# Drug Interaction with Magnesium in Pregnancy and Delivery

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## Zusammenfassung

Der Nachweis eines positiven Einflusses einer Magnesiumsubstitution während der Schwangerschaft auf Mutter und Kind und die damit notwendig gewordene häufigere Einnahme von Magnesium hat es notwendig werden lassen, nach möglichen Interaktionen zwischen Magnesium und anderen Substanzen, die unter Umständen während der Schwangerschaft und unter der Geburt verabreicht werden, zu fahnden. In der normalen Schwangerschaft behindert die Eisensubstitution nicht die Magnesiumutilisation aus der Nahrung. Ob eine hochdosierte Magnesiumsubstitution mit einer Eisengabe agiert, ist nicht bekannt. Kalzium und Magnesium hemmen kompetitiv ihre Resorption. Erst eine höchstdosierte Einnahme von Vitamin B6 kann den Magnesiumgehalt im Erytrozythen erhöhen. Magnesiumhaltige Antazide können die Resorption von Trimethoprim, Nitrofurantoin, Phenotiaziden und Indometazin hemmen. Die Resorptionsgeschwindigkeit von Digoxin ist verlängert. Aminoglykoside können die nervenblockierende Wirkung hoher Magnesiumkonzentrationen im Serum verstärken. So kann die Gabe von Gentamycin einen Atem- und Kreislaufstillstand hervorrufen. Im Magnesiummangel können Medikamente ihre Wirkungen durch eine Verringerung des physiologischen Kalzium antagonisten Magnesium verstärken. Die Digitalisempfindlichkeit steigt. Unter katecholaminen und Kortikoiden gleichzeitig im Magnesiummangel appliziert sind Herzmuskelnekrosen beschrieben. In der Anästhesiologie ist unter einem hohen Magnesiumserumspiegel eine mögliche Potenzierung der Narkotika zu berücksichtigen. Im Vergleich zum Nutzen einer Magnesiumsubstitution/ Therapie sind besonders im Bereich der Geburtshilfe mögliche negative Medikamenteninteraktionen von untergeordneter Bedeutung.


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## Summary

Evidence for the sulutary effect of magnesium replacement on mother and child during pregnancy has given rise to a more frequent ingestion of magnesium by pregnant women. Thus, studies are needed to determine any possible interactions with drugs that are likely to be administered during pregnancy and delivery. In normal pregnancy, iron replacement does not seem to impair the utilization of magnesium ingested with food. We do not know whether high-dose magnesium substitution interacts with the administration of iron. Calcium and magnesium have been shown to compete for a common absorptive site. Extremely high doses of vitamin $B_6$ may increase red blood cell magnesium. Magnesium containing antacids may interfere with the absorption of trimetoprim, nitrofurantoin, phenothiazines and indomethacin. The absorption rate of digoxin was found to be reduced. Amino glycosides may reinforce the nerve blocking action of high serum magnesium concentrations. In this respect the administration of gentamycin may produce respiratory and cardiac arrest. In the presence of magnesium deficiency, the effects of certain drugs may be potentiated owing to the reduced levels of this physiologic calcium antagonist. This may lead to increased sensitivity to digitalis. In magnesium depletion animals receiving catecholamines and corticoids were found to develop cardiac necrosis. In anaesthesiology the possibility of potentation of the effect of anaesthetics should be considered. On account of the therapeutic benfit derived from magnesium replacement and treatment, particularly in obstetrics, any possible adverse interactions with other drugs seem to be of minor importance.



## Résumé

Comme il existe des arguments plaidant en faveur de l'effet bénéfique (maternel et foetal) d'une supplémentation en magnésium pendant la grossesse, les femmes enceintes prennent aujourd'hui plus souvent du magnésium. Il convient donc de mener des études pour déterminer s'il y a un risque d'interaction avec les médicaments susceptibles d'être prescrits pendant la grossesse et l'accouchement. Pendant la grossesse normale, une supplémentation en fer ne paraît pas entraver l'utilisation du magnésium ingéré avec l'alimentation. Nous ignorons si un traitement substitutif par le magnésium à forte dose interfère avec l'administration de fer. Il est démontré que le calcium et le magnésium entrent en compétition pour occuper les sites de résorption communs. Des doses extrêmement élevées de vitamine $B_6$ peuvent augmenter la teneur des érythrocytes en magnésium. Les antiacides contenant du magnésium peuvent interférer dans la résorption du triméthoprime, de la nitrofurantoïne, des phénothiazines et de l'indométacine. On a montré que le taux de résorption de la digoxine était diminué. Les aminoglycosides peuvent renforcer le blocage nerveux induit par les concentrations sériques élevées de magnésium. C'est pourquoi l'administration de gentamicine peut induire un arrêt respiratoire ou cardiaque. En cas de déficit en magnésium, l'effet de certains médicaments peut être potentialisé étant donné que le magnésium est un inhibiteur calcique physiologique. On peut donc enregistrer une augmentation de la sensibilité aux digitaliques. Chez des animaux carencés en magnésium, les catécholamines et corticoïdes provoquent des nécroses cardiaques. En anesthésiologie, il faut tenir compte du risque de potentialisation de l'effet des anesthésiques. Au regard du bénéfice thérapeutique apporté par les supplémentations ou traitements curatifs par le magnésium, notamment en obstétrique, les éventuelles interactions avec d'autres médicaments paraissent mineures.


# A. Introduction

The administration of magnesium has become increasingly

trics. This is due to the relationship existing between magnesium deficiency and the risk for premature delivery [43]. Recent data collected in a double-blind study show that magnesium replacement during pregnancy reduces the incidence of premature delivery and improves the adapatation of the newborn children. Thus, admission to a neonatal intensive care unit was less often required. Without magnesium replacement, inpatient treatment was necessary twice as often, usually as a result of incompetent cervix and premature labour [46]. Therefore, magnesium replacement throughout pregnancy seems to be highly desirable. Owing to the large number of pregnant women likely to receive magnesium and to the fact that intravenous magnesium injections have been used for a long time in the management of eclampsia, investigations concerning the interactions between magnesium and other compounds employed in pregnancy are required. The number of compounds to be studied is greatly reduced on account of a large number of contraindications and since any medication should be given by strong indications. Drugs likely to interact with magnesium in pregnancy will be discussed in accordance with their range of application: a) normal pregnancy, b) disturbed pregnancy, c) delivery.

# B. Survey

## 1. Normal Pregnancy

### 1.1. Iron

**Iron** obviously is the substance most frequently substituted. Patients have been advised against simultaneous ingestion of iron and magnesium [27]. The question arises whether magnesium competes with other compounds for absorptive sites or whether the dissociated part of the molecule is bound to another substance. This applies above all to the antacids, which are discussed below. In a recent study, no effect of magnesium hydroxide on iron absorption has been noted [34]. Iron replacement does not interfere with the utilization of magnesium ingested with food [40].

### 1.2. Calcium, Potassium, Vitamin $D_3$, Vitamin $B_6$

Iron is often administered together with preparations containing a large number of vitamins, elements and trace elements. In case of concurrent use of **calcium,** the competitive inhibition of magnesium absorption should be taken into account [49–51, 17]. Newest results do not show any influence of magnesium absorption by calcium [47]. The ingestion of large amounts of **potassium** might impair magnesium absorption [23]. **Vitamin $D_3$** increases the magnesium concentration in bone and reduces the serum magnesium levels [1]. Acute hypercalcaemia has been reported after concurrent administration of magnesium and vitamin $D_3$ [5]. Elevated tissue magnesium levels were seen in the experimental animal receiving magnesium in combination with **vitamin $B_6$** [54], while in human subjects suffering from magnesium deficiency, red cell magnesium was found to rise after pyridixine hydrochlorid doses exceeding 1 g daily [20]. Thus concurrent administration of magnesium and vitamin $B_6$ is considered unnecessary.

## 2. Disturbed Pregnancy

### 2.1. Excessive Gastric Acidity

Individuals affected with heartburn often use antacids containing **magnesium hydroxide** or **magnesium trisilicate.** A large number of interactions between these drugs and other compounds have been described. However, owing to the special circumstances prevailing in pregnancy, only some of these compounds has to be discussed. Contrary to former reports, magnesium does not directly interfere with the bioavailability of the histamine receptor blocker **cimetidine** [4, 38]. Magnesium trisilicate impairs the absorption of the anti-infectious agents **nitrofurantoin** [33] and **trimetoprim** [8]. Furthermore, the absorption of **phenothiazine** derivatives is affected by magnesium trisilicate [21]. The questions ar-

Tab. 1: Interaction of ingested drugs with Magnesium in pregnancy

| drug (enteral) | action |
|---|---|
| FE++ | no inhibition of Mg resorption (vice versa) |
| Ca++ | no inhibition of Mg resorption |
| vitamin $B_6$ | 1) Mg in tissue ↗<br>2) only highest doses erythrocytes Mg ↗ |
| vitamin $D_3$ | Mg in bone ↗, Mg in serum ↓ |
| alcohol | Mg excretion ↗ |
| Mg-hydroxid<br>Mg-trisilicate | resorption ↓ of Nitrofurantoin<br>Trimetoprim<br>Phenothiacine<br>Indomethacine<br>prolonged resorption of Digoxin |

ising in connection with iron replacement have been discussed above. There is yet no evidence for an influence of magnesium hydroxide on the amount of **digoxin** being absorbed [11, 30], while the rate of absorption was found to be markedly reduced [3]. The bioavalability of the prostaglandin synthetase inhibitor **indomethacin** has been shown to be greatly reduced [25].

### 2.2. Infection

Gentamycin has been reported to lower the serum concentrations of magnesium, but also those of calcium and potassium [9, 52, 16]. Magnesium reinforces the curare-like effect of amino glycosides [35]. Respiratory and cardiac arrest were seen 90 minutes after the administration of gentacmycin in a newborn whose mother had been treated with magnesium sulfate infusions for toxaemia [31].

### 2.3. Magnesium Deficiency

There is some evidence that pregnancy constitutes a state of magnesium deficiency [45]. As a result, disorders precipitated by magnesium depletion may develop. Less **vitamin $B_1$ (thiamine)** is incorporated into tissue [28, 19]. In most cases, such disorders are due to a deficiency of the physiologic **calcium** antagonist magnesium. Calcium infusions aggravate the signs of magnesium depletion [39]. There is a hypersensitivity to digitalis [41, 53]. Magnesium deficiency leads to myocardial calcium overload [48] which may cause cardiac necrosis in experimental animals receiving **catecholamines** and **corticoids** [14]. Tocolytic treatment with **beta mimetic agents** and induction of the pulmonary maturation of the fetus with corticoids can affect the heart adversily. Thus, women undergoing tocolytic therapy with beta mimetics should be given magnesium supplementation [44]. The pathogenic influence of catecholamines is to be emphasized: Thus, **terbutaline,** a beta mimetic agent, may produce an additional reduction in serum magnesium levels [12]. On the other hand, magnesium was shown to have no effect on **verpamil,** which is sometimes used as calcium antagonist in tocolytic treatments with beta mimetic agent [7]. Furthermore, it should be borne in mind that **alcohol** increases the excretion of magnesium [22]. Alcohol is sometimes employed as tocolytic agent [24]. Magnesium deficiency may also be due to abuse of laxatives [37, 15].

## 3. Delivery

### 3.1. Spontaneous Delivery

Labour during delivery is controlled by endogenous **oxytocin** and **prostaglandins.** The exogenous supply of these compounds should be considered in the presence of poor contractions. Magnesium is required for the myometrial response to oxytocin and the prostaglandins [13]. In vitro studies and animal experiments have shown that rising serum magnesium levels cause a diminished response to oxytocin [6, 55]. Moreover, the in vitro reactivity of smooth muscle to the prostaglandins $F_2$ alpha and $E_2$ was found to be reduced [36]. **Local anaesthetics** are needed for peridural anaesthesia, local infiltration of the pudendal nerve and the perineum. Animal studies have demonstrated that magnesium increases the efficacy of these drugs [2]. A similar effect would be expected in human therapy.

### 3.2. Surgical Delivery

Magnesium infusions are most commonly used in patients at risk of developing eclampsia. In the presence of high serum magnesium concentrations, i.v. infusion of magnesium may have a

Tab. 2: Interaction of parenteral applicated drugs with Magnesium in pregnancy and delivery.

| drug (parenteral) | action |
|---|---|
| Aminoglycoside<br>Gentamycin | "curare"-like action by Mg ↗<br>serum Mg ↓ |
| Terbutalin | serum Mg ↓ |
| Oxytocin<br>PG $F_2$alpha, PG $E_2$ | ↓ under high serum Mg |
| lokal anesthetics | ↗ under high serum Mg |
| Curare<br>Pancuronium | ↗ under high serum Mg |
| Succinyl | no influence of high serum Mg |

Tab. 3: Drug interaction in magnesium deficiency in pregnancy

| drug | action in magnesium deficiency |
|---|---|
| vitamin $B_1$ | ↓ incorporation |
| Ca (iv) | signs of Mg-deficiency ↗ |
| Catecholamines +<br>Corticosteroids | myocardial infarction |

nerve blocking effect. This effect may be potentiated by **curare** [26, 18]. Respiratory arrest was seen in a patient under general anaesthesia [10]. Large amounts of i.v. magnesium sulfate were found to potentiate the effect of **pancuronium** prolonging the neuromuscular blockade [37, 42]. However, elevated serum magnesium concentrations are supposed to have no influence on the features of the nerve blockade caused by succinyl [29].

## 4. Resuming Comment

Three types of treatment should be considered in connection with interactions between magnesium and other drugs:

1. oral administration of magnesium.
2. intravenous infusion of magnesium.
3. drug treatment of magnesium deficiency.

### 4.1. Oral Administration Magnesium

Magnesium absorption as well as the effect of drugs used in pregnancy my be impaired. Whether magnesium supplements interfere with iron absorption (or iron supplements with magnesium absorption) is not settled. The possibility of diminished absorption leading to unexpected underdosage should be considered upon ingestion of magnesium-containing antacids.

### 4.2. Intravenous Infusion of Magnesium

Interactions with elevated serum magnesium levels are most commonly seen in women at risk of developing eclampsia and receiving high-dose magnesium infusions. In such cases, the possible potentiation of the effect of anaesthetics should be taken into account.

### 4.3. Drug Treatment during Magnesium Deficiency

Some drugs were shown to reduce the magnesium content of the tissue. The pathologic effect of other drugs such as catecholamines or digitalis is more prominent in subjects suffering from magnesium deficiency. This is usually due to the absence of this physiologic calcium antagonist. At this point it is well to reemphasize the fact that magnesium deficiency has a wide variety of discorders unrelated to drug interactions. The remarks about increased morbidity of mother and child at the beginning of this paper refer only to a small number of such disorders. The lack of magnesium supplementation during pregnancy can do more harm than unfavourable sequelae of all conceivable drug interactions with magnesium in pregnancy and delivery.

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