belongs to uncommon medical conditions (11), usually having iatrogenic causes. Other causes are worsening kidney function, bowel disorders, and age-related conditions (11). In pregnancy, hypermagnesaemia may occur in pre-eclamptic women after magnesium therapy (2). Overtreatment with magnesium can result in magnesium toxicity (5, 16). Hypermagnesaemia is absent in normal renal magnesium excretory processes (14).

Magnesium use may lower the risk of pregnancy complications

Magnesium therapy with off-label usage is used in adult non-pregnant patients with migraine (38), status asthmaticus (38), and arrhythmias (38). In pregnancy, magnesium can be indicated in the case of eclampsia or preeclampsia (38), where it is capable of preventing seizures or lowering the strength of seizures (38). In a study by Zarean et al. (2017), it was also confirmed that, in the oral magnesium supplement group, there was a decrease in preeclampsia rates (9). Magnesium supplementation can lower the risk of induced high blood pressure (49). The use of magnesium in the setting of preterm labour belongs to off-label indications (38). Magnesium supplementation can be helpful in preventing leg cramps (9) and in women with gestational diabetes mellitus (1).

Foetal hypomagnesaemia and overview of increased risk for foetal complications

A foetus is dependent on maternal magnesium levels (50). **Table 4** describes possible foetal complications that can arise due to lowered maternal magnesium levels or magnesium restrictions. Some of the conditions mentioned in the table are the subject of further research. The summary of foetal complications was obtained from sources describing hypomagnesaemia primarily from animal data, as well as from human data or theoretical data.

Magnesium safety in pregnancy and relationship with pharmaceutical dosage form

Magnesium supplementation seems to be safe for maternal and infant health (55), but patient compliance is required. Severe side effects may occur in patients with renal insufficiency (56). Oral administration of magnesium is recommended as a prophylactic strategy for pregnant patients without clinical symptoms; if clinical symptoms are present, it is advisable to increase the dosing, and the health care professional should consider each patient individually taking into account the cause of deficiency and the health status of the pregnant patient (56). In more severe cases, parenteral administration of magnesium is possible (56). Magnesium sulphate is used in obstetric practice, where the benefits should outweigh the potential risks (54). During $MgSO_4$ therapy, magnesium levels should be carefully checked (56) and safe practice procedures and monitoring should be followed (54, 56). The only indication for intravenous administration of magnesium sulphate in obstetrics is prophylaxis of seizures in pre-eclampsia and eclampsia (56, 57, 58).

The use of magnesium sulphate for inhibition of preterm birth is, according to FDA 2013 (U.S. Food and Drug Administration), off-label usage, and it is not recommended to use magnesium sulphate injection for more than 5–7 days to stop preterm birth (56, 59), because it can cause low calcium levels (59), osteopenia or pathologic fractures in the foetus (56). Parenteral administration of magnesium suphate can contribute to increase in maternal magnesium levels above normative levels, if not monitored, which can possibly lead to neonatal complications (60). The safety of the magnesium unfolds based on oral and parenteral administration during pregnancy. Allen et al. (2023), Calda (2013), and FDA report that magnesium sulphate was changed to safety class D (59) and is not recommended for use in the setting of preterm birth for longer than 5 to 7 days (38, 56). Therefore, there is an

Tab. 4. *Increased risk for foetal complications caused by lowered maternal magnesium levels or due to magnesium restrictions*

Anatomical foetal body systems	Increased risk for foetal complications by magnesium deficiency
exocrine or integumentary systems	insufficient data
skeletal system	insufficient data
muscular system	insufficient data
nervous system	anxiety in the offspring in adulthood[2] decrease in foetal neuroprotection[2, 51] worsened cognitive outcomes[2]
respiratory system	insufficient data
gastrointestinal and excretory systems	insufficient data
endocrine system	IUGR[2]/foetal growth restriction[50] problems in foetal development[2] increase in body fat[2] induced insulin resistance and impaired glucose tolerance[2] small for gestational age[2]/foetal growth retardation[9] lower birth weight[9]
circulatory and cardiovascular systems	foetal anaemia[52]
immune and lymphatic systems	insufficient data
renal and urinary systems	insufficient data
reproductive system	insufficient data
other foetal complications	foetal programming theory of diseases later in life[2] increased risk for metabolic syndrome later in life[2] premature birth[1, 2, 9, 49, 53] epigenetic dysregulation[2] foetal malformation[52] placental dysfunction[9] worsened placental development[50] worsened foetal growth[50] foetal loss[50] increased ROS production between maternal-foetal units[54] indirect decrease in antioxidant defence[54]

Note: Insufficient data: more detailed information that could provide a closer explanation is not available. IUGR (intrauterine growth restriction) and SGA (small for gestational age) pathologies may overlap with those of other conditions that can be influenced by nutrition.[1]

increased risk that intravenous administration can lead to the development of foetal skeletal demineralization and hypocalcaemia which can occur after the fifth day of administration (38, 56). These limitations are not related to the oral form (56).

Recommendations whether to supplement or not

Approximately half of the women in the United Kingdom and the United States of America between 19 and 50 years old do not meet the requirements for magnesium intake (61), and during pregnancy, a 10% higher supply of magnesium is required (2). Normomagnesaemia may not rule out magnesium deficiency (4). Maternal hypomagnesaemia has clinical symptoms, but may also occur without clinical symptoms (56). Oral form of magnesium is safer than parenteral administration, which has limitations and belongs in the hands of healthcare specialists (56). In non-pregnant patients, hypomagnesaemia can manifest with the highest frequency at the cardiovascular level, but symptoms can also be observed in the nervous and muscular systems (5); we suppose this to be similar in the case of pregnant patients. In obstetrics and gynaecology, magnesium is used as a vasodilator and muscle relaxant, and its effect on the cardiovascular system is used to regulate blood pressure and in addition also to lower the levels of prostaglandins (62). However, a study by Makrides et al. (2014), explains that there is not enough high-quality evidence for confirmation that dietary magnesium supplementation during pregnancy is beneficial (63). To sum up, maternal hypomagnesaemia can increase the risk for pregnancy complications and, in certain cases, lead to foetal hypomagnesaemia, which can have a far-reaching impact on the future health of the offspring.

Conclusion

Magnesium has a crucial role in normal cellular and organ functioning and in the metabolic and biochemical pathways of the cells of maternal and foetal organisms. During pregnancy, there is an increased need for magnesium. The maternal serum magnesium values during trimesters may fluctuate slightly, but more significantly so when approaching the third trimester. Maternal hypermagnesaemia during pregnancy is a rather rare medical condition, and maternal hypomagnesaemia can be caused by pregnancy-related or pregnancy-unrelated factors. Lowered maternal magnesium levels or magnesium restriction can lead to foetal complications; however, there is still limited data. If required, magnesium supplementation seems to be safe for maternal and foetal health with appropriately adjusted doses in the form of oral administration. Parenteral magnesium administration belongs in the hands of healthcare specialists and requires careful monitoring.

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