Magnesium and preeclampsia/eclampsia. Monitoring common risks or protection and their role in oxidative damage.

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Short title: Magnesium and their role in oxidative damage

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Abstract: Magnesium sulfate is a widely used therapy in patients with preeclampsia, a hypertensive disorder of pregnancy. The newborn children of mothers, who received parenteral magnesium sulfate during labor state, may exhibit toxicity with serum magnesium levels, and low levels of magnesium are associated with chronic inflammatory stress.
Mg+2concentrations in plasma or serum may be monitored for efficacy and safety or to confirm the diagnosis in potential poisoning victims. The most common symptoms of overdose are nausea, vomiting, and diarrhea; other symptoms include hypotension, confusion, slowed heart and respiratory rate, deficiencies of other minerals, coma, cardiac arrhythmia, and death from cardiac arrest.
Magnesium (Mg+2) and their important interaction with phosphate ions makes magnesium essential to the basic nucleic acid chemistry of all cells of all known living organisms. More than 300 enzymes require magnesium ions for their catalytic action, including all enzymes for synthesis of ATP and that use other nucleotides to synthesize DNA and RNA, which may exhibit oxidative damage or important changes against free radicals.
This paper reviews the possible mechanisms of magnesium and their interactions with free radicals or metabolites involved in pre-eclampsia compared with homeostasis state.

Key words: Magnesium, pre-eclampsia, free radicals, antioxidant.

Magnesium

Magnesium and some nutritional factors during pregnancy are associated with a decreasedlinear growth in utero and childhood [1], the adverse effects of maternal Mg deficiency on fetal weight and placental function, including transport and proliferationmay explain the fetal growth restriction observed with moderate Mg deficiency [2], due low levels of magnesium are associated with chronic inflammatory stress [3].

The interaction between phosphate and magnesium ions makes magnesium essential to the basic nucleic acid chemistry of all cells [4]. More than 300 enzymes require magnesium ions for their catalytic action, including all enzymes that use or synthesizeATP and those that use other nucleotides to synthesize DNA and RNA [5], although magnesium is essential to maintain DNA integrity [6].

Preeclampsia is a pregnancy-specific disorder characterized by development of concurrent hypertension, proteinuria, and placental oxidative stress. Poor placentation, which manifests as preeclampsia and fetal growth restriction, is a major pregnancy complication [7]. During the last trimester of gestation, maternal-to-fetal transport of minerals is dramatically increased and becomes tightly mediated by ion channels that are highly permeable to various divalent cations, such as Ca^{2+}, Mg^{2+}, and Zn^{2+} [8].

Preeclampsia is associated with oxidative stress in the maternal circulation and in utero, this may be an important determinant of mortality and morbidity in preterm infants [9]. This condition decrease magnesium levels and elevates levels of malondialdehyde (marker of lipid peroxidation) [10].

Magnesium sulfate ($MgSO_4$) is the most effective treatment and widely used therapy to prevent the progression of preeclampsia, to eclampsia. Eclampsia, manifested as unexplained seizures and/or coma during pregnancy or postpartum, accounts for ~13% of maternal deaths [11]. In some Countries pre-eclampsia/eclampsia (PE/E) [12], causes an

estimated 21% of maternal deaths annually and contributes to adverse neonatal birth outcomes, and to generalizevascular endothelial damage. In fact platelets are known to be activated in early pregnancy, and also play a pivotal role in the process of inflammation [13].

Chronically low serum magnesium levels are associated with metabolic syndrome and diabetes mellitus type 2 (DM2). It has been documented that patients receiving 250mg of magnesium supplementation among women with Gestational DM had beneficial effects on metabolic status and pregnancy outcomes [14].

Magnesium sulfate administration is recommended for women at high risk of imminent preterm birth before 32 weeks [15]. A 33-year-old woman at 26 weeks of gestation received intravenous magnesium sulfate in Ringer's lactate solution and corticosteroids for preterm uterine contractions without preeclampsia. She developed polyuria of more than 18L in 48 hours; with urine chemistries documenting that magnesium sulfate contributed 30% of the solute in this massive isosthenuric diuresis [16]. The most common symptoms of overdose are nausea, vomiting, and diarrhea; other symptoms include hypotension, confusion, bradycardia and bradypnea, deficiencies of other minerals, coma, cardiac arrhythmia, and death from cardiac arrest. In pregnant women, magnesium sulfate infusions are commonly used for preeclampsia and as a tocolytic agent, although maternal severe adverse effects may occur with all tocolytics [17].

An adequate treatment regimen with MgSO4 leads to a therapeutic level of 2.8 ± 0.6 mmol/L Mg in plasma, which offers neuroprotection by preventing placental ischemia, cerebral edema and reduced levels of cytokines/chemokines in the cerebrospinal fluid [11]. $MgSO_4$also plays a neuroprotective role against eclampsia seizure by reducing

neuroinflammation and brain edema, because inflammation is deleterious to organs with reduced capacity of regeneration.

Peripheral inflammation leads to immune responses in brain characterized by microglial activation, elaboration of proinflammatory cytokines, reactive oxygen species, and secondary neuronal injury. The inducible cyclooxygenase (COX), COX-2, mediates a significant component of this response in brain pathway downstream proinflammatory PG signaling [18]. Shiand col. report that PGE2 EP4 signaling mediates an anti-inflammatory effect in brain byblocking LPS-induced proinflammatory gene expression in mice, and suggest that EP4 selective agonist decreased LPS-induced proinflammatory gene expression in hippocampus and in isolated adult microglia.Pro-inflammatory cytokines (TNF-alpha and IL-1), secretory phospholipase A2 IIA and lipoprotein-PLA2 are implicated in vascular inflammation. These inflammatory responses promote atherosclerotic plaques, formation and release of the blood clot that can induce ischemic stroke. TNF-alpha (TNF-α)and IL-1 alter lipid metabolism and stimulate production of eicosanoids, ceramide, and reactive oxygen species that potentiate CNS injuries and certain neurological disorders [19].Thus, reducing neuroinflammation may be one mechanism by which MgSO4 prevents eclampsia [20]. $MgSO_4$ also inhibit elevated TNF-α mRNA expression induced by lipopolysaccharides (LPS) [21].

Uterine hypoxia has been associated with neuronal damage in the fetal brain, such as nuclear membrane alterations and genomic fragmentation [22]; these can be prevented with the administration of $MgSO_4$. On the other hand, Mg has been correlated with enzyme activity including catalases, glutathione peroxidase. Interleukin-6 and TNF-α are able to increase magnesium and decreases urinary 8-isoprostane, that is the reason why these are considered predictors of preeclampsia [23].

$MgSO_4$ reduces the lipid peroxidation of their red blood cell membranes to normal levels and leads to a significant reduction in the osmotic fragility of the red blood cells that is increased during preeclampsia, probably through interactions with alkyl radicals (R) and halogens (X) [24].Therefore, attack peroxides and generates alcohols or aldehydes (Figure 1).

$$R - X + Mg: \rightarrow R\ Mg\ X$$

$$H - C\ O - OH + R\ Mg\ X \rightarrow R_2OH + Mg\ X]$$

Figure 1. Reactions of magnesium with peroxides

In fact, inducible nitric oxide synthase (iNOS)is the major contributor to initiation/exacerbation of the central nervous system (CNS) inflammatory/degenerative conditions through the production of excessive NO, which generates reactive nitrogen species (RNSs). Activation of iNOS and NO generation has come to be accepted as a marker and therapeutic target in neuroinflammatory conditions such as those observed in ischemia and inherited peroxisome and lysosomal disorders. Inducible nitric oxide synthase (iNOS) is one of three NOS isoforms generating nitric oxide (NO) by the conversion of l-arginine to l-citrulline [25]. NO generated from GSNO acts as second messenger molecular which through S-nitrosylation has been shown to control important cellular processes by regulation of expression/activity of certain proteins such as NF-kappaB.

Glutathione (GSH) micronutrient deficiency during pregnancy is associated with several complications, plasma total glutathione levels (1791 ± 566 vs. 1434 ± 622 µmol/l, p=0.04) of the newborns, whose mothers received multivitamin-mineral were higher than those whose mothers received multivitamin supplements [26]. Although elevated serum heavy metals (cadmium and lead) and reduction of essential micronutrients may contribute to recurrent spontaneous abortion [27]. The reduced levels of trace elements associated with inadequate amount of antioxidant enzymes may be important contributing factor associated with oxidative stress leading to endothelial dysfunction in pre-eclamptic/eclamptic mothers [10]. Micronutrient mineral and vitamin needs are addressed in the context of exposure to oxidative stress and inflammatory disorders, and magnesium facilitates glucose catabolism.

According to this review, adequate supplementation with $MgSO_4$, micronutrients and vitamins, is very important during pregnancy as it helps prevent damage neuronal and cellular in newborns, products of mothers with preeclampsia.

Therefore, magnesium sulphate can prevent some of the adverse neonatal outcomes and it will promote good health.

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