

## Optimizing antenatal corticosteroid therapy

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### ABSTRACT

Treatment with antenatal corticosteroids (ACS) is standard of care for women at risk of preterm birth between 24 and 34 weeks' gestation. ACS are increasingly used for other indications, including threatened or indicated late preterm birth, elective cesarean, and in at-risk pregnancies for periviable gestations. However, the various drugs and doses being used worldwide have not been rigorously evaluated to optimize clinical responses and to minimize potential risks. Translational research in animal models indicate that a constant, low concentration fetal exposure to ACS is sufficient for lung maturation, resulting in lower fetal exposures. Clinical trials to develop dosing strategies with inexpensive and widely available drugs could promote greater use in low resource environments.

### 1. Introduction

Maternal treatment with antenatal corticosteroids (ACS) is the standard of care worldwide for fetuses at risk of adverse outcomes from preterm birth. Liggins and Howie demonstrated by randomized controlled trial (RCT) in the 1970s that ACS decrease the risk of respiratory distress syndrome (RDS) and neonatal death [2]. More than 20 RCTs were published before 1993 to evaluate a single course of ACS with subsequent extensive meta-analyses [3]. The Declaration of Helsinki quotation is relevant because ACS are an old therapy that must be re-evaluated in the era of modern perinatal care to verify continued safety and effectiveness [1]. Significant knowledge gaps continue to exist, including the magnitude of benefit for periviable pregnancies and in infants born prior to 28 weeks' gestation, the risk-to-benefit ratio for expanded uses of ACS such as late preterm birth and elective cesarean at term, and the efficacy and safety of ACS in low resource environments [4].

Another major knowledge gap is the lack of information about optimization of corticosteroid drug regimens, which is in part explained by the history of research into ACS. Liggins first demonstrated the lung maturational effects of corticosteroids using infusions in fetal sheep in 1969 [5]. He selected for the initial clinical trial, the potent fluorinated corticosteroid betamethasone that was available as a 1-1 prodrug mixture of soluble betamethasone phosphate, and a slow release particulate, betamethasone acetate. This combination yielded

unconjugated betamethasone to cross the placenta and provide a relatively long fetal exposure to betamethasone to replicate his fetal infusion studies. His empiric selection of this drug combination at a dose of 12 mg (6 mg betamethasone phosphate and 6 mg betamethasone) given by maternal intramuscular injection at recognition of a risk for preterm birth, and a second dose 24 h later, proved to be effective and has become the most-used and tested antenatal corticosteroid regimen [6]. Pharmacologic studies of drug type and dose were not performed, as the therapy was not systematically evaluated or licensed by commercial pharma. The other widely used antenatal corticosteroid treatment is four 6 mg doses of dexamethasone phosphate given by maternal intramuscular injection at 12 h intervals to achieve a continuous fetal exposure for about 48 h, based on estimates of maternal and fetal drug levels (Fig. 1) [7]. Betamethasone and dexamethasone are generally considered to have similar efficacy when used for preterm birth [6], although they have distinct pharmacology. Dexamethasone is recommended by the World Health Organization as it is less expensive and widely available in low resource environments [8]. Other drug and dosing schedules such as two doses of either 12 mg betamethasone phosphate or dexamethasone phosphate given at 24 h intervals are used but not validated as to effectiveness by RCTs. Thus, there has not been substantial clinical research to optimize treatment with ACS.

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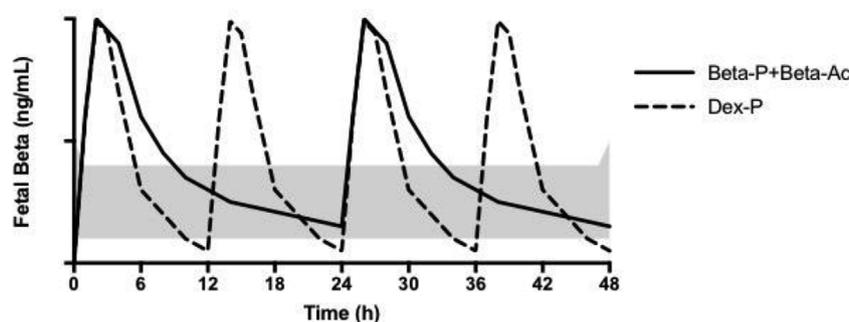


Fig. 1. Sketch of fetal blood levels of Beta or Dex after treatment with 2 doses of 12 mg/kg Beta-P + Beta-Ac or 4 doses of 6 mg Dex-P. The shaded area represents the concept of an ideal target range for minimizing fetal exposure (adapted from Ballard and Liggins) [7].

Table 1

Elements for an optimal antenatal corticosteroid treatment.

- An effective and durable maturational response – efficacy
- A treatment with the lowest fetal drug exposure – safety
- Convenient treatment routes and dosing intervals – ease of use
- Inexpensive and available drug for low resource environments – widespread use
- Treatment only of pregnancies that can benefit from antenatal corticosteroid – targeted therapy

## 2. What is the optimal antenatal corticosteroid treatment?

The clear goals of antenatal corticosteroid therapy are to decrease the newborn diseases associated with preterm birth, including RDS, intraventricular hemorrhage, necrotizing enterocolitis and late onset sepsis, and mortality (Table 1). The fact that ACS decrease the rates of all these adverse outcomes indicates pleiotropic effects on the fetus that are generalized organ maturational responses. These effects will differ for expanded uses of ACS such as for late preterm birth [9]. The “gold standard” for treatment with ACS is two doses of a combined preparation of 6 mg betamethasone phosphate and 6 mg betamethasone acetate, 24 h apart, as it has been the most tested. Higher doses, lower doses and different treatment intervals have been minimally tested for maturational responses [6]. An untested assumption is that the “gold standard” actually provides the optimal fetal response. A critical element of an optimal fetal response is a durable maturational response that occurs as early as possible after the initial dose and that persists for the longest period after treatment. The RCT data indicate that combination treatment with betamethasone phosphate and betamethasone acetate causes a clinically significant maturational response within 24 h that persists for about 7 days [3]. This response timing is based on subgroup analysis of trial data and is consistent with clinical experience but has not been rigorously tested [4]. Efficacy may differ for different causes of prematurity or across gestational ages based on drug dose. These variables have been minimally evaluated clinically. Thus, optimization of efficacy remains to be carefully explored.

ACS seem to have very low risk of maternal or newborn adverse effects. This is somewhat surprising as the dose of corticosteroid and the fetal exposure is substantial. A large experimental literature in animal models from rodents to primates has shown adverse developmental, behavioral, and transgenerational effects of ACS [10]. ACS decrease birth weight by a small amount and may increase the risk of hypoglycemia in late preterm infants [9].

A significant concern with fetal exposure to ACS is the potential for adverse cardiovascular and metabolic effects in later life [11]. While there are no strong indicators of such effects in follow up studies from the initial RTCs [12], those studies were mostly in larger preterm infants (birth weight of approximately 2.3 kg), a population quite different from the very preterm infants exposed routinely to ACS today. Thus, caution supports using the lowest possible effective dose to minimize even theoretical risks that may occur later in life.

ACS treatments should be convenient and easy to administer. The goal of a continuous calibrated fetal exposure can be achieved with maternal infusions, although this is an impractical and expensive option [13]. The standard route of treatment since the 1970s has been maternal intramuscular injection. However, for most other medical indications, betamethasone phosphate and dexamethasone phosphate are normally given orally. One trial published in 1998 evaluated oral versus intramuscular dexamethasone phosphate but was stopped early due to increased rates of neonatal sepsis and intraventricular hemorrhage in the oral treatment group [14], and there have been no further evaluations of oral dosing. There has also been little research on dosing interval, and this remains to be refined based on information about the pharmacokinetics of the drugs in pregnancy.

Although ACS were assumed to be effective in low resource environments, where most of the world's mortality from prematurity occurs, they are used only sporadically and not in the environments with the highest mortality from prematurity [15,16]. A recent large international trial of ACS in India, Africa, Pakistan, Guatemala and Argentina found no mortality benefit from ACS for very low birth weight infants [17]. Most concerning was an increase in mortality in larger and more mature infants exposed to ACS, and a secondary analysis suggested this was due to an increase in deaths from infection [18]. Ongoing trials evaluating ACS in low resource environments will hopefully identify if the benefits of ACS therapy can be achieved in these populations. Optimum treatment with inexpensive and readily available corticosteroids and oral dosing would be desirable.

Ideally, ACS would only be used when there is a high probability of achieving neonatal benefit. As the number of women exposed to ACS increases with expanding indications, the benefit-to-risk ratio changes. The risks may not be comparable across gestational ages or for different modes of delivery. Since the NIH consensus conference in 1993 [19], the use of ACS has been appropriately very high among women with threatened or planned preterm birth at 24–34 weeks' gestation. However, neonatal morbidity and mortality related to preterm birth have greatly decreased since 1993. The risk of RDS is low in infants born at 32–34 weeks', and many very preterm infants do not develop significant RDS or other adverse outcomes. Neonatal complications in late preterm infants are less severe than in very preterm infants and the incidences are much lower. The best way to avoid any potential risks from ACS is to avoid using ACS in pregnancies that will not benefit. Presently, more than 50% of pregnancies treated with ACS do not deliver within the presumed 1–7 day efficacy window, and many will deliver after 34 weeks' gestation or at term [20]. Thus, many women at 24–34 weeks' gestation do not need treatment with ACS when first assessed. Efficient and reliable tests to predict timing of delivery could decrease exposure to ACS. Further, time of delivery assessments combined with assessments of potential fetal benefit from ACS could further decrease exposure to ACS. Fetal assessment of lung maturity using amniotic fluid is seldom used today. However, fetal lung maturity can be predicted by ultrasound, and analysis of maternal plasma for fetal mRNA or proteins

associated with early maturation should be possible in the near future [21–23]. Thus, combining new diagnostic tools and clinical data may lead to better identification of women who will benefit from ACS.

### 3. Translational research to optimize antenatal corticosteroid treatment

#### 3.1. Corticosteroid treatment for lung maturation - sheep

Since Liggins' original work with corticosteroid infusions in sheep, researchers have utilized multiple animal models to verify the maturational effects of ACS, including rodents, sheep, and primates [10]. Liggins and Howie demonstrated that a continuous fetal exposure of corticosteroids induced lung maturation [5]. However, clinical dosing with betamethasone phosphate (including as a combined preparation of betamethasone phosphate and acetate) or dexamethasone phosphate results in high early maternal blood levels because the drugs are rapidly dephosphorylated to betamethasone or dexamethasone, respectively, which in turn cross the placenta to expose the fetus to high peak drug levels that then decrease over hours to low levels [24]. We investigated whether the high early peak levels from phosphorylated betamethasone or dexamethasone contribute to the fetal maturational response [25]. In sheep, a single maternal dose of 0.5 mg/kg betamethasone phosphate did not cause fetal lung maturation, while four doses of betamethasone phosphate induced lung maturation comparable to two doses of betamethasone phosphate and acetate mixture. As two doses of 12 mg dexamethasone phosphate or betamethasone phosphate given at 24-h intervals are being used clinically, and this regimen of dexamethasone phosphate is being compared to two doses of 11.4 mg betamethasone (as Celestone Chronodose 7.8 mg betamethasone phosphate, 6 mg betamethasone acetate) in the A\*STEROID clinical trial [26], we tested this 24-h dosing schedule in the sheep [27]. However, neither dexamethasone phosphate nor betamethasone phosphate alone were as effective as a combined preparation of betamethasone phosphate and acetate, although some lung maturation did occur [27].

These results suggest that betamethasone acetate is the critical component of the standard antenatal corticosteroid treatment, and that the phosphorylated drugs alone are less effective than the standard combined betamethasone preparation unless given four times. We tested this possibility by treating ewes with a single intramuscular dose of 0.125 mg/kg betamethasone acetate, and fetuses were delivered 2 days after treatment to assess lung function [24]. This single maternal dose was as effective as one or two doses of 0.25 mg/kg betamethasone phosphate and acetate mixture. Further, a four-fold higher dose of betamethasone acetate did not increase the fetal lung response (Fig. 2). Therefore, in sheep, 25% of the standard clinical two-dose treatment, when given as acetate, achieved the same lung maturation response. In pharmacokinetic studies, the betamethasone phosphate and acetate mixture increased maternal levels to almost 100 ng/mL at 30 min and fetal levels to 10 ng/mL at 2–4 h (Fig. 2). In contrast, the slowly deacetylated betamethasone yielded peak maternal betamethasone levels of about 20 ng/mL by 4 h, and fetal betamethasone levels of 1–4 ng/mL for 24 h. With maternal treatment of 0.125 mg/kg betamethasone phosphate, fetal levels were below 1 ng/mL by 24 h. Therefore, the fetal exposure that was associated with optimal lung maturation was achieved with a maternal dose of 0.125 mg/kg betamethasone acetate, resulting in fetal blood levels of 1–4 ng/mL for at least 24 h. Note that maternal and fetal blood levels with 0.25 mg/kg betamethasone phosphate and acetate mixture and 0.125 mg/kg betamethasone acetate were equivalent from about 8 to 24 h because levels during this period reflect deacetylated betamethasone once dephosphorylated betamethasone has been cleared.

#### 3.2. Corticosteroid treatments for lung maturation - rhesus macaque

The slow release betamethasone acetate that achieved low fetal

blood betamethasone levels for at least 24 h in fetal sheep was then tested in rhesus macaques to verify that lower clinical exposures than presently used are generalizable. Pregnant monkeys were given a single intramuscular injection of 0.25 mg/kg betamethasone phosphate and acetate mixture, 0.125 mg/kg betamethasone acetate or 0.06 mg/kg betamethasone acetate, and lung maturation was evaluated 5 days later at about 132 days' gestational age (term is 165 days' gestational age). The effect of 0.125 mg/kg betamethasone acetate on improving pressure-volume curves was equivalent to two doses of 0.25 mg/kg of betamethasone phosphate and acetate mixture, while a lower dose of 0.06 mg/kg betamethasone acetate yielded a partial maturational response [28]. Saturated phosphatidylcholine in alveolar washes, a measure of surfactant production, also was increased similarly by the two treatments. Betamethasone levels in fetal blood samples from the monkeys was about 5 ng/mL at 8 h and 4 ng/mL at 24 h after the maternal intramuscular treatment with 0.125 mg/kg betamethasone acetate. Thus, results are consistent between sheep and monkeys, demonstrating that a low continuous fetal exposure to betamethasone can cause fetal maturation with avoidance of the high peak drug exposures from the phosphorylated corticosteroid.

#### 3.3. Testing of fetal dosing for maturation using maternal infusions of betamethasone phosphate - sheep

Another approach to evaluating the fetal drug exposure required to achieve a lung maturational response is to use maternal infusions of betamethasone phosphate to achieve the desired fetal blood levels. Infusions of betamethasone phosphate into ewes that included a loading dose and constant infusions to achieve 2 ng/mL for 12 h caused no lung maturation at 2 days, and less lung maturation at 10 ng/mL or 20 ng/mL than with 2 doses of intramuscular 0.25 mg/kg betamethasone phosphate and acetate mixture [29]. In contrast, a 26-h maternal betamethasone phosphate infusion to target a fetal plasma betamethasone level of 2 ng/mL caused equivalent lung maturation to two maternal intramuscular doses of betamethasone phosphate and acetate mixture [30]. These and the preceding experiments lead to the same conclusion concerning betamethasone acetate: in sheep, a low fetal exposure for 26 h is sufficient to achieve a lung maturational response and higher peak fetal drug levels do not appear to have any additional benefit for fetal lung maturation. Infusion studies have not been attempted in rhesus macaque because of the difficulties using chronic catheters in monkeys.

#### 3.4. Durability of lung maturation responses - sheep

It is generally assumed that the fetal lung maturation response involves a pleotropic change in maturational trajectory that persists. Surfactant will increase and improve lung function in the preterm infant. However, the lung maturational responses are far more complex than simply an increase in surfactant. In sheep, fetal lung mechanics and anatomy can change within 12 h of ACS exposure due to decreases in lung mesenchyme and decreased epithelial permeability but surfactant lipids and proteins are not increased for several days [31]. Surfactant protein mRNAs increase in fetal lung explants exposed to corticosteroids, but the increases persist only with continued exposure to corticosteroids [32,33]. Therefore, functional lung maturation may be reversible in the fetus.

In the above fetal dose studies, lung maturation was initially assessed at 2 days [24,34]. Treatment of ewes with a single dose of betamethasone phosphate and acetate mixture (24–26 h of fetal exposure) was equivalent to two doses 24 h apart (48 h of fetal exposure) when assessed at 2 days. However, when the initiation from treatment to delivery interval was 5 days, there were no lung maturation responses to betamethasone acetate [35]. Therefore, another variable for optimizing lung maturation is the period of exposure to achieve the maximal durability of the lung maturation, a treatment variable that has not

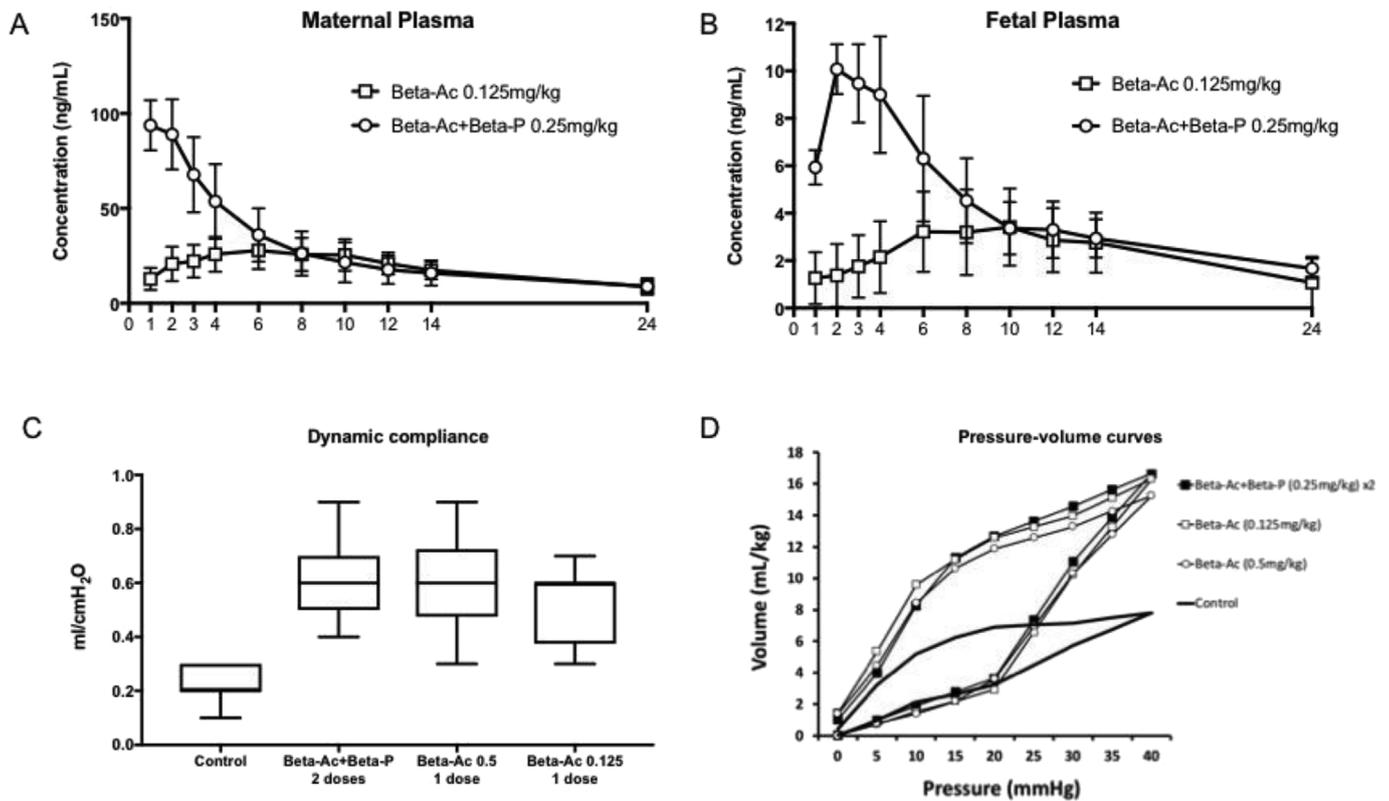


Fig. 2. Maternal and fetal plasma concentrations of Beta and fetal lung responses in sheep. The maternal (A) and fetal (B) Beta levels were measured for timed paired maternal and fetal blood sampling in chronically catheterized sheep given 0.125 mg/kg Beta-Ac or 0.25 mg/kg of a 1 to 1 mixture of Beta-Ac + Beta-P. The dynamic compliance (C) and static pressure-volume curves (D) were measured 2 d after the initiation of treatments and 30 m after preterm delivery at 122 d gestational age. Beta-Ac mediated improvements were comparable to the 2 dose treatment with Beta-P + Beta-Ac. Data redrawn from Schmidt et al. [24].

been explored experimentally.

### 3.5. Oral antenatal corticosteroid treatment

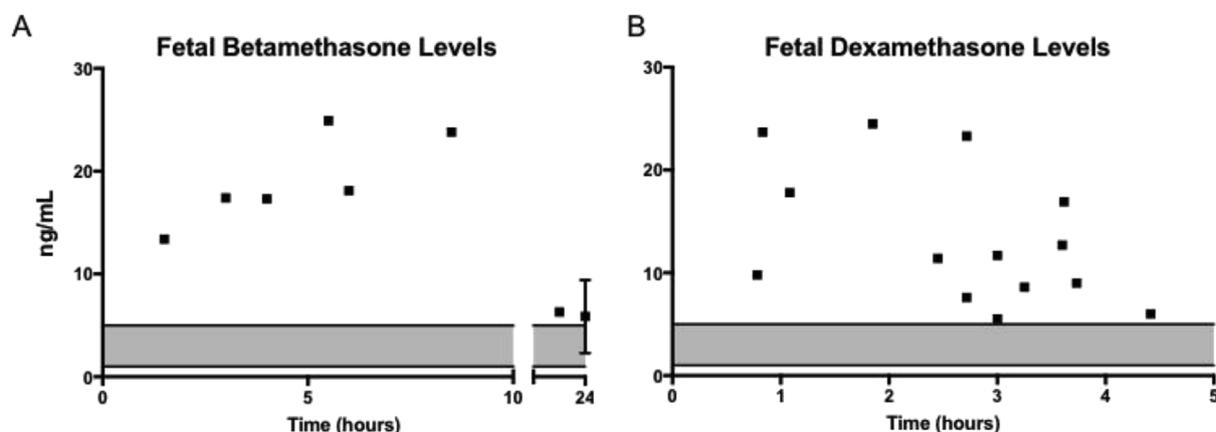
Oral ACS should be effective, and the pharmacokinetic profiles for oral dexamethasone phosphate or betamethasone phosphate have slower absorption with prolonged plasma levels compared to intramuscular treatments. Thus, oral ACS will minimize the high peak fetal drug levels from intramuscular treatments. As proof of principle, in sheep oral dosing based on maternal and fetal betamethasone levels caused two-day lung maturational responses equivalent to two doses of combined betamethasone phosphate and acetate [36]. These early results need further evaluation for durability of responses and optimal dosing to minimize fetal exposures, and to assess for any potential adverse effects with oral betamethasone.

## 4. Optimizing dosing in humans

Several critical pieces of information from animal models can guide considerations for new dosing strategies in humans. Assuming that the corticosteroid exposure required for fetal maturation in humans is similar to sheep and monkeys, the target fetal corticosteroid levels established in these animals (range of 1–4 ng/mL) can be used to plan new treatment strategies in humans [37]. Although reports of cord blood betamethasone and dexamethasone levels in humans are limited, data from several sources support the presumed target range of 1–4 mg/mL (Fig. 3). The fetal plasma values from 12 mg of betamethasone phosphate and acetate mixture or 6.6 mg dexamethasone phosphate are substantially above this target range in the early period after maternal treatment. At 24 h, cord blood levels appear to approach this target range [38–40]. There is a pressing need to evaluate if current dosing is excessive in humans.

There is no compelling information to suggest that antenatal treatment with corticosteroids other than dexamethasone or betamethasone would be beneficial. The decision about which drug to use will likely depend on available formulations, results from awaited trials, and the pharmacokinetics of intramuscular and oral treatment routes. An ideal treatment would minimize the risk of high fetal plasma levels soon after maternal treatment, maximize the period that fetal plasma levels are in the target range (whatever that may be), and minimize the number of doses needed to have a durable maturational response. A complete model for selecting treatment options will require pharmacokinetic data for bioavailability, the peak maternal blood levels achieved, clearance rate for the drug, the protein binding in maternal and fetal plasma, and the drug ratio of fetal to maternal blood levels. Although there are some estimates of these variables for pregnant humans for the drugs of interest, no integrated model for antenatal corticosteroid dosing has been developed. The challenge to the field is to test lower doses given at appropriate treatment intervals. The oral route may provide convenient ways to keep fetal exposures low using the low cost and the readily available betamethasone phosphate or dexamethasone phosphate pills. However, the possible effects of body mass index or meals on the bioavailability of orally administered drugs needs to be considered. Betamethasone acetate is close to an ideal drug for antenatal therapy. However, the drug is not available for intramuscular use except as a component of the betamethasone phosphate and acetate mixture. As pharma is most reluctant to develop drugs for preterm fetuses, an industry sponsored drug development program for betamethasone acetate may be unrealistic.

In conclusion, although ACS have been used for almost 50 years, fetal exposures to these potent agents are high, and potential risks could be decreased by optimizing the dosing strategy. The current variations in treatment worldwide appear to be largely empiric. New dosing strategies will require pharmacokinetic modelling and non-inferiority



**Fig. 3.** Maternal and fetal cord blood Beta levels for IM maternal steroids. A. Women in preterm labor received 12 mg Beta-P + Beta-Ac treatments and maternal, and cord blood were collected at delivery at the times indicated on the X axis as reported by Ballabh et al. [38]. The 24 h value with the standard deviation is for 10 samples reported by Gyamfi et al. [39]. B. Maternal and cord blood values for 14 women given 6.6 mg Dex-P prior to C-section delivery at term as reported by Tsuei et al. [40]. The shaded 1–4 ng/dL range indicates the Dex concentrations sufficient for lung maturation in sheep and monkey models.

testing against the current standard of care. The quotation from Declaration of Helsinki provides justification for a search for a better antenatal corticosteroid treatment strategy [1].

#### 4.1. Research directions

- Assess magnitude of benefits of ACS in contemporary populations.
- Develop up to date pharmacology profile of corticosteroid drugs used for antenatal therapy.
- Test new treatment strategies to minimize fetal exposure to ACS.

#### 4.2. Practice points

- ACS save lives and improve outcomes when given to the right women at the right time.
- ACS efficacy is strongly impacted by the treatment-to-delivery interval.
- The use of repeat ACS, or ACS > 34 weeks' gestation should be considered cautiously.
- Data from animal studies confirm that additional work to optimize ACS dosing strategies is warranted.

#### Disclosure statement

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