

The Impact of Type, Dosage and Time of Prenatal Steroid Administration on Neonatal Outcome

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Abstract

Background: In 1972, Liggins and Howie demonstrated that antenatal steroid administration reduced the incidence of respiratory distress syndrome and perinatal mortality in neonates. Since the publication of these findings, perinatal and long-term results of steroid therapy have been evaluated in numerous studies. The aim of the review was to compare the impact of type, dosage, and time of prenatal steroid administration on perinatal outcomes in neonates and in mothers.

Summary: Although the results of the studies are ambiguous, one should consider the potential benefits of dexamethasone in cases of risk of preterm delivery due to abnormalities in fetal health assessments. Dexamethasone may also lead to better results when preterm neonates are burdened with cardiovascular defects or diseases. The opposite holds true for abnormal flows within UA or fetal MCA, i.e., one should consider whether betamethasone is the appropriate drug of choice. Steroid treatment after 34 weeks of gestation is not beneficial. Administration of the full course of steroid treatment (24 mg) in lower single doses is probably more favorable for the mother. On the other hand, a shorter time interval between the doses may allow more women in preterm birth to receive the full course of steroids. Further studies are required to answer these questions, and better methods for predicting preterm birth should be determined.

Keywords: Antenatal steroids; Pregnancy; Dexamethasone; Betamethasone; Preterm delivery

Introduction

In 1972, Liggins and Howie [1] demonstrated that antenatal steroid administration reduced the incidence of respiratory distress syndrome (RDS) and perinatal mortality in neonates. Since the publication of these findings, perinatal and long-term results of steroid therapy have been evaluated in numerous studies. Antenatal steroid administration (betamethasone or dexamethasone) has been shown to reduce the risk of the following complications of preterm delivery while not increasing the risk of infections in mothers and neonates: respiratory distress syndrome (RDS) (RR 0.66), intraventricular hemorrhage (IVH) (RR 0.54), necrotizing enterocolitis (NEC) (RR 0.46), and neonatal death (RR 0.69) [2].

Currently, a single course of steroid therapy including intramuscular administration of 24 mg of steroid over 24 hours is recommended; this includes betamethasone 2 × 12 mg every 24 hours or dexamethasone 4 × 6 mg every 12 hours [3,4].

Numerous studies have compared the effects of the route of administration, the type and the dose of the steroid as well as the timing on perinatal outcomes in neonates and in mothers.

Route of administration

In 1998, a study compared oral (4 × 8 mg every 12 hours) and intramuscular (4 × 6 mg every 12 hours) routes of dexamethasone administration in the reduction of RDS incidence in preterm neonates

[5]. The study was discontinued due to the obtained results (170 mothers; 188 fetuses). The authors observed no difference in the incidence of RDS between the groups, but oral administration was associated with an increased risk of IVH (15.9% vs. 3.3%, $P = 0.03$) and sepsis (15.9% vs. 1.6%, $P = 0.009$) in neonates. Intravenous dexamethasone was also effective in reducing perinatal mortality from respiratory distress syndrome in premature infants delivered between 28 to 33 weeks' gestation [6].

Type of steroid

To date, the dispute of whether betamethasone or dexamethasone should be used has not been solved. Betamethasone is characterized by a longer half-life (12 hours) and is less likely to cause periventricular leukomalacia than dexamethasone [7]. Dexamethasone is characterized by a stronger affinity for steroid receptors and a greater reduction in the risk of IVH while containing potentially neurotoxic sulfonate groups [8].

In the 1990s, several studies were published on the impact of steroid treatment on fetal cardiac function and/or biophysical profile [9-11]. In a double-blind, randomized study, Magee et al. [9] administered 24 mg of betamethasone (2 × 12 mg every 12 hours) or 24 mg of dexamethasone (according to the same dosing regimen) to 59 women in with single pregnancies at risk of preterm delivery. The authors concluded that both steroids led to a reduction in basic fetal heart rate and increased the variability of both short-term and long-term heart function on the first day after administration while reducing fetal heart rate amplitude and potentially causing heart rate deceleration on the

second day after administration. The authors noted that these are physiological effects of the steroids.

In the same year, Dutch authors [11] observed that betamethasone (24 mg; 2×12 mg every 24 hours) reduced the acceleration of fetal heart rate and fetal breathing movements. Dexamethasone (24 mg; 2×12 mg every 24 hours) led to increased short-term variability on the first day of treatment. All the above changes were unobservable on the fourth day after completion of the treatment. Similar results were obtained by Israeli researchers [12].

A year later, Senat et al. [10] published a study that compared the effects of dexamethasone (4×6 mg every 12 hours) and betamethasone (4×6 mg every 12 hours) administered intramuscularly to accelerate the maturity of the respiratory system and fetal heart function in a non-blinded randomized study. Computerized cardiotocogram (CTG) parameters obtained before, during and after treatment were compared. No differences were observed between the groups with regard to neonatal outcomes. Reduced fetal heart rate oscillations were observed in the betamethasone group ($n=42$). The changes resolved within a week after treatment completion. No significant changes were observed in the dexamethasone group ($n=40$). The authors concluded that steroid treatment should also be accompanied by fetal health assessment methods other than CTG and that dexamethasone should be the medication of choice when steroid treatment is required.

In the next year, the results of a randomized study regarding the impact of steroid therapy on fetal heart function and biophysical profile were published [13]. The study compared the effects of 24 mg of dexamethasone (4×6 mg every 12 hours) and 24 mg of betamethasone (2×12 mg every 24 hours). Both medications altered the fetal heart function (reduced acceleration, long-term and short-term variability) and biophysical profile (reduced number of fetal movements as well as fetal breathing movements) over 48 hours; the changes were greater following betamethasone administration.

Several years later, Subtil et al. [14] compared the effects of 24 mg of betamethasone acetate and betamethasone phosphate (2×12 mg every 24 hours) as well as 24 mg of dexamethasone (4×6 mg every 12 hours) on fetal heart function in 105 mothers at risk of preterm delivery. The changes observed by the authors included an increase in oscillations and numbers of fetal movements perceived by the mother during the treatment (day 1) as well as a reduction in oscillations and acceleration after treatment completion (days 2 and 3); the changes were no longer observed on day 4.

The authors of the aforementioned studies noted that changes in fetal heart function resulting from steroid administration might be the cause of iatrogenic preterm delivery if caution is not exercised.

In 2005, Polish researchers assessed the effects of steroid treatment on the blood flow within the middle cerebral artery of the fetus as well as in the umbilical artery by testing the flow rates before treatment as well as 24 and 72 hours after administration of the first dose [15]. The authors observed that 24 mg of dexamethasone ($n=34$) delivered intramuscularly (4×6 mg every 12 hours) reduced the pulsatility index (PI) within the median cerebral artery (MCA) 72 hours after administration of the first dose while not affecting the PI within the umbilical artery (UA). No changes in the pulsatility index were observed in either the fetal MCA or UA following the administration of 24 mg of betamethasone ($n=33$) (2×12 -mg every 24 hours).

According to the results of randomized, double-blind studies to assess the effects of intramuscular administration of 24 mg of dexamethasone (4×6 mg every 12 hours) and betamethasone (2×12 mg every 24 hours) on the morbidity and mortality of preterm neonates, the latter drug led to more frequent incidence of neonatal IVH (RR 2.97, 95% confidence interval [CI] 1.22–7.24, $P=.02$) [16].

Danesh et al. [17] compared the effects of 24 mg of dexamethasone (4×6 mg every 12 hours) and 24 mg of betamethasone (2×12 mg every 24 hours) on maternal inflammatory markers to conclude that in the case of symptoms of preterm labor with PPRM, dexamethasone significantly increased maternal leukocytosis. No differences were observed regarding inflammatory markers in pregnant mothers with preterm labor symptoms and retained amniotic fluid in both groups.

Steroid dosage

The best treatment effects of antenatal steroid administration are observed when the delivery occurs within 7 days from administration of the full steroid dose [2]. After this time, no significant reduction is observed in the incidence of RDS, cerebral hemorrhage or blood breakthrough into the ventricular system [2]. If the delivery is expected to occur before the completion of the full course of steroid treatment, the treatment should be initiated all the same. Even the first dose of betamethasone has been shown to reduce the risk of IVH and neonatal death [18-21].

In 2015, the results of a multicenter study assessing the appropriate use of steroid therapy [22] in 246,459 pregnant patients during 1988-2012 were published. The authors declared that during the study period, the steroid use rates increased from 10 to 23% for optimal drug doses (OR 2.7, 95% CI 1.6-4.5), from 7 to 34% for suboptimal drug doses (OR 6.7, 95% CI 3.9-11.6) and from 0.2 to 1.7% for questionably appropriate administration (OR 7.5, 95% CI 4.9-11.3). In addition, 52% of mothers who received steroids gave birth at week 35 or later. Therefore, better methods of predicting preterm birth should be determined.

Khandelwal et al. [23] observed that 24 mg of betamethasone administered as 2×12 mg every 24 hours or every 12 hours did not change the risk of RDS (36.5% vs. 37.3%; $P =$ not significant), whereas necrotic enterocolitis developed in neonates born from the group that received the drug at shorter intervals (6.2% vs. 0%; $P=0.03$).

In a study conducted at our institution comparing the neonatal and maternal results depending on the regimen of administration of 24 mg of betamethasone, i.e., 6×4 mg every 8 hours (study group) and 2×12 mg every 24 hours (control group), we observed a significant increase in maternal leukocytosis as well as reduced erythrocyte counts, hemoglobin levels and hematocrit in the control group compared with the study group [24]. No differences were observed between the study group and the control group in terms of complications such as moderate or severe respiratory disorders, IVH, NEC, retinopathy, infection, hyperbilirubinemia or anemia in neonates. Mild respiratory disorders were observed more frequently in the study group.

Timing of steroid treatment

The time limit for the use of steroids in pregnancy is also a matter of dispute. In 2011, BMC published the results of a prospective, double-blind randomized study comparing the effects of intramuscular betamethasone administered over two 12-mg doses at a 24 hour interval with placebo on complications occurring in late preterm

neonates (week 34-36.7: 143 in the treatment group vs. 130 in the placebo group) [25]. No differences between groups were observed with respect to the incidence of RDS (1.4% vs. 0.8%; $p=0.54$) and transient tachypnea (24% vs. 22%; $p=0.77$) as well as regarding the need for respiratory support (approximately 20% in both groups) and neonatal morbidity (62% vs. 72%; $p=0.08$). No differences were observed between the groups with regard to the gestational age at delivery, birth weight, 1-minute and 5-minute Apgar scores, surfactant treatment, neonatal intensive care unit (NICU) admissions, or the incidence of sepsis. The groups differed in the incidence of jaundice that required phototherapy (24% in the treatment group vs. 38% in the placebo group; $p=0.01$).

Kamath-Rayne et al. [26] and Yinon et al. [27] also demonstrated that steroid treatment applied at gestational week 34 and onward did not reduce the morbidity associated with respiratory diseases.

According to the results of a meta-analysis, steroid treatment is beneficial in preterm deliveries when administered by gestational week 34, day 6 [2].

Repeated treatment courses

Because the beneficial effects of steroids wane over time, repeated courses of steroids were routinely used even at the beginning of this century despite the fact that a study demonstrating the unfavorable effects of repeated steroid courses in animals was published in 1995 [28]. The authors demonstrated that repeated courses of steroids might cause intrauterine growth restriction (IUGR), reduced neonatal birth weights, and optic nerve myelination disturbances.

In humans, studies were conducted in this respect only at the beginning of the current century. French et al. demonstrated that

repeated administration of steroid doses between gestational weeks 24 and 33 reduced the birth weight and head circumference as well as increased the incidence of aggressive, destructive, and hyperkinetic behavior at a later age (3 and 6 years) [29,30].

In 2008, a Canadian multicenter, double-blind randomized study assessing the effects of repeated doses of steroids on perinatal outcomes was published [31]. Included in the study were 1858 women at gestational weeks 25 to 32 who had received a single course of steroids due to preterm labor and did not give birth after the following 14-21 days. Due to the continued risk of preterm delivery, the patients received steroid therapy ($n=937$) (2×12 mg at a 24-h interval) or placebo ($n=921$) every 14 days until the delivery or completion of pregnancy at week 33. In the steroid therapy group, 41% of women received 1 course of treatment, 33% of women received 2 courses of treatment, 16% of women received 3 courses of treatment, and 10% of women received 4 courses of treatment. No differences were observed between the groups with regard to neonatal morbidity and mortality. Neonates subjected to repeated courses of steroid therapy were born with lower birth weights (2216 g vs. 2330 g, $p=0.0026$), lower body lengths (44.5 cm vs. 45.4 cm, $p<0.001$) and lower head circumferences (31.1 cm vs. 31.7 cm, $p<0.001$). No differences were observed between the groups with regard to maternal outcomes.

In 2014, Elfayomy and Almasry [32] also demonstrated that repeated doses of dexamethasone caused lower birth weights, body lengths and head circumferences in neonates as well as lower placental weights in mothers. The authors also observed lowered serum levels of vascular endothelial growth factor (VEGF) in mothers subjected to repeated courses of steroid therapy, leading to reduced placental vascularity (Table 1).

Study	Year	Number of neonates	Subject	Major findings
Egerman R et al.	1998	188	4 × 8 mg every 12 hours oral dexamethasone vs 4 × 6 mg every 12 hours intramuscular dexamethasone	oral dexamethasone increased risk of neonatal IVH and sepsis
Magee LA et al.	1997	59	2 × 12 mg every 12 hours betamethasone vs 2 × 12 mg every 12 hours dexamethasone	both: reduction in basic fetal heart rate and increase the variability of short and long-term heart; reducing fetal heart rate amplitude
Wong D et al.	2014	2549	none, incomplete, complete	complete course: higher infant survival rates, lower rates of severe IVH and NEC any exposure: reduces the risk of moderate cerebral palsy
Lee BH et al.	2008	1124	steroid exposure: betamethasone vs dexamethasone vs no steroid exposure	betamethasone exposure increased likelihood of unimpaired neurodevelopmental status and reduced risk of hearing impairment compared with prenatal dexamethasone exposure or no prenatal steroid exposure
Elimian A et al.	2003	229	12-mg dose of betamethasone vs no steroid exposure	incomplete course of steroids reduce the rate of intraventricular hemorrhage, neonatal death and the need for vasopressors
Senat MV et al.	1998	97	dexamethasone vs betamethasone	betamethasone decreases variability of fetal heart rate
Rotmensch S et al.	1999	46	dexamethasone vs betamethasone	dexamethasone and betamethasone (more pronounced effect) induce a profound, albeit transient, suppression of fetal heart rate and biophysical activities
Mushkat Y et al.	2001	40	dexamethasone vs betamethasone	betamethasone induced a significant decrease in fetal movements

Elfayomy AK et al.	2014	71	single course or multiple courses	multiple antenatal courses of dexamethasone compromised fetal and placental growth
Urban R et al.	2005	67	dexamethasone vs betamethasone	decrease in fetal middle cerebral artery impedance at 72 h after first dose of dexamethasone
Porto AM et al.	2011	273	2 × 12 mg of betamethasone vs placebo	steroids at 34-36 weeks of pregnancy does not reduce the incidence of respiratory disorders
French NP et al.	2004	541	multiple courses of steroids	multiple antenatal courses of corticosteroids may protect against cerebral palsy but are associated with hyperactivity later in childhood
Murphy KE et al.	2008	1858	multiple courses vs placebo	multiple courses do not improve preterm-birth outcomes, and are associated with a decreased weight, length, and head circumference at birth

Table 1: Included studies.

Conclusions

One should consider the potential benefits of dexamethasone in cases of risk of preterm delivery due to abnormalities in fetal health assessments (abnormal CTG records, reduced biophysical profile). Dexamethasone may also lead to better results when preterm neonates are burdened with cardiovascular defects or diseases. The opposite holds true for abnormal flows within UA or fetal MCA, i.e., one should consider whether betamethasone is the appropriate drug of choice.

- Steroid treatment after 34 weeks of gestation is not beneficial.
- Administration of the full course of steroid treatment (24 mg) in lower single doses is probably more favorable for the mother.
- A shorter time interval between the doses may allow more women in preterm birth to receive the full course of steroids.
- Further studies are required to find better methods for predicting preterm birth.

Considering the benefits and the risks of antenatal steroid treatment, the type and the dosage of prenatal steroid should be determined carefully by the team of physicians, care managers and the patients [33]. That may attribute to the optimal perinatal outcome [34].

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