Comparison of magnesium sulfate and salbutamol for the management of preterm labour

Jaweria Faisal[1], Sadia Kanwal[2], Zeba Munzar[1], Hira Omair[3]

ABSTRACT

Objective: To determine the efficacy of magnesium sulfate and salbutamol in preterm labour management and compare frequency and severity of their side effects.

Study Design: Randomized control trial.

Place and Duration: Mother and Child Health Unit II, Pakistan Institute of Medical sciences Islamabad, from 1st January 2007 to 1st July 2007.

Methodology: The patients with singleton pregnancy and preterm labor pains at 24-36 weeks of gestation were randomly allocated to Group A (Magnesium Sulfate (MgSO4)) and Group B (Salbutamol. All patients were checked for duration of treatment means time from start of treatment till contractions were ceased and time of delay of delivery, taken from start of treatment till parturition; that was further divided into <24 hour, 24-48 hours, 2-7 days,7-28 days and >28 days to see prolongation of pregnancy. Efficacy was taken as less duration of treatment and more time duration in delaying of delivery by each drug. The patients were observed for appearance of relevant side effects and those were further categorized into no side effects, mild and severe side effects.

Results: Maternal demographic features were similar in both groups. Average duration of treatment of both drugs was similar (20 ±5.5 vs. 19±5.2) hours with non-significant p value. Average time gained in delaying delivery by salbutamol was more than magnesium sulphate (6.2 vs. 5.8 days) with p value of 0.04, signifying its better efficacy. In MgSO4 group mild side effects i.e. flushing 70%, mild headache and slight dry mouth 56.6% each, were experienced more than severe side effects like severe vomiting, dizziness and headache in 3.3% each, dry mouth and sweating in 6.6% patients each. In salbutamol group more events were of severe intensity as compared to mild and they occurred in majority of patients, as 40% patients had severe maternal tachycardia and anxiety, 36.6% patients had severe fetal tachycardia. Total 79.9% patients had palpitations and in 33.3% patients it was of severe intensity.

Conclusion: Salbutamol was superior in efficacy but it was associated with more side effects of severe intensity as compared to Magnesium Sulfate (MgSO4) that was better tolerated with less side effects mostly of mild intensity so salbutamol is more efficacious than MgSO4 but should be used with caution.

Keywords: Magnesium sulphate, Salbutamol, Preterm labour, Management, Tocolysis, Prematurity, Side effects.

How to Cite This:

Faisal J, Kanwal S, Munzar Z, Omair H. Comparison of magnesium sulfate and salbutamol for the management of preterm labour. Isra Med J. 2019; 11(1): 10-15.

1. Associate Professor of Gynae & Obs, Al Nafees Medical College and Hospital, Islamabad
2. Assistant Professor of Gynae & Obs, Al Nafees Medical College and Hospital, Islamabad
3. Consultant Gynecologist of Gynae & Obs, City Hospital, Toba Tek Sing

Correspondence to:
Dr. Jaweria Faisal
Associate Professor of Gynae & Obs
Al Nafees Medical College and Hospital, Islamabad
Email: jaweria_faisal@hotmail.com

Received for Publication: 15-11-17
1st Revision of Manuscript: 26-05-18
2nd Revision of Manuscript: 18-11-18
3rd Revision of Manuscript: 11-02-19
4th Revision of Manuscript: 17-02-19
Accepted for Publication: 24-02-19

INTRODUCTION

Preterm labor, occurring in 5% to 17% of all pregnancies, remains a major unsolved problem in perinatal medicine[1]. Prematurity is the most common cause of perinatal morbidity and mortality after congenital malformations[2,3] . It is also responsible for the death of under five years old children and contributes to their long-term growth impairment if they survive[4] Preterm labour refers to onset of labour after age of viability and before 37 completed weeks of gestation[5]. Advanced neonatal care has improved survival of premature infants but they remain at increased risk of range of adverse neonatal outcomes including respiratory distress syndrome (RDS), interventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis and cerebral palsy[6-8]. It is essential to suppress preterm labor until the fetus becomes mature enough, unless it is contraindicated due to intrauterine infections, fetal distress or bleeding[9]. Tocolytics are the drugs that can stop the uterine contractions and thus may improve neonatal outcomes[10] Tocolysis prevents labor for at least 48 hours, which is the critical

period for antenatal steroid administration or in utero transfer of fetus to tertiary health center[11, 12]. Single course of antenatal steroids is associated with a significant reduction in Respiratory distress syndrome (RDS), interventricular hemorrhage, necrotizing enterocolitis and neonatal death[13,14]

The ideal tocolytic agent should be easy to administer, inexpensive, without significant fetomaternal side effects and effective at delaying preterm birth at least long enough to permit the use of prenatal corticosteroids[15]. Wide variety of tocolytics are available i.e. beta agonists, Magnesium Sulfate (MgSO4), Atosiban and calcium channel blockers[10, 16]. Beta agonists are widely used for prevention of preterm labor but their several side effects are not uncommon as tachycardia, palpitations and tremors[17,18]. MgSO4 has emerged as a new option that has neuroprotective role along with its tocolytic action[19, 20]. It is an inexpensive, widely available drug and along with preterm labour it is also used for preeclampsia[21]. It has narrow therapeutic range but based on high quality evidence, its risk benefit ratio is in favor of its use so currently it is recommended for tocolysis and also for prevention of cerebral palsy in very preterm infants[22, 23]. The use of MgSO4 is recommended by RCOG and NICE, in Preterm labor and birth guidelines[24].

Due to associated risk factors such as inadequate health services, uncontrolled medical disorders, previous abortions and anemia the burden of preterm labour and its associated perinatal morbidity and mortality is high in our country[25,26]. For its narrow therapeutic range and fear of severe side effects, MgSO4 is not commonly used in our country. Despite applying international data on our patient, we decided to perform this study in our setup. This study will add in existing knowledge along it will help to find out effectiveness and side effects these tocolytics in our patients. So this study was conducted to determine the efficacy of magnesium sulfate and salbutamol in preterm labour management and compare frequency and severity of their side effects.

METHODOLOGY

This randomized control trial was conducted in Mother and Child Health Unit II, Pakistan Institute of Medical Sciences Islamabad, over a period of six months from 1st January 2007 to 1st July 2007. Non-probability consecutive sampling was employed to select 60 patients who were admitted with singleton pregnancy and labor pains at 24-36 weeks of gestation. Detailed history was taken along with examination. Patients who had vaginal bleeding, fetal anomalies, ruptured membranes, placental abruption, placenta previa, previous caesarean section, cervical dilatation of 4cm and serious medical diseases were excluded. Preterm labor was defined as the presence of at least 2 uterine contractions in 10minutes and the cervical dilatation of 0- 3 cm with less than 50% of cervical effacement in patients of 24-36 weeks of gestation. These patients were divided in two groups comprising of 30 members in group A and B respectively. Informed consent was taken after explaining the procedure, pros and cons of study.

All patients were initially advised bed rest, sedation and intravenous hydration. If contraction didn't settle, they were randomly allocated to Magnesium sulfate, MgSO4 (Group A) and salbutamol (Group B). Randomization was done by block method. All patients were given I/M injection Dexamethasone for fetal lung maturity.

For Magnesium sulfate group, 4 gram (8cc) of drug and 12 cc D/W mixed in 20 cc disposable syringe, making 20% solution was given intravenous over 20 minutes. Then 2 grams I/V infusion per hour was given until contractions were stopped, maximum till 48 hours. MgSO4 infusion was continued for 12 hours after cessation of contractions. Patients were observed for any toxic effects of MgSO4 as bradycardia, absent reflexes with poor urine output Salbutamol infusion was prepared by adding 8 ampules of Ventolin (500 microgram/ ampule) in 500 ml of infusion solution such as sodium chloride to provide a salbutamol dose of 8 micrograms per ml of solution. A starting dose of 8 micrograms (16 drops per minute) increasing the rate by 8 micrograms at 30 min intervals until there was diminution in strength, frequency or duration of contraction. Once uterine contractions were ceased the infusion rate was maintained at the same level for one hour and then reduced by 50% decrements at 6 hourly intervals in all patients, fetal heart rate, blood pressure, pulse rate, and uterine contractions were observed. Maximum duration of treatment was 48 hours. All patients were checked for duration of treatment that was taken between start of treatment till contraction ceased and time of delay of delivery means time between start of treatment till parturition, that was further divided into for <24 hour, 24-48 hours, 2-7 days,7-28 days and >28 days to see prolongation of pregnancy. Efficacy was taken as less duration of treatment and more time duration in delaying delivery by each drug. The patients were observed for appearance of relevant side effects and they were further categorized into mild, severe and nil. Group A was observed for flushing, burning at injection site, vomiting, headache, sweating, dry mouth and dizziness. Group B was observed for tremors, tachycardia, anxiety, hypotension, palpitations and fetal tachycardia.

Data Analysis: Data was entered on pre-designed Pro forma and was analyzed by using SPSS version 10. Descriptive statistics were calculated. Mean ± S.D was calculated for all quantitative variables. Frequency and percentages were presented for Parity, adverse effect and prolongation of pregnancy. In order to observe statistical significance, patient data including age, parity and duration of treatment in each group was compared using t test. Duration of delay of delivery and mode of delivery were analyzed by using chi- square test. A p value of less than 0.05 was considered statistically significant.

RESULTS

Total numbers of sixty patients with preterm labour were enrolled in this study. Maternal demographic features and clinical characteristics at randomization were similar in both groups. Mean age was 25 years and mean gestational age was 32.1 weeks in both groups. Relationship of parity shows that nulliparous women were 33 vs. 30 and multiparous women were

66 vs.70 in group A & B respectively. Similar were the case with duration of labour pains (17.4±9.4vs.16.6±6.3), fundal height (32±1.8 vs. 32±1.7), palpable contractions/10 minutes (2.5±0.5 vs. 2.4±0.7), bishop score (4.1±0.8 vs.3.9±0.9), vaginal leaking (0.0% vs.0.0%) and discharge (16±1.6 vs. 17±1.8). All these values were statistically not significant. (Table-I)

Table-I: Frequency of baseline characteristics of study patient, (N= 60)

Variables Mean ± SD	Group A (MgSO4) n= 30	Group B (salbutamol) n=30	p-value
Age (years)	25 ± 5.8	25±3.9	N.S
Gestational age (weeks)	32±1.9	32±1.8	N.S
Fundal height (cm)	32±1.8	32±1.7	N.S
Palpable contraction/10 min	2.5±0.5	2.4±0.7	N.S
Bishop score	4.1±0.8	3.9±0.9	N.S
Vaginal leaking	0±0	0±0	N.S
Vaginal discharge	16±1.6	17±1.8	N.S
Duration of labor pains (hours)	17.4±9.4	16.6±6.3	N.S
Nulliparous	10(33.3%)	9(30%)	N.S
Multiparous	20(66.6%)	21(70%)	N.S

Maximum duration of treatment defined in study was 48 hours in both groups. Average duration of treatment in Group A was 20 ±5.5 hours while in Group (B), it was 19±5.2 hours, with non-significant p value. Average time gained in delaying delivery gained by Magnesium sulfate (MgSO4) therapy was 141±150 hours (5.8 days) and 149±110.2 hours (6.2 days) in salbutamol therapy with significant p value. This signifies that efficacy of salbutamol in delaying delivery was more than MgSO4 with same duration of treatment. (Table-II)

The time duration of delay of delivery was <24 hour in 13.3% vs. 6.6%, 24-48 hours in 33% vs 9.9 %., for 2-7 days in 30% vs. 46.6%, 7-8 days in 20 % vs. 33.3% and for > 28 days in 3.3% vs 3.3% in group A& B respectively showing that salbutamol was superior in delaying delivery for longer durations (Table-III)

Regarding adverse effects, in group A, the majority of patients were free of side effects and side effects that occurred were of mild intensity in most cases. Most common side effect was flushing but that it was of mild intensity in 21(70%) patients and was severe in only 3(10%) women. Other adverse effects of severe intensity occurred in small number of patients as vomiting, dizziness and headache in 1(3.3%), dry mouth and sweating in 2(6.6%) patients each. (Fig-1). In salbutamol group more events were of severe intensity and they occurred in majority of patients, as 12(40%) patients had severe maternal tachycardia and anxiety, 11(36.6%) patients had severe fetal tachycardia other had mild effect. Total 24(79.9%) patients had palpitations and in 10(33.3%) patients it was of severe intensity. (Fig-2)

Table-II: Duration of treatment and time of Delaying delivery (efficacy), (N=60)

Variables Mean ± SD	Group A (MgSO4) n=30	Group B (Salbutamol) n=30	p –value
Duration of treatment (hours)	20 ± 5.5	19±5.2	N.S
Delay in delivery by treatment (hours)	141±150.0	149±110.2	0.04*

*P – value significant at 5% level of significance

Table-III: Time duration of delaying delivery, Efficacy, (N=60)

Delay of delivery/Pregnancy prolonged	MgSO4 group, n (% age)	Salbutamol, n (% age)
< 24 hours	4 (13.333%)	2 (6.6%)
24-48 hours	10 (33.333%)	3 (9.9%)
2-7days	9(30%)	14(46.6%)
7-28 days	6(20%)	10(33.3%)
>28 days	1(3.333%)	1(3.3%)

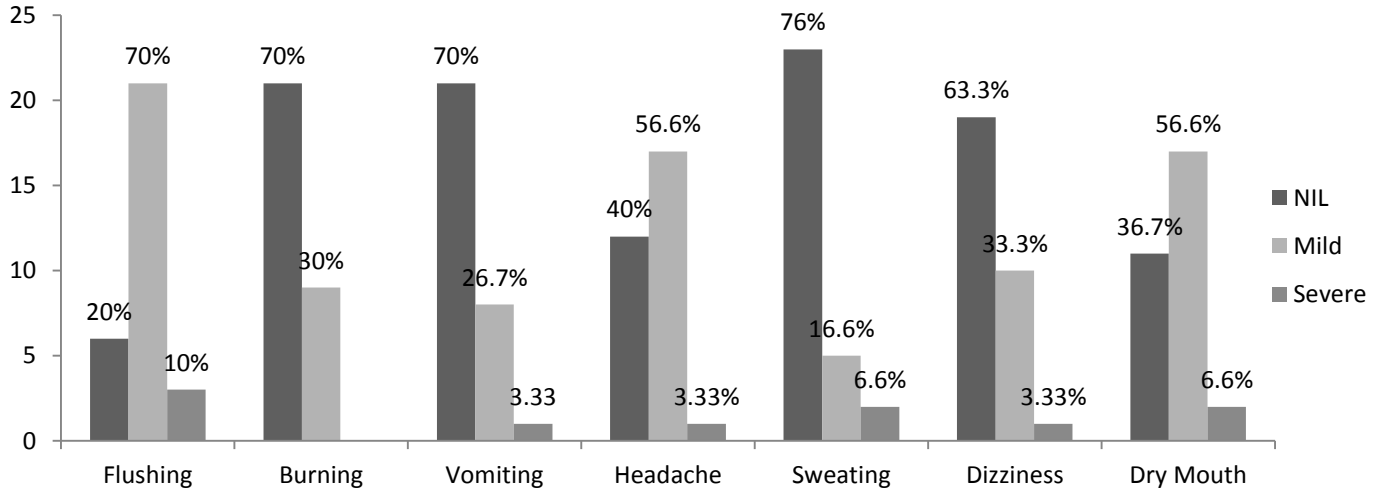

Fig-1: Frequency & Severity of side effects, Group A (MgSO4): (N=30)

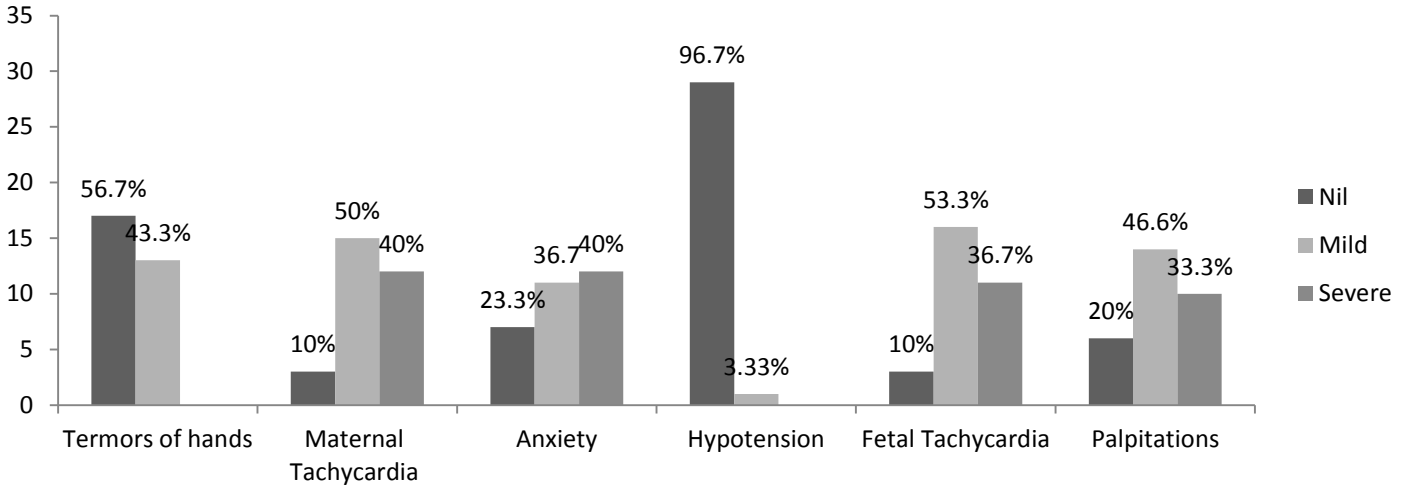

Fig-2: Frequency and Severity of side effects, Group B (Salbutamol): (N=30)

DISCUSSION

In our study, the mean age of patients was 25 years, which is similar to other studies. We found that delay in delivery was more in salbutamol group but this was associated with many side effects. The findings of our study are consistent with previous studies that have shown that beta agonists are effective tocolytic agents but are accompanied by side effects[27, 28]. As also seen by Mawaldi et al, who compared subcutaneous Terbutaline with nifedipine for prolongation of gestation and found that both equally effective[17].

Mean duration of treatment for MgSO4 was 20 hours that delayed delivery for 5.8 days that was significantly less than salbutamol in our study that helped in prolonging of pregnancy for mean of 6.2 days. This shows that MgSO4 is also a good tocolytic agent but its effectiveness is less than beta agonists. Saadati N et al in 2014 compared Celecoxib with $MgSO_4$ for tocolysis[29] and found MgSO4 as an effective drug. Similar findings were also observed by Borna and Saeidi, where preterm labour was suppressed in 87% patients by MgSO4[29]. Kawagoe observed in randomized trial that even beta agonists become more potent in stopping preterm labor with adjuvant Magnesium Sulphate[30]. But these results are in contrary to seen by Crowther CA, who found Magnesium sulfate ineffective at delaying birth, with no apparent advantages[31]. The results of our study correspond to the findings of Klauser et al who observed in a Randomized trial that MgSo4 was effective for tocolysis even at advance cervical dilatation[32].

In 2010, Motazedian et al [27]found that salbutamol is associated with more complications of severe intensity including tachycardia, palpitation, anxiety and chills like in our study where most patients had fetomaternal tachycardia and palpitations and these complications were of severe intensity in many patients. Phupong et al studied the effect of salbutamol on prolongation of pregnancy in women with PTL and fond that tachycardia was the most common side effect, which was experienced by 85.6% of the individuals[28]. This is in consistence with our study where most common side effect was maternal tachycardia. Malwaldi and Duminy also found, in a Randomized trial that beta agonists are associated with many sideeffcts,[17] these observations were like our study. Most side effects of magnesium therapy occur at higher dose[33]. Flushing is common side effect of magnesium therapy but sometimes it become severe enough that patient has to discontinue therapy. In our study most patients in magnesium sulfate group had mild flushing but it was severe in 3 patients. In an RCT done Nikbkhtin in 2014, 2% patients in the magnesium sulfate group, had to discontinue therapy because of severe flushing[5]. Bain reported in 2013 that the most frequently reported side effects of magnesium sulfate therapy are warmth or flushing, arm discomfort or problems at the IV site and sweating without an increase in major complications (respiratory arrest, cardiac arrest, death)[34,35]. These findings correspond well with our study. Saadati also mentioned that MgSO4 is associated with arm discomfort and pain at injection site[29].

CONCLUSION

Salbutamol was superior in efficacy but it was associated with more side effects mostly of severe intensity, however; Magnesium Sulfate (MgSO4) was better tolerated than salbutamol along with less severe side effects thus salbutamol is more efficacious but should be used with caution.

CONTRIBUTION OF AUTHORS

Faisal J: Literature search, Literature review, Data interpretation, Statistical analysis, Manuscript writing, Manuscript final reading and approval

Kanwal S: Conceived idea, Designed research methodology, Data collection

Statistical analysis

Munzar Z: Literature search, Literature review, Statistical analysis

Omair H: Literature search, Literature review

Disclaimer: None.
Conflict of Interest: None.
Source of Funding: None.

REFERENCES

1. Carmichael SL, Cullen MR, Mayo JA, Gould JB, Loftus P, Stevenson DK, et al. Population-Level Correlates of Preterm Delivery among Black and White Women in the U.S. PLoS One. 2014; 9(4): e94153.
2. Conde-agudelo A, Romero R .Transdermal nitroglycerin for the treatment of preterm labor: a systematic review and meta-analysis. Am J Obstet Gynecol. 2013; 209(6): 551.e1–551.e18.
3. Heron M, Sutton PD, Xu J, Ventura SJ, Strobino DM, Guyer B. Annual summary of vital statistics: 2007. Pediatrics 2010; 125:4–15
4. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012; 379(9832):2151-61.
5. Nikbakht R, Moghadam MT , Ghane'ee H. Nifedipine compared to magnesium sulfate for treating preterm labor: A randomized clinical trial. Iran J Reprod Med. 2014; 12(2): 145–50.
6. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013; 55(6):509-19.
7. Dolan SM, Gross SG, Merkatz IR, Faber V, Sullivan LM. The contribution of birth defects to preterm birth and low birth weight. Obstet Gynecol. 2007; 110: 318–24.
8. Bolisetty S, Dhawan A, Abdel Latif M, Bajuk B, Stack J, Lui k, et al. New South Wales and Australian Capital Territory Neonatal Intensive Care Units' Data Collection. Intraventricular hemorrhage and neurodevelopment outcomes in extreme preterm infants. Pediatrics. 2014; 133: 55-62
9. Tan MY, To M. Recent advances in the prevention and management of preterm birth. F 1000 Prime Rep. 2015; 7: 40.
10. Thornton S, Miller H, Valenzuela G, Snidow J, Stier B, Fossle MJ, et al. Treatment of spontaneous preterm labour with retosiban: a phase 2 proof-of-concept study Br J Clin Pharmacol. 2015; 80(4): 740–49
11. Locatelli A, Consonni S, Ghidini A. Preterm labor: approach to decreasing complications of prematurity. Obstet Gynecol Clin North Am. 2015; 42(2): 255-74.
12. Schmitz T. Prevention of preterm birth complications by antenatal corticosteroid administration. J Gynecol Obstet Biol Reprod (Paris). 2016; 45(10):1399-417.
13. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016; 374(14): 1311-20.
14. Sotiriadis A, Tsiami A, Papatheodorou S, Baschat AA, Sarafidis K, Makrydimas G, et al. Neurodevelopmental Outcome After a Single Course of Antenatal Steroids in Children Born Preterm: A Systematic Review and Meta-analysis. Obstet Gynecol. 2015; 125 (6):1385-96.
15. De Heus R, Mulder EJ, Visser HA. Management of preterm labor: atosiban or nifedipine? Int J Women's Health. 2010;2:137–42.
16. Navathe R, Berghella V. Tocolysis for Acute Preterm Labor: Where Have We Been, Where Are We Now, and Where are We Going? Am J Perinatol. 2016; 33(3):229-35
17. Mawaldi L, Duminy P, Tamim H. Terbutaline versus nifedipine for prolongation of pregnancy in patients with preterm labor.Int J Gynaecol Obstet. 2008; 100(1):65-68
18. Croen LA, Connors SL, Matevia M, Qian Y, Newschaffer C, Zimmerman AW, et al. Prenatal exposure to β2-adrenergic receptor agonists and risk of autism spectrum disorders. J Neurodev Disord. 2011; 3(4): 307–15.
19. Horton AL, Lai Y, Rouse DJ, Spong CY. Leveno KJ, Varner MW, et al. The effect of magnesium sulfate administration for neuroprotection on latency in women with preterm premature rupture of membranes. Am J Perinatol. 2015; 32(4): 387–92.
20. 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 Syst Rev. 2009; (1): CD 004661
21. Wolf HT, Huusom L, Weber T, Piedvache A, Schmidt S, Norman M, Zeitlin J, et al. Use of magnesium sulfate before 32 weeks of gestation: a European population-based cohort study. BMJ Open. 2017; 7(1):e013952.
22. Usman S, Foo L, Tay J, Bennett PR, Lees C. Use of magnesium sulfate in preterm deliveries for neuroprotection of the neonate. The Obstet Gynaecol. 2017; 19: 21-28
23. Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and Safety of Magnesium Sulfate on Neuroprotection. A Meta-Analysis Based on PRISMA Guidelines. Medicine (Baltimore). 2016; 95(1): 2451.
24. National Collaborating Centre for Women's and Children's Health (UK). Preterm Labour and Birth. National Institute of Health Care Excellence. Guideline 25; November 2015. Website: [https://www.nice.org.uk/guidance/ng25/evidence/full-guideline-pdf-2176838029]
25. Swingle HM, Colaizy TT, Zimmerman MB, Morriss FH Jr. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analyses. J Reprod Med. 2009; 54(2):95-108.
26. Baig SA, Khan N, Baqai T, Fatima A, Karim SA, Aziz S. Preterm birth and its associated risk factors. A study at tertiary care hospitals of Karachi, Pakistan. J Pak Med Assoc. 2013; 63(3): 414-48
27. Motazedian S, Ghaffarpasand F, Mojtahedi K , Asadi N. Terbutaline versus salbutamol for suppression of preterm labor: a randomized clinical trial. Ann Saudi Med. 2010; 30(5): 370– 75.
28. Phupong V, Charakorn C, Charoenvidhya D. Oral salbutamol for treatment of preterm labor. J Med Assoc Thai. 2004; 87(9): 1012-16

29. Saadati N, Moramezi F, Cheraghi M, Sokhray L. Using Celecoxib for the Suppression of Preterm Labor Instead of Magnesium Sulfate. J Pregnancy. 2014; 2014: 869698.
30. Kawagoe Y, Sameshima H, Ikenoue T, YasuhiI, Kawarabayashi T. Magnesium Sulfate as a Second-Line Tocolytic Agent for Preterm Labor: A Randomized Controlled Trial in Kyushu Island. J Pregnancy. 2011; 2011: 965060.
31. Crowther CA, Brown J, McKinlay CJ, Middleton P. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst Rev. 2014; (8): CD001060.
32. Klauser CK, Briery CM, Tucker AR, Martin RW, Magann EF, Chauhan SP, et al. Tocolysis in women with advanced preterm labor: a secondary analysis of a randomized clinical trial. J Matern Fetal Neonatal Med. 2016; 29(5):696-700.
33. Wilson MS, Ingersoll M, Meschter E, Bodea-Braescu AV, Edwards RK. Evaluating the side effects of treatment for preterm labor in a center that uses "high-dose" magnesium sulfate. Am J Perinatol. 2014; 31 (8):711-16
34. Bain ES, Middleton PF, Crowther CA. Maternal adverse effects of different antenatal magnesium sulphate regimens for improving maternal and infant outcomes: a systematic review. BMC Pregnancy Childbirth. 2013; 13: 195.
35. Zeng X, Xue Y, Tian Q, Sun R, Ruifang An. Effects and Safety of Magnesium Sulfate on Neuroprotection A Meta-analysis Based on PRISMA Guidelines. Medicine (Baltimore). 2016; 95(1): 2451.