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Antenatal Corticosteroids for Fetal Lung Maturity – Too Much of a Good Thing?

Lenka Hrabalkova[1], Tsukasa Takahashi[2], Matthew W. Kemp[2,3], Sarah J. Stock[1,4Ω]

[1] Tommy's Centre for Maternal and Fetal Health at the MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, United Kingdom.

[2]Tohoku University Hospital, Sendai, Miyagi, Japan.

[3]Division of Obstetrics and Gynaecology, University of Western Australia, Perth, Australia.

[4] Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, United Kingdom.

[Ω]Corresponding Author

Sarah J. Stock (Sarah.Stock@ed.ac.uk).

Abstract

Background: Between 5-15% of babies are born prematurely worldwide, with preterm birth defined as delivery before 37 completed weeks of pregnancy (term is at 40 weeks of gestation). Women at risk of preterm birth receive antenatal corticosteroids as part of standard care to accelerate fetal lung maturation and thus improve neonatal outcomes in the event of delivery. As a consequence of this treatment, the entire fetal organ system is exposed to the administered corticosteroids. The implications of this exposure, particularly the long-term impacts on offspring health, are poorly understood.

Aim: This review will consider the origins of antenatal corticosteroid treatment and variations in current clinical practices surrounding the treatment. The limitations in the evidence base supporting the use of antenatal corticosteroids and the evidence of potential harm to offspring are also summarised.

Results: Little has been done to optimise the dose and formulation of antenatal corticosteroid treatment since the first clinical trial in 1972. International guidelines for the use of the treatment lack clarity regarding the recommended type of corticosteroid and the gestational window of treatment administration. Furthermore, clinical trials cited in the most recent Cochrane Review have limitations which should be taken into account when considering the use of antenatal corticosteroids in clinical practice. Lastly, there is limited evidence regarding the long-term effects on the different fetal organ systems exposed in utero, particularly when the timing of corticosteroid administration is sub-optimal.

Conclusion: Further investigations are urgently needed to determine the most safe and effective treatment regimen for antenatal corticosteroids, particularly regarding type of corticosteroid and optimal gestational window of administration. A clear consensus on the use of this common treatment could maximise the benefits and minimise potential harms to offspring.

Introduction

Preterm birth is defined as birth occurring prior to 37 completed weeks of gestation (with term being 37-42 weeks gestation) and can subcategorised based on gestational age into extremely preterm birth (less than 28 weeks), very preterm birth (28 to 32 weeks) and moderate to late preterm birth(32 to 37 weeks). There is marked geographical variation in the rate of preterm birth, ranging from 5% to 15% worldwide, resulting in more than 15 million preterm babies born per annum globally (1). Approximately one third of preterm births are the result of delivery indicated by maternal medical or obstetric conditions such as pre-eclampsia or suspected fetal compromise such as fetal growth restriction, where the risks of continuing a pregnancy outweigh the risks of delivery. The remaining two thirds follow the spontaneous onset of labour, which may be preceded by pre-labour rupture of membranes (one third of spontaneous preterm births), or may result from spontaneous onset of contractions (two thirds of preterm births) (2). The risks of adverse outcomes associated with prematurity are higher the earlier in gestation delivery occurs. Even with advanced neonatal care, only a very small proportion of babies born at 22 weeks gestation survive until hospital discharge (2%), rising to around 40% of babies born at 24 weeks gestation and 77% of babies born at 26 weeks gestation (3). Such extreme preterm birth is comparatively rare (only 5% of all preterm births) but surviving babies are at high risk of significant morbidity (4). Outcomes are much better for late preterm babies born between 34-36 weeks of gestation. As late preterm births are much more common than extreme and early preterm births, they are overall the biggest contributor to burden of disease that results from prematurity (5). The cost of late preterm deliveries (34-36 weeks gestation) on the health service from birth until 24 months has been estimated at £5823 compared with £2056 for children born at term (6). Overall, the economic burden of preterm birth is considerable with the total cost to the public sector estimated to be £2.9 billion in the UK and $26 billion in the US (7, 8).

Women at risk of preterm birth receive antenatal corticosteroids (ACS) as part of standard care to improve neonatal outcomes in case of delivery. ACS work by accelerating fetal lung maturation thereby reduce the number of babies that die or suffer from breathing problems. However, it is not solely fetal lungs which are exposed to corticosteroids during ACS treatment; the entire organ system is exposed. The implications of ACS treatment are not fully understood, with many questions still unanswered. In this article, we aim to review how the use of ACS began, what the current clinical practices are, the limitations of evidence regarding its benefits and the evidence of potential harms.

Endogenous corticosteroids and preparation for ex-utero life

Towards the end of pregnancy a complex maturation process of multiple fetal organs occurs in preparation for the fetus to transition from the *in utero* environment to *ex-utero* upon birth (reviewed by (9)). This process is crucial for neonatal survival and key mediators include the adrenocortically produced corticosteroid hormones called glucocorticoids (cortisol in most mammals but corticosterone in mice and rats) (10). In the early and mid-stages of pregnancy the fetus is only exposed to low levels of glucocorticoids because fetal glucocorticoid synthesis is limited until late gestation and maternal glucocorticoids are inactivated by the enzyme 11β-hydroxysteroid dehydrogynease-2 (11β-HSD-2). This enzyme converts the active glucocorticoid cortisol to inactive cortisone and is primarily produced by the placenta but is also present in fetal tissues (reviewed by (11, 12)). The fetus also actively transports glucocorticoids across to the maternal side further controlling the amount of fetal glucocorticoids exposure (13). In late gestation, both maternal and fetal glucocorticoid production increases substantially, whilst placental 11β-HSD-2 activity declines, resulting in a rise of glucocorticoids. This rise stimulates fetal maturation, promoting a switch from cell proliferation to differentiation (10). If the fetus is exposed to high levels of glucocorticoids in early to mid-pregnancy, due to for example stress or maternally administered ACS, it may be more apt to survive but the exposure may also have adverse implications for the natural development of different organs systems with potential consequences for health later in life (12).

Exogenous antenatal corticosteroids (ACS)

The discovery that maternally administered exogenous ACS mitigate the adverse effects of preterm birth is considered a milestone of antenatal care. In 1972 Liggins and Howie were the first to demonstrate the benefits of ACS treatment following the first randomised clinical trial (15). The basis for the clinical trial was Liggins' previous work investigating the role of glucocorticoids in labour using an ovine model. Liggins was interested in discovering what triggers the process of labour with an intent to prevent preterm birth and found that in sheep labour is initiated by an increase in fetal glucocorticoid production but that this is not the case

in humans. However, Liggins noticed that in addition to triggering labour, the administration of glucocorticoids led to the survival of prematurely born lambs that would normally die soon after birth. When sacrificed, the lungs of prematurely born lambs remained partially expanded in contrast to controls (16-18). This observation was soon confirmed by DeLemos et al. in 1970 who also provided direct evidence that glucocorticoids stimulate the production of lung surfactant (19). This then led to the hypothesis that synthetic glucocorticoids have the potential to prevent fetal respiratory distress syndrome (RDS) resulting from pulmonary immaturity in preterm born babies and a clinical trial followed. Between December 1969 and October 1971, 282 women admitted in preterm labour between 24 to 36 weeks or in whom preterm delivery was planned, were randomised to receive either a mixture of 6 mg of betamethasone phosphate and 6mg betamethasone acetate or a control of 6 mg of cortisone acetate which has a much lower potency (a placebo control group was not included) (15). Unless delivery occurred, a second injection of the same material as the first was given 24 hours later. In the treatment group, neonatal mortality was 3.2% in contrast to 15% in the control group and RDS was less frequent (9%) than in controls (25.8%) (15). Following this initial trial others followed confirming improvements in neonatal outcomes, however, it wasn't until two decades later, that clinical practice changed. This was largely due to a systematic review published by Crowley et al. in 1990 (20) which was considered so seminal that it's meta-analysis plots were, and still are, used as the logo of the Cochrane Collaboration. This review was considered to be seminal, such that the forest plot of the meta-analysis was made the logo for the Cochrane Collaboration. The meta-analysis included data from 12 controlled trials, involving over 3000 participants and showed a reduction in RDS, intraventricular haemorrhage (IVH) and necrotizing enterocolitis (NEC) (20). The use of ACS further increased following the publication of the consensus reached by the National Institutes of Health Review in 1995, following an assessment of the available scientific evidence by a 16-member consensus panel, with the conclusion that "ACS therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs" (21). The first Cochrane Review of ACS was published in 2000 which gathered and further supported the use of ACS based on evidence from 18 trials which included data on over 37000 babies and showed a significant reduction in neonatal mortality and morbidity associated with preterm birth in the first 48 hours of life of neonates (22). Since then, the Cochrane reviews have been regularly updated with the most recent published in 2017 (23).

Antenatal Corticosteroid Regimens

It is striking that despite ACS being one of the most commonly used treatments in pregnancy, very little work has been done to optimise the dose and formulation since the initial trial in 1972 (15). The optimal interval from treatment administration to delivery is widely considered to be 24 hours and up to 7 days, however, trials which have investigated the optimal time give differing reports (24-30). The most recent analysis by WHO in 2015 concluded that a 24 to 48 hour treatment to delivery interval is most commonly associated with significant benefits and no benefits are observed when the interval exceeds 7 days (31).

The most commonly used regimen of ACS is 12mg of betamethasone acetate/phosphate in a 1:1 ratio mix, given intramuscularly in 2 doses 24 hours apart. This regimen is based on Liggins' pre-clinical experiments, with no further modification and is commonly used in the USA, Australia and some European countries. In other countries, such as the UK and India, betamethasone is only available as the soluble form betamethasone phosphate.

Betamethasone is a synthetic fluorinated corticosteroid which can cross the placenta from mother to fetus (32). The betamethasone phosphate component is soluble and rapidly released, whereas, the betamethasone acetate component is largely insoluble and de-acetylated more slowly (33). Intramuscular administration of betamethasone phosphate/acetate yields a peak concentration of 80-115 ng/mL of betamethasone in maternal plasma between 30 and 50 minutes after dosing (34), with an initial half-life of approximately 6 hours. Betamethasone levels are then shown to return to baseline 48 hours after treatment (35). In cord blood, betamethasone is detectable as early as one hour after maternal administration, with a materno-fetal steroid concentration gradient of approximately 1:3. Animal studies have suggested that the initial peak generated by betamethasone phosphate is not necessary for fetal lung maturation (36-39). Using an ovine model of pregnancy, it has been shown that maintaining a low fetal betamethasone exposure of 1-4ng/mL for ~26 hours, (either by constant maternal betamethasone phosphate infusion or by maternal injection of low-dose betamethasone acetate) achieves lung maturation equivalent to that given with a standard clinical course of ACS (2 x 0.25mg/kg doses of betamethasone phosphate/acetate spaced by 24h). Earlier studies, also in pregnant sheep, have reported that brief (12h), high concentration fetal exposures do not improve fetal pulmonary gas exchange (36). Together these data suggest that the dose of betamethasone phosphate/acetate mix used clinically (6mg of each form) is several fold higher than necesary to achieve lung maturation, and if 12mg betamethasone phosphate alone is used, the degree of overtreatment is even greater. Only one trial to date has compared betamethasone

acetate/phosphate regimen versus betamethasone phosphate which found that there were no significant differences in infant outcomes (40). Khadelwal et al. investigated betamethasone dosing intervals using 12mg dose of betamethasone either 12 or 24 hours apart with no significance difference in RDS found (41).

The alternative ACS to betamethasone is dexamethasone, often used as dexamethasone sodium phosphate. The recommended regimen for dexamethasone is four 6mg intramuscular injections given at 12 hour intervals (31). Like betamethasone, it is a fluorinated synthetic corticosteroid with a similar molecular structure and pharmacokinetic properties (33). Dexamethasone has a higher affinity for corticosteroid receptors than betamethasone (7.1 and 5.4 fold in comparison to endogenous cortisol respectively) but betamethasone has a longer half-life (42). Betamethasone is slightly cheaper and does not require refrigeration meaning it may be preferred in low income settings. It is unclear whether betamethasone or dexamethasone is a superior agent for lung maturation. A review of ten trials with 1159 women and 1213 infants comparing betamethasone to dexamethasone (with the betamethasone regimen type often not specified) found no statistically significant difference with regards to neonatal mortality and the majority of morbidities associated with preterm birth (42). However, dexamethasone was associated with a decreased risk of IVH (RR 0.44, 95% CI 0.21 to 0.92; four trials) although no difference was seen for severe IVH (RR 0.40, 95% CI 0.13 to 1.24) (42). An investigation into the effect of ACS treatment on fetal heart rate, betamethasone showed an absence of impact whereas dexamethasone was associated with a reduced fetal heart rate variability but neonatal outcomes were similar in both(43). Another randomised controlled trial showed that both betamethasone and dexamethasone decreased baseline fetal heart rate and caused transient changes in fetal heart rate variability in the two days following administration (44).

Baud and colleagues reported that betamethasone but not dexamethasone was associated with a reduced risk of cystic periventricular leukomalacia (a major cause of cerebral palsy) in low birthweight (≤1.75 kg) infants (45) whereas another trial reported that both were associated with a reduced risk (46).

International guidelines for the use of antenatal corticosteroids vary and lack clarity regarding which corticosteroid drug should be used (Table 1.) (31, 47-50) . With the exception of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, most guidelines do not specify which betamethasone (betamethasone acetate/phosphate mix or betamethasone phosphate only) they recommend for use (31, 47-50). Systematic reviews also frequently lack clarity on the formulation used in trials. It is clear that further investigations are

urgently needed to determine the most efficient corticosteroid type and administration regimen to maximise benefits and minimise both short and long-term side effects.

	Recommended ACS treatment	Recommended gestational window of ACS administration
World Health Organization (WHO)	intramuscular dexamethasone or betamethasone (total 24mg in divided doses)	24 - 34 weeks
Royal College of Obstretricians and Gynaecologoists (RCOG)	no specifications	26^{+0} -33^{+6} weeks (should be considered between 24^{+0} - 25^{+6} weeks and 34^{+0} - 35+6 weeks)
Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)	two 11.4mg intramuscular betamethasone acetate and phosphate mix 24 hours apart or four 6mg intramuscular dexamethasone phosphate 12 hours apart	34+6 weeks or less
The American College of Obstetricians and Gynecologists (ACOG)	two 12mg intramuscular betamethasone 24 hours apart or four 6mg intramuscular dexamethasone 12 hours apart	24^{+0} - 33^{+6} weeks (should be considered - starting at 23+0 weeks)
The Society of Obstetricians and Gynaecologists of Canada (SOGC)	two 12mg intramuscular betamethasone 24 hours apart or four 6mg intramuscular dexamethasone 12 hours apart	24 - 34 weeks
Japan Society of Obstretrics and Gynecology (JSOG)	two intramuscular betamethasone injections 24 hours apart	22-33 weeks

Table 1. International guidelines for antenatal corticosteroid treatment. Gestational window given as weeks[+days] where possible; WHO, RANZOG, SOGC and JSOG only specify weeks in their recommendations.

Current Antenatal Corticosteroid Use and Limitations of Evidence

The 2017 Cochrane Review by Roberts et al. provides strong evidence that ACS can be lifesaving (23). However, there are limitations to the trial data included in the review which need to be taken into account when considering ACS as used in current clinical practice (51). Firstly, the majority of trial evidence about ACS is based on data from women with singleton

pregnancies between 28 and 34 weeks gestation. Women with pregnancies complicated by conditions such as chorioamnionitis, diabetes or fetal growth restriction often excluded from trials. This is not representative of current clinical practice where ACS are commonly given to all women thought to be at risk of preterm delivery from the threshold of viability (~22 weeks of gestation) (52) to late preterm delivery (34-37 weeks of gestation), regardless of co-morbidities (53). Since the 2017 Cochrane review, a large multicentre observational study showed that any exposure to ACS (partial or complete doses of either betamethasone or dexamethasone) is associated with lower mortality in extremely preterm infants (born between 22-28 weeks of gestation) before discharge when compared to those not exposed to any ACS treatment(54). It is important to note that the majority of women which made up the group which did not receive any ACS treatment were admitted in advanced labour creating a risk for bias, which may have impacted the findings. Many of the trials included in the Cochrane review were carried out more than three decades ago, with the comparator being standard neonatal care at that time which has changes considerably over the years. Management of RDS has improved markedly and is no longer a major cause of neonatal mortality in high-income countries. Furthermore, surfactant treatment, less invasive approaches to respiratory support (such as continuous positive airway pressure ventilation) and improvements in neonatal care of low birthweight infants mean that the potential benefits of ACS may not be as great in the modern era of advanced neonatal care (55). Lastly, most of the trials included in the Cochrane Review had extremely high rates of delivery within seven days of treatment – either because trial recruitment was restricted to women with a very high-risk of early delivery or because of censoring if delivery in the ensuing weeks did not occur. This is not reflective of clinical practice, where preterm birth is notoriously difficult to predict. Observational studies in high-income settings show that up to 9% of pregnant women receive ACS treatment at some point in their pregnancy (56-58). At least half of these are inappropriately timed - in more than 50% of women given ACS, pregnancy continues for more than seven days (after which the benefits of ACS are thought to be minimal) (Figure 1.) or delivery is at term (when the benefits are less clear) (57). This overuse of ACS is acceptable only if they do not cause harm. However, it is biologically plausible that ACS could cause serious and long-term harms.
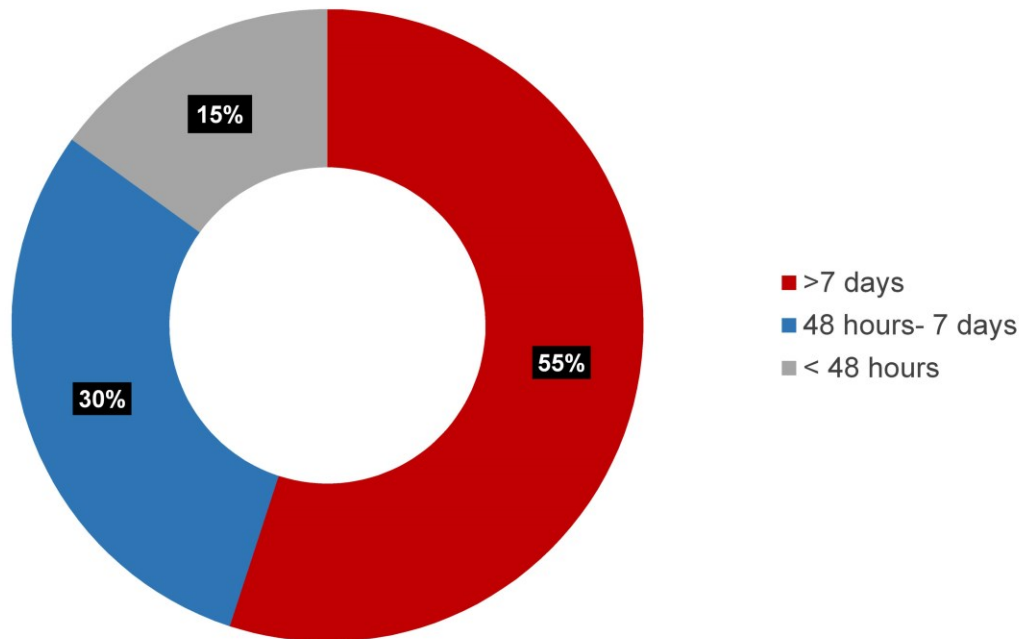
Figure 1. Chart summarising the percentage of women who receive ACS optimally (48hours-7 days prior to deliver) and the percentage who receive treatment sub-optimally (> 7 days or <48 hours prior to delivery). Based on data from Makhija et al. 2016 *(58)*.

ACS in low and middle income (LMIC) settings

The Global Network Antenatal Corticosteroid Trial (ACT), a multi-country cluster randomized trial conducted across 7 research sites in 6 LMIC countries including India, Pakistan, Zambia, Kenya, Guatemala and Argentina) set out to determine whether a multicomponent intervention increased the administration of ACS in the women at risk of preterm birth and whether it reduced neonatal mortality among that group (59, 60). Surprisingly, the trial showed an absence of a positive effect on 28-day mortality in infants less than the 5th percentile for birthweight (used as a proxy for preterm birth because ultrasound wasn't generally available and gestational age was sometimes unknown). Perhaps even more surprising was the finding that overall neonatal mortality in the intervention clusters increased with an excess of 3.5 neonatal deaths per 1000 live births. Furthermore, suspected maternal infection was marginally increased in comparison to the control group (60). Following these concerning results, the WHO are currently conducting further randomised trials in LMICs: The Antenatal Corticosteroids for Improving Outcomes in preterm Newborns I and II (ACTION-I and ACTION-II) trials. These

trials include centres in Bangladesh, India, Kenya, Nigeria and Pakistan and are comparing the effects of dexamethasone to placebo when given to women at risk if imminent preterm birth between either 26-33 weeks of gestation (ACTION-I) or 34-36 weeks of gestation (ACTION-II). Primary outcomes include stillbirth and neonatal death/survival, severe neonatal respiratory distress and maternal bacterial infections. Although the findings of the ACT trial are yet to be confirmed by the ACTION-I and ACTION-II trials, it strongly suggests that benefits of ACS found in high-income settings do not necessarily translate to LMIC settings where the majority of facilities lack neonatal intensive care equipment and equipment to accurately determine gestational age thus potentially increasing sub optimally-timed ACS treatment.

Potential Harms associated with Antenatal Corticosteroid Treatment

In a recent review, Jobe et al. assessed the benefits and potential risk of ACS (61). Exposure of the fetus to excessive levels of glucocorticoids can result in adverse effects on the developing organs as well as long-term programming of the hypothalamic-pituitary-adrenal (HPA) axis function (62). Changes in the HPA function have been shown to be associated with altered brain growth, behavior and increased risk of metabolic and cardiovascular disease later in life (62-64). Outcomes are likely to vary depending on the gestational age at which the fetus is exposed as well as the regimens used.

Renin-angiotensin-aldosterone and cardiovascular outcomes

Animal studies

In sheep and rats it has been shown that corticosteroid exposure during early development results in reduced nephron numbers and consequently hypertension in adulthood (65, 66). Furthermore, experimental work in sheep has shown that maternal exposure to high levels of cortisol in late gestation results in cardiac changes such as reduced cardiac mitochondrial number and function and this coincides with an increased incidence of perinatal stillbirth (67, 68). A study investigating chronic maternal exposure to cortisol showed an increased proliferation of fetal cardiomyocytes and increased apoptosis of cardiac Purkinje fibers (69). These changes have the potential to impact long-term cardiovascular health. Furthermore, altered fetal electrocardiogram, heart rate and depressed aortic pressure readings were also observed just prior to delivery. The authors speculate that the chronic maternal exposure to

glucocorticoid in late gestation results in altered fetal cardiac features that contribute to cardiac dysfunction, creating vulnerability to death during the stressful event of labour.

Clinical studies

The effects of ACS on the heart have recently been reviewed by Agnew et al (70). Preterm birth itself is associated with an increased risk of cardiovascular disease later in life but there is evidence that ACS have independent effects on renin-angiotensin-aldosterone and cardiovascular outcomes.

A follow up study of children at 2 years of age which were either repeatedly exposed to ACS or placebo, showed no effect on blood pressure (71). A single course of betamethasone at 6 years of age also showed no differences in blood pressure measurements (72). However, a follow up study at the age of 14 showed that ACS exposure leads higher systolic and diastolic pressure, although only a few of the children were in the hypertensive range (73). Follow up of adults at the age of 30 following a single course of ACS showed no differences in blood pressure, blood lipids or cortisol between those exposed to treatment versus placebo (74). However, most of the subjects in this study were born late preterm and therefore relatively mature compared to extremely early and early preterm babies. Other follow-up cohort studies focusing primarily on low birth weight babies showed that exposure to ACS led to higher systolic and diastolic pressure (73), decreased aortic distensibility (75) reduced heart rate variability which is associated with development of adverse cardiometabolic outcomes (76). The most recent cohort study of adolescents born prematurely showed that the use of ACS was associated with alterations in the renin-angiotensin-aldosterone system which over time could lead to renal inflammation and fibrosis and ultimately hypertension and renal disease (77).

Metabolic outcomes

Animal studies

In 2007 studies in sheep showed that early exposure to ACS has sex specific effects on glucose homeostasis and induces hyperinsulinemia (78). However, a more recent study which also used sheep as a model of preterm birth and ACS exposure did not result in impaired insulin action in adulthood (79) other

Clinical studies

ACS exposure has also been shown to be associated with neonatal hyperbilirubinemia and hypoglycemia (80). Fetal hypoglycemia could be a consequence of fetal adrenal gland suppression or ACS-induced maternal hyperglycemia that could cause fetal pancreatic beta cell hyperplasia/hyperinsulinemia (81). With regards to long-term outcomes there is evidence that ACS exposure can result in insulin resistance (74) and altered glucose metabolism (75). A follow up study of adults at the age of 30, ACS exposure did not result in any differences in body size, lipid levels or the incidence of diabetes (74). However, a slight increase in insulin following a glucose tolerance test was observed (74).

Effect on growth

Animal studies
Investigations in mice have shown that multiple courses of ACS result in intrauterine growth restriction with subsequent reduced birth weight, body length and head width at birth (82, 83). In sheep, preterm lambs exposed to multiple courses of ACS were lighter from birth until adolescence than term lambs, with females gradually catching-up but males remaining lighter. However, preterm sheep remained smaller in stature than controls throughout life (84).

Clinical studies
A retrospective cohort study showed that betamethasone exposure reduces fetal weight gain in a dose-dependent manner without improving neonatal morbidity or mortality (85). Birthweight has been shown to be unaltered following a single course of ACS but repeated ACS exposure decreases birth weight where for each additional course of antenatal corticosteroids, there is a trend toward an incremental decrease in birth weight, length, and head circumference (86). Furthermore, in babies born at term rather than preterm ACS was associated with a reduction in birth length, weight and head circumference when compared with matched controls (87). A randomised controlled trial which investigated multiple courses of antenatal corticosteroids for preterm birth (MACS) in women who continued to be at high risk of preterm birth reported an association of the multiple courses with a decreased weight, length of infants at birth (88).

Neurodevelopmental outcomes

Animal studies

In primates maternal dexamethasone causes dose dependent morphological hippocampal injury and multiple injections induce more severe damage than single injections of the same total dose (89). Studies in mice show that ACS has an effect on hippocampal volume, apoptosis and importantly proliferation all of which may have important implications for hippocampal network function later in life (90). In guinea pigs, ACS in late gestation alters developmental trajectories of transcription, glucocorticoid receptor DNA binding, and DNA methylation in the hippocampus and the authors suggest that this may be one potential mechanism by which ACS may lead to metabolic, endocrine, and behavioral phenotypes later in life (91). Interestingly, effects of ACS on the epigenome and gene expression in the brain appear to be transgenerational as shown in both guinea pigs and rats (91-94). Other rodent studies have shown that ACS exposure leads to alterations in brain morphology (blood-brain barrier, paraventricular nucleus of the hypothalamus) (95), gene expression (markers associated with brain vascularization and/or differentiation) (96), and inflammatory state (activation of the oligodendrocyte inflammasome) (97).

Clinical studies

Investigation of necropsy specimens from human neonates treated antenatally with ACS showed a lower density of neurons in the hippocampus (98). The use of repeat ACS leads to a decreased in head circumference (23, 88, 99) and although not significant, it was found to be associated with a higher rate in the incidence of cerebral palsy (100). A follow up study of children at 2 years of age which were at a high risk of preterm birth but were delivered at term, of which 100% received ACS treatment, showed that ACS exposure was associated with impaired cognitive development relative to children born at term with no ACS exposure (101). Liggins' original trial follow-up at 4 and 7 years of age concluded that there was no hazardous effect on physical and neurocognitive function assessed by detailed tests of psychological development (102, 103). In contrast to this, follow up study published in 2012 showed that females exposed to but born at term ACS showed increased cortisol reactivity to acute psychosocial stress at the age of 6-11 years (104). The most recent study investigating children's intelligence argues that it is conditions related to a threatening preterm delivery rather than ACS treatment itself responsible for the decrease in intelligence observed (105).

Overall, there is a lot of contradictory evidence relating to the effects of ACS on the different organ systems. It would be useful if future clinical studies analysed different cohorts based on the type and dose of ACS used, whether the treatment was partial, complete and/or repeated

and gestational age at the time of delivery. These factors are likely impact the outcomes observed therefore ignoring these differences may mask significant effects.

Future research directions

Much of the research into the effects of ACS has focussed on outcomes in babies born preterm. Outcomes in babies born at term have been largely ignored. A new project, the Consortium for the study Of Pregnancy Treatments (Co-OPT) plans to address this. This collaborative project will bring together data from 13 datasets (1.5 million women and their children who received ACS). The aim is to describe how antenatal corticosteroid treatment is used across a variety of setting and determine the short and long-term outcomes of ACS, particularly focussing on outcomes when ACS were given unnecessarily (did not deliver preterm) and or were inappropriately timed. Analysis of data at scale will allow exploration of influences maternal and infant outcomes and develop predictive models to help improve ACS prescribing.

In conclusion, we need to be more sophisticated in how ACS are used, as many of the questions raised by Liggins and Howie in 1972 still lack a clear and definite answer. The introduction of ACS into clinic has indeed been revolutionary and has saved millions of preterm babies worldwide. Ironically, this success may well be what has impeded further research and understanding of the treatment.

Acknowledgements

List of abbreviations

11β-HSD-2	11β-hydroxysteroid dehydrogynease
ACS	Antenatal Corticosteroids
HPA	Hypothalamic-pituitary-adrenal axis
IVH	Intraventricular Hemorrhage
NEC	Necrotizing Enterocolitis
RDS	Respiratory Distress Syndrome

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