Published in final edited form as:
Int J Gynaecol Obstet. 2011 December ; 115(3): 215–219. doi:10.1016/j.ijgo.2011.07.017.

A conference report on prenatal corticosteroid use in low- and middle-income countries

Elizabeth M. McClure[a,*], **Joseph de Graft-Johnson**[b], **Alan H. Jobe**[c], **Steve Wall**[d], **Marge Koblinsky**[e], **Allisyn Moran**[b], **Linda L. Wright**[f], **Winifride Mwebesa**[b], **Marion Koso-Thomas**[f], and **Robert L. Goldenberg**[g] **Maternal and Child Health Integrated Project (MCHIP) Antenatal Corticosteroid Conference Working Group**[1]

[a]Research Triangle Institute, Durham, USA

[b]Maternal and Child Health Integrated Project, Washington, USA

[c]Cincinnati Children's Hospital, Cincinnati, USA

[d]Save the Children, Washington, USA

[e]John Snow Incorporated, Washington, USA

[f]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, USA

[g]Drexel University, College of Medicine, Philadelphia, USA

Abstract

Objective—To evaluate the evidence for prenatal corticosteroid use in low- and middle-income countries and to make recommendations regarding implementation and further research.

Methods—Studies and meta-analyses on prenatal corticosteroids relevant to low- and middle-income countries were identified and reviewed at the Maternal and Child Health Integrated Project (MCHIP) Antenatal Corticosteroid Conference held in Washington on October 19, 2010.

Results—There is strong evidence regarding the effectiveness of prenatal corticosteroid use in hospitals in high- and middle-income countries, usually in settings with high-level newborn care. For births occurring in hospitals in low-income countries without high-level neonatal care or for

[*]Corresponding author: Elizabeth M. McClure, Department of Epidemiology and Biostatistics, Research Triangle Institute, 3040 Cornwallis Road, Durham, NC 27709, USA. Tel.: +1 919 316 3773; fax: +1 919 647 4160. mcclure@rti.org.

[1]Conference attendees: Koki Agarwal (MCHIP); Debra Armbruster (USAID); Massee Bateman (Save the Children, Saving Newborn Lives); Neal Brandes (USAID); Pierre Buekens (Tulane School of Public Health and Tropical Medicine); Joseph de Graft-Johnson (MCHIP); Michael Gravett (Global Alliance for Prevention of Preterm and Stillbirth); Robert L. Goldenberg (Drexel University College of Medicine); Steve Hodgins (MCHIP); Alan H. Jobe (University of Cincinnati, Cincinnati Children's Hospital); Tina Johnson (American College of Nurse Midwives); Lily Kak (USAID); Marge Koblinsky (John Snow Incorporated, MCHIP); Marion Koso-Thomas (NICHD); Eve Lackritz (Centers for Disease Control); Nahed Matta (USAID); Elizabeth M. McClure (Research Triangle Institute); Allisyn Moran (Save the Children, Saving Newborn Lives); Winnie Mwebesa (MCHIP, Save the Children); Doyin Oluwole (Africa 2010); Anne Pfitzer (Save the Children, Saving Newborn Lives); Harshad Sanghvi (Jhpiego); Steve Wall (Save the Children, Saving Newborn Lives); Defa Wane (MCHIP, Save the Children); Linda L. Wright (NICHD). Rapporteurs: Rachel Taylor; Lara Martin; Deborah Sitrin (all MCHIP, Save the Children, Saving Newborn Lives).

Conflict of interest The authors have no conflicts of interest.

births outside hospitals, no studies have been conducted to evaluate prenatal corticosteroid use. The efficacy and safety of prenatal corticosteroid use in these settings must be evaluated.

Conclusions—The conference working group recommended expanding the use of prenatal corticosteroids in hospitals with high-level newborn care in low-income countries. For other low-income country settings, further research regarding efficacy and safety should precede the widespread introduction of prenatal corticosteroids.

Keywords

Low-resource countries; Prenatal corticosteroids; Preterm birth

Introduction

An estimated 9.6% of births worldwide are preterm (approximately 13 million births annually), with rates ranging from 7%–12% in high-income countries (HICs) to as high as 20% in some areas of Africa [1]. With few, if any, effective prevention measures on the horizon, the rate of preterm birth is expected to remain the same or increase worldwide, as it has in many HICs—predominantly because of physician-initiated deliveries for various maternal and fetal conditions, driven in part by the improving survival of these newborns in intensive care units. It is likely that a similar phenomenon will occur as preterm survival increases in low- and middle-income countries (LMICs) [1-3]. Preterm birth contributes to more than 1 million neonatal deaths worldwide each year [2]. Among infants born preterm, respiratory distress syndrome (RDS) is the most common cause of death [4]; those who survive are at significantly increased risk of morbidities such as cerebral palsy, learning disabilities, and respiratory disorders [5].

The administration of prenatal corticosteroids occurs routinely in HICs for women at risk of delivering preterm infants at less than 34 weeks, in order to improve maturation of the lungs and other organs. This therapy—generally, a suspension of betamethasone phosphate plus betamethasone acetate or dexamethasone—is administered via 2–4 injections in a 48-hour period within 1 week of delivery. The original report on the use of prenatal corticosteroids to improve newborn outcome was by Liggins and Howie in 1972 [6]. More than 20 subsequent randomized controlled trials were summarized in a comprehensive meta-analysis in 1995 and updated in 2006 [7,8]. The primary benefits to infants whose mothers receive prenatal corticosteroids at least 12 hours before delivery are decreases in RDS, intraventricular hemorrhage (IVH), and neonatal mortality. Prenatal corticosteroid use has no contraindications, other than clinical chorioamnionitis (imminent delivery is sometimes listed as a contraindication, not because of potential harm but because of lack of efficacy) [9]. The use of prenatal corticosteroids at 34–38 weeks has also been studied but it has a less clear role in improving neonatal outcome. In HICs, where high-level perinatal care can be provided to the mother and the infant, nearly 90% of women at risk of preterm birth at <34 weeks receive this therapy [10].

Prenatal corticosteroids are inconsistently used in LMICs. Evidence highlighted in the present paper will show that, across LMICs, prenatal corticosteroid coverage for at-risk women is likely to be less than 10%. One meta-analysis indicated that the benefits of prenatal corticosteroids may be similar in middle-income countries (MICs) and HICs [11]. Few, if any, studies have evaluated prenatal corticosteroid efficacy or safety in low-income country (LIC) settings, specifically among deliveries for which advanced maternal and infant care is unavailable.

On October 19, 2010, the US Agency for International Development (USAID)'s Maternal and Child Health Integrated Project (MCHIP), Save the Children, the National Institute of

Child Health and Human Development (NICHD)'s Global Network for Women's and Children's Health Research, Research Triangle Institute, and other organizations convened a meeting to review the evidence for use of prenatal corticosteroids in LMICs in Washington, USA. Specifically, the meeting aimed to review the evidence of improved newborn outcomes through the use of prenatal corticosteroids, and the approaches needed to increase the use and coverage of this intervention in LMICs. In addition, it sought to identify key research gaps, program-monitoring and evaluation indicators, and potential for programmatic implementation in LMICs.

Prenatal corticosteroid use in high-income countries

The general consensus, based on studies from HICs, is that prenatal corticosteroids are effective at decreasing neonatal mortality in infants born at 24–34 weeks [8,9,12-14]. A meta-analysis of 21 clinical trials concluded that prenatal corticosteroids were effective at reducing neonatal mortality (relative risk [RR] 0.69; 95% confidence interval [CI], 0.58–0.81) and RDS (RR 0.66; 95% CI, 0.59–0.73) among all races, in infants of both sexes, at 31–34 weeks, as well as before 31 weeks and possibly after 34 weeks [8]. Prenatal corticosteroids also decreased IVH in infants at 24–31 weeks of gestation, in infants treated with tocolytics, and in infants with severe RDS. In addition, compared with placebo treatment, prenatal corticosteroid administration was not associated with an increased risk of maternal or neonatal infection when given either with intact membranes or with premature rupture of membranes [8]. Furthermore, studies evaluating the long-term outcomes of children exposed to prenatal corticosteroids found no associated negative effects [4]. The National Institute of Health Consensus Panel concluded that the benefits of any prenatal corticosteroid therapy to fetuses at risk of preterm delivery in HICs vastly outweigh the potential risks [15]. Benefits include not only a reduction in the risk of RDS but also a substantial reduction in neonatal mortality and IVH [16,17]. The use of prenatal corticosteroids, specifically betamethasone, is among the best-studied interventions in perinatal and neonatal medicine.

Despite widespread agreement in HICs regarding the benefits of prenatal corticosteroid use at 24–33 weeks, several questions remain. For example, as the survival of infants born at early gestational ages has increased, questions regarding the efficacy of the intervention at 22 and 23 weeks have been raised [18]. Similarly, because there is growing evidence of increased respiratory distress and other adverse outcomes among infants born at 34–38 weeks compared with those born at 39 and 40 weeks, the potential for prenatal corticosteroid use among women expecting delivery at 34–38 weeks is being queried [19]. For women undergoing elective cesarean at 34 weeks or later, there is also emerging evidence that prenatal corticosteroid use may reduce post-delivery neonatal respiratory distress [20]. Finally, there remain questions about the most efficacious prenatal corticosteroid preparation [21]. Several studies indicate that betamethasone may be more efficacious than dexamethasone, in addition to potentially having fewer adverse effects, and that the suspension of betamethasone phosphate and betamethasone acetate may be more efficacious than other betamethasone preparations [8].

Prenatal corticosteroids in low- and middle-income countries

Few studies have evaluated the use of prenatal corticosteroids in LMICs. In Southeast Asia, the administration of prenatal corticosteroids to women at less than 34 weeks varied widely between countries (from 9% to 73%), and within these countries appropriate usage varied widely between hospitals (from 0% to 86%) [22]. Of interest, dexamethasone was the only type of prenatal corticosteroid used in the participating countries. In another review of LMIC prenatal corticosteroid studies, the highest rates of use were in MICs, where up to

30% of eligible women may receive prenatal corticosteroids [11]. However, in many areas of Africa, less than 5% of eligible pregnant women receive prenatal corticosteroids, and in many areas this treatment is not available at all [23].

Four trials to evaluate efficacy were conducted in MIC hospitals at which neonatal support was generally available [24-27] (Table 1). The efficacy was similar to that reported in HIC studies. A recent meta-analysis noted that the reduction in neonatal mortality associated with prenatal corticosteroid use varied according to baseline mortality rate, with a larger reduction in MICs—where there were higher mortality rates—than in HICs [11]. There was a notable absence of comparable studies from LICs.

As noted, prenatal corticosteroids have been established as being beneficial to women who are at risk of preterm delivery at 24–33 weeks. However, in the absence of ultrasound, determining accurate gestational age and, therefore, who to treat with corticosteroids is an important issue to consider in LMICs, where many women receive only minimal prenatal care [28]. In these areas, there will likely be over-treatment of women who deliver at term and under-treatment of those who deliver prematurely, which could not only waste limited resources but also be associated with increased risk. Thus, the overall mortality and morbidity rates associated with prenatal corticosteroid use may be different from that in HICs.

Another consideration is that the studies of prenatal corticosteroid use in HICs were nearly all performed in hospitals with a high level of newborn care (which may be defined as the ability to maintain adequate temperature; to provide nutritional support; and to give antibiotics, oxygen, and neonatal respiratory support to the level of continuous positive airway pressure), and most often with newborn intensive care available. Thus, evidence of prenatal corticosteroid effectiveness is available only for those types of setting. In LMICs, in the absence of high-level neonatal care, a potential outcome is that the use of prenatal corticosteroids would lead to a reduction in neonatal mortality as a result of decreases in the incidences of RDS and IVH—similar to the effects in HICs. Furthermore, lung maturation induced by prenatal corticosteroids may be more crucial in LMICs than in HICs with regard to the survival of moderately preterm infants or even early term infants, whereas there may be fewer benefits for the most preterm infants in LMICs—where high-level neonatal care may be lacking. The higher prevalence of mortality among moderately preterm infants compared with extremely preterm infants may lead to a larger proportion of lives saved in LMICs than in HICs as a result of prenatal corticosteroid use.

However, there is concern that, even if deliveries occur in a hospital, prenatal corticosteroid treatment in the absence of high-level neonatal and obstetric care could worsen some maternal and neonatal outcomes. For example, corticosteroids used for other indications decrease immune function and increase susceptibility to a variety of infections. In many LMICs, the infectious disease burden is higher and the level of antiseptic precautions is lower than in HICs. In these settings, prenatal corticosteroids may increase susceptibility to acute bacterial infections and may lead to higher maternal and neonatal case fatality rates. In addition, the effect of prenatal corticosteroids on prevalent chronic maternal infectious conditions in LICs (e.g. HIV, malaria, and tuberculosis) is largely unknown, but a concern. Because half of all infants in LICs are born at home and many others are born in poorly staffed and poorly equipped clinics, such concerns are increased for infants delivered in these settings [28].

Furthermore, although prenatal corticosteroid use has not been associated with long-term developmental impairment in HICs, there is concern that, even if neonatal mortality in LMICs is reduced by this intervention, the infants who survive may have a high risk of

developmental handicap. This is of potential concern in areas where there is minimal support to care for preterm infants and those with impairment.

In summary, prenatal corticosteroid use is standard care in HICs for women at risk of preterm delivery. Furthermore, there is evidence that, in geographic areas with access to high-level neonatal care but with low rates of prenatal corticosteroid use, significant improvements in outcome associated with preterm birth could be achieved. There are no data regarding the efficacy or safety of prenatal corticosteroids in any LICs with or without access to high-level newborn care; thus, a number of important questions remain about scaling-up the use of this intervention in these settings.

Considerations for corticosteroid use in low-income countries

The conference working group addressed a number of questions regarding the use of prenatal corticosteroids, especially in LICs. One of these questions was whether, based on available evidence, there were LIC settings in which prenatal corticosteroid use should be expanded at the present time. The group concluded that such use should not be based on whether the site was in an LIC, an MIC, or an HIC, but instead should be based on the level of care at the facility at which the delivery was to take place. The conference members agreed that the evidence of prenatal corticosteroid efficacy was sufficiently strong that hospitals providing a reasonable level of maternal care and high-level newborn care should use this treatment. There was also a consensus that the lack of evidence of prenatal corticosteroid efficacy and safety in geographic areas without high-level newborn care for preterm infants did not support its use.

Programmatic considerations for prenatal corticosteroids in low-income countries

Prenatal corticosteroids were introduced more than 10 years ago in tertiary hospitals in several LICs, including Nepal, Kenya, Uganda, and Tanzania. Current prenatal corticosteroid availability/usage has not been well tracked but is estimated to be less than 5% of eligible women [29]. Considering the working group's conclusions regarding efficacy and the very low use of prenatal corticosteroids in many LMIC hospitals (even those with high-level newborn care), the first programmatic priority is to increase the appropriate use of this intervention in these hospitals. Programmatic issues related to increasing use in hospitals with high-level newborn care could be considered by a number of levels, including those related to international agencies, national programs, health systems, and hospitals, and at the community level with the women themselves. At the global level, the group recommended the engagement of organizations such as World Health Organization (WHO), United Nations Population Fund (UNFPA), and International Federation of Gynecology and Obstetrics (FIGO) to review existing guidelines and develop a joint statement on the use of prenatal corticosteroids. Furthermore, a landscape analysis of countries that either used or were poised to introduce and/or expand use of prenatal corticosteroids was recommended. The previously mentioned international health and donor agencies could, for example, establish guidelines for prenatal corticosteroid use, recommend appropriate formulations, and provide support for countries that adopt those guidelines. At the country level, after assessing the current situation regarding prenatal corticosteroid utilization and associated barriers in health facilities, guidelines for use of the intervention could be developed and a formulation could be chosen, approved for obstetric use, and made widely available through public and private pharmacies. Countries could also identify, and perhaps expand, the types of providers who can determine the need for treatment and administer prenatal corticosteroid injections. From the health system perspective, hiring and/or training skilled birth attendants who can identify women at risk of preterm births, who have knowledge regarding

appropriate timing and use of prenatal corticosteroids, and who can refer mothers to higher levels of care is required for effective scale-up of prenatal corticosteroid use. Developing or supporting policies and mechanisms to transport women at risk of preterm delivery to hospitals with prenatal corticosteroids would also be important.

At hospitals where prenatal corticosteroid use is considered appropriate, several programmatic questions also arise. The most important is how to increase prenatal corticosteroid use, including training of providers, maintenance of the supply chain, and making sure that the treatment can be administered in a timely manner. There are also a number of crucial issues in communities where the majority of births and related care occur in home settings: for example, how to engage mothers who intend to deliver at home and their caregivers to identify early signs of preterm labor, and to encourage families to seek care at hospitals that provide prenatal corticosteroids and newborn care. Including the community will be important for the success of most strategies aimed at addressing preterm birth in LMICs. Although programmatic strategies to increase prenatal corticosteroid use in LMIC hospitals will differ by country (middle-income versus low-income) and health system, a concerted effort at multiple levels will be required to increase its use substantially in most areas. If prenatal corticosteroids proved to be safe and effective in LIC settings beyond hospitals with high-level newborn care, several other programmatic issues would arise that may impact their availability and use in those settings.

Research questions in low- and middle-income countries

As noted, there is a clear consensus about the efficacy of prenatal corticosteroid use for women at 24–34 weeks in reducing the risk of neonatal RDS and mortality in HICs and MICs with access to high levels of neonatal care. Research questions in these settings relate to extending the criteria for prenatal corticosteroid use to earlier and later gestational ages and for use among women undergoing cesarean at later gestational ages. For example, prenatal corticosteroids are being evaluated for infants born between 34 and 38 weeks (e.g. ClinicalTrials.gov-registered NCT00675246). Evidence of efficacy in infants born at 34–38 weeks is especially important in LICs, where mortality among such infants remains high. If prenatal corticosteroids were found to be effective beyond 34 weeks, it would make it easier to use them in LICs, where determination of gestational age is often problematic. Additionally, it has not been firmly established whether prenatal corticosteroid use among women undergoing cesarean at later gestational age is beneficial (e.g. Clinical Trials.gov-registered NCT00446953). With the increasing prevalence of cesarean delivery worldwide, this evidence may be especially important. Finally, research should be conducted to define the most efficacious prenatal corticosteroid preparation.

Research questions also remain regarding the efficacy of prenatal corticosteroids in LMIC settings, in which basic newborn care may be limited, high-level newborn care is often not available, and the infection burden may be high. The infants benefitting from prenatal corticosteroids, especially in LICs, may differ with regard to location of care, provider skills, and gestational age from those in HICs, so rethinking the target population for prenatal corticosteroid use in LICs is important.

The safety of prenatal corticosteroids for both the mother and the fetus has been well demonstrated in HICs. However, in LICs—where poor hygiene and potential delays in the recognition and treatment of maternal and neonatal infections are significant concerns—the use of this intervention may not have the same safety profile. Determining whether its use increases susceptibility to maternal and neonatal infections in LIC settings, especially where there is inadequate maternal and newborn care, is crucial prior to widespread introduction of the intervention.

Little is known about effective strategies to provide high coverage of prenatal corticosteroids to women in LICs, although initial expansion of use through tertiary, secondary, and primary health facilities seems the most likely delivery strategy. The use of community-based strategies to identify and treat women who have limited access to and/or frequent delays in reaching health facilities would also be crucial in settings in which home delivery is predominant. A trial is currently underway to evaluate the impact of prenatal corticosteroids in community-based settings in 6 LMICs with varying levels of coverage (ClinicalTrials.gov-registered NCT01084096). Finally, there is little information regarding the required supportive neonatal care for preterm infants. For example, kangaroo (skin-to-skin) care has been suggested as an alternate method for providing warmth and support for preterm newborns when high-level care is unavailable, but its efficacy for reducing neonatal mortality and morbidity in conjunction with prenatal corticosteroids has not been demonstrated.

Because increased coverage of prenatal corticosteroid use in LMICs was recommended, a conference subcommittee also met to review potential considerations in monitoring and evaluation of the intervention in these settings. For settings with low coverage, the group recognized that a phased approach to scaling-up use of prenatal corticosteroids would likely be required, which would enable evaluation of the effect of the introduction/expansion of prenatal corticosteroids. Issues to be addressed might include: availability of prenatal corticosteroids at clinics and hospitals; authorization for providers to use prenatal corticosteroids at home, clinics, and hospitals; number of pregnant women admitted to hospitals and clinics, and gestational age at delivery (best obstetric estimate); rates of prenatal corticosteroid use at hospitals and clinics; and outcomes for mothers, fetuses, and infants with prenatal corticosteroid use. The amount of data collected and the method of collection would need to be tailored to local settings; however, the primary goal would be to include mechanisms to evaluate the safety and efficacy of prenatal corticosteroid use in settings in which it is newly introduced or expanded. Rates of use, as well as important outcomes such as mortality and RDS, should be evaluated over time. To evaluate the effectiveness of this intervention, these outcomes should be assessed in comparison sites at which prenatal corticosteroids have not yet been introduced.

Conclusion

In HICs and some MICs, prenatal corticosteroids effectively reduce neonatal mortality and RDS associated with preterm birth (at 24–34 weeks). Some questions remain regarding the optimal timing and preparation of use, in addition to the potential for use among certain subpopulations of women. In LICs with referral facilities providing high-level newborn care, prenatal corticosteroids should reduce neonatal mortality and morbidity associated with preterm birth. Studies in MICs have indicated that the size of the effect may be greater in areas with higher mortality rates and where late preterm deliveries account for a high proportion of deaths. However, prenatal corticosteroids have not been tested in LIC settings without high-level neonatal care. Furthermore, for births that occur in the community (i.e. in a health center or at home), there are no data to evaluate the impact of prenatal corticosteroid use. Because this intervention transiently suppresses the immune response, there are potential risks to the use of prenatal corticosteroids in settings with high rates of maternal and neonatal infections.

Based on the review by the conference members, the best opportunity to reduce neonatal mortality in LMICs through use of prenatal corticosteroids is through promoting the use of this intervention in health facilities with high-level neonatal care, where current rates of availability and use are low. In these settings, ensuring that health providers are trained on prenatal corticosteroid usage, that prenatal corticosteroids are routinely available, and that

all eligible women receive timely administration would be important first steps in reducing neonatal mortality and morbidity associated with preterm birth.

Acknowledgments

The MCHIP Antenatal Corticosteroid Conference was supported through USAID grants to MCHIP. The work was also supported through grants from the NICHD Global Network for Women's and Children's Health Research.

References

1. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ. 2010; 88(1):31–8. [PubMed: 20428351]
2. Lawn JE, Cousens S, Zupan J. Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? Lancet. 2005; 365(9462):891–900. [PubMed: 15752534]
3. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008; 371(9606):75–84. [PubMed: 18177778]
4. Kamath BD, Macguire ER, McClure EM, Goldenberg RL, Jobe AH. Neonatal mortality from respiratory distress syndrome: lessons for low-resource countries. Pediatrics. 2011; 127(6):1139–46. [PubMed: 21536613]
5. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008; 371(9608):261–9. [PubMed: 18207020]
6. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics. 1972; 50(4):515–25. [PubMed: 4561295]
7. Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Am J Obstet Gynecol. 1995; 173(1):322–35. [PubMed: 7631713]
8. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006; 3:CD004454. [PubMed: 16856047]
9. Miracle X, Di Renzo GC, Stark A, Fanaroff A, Carbonell-Estrany X, Saling E, et al. Guideline for the use of antenatal corticosteroids for fetal maturation. J Perinat Med. 2008; 36(3):191–6. [PubMed: 18576926]
10. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010; 126(3): 443–56. [PubMed: 20732945]
11. Mwansa-Kambafwile J, Cousens S, Hansen T, Lawn JE. Antenatal steroids in preterm labour for the prevention of neonatal deaths due to complications of preterm birth. Int J Epidemiol. 2010; 39(Suppl 1):i122–33. [PubMed: 20348115]
12. Crane J, Armson A, Brunner M, De La Ronde S, Farine D, Keenan-Lindsay L, et al. Antenatal corticosteroid therapy for fetal maturation. J Obstet Gynaecol Can. 2003; 25(1):45–52. [PubMed: 12548324]
13. Royal College of Obstetricians and Gynaecologists. Antenatal Corticosteroids to Reduce Neonatal Morbidity. www.rcog.org.ukhttp://www.rcog.org.uk/files/rcog-corp/GTG%207.pdf. Published 2010
14. Committee on Obstetric Practice. ACOG committee opinion. Antenatal corticosteroid therapy for fetal maturation. American College of Obstetricians and Gynecologists. Int J Gynecol Obstet. 2002; 78(1):95–7.
15. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Statement. 1994; 12(2):1–24.
16. Doyle LW, Ehrenkranz RA, Halliday HL. Dexamethasone treatment in the first week of life for preventing bronchopulmonary dysplasia in preterm infants: a systematic review. Neonatology. 2010; 98(3):217–24. [PubMed: 20389126]

17. Been JV, Rours IG, Kornelisse RF, Lima Passos V, Kramer BW, Schneider TA, et al. Histologic chorioamnionitis, fetal involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. Am J Obstet Gynecol. 2009; 201(6):587.e1–8. [PubMed: 19729143]

18. Abbasi S, Oxford C, Gerdes J, Sehdev H, Ludmir J. Antenatal corticosteroids prior to 24 weeks' gestation and neonatal outcome of extremely low birth weight infants. Am J Perinatol. 2010; 27(1):61–6. [PubMed: 19544249]

19. Shanks A, Gross G, Shim T, Allsworth J, Sadovsky Y, Bildirici I. Administration of steroids after 34 weeks of gestation enhances fetal lung maturity profiles. Am J Obstet Gynecol. 2010; 203(1): 47.e1–5. [PubMed: 20478551]

20. McEvoy C, Schilling D, Peters D, Tillotson C, Spitale P, Wallen L, et al. Respiratory compliance in preterm infants after a single rescue course of antenatal steroids: a randomized controlled trial. Am J Obstet Gynecol. 2010; 202(6):544.e1–9. [PubMed: 20227053]

21. Strickland DM. Antenatal betamethasone compared with dexamethasone (betacode trial): a randomized controlled trial. Obstet Gynecol. 2007; 110(4):930. [PubMed: 17906034]

22. Pattanittum P, Ewens MR, Laopaiboon M, Lumbiganon P, McDonald SJ, Crowther CA, et al. Use of antenatal corticosteroids prior to preterm birth in four South East Asian countries within the SEA-ORCHID project. BMC Pregnancy Childbirth. 2008; 8:47. [PubMed: 18925968]

23. Tita AT, Selwyn BJ, Waller DK, Kapadia AS, Dongmo S. Factors associated with the awareness and practice of evidence-based obstetric care in an African setting. BJOG. 2006; 113(9):1060–6. [PubMed: 16956337]

24. Pattinson RC, Makin JD, Funk M, Delport SD, Macdonald AP, Norman K, et al. The use of dexamethasone in women with preterm premature rupture of membranes--a multicentre, double-blind, placebo-controlled, randomised trial. Dexiprom Study Group. S Afr Med J. 1999; 89(8): 865–70. [PubMed: 10488363]

25. Amorim MM, Santos LC, Faúndes A. Corticosteroid therapy for prevention of respiratory distress syndrome in severe preeclampsia. Am J Obstet Gynecol. 1999; 180(5):1283–8. [PubMed: 10329891]

26. Fekih M, Chaieb A, Sboui H, Denguezli W, Hidar S, Khairi H. Value of prenatal corticotherapy in the prevention of hyaline membrane disease in premature infants. Randomized prospective study. Tunis Med. 2002; 80(5):260–5. [PubMed: 12534029]

27. Qublan HS, Malkawi HY, Hiasat MS, Hindawi IM, Al-Taani MI, Abu-Khait SA, et al. The effect of antenatal corticosteroid therapy on pregnancies complicated by premature rupture of membranes. Clin Exp Obstet Gynecol. 2001; 28(3):183–6. [PubMed: 11530870]

28. Darmstadt GL, Bhutta ZA, Cousens S, Adam T, Walker N, de Bernis L, et al. Evidence-based, cost-effective interventions: how many newborn babies can we save? Lancet. 2005; 365(9463): 977–88. [PubMed: 15767001]

29. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS. Bellagio Child Survival Study Group. How many child deaths can we prevent this year? Lancet. 2003; 362(9377):65–71. [PubMed: 12853204]

Table 1

Randomized controlled trials of corticosteroid use in middle-income countries

Location, year	Number enrolled	Drug studied	Relative risk (95% confidence interval)	
			Neonatal death	Respiratory distress syndrome
Brazil (1997–1998) [25]	220	Betamethasone	0.50 (0.28–0.89)	0.53 (0.35–0.82)
South Africa (1999) [24]	206	Dexamethasone	0.48 (0.15–1.55)	1.16 (0.75–1.79)
Tunisia(1998–1999) [26]	131	Betamethasone	0.46 (0.23–0.93)	0.17 (0.05–0.55)
Jordan (1997–1999) [27]	137	Dexamethasone	0.45 (0.29–0.70)	0.54 (0.31–0.95)
Total [a]	694	—	0.47 (0.35–0.64)	0.63 (0.49–0.81)

[a] Meta-analysis of relative risk [11].