The Effect of Antenatal Corticosteroid Use on Offspring Cardiovascular Function: A Systematic Review

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Abstract

Background Antenatal corticosteroids (ACS) are recommended in threatened preterm labour to improve short term neonatal outcome. Preclinical animal studies suggest detrimental effects of ACS exposure on offspring cardiac development; their effects in humans are unknown. Objectives To systematically review the human clinical literature to determine the effects of ACS on offspring cardiovascular function. Main results Twenty-six studies including 1921 patients were included, of which most were cohort studies of mixed quality. The type of ACS exposure, gestational age at exposure, dose and number of administrations varied widely. Offspring cardiovascular outcomes were assessed from one day to 36 years postnatally. The most commonly assessed parameter was arterial blood pressure (18 studies), followed by echocardiography (8 studies), heart rate (5 studies), electrocardiogram (ECG, 3 studies) and cardiac magnetic resonance imaging (MRI, 1 study). There were no clinically significant effects of ACS exposure on offspring blood pressure. However, there were insufficient studies assessing cardiac structure and function using echocardiography or cardiac MRI to be able to determine an effect. Conclusions Administration of ACS is not associated with long-term effects on blood pressure in exposed human offspring. The effects on cardiac structure and other measures of cardiac function were unclear due to the small number of studies, study heterogeneity and mixed quality. Given the emerging preclinical evidence of harm following ACS exposure, there is a need for further research to assess central cardiac function in human offspring exposed to ACS. Keywords: Antenatal corticosteroids, ACS, cardiovascular, offspring, blood pressure

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Abstract

Background

Antenatal corticosteroids (ACS) are recommended in threatened preterm labour to improve short term neonatal outcome. Preclinical animal studies suggest detrimental effects of ACS exposure on offspring cardiac development; their effects in humans are unknown.

Objectives

To systematically review the human clinical literature to determine the effects of ACS on offspring cardiovascular function.

Search strategy and selection criteria

A systematic review was performed according to PRISMA guidelines in MEDLINE, EMBASE and Cochrane databases. Offspring who had been exposed to ACS during fetal life in comparison to those not receiving steroids, those receiving a placebo or population data were included. Studies not performed in humans or which did not assess cardiovascular function were excluded.

Data collection and analysis

Two authors independently screened studies, extracted data and assessed quality of studies. Results were combined descriptively and analysed using a standardised Excel form.

Main results

Twenty-six studies including 1921 patients were included, of which most were cohort studies of mixed quality. The type of ACS exposure, gestational age at exposure, dose and number of administrations varied widely. Offspring cardiovascular outcomes were assessed from one day to 36 years postnatally. The most commonly assessed parameter was arterial blood pressure (18 studies), followed by echocardiography (8 studies), heart rate (5 studies), electrocardiogram (ECG, 3 studies) and cardiac magnetic resonance imaging (MRI, 1 study). There were no clinically significant effects of ACS exposure on offspring blood pressure. However, there were insufficient studies assessing cardiac structure and function using echocardiography or cardiac MRI to be able to determine an effect.

Conclusions

Administration of ACS is not associated with long-term effects on blood pressure in exposed human offspring. The effects on cardiac structure and other measures of cardiac function were unclear due to the small number of studies, study heterogeneity and mixed quality. Given the emerging preclinical evidence of harm following ACS exposure, there is a need for further research to assess central cardiac function in human offspring exposed to ACS.

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Keywords:

Antenatal corticosteroids, ACS, cardiovascular, offspring, blood pressure

Tweetable abstract:

Exposure to antenatal corticosteroids does not have long-term effects on blood pressure.

Introduction

Over the last 40 years, the administration of antenatal corticosteroids (ACS) has become routine practice in mothers with threatened preterm labour between 24 and 34 weeks of gestation[1]. In this circumstance, they are proven to reduce short-term neonatal morbidity - especially that caused by respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis and sepsis - and mortality[2 3]. Prophylactic treatment with ACS is designed to mimic the maturational effects of the normal endogenous, prepartum increase in fetal plasma cortisol concentration that occurs close to term in humans and other species[4]. Glucocorticoids are known to switch tissue accretion to differentiation. Therefore, ACS accelerate maturation of many fetal organs and systems, enhancing the preterm baby's successful transition to neonatal life[4 5].

Despite clear life-saving benefits of ACS, there is increasing awareness of possible adverse off-target effects[5 6 7]. A systematic review in humans showed improved major neurodevelopmental outcomes (e.g. lower rates of cerebral palsy) in children exposed to ACS[8], but a large amount of animal data have suggested an association between ACS administration and a range of neuro-anatomical and neuro-behavioural changes [7 9 10]. The developing cardiovascular system is also affected by glucocorticoid signalling. Preclinical animal studies have suggested that ACS may have long-term adverse effects on the heart and the circulation[5 6 7 11] but much less is known about cardiovascular consequences of ACS exposure in humans. Therefore, the aim of this study was to systematically review the human clinical literature to determine the effects of ACS on offspring cardiovascular function.

Methods

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidance[12]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42020178521).

Eligibility criteria

Eligible studies were those in which cardiovascular function had been assessed in humans who had been exposed to ACS during fetal life in comparison to those not receiving steroids, those receiving a placebo or population data. Studies not performed in humans or which did not assess cardiovascular function were excluded. Randomised trials and observational studies (cohort and case-control) were included, as were case series with n[?]3. There is no accepted numerical definition of a case series[13]. We used an empirical cut-off of at least three cases however, because of the risk of publication bias with individual case reports. Systematic and narrative reviews were excluded after checking reference lists for primary studies. Publications from 1990 to January 2021 were considered eligible and no language restrictions were applied.

Search strategy

A systematic review was conducted in MEDLINE, EMBASE and Cochrane databases using a combination of Medical Subject Headings (MeSH) and free text as follows:

antenatal corticosteroid OR antenatal glucocorticoid OR antenatal steroid OR prenatal steroid OR dexamethasone OR betamethasone

AND

cardiovascular OR heart OR echocardiography OR blood pressure

Subsequently, a grey literature (first 100 hits in Google Scholar and Pubmed) search was performed, and reference lists of relevant review articles were manually checked. Forward citation searching was also performed, whereby key papers identified were located in Web of Science to identify other work where they may have subsequently been cited; references of these papers were also checked. Covidence software (Veritas Health Innovation Ltd, Melbourne, Australia) was used to eliminate duplicate articles and manage study screening.

Study selection

Two authors (A.S. and E.C.) independently screened all studies by title and abstract and subsequently assessed full-text articles. Disagreements were resolved by consensus.

Data extraction

Two authors (A.S. and E.C.) independently extracted data from all studies and entered them into a standardised Excel (Microsoft, Washington, USA) form. Data which did not match were discussed, and the study was reviewed to reach a consensus.

Quality assessment of studies

Two authors (A.S. and E.C.) assessed study quality and risk of bias independently using a standardised Excel form. Randomised trials were analysed using the Cochrane Collaboration's tool[14] for assessing risk of bias. Case-control and cohort studies were analysed using the Newcastle-Ottawa scale[15] for assessing the quality of non-randomised studies. An adaptation of the Murad tool[16] was used for case series.

Statistics

Results were combined descriptively and analysed using a standardised Excel form. Due to the anticipated rarity of studies and heterogeneity of parameters investigated, meta-analysis was not planned.

Results

Study selection

The electronic literature search identified 3938 studies (Figure 1); search of the grey literature and reference lists identified a further 19 studies. Following import of the literature search results, 1337 studies were immediately removed as duplicates. Screening by title and abstract of 2620 studies was performed and 2529 studies were excluded as irrelevant. The full texts of 69 remaining articles were reviewed and 43 studies were excluded as shown in Figure 1. Eventually 26 studies were included in this systematic review.

Study characteristics

Characteristics of included studies are shown in Table 1. The majority of studies were cohort studies (19/26, 73.1%); the remainder were randomised controlled trials (5/26, 19.2%), case control studies (1/26, 3.8%) and case series (1/26, 3.8%). A total of 1921 patients were described in the included studies.

Quality assessment

Quality assessment of included studies is given in Figure 2. The majority of studies were cohort studies of mixed quality. Case representativeness, demonstration that cardiac problems were not present before the intervention, and both duration and completeness of follow up were all areas of low quality. For randomised trials, there was an unclear risk of bias for most parameters.

Antenatal corticosteroid exposure

The gestational age of maternal ACS administration was not stated in 11/26 studies (42.3%). The remaining 15 studies reported maternal administration of ACS between 22-36 weeks of gestation. ACS exposure in terms of preparation of drug used, dose and number of doses varied widely between studies (Table 2).

Age at delivery and testing

The gestational age at delivery was given as a range in most studies. Combining all studies gave a range of gestational age at delivery of 23-41 weeks for patients described. The age at which cardiovascular testing was undertaken ranged from 1 day old to 36 years (Figure 3).

Types of cardiovascular test

Figure 3 shows the types of cardiovascular test undertaken according to age of participants at follow-up. Blood pressure (either peripheral or central) was assessed in eighteen studies, echocardiography in eight studies, heart rate in five studies, electrocardiogram (ECG) in three studies and cardiac magnetic resonance imaging (MRI) in one study. Several studies assessed more than one outcome measure and/or determined outcome measures at more than one time point.

Blood pressure (BP)

Peripheral blood pressure in offspring exposed to ACS was assessed in eighteen studies [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34]. Three of the eighteen studies also assessed central blood pressure [29] [31] [32]. The findings of these studies are shown in Table 3. Twelve studies found no difference in blood pressure (peripheral or central, systolic or diastolic) between offspring exposed to ACS and controls. Six studies showed an increase in mean arterial pressure (MAP) in offspring exposed to ACS compared to controls [17] [19] [22] [28] [30] [31]. These studies were all performed in the early neonatal period, and they reported that an increase in the MAP of the infant which the authors either reported was either clinically beneficial (reducing the need for vasopressor BP support) or the authors reported was clinically irrelevant (a small change which did not persist).

Echocardiography

Offspring echocardiography following ACS exposure was assessed in eight studies. Five of these studies assessed only the presence or absence of patent ductus arteriosus (PDA) - three found no difference in offspring exposed to ACS compared to controls [35] [30] [31], and two found that the incidence of PDA was reduced in infants who had been exposed to ACS at specific time points or in subgroup analyses [36] [37]. The remaining three studies assessed cardiac structure and function using a wide range of echocardiographic parameters. Two of these studies found no difference between offspring exposed to ACS and controls [18] [24]. One showed transient hypertrophic cardiomyopathy in neonates exposed to multiple ACS doses when comparing echocardiographic parameters to population norms [38].

Heart rate

Five studies determined changes in offspring heart rate following ACS exposure. Three of these studies showed no difference in heart rate between ACS exposure and controls [18] [24] [39]. Two studies found an increase in heart rate in ACS exposed infants - one found that in the first 72 hours after birth, unexposed infants had lower mean peak heart rate than those were exposed to ACS, which the authors describe as clinically irrelevant [19]. The other study showed that infants exposed to ACS had a higher heart rate response to a stress test (heel prick) than those who had not been exposed ACS [40].

ECG

ECG was assessed in three studies. Two studies showed no difference in ECG parameters (respiratory sinus arrhythmia and heart rate variability) between offspring exposed to ACS and those who were not exposed[41] [39]. One study showed in subgroup analysis that non-black offspring exposed to ACS had lower heart rate variability than those not exposed [42]. This effect was greater in non-black females compared to non-black males, and no difference was found in black offspring.

Cardiac MRI

One study assessed cardiac MRI [29]. This showed an increase in aortic arch stiffness (decreased aortic arch distensibility and increased aortic arch pulse wave velocity) in offspring exposed to ACS compared to controls. Exposure to ACS was associated with a localised increase in aortic arch stiffness, similar in magnitude to term-born individuals a decade older[29].

Discussion

This systematic review identified 26 studies in humans assessing cardiovascular function following antenatal corticosteroid (ACS) exposure where appropriate controls such as no exposure, placebo or population norms were included. Overall, no significant differences in measures of cardiovascular function were demonstrated. In particular, the majority of these studies focused solely on assessment of arterial blood pressure, finding either no effect or, in the neonatal period specifically, finding an increase in the MAP of the infant was either clinically beneficial (reducing the need for vasopressor BP support) or clinically irrelevant.

Comparatively fewer studies however determined the effect on ACS exposure on cardiac function, using for example echocardiography or cardiac MRI. We found 8 human clinical studies in children that determined effects of ACS exposure on cardiac function by echocardiography. Of these, 5 focused on the presence or absence of PDA[30 31 35 36 37], while the other three studies explored central cardiac function [17 23 37]. One study described a case series of three newborn infants exposed to ACS who showed evidence of hypertrophic cardiomyopathy when echocardiographic parameters such as left ventricle end systolic/diastolic dimension, ventricular septum thickness in systole/diastole and posterior wall thickness in systole/diastole were compared to population norms[38]. These changes were no longer present at six month follow up. The second study assessed 29 children aged 6 to 10 years whose mothers had received ACS compared to a cohort born at the same gestational age who had not been exposed to ACS[18]. Echocardiogram parameters were not different between the two groups. The third study assessed 51 children aged 7 to 10 years whose mothers had received ACS compared to a cohort born at the same gestational age who had not been exposed to ACS[24]. Echocardiographic parameters assessing systolic function, diastolic function and wall thickness were again not different between the two groups. Another human clinical study involved cardiac MRI in young men and women whose mothers were treated with ACS[29]. This study reported that *in utero*exposure to ACS was associated with long-term localised changes in aortic stiffness and function, measured in offspring approximately 25 years later. Combined, therefore, the available human clinical data show variable effects of ACS on cardiac and aortic structure and function, highlighting a significant knowledge gap in this specific area.

Maternal ACS are administered to women at risk of preterm birth so as to reduce the risk of serious illness and death in newborns[43]. It is estimated that ACS reduce perinatal death by a risk ratio (RR) of 0.85 (95% CI 0.77-0.93), reduce neonatal death (RR 0.78 (95% CI 0.70-0.87)) and respiratory distress syndrome (RR 0.71 (95% CI 0.65-0.78)), Importantly the evidence demonstrates improved outcomes in preterm infants (24–34 weeks) delivered between 1 and 7 days after the administration of a single course of ACS. Often women in threatened preterm labour however do not deliver within this short time frame following ACS administration, and more go on to deliver after 34 weeks of gestation, when ACS are not recommended[44]. The administration of ACS to mature the fetal lung remains contentious, especially as treatment doses and regimens are largely unoptimised. A focus on human clinical studies determining effects of ACS on offspring cardiac structure and function is important.

Accumulating evidence derived from experimental animal models suggests that synthetic glucocorticoids can have profound effects on the cardiovascular system of offspring, without necessarily inducing alterations in blood pressure. A focus on human clinical studies determining the effects of ACS on offspring cardiovascular structure and function is therefore important. Studies in ovine, rodent and avian model systems all demonstrate that exposure to antenatal glucocorticoids, such as dexamethasone or betamethasone, administered in clinically relevant doses, can affect cardiac morphology, metabolism and function [5 6 745 46 4748 49 5051 52 5354 55]. Reported effects include a premature switch from tissue accretion to differentiation, increased

oxidative stress, alterations in mitochondrial fatty acid oxidation and activation of cellular senescence in fetal cardiomyocytes. Long-term adverse effects of synthetic steroids on cardiac function in offspring reported in preclinical experimental studies include weakened systolic function, an impaired cardiac functional reserve and left ventricular hypertrophy[5 6 745 46 4748 49 5051 52 5354 55]. Therefore, data derived from preclinical animal models suggest potent effects of the synthetic glucocorticoids that are used in human clinical practice on cardiac function that are independent of changes in arterial blood pressure and independent of prematurity. The implication is that the widespread use of ACS may induce potential damaging long-term effects on cardiovascular function in offspring, that may only manifest in late adulthood, such as for example an increased risk of cardiac failure and myocardial infarction. This systematic review is unable to determine if there is such an effect in humans due to insufficiently available data.

A strength of our study is that it was conducted using validated systematic review methodologies and ensured that appropriate controls were included in all eligible studies. However, the eligible studies had wide variation in the type or dose regimen of ACS used, the gestational age at administration, the gestational age at delivery, the age at follow-up and the type of cardiovascular assessment performed. Gestational age at delivery is a particular confounder, ranging from 23 to 41 weeks in included studies. It is therefore difficult to isolate any potential adverse effects of ACS on cardiovascular outcomes in the offspring independent of prematurity.

Conclusion

This systematic review found that administration of ACS is not associated with long-term effects on blood pressure in exposed human offspring. The effects on cardiac structure and other measures of cardiac function were unclear due to study heterogeneity mixed quality. Given the widespread use of ACS and the emerging preclinical evidence that ACS exposure compromises cardiac development, ascertaining their potential direct long-term effects on cardiovascular structure and function in exposed children should be a clinical priority going forward. We would therefore recommend further clinical research on the effects of ACS specifically on cardiac function in children both born preterm and at term.

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Contribution

AS, DG, AD and NM conceived and planned the study. AS and EC performed searches, screening, data extraction and quality analysis. All authors contributed to writing and editing the manuscript.

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Disclosures

None

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