Meta-Analysis

A Meta-Analysis on the long-term effects of repeated exposure to antenatal corticosteroids given to women at risk of preterm birth

Karein Therese Alparas* and Zarinah Gonzaga
Department of Obstetrics and Gynecology, The Medical City, Ortigas Avenue, Pasig City
*Contact Details: karein_12@hotmail.com

ABSTRACT: Randomized controlled trials have shown that repeated exposure to antenatal corticosteroids improve specific neonatal outcomes in infants born preterm but increases the risk of small for gestational age and low birth weight infants. Our study determined the effects of repeated exposure to antenatal corticosteroids on the development of cerebral palsy. A comprehensive search on PubMed, Science Direct, MEDLINE, Cochrane CENTRAL, HERDIN, and Google Scholar was done to identify randomized controlled trials, and three articles were included. The study population comprised of parturients between 24 1/7 to 34 6/7 weeks who were exposed to repeated doses of prenatal corticosteroids versus placebo. Our primary outcome was to determine the benefits of antenatal corticosteroids in reducing neonatal morbidities after preterm birth. Children exposed who experienced multiple treatments of antenatal corticosteroids had similar rates of developing cerebral palsy compared to those who were given a single course. Multiple doses of corticosteroid therapy given weekly or every 2 weeks did not provide an increased risk of developing cerebral palsy compared with a single course. However, long-term monitoring is necessary to determine its behavioral and cognitive effects during adolescence and adulthood.
Keywords: *antenatal corticosteroids, preterm birth, preterm labor, repeat, rescue dose*

INTRODUCTION

Preterm neonates are estimated to comprise 11.1% of all live births and preterm birth is a risk factor for at least 50% of all neonatal deaths.[2] The Philippines ranks 8th out of 184 countries with preterm births and ranks 17th in total number of deaths caused by complications of prematurity. This increasing trend has been attributed to the increasing number of teenage pregnancies and lack of public awareness.[3]

Preterm delivery, regardless of the gestational age, causes short- and long-term neonatal morbidities including impaired neurodevelopmental functions, infection, learning impairment, visual disorders, and pulmonary complications.[3] Since the pulmonary system is the last to develop, the lungs are the most commonly affected. Hence, prevention of preterm birth is the ultimate goal. One established intervention is the administration of antenatal corticosteroids to mothers at risk of preterm delivery. A randomized controlled trial on maternal administration of betamethasone showed a decreased incidence of respiratory distress syndrome in preterm infants from 15.6% to 10.0% as well as a reduction in neonatal mortality from 11.6% to 6.0%.[1,2] Since then, the National Institutes of Health (NIH) along with American Congress of Obstetricians and Gynecologists (ACOG), has recommended the use of antenatal corticosteroids for women at risk of preterm birth between 24 and 34 weeks age of gestation.[2] However, steroid effect diminishes through time and has raised concern in the management of women initially given a single course of steroids but still at risk of preterm delivery.

During the 1990's, administration of repeated doses of antenatal corticosteroids became rampant triggering the National Institutes of Health (NIH) to caution on limiting the use of repeated corticosteroids to patients participating in randomized trials.

It has been standard practice in the Philippines to provide pregnant women between 24 to 34 weeks of gestation, at risk of preterm delivery, antenatal corticosteroids to enhance fetal lung maturity. If these patients remain pregnant after an initial course of corticosteroids, some obstetricians opt to give a rescue dose while others question its necessity. Despite multiple studies, a consensus regarding steroid duration has yet to be reached.

We aimed to assess the risk of repeated corticosteroid exposure of pregnant women at risk of preterm birth and focused on cerebral palsy as the primary outcome. We also aimed to combine current and relevant data from various studies to come up with a recommendation that can be integrated into standard practice.

METHODS

A meta-analysis of retrospective observational studies on the long term neurodevelopmental effects of repeated exposure to antenatal corticosteroids was performed.

Criteria for Considering Studies for this Review

Types of Studies

All published retrospective observational cohort studies that met the following criteria were included: (1) studies that compared the long term effects of multiple doses of prenatal corticosteroids versus placebo; (2) retrospective cohort studies that involved repeated exposure of pregnant women between 23-32 weeks age of gestation to multiple courses of prenatal corticosteroids; (3) retrospective cohort studies that followed-up exposed patients from up to early school age

Exclusion criteria were the following: (1) Articles involving animal subjects; (2) Papers using other study designs; (3) Clinical trials with different outcomes measured; (4) Clinical trials that administered only a single rescue dose; (5) Articles with no English translation; (6) studies that focused on the effects of a single dose versus multiple exposure to corticosteroids

Types of participants

Study participants were pregnant women between the ages of 23-32 weeks age of gestation who remained at risk of preterm birth despite treatment and initial administration of antenatal corticosteroids. Women were included regardless of their parity and age. Infants were followed up until early childhood age to assess for any neurologic or behavioral changes related to their exposure to repeated doses of corticosteroids.

Outcome measures

The primary outcome measured was the development of a neurocognitive impairment, specifically, cerebral palsy.

Search Methods Incorporation of Studies

A literature search for full papers and abstracts between January 2000-January 2016 using PubMed, Science Direct, MEDLINE, Cochrane CENTRAL, and HERDIN was done to determine the long term effects of repeated exposure to antenatal corticosteroids during threatened preterm labor. The keywords used were “antenatal/prenatal corticosteroids”, “glucocorticoid”, “Betamethasone”, “Dexamethasone”, “rescue”, “repeat”, “multiple” and “cerebral palsy”. Filters were activated to limit the search to retrospective observational cohort studies that were published within the last 16 years. Language restriction was limited to the English language.

Data Collection and Analysis

Selection of trials and Assessment of methodological quality

During the literature search, various abstracts were identified. Full articles were retrieved and assessed for methodological quality using the standards set by the Cochrane Handbook for Systematic Reviews of Interventions.

Data Analysis

Statistical analysis was done using the Review Manager 5 Software (RevMan5 2014). Extracted data from the three included studies were quantitative. The analysis of the primary outcome was set to a fixed effect model with a 95% confidence interval (CI). The development of cerebral palsy was categorized as dichotomous data and risk ratio (RR) under Mantel-Haenszel (M-H) was used for analysis.

RESULTS

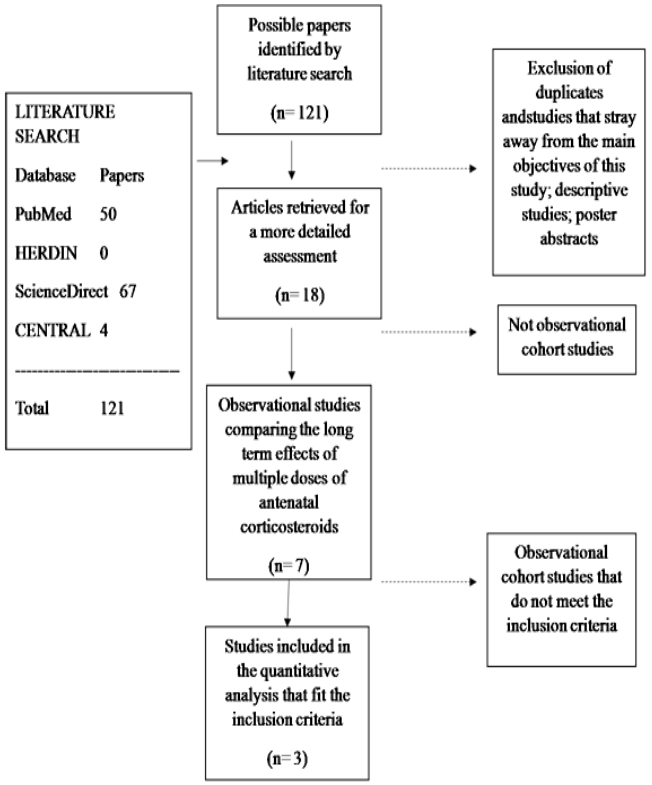
Three retrospective observational cohort studies satisfied the inclusion criteria. Data from these trials were computed to determine the risk of developing cerebral palsy. No local trials were identified by the search.

Figure 1 shows the search scheme through which trials were included in the study. Full papers and abstracts were manually reviewed for inclusion in the study.

Figure 2 presents the data that were collected from the three included studies on the number of infants who developed cerebral palsy during the follow-up period. Asztalos et. al. (2010) (RR=0.93, 95%CI=0.53, 1.62)[4] and Crowther et. al. (2007) (RR=0.89, 95% CI 0.51, 1.56)[5] claim that multiple exposure to antenatal corticosteroids increase the risk of developing cerebral palsy compared to patients who were given placebo. In contrast, the study of Wapner et. al. (2007) (RR=5.76, 95% CI=0.70, 47.47)[6] indicated that multiple exposure to antenatal corticosteroid may not increase the risk of developing cerebral palsy. This study also has a wide range of confidence interval, indicating an uncertainty in the true effect of its results.

The Forest Plot (Figure 2) shows that there is no significant difference between the two treatments. All three studies give an I2 statistic value of 31%, giving a non-significant test for heterogeneity.

Figure 1. PRISMA flow diagram of study inclusion in the Meta-Analysis



DISCUSSION

Since the assembly of the NIH in 2000, the use of repeat courses of antenatal corticosteroids has been restricted to patients enrolled in randomized controlled clinical trials of sufficient power to evaluate both short-term and long-term efficacy and safety.[7] These trials concluded that treatment of women at risk of preterm birth with repeat courses of antenatal corticosteroids significantly reduced the risk of neonatal respiratory distress syndrome, serious infant morbidity and severe lung disease.[8] However, along with these findings, some studies also reported a mean reduction in birth weight and increase in small for gestational age infants.[6]

Although there have been multiple trials on the use of antenatal corticosteroids, data is conflicting. In the multiple courses of antenatal corticosteroids for preterm birth (MACS) trial, women who were given corticosteroids every 14 days did not appreciate neonatal benefits at birth but instead noted a reduced size at birth compared with a single course.[9] In a randomized controlled trial by Guinn et al., no reduction in composite neonatal morbidity was noted in weekly courses of antenatal corticosteroids compared to a single treatment.[10] Statistical significance in the decreased composite neonatal morbidity was only achieved in neonates delivered at <28 weeks age of gestation.

While results on the short term effects are conflicting, long-term studies, especially on neurodevelopmental effects are scarce and limited to cohort studies.

Based on the results of the meta-analysis, the relative risk of developing cerebral palsy was higher in those exposed to multiple treatments of corticosteroids compared to those studies in which placebo is given.[4,5] Another study showed an increased risk in those patients given placebo, but with a wide confidence interval, the estimated effect of its results may be uncertain.[6] Overall, the three studies gave no statistically significant differences between the repeat corticosteroid group compared to the placebo (RR 1.01, 95%CI=0.69, 1.47). The computed value of I2 statistic was less than 50%, indicating that the effects of the studies were reliable and not due to chance alone.

An in-depth analysis of the methodology of the studies revealed that Asztalos et. al. (2010) and Wapner et. al. (2007) both administered weekly courses of corticosteroids until 32 weeks or delivery, whereas, Crowther & Harding (2007) repeated the treatment every 14 days. The maximum number of treatment course that was given in all trials was 4 due to safety concerns about excessive dosing. Six infants in the repeat treatment group, born at or after 34 weeks, developed cerebral palsy cautioning the repetitive use of this treatment.[6] This contradicts the study by French et al. who found that children exposed to repeated courses are protected from cerebral palsy.[11]

The result of this meta-analysis is potentially reassuring. Clinicians can opt to maximize the benefits of repeated corticosteroid administration. However, long term follow-up studies are necessary to determine other outcomes as studies only included children up to two years of age.

Table 1. Included observational cohort studies

Study and Location	GA at randomization, week	Minimal interval from first steroids to randomization	Intervention	Number of women randomized (live fetuses)	Mean GA at birth, week	Number of study treatments received= parturients
MACS-2 Asztalos et al, 2010, Canada	25-32	14-21	Betamethasone 24mg (divided) or placebo every 14 days until 33 weeks AOG if undelivered	1858 (2309)	33-36	0 = 4 1 = 351 2 = 280 3 = 139 4 = 84
Wapner et al, 2007, USA	23-31	7	Betamethasone 12mg or placebo every week if still undelivered by <34 weeks AOG	495 (594)	34	4
Crowther et al, 2006 (ACTORDS), Australia and New Zealand	<32	7	Betamethasone 11.4mg or placebo IM every 7 days if undelivered <32 weeks AOG	982 (1146)	32	0 = 4 1 = 185 2 or 3 = 155 ≥ 4 = 120

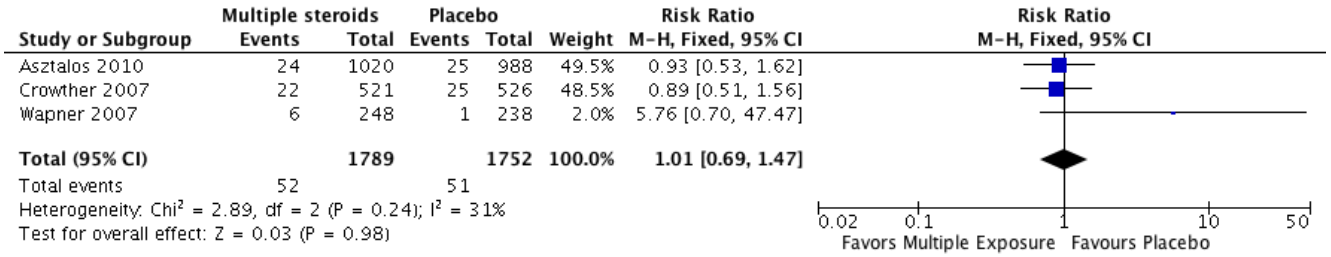


Figure 2. Meta-Analysis of risk ratio for cerebral palsy for multiple exposure to antenatal corticosteroids versus placebo using fixed effects

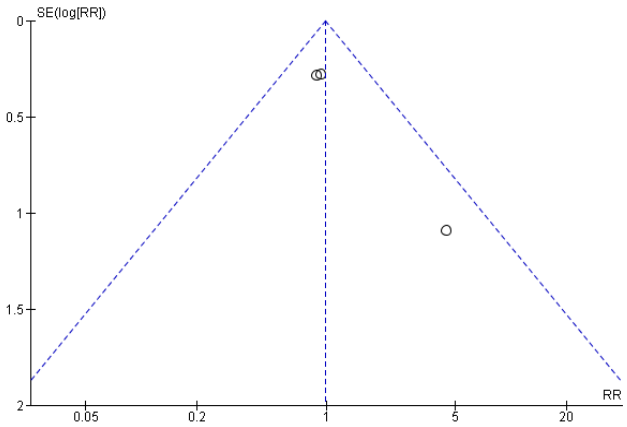


Figure 3. Funnel Plot for publication bias of included studies

CONCLUSION

Multiple courses of antenatal corticosteroids given weekly or every 14 days until 32 weeks age of gestation does not seem to increase the risk of developing cerebral palsy compared with a single treatment. However, the studies were observational in nature and definitive conclusions about the risks of repeated corticosteroid therapies cannot be made. When steroids are used, it is still prudent to weigh the benefits against the possible complications of this treatment regimen. Additional, large scale randomized studies with long-term follow-up is necessary to determine the risks of repeated corticosteroid administration.

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