Ministry of Higher Education.
And Scientific & Research.
2020-2021

University of Diyala
College of Medicin

Review article

Tocolytic drug in preterm labor

,Submitted to the council of the College of Medicines, Diyala University In partial Fulfillment of Requirements for the Bachelor degree in Medicine

Prepared by

Zeynap Alham Khalaf

Supervised by

Dr.Assma Najm

Abstract

The aim of this article is to review available data about drugs for preventing preterm labour. Tocolytic therapy includes β adrenergic receptor agonists, NO donors, magnesium sulphate, prostaglandin-synthase inhibitors, oxytocin receptor antagonists, calcium-channel blockers, progesterone, 17-α-hydroxyprogesterone caproate, and antibiotics. Their specific effects on myometrial contractility, their safety, their efficiency, and side effects profile for the mother and the fetus are presented. The main question of why and for what reasons tocolysis should be administrated is discussed.

Conclusion

Prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal and maternal outcomes

Keyword

Premature labor, tocolytic magnesium sulfate, β-adrenergic receptor agonists, calcium channel blockers, NO Donors
Prostaglandin-Synthase Inhibitors, Oxytocin Receptor Antagonists, Progesterone and 17-α-Hydroxyprogesterone Caproate

Introduction

Pre term delivery is a birth that occurring before 37 weeks of gestation or before 259 days from the last menstrual period. Prematurity multifactorial and incidence of it increased during the last decade in most Occidental countries (1_3)

Preterm labour Mechansim are still unclear. It could be associated with premature activation of physiological contractions or with pathological factor responsible for leading to pre term labor (1_3)

Among preterm labour pathway , the are uterine overdistension due to multiple pregnancies or polyhydramnios ,cervical diseases,placental ischaemia , imunologic and allergic phenomena,decidual or retroplacental hemorrhage, intrauterine infection and inflammatory processes,fetal endocrine activation (1_4)

Drugs safety and side effect profile is major concern not only for pregnant women but also for foetus (4_6)

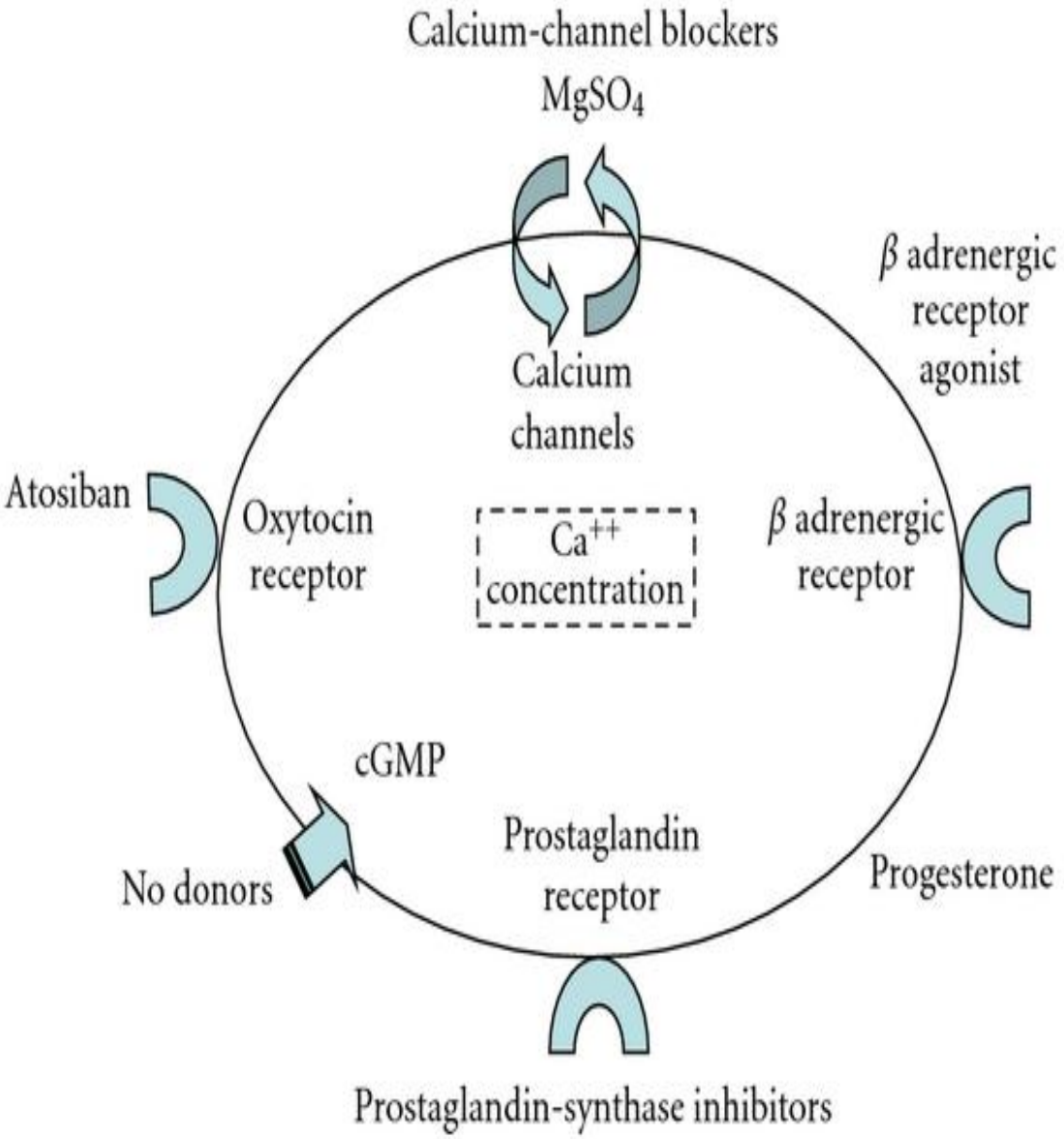
Tocolysis aims not only Inhibit uterine contractions but also to allow safe transfer of pregnant to a tertiary care centre (5_7)

Mechanisms of Tocolysis

the myometril contractility is complex process based on myocytes function. It involve the presence of hormonal receptor, ions channels, intercell gap junctions, and regulatory protein such as oxytocin,tachykinin, endothelin and angiotensin (8_9)
Increase of intracellular calcium concentration is essential for uterine smooth muscle contraction (9)

As shown below uterine relaxation obtained by interfering with intracellular messenger responsible for contractile protein effect : B adrenergic receptor agonists,nitric oxide(NO) donor , magnesium sulphate and calcium channel Blocker is tocolytic drug aiming to this (1,2,6,9). Other pathway involves the inhibition of contracting factor synthesis .Atosiban an oxytocin receptor

antagonist and prostaglandin synthetase inhibitors have this effect by interfering with endogenous myometrial stimulator (1,2,6,9)



Type of Tocolytic Treatment

β Adrenergic Recepto ceptor Agonists Selective β 2 agonists such as ritodrine and salbutamol used in clinical practice for preterm labour since 1980s. This drug impair the intracellular cyclic AMP concentration and facilitate myometrial relaxation (9,10).
Randomized control studies and meta_analysis reported that these agent was more efficient than placebo to delaying preterm birth for two days. There is no benefit for long term (the effect of tocolytic restricted to 7 days) and perinatal morbidity and mortality rate was found(5,10,11).

NO Donors. NO is power vasodilator synthesized during amino acid oxidation process catalyzed by NO synthase. There is a specific link between NO production and Uterine relaxation and it present in myometrial cell(8,9)

Magnesium Sulphate. the relaxation effect of Magnesium sulphate in vitro and in vivo on human uterine contractility was widely reported. The Magnesium is calcium antagonist,it decreases calcium intracellular concentrations and inhibits contractions process (2,4,9)

Prostaglandin -Synthase Inhibitors
Prostaglandin synthase or cyclooxygenase (COX) isoforms COX_1 and _2 are essential enzymes to converting arachidonic acid to prostaglandin.
Prostaglandin also works by enhancing myometrial gap junctions and increase intracellular calcium concentrations (2,4,5,9)

Oxytocin Receptor Antagonists
This agent are in competition with the myometrial and decidual oxytocin receptors. The only drug used in clinical practice is atosiban. It blocks in a reversive manner intracytoplasmic
calcium release associated with contractions and downregulates prostaglandin synthesis (2, 9). A first multicentric randomised trial comparing atosiban and ritodrine demonstrated a similar tocolytic effect but fewer adverse effects with atosiban (4, 6)

Calcium-Channel Blockers.
These agents are interfering
with the calcium ions transfer through the myometrial cell membrane. They decrease intracellular free calcium concentration and induce myometrial relaxation (2–4) Nifedipine is the most commonly used drug for preterm labour inhibition at a daily dose of 30–60 mg daily (20)

Progesterone and 17-α-Hydroxyprogesterone Caproate.

Progesterone is a steroid hormone secreted by the corpus luteum and by the placenta after 8 weeks of gestation.It has a physiological effect on uterine quiescence mediated
by a direct effect on intracellular calcium concentration and
prostaglandin synthesis (1, 2, 5, 9)

Antibiotics. Infection is one of causal factors of preterm labour with an incidence of 20–40%, especially before 30 weeks (1, 2) . Antibiotics use for preventing preterm labour has been largely studied (5, 28–30)

Result

Between March 1995 and February 1996, 34 women (39 babies) were recruited. The baseline characteristics of the two groups were similar. No patient was lost to follow up. In the indomethacin group, gestation was prolonged by > 48 hours in 13/16 (81%) of women vs 10/18 (56%) in the placebo group. The incidence of perinatal mortality or severe neonatal morbidity was not significantly different between the groups, but occurred in twice as many babies in the indomethacin group as in the placebo group d/l9 (32%) vs 3/20 (15%) OR (95% CI) 2.62 (0.44–18.8). There was one perinatal death, of a baby delivered at 24 weeks of gestation. This occurred in the indomethacin group.
In 2005 two trials (651 women) compared atosiban with placebo. Atosiban did not reduce the risk of preterm birth or improve neonatal outcome. In one trial (583 infants), atosiban was associated with an increase in infant deaths at 12 months of age compared with placebo (relative risk (RR) 6.15; 95% confidence intervals (CI) 1.39 to 27.22). However, this trial randomised significantly more women to atosiban before 26 weeks' gestation. Use of atosiban resulted in lower

infant birthweight (weighted mean difference ‐138.31 gm; 95% CI ‐248.76 to ‐27.86) and more maternal adverse drug reactions (RR 4.02; 95% CI 2.05 to 7.85, 2 trials, 613 women).

Four trials (1044 women) compared atosiban with betamimetics. Atosiban increased the numbers of infants born under 1500 gm (RR 1.96; 95% CI 1.15 to 3.35, 2 trials, 575 infants), and resulted in fewer maternal drug reactions requiring treatment cessation (RR 0.04; 95% CI 0.02 to 0.11, number needed to treat 6; 95% CI 5 to 7, 4 trials, 1035 women).
In 2010 the study finding that areOf 269 relevant reports, including 5607 women, adverse fetomaternal events varied according to the total dose of nifedipine and study design. Adverse events were highest amongst women given more than 60 mg total dose of nifedipine [odds ratio (OR) 3.78, 95% confidence interval (CI) 1.27–11.2, p = 0.017] and in reports from case series compared to controlled studies (OR 2.45, 95% CI 1.17–5.15, p = 0.018).

In 2012 Of the 3263 titles initially identified, 95 randomized controlled trials of tocolytic therapy were reviewed. Compared with placebo, the probability of delivery being delayed by 48 hours was highest with prostaglandin inhibitors (odds ratio 5.39, 95% credible interval 2.14 to 12.34) followed by magnesium sulfate (2.76, 1.58 to 4.94), calcium channel blockers (2.71, 1.17 to 5.91), beta mimetics (2.41, 1.27 to 4.55), and the oxytocin receptor blocker atosiban (2.02, 1.10 to 3.80). No class of tocolytic was significantly superior to placebo in reducing neonatal respiratory distress syndrome. Compared with placebo, side effects requiring a change of medication were significantly higher for beta mimetics (22.68, 7.51 to 73.67), magnesium sulfate (8.15, 2.47 to 27.70), and calcium channel blockers (3.80, 1.02 to 16.92). Prostaglandin inhibitors and calcium channel blockers were the tocolytics with the best probability of being ranked in the top three medication classes for the outcomes of 48 hour delay in delivery, respiratory distress syndrome, neonatal mortality, and maternal side effects (all cause).

In 2015 There were no differences seen between high‐dose magnesium sulphate regimens compared with low‐dose magnesium sulphate regimens for the primary outcome of fetal, neonatal and infant death (risk ratio (RR) 0.43, 95%

confidence interval (CI) 0.12 to 1.56; one trial, 100 infants). Using the GRADE approach, the evidence for fetal, neonatal and infant death was considered to be very low quality. No data were reported for any of the other primary maternal and infant health outcomes (birth less than 48 hours after trial entry; composite serious infant outcome; composite serious maternal outcome).

There were no clear differences seen between high‐dose magnesium sulphate regimens compared with low‐dose magnesium sulphate regimens for the secondary infant health outcomes of fetal death; neonatal death; and rate of hypocalcaemia, osteopenia or fracture; and secondary maternal health outcomes of rate of caesarean birth; pulmonary oedema; and maternal self‐reported adverse effects. Pulmonary oedema was reported in two women given high‐dose magnesium sulphate, but not in any of the women given low‐dose magnesium sulphate.

And in other study calcium channel blocker were associated with statistically and clinically significantly better neonatal outcome and fewer maternal side effects than any other tocolytic. So calcium channel blocker would be preferred first line tocolytic with regard to several important outcomes

In a single trial of high and low doses of magnesium sulphate for tocolysis including 100 infants, the risk of respiratory distress syndrome was lower with use of a high‐dose regimen compared with a low‐dose regimen (RR 0.31, 95% CI 0.11 to 0.88; one trial, 100 infants). Using the GRADE approach, the evidence for respiratory distress syndrome was judged to be low quality. No difference was seen in the rate of admission to the neonatal intensive care unit. However, for those babies admitted, a high‐dose regimen was associated with a reduction in the length of stay in the neonatal intensive care unit compared with a low‐dose regimen (mean difference ‐3.10 days, 95% confidence interval ‐5.48 to ‐0.72).

In 2019 the evidence to support the use of magnesium sulfate or nitric oxide donors as a tocolytic is poor. Compared to placebo or no treatment, there is evidence to support the efficacy of calcium channel blockers (mainly nifedipine), prostaglandin synthetase inhibitors (mainly indomethacin and sulindac), oxytocin receptor antagonists (mainly atosiban) and β2-agonists (mainly ritodrine, terbutaline, salbutamol and fenoterol). Maternal safety

concerns have reduced the use of β2-agonists. Fetal safety and gestational age restrictions have largely condemned prostaglandin synthetase inhibitors to second-line therapy. First-line therapy in Europe and other parts of the world outside the USA and Australia is limited to calcium channel blockers and oxytocin receptor antagonists. With respect to efficacy, atosiban and nifedipine are similar, but the robustness of the evidence favours atosiban. With respect to safety, atosiban is clearly the safest tocolytic as there are fetomaternal concerns with nifedipine, particularly in high daily doses

Conclusion

Pre term labor prevalence has increased during the last decades and it is real public health concern. The use of tocolytic drug aim to stop uterine contractions and to prevent neonatal risk associated with prematurity in utero transfer of pregnant patient in tertiary specialized centre and corticosteroids used (1,2,7)

Our review of several studies confirm the efficacy of β adrenergic receptor agonists, prostaglandin-synthetase inhibitors, and atosiban
for delaying delivery for 24–48 hours (2, 5, 6, 10, 11, 17)

In terms of maternal and fetal safety the prevalence of sever side effects
With Tocolysis is about 1% and is more frequent in multiple therapies , preterm rupture of membranes and multiple gestation (27)

Atosiban is first choice drugs safety following prostaglandin synthase inhibitors and nifedipine (2,5,6,12,27)

For future tocolytic drug development should aim to reach better efficacy in term of pregnancy prolongation and lower adverse effect profile. Should use new strategies for better understanding of regulation of myometrial contraction and for detection of specific maternal or fetal parameters. The last generation of oxytocin receptors antagonist such as barusiban could be more efficient and less affinity for vasopressin receptors (9).The specific COX_2 inhibitors or "coxibs" prostaglandin receptors antagonist could promise tocolytic alternatives (2,4,9,18)

References

[1] L. J. Muglia and M. Katz, “The enigma of spontaneous preterm birth,” The New England Journal of Medicine, vol. 362, no. 6, pp. 529–535, 2010.
[2] H. N. Simhan and S. N. Caritis, “Prevention of preterm delivery,” The New England Journal of Medicine, vol. 357, no. 6, pp. 477–487, 2007.
[3] R. Romero, J. Espinoza, J. P. Kusanovic et al., “The preterm parturition syndrome,” BJOG: An International Journal of Obstetrics and Gynaecology, vol. 113, supplement 3, pp. 17–42, 2006.
[4] V. Tsatsaris, D. Cabrol, and B. Carbonne, “Pharmacokinetics of tocolytic agents,” Clinical Pharmacokinetics, vol. 43, no. 13, pp. 833–844, 2004.
[5] V. Smith, D. Devane, C. M. Begley, M. Clarke, and S. Higgins, “A systematic review and quality assessment of systematic reviews of randomised trials of interventions for preventing and treating preterm birth,” European Journal of Obstetrics and Gynecology and Reproductive Biology, vol. 142, pp. 3–11, 2009.
[6] S. Caritis, “Adverse effects of tocolytic therapy,” British Journal of Obstetrics and Gynaecology, vol. 112, supplement 1, pp. 74–78, 2005.
[7] J. C. Di Renzo, E. El Saleh, A. Mattei, I. Koutras, and G. Clerici, “Use of tocolytics: what is the benefit of gaining 48 hours for5 the fetus?” BJOG: An International Journal of Obstetrics and Gynaecology, vol. 113, supplement 3, pp. 72–77, 2006.
[8] R. C. Young, “Myocytes, myometrium, and uterine contractions,” Annals of the New York Academy of Sciences, vol. 1101, pp. 72–84, 2007.

[9] A. L. Bernal, “The regulation of uterine relaxation,” Seminars in Cell and Developmental Biology, vol. 18, no. 3, pp. 340–347, 2007.
[10] S. Anotayanonth, N. V. Subhedar, P. Garner, J. P. Neilson, and S. Harigopal, “Betamimetics for inhibiting preterm labour,” Cochrane Database of Systematic Reviews, no. 4, article CD004352, 2004.
[11] Worldwide Atosiban Versus Betaagonists Study Group, “Effectiveness and safety of the oxytocin antagonist atosiban versus beta adrenergic agonists in the treatment of preterm labour,” British Journal of Obstetrics and Gynaecology, vol. 108, no. 2, pp. 133–142, 2001.
[12] J. Wex, M. Connolly, and W. Rath, “Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation,” BMC Pregnancy and Childbirth, vol. 9, article 23, 2009.
[13] C. A. Crowther, J. E. Hiller, and L. W. Doyle, “Magnesium sulphate for preventing preterm birth in threatened preterm labour,” Cochrane Database of Systematic Reviews, no. 4, article CD001060, 2002.
[14] R. Mittendorf and P. G. Pryde, “A review of the role for magnesium sulphate in preterm labour,” BJOG: An International Journal of Obstetrics and Gynaecology, vol. 112, supplement 1, pp. 84–88, 2005.
[15] C. A. Crowther, J. E. Hiller, L. W. Doyle, and R. R. Haslam, “Effects of magnesium sulphate for preterm neuroprotection before preterm birth,” Journal of the American Medical Association, vol. 290, no. 20, pp. 2669–2676, 2003.
[16] S. A. Reeves, R. S. Gibbs, and S. L. Clark, “Magnesium for fetal neuroprotection,” American Journal of Obstetrics and Gynecology, vol. 204, pp. 202e1–202e4, 2011.
[17] J. F. King, V. Flenady, S. Cole, and S. Thornton, “Cyclooxygenase (COX) inhibitors for treating preterm labour,”

Cochrane Database of Systematic Reviews, no. 2, article CD001992, 2005.
[18] R. Savoly, D. Slater, N. M. Fisk, D. K. Edmonds, and P. Bennett, "Use of a cyclo-oxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery," The Lancet, vol. 350, no. 9073, pp. 265–266, 1997.
[19] D. Papatsonis, V. Flenady, S. Cole, and H. Liley, "Oxytocin receptor antagonists for inhibiting preterm labour," Cochrane Database of Systematic Reviews, no. 3, article CD004452, 2005.
[20] H. P. Van Geijn, J. E. Lenglet, and A. C. Bolte, "Nifedipine trials: effectiveness and safety aspects," British Journal of Obstetrics and Gynaecology, vol. 112, supplement 1, pp. 79–83, 2005.
[21] J. F. King, V. J. Flenady, D. N. M. Papatsonis, G. A. Dekker, and B. Carbonne, "Calcium channel blockers for inhibiting preterm labour," Cochrane Database of Systematic Reviews, no. 1, article CD002255, 2003.
[22] A. Conde-Agudelo, R. Romero, and J. P. Kusanovic, "Nifedipine in the management of preterm labor: a systematic review and metaanalysis," American Journal of Obstetrics and Gynecology, vol. 204, no. 2, pp. 134.e1–134.e20, 2011.
[23] P. J. Meis, M. Klebanoff, E. Thom et al., "Prevention of recurrent preterm delivery by 17 alpha hydroxyprogesterone caproate," The New England Journal of Medicine, vol. 348, no. 24, pp. 2379–2385, 2003.

[24] E. B. Fonseca, E. Celik, M. Parra, M. Singh, and K. H. Nicolaides, "Progesterone and the risk of preterm birth among women with a short cervix," The New England Journal of Medicine, vol. 357, no. 5, pp. 462–469, 2007.
[25] G. C. Di Renzo, A. Rosati, A. Mattei, M. Gojnic, and S. Gerli, "The changing role of progesterone in preterm labour," BJOG: An International Journal of Obstetrics and Gynaecology, vol.

112, no. 1, pp. 57–60, 2005.
[26] A. P. Kenyon and D. Peebles, “Myth: tocolysis for prevention of pretermbirth has a major role in modern obstetrics,” Seminars in Fetal & Neonatal Medecine, vol. 16, pp. 242–246, 2011.
[27] R. de Heus, B. W. Mol, J. J. H. M. Erwich et al., “Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study,” BMJ, vol. 338, no. 7697, article b744, 2009.
[28] J. King and V. Flenady, “Prophylactic antibiotics for inhibiting preterm labour with intact membranes,” Cochrane Database of Systematic Reviews, no. 4, article CD000246, 2002.
[29] S. Kenyon, M. Boulvain, and J. Neilson, “Antibiotics for preterm rupture of membranes,” Cochrane Database of Systematic Reviews, no. 2, article CD001058, 2003.
[30] H. M. MacDonald, P. Brocklehurst, and A. Gordon, “Antibiotics for treating bacterial vaginosis in pregnancy,” Cochrane Database of Systematic Reviews, no. 1, article CD000262, 2007.
[31] J. G. Thornton, “Maintenance tocolysis,” BJOG: An International Journal of Obstetrics and Gynaecology, vol. 112, no. 1, pp. 118–121, 2005.
[32] H. Helmer, “Frequently asked questions about tocolytics,” British Journal of Obstetrics and Gynaecology, vol. 112, supplement 1, pp. 94–96, 2005.

[33]↵Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. Obset Gynecol2009;113:585-94.Google Scholar
[34]↵Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev2006;(3):CD004454.Google Scholar
[35]↵Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2008. Natl Vital Stat Rep2010;58:1-17.PubMedGoogle Scholar

[36]↵ACOG practice bulletin. Management of preterm labor. No 43, May 2003. Obstet Gynecol2003;101:1039-47.CrossRefPubMedGoogle Scholar
[37]↵Goldenberg RL. The management of preterm labor. Obstet Gynecol2002;100:1020-37.CrossRefPubMedWeb of ScienceGoogle Scholar
[38]↵Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst Rev 2006;(3):CD001060.Google Scholar
[39]Caldwell DM, Welton NJ, Ades AE. Mixed treatment comparison analysis provides internally coherent treatment effect estimates based on overviews of reviews and can reveal inconsistency. J Clin Epidemiol2010;63:875-82.CrossRefPubMedWeb of ScienceGoogle Scholar
[40]Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM, Sutton PD. Births: final data for 2001. National Statistics Report 2002;51(2):1-104.
[41]Haas DM, Benjamin T, Sawyer R,Quinney SK. Short-term tocolytics for preterm delivery - current perspectives. Int J Womens Health. 2014;6:343-9.

[42]Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. Obset Gynecol 2009;113:585-94. [PubMed] [Google Scholar]
[43] Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;(3):CD004454. [PubMed] [Google Scholar]
[44] Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2008. Natl Vital Stat Rep 2010;58:1-17. [Google Scholar]
[45] ACOG practice bulletin. Management of preterm labor. No 43, May 2003. Obstet Gynecol 2003;101:1039-47. [PubMed] [Google Scholar]

[46] Goldenberg RL. The management of preterm labor. Obstet Gynecol 2002;100:1020-37. [PubMed] [Google Scholar]
[47]Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst Rev 2006;(3):CD001060. [PubMed] [Google Scholar]