SYSTEMATIC REVIEW

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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 pre-term 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: A systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in MEDLINE, EMBASE and Cochrane databases.

Selection criteria: Offspring who had been exposed to ACS during fetal life, in comparison with those not receiving steroids, those receiving a placebo or population data, were included. Studies not performed in humans or that did not assess cardiovascular function were excluded.

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

Main results: Twenty-six studies including 1921 patients were included, most of which 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 1 day to 36 years postnatally. The most commonly assessed parameter was arterial blood pressure (18 studies), followed by echocardiography (eight studies), heart rate (five studies), electrocardiogram (ECG, three studies) and cardiac magnetic resonance imaging (MRI, one 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: The 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 because of the small number,

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heterogeneity and mixed quality of the studies. Given the preclinical and human evidence of potential 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, blood pressure, cardiovascular, offspring

1 | 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, ACS 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 the maturation of many fetal organs and systems, enhancing the preterm baby's successful transition to neonatal life.[4,5]

Despite the clear life-saving benefits of ACS, there is an 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 volume 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 the 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.

2 | METHODS

2.1 | 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). Patients were not involved in the development of this review as no primary research was conducted.

2.2 | 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 with those not receiving steroids, those receiving a placebo or population data. Studies not performed in humans or that did not assess cardiovascular function were excluded. Randomised trials and observational studies (cohort and case–control) were included, as were case series with $n \geq 3$. 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.

2.3 | 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 the key papers identified were then located in Web of Science to identify other work where they may have been subsequently cited; the references of these papers were also checked. Covidence software (Veritas Health Innovation Ltd, Melbourne, Australia) was used to eliminate duplicate articles and to manage study screening.

2.4 | Study selection

Two authors (AS and EC) independently screened all studies by title and abstract and subsequently assessed

full-text articles. Disagreements were resolved by consensus.

2.5 | Data extraction

Two authors (AS and EC) independently extracted the data from all studies and entered them into a standardised Excel (Microsoft, WA, USA) form. Data that did not match were discussed, and the study was reviewed to reach a consensus.

2.6 | Quality assessment of studies

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

2.7 | Statistics

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

3 | RESULTS

3.1 | Study selection

The electronic literature search identified 3938 studies (Figure 1); the search of grey literature and reference lists identified a further 19 studies. Following the 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 the 69 remaining articles were reviewed and 43 studies were excluded, as shown in Figure 1. Eventually, 26 studies were included in this systematic review.

3.2 | Study characteristics

The characteristics of the 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.
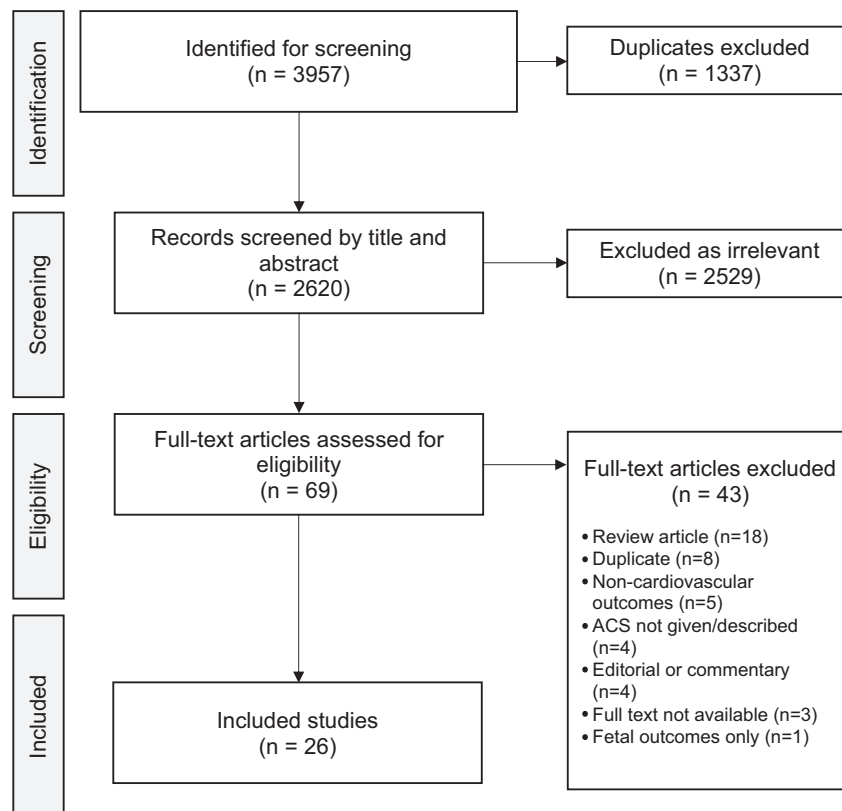

FIGURE 1 Flow diagram of study selection, adapted from PRISMA 2009[10]

TABLE 1 Included studies

First author and year of publication	Study design	Number of patients
Batton 2009[16]	Case–control	125
Chen 2008[17]	Cohort	29
Cinar Yakar 2013[18]	Cohort	80
Costa 2007[19]	Cohort	170
Dalziel 2004[20]	Randomised controlled trial	121
Dalziel 2005[21]	Randomised controlled trial	253
Davis 2006[22]	Cohort	14
Demarini 1999[23]	Cohort	80
Dessens 2000[24]	Randomised controlled trial	48
DeVries 2008[25]	Cohort	51
Dimitriou 2005[26]	Cohort	48
Doyle 2000[27]	Cohort	89
Eronen 1993[28]	Randomised controlled trial	28
Finken 2008[29]	Cohort	84
Gwathmey 2013[30]	Cohort	22
Kari 1994[31]	Randomised controlled trial	91
Kelly 2012[32]	Cohort	16
Moise 1995[33]	Cohort	59
Nair 2009[34]	Cohort	136
Nixon 2017[35]	Cohort	79
Norberg 2013[36]	Cohort	58
Savoy 2019[37]	Cohort	28
Schaffer 2010[38]	Cohort	23
South 2017[39]	Cohort	92
Washburn 2017[40]	Cohort	94
Yunis 1999[41]	Case series	3
	TOTAL	1921

3.3 | Quality assessment

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

3.4 | Antenatal corticosteroid exposure

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

3.5 | 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 the patients described. The age at which cardiovascular testing was undertaken ranged from 1 day old to 36 years (Figure 3).

3.6 | 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 18 studies, echocardiography was assessed in eight studies, heart rate was assessed in five studies, electrocardiogram (ECG) was assessed in three studies and cardiac magnetic resonance imaging (MRI) was assessed in one study. Several studies assessed more than one outcome measure and/or determined outcome measures at more than one time point.

3.7 | Blood pressure (BP)

Peripheral BP in offspring exposed to ACS was assessed in 18 studies.[17–34] Three of the 18 studies also assessed central BP.[29,31,32] The findings of these studies are presented in Table 3. Twelve studies found no difference in BP (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 with controls.[17,19,22,28,30,31] These studies were all performed in the early neonatal period and reported an increase in the MAP of the infant that was either clinically beneficial (i.e. reducing the need for vasopressor BP support) or clinically irrelevant (i.e. a small change that did not persist).

3.8 | 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 with controls;[30,31,35] 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 with population norms.[38]
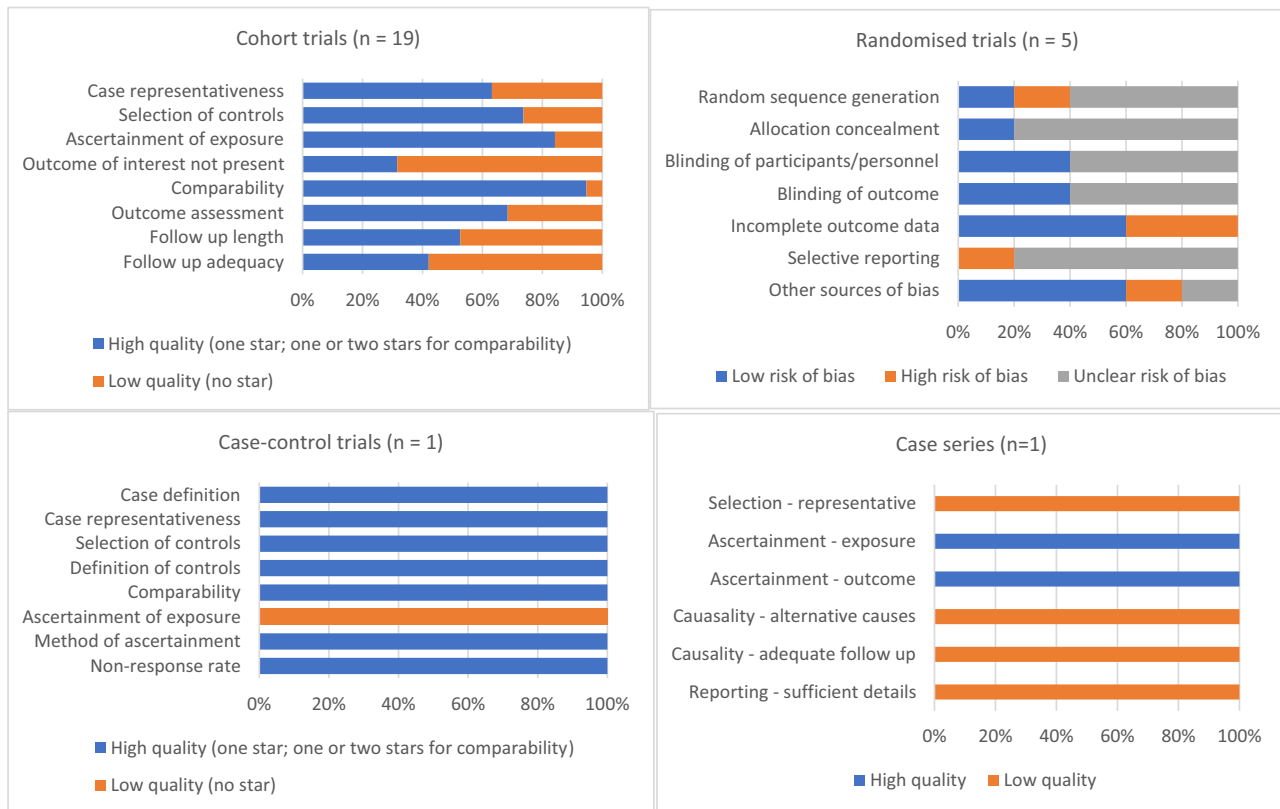
FIGURE 2 Quality assessment of studies using the Cochrane Collaboration tool for randomised trials,[11] the Newcastle–Ottawa scale for case–control and cohort studies,[12] and the Murad tool for case series [13]

3.9 | 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 infants exposed to ACS. One found that in the first 72 hours after birth, unexposed infants had a lower mean peak heart rate than infants who had been exposed to ACS, which the authors described 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 infants who had not been exposed to ACS.[40]

3.10 | ECG

Electrocardiograms (ECGs) were 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 offspring who were not exposed.[39,41] One study showed in subgroup analysis that non-black offspring exposed to ACS had lower heart rate variability than offspring not exposed to ACS.[42] This effect was greater in non-black females compared with non-black males, and no difference was found in black offspring.

3.11 | 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 with controls. Exposure to ACS was associated with a localised increase in aortic arch stiffness, similar in magnitude to term-born individuals who were a decade older.[29]

4 | DISCUSSION

This systematic review identified 26 studies in humans assessing cardiovascular function following ACS exposure, where appropriate controls such as no exposure, placebo or population norms were included. The majority of these studies focused solely on the assessment of arterial BP. Such studies reported either no effect or, in the neonatal period specifically, an increase in the MAP of the infant. This was seen as either clinically beneficial, reducing the need for vasopressor BP support, or clinically irrelevant. Comparatively fewer studies, however, determined the effect of ACS exposure on cardiac function, using for example echocardiography or cardiac MRI. We found eight human clinical studies in children that determined the effects of ACS exposure on cardiac function

by echocardiography. Of these, five focused on the presence or absence of PDA,[30,31,35,36,37] whereas 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

TABLE 2 Antenatal corticosteroid exposure

ACS details	Number of studies (%)
Type of ACS	
Not stated	4 (15.4)
Betamethasone	15 (57.7)
Dexamethasone	4 (15.4)
Betamethasone and dexamethasone	3 (11.5)
Dose of ACS	
Not stated	10 (38.5)
6 mg	3 (11.5)
8 mg	1 (3.8)
12 mg	9 (34.6)
6 mg short-acting + 6 mg long-acting	3 (11.5)
Number of doses	
Not stated/variable within study	5 (19.2)
1 dose	1 (3.8)
2 doses	9 (34.6)
4 doses	3 (11.5)
1–5 doses	5 (19.2)
5–15 doses	3 (11.5)

septum thickness in systole/diastole and posterior wall thickness in systole/diastole were compared with population norms.[38] These changes were no longer present at the follow-up at 6 months. The second study assessed 29 children aged 6–10 years whose mothers had received ACS, compared with a cohort born at the same gestational age who had not been exposed to ACS.[18] The Echocardiogram parameters were not different between the two groups. The third study assessed 51 children aged 7–10 years whose mothers had received ACS, compared with a cohort born at the same gestational age who had not been exposed to ACS.[24] Again, the echocardiographic parameters assessing systolic function, diastolic function and wall thickness did not differ 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 reduce 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 do not deliver
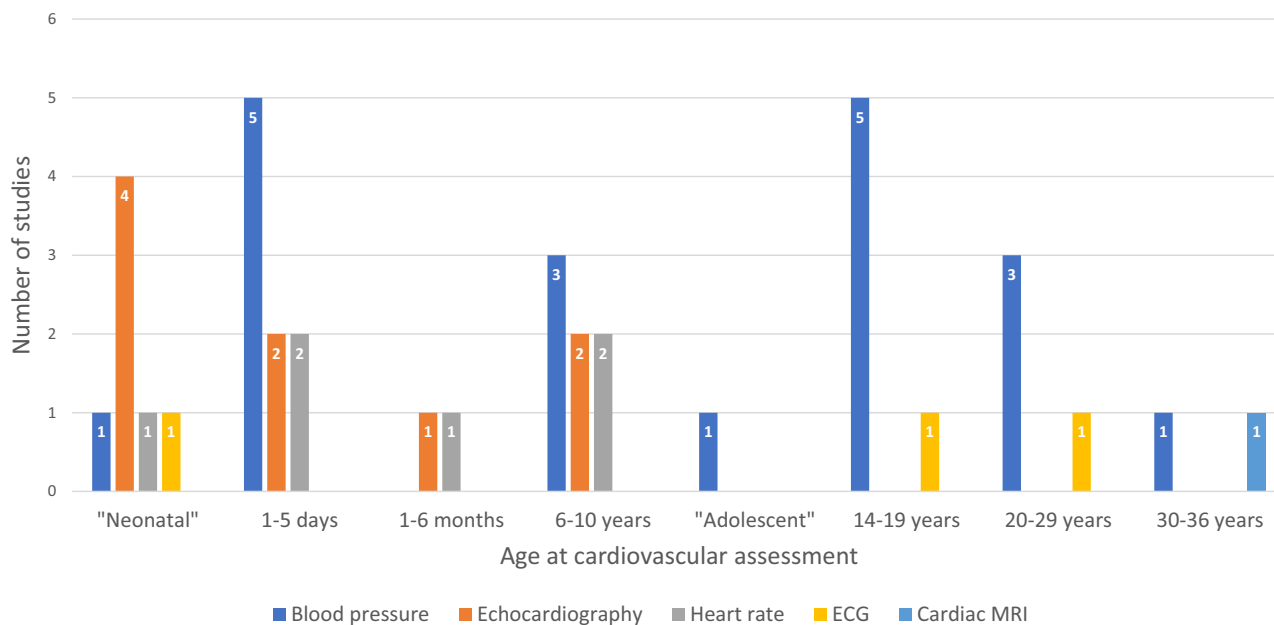

FIGURE 3 Cardiovascular testing type and age of participants. Bars show number of studies (*n*). ECG, electrocardiogram; MRI, magnetic resonance imaging

TABLE 3 Effects of ACS on blood pressure

BP parameter studied	Effect in offspring exposed to ACS vs controls (no. of studies)		
	Increased	Decreased	No difference
Peripheral BP			
Systolic	1	1	1
Diastolic	0	0	0
Systolic + diastolic	1	0	10
MAP	6	0	2
Clinical hypertension	0	0	1
Central BP			
Systolic	0	0	0
Diastolic	0	0	0
Systolic + diastolic	0	0	3

Note: Controls included those not receiving steroids, those receiving a placebo or population data.

Abbreviations: ACS, antenatal corticosteroids; BP, blood pressure; MAP, mean arterial pressure.

within this short time frame following ACS administration, however, 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 remain largely not optimised. The cluster-randomised Antenatal Corticosteroids Trial (ACT) found that the use of ACS in low-birthweight infants did not improve neonatal mortality in this group and was associated with an increase in overall population mortality.[45] This study was not included in our systematic review as it did not include the cardiovascular follow-up of infants, but serves as an example of the difficulty in evaluating ACS effects.

The absence of human clinical studies determining the effects of ACS on offspring cardiovascular outcomes other than the measurement of arterial BP is a significant gap of knowledge in the literature, as 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 BP. Independent studies in several laboratories in non-human primate, ovine, rodent and avian model systems have all demonstrated that exposure to antenatal glucocorticoids, such as dexamethasone or betamethasone, administered in clinically relevant doses, can affect cardiac morphology, metabolism and function.[5,6,7,46,47,48,49,50,51,52,53,54,55,56,57] 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.[5,6,7,46,47,48,49,50,51,52,53,54,55,56] An interesting study

by Kuo et al. reported that administration of the synthetic glucocorticoid betamethasone to pregnant baboons, at doses and stages of fetal life equivalent to human obstetric practice, produced offspring that at 10 years of adult life (the human equivalent to 40 years of age) showed pericardial and hepatic steatosis.[57] These findings highlight that ACS can cause abnormal fat deposition and adult body composition in midlife primate offspring, raising concerns regarding future cardiac lipid accumulation and lipotoxicity.[57] Combined, therefore, data derived from several preclinical animal models, including non-human primates, suggest potent effects of the synthetic glucocorticoids that are used in human clinical practice on cardiac function that are independent of changes in arterial BP and independent of prematurity. The implication is that ACS can be a developmental programming stimulus, giving rise to fetal origins of cardiac dysfunction that may lie dormant for many years and emerge much later in adult life, particularly in response to a 'second hit', such as an increased risk of cardiac failure and myocardial infarction. This systematic review is unable to determine if there is such an effect in humans because of insufficiently available data. However, our review highlights the importance of a focus on human clinical studies to determine the effects of ACS on offspring cardiac structure and function.

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 independently of prematurity.

5 | CONCLUSION

This systematic review found that the administration of ACS is not associated with long-term effects on BP in exposed human offspring. The human data on other adverse long-term cardiovascular consequences of ACS exposure are insufficient to exclude important harmful effects. Given the evidence from animal and human studies, the administration of ACS should be limited to clinical settings where there is a high degree of certainty that preterm birth is imminent, to reduce the risk that as yet poorly understood adverse effects might outweigh the known clinical benefits. Ascertaining the potential direct long-term effects of ACS on cardiovascular 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 structure and function in children born both preterm and at term.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTERESTS

NM reports personal fees from InfanDx and Novartis, outside of the submitted work. All other authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.