



ORIGINAL ARTICLE

Prenatal treatment with magnesium sulphate: Initial clinical outcomes in pre-term infants less than 29 weeks and correlation with neonatal magnesium levels[☆]



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KEYWORDS

Magnesium sulphate;
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Abstract

Introduction: Antenatal magnesium sulphate (MgSO₄) administration has shown to be effective in minimising cerebral palsy and severe motor dysfunction at the age of 2 years.

The aim of this study is to analyse the initial clinical outcome of preterm neonates less than 29 weeks who have received prenatal MgSO₄, as well as to determine the relationship between the magnesium dose delivered to the mother and the magnesium concentration in the neonates.

Material and methods: A prospective cohort study was conducted on neonates of less than 29 weeks gestation admitted to the Neonatal Intensive Care Unit (NICU) of Hospital Universitario de Vigo from December 2012 to July 2015. Comparative analysis was performed on the perinatal outcomes, neonatal morbidity, mortality, and magnesium levels between the groups of neonates exposed to magnesium sulphate and the control group.

Results: A total of 42 neonates were included in the study. The mothers of 28 of them had received MgSO₄ as a neuroprotective agent.

Statistical significance was obtained in the mortality variable. There were no significant differences in the rest of studied variables. There was a significant correlation between the full dose of MgSO₄ received by the mother and the levels of magnesium in the neonate in the first 24 h of life (r^2 0.436; $P < 0.001$).

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PALABRAS CLAVE

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Conclusions: A lower mortality was observed in the group that had been exposed to MgSO₄. No significant side effects were found as a result of administering of MgSO₄. The MgSO₄ dose received by mother has a linear relationship with the magnesium levels obtained in neonates.

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Terapia prenatal con sulfato de magnesio: evolución clínica de los recién nacidos pretérmino menores de 29 semanas y correlación con la magneemia neonatal

Resumen

Introducción: La administración prenatal de MgSO₄ ha mostrado su eficacia en reducir la parálisis cerebral y la disfunción motora severa a los 2 años de edad.

El objetivo de este trabajo es estudiar la evolución clínica inicial de los neonatos menores de 29 semanas, que han recibido prenatalmente MgSO₄ con indicación neuroprotectora y dilucidar la asociación entre la dosis de magnesio administrada a la madre y las concentraciones de magnesio en suero neonatal.

Material y métodos: Estudio prospectivo de cohortes en el que se incluyó a los neonatos menores de 29 semanas ingresados en la Unidad de Cuidados Intensivos Neonatales del Hospital Universitario de Vigo desde diciembre del 2012 hasta julio del 2015. Análisis comparativo de resultados perinatales, de morbimortalidad neonatal y magneemia entre el grupo expuesto prenatalmente al sulfato de magnesio y un grupo control.

Resultados: Se incluyó a un total de 42 recién nacidos, en 28 de los cuales sus madres habían recibido MgSO₄.

Se encontró significación estadística en la variable mortalidad. No hubo diferencias significativas en el resto de las variables estudiadas. Se obtuvo una correlación significativa entre la dosis total de MgSO₄ recibida por la madre y los niveles de magnesio del recién nacido en las primeras 24 h de vida (r^2 0,436; $p < 0,001$).

Conclusiones: Se ha obtenido una menor mortalidad en el grupo expuesto a MgSO₄. No se han encontrado efectos secundarios significativos derivados de la administración de MgSO₄. La dosis de MgSO₄ recibida por las madres tiene una relación lineal con los niveles de magnesio obtenidos en los recién nacidos.

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Introduction

Although the survival rates of preterm newborns have increased significantly in the past 20 years, the incidence of cerebral palsy (CP) in children has remained stable through time, probably due to the increased survival of extremely preterm NBs and the associated morbidity and neurosensory impairment.^{1,2}

The main risk factor for CP in children is preterm birth, and 35% of cases occur in children born at less than 34 weeks' gestation.³ Cerebral palsy is 70 times more frequent in children born at less than 28 weeks and 40 times more frequent in children born at 28–32 weeks compared to children born to term.^{4–7} The risk is inversely proportional to gestational age.

A Cochrane systematic review⁸ published in 2009 concluded that administration of magnesium sulphate (MgSO₄) to women at risk of preterm birth, regardless of its purpose

or route of administration, significantly reduces the incidence of cerebral palsy and severe motor dysfunction at age 2 years in children born before 32 weeks' gestation.

Two metaanalyses^{9,10} published in 2009 suggest that the number needed to treat to prevent one case of CP is 63 pregnant women.

However, few studies have assessed the initial outcomes of newborns exposed to MgSO₄ before birth or described their clinical course during admission in the neonatal period. Studies in the literature have reported an increased incidence of hypotonia, intubation in the delivery room, a higher need for mechanical ventilation and patent ductus arteriosus, among other respiratory, haemodynamic,¹¹ neurologic and gastrointestinal^{7,12} adverse effects.

On the other hand, there is currently no consensus regarding the dose, standard regimen, therapeutic window and safety of the use of MgSO₄ for neuroprotection. The cumulative dose of magnesium received by the mother that

is safe to the newborn is not known, as its association with the serum levels of magnesium in the newborn has not been sufficiently studied.¹³ Thus, although there is a therapeutic window in which the neuroprotective effects of magnesium are observed, it is known that neonatal morbidity and mortality increase after serum magnesium exceeds certain levels in the newborn.¹⁴

The main aim of our study was to assess the initial clinical outcomes of patients admitted to a tertiary level neonatal intensive care unit (NICU) that received prenatal MgSO₄ for neuroprotection, to analyse the potential side effects of its administration, and last of all to determine the association between the dose of magnesium given to the mother and the serum levels of magnesium in the newborn.

Materials and methods

We conducted a prospective cohort study from December 2012 to July 2015. We included newborns delivered at less than 29 weeks' gestation to mothers that were given MgSO₄ for neuroprotection admitted to the NICU of the Complejo Hospitalario Universitario de Vigo. We compared these preterm newborns to a control group of the same gestational age born during the same period. We excluded newborns with other risk factors leading to immediately poor outcomes, which in our series included one patient with polymalformation syndrome and one that died a few hours after birth following placental abruption. We chose newborns of less than 29 weeks of gestational age because this group is more likely to require advanced resuscitation measures in the delivery room or respiratory support with invasive mechanical ventilation, and is at higher risk of neurological sequelae.^{1,5}

We collected data for the following perinatal variables: gestational age, weight, small for gestational age (defined as birth weight below the 10th percentile), sex, twin pregnancy, caesarean delivery, exposure to prenatal corticosteroids, chorioamnionitis (diagnosed by histological examination), preeclampsia, gestational diabetes and timing of rupture of membranes.

We analysed the need in the first hour of life of advanced or intensive cardiopulmonary resuscitation (CPR) (defined as any of the following: intubation, chest compressions, administration of epinephrine), the Apgar score at 1 and 5 min, and the umbilical artery pH.

We studied a series of haemodynamic, respiratory, neurologic, gastrointestinal, ophthalmologic and infectious variables.

The haemodynamic analysis included the sonographic assessment for patent ductus arteriosus, the need for volume expansion and the administration of inotropic agents for low blood pressure.

To assess the impact of MgSO₄ from a respiratory perspective, we took into account the need for invasive mechanical ventilation, surfactant administration, the total duration of oxygen therapy (in days), the presence of bronchopulmonary dysplasia (BPD) and its severity (based on the definition given by the Standards Committee of the Sociedad Española de Neonatología [Spanish Society of Neonatology], 2013)¹⁵ and administration of intravenous corticosteroids for BPD.

The study of gastrointestinal variables included the presence of necrotising enterocolitis (NEC),¹⁶ the day since birth at which enteral feedings were initiated, and the day when exclusive enteral feeding without need for any type of parenteral supplementation was achieved.

We also analysed neurologic outcomes (development of intraventricular haemorrhage [HIV] and periventricular-leukomalacia), ophthalmologic outcomes (retinopathy of prematurity), infectious outcomes (nosocomial sepsis, defined as elevated acute phase reactants combined with clinical manifestations of sepsis) and mortality.

In our hospital, the MgSO₄ regimen used for neuroprotection is the same that has been used for the treatment of preeclampsia and/or prevention of eclampsia.¹³ Treatment with MgSO₄ is initiated with a loading dose of 4 g delivered over half an hour and continues with infusion of 1 g/hour until delivery. Administration of MgSO₄ should be discontinued if delivery does not occur within 24 h of initiating infusion. If the risk of imminent preterm birth recurs after discontinuation, treatment with MgSO₄ should be resumed. If less than 6 h have elapsed from discontinuation, treatment should resume with the maintenance dose, and otherwise should be reinitiated with a loading dose.

To study the association between the cumulative dose of magnesium received by mothers and the levels of magnesium in the newborn, we measured these levels in the first 24 h from birth in all preterm newborns whose mothers had received MgSO₄ by adding this parameter to blood tests performed for other reasons.

We analysed the data with SPSS version 21. We used the Kolmogorov–Smirnov test to analyse distribution of the variables, and based the analysis of quantitative variables on its results, using Student's *t* test and ANOVA for normally distributed variables and the Mann–Whitney *U* test for nonparametric variables. We analysed differences between nominal variables by means of the chi square test. We conducted linear regression analysis to determine the statistically significant correlations between qualitative variables. We considered differences to be statistically significant when the *p*-value obtained in any of the tests mentioned above was less than 0.05.

Results

The total sample consisted of 42 newborns of less than 29 weeks of gestational age, of whom 28 were exposed to MgSO₄ prenatally, and 14 were not.

Both groups had similar perinatal characteristics, which allowed the comparison of the treatment and control groups. The percentage of caesarean deliveries (85.7%) and twin pregnancies (46.4%) was higher in the group treated with MgSO₄ (Table 1), and these differences were statistically significant.

We did not find any differences in the outcomes of the two groups in terms of need for advanced CPR, Apgar score, umbilical artery pH, respiratory variables, neurologic variables, retinopathy (grade >2), and nosocomial sepsis (Table 2). However, the mortality was greater in the group that was not treated with MgSO₄ (21.4%), a difference that was statistically significant. Furthermore, while the incidence of BPD was similar in both groups, the subset of patients born

Table 1 Perinatal variables.

| | MgSO ₄ | No MgSO ₄ | P |
|--------------------------------------|-------------------|----------------------|-------|
| Frequency (%) | 28 (66.7) | 14 (33.3) | |
| Weight in g (mean ± SD) | 869.68 ± 207.19 | 951.43 ± 244.07 | NS |
| Gestational age in weeks (mean ± SD) | 27.26 ± 1.18 | 26.84 ± 1.93 | NS |
| Male sex (%) | 14 (50) | 8 (57.1) | NS |
| Small for gestational age (%) | 6 (21.4) | 2 (14.3) | NS |
| Prenatal corticosteroids (%) | 28 (100) | 13 (92.9) | NS |
| Chorioamnionitis (%) | 13 (48.1) | 9 (69.2) | NS |
| Preeclampsia (%) | 5 (17.9) | 0 | NS |
| HBP (%) | 2 (7.1) | 0 | NS |
| Twin (%) | 13 (46.4) | 1 (7.1) | 0.016 |
| Caesarean (%) | 24 (85.7) | 7 (50) | 0.022 |
| Gestational diabetes (%) | 2 (7.1) | 3 (21.4) | NS |

HBP, high blood pressure; MgSO₄, prenatal treatment with magnesium sulphate; No MgSO₄, no prenatal treatment with magnesium sulphate; NS, not significant; SD, standard deviation.

before 29 weeks' gestation and not treated with MgSO₄ had a higher incidence of moderate-to-severe BPD (five cases of moderate-severe BPD compared to 2).

All newborns and their mothers were included in the analysis of the association between maternal magnesium dose and neonatal magnesium levels. In the group treated with MgSO₄, the prenatal exposure was of 4 g in

eight newborns, more than 8 g in twelve newborns, and between 4 and 8 g in the rest. The mean cumulative dose of MgSO₄ given to mothers was 10.09 g, with a median of 7.5 g.¹⁴ The mean serum levels of magnesium in exposed newborns was 2.68 mg/dL (median, 2.65 mg/dL), which differed significantly from magnesium levels measured the first day of life in newborns that were not treated with

Table 2 Neonatal outcomes.

| | MgSO ₄ | No MgSO ₄ | P |
|---|-------------------|----------------------|--------|
| Serum magnesium (mg/dL) (mean ± SD) | 2.68 ± 0.10 | 1.89 ± 0.66 | <0.001 |
| Serum calcium (mg/dL) (mean ± SD) | 4.87 ± 0.88 | 5.2 ± 0.98 | NS |
| Advanced CPR (%) | 18 (64.3) | 10 (71.4) | NS |
| Umbilical artery pH (mean ± SD) | 7.27 ± 0.11 | 7.21 ± 0.17 | NS |
| Apgar 1 (mean ± SD) | 7.03 ± 1.15 | 6.36 ± 1.15 | NS |
| Apgar 5 (mean ± SD) | 8.34 ± 0.72 | 8.00 ± 0.88 | NS |
| IMV (%) | 23 (82.1) | 13 (92.9) | NS |
| Surfactant (%) | 23 (82.1) | 12 (85.7) | NS |
| Total days of O ₂ (mean ± SD) | 42.10 ± 21.25 | 47.09 ± 25.50 | NS |
| BPD (%) | 21 (75) | 8 (72.7) | NS |
| Moderate-severe BPD (%) | 2 (9) | 5 (62.5) | 0.007 |
| IV corticosteroids (%) | 6 (20.7) | 0 | NS |
| Inotropes (%) | 15 (53.6) | 9 (64.3) | NS |
| PDA (%) | 12 (42.9) | 7 (50) | NS |
| Initiation enteral nutrition (days) (mean ± SD) | 2.41 ± 0.98 | 3.38 ± 1.80 | NS |
| Full enteral nutrition (days) (mean ± SD) | 20.48 ± 15.55 | 25.09 ± 13.59 | NS |
| Death (%) | 0 | 3 (21.4) | 0.029 |
| IVH (%) | 7 (25) | 6 (42.9) | NS |
| IVH grade III-IV (%) | 5 (17.9) | 5 (35.7) | NS |
| NEC (%) | 5 (17.9) | 4 (30.8) | NS |
| PVL (%) | 4 (14.3) | 0 | NS |
| ROP > 2 (%) | 10 (35.7) | 2 (18.2) | NS |
| Nosocomial sepsis (%) | 17 (60.7) | 8 (61.5) | NS |

BPD, bronchopulmonary dysplasia; CPR, cardiopulmonary resuscitation; IMV, invasive mechanical ventilation; IV, intravenous; IVH, intraventricular haemorrhage; MgSO₄, prenatal treatment with magnesium sulphate; No MgSO₄, no prenatal treatment with magnesium sulphate; NS, not significant; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP > 2, retinopathy of prematurity grade > 2; SD, standard deviation.

Table 3 Mean levels of magnesium, and levels by cumulative maternal dose.

| | MgSO ₄ | No MgSO ₄ | <i>P</i> | |
|---------------------------------|----------------------|-------------------------|----------------------------------|-------------------------|
| Newborns (N) | 28 | 14 | | |
| Mg (mg/dL) (mean ± SD) | 2.68 ± 0.10 | 1.89 ± 0.66 | <0.001 | |
| | No MgSO ₄ | MgSO ₄ ≤ 4 g | MgSO ₄ > 4 g and <8 g | MgSO ₄ ≥ 8 g |
| Newborns (N) | 14 | 8 | 8 | 12 |
| Neonatal Mg (mg/dL) (mean ± SD) | 1.89 ± 0.66 | 2.39 ± 0.13 | 2.40 ± 0.11 | 3.07 ± 0.16 |
| | <i>p</i> = 0.002 | | | |

MgSO₄ (Table 3). We found a statistically significant linear correlation between the MgSO₄ dose received by mothers and the magnesium serum levels measured in newborns in the first 24 h of life ($r^2 = 0.436$; $p < 0.001$). In our series, the highest serum level of magnesium was 4.04 mg/dL and corresponded to a newborn whose mother had received 20 g of MgSO₄.

Using the cumulative dose of magnesium received by the mother and the serum levels of magnesium in the newborn (Table 3), we conducted an analysis to assess the correlation between birth weight and serum magnesium levels, but found no statistically significant differences.

We also compared the levels of magnesium in preterm newborns whose mothers had only received the loading bolus with 4 g of MgSO₄ with the levels in newborns of mothers that were not treated with MgSO₄. The group with mothers that received the loading dose of 4 g of MgSO₄ had a mean serum level of magnesium of 2.39 mg/dL (median, 2.3 mg/dL), while the group that was not exposed to magnesium had a mean serum level of magnesium of 1.89 mg/dL (median, 1.86 mg/dL), a difference that was statistically significant.

Discussion

When it came to the initial outcomes in the delivery room, we found no significant differences in the need for advanced CPR, Apgar score or umbilical artery pH. These results were consistent with those of other cohort studies that already supported the safety of the use of MgSO₄ under these circumstances.¹⁷

From a respiratory perspective, there were no differences in the need for invasive mechanical ventilation, use of surfactant and total days of oxygen therapy, so we could not attribute any respiratory side effects to MgSO₄, contrary to what has been assumed historically, as treatment with MgSO₄ was associated with an increased incidence of respiratory depression.¹⁸ Bronchopulmonary dysplasia was less severe in the treated group.

From a haemodynamic perspective, the absence of adverse effects was also consistent with the finding of other studies, as we did not observe an increased prevalence of patent ductus arteriosus or increased use of inotropic agents.¹⁹ We did not find differences in the remaining outcome variables during the stay in the NICU, and we observed that, at the neurologic level, the incidence of

IVH and leukomalacia were similar in both groups. In this regard, it would be interesting to conduct a long-term followup of these patients to study their psychomotor development. We also found no differences at the gastrointestinal level in either the development of NEC, initiation of enteral nutrition or the number of days post birth at which full enteral nutrition was achieved. Furthermore, we observed similar outcomes in relation to the development of retinopathy of prematurity from an ophthalmologic perspective, and of nosocomial sepsis from an infectious perspective.

We did find differences in mortality in the group treated with MgSO₄. Once again, the small sample size requires that we interpret this result with caution and continue collecting data for future comparisons. We must keep in mind that the Cochrane systematic review of 2009¹³ established that when MgSO₄ was administered for the sole purpose of neuroprotection, there was a reduction in the composite outcome of death and cerebral palsy at age 2 years in exposed children.^{9,20}

It would be worth exploring whether the association of MgSO₄ exposure with a decrease in childhood mortality starts as early as the neonatal period. Other studies in the literature have also found a lower mortality in the group treated with MgSO₄,¹⁷ although its mechanism of action remains unclear. Studies conducted in recent years have found an association between antenatal MgSO₄ and decreased oxygen consumption in the newborn brain, with a decreased cerebral fractional tissue oxygenation extraction (cFTOE).²¹

When it came to the dose of MgSO₄ administered to the mothers, we found a linear correlation between the cumulative dose and magnesium levels in newborns of less than 29 weeks of gestational age in the first 24 h post birth. This finding allows the establishment of safe maternal doses to prevent the development of side effects in preterm newborns.

The mean level of magnesium in the newborns was 2.68 mg/dL, below the 4.5 mg/dL threshold potentially associated with the development of side effects and poor clinical outcomes in the neonatal period.²² It is very likely that the absence of side effects from the use of MgSO₄ in our series was due to the generally low doses administered to the mothers. In the group of exposed children in our study, the highest level of magnesium was 4.04 mg/dL and corresponded to a boy whose mother had received 20 g of MgSO₄. Therefore, we could establish

a safety threshold of 20g for the cumulative dose and 16h of continuous infusion, after which the dose would come dangerously close to levels associated with worse outcomes.

In eight out of the twenty-eight newborns of mothers treated with MgSO₄, the mother was only given the loading bolus with 4g due to the short time elapsed to delivery. Even these newborns had a statistically significant increase in magnesium levels compared to the newborns of mothers that had not received MgSO₄. For this reason, we recommend that at least the loading dose of 4g be given to mothers at risk of giving birth at less than 29 weeks' gestation, even if the birth is imminent.

We also recommend the measurement of magnesium levels in all newborns of mothers treated with MgSO₄ before birth. The reasons for this are, first, the increased mortality detected in association with serum levels of magnesium greater than 4.5 mg/dL²² and, second, the adjustments that need to be made in the composition of the parenteral feeds administered to these newborns in the first days of life until their magnesium levels normalise.

In conclusion, our study found that MgSO₄ was safe at the administered dose, with a linear correlation between serum levels of magnesium in the newborn in the first 24h of life and the cumulative dose of magnesium received by the mother.

Long-term follow-up studies of the patients included in this study are required to assess the impact of MgSO₄ therapy on future neurodevelopmental outcomes.

Conflict of interests

The authors have no conflict of interests to declare.

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References

- Jacobsson B, Hagberg G, Hagberg B, Ladfors L, Niklasson A, Hagberg H. Cerebral palsy in preterm infants: a population-based case-control study of antenatal and intrapartum risk factors. *Acta Paediatr.* 2002;91:946–51.
- Clark SM, Ghulmiyyah LM, Hankins GD. Antenatal antecedents and the impact of obstetric care in the etiology of cerebral palsy. *Clin Obstet Gynecol.* 2008;51:775–86.
- Centers for Disease Control and Prevention (CDC). Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment-United States, 2003. *Morb Mortal Wkly Rep.* 2004;53:57–9.
- Himmelman K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995–1998. *Acta Paediatr.* 2005;94:287–94.
- Van de Bor M, Verloove-Vanhorick SP, Brand R, Keirse MJ, Ruys JH. Incidence and prediction of periventricular-intraventricular hemorrhage in very preterm infants. *J Perinat Med.* 1987;15:333–9.
- Leviton A, Kuban KC, Pagano M, Brown ER, Krishnamoorthy KS, Allred EN. Maternal toxemia and neonatal germinal matrix hemorrhage in intubated infants less than 1751 grams. *Obstet Gynecol.* 1988;72:571–6.
- Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birth weight infants? *Pediatrics.* 1995;95:263–9.
- Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulfate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev.* 2009;1:CD004661.
- Doyle LW, Crowther CA, Middleton P, Marret S. Antenatal magnesium sulfate and neurologic outcome in preterm infants: a systematic review. *Obstet Gynecol.* 2009;113:1327–33.
- Constantine MM, Weiner SJ, Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis. *Obstet Gynecol.* 2009;114:354–64.
- Crowther CA, Hiller JE, Doyle LW, Haslam RR, Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO₄) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA.* 2003;290:2669–76.
- Mittendorf R, Dambrosia J, Pryde PG, Lee K-S, Gianopoulos JG, Besinger RE, et al. Association between the use of antenatal magnesium sulfate in preterm labor and adverse health outcomes in infants. *Am J Obstet Gynecol.* 2002;186:1111–8.
- Bain E, Middleton P, Crowther CA. Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth. *Cochrane Database Systematic Rev.* 2012;2:CD00932.
- McPherson JA, Rouse DJ, Grobman WA, Palatnik A, Stamilio DM. Association of duration of neuroprotective magnesium sulfate infusion with neonatal and maternal outcomes. *Obstet Gynecol.* 2014;124:749–55.
- Sánchez Luna M, Moreno Hernando J, Botet Mussons F, Fernández Lorenzo JR, Herranz Carrillo G, Rite Gracia S, et al., Comisión de Estándares de la Sociedad Española de Neonatología. Displasia broncopulmonar: definiciones y clasificación. *An Pediatr.* 2013;79(262.):e1–6.
- Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am.* 1986;33:179–201.
- Weisz DE, Shivananda S, Asztalos E, Yee W, Synnes A, Lee SK, et al., Canadian Neonatal Network. Intrapartum magnesium sulfate and need for intensive delivery room resuscitation. *Arch Dis Child Fetal Neonatal Ed.* 2015;100: F59–65.
- Magee L, Sawchuck D, Synnes A, von Dadelszen P. Magnesium sulphate for fetal neuroprotection. *J Obstet Gynaecol Can.* 2011;33:516–29.
- De Jesus LC, Sood BG, Shankaran S, Kendrick D, Das A, Bell AF, et al., Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Antenatal magnesium sulfate exposure and acute cardiorespiratory events in preterm infants. *Am J Obstet Gynecol.* 2015;212:4e1–7e.
- American College of Obstetricians and Gynecologists. Committee on Obstetric Practice; Society for Maternal-Fetal Medicine. Committee opinion No 455. Magnesium sulfate

- before anticipated preterm birth for neuroprotection. *Obstet Gynecol.* 2010;115:669–71.
21. Stark Michael J, Hodyl Nicolette A, Andersen Chad C. Effects of antenatal magnesium sulfate treatment for neonatal neuro-protection on cerebral oxygen kinetics. *Pediatr Res.* 2015;78:310–4.
 22. Borja del Rosario P, Basu SK, Haberman S, Bhutada A, Rastogi S. Neonatal serum magnesium concentration are determined by total maternal dose of magnesium sulfate administered for neuroprotection. *J Perinat Med.* 2014;42:207–11.