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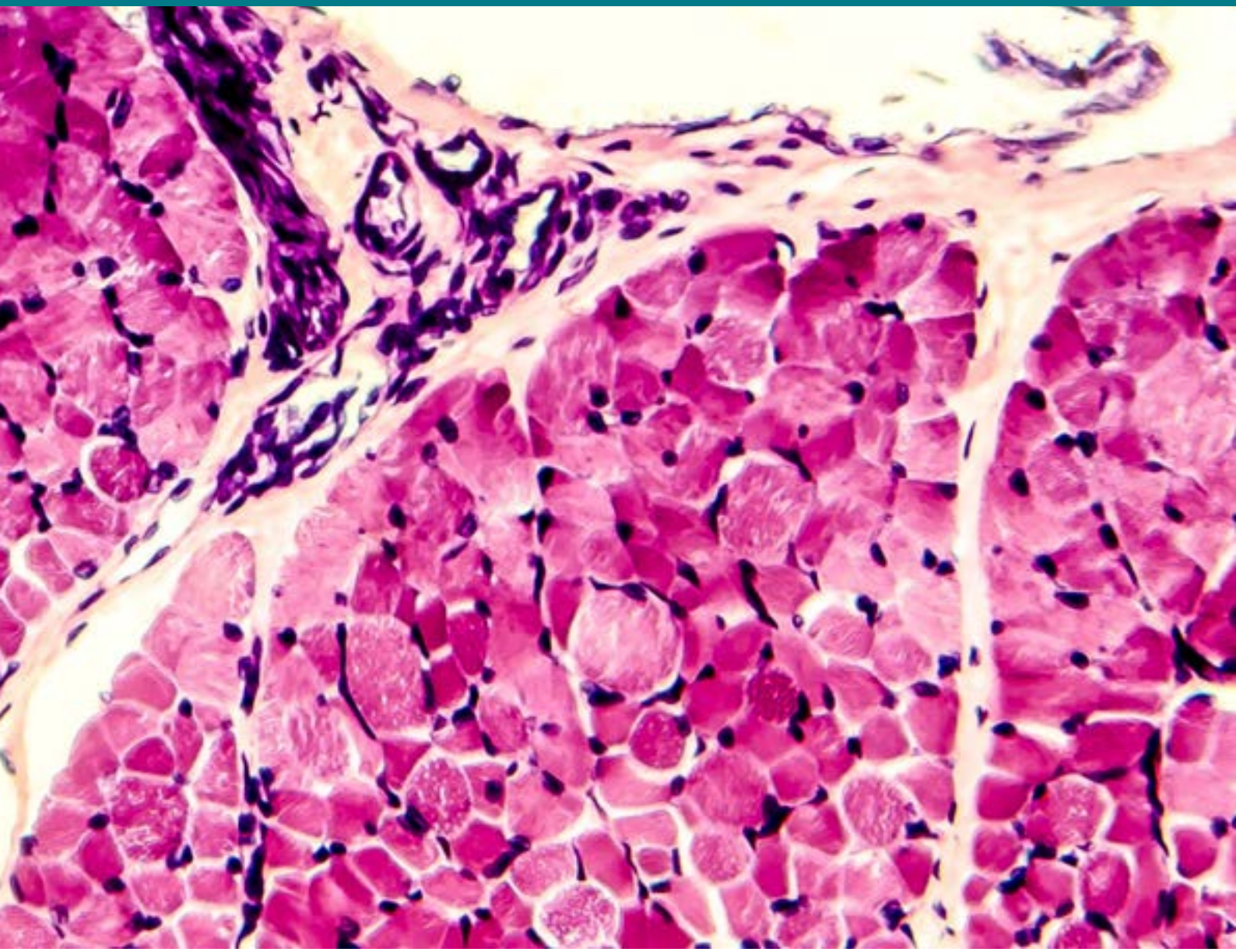

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CAN MAGNESIUM GLUCONATE BE USED AS AN ALTERNATIVE THERAPY FOR PREECLAMPSIA?

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ABSTRACT
Magnesium (Mg^{+2}) in the body plays a structural and regulatory role and it is involved in fundamental cellular reactions. It is known that Mg^{+2} blood levels decrease during pregnancy, which has been related to preeclampsia and premature delivery, as well as other pathologies such as cardiovascular alterations and renal, gastrointestinal, neurological, and muscular dysfunctions among others. Mg^{+2} salts are used to treat its deficiency, and parenteral magnesium sulfate ($MgSO_4$) is relatively effective in preeclampsia and eclampsia. The use of $MgSO_4$ has the main disadvantage that it is mainly administered intravenously which leads to significant toxicity risks. Currently, other magnesium salts are being studied as alternative treatments. Magnesium gluconate (Mg-gluconate) has been used to prevent pregnancy-induced hypertension, showing a greater antioxidant capacity than $MgSO_4$. Mg-gluconate can scavenge hydroxyl and alkoxyl radicals and it has been shown that it can inhibit lipid peroxidation in microsomal membranes treated *in vitro* with the Fenton reaction. Mg-gluconate seems to be an excellent candidate to replace $MgSO_4$ as a therapy for preeclampsia with severe features.
Keywords: Magnesium deficiency, preeclampsia, magnesium sulfate, magnesium gluconate, oxidative stress

RESUMEN
El magnesio (Mg^{+2}) en el organismo, juega un papel estructural y regulador, y participa en reacciones celulares fundamentales. Se sabe que los niveles séricos de Mg^{+2} disminuyen durante el embarazo, lo cual se ha relacionado con la preeclampsia y el parto prematuro, así como con otras patologías como alteraciones cardiovasculares y disfunciones renales, gastrointestinales, neurológicas, musculares, entre otras. Las sales de Mg^{+2} se utilizan para tratar su deficiencia, y el sulfato de magnesio parenteral ($MgSO_4$) ha demostrado ser relativamente eficaz en la preeclampsia y la eclampsia. El uso de $MgSO_4$ tiene el principal inconveniente de que se administra principalmente por vía intravenosa, lo cual conlleva a riesgos importantes de toxicidad. Actualmente, se están estudiando otras sales de magnesio como tratamientos alternativos. El gluconato de magnesio (Mg-gluconato) se ha utilizado para prevenir la hipertensión inducida por el embarazo, mostrando una mayor capacidad antioxidante que el $MgSO_4$. El Mg-gluconato es capaz de eliminar radicales hidroxilo y alcoxilo e inhibir la peroxidación lipídica en membranas microsomales tratadas *in vitro* con la reacción de Fenton. El Mg-gluconato parece ser un excelente candidato para sustituir al $MgSO_4$ como terapia para la preeclampsia con características graves.
Palabras clave: Deficiencia de magnesio, preeclampsia, sulfato de magnesio, gluconato de magnesio, estrés oxidativo.

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Introduction

Magnesium (Mg^{2+}) is the most abundant cation in the body and is the second most abundant cation in the intracellular compartment. The average total Mg^{2+} in the body is approximately 2,000 mEq (about 24 g). It is mostly located in the intracellular compartment (99%), whereas only 1% is found in the extracellular fluid [1]. The average daily intake for an adult is approximately 20 to 30 mEq (240-365 mg) of Mg^{2+} obtained from green vegetables, being necessary to maintain an optimal balance of a daily intake of 0.5 - 0.7 mEq/kg body weight [2].
An important fraction of the intracellular Mg^{2+} is localized in bone, where two compartments have been described: cortical and trabecular. The Mg^{2+} located in bone is potentially mobilizable and exchangeable with serum Mg^{2+} [3]. Inside the cells, most of this ion is bound to chelators, such as citrate, proteins, ADP, ATP, and nucleic acids. Less than 10% is found in free form and is essential for regulating intracellular Mg^{2+} content as well as for metabolic and ion exchange processes [4].
This mineral is essential as it is involved in more than 300 enzymatic reactions, including all phosphate transfer reactions involving adenosine triphosphate and other nucleotide triphosphates [1]. This ion plays an important role as a structural element and regulator of various functions, acting as a cofactor of different enzymatic systems involved in energy metabolism, the synthesis of proteins and nucleic acids, the maintenance of the electrical potential of nervous tissue, muscle, and cell membranes and mitochondrial function [2]. Figure 1 shows a scheme of the main elements that participate in the body distribution and storage of Mg^{2+}.

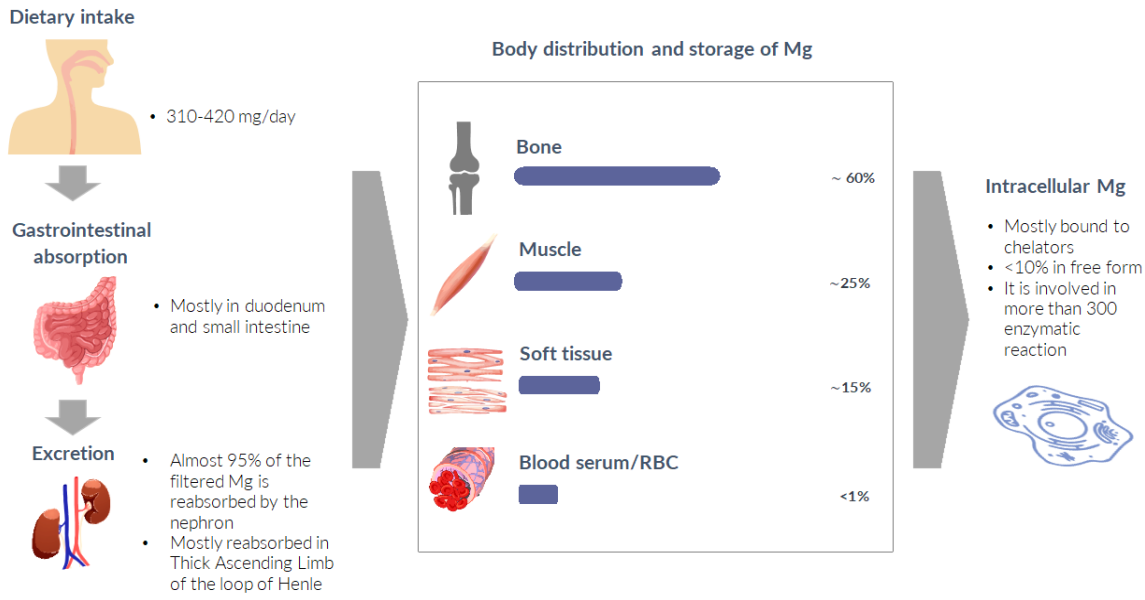

Figure 1. Schematic view of the main elements that participate in the body distribution and storage of Mg^{2+}. The balance of the dietary intake, gastrointestinal absorption, and the renal excretion of Mg^{2+}, allows for controlling the serum Mg^{2+}. In the whole body, most of Mg^{2+} is accumulated in the bone, muscle, and soft tissues. In the blood serum as well as the red blood cells (RBC) there is less than 1% of the total body Mg^{2+}. The intracellular homeostasis of Mg^{2+} is the result of several mechanisms of influx, efflux, and passive movement through Mg^{2+} channels in the cell membrane and mitochondria, as well as interaction with intracellular chelators.

This cation is involved in vascular and cardiac function. At the subcellular level, Mg^{2+} regulates contractile proteins and modulates the membrane transport of Ca^{2+}, Na^{+}, and K^{+}, among others. Experimental and epidemiological results suggest a physiological relationship between Mg^{2+} and blood pressure [5]. It has been shown that at the vascular level, endothelial dysfunction and increased vascular tone leading to elevated blood pressure are associated with a decrease in Mg^{2+} levels [6]. Although the mechanism by which it regulates vascular tone is not well understood, it is proposed

that Mg^{2+} may act as an antagonist of intracellular Ca^{2+} and modulate its vasoconstrictor effect on smooth muscle cells [7]. Likewise, a decrease in Mg^{2+} causes an increase in intracellular Ca^{2+}, which is associated with increased vasoconstriction and vascular tone, also seen in preeclampsia [7,8]. Given the vasodilator property and therapeutic effects of Mg^{2+}, it has been proposed that a deficiency of Mg^{2+} may contribute to the development of vasoconstriction in preeclampsia [9].

Hypomagnesemia, pregnancy, and preeclampsia

Mg^{2+} deficiency (hypomagnesemia) is a relatively common condition. Hypomagnesemia has been reported in 65% of intensive care unit patients [10]. Some chronic diseases, such as arterial hypertension, coronary artery disease, heart failure, hypercholesterolemia, and diabetes mellitus, have been associated with Mg^{2+} deficiency [11]. Increased free radical production has also been reported in rats receiving a Mg^{2+}-deficient diet as compared with animals receiving a normal diet [12].

Several studies have evaluated Mg^{2+} levels in gestation and it is known that a decrease in serum levels occurs during pregnancy. However, gestation is not considered one of the causes of hypomagnesemia [9]. Studies have described low levels of Mg^{2+} in pregnant women both at serum and intracellular levels, but not in hypomagnesemia ranges, and insufficient to reflect disorders in Mg^{2+} metabolism [13,14], although there are reports that indicate that Mg^{2+} deficiency may contribute to the development of preeclampsia [15]. In one study, urinary Mg^{2+} was evaluated as a predictor of preeclampsia, finding hypomagnesemia in 60% of the cases [16]. In 2008, a study by Yamamoto-Seto *et al.* [9] found hypomagnesemia in 37.5% of preeclamptic pregnant women and 5.6% in normal pregnant women.

Mg^{2+} deficiency has been observed to increase the probability of preeclampsia and preterm birth. A study in Nigeria [17] confirmed that serum Mg^{2+} values are reduced during pregnancy [18] and suggested reasons for low Mg^{2+} levels during pregnancy include metabolic increase, physiological hemodilution, and increased parity (in obstetrics, the total number of pregnancies). Previous work has investigated Mg^{2+} levels in pregnancy and found a link between Mg^{2+} depletion and pregnancy-induced hypertension in both humans and animals [17,19]. Enaruna *et al.* [17] found a significant association between low serum Mg^{2+} and preterm delivery. A possible mechanism of action of Mg^{2+} in attenuating preterm labor is by competing with intracellular calcium at its binding sites, thereby decreasing muscle contractility and stabilization of membrane potential [17].

Mg^{2+} deficiency in some cases is treated with parenteral magnesium sulfate ($MgSO_4$), when rapid replacement is necessary, as in eclampsia, arrhythmia, or symptomatic hypomagnesemia [1]. However, its use requires intrahospital treatment because $MgSO_4$ is administered intravenously and its serum levels must be carefully monitored due to a high risk of toxicity.

Despite the current novel therapeutic research, the treatment of preeclampsia has not changed in decades and consists of rest, administration of antihypertensive drugs, in case of preeclampsia with severe features administration of anticonvulsant or antiepileptic agents for the prophylaxis, and prevention of seizures [20]. $MgSO_4$ has been one of the most effective agents in the prevention of eclampsia [21]. Studies have shown that $MgSO_4$ decreases the pulsatility index in uterine, umbilical, and fetal arteries, as well as increases cerebral blood flow, decreases the vascular systemic resistance index, and increases uterine blood flow, among others [22].

Intracellular Ca^{2+} homeostasis, preeclampsia, and Mg^{2+}

Several mechanisms participate in intracellular Ca^{2+} homeostasis: channels, transporters, and exchangers [23]. Together, all these mechanisms end up distributing the excesses in cytoplasmic Ca^{2+} levels, both towards the extracellular space and towards the interior of the organelles [24]. Experimentally, an association between preeclampsia and alterations in Ca^{2+} metabolism has been supported. Our group has demonstrated that during preeclampsia there is a decrease in the activity of plasma membrane Ca^{2+}-ATPase (PMCA) as well as an increase in the levels of lipid peroxidation in red blood cells, myometrium, basal membrane, and placental microvilli from preeclamptic pregnant women [25]. Likewise, placental explants from normal pregnant women incubated under

hypoxia show a diminution of the PMCA activity and a rise in the levels of lipid peroxidation. Both parameters are altered in both basement membranes (BM) and microvillous membranes (MVM) of the syncytiotrophoblast (SCT), mimicking what occurs in both membranes of the SCT of the term human placenta of preeclamptic pregnant women [26].

Kisters *et al.* [13], observed that there are no differences between magnesium concentrations in blood plasma, nor in intracellular magnesium concentration, at least in red blood cells, for normotensive and preeclamptic pregnant women. This group found a lower Mg^{2+} content and a higher Ca^{2+} content in the membranes of the red blood cells of preeclamptic pregnant women compared to the red blood cells of normotensive pregnant women, suggesting that plasma membrane magnesium contents in preeclampsia may contribute to the development of hypertension in pregnancy. Chiarello *et al.* [26] found that, in SCT membranes, an increased Ca^{2+}/Mg^{2+} ratio translates into increased levels of lipid peroxidation, associated with decreased PMCA activity, which is characteristic of preeclampsia. Consequently, a minimum Mg^{2+} content is required to protect membranes and prevent increased membrane lipid peroxidation, which can be achieved with an increase in serum Mg^{2+} levels [26]. These results opened the possibility of establishing a prophylactic therapy with some other Mg^{2+} salt that, unlike $MgSO_4$, can be ingested orally.

Mg-gluconate and pregnancy

By the 1950s the benefits of Mg-gluconate, its lack of toxicity, and better tolerance compared to $MgSO_4$ were already known [27-29]. In a study carried out in the city of Buenos Aires, Argentina, it was demonstrated that the daily use of Mg-gluconate intramuscularly, during one or two months in some cases and doses of 1.25 g/day, did not cause any adverse effects and was efficient in preventing miscarriages or premature deliveries [29]. In this study, the investigators evaluated Mg-gluconate as a prophylactic for spasmodic labor contractions. Analysis of observations made on a group of vagotonic pregnant women treated with this Mg^{2+} salt showed that their deliveries proceeded with normal contractions [29].

Several studies have indicated that the dose for oral administration of Mg-gluconate to act as a tocolytic agent is 1 g every 4 h. These studies indicate that Mg-gluconate administered in this manner appears to be relatively safe and free of adverse side effects, and no cases have been found with symptoms of associated Mg^{2+} systemic toxicity [27,28]. However, the number of clinical cases has not been sufficient to prove the effectiveness of this Mg^{2+} salt as a tocolytic agent.

In 1987, Martin *et al.* conducted [27] a study on tocolysis with oral Mg^{2+}. This group investigated the effect of orally administered Mg-gluconate for tocolysis in patients with arrested uterine activity. In this study, none of the patients developed any symptoms of Mg^{2+} toxicity when Mg-gluconate was administered parenterally or orally. Data from this study revealed that oral Mg-gluconate can be administered to patients after tocolysis with $MgSO_4$ and none of the patients had a recurrent uterine activity or required further parenteral treatment. Subsequently, the same group evaluated the effectiveness of Mg-gluconate compared with ritodrine hydrochloride, which is a β-adrenergic receptor agonist [28]. The results of this study revealed that approximately 80% of patients who received orally administered Mg-gluconate completed 36 weeks of gestation, showing similar results with ritodrine. In this study, 4 patients presented side effects with the use of oral Mg^{2+} (1 patient with nausea and vomiting, 3 patients with diarrhea), but only one patient with severe symptoms had her treatment discontinued. On the other hand, 10 patients treated with ritodrine had side effects and 3 patients in this group had to discontinue treatment, so there was a trend toward more patients having side effects and having their treatment discontinued in the group treated with the β-adrenergic agonist as compared with the group treated with oral Mg^{2+}. These results indicate that orally administered Mg-gluconate is as effective as a β-agonist in preventing recurrent episodes of preterm labor and in continuing gestation to term, in addition to having fewer side effects [28].

In 1992, Martin *et al.* [30] conducted a prospective study to evaluate whether oral Mg^{2+} treatment reduces the incidence of preterm labor and delivery in women at high risk. Fifty-four women at high risk of preterm delivery were selected for this study and were administered 1 g of oral Mg-gluconate

or placebo every 6 h. They found that 4 times daily administration of 1 g of Mg-gluconate did not change the incidence of preterm delivery or low birth weight infants in this group of high-risk pregnant women. Uterine activity was also not affected by this dose of Mg^{2+}, so they concluded that women with risk factors whose serum Mg^{2+} levels did not increase during treatment with oral Mg^{2+} may have an increased risk of preterm delivery [30].
On the other hand, it has been shown that low-dose Mg-gluconate can effectively prevent pregnancy-induced hypertension in high-risk women [31]. In this study, 4% of pregnant women were found to develop pregnancy-induced hypertension, which was substantially lower than the control group (16%).

Mg-gluconate as an antioxidant

Mg-gluconate could be considered an important antioxidant. This salt has ten -OH groups in its two anions. In this regard, a study evaluated the anti-radical potential and cryoprotective effects of Mg-gluconate on microsomal membranes of bovine aortic endothelial cells peroxidized with superoxide anion ($^{\bullet}O_2^-$), and the iron-catalyzed oxy-radical system (R*= dihydroxyfumarate + Fe^{2+}) [32]. Mg-gluconate was found to inhibit lipid peroxidation measured as thiobarbituric acid reactive substances (TBARS) formation in a concentration-dependent manner, with 2.3 mM being the inhibitory concentration (IC50). This study found that pretreatment with 0.25-4 mM Mg-gluconate before R* exposure prevented GSH loss to varying degrees. Mg-gluconate salt and no other salt significantly inhibited the formation of hydroxyl radicals ($^{\bullet}OH$) in a Fenton reaction system consisting of Fe^{2+} + H_2O_2. It was also found that Mg-gluconate inhibits in a dose-dependent manner the iron-catalyzed degradation of deoxyribose, suggesting that this Mg^{2+} salt could displace iron from the "catalytic sites" of oxidative damage. These data suggest that Mg-gluconate may serve as an advantageous Mg^{2+} salt for clinical use because of its additional anti-radical and cryoprotective activities [32].
In a study by Murthi *et al.* [33], the cardioprotective effect of Mg-gluconate, its respective anion, and compared with $MgSO_4$ and its related anion, was evaluated in rat heart stressed by ischemia and reperfusion (I/R) processes. They found that both Mg-gluconate and $MgSO_4$ significantly reduce membrane damage produced by lipid peroxidation. However, Mg-gluconate offered substantially greater protection than $MgSO_4$, which was observed during the first minutes of reperfusion in addition to providing significant protection of coronary flow throughout reperfusion. The data obtained in this work suggest that the protective efficacy of Mg^{2+} varies depending on its salt form. This work represents the first report demonstrating the advantages of using Mg-gluconate over $MgSO_4$ in the I/R model. Data from this study also indicate that the anion gluconate may have antioxidant properties related to the direct removal of the $^{\bullet}OH$ radical rather than the removal of alkoxyl radicals. The likelihood that Mg^{2+} and the anion gluconate separately contributed to an overall additive protective effect was supported by the findings that post-ischemic hearts treated with sodium gluconate (Na-gluconate) exhibited a 25% decrease in alkoxyl production.
The effectiveness of Mg-gluconate as a neuroprotectant in traumatic brain injury (TBI) has also been evaluated [34] and compared with $MgSO_4$. Both Mg^{2+} salts were shown to significantly decrease the acute functional deficit after severe TBI in rats. Although both $MgSO_4$ and Mg-gluconate are equally neuroprotective following TBI, Mg-gluconate alone may be more effective in ischemia-producing conditions if high concentrations of ROS are generated [34].
Mg-gluconate has been shown to have greater therapeutic efficacy than $MgSO_4$ in pathobiological conditions resulting from excessive free radical production *in vivo*, such as myocardial infarction, stroke, organ preservation for transplantation, and other acute I/R injury conditions [34].

Mg-gluconate and preeclampsia

The proposal to use Mg-gluconate as a substitute for $MgSO_4$ requires further studies. In this sense, in our laboratory, we have evaluated the effect of Mg-gluconate treatment using two experimental models. The first consists of using an *in vitro* model with placental explants from normotensive pregnant women, cultured under hypoxic conditions. With this preparation, the levels of lipid

peroxidation of SCT membranes are elevated, while the PMCA activity of these membranes is decreased, which has been found in SCT membranes of preeclamptic pregnant women. The presence of 4 mM Mg-gluconate in the culture medium prevents the alteration of both lipid peroxidation levels and PMCA activity (unpublished data).

Additionally, we have used an animal model of preeclampsia with pregnant rats subjected to saline overload during the last week of gestation. With this animal model, we found that the presence of Mg-gluconate during saline overload prevents: a) the increase in blood pressure, proteinuria, and the level of lipid peroxidation and b) the concomitant decrease in the PMCA activity of their red blood cell membranes, reaching values similar to those of the control pregnant rats [35]. Consequently, treatment of preeclamptic pregnant women with Mg-gluconate could reverse the increased oxidative stress characteristic of this pathology (Figure 2). The possible antioxidant role of Mg-gluconate during preeclampsia in no way excludes that this salt, for example, could be contributing to the stabilization of oxidized plasma membranes, interacting with other cellular components, and participating in the treatment of mitochondrial dysfunction observed in preeclamptic pregnant women.

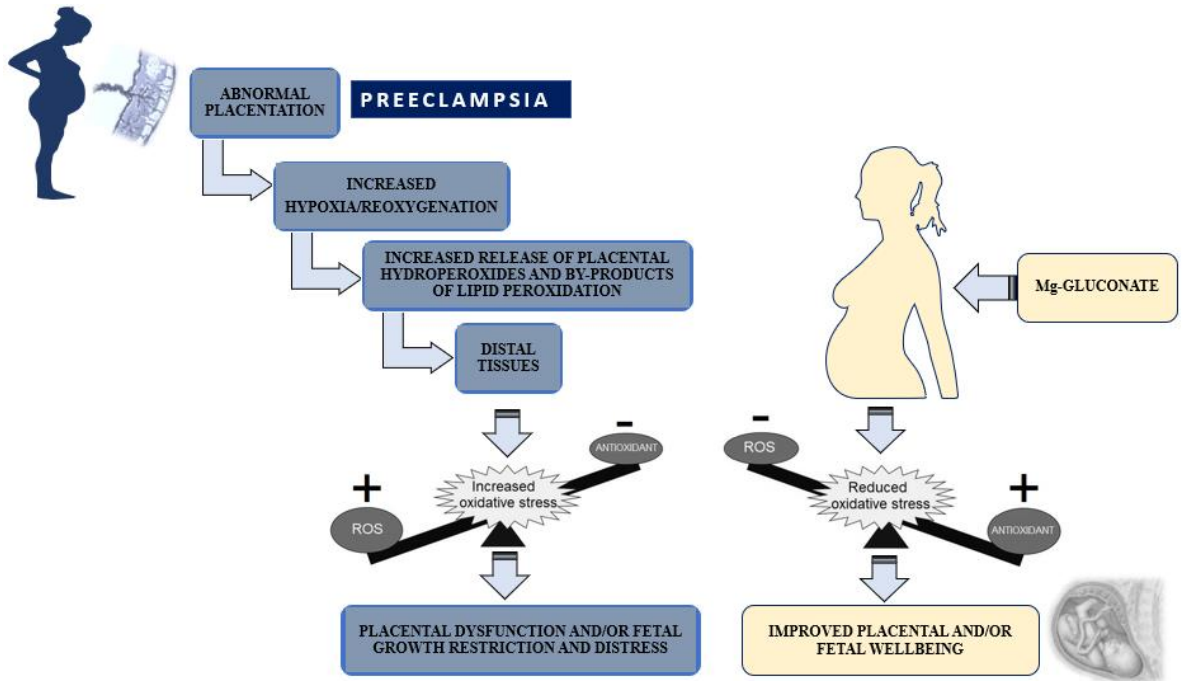

Figure 2. A hypothetical scheme of the possible role of Mg-gluconate as an antioxidant in preeclampsia.

In conclusion, it seems that oral treatment with Mg-gluconate may be an excellent candidate to replace intravenous therapy with $MgSO_4$ in preeclamptic pregnant women.

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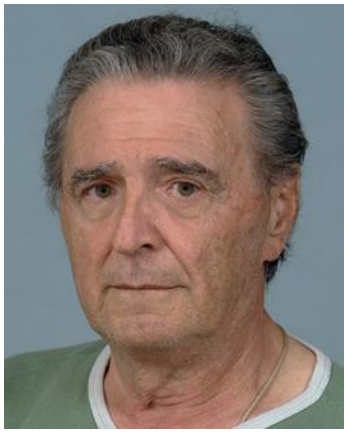

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