

## 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.

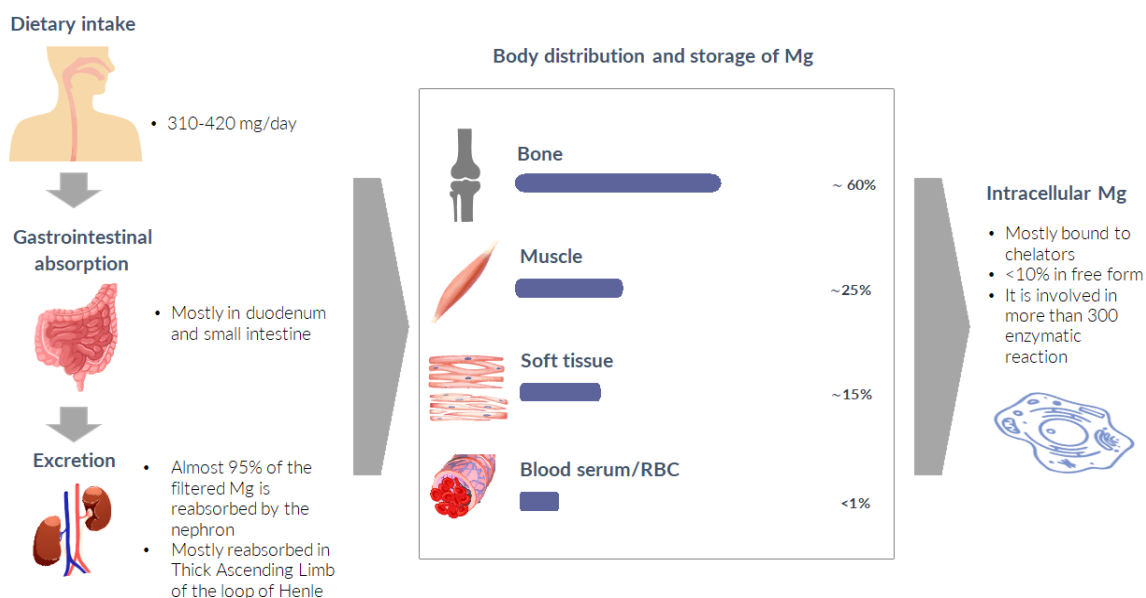
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## Introduction

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  $\beta$ -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  $\beta$ -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  $\beta$ -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 ( $\cdot O_2^-$ ), 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 ( $\cdot OH$ ) 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  $\cdot OH$  radical rather than the removal of alkoxy 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 alkoxy 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].

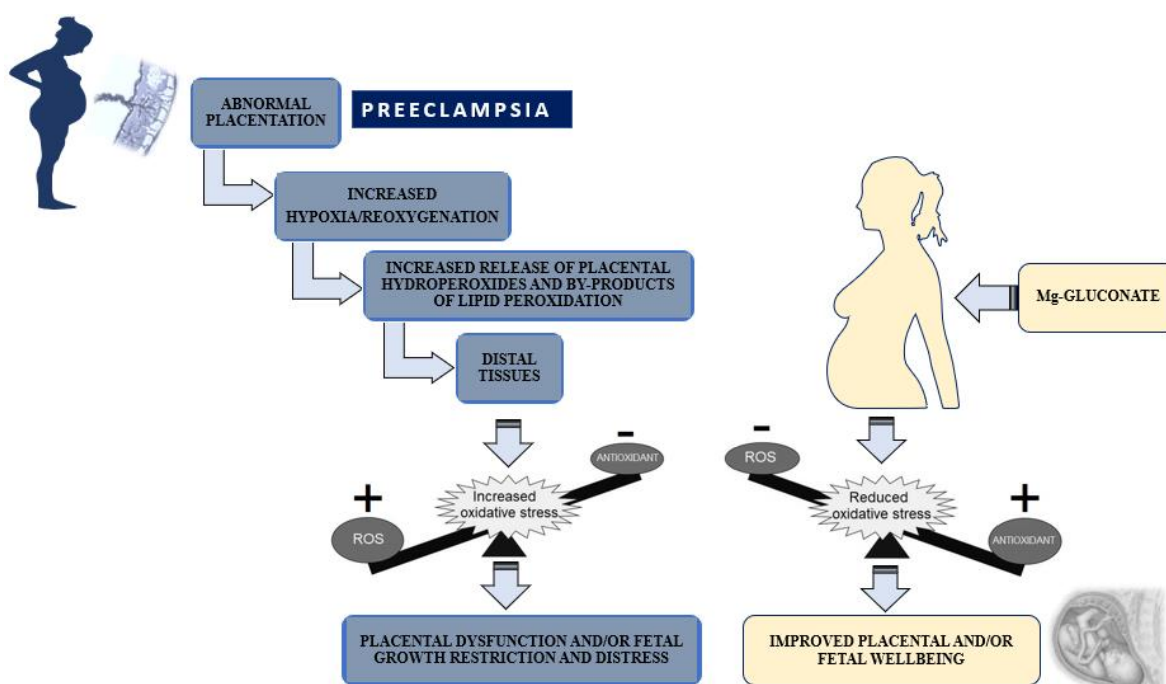
Mg-gluconate has been shown to have greater therapeutic efficacy than  $MgSO_4$  in pathobiological conditions resulting from excessive free radical production *in vivo*, such as myocardial infarction, stroke, organ preservation for transplantation, and other acute I/R injury conditions [34].

### **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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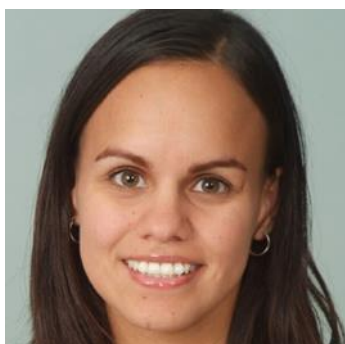
**Ph.D. Heicher Leen Rangel Sánchez.** During her studies at IVIC, she has worked on the study of plasma membrane ATPase activities and their role in health and disease. In the last 10 years, she studied oxidative stress in the human placenta, particularly in pregnant women with preeclampsia, with emphasis on the study of magnesium gluconate as an antioxidant in pregnant women with preeclampsia.



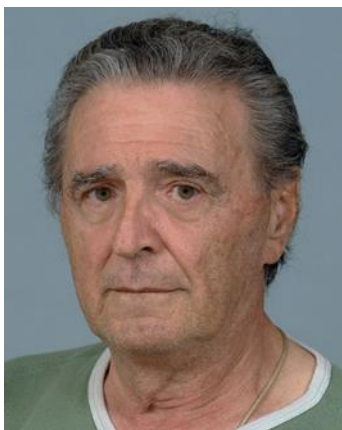
**Ph.D. Cilia Lourdes Abad Marcano** is a Postdoctoral Researcher at the Department of Pharmacology & Toxicology, Pharmacy Faculty, Charles University. As a scientific researcher in Biochemistry and Physiology of Human Reproduction, focused on placenta functions, working in placenta explants and pregnancy diseases on human and non-human models. Experience in oxidative stress, membrane transport, and metabolic pathways. Proven experience in the design and execution of scientific research projects which includes the management and execution of budgets with success.



**Ph.D. Delia Indira Chiarello Peñaranda** is an Assistant Professor at the Faculty of Medicine, Universidad de San Sebastián, Santiago de Chile. She completed postdoctoral studies at the Pontificia Universidad Católica de Chile. Her research experience has focused on the study of the biochemical and cellular aspects related to placental function and maternal-fetal communication, in the context of pregnancy pathologies such as preeclampsia. Currently, Dr. Chiarello's research interest focuses on the vascular and placental effects of air pollution.



**M.Sc. Deliana Valentina Rojas Marcano.** During her studies at IVIC, she has worked on the study of plasma membrane ATPase activities and their role in health and disease. In the last 10 years, she studied an animal model of preeclampsia with pregnant rats under salt overload during the last week of pregnancy. In this model, she has studied the role of magnesium gluconate as possible replacement therapy for preeclampsia.



**Ph. Fulgencio Proverbio.** During his career at IVIC, he was the leader of the team responsible for the study of plasma membrane ATPase activities and their role in health and disease. He conducted several studies on the activity of the Na,K-ATPase in red blood cells in collaboration with Joseph F. Hoffman from Yale University, where he demonstrated the existence of an ATP-membrane pool that is preferentially used by the ATPases than the cytosolic ATP or bulk ATP. He also was the first to describe the phosphorylated intermediate of the Ca-ATPase, as an independent entity from the Na,K-ATPase. He demonstrated that the ouabain-insensitive active transport of Na in the basolateral plasma membranes from proximal tubules is due to the presence of an ouabain-insensitive Na-ATPase. He published over 100 successful manuscripts.



**Ph.D. Reinaldo Luis Marín Hernández.** During his career at IVIC he had worked on the study of plasma membrane ATPase activities and their role in health and disease. In the last 30 years, H studied oxidative stress in the human placenta, particularly in pregnant women with preeclampsia, unraveling the molecular role of magnesium sulfate as an antioxidant and stabilizer of the plasma membrane.