Sys Rev Pharm 2021;12(1):1624-1629
A multifaceted review journal in the field of pharmacy

Correlation of the Magnesium Serum Levels in Maternal and Fetal over the Fetal Brain-Derived Neurotrophic Factor (BDNF) after Antenatal Magnesium Sulphate ($MgSO_4$) Provision in the Preterm Birth Neuroprotection Strategy

Sri Sulistyowati[1], Muhammad Adrianes Bachnas[2]*, Septiana Ekasari[2], Agung Sari Wijayanti[2]

[1]Departement of Obstetrics and Gynecology, Faculty of Medicine, Sebelas Maret University, Sebelas Maret University Hospital, Surakarta, Indonesia
[2] Departement of Obstetrics and Gynecology, Faculty of Medicine, Sebelas Maret University, Dr. Moewardi General Hospital, Surakarta, Indonesia

ABSTRACT

Background: Cerebral palsy (CP) is one of the most feared poor outcomes in preterm birth. The strategy to decrease CP incidence is by giving antenatal magnesium sulphate (MgSO4) prior to the inevitable preterm delivery. The neuroprotective effects of $MgSO_4$ are driven by the stimulation of magnesium on Brain-Derived Neurotrophic Factor (BDNF) production, which improves neurogenesis and neuronal resilience. The dynamics of magnesium levels in maternal serum and umbilical cord blood with BDNF levels needs further investigation.

Aim: To investigate the correlation between maternal serum and umbilical cord blood magnesium levels over the umbilical cord blood BDNF levels.

Methods: This was a study with a cross-sectional design, involving 72 patients with gestational age 28-34 weeks, who were given $MgSO_4$ with a loading dose of 4 g followed by maintenance 1-2 g/h until birth or for a maximum 24 hour. Samples of maternal blood and premature newborn umbilical cord blood were collected immediately after delivery. The correlation between maternal serum and umbilical cord blood levels of magnesium over BDNF levels were statistically analyzed using the Spearman correlation test.

Results: There was a modest positive correlation between maternal serum magnesium and umbilical cord blood BDNF levels ($r=0.367$, $p<0.05$), and also a weak positive correlation between umbilical cord blood magnesium and BDNF levels ($r=0.269$, $p<0.05$). Other factors that showed to influence the BDNF levels were the total dose of $MgSO_4$ ($p <0,05$) and preeclampsia ($p <0,05$).

Conclusion: The antenatal MgSO4 for neuroprotection strategy in preterm birth gives impact on the increasing production of BDNF via higher maternal and fetal magnesium serum levels, and a higher dose is supposed to give higher production.

Keywords: Antenatal MgSO4, maternal serum magnesium levels, umbilical cord blood magnesium levels, BDNF, prematurity

Correspondence:
Muhammad Adrianes Bachnas
Department of Obstetrics and Gynecology, Faculty of Medicine Sebelas Maret University, Dr. Moewardi Hospital, Surakarta, Indonesia
E-mail: adrianesbachnas@staff.uns.ac.id / adrianesbachnas@yahoo.com

INTRODUCTION

Preterm delivery is known to be the leading cause of neonatal mortality and morbidity. It is estimated that 15 million babies are born prematurely in the world in each year, and this number is increasing rapidly in this decade.[1] Preterm birth is significantly associated with various long-term risks to the neonates, such as neurological deficits, pulmonary dysfunction, ophthalmological abnormalities, and impaired motor and intellectual function. Those are could potentially affect 35% of infants born at 32 weeks of gestational age or less.[2] Long-term problems of prematurity contribute to 40-50% of cases of cerebral palsy (CP), a condition with permanent motor control disorders that is accompanied by disturbances in sensation, perception, cognition, communication, and behavior and is associated with epilepsy.[3,4]

The risk of CP in preterm infants decreases with increasing gestational age, namely 15% at 22-27 weeks, 6.2% at 28-31 weeks, 0.7% at 32-36 weeks, and 0.1% at full-term.[5] This risk reduction is associated with a neurotrophic hormone that is essential for the maturation and protection of brain cells. The neurotrophic protein is produced endogenously in full-term infants but is not being synthesized sufficiently in preterm infants.[6] Antenatal administration of $MgSO_4$ could provide nerve protection by inhibiting calcium receptors, providing a vasodilator effect, inhibiting cerebral ischemia, and decreasing the production of pro-inflammatory cytokines.[7] Antenatal administration of $MgS0_4$ can also increase the synthesis of Brain-Derived Neurotrophic Factor (BDNF), which functions as a brain protector and plays an essential role in neurogenesis.[7,8] BDNF concentrations were found to be lower in preterm infants compared to full-term infants. Under normal conditions, BDNF concentrations in umbilical cord blood would increase its concentration with the increasing of gestational age.[9]

Brain-derived neurotrophic factor (BDNF) is believed to be a neurotrophic protein that provides neuroprotective properties and has an essential role in reducing the risk of CP. BDNF provides neuroprotective effects through anti-inflammatory, anti-apoptotic mechanisms, promotes neural cell regeneration, and protects against periventricular leukomalacia.[10] When inflammation occurs, BDNF promotes microglial proliferation and microglial in vitro phagocytic activities, which will increase the number of phagocytic microglial, and produces BDNF. The hypoxia-ischemic process secretes IL-1β, IL-6, IL-8, dan TNF-α cytokines.[8] BDNF is known to suppress inflammatory cytokines and induce the production of IL-10, which has anti-inflammatory properties and protects neurons in ischemic conditions.[8,10] The mechanism of BDNF as a neuroprotector for prematurity in the hypoxic-ischemic condition is not

precisely known. The administration of magnesium intrauterine stimulates the formation of BDNF. The magnesium ion is competitive with glutamate, causing a bond with the NMDAr receptor, which releases and causes intracellular calcium ion (Ca^{2+}) influx and stimulates BDNF to release from postsynaptic neuron cells (dendrite).[11] Another mechanism explains that magnesium ions in neuron cells or other non-neural cells will activate PI3K (phosphatidyl inositol-3 kinase) pathway that stimulates CREB (cAMP-response-element-binding-protein), which regulates gene expression and expresses proteins involved in neural plasticity, stress resistance, and neuron cell defense.[11,12]

The dose of antenatal magnesium administration is associated with the reduction of the incidence of CP. From a previous study, BDNF levels were found significantly higher in the MgSO4 group 1-2 g/h than those given only the initial 4 g bolus.[13] We also found that the increase in magnesium levels is positively correlated with the dose and duration of antenatal magnesium administration.[14–17] Current knowledge about magnesium disposition in pregnant women after administration of $MgSO_4$ therapeutic protocols is limited to the therapeutic levels of magnesium needed to prevent seizures and the safe levels of magnesium from its toxicity. Although the previous study has explained that $MgSO_4$ administration impacted the increasing of BDNF levels,[8] no study demonstrates the interaction of maternal serum and umbilical cord blood magnesium levels to BDNF levels. The correlation between magnesium levels in maternal serum and umbilical cord blood to BDNF levels in premature infants is still unknown, and similar studies have not been established yet.

SUBJECTS AND METHODS

Subjects

All samples were taken from the maternal ward and delivery room at Dr. Moewardi General Hospital, Surakarta, from July 2020 to November 2020, which met the inclusion and exclusion criteria and agreed to participate in this research. This study has received approval from the Ethics Committee of Dr. Moewardi General Hospital, Surakarta (No 1.046/ IX/HREC/2020 and No 1.229/IX/HREC/2020).

The subjects of the study were patients in the maternal ward or delivery room at Dr. Moewardi General Hospital, Surakarta, with inevitable preterm labor who have agreed with consent and met the inclusion/ exclusion criteria.

The inclusion criteria of this study are women aged 20-35 years, 28-34 weeks of gestation, in a threatened labor phase, or pregnancy termination for medical reasons. The exclusion criteria of this study are multiple pregnancies, intrauterine fetal death, a fetus with major and minor congenital abnormalities, pregnancies with severe renal insufficiency, and the patients who refused to attend the study. The patients received the initial dose of $MgSO_4$ 4 g followed by 1-2 g/h until birth or for maximum 24 h. By the statistical inquiry the minimum sample needed was 72 patients.

METHODS

This research was a quantitative analytic study using a cross-sectional design on a clinical test of maternal serum magnesium levels, umbilical cord blood magnesium levels, and umbilical cord blood BDNF levels in premature infants. This research was conducted from July to November 2020 at the maternity ward and delivery room of Moewardi Hospital Surakarta.

Maternal serum of magnesium levels was analyzed from ± 5 cc of maternal blood. Magnesium and BDNF levels were analyzed from ± 5 cc umbilical cord blood of a premature fetus, taken immediately after birth. Blood samples were centrifuged for 15 minutes at a speed of 3000 RPM, and then the samples were stored at 4^0C temperature within 24 hours from the time of sampling. BDNF levels detection test used enzymes to detect the presence of a ligand (protein) in a fluid sample using one or a pair of antibodies, with Quantikine Human BDNF Free Immunoassay reagent (R and D systems). The BDNF levels were measured by the ELISA method.

The data were analyzed using SPSS statistical application version 25. This research examined the correlation between maternal serum magnesium levels and umbilical cord blood BDNF levels using the Spearman correlation test. The correlation between magnesium levels of the umbilical cord and BDNF levels were analyzed with the Spearman correlation test. A p-value <0.05 was considered statistically significant, with a 95% confidence interval.

RESULTS

In this study, a total of 72 patients met the inclusion and exclusion criteria as research subjects. The research subjects experienced preterm labor and had been given the neuroprotector $MgSO_4$ with various doses. Characteristics data of the issues are presented in Table 1. The patient's mean age in this study was 29,83±5,24 years, with the average body weight being 64,26±7,67 kg. The mean gestational age of patients in this study were 32,15±2,01 weeks. The mean interval time between initial MgSO4 administration to birth was 16,71±9,30 h. All patients received corticosteroid therapy as a mandatory protocol for lung maturation in preterm birth have been give the mean dose of 14,03±5,91 g dexamethasone. The mean total dose of $MgSO_4$ administered was 19,72±13,28 g. The mean maternal magnesium levels were 3,02±1,02 mg/dl, while the mean umbilical cord magnesium levels were 3,16±0,93 mg/dl. The mean umbilical cord BDNF levels of the subjects were 11674,58±5074,74 pg/ml. The mean birth weight was 1696,81±423,98 g.

Factors affecting maternal serum magnesium levels and umbilical cord blood magnesium levels are presented in Table 2. Table 3 showed the correlation between maternal magnesium blood levels and umbilical cord blood magnesium levels, which gave a strong positive correlation (p< 0.05; r=0.753).

Table 4 showed the results of the Spearman correlation analysis. The table consists of the correlation coefficient, the p-value Sig. (2-tailed), and the number of subjects (N). The Spearman correlation test was used to evaluate the correlation of maternal serum magnesium levels and umbilical cord blood magnesium levels to umbilical cord blood BDNF levels. The results showed there was a modest positive correlation between maternal serum magnesium levels to umbilical cord blood BDNF levels (p <0.05; r=0.367), and week positive correlation between umbilical cord blood magnesium levels to umbilical cord blood BDNF levels (p< 0.05; r=0.269). The positive correlation coefficient suggests that the increasing maternal magnesium blood levels and umbilical cord magnesium levels will result in increasing BDNF levels. The magnesium serum levels were shown also to be affected

by the total dose of MgSO4 given (p=0.000 on maternal blood and p=0.012 on umbilical cord blood), as seen on the table 2. This suggested that higher dose of magnesium sulphate is needed to drive higher production of BDNF.
In our study, we did not aim to evaluate maternal and neonatal side effect with the administration of MgSO4. However, we did not receive any maternal and neonatal side effect report that is correlated with antenatal magnesium administration.

Table 1: Research subject characteristic

Variable	Mean ± SD
Maternal age (years)	29,83±5,24
Maternal weight (kg)	64,26±7,67
Gestational age (weeks)	32,15±2,01
Interval of termination (days)	16,71±9,30
Corticosteroid administration (mg)	14,03±5,91
Total dose of $MgSO_4$ (mg)	19,72±13,28
Maternal serum magnesium levels (mg/dl)	3,02±1.02
Umbilical cord magnesium levels (mg/dl)	3,16±0,93
BDNF levels (pg/ml)	11674,58±5074,74
Birth weight (g)	1696,81±423,98

Table 2 : Factors affecting maternal and umbilical cord magnesium levels.

Variable	Maternal serum magnesium levels	Umbilical cord magnesium levels
	(p value)	(p value)
Total dose of MgSO4 (mg)[a]	0.000[d]	0.012[d]
Gestational age (weeks)[a]	0.694[e]	0.537[e]
Birth weight (g)[b]	0.554[e]	0.293[e]
Preeclampsia[c]	0.008[d]	0.012[d]

[a] Statistical test : Spearman correlation test
[b] Statistical test : Pearson correlation test
[c] Statistical test : Independent t-test
[d] Statistically significant result (p< 0.05)
[e] Statistically insignificant result (p> 0.05)

Table 3 : The correlation between maternal magnesium levels and umbilical cord magnesium levels

		Umbilical cord magnesium levels (pg/ml)	
Correlation test Spearman's rho	**Maternal magnesium levels (mg/dl)**	Correlation Coefficient	0,753
		Sig. (2-tailed)	0.000[d]
		N	72

[d] Statistically significant result (p< 0.05).

DISCUSSION

Several studies had shown that $MgSO_4$ administration was proved to reduce the incidence of cerebral palsy (CP), where the reduced risk of CP in premature infants is associated with increased BDNF levels achieved as one of the expected effects after $MgSO_4$ administration.[8,18]
Our study shows a positive correlation with a significant relationship between maternal serum magnesium levels and umbilical cord BDNF levels (p<0.05). The study is in line with a previous study shown that $MgSO_4$ administration would increase magnesium levels, which would trigger an increase in BDNF levels in preterm infants.[8] The Spearman analysis between umbilical cord magnesium levels and umbilical cord BDNF levels shows a positive correlation, in which an increase of umbilical cord magnesium levels will increase the BDNF levels significantly (p<0.05). In previous studies, antenatal administration of $MgSO_4$ as a neuroprotectant had a significant correlation with the increase in BDNF, notably in the 28-50 g dose group.[13]
Several factors were analyzed concerning the effect of maternal serum magnesium levels. After birth, some factors play a role in serum magnesium concentrations during the first days of life.[15,17] The total dose of MgS04 and the incidence of preeclampsia were factors that influenced the maternal serum magnesium levels and umbilical cord magnesium levels in this study. The factors have been described in Table 2. The total dose of magnesium sulphate will affect magnesium levels in maternal blood serum. The greater the quantity given, the greater the maternal blood magnesium level achieved. Intravenous loading dose between 4 and 6 g was associated with a doubling of this baseline concentration half an hour after the injection. The maintenance infusion of 1 g/hr consistently produced concentrations below 2 mmol/l. The maintenance infusion at 2 g/hr and the Pritchard intramuscular regimen had a higher but inconsistent probability of making concentrations between 2 and 3 mmol/l.[19] The fetal serum magnesium concentration will increase within one hour after MgSO4 administration and accumulate in amniotic fluid 3 hours after MgSO4 exposure through fetal urine excretion on MgSO4 tocolytic administration.[20] Maternal serum magnesium will cross the placenta and be involved in many intracellular processes, causing several responses such as cerebral vasodilation effects, reduction of inflammatory cytokines, and inhibition of the entry of calcium in cells, which will have an impact on increasing BDNF.[7] This is in line with this study that there was a significant correlation between maternal serum magnesium levels and umbilical cord magnesium levels when administering MgSO4 as a neuroprotector (p<0.001), which was followed by an increase in umbilical cord BDNF levels.
A study in 2014 described a statistically significant positive correlation between the total dose of MgS04 administration and neonatal serum magnesium concentration [r=0.55, (p<0,0001) and r=0.35, (p<0,0001), respectively]. Neonatal serum magnesium concentrations were associated with the total dose of magnesium administered to the mother, and this correlation remained significant when magnesium was administered for a longer time. However, there was no statistically significant correlation between the total dose of $MgSO_4$ administration on maternal serum magnesium levels [r=0,004, (p=0,98) and r=0,14, (p=0,21)].[15]

Table 4 : The correlation of maternal and umbilical cord magnesium levels to umbilical cord BDNF levels

			Umbilical cord BDNF (pg/ml)
Correlation test Spearman's rho	**Maternal magnesium (mg/dl)**	Correlation Coefficient	0,367
		Sig. (2-tailed)	0.002[d]
		N	72
	Umbilical cord magnesium (mg/dl)	Correlation Coefficient	0,269
		Sig. (2-tailed)	0.022[d]
		N	72

[d] Statistically significant result (p< 0.05).

There was a significant difference in maternal blood magnesium levels in patients with preeclampsia and without preeclampsia. This is associated with conditions that occur in preeclampsia, which affect drug pharmacokinetics. Endothelial dysfunction involves organ dysfunction; one of them is the kidney. It will have an impact on the leakage of albumin filtration and decrease renal clearance, which results in total protein, albumin, and creatinine levels in the body. It can also affect the process of drug transport and elimination.[21] Moreover, the increase of extracellular fluid in preeclampsia-eclampsia will affect the distribution volume of magnesium, resulting in higher serum magnesium levels in preeclampsia patients.[22] This is in line with this study that the mean maternal magnesium levels and umbilical cord blood magnesium levels in the preeclampsia patients give higher levels than in the non-preeclampsia patients (respectively, p = 0.08; p = 0.012). Linear regression analysis in a 2017 study also found that high neonatal magnesium concentrations were not only related to maternal magnesium levels but also maternal preeclampsia.[16]

Our study also shows a significant correlation between maternal magnesium and umbilical cord magnesium levels (p<0,05). This finding indicates that maternal magnesium can cross the placental blood barrier and the umbilical cord magnesium levels at birth correlate with maternal magnesium levels. These results are consistent with previous studies that found a positive correlation between maternal magnesium levels and neonatal magnesium levels.[16,23]

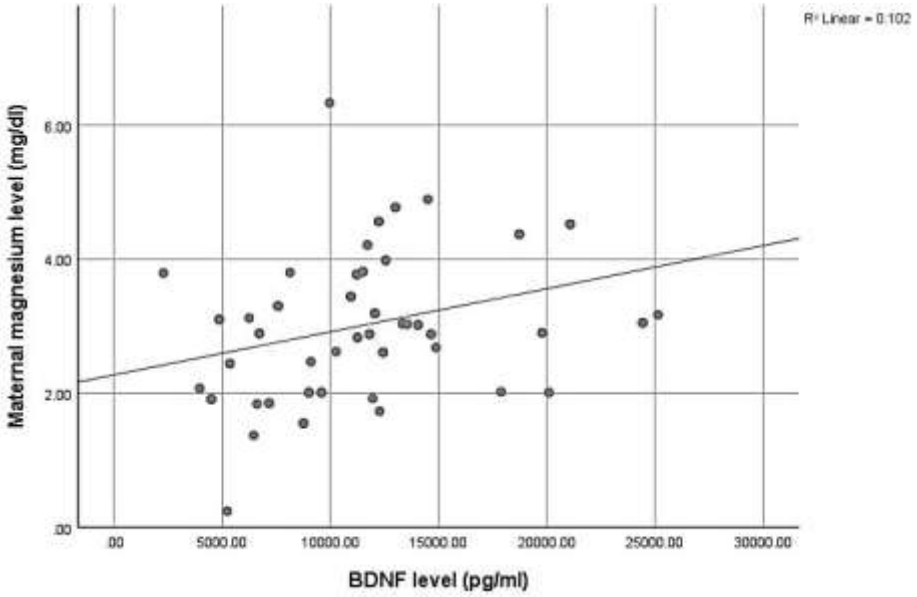

Figure 1 : Analysis correlation between maternal serum magnesium levels and BDNF levels

It is still necessary to evaluate the correlation between the total dose of $MgSO_4$ administration on the umbilical cord magnesium level. It is also essential to understand that there are direct adverse effects associated with neonatal serum magnesium concentrations or the toxicity of magnesium to infants, such as the presence of brain lesions and even death.[24] A study in 2012 reported that there was an increased incidence of intubation, broncho-pulmonary dysplasia, patent ductus arteriosus, and retinopathy of prematurity, which was associated with neonatal magnesium concentrations of >4,5 mEq/L, with a significant incidence of mortality compared to lower serum magnesium levels.[25]

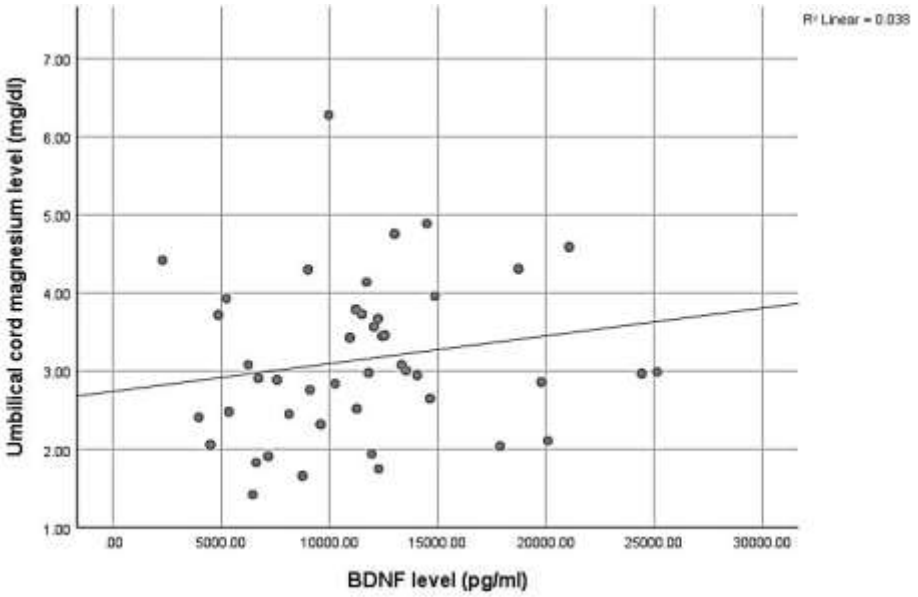

Figure 2 : Analysis correlation between umbilical cord magnesium levels and BDNF levels

In this study, the mean magnesium levels of the umbilical cord were 3.51±0.92 mg/dl, which still below the range of magnesium toxicity levels in neonates studied in previous studies. This finding suggests that it is essential to keep neonatal serum magnesium levels within the therapeutic range despite the need to increase the higher BDNF production by giving higher dose of antenatal magnesium sulphate.[26]

LIMITATIONS OF RESEARCH

This study only assessed the final results of maternal serum magnesium levels and umbilical cord BDNF levels achieved at the termination of pregnancy. Still, the study did not periodically evaluate the BDNF levels at the time of evaluation of $MgSO_4$ administration, so it might not describe time-by-time dynamics of magnesium effect on fetal BDNF.

This study also analyzed only the relationship between maternal serum magnesium levels and umbilical cord BDNF levels. It did not observe the effect of maternal BDNF levels on umbilical cord blood BDNF levels as a response to $MgSO_4$ administration. So, it could not evaluate whether the increase in cord blood BDNF levels occurred as a direct response to the rise of cord blood magnesium levels on the fetus or as a result of the rise on maternal BDNF levels after the $MgSO_4$ administration in the maternal circulation, which will be transported into the fetal umbilical cord.

Further research with larger number of subjects and multi-center basis is needed to maximize the potential variety of individual characteristics and broader parameters. We also recommend further research on the correlation of umbilical cord BDNF levels through the short and long-term effects of neonates.

CONCLUSION

The maternal magnesium blood levels and the umbilical cord magnesium levels have a significantly correlate with BDNF levels, in a positive trend. The higher magnesium levels in the maternal blood, the higher BDNF levels in the umbilical cord blood. We also conclude that the higher the umbilical cord magnesium levels, the higher the BDNF levels. Our study shows maternal magnesium blood levels and umbilical cord magnesium levels were influenced by various factors, including the total dose of antenatal $MgSO_4$ administration and the incidence of preeclampsia. This study has provided evidence to recommend $MgSO_4$ administration as a neuroprotector in preterm pregnancy with ongoing spontaneous birth or medically indicated preterm birth. Higher dose of antenatal MgSO4 is needed to increase BDNF production, but should not exceed the limit of umbilical cord blood magnesium levels allowance.

ACKNOWLEDGMENTS

The research efforts were held in Dr. Moewardi hospital, Surakarta. The authors would like to thank the Head of the hospital and all of the medical staffs in the Obstetrics and Gynecologic Department of Dr. Moewardi hospital, Surakarta.

CONFLICTS OF INTEREST

The authors have stated explicitly that are no conflicts of interest in connection with this article.

FUNDING

No financial support was received for this study.

REFERENCES

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born Too Soon: The global epidemiology of 15 million preterm births. Reprod Health. 2013;10(SUPPL. 1).
2. Doll E, Wilkes J, Cook LJ, Korgenski EK, Faix RG, Yoder BA, et al. Neonatal magnesium levels correlate with motor outcomes in premature infants: A long-term retrospective cohort study. Frontiers in Pediatrics. 2014;2:120.
3. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: A clinical overview. Transl Pediatr. 2020;9(1):S125–35.
4. Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O. Cerebral palsy-trends in epidemiology and recent development in prenatal mechanisms of disease, treatment, and prevention. Vol. 5, Frontiers in Pediatrics. 2017;5:21.
5. Himpens E, Van Den Broeck C, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and

severity of cerebral palsy in relation to gestational age: A meta-analytic review. Developmental Medicine and Child Neurology. 2008;50(5):334–40.
6. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009;8(1):110–24.
7. Usman S, Foo L, Tay J, Bennett PR, Lees C. Use of magnesium sulfate in preterm deliveries for neuroprotection of the neonate. Obstet Gynaecol. 2017;19(1):21–8.
8. Bachnas MA, Mose JC, Effendi JS, Andonotopo W. Influence of antenatal magnesium sulfate application on cord blood levels of brain-derived neurotrophic factor in premature infants. J Perinat Med. 2014;42(1):129–34.
9. Rao R, Mashburn CB, Mao J, Wadhwa N, Smith GM, Desai NS. Brain-derived neurotrophic factor in infants <32 weeks gestational age: Correlation with antenatal factors and postnatal outcomes. Pediatr Res. 2009;65(5):548–52.
10. Chen A, Xiong LJ, Tong Y, Mao M. The neuroprotective roles of BDNF in hypoxic ischemic brain injury. Biomed Reports. 2013;1(2):167–76.
11. Murray PS, Holmes P V. An overview of brain-derived neurotrophic factor and implications for excitotoxic vulnerability in the hippocampus. Int J Pept. 2011;2011:1-12.
12. Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical Implications. Arch Med Sci. 2015;11(6):1164–78.
13. Sulistyowati S, Bachnas MA, Astetri L. Pengaruh perbedaan dosis pemberian magnesium sulfat terhadap kadar brain-Derived Neurotrophic Factor darah tali pusat bayi lahir prematur. Thesis, Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia. (2019).
14. Altraigey A, Mostafaa ST. Correlation of neonatal and maternal serum magnesium levels in pre-eclamptic women. MOJ Womens Heal. 2019;8(3):232–5.
15. Borja-Del-Rosario P, Basu SK, Haberman S, Bhutada A, Rastogi S. Neonatal serum magnesium concentrations are determined by total maternal dose of magnesium sulfate administered for neuroprotection. J Perinat Med. 2014;42(2):207–11.
16. Narasimhulu D, Brown A, Egbert NM, Rojas M, Haberman S, Bhutada A, et al. Maternal magnesium therapy, neonatal serum magnesium concentration and immediate neonatal outcomes. J Perinatol. 2017;37(12):1297–303.
17. Rigo J, Pieltain C, Christmann V, Bonsante F, Moltu SJ, Iacobelli S, et al. Serum magnesium levels in preterm infants are higher than adult levels: A systematic literature review and meta-analysis. Nutrients. 2017;9(10):1–24.
18. Brookfield KF, Vinson A. Magnesium sulfate use for fetal neuroprotection. Curr Opin Obstet Gynecol. 2019;31(2):110–5.
19. Okusanya BO, Oladapo OT, Long Q, Lumbiganon P, Carroli G, Qureshi Z, et al. Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia. BJOG An Int J Obstet Gynaecol. 2016;123(3):356–66.
20. Gortzak-Uzan L, Mezad D, Smolin A, Friger M, Huleihel M, Hallak M. Increasing amniotic fluid magnesium concentrations with stable maternal serum levels: A prospective clinical trial. J Reprod Med Obstet Gynecol. 2005;50(11):817-20
21. da Costa TX, Azeredo FJ, Ururahy MAG, da Silva Filho MA, Martins RR, Oliveira AG. Population Pharmacokinetics of Magnesium Sulfate in Preeclampsia and Associated Factors. Drugs R D. 2020;20(3):257–66.
22. Brookfield KF, Su F, Elkomy MH, Drover DR, Lyell DJ, Carvalho B. Pharmacokinetics and placental transfer of magnesium sulfate in pregnant women Presented in part at the Society for Maternal Fetal Medicine 35th Annual Meeting, San Diego, CA, February 1-6, 2015. Am J Obstet Gynecol. 2016;214(6):737.e1-737.e9.
23. Sherwin CMT, Balch A, Campbell SC, Fredrickson J, Clark EAS, Varner M, et al. Maternal magnesium sulphate exposure predicts neonatal magnesium blood concentrations. Basic Clin Pharmacol Toxicol. 2014;114(4):318–22.
24. Mittendorf R, Dambrosia J, Pryde PG, Lee KS, 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(6):1111–8.
25. Basu SK, Chickajajur V, Lopez V, Bhutada A, Pagala M, Rastogi S. Immediate clinical outcomes in preterm neonates receiving antenatal magnesium for neuroprotection. J Perinat Med. 2012;40(2):185–9.
26. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2009.