Maternal and neonatal outcomes following antenatal corticosteroids in pregnancies complicated by diabetes: a scoping review

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OBJECTIVE: To examine the current literature surrounding the administration of antenatal corticosteroids in pregnancies complicated by diabetes and summarize the reported neonatal and maternal outcomes in exposed and unexposed groups.

DATA SOURCES: A systematic search was performed in November 2023 using Ovid Medline and Embase databases to identify relevant studies.

STUDY ELIGIBILITY CRITERIA: Articles that reported on the maternal or neonatal outcomes in pregnancies complicated by pre-gestational or gestational diabetes after exposure to antenatal corticosteroids were included in this review. Articles were excluded if they did not separately report on the outcomes experienced by women with diabetes.

METHODS: Maternal and neonatal outcomes of interest included neonatal respiratory distress syndrome, neonatal hypoglycemia, and maternal hyperglycemia. Key words in this search included combinations of the terms related to pre-gestational and gestational diabetes, antenatal corticosteroids, respiratory distress syndrome, hypoglycemia, and hyperglycemia. Title and abstract screening was conducted in duplicate.

RESULTS: There were 19 studies that met the inclusion criteria. There were 13 studies that presented results pertaining to neonatal respiratory distress syndrome, 14 studies discussed neonatal hypoglycemia and 5 studies discussed maternal hyperglycemia. Only 2 included studies were randomized controlled trials with the remaining 17 studies being observational. There was heterogeneity in clinical settings, study populations, type of corticosteroid administered and timing of administration across the included studies. This review found that there is no clear evidence of beneficial effect of corticosteroid administration on neonatal respiratory outcomes in pregnancies complicated by diabetes. Additionally, there was discrepancy between studies reporting on neonatal hypoglycemia with 6 studies reporting an increased incidence in this outcome after antenatal corticosteroid exposure whilst 4 studies found no difference between exposed and unexposed groups. This review identified a specific gap in the reporting of maternal hyperglycemia following antenatal corticosteroids. The limited number of studies that did report this outcome unanimously reported an increased incidence of maternal hyperglycemia after corticosteroid exposure. The majority of studies had small sample sizes of pregnancies both complicated by diabetes and exposed to corticosteroids and therefore lacked sufficient power to make robust conclusions about the influence of antenatal corticosteroids in this group.

CONCLUSION: This review concludes that there are insufficient data regarding the risks and benefits of antenatal corticosteroid administration in pregnancies complicated by diabetes.

Key words: antenatal corticosteroids, diabetes in pregnancy, neonatal hypoglycemia, maternal hyperglycemia, respiratory morbidity

Introduction

The administration of antenatal corticosteroids (ACS) is one of the most successful interventions for the prevention of neonatal respiratory morbidity and neonatal death in infants born preterm.[1] The landmark trial by Liggins and Howie conducted over 50 years ago was the first to demonstrate that administration of ACS remarkably reduced the incidence of respiratory distress syndrome (RDS) and neonatal mortality.[2] Since this initial trial, multiple randomized trials, summarized in a recent Cochrane systematic review, have confirmed the beneficial effects of ACS on other complications of prematurity including transient tachypnoea of the

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The authors report no conflict of interest.

Patient consent is not required because no personal information or details have been used.

This study reviews the reported outcomes of antenatal corticosteroids administered in pregnancies complicated by diabetes.

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2666-5778/$36.00

http://dx.doi.org/10.1016/j.xagr.2024.100416

AJOG Global Reports at a Glance

Why was this study conducted?

There is currently no consensus on whether the potential benefits of antenatal corticosteroids in reducing neonatal respiratory morbidity outweigh the potential risks of neonatal hypoglycemia and maternal hyperglycemia in women with diabetes.

Key findings

This review found that there are insufficient data regarding the risks and benefits of antenatal corticosteroid administration in pregnancies complicated by diabetes.

What does this study add to what is already known?

This review highlights the need for high quality randomized controlled trials of antenatal corticosteroids in pregnancies complicated by diabetes to ensure well informed clinical practice for these women and their infants.

newborn (TTN), intraventricular hemorrhage and necrotizing enterocolitis with no apparent adverse maternal effects.[1] This research has informed clinical guidelines globally with the World Health Organization recommending antenatal corticosteroid therapy for women who are likely to give birth between 24 and 34 weeks' gestation.[3]

Despite the known benefits for fetal lung maturation in preterm pregnancies, there are emerging reports of potential risks associated with ACS administration. Gyamfi-Bannerman et al.[4] reported that the incidence of neonatal hypoglycemia was 60% more likely to occur in ACS exposed infants (relative risk 1.60, 95% CI 1.37−1.87, $P<.001$) in a randomized trial of pregnant women at risk of late preterm birth (34^{+0} to 36^{+7} weeks).[4] Sifianou et al.[5] observed a significant increase in c-peptide concentration in cord blood of neonates exposed to ACS (median 2.85mcg/L vs 1.19mcg/L, 95% CI 2.44 −3.47 vs 1.09−1.29, $P<.0001$), suggesting fetal hyperinsulinemia which may lead to neonatal hypoglycemia.[5] Likewise, maternal hyperglycemia is a widely recognised consequence of ACS administration, regardless of the presence of diabetes due to the stimulation of gluconeogenesis.[6]

Considering these complications associated with ACS, particularly maternal hyperglycemia, it is alarming that women with diabetes have historically been excluded from studies investigating ACS.[7] Women with pre-gestational diabetes (PGDM) (including type 1 or type 2 diabetes mellitus) or gestational diabetes (GDM) are more likely to experience pregnancy complications such as fetal macrosomia, pre-eclampsia, and stillbirth compared with those without diabetes.[8-10] They are also more likely to require caesarean birth[10,11] and their neonates are more likely to have hypoglycemia.[12] Babies born to women with PGDM or GDM are more likely to have respiratory morbidity (Adjusted Odds ratio (OR) for type 1 diabetes, 2.5; 95% CI 1.4−4.4)[12](OR GDM, 1.1; 95% CI 1.0-1.4).[11] Considering the risk of neonatal respiratory complications, ACS may be beneficial for infants born to women with diabetes to help reduce this risk. Fetal hyperinsulinemia associated with maternal diabetes may impact surfactant production in the fetal lung, increasing the risk of neonatal respiratory morbidity.[5] What is not known yet, is whether surfactant production and therefore risk of neonatal respiratory morbidity is improved following ACS in pregnancies complicated by diabetes or whether ACS exacerbates associated complications. With the incidence of diabetes in pregnancy increasing substantially over the past decade,[13] there is an urgent need to determine the safety and efficacy ACS in these women.

There is currently no consensus on whether the potential benefits of ACS in reducing neonatal respiratory morbidity outweigh the potential risks of neonatal hypoglycemia and maternal hyperglycemia in women with diabetes. The most recent Cochrane review highlighted the insufficient evidence available for the use of ACS in this group of women[1] emphasizing the need for further research in this population. Peak bodies acknowledge this key gap in research in their recommendations on ACS including the American College of Obstetricians and Gynaecologists,[14] World Health Organisation[15] and the National Institute for Health Excellence[16] who have all highlighted that the benefit of ACS in women with diabetes is currently unknown. Guidelines that do recommend ACS in this population clarify that administration should be accompanied by appropriate glycemic monitoring and management.[17]

This review therefore aims to examine the available literature surrounding the administration of ACS in women with diabetes and summarize key neonatal and maternal outcomes: neonatal respiratory morbidity, neonatal hypoglycemia, and maternal hyperglycemia.

Methods

A literature search of the databases Ovid Medline and Embase was conducted (final search on 15th of November 2023). General search terms pertained to PGDM, GDM and antenatal corticosteroids. Key outcome terms included neonatal hypoglycemia, maternal hyperglycemia, and respiratory morbidity. Boolean operators AND and OR were used to combine these key themes. A detailed search strategy is summarized in Supplementary Table 1.

Once duplicate articles had been removed, the resulting publications were screened based on their title and abstract. Relevant publications then underwent full text screening. Publications that did not provide evidence of separate data or analysis of outcomes for participants with diabetes were excluded from this review. This exclusion criterion was implemented to ensure that the data presented in this review is specific to outcomes experienced by women with diabetes and their infants after ACS exposure.

This systematic review was prospectively registered with Open Science Frameworks on 12th November 2023 (https://doi.org/10.17605/OSF.IO/VQ7RF).

Results

A total of 19 publications[18-36] were included in this review (Table 1). The results of our literature search and reasons for article exclusion are depicted in Figure 1.

Notably, the exclusion criteria removing any study that did not conduct a separate analysis on the outcomes of participants with diabetes resulted in a large number of studies being excluded from this review. Despite their relevance to the discourse on the use of ACS, the absence of separate data relating to the outcomes of patients with diabetes prevents determining whether these outcomes are unique in pregnancies complicated by diabetes. Studies that used corticosteroids for purposes other than the prevention of neonatal RDS were also excluded. Additionally, studies that were not available in English were excluded. A summary of these studies which were excluded during full publication screening is outlined in Supplementary Table 2.

Of the 19 studies included, only 2 were randomized controlled trials.[23,32] The remaining 17 studies were

FIGURE 1
PRISMA diagram of Embase and Medline search

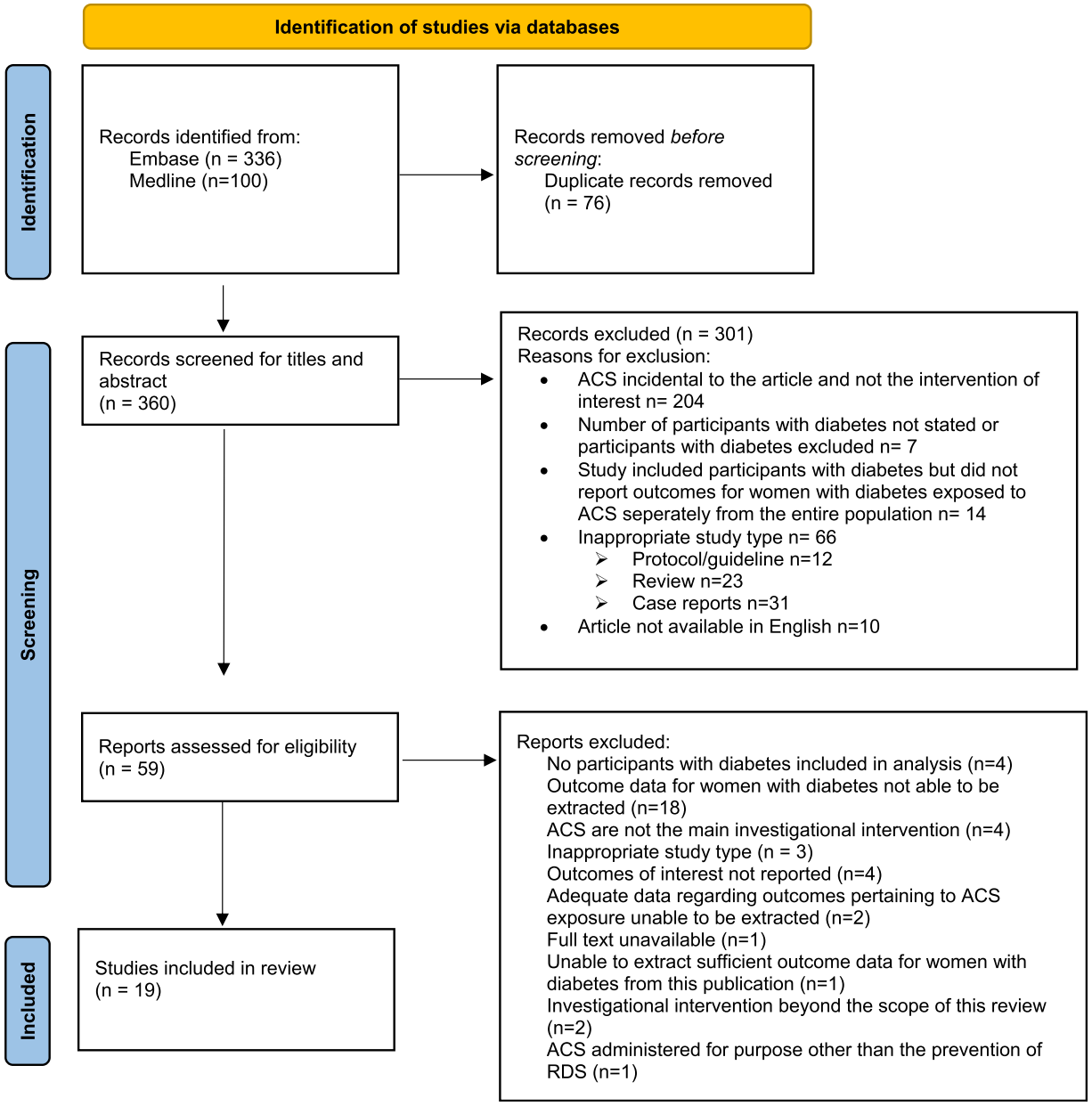

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TABLE 1
Summary of papers included in this review

Authors	Study type	Sample size	Population studied	Intervention	Outcomes assessed
Ali H, et al 2020[18]	Retrospective analysis using routinely collected hospital data	• 13,976 infants • 3895 women with diabetes • 80 received ACS • 18 received ACS ≤14 d from delivery	Singleton births after 34 weeks' gestation	Two intramuscular injections of 12 mg betamethasone phosphate, 24 h apart in mothers. All patients except 3 received a complete regimen of 2 doses	RDS, TTN, NICU admission, neonatal hypoglycaemia based on ICD-10 coded diagnoses or data entered into medical records
Battarbee AN, et al 2022[19]	Secondary analysis of an observational cohort from 25 US hospitals from March 2008 to February 2011	• 4429 women and 5259 neonates • 510 women with diabetes (181 PGDM, 329 GDM) • 439 received ACS	Women with singleton pregnancies who delivered at 23^{+0} to 33^{+6} weeks' gestation and received antenatal corticosteroids were compared with those who did not receive antenatal corticosteroids.	One dose of 12 mg intramuscular betamethasone) or a full course (2 doses of 12 mg intramuscular betamethasone spaced 24 h apart)	Neonatal RDS or death within 48 h. RDS was defined as a clinical diagnosis of respiratory distress syndrome, hyaline membrane disease, or respiratory insufficiency requiring oxygen therapy with FiO2 ≥ 0.40 started within the first 24 hours after birth and continued for ≥ 24 h or until neonatal demise. Secondary outcomes included mechanical ventilation and a composite of neonatal morbidity including respiratory distress syndrome, necrotizing enterocolitis, grade 3 or 4 intraventricular hemorrhage, sepsis, or neonatal demise.
Cassimatis IR et al. 2020[20]	Three site retrospective cohort study between April 2014 to May 2017	• 54 women with pre-gestational diabetes • 18 received ACS	Women with PGDM with singleton pregnancies who delivered in the late pre term period (34^{+0} to 36^{+6} weeks)	Betamethasone administration. Dose and timing not stated.	Length of neonatal hospitalization, composite respiratory morbidity (defined as continuous positive airway pressure ≥2 h, O2 ≥ 4 h, or mechanical ventilation) and neonatal hypoglycaemia (<40 mg/dL or 2.2mmol/L)
Dude AM et al. 2021[21]	Single centre, retrospective cohort study comparing 2 cohorts before (1 November 2012 to 31 October 2013) and after 1 April 2016 to 30 March 2017) introduction of a protocol for late preterm steroids	• 123 women with diabetes • Births during the pre-ACS protocol period (n=58) compared with the post-ACS protocol period (n=65) • Only 50 of 65 people eligible to receive corticosteroids in the post-protocol period (76.9%) received corticosteroids during the late preterm period	Patients with any diabetes diagnosis and singleton gestation, between 34^{+0} and 36^{+6} gestation at risk of birth before 37 weeks GA.	Two doses of Betamethasone acetate 12mg administered intramuscularly 24 hours apart exposure compared to those who were note exposed	Neonatal hypoglycaemia, defined as any glucose ≤ 60 mg/d (3.3mmol / L) within the first 24 h of life, Secondary outcomes included neonatal hypoglycaemia defined as any glucose ≤ 40 mg/dL (2.2mmol/ L) in the first 24 h of life, receipt of intravenous dextrose, TTN, RDS, surfactant administration, and hospital length of stay. Respiratory distress syndrome diagnosis was made based on typical chest X-ray and need for supplemental oxygen. Transient tachypnea of the newborn was diagnosed by chest X-ray finding of perihilar linear streaking. Those neonates requiring oxygen, but with normal chest X-ray findings, were individually reviewed for a diagnosis by a neonatologist.
Gupta K et al. 2020[22]	Single centre, Retrospective study between 1 May 2016 and 30 April 2018.	• 102 women with diabetes (95 GDM, 4 Type 2 diabetes, 3 Type 1 diabetes) • 33 received ACS	Women with any form of diabetes in pregnancy undergoing elective CS with a singleton pregnancy were included. (37+0 to 38+6 weeks' gestation)	Type of corticosteroids, dose, and timing in relation to caesarean section is not stated.	Neonatal hypoglycaemia defined as a as a heel-prick blood glucose of <2.6 mmol/L. RDS/TTN defined as respiratory distress requiring support (and admission to NICU), including subcostal recession, or a respiratory rate of >60 breaths per minute.
Gyamfi-Bannerman C et al. 2023[23]	Secondary analysis of randomized controlled trial	• 2609 infants, 283 women with diabetes • Number exposed to betamethasone not specified	Women at risk for late preterm delivery between 34+0 and 36+5 weeks' gestation were randomized to betamethasone or placebo	Two intramuscular injections containing either 12 mg of betamethasone (equal parts betamethasone sodium phosphate and betamethasone acetate) or matching placebo administered 24 hours apart	Duration of neonatal hypoglycaemia <40mg/dL, lowest reported blood glucose, treatment for hypoglycaemia and incidence of prolonged, persistent hypoglycaemia defined as hypoglycaemia which persisted for ≥72 hours after birth.

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TABLE 1
Summary of papers included in this review *(continued)*

Authors	Study type	Sample size	Population studied	Intervention	Outcomes assessed
Jolley JA et al. 2016[24]	Prospective observational study	• 33 total • 11 women with diabetes (9 GDM, 2 PGDM) • All exposed to ACS	Women with singleton or twin pregnancies who were candidates for betamethasone administration due to risk for preterm delivery for any reason between 24+0 and 33+6 weeks gestation.	Betamethasone (dose not specified)	Maternal hyperglycemia measured by capillary blood glucose every 4 hours for 48 hours after administration of corticosteroids. Significant hyperglycemia defined as a blood glucose level ≥140 mg/dL, and ≥160 mg/dL
Kakoulidis I et al. 2019[25]	Observational cohort study from August 2016 to December 2017	• 99 women with GDM (47 controlled with diet and 52 on insulin), all received ACS	Women with singleton pregnancies, 23—34 weeks' gestation who are at increased risk of preterm delivery	One or 2 doses of 12 mg of betamethasone given intramuscularly, 24 h apart	Maternal glycaemic profile measured by 6 to 7 capillary plasma blood glucose measurements per day (pre and 1 h postprandial, plus an overnight measurement) with point of care devices
Krispin E et al. 2018[26]	Single centre retrospective cohort study between 2012 and 2016.	• 2262 women with GDM • 47 received ACS prior to 34^{+0} weeks and delivered in the late pre-term. • 82 received ACS prior to 34^{+0} weeks and delivered at term	Women with singleton viable fetus delivering after 34 weeks' gestation. (Subdivided into late preterm (34^{+0} to 36^{+6}) and term (37^{+0} to 41^{+6})	Two doses of betamethasone 12mg administered intramuscularly 24 hours apart administered once in the setting of risk of preterm birth between 24^{+0} to 33^{+6} weeks.	Neonatal adverse composite outcome including respiratory composite outcome, hypoglycaemia, and necrotizing enterocolitis. Secondary outcomes were neonatal respiratory composite outcomes, including any of the following: TTN, RDS, mechanical ventilation and meconium aspiration syndrome.
Langen ES et al. 2014[27]	Prospective observational trial from August 2010 to May 2011	• 15 women total between 24+0 and 34+0 weeks' gestation. • 4 women with diabetes (3 with GDM and 1 with Type 2 diabetes) who all received ACS	Women receiving clinically indicated betamethasone between 24+0 and 34+0 weeks' gestation	Two doses of 12 mg of betamethasone intramuscularly 24 hours apart.	Maternal glycaemia measured using continuous glucose monitoring. Proportion of time spent with glucose levels above 110, 144, 180mg/dL (6.1, 8.0 10.0mmol/L) thresholds.
Li J et al. 2022[28]	Retrospective cohort study	1165 women with diabetes • 427 received ACS • 159 received ACS within 2 days • 131 received ACS within 2-7 days of birth • 137 received ACS >7 days prior to birth	Women having a planned CS at 37^{+0} to 38^{+6} weeks with GDM (WHO criteria) or Diabetes in Pregnancy (fasting glucose ≥7mmol/L and 2 hour glucose ≥11.mmol/L on OGTT	Dexamethasone 6mg x 4 doses given 12 hours apart. Exposure defined as receiving at least 1 dose prior to birth. Decision regarding administration was left to discretion of treating team.	Respiratory distress syndrome defined according to clinical criteria and presence of typical findings of either RDS or TTN on Chest x-ray. Neonatal hypoglycaemia defined as blood glucose ≤2.2mmol/L within 24 hours after birth. All infants with blood glucose ≤2.6mmol/L were treated with intravenous dextrose and close surveillance.
Liang FW et al. 2021[29]	Population-based retrospective study	• 70946 total • 4233 infants born to women with GDM • 746 were exposed to ACS • (Women with PGDM excluded)	Women presenting with early or threatened preterm labour between 20 and 36^{+6} weeks of gestation who gave birth to an infant after 33 weeks' gestation.	ACS exposure between 34^{+0} and 36^{+6} weeks' gestation. No details provided regarding type and timing of ACS	Neonatal respiratory morbidity (RDS) including utilisation of CPAP, mechanical ventilation, and oxygen. Neonatal 'glucose' use (not specifically defined as intravenous or oral)
Paul R et al. 2019[30]	Retrospective case control study	• 60 women with GDM • 30 received ACS	Women with a singleton pregnancy and GDM who delivered via caesarean section ≥37 weeks' gestation	Two doses of Betamethasone 11.4mg administered 24 hours apart intramuscularly prior to delivery. The decision to treat was at the discretion of the treating team. All women who received ACS were admitted for an insulin and dextrose infusion. Controls were selected (1:1) to match for cases by ethnicity, mode of birth and year of birth.	Number of admissions to NICU for RDS and/or TTN, the mean length of stay in NICU for respiratory complications. Incidence of neonatal hypoglycaemia (defined as glucose levels ≤2.5 mmol/L) within 24 h post-delivery and the mean nadir neonatal glucose level.

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TABLE 1
Summary of papers included in this review *(continued)*

Authors	Study type	Sample size	Population studied	Intervention	Outcomes assessed
Raj-Derouin et al. 2023[31]	Retrospective single centre case control study	• 169 women with diabetes (162 GDM, 6 Type 2 DM) • 87 received ACS	Individuals with diabetes who delivered between 34^{+0} and 37^{+6} weeks' gestation	Betamethasone (dose not specified) 36 participants received 2 doses of betamethasone and 51 received one dose	Prevalence of neonatal hypoglycaemia defined as heel stick less than 40mg/dL within the first 4 hours of life or less than 45mg/dL at 4 to 24 hours of life
Said JM et al. 2023[32]	Single centre, triple blind pilot randomized control trial	• 47 women with diabetes • GDM • Type 1 diabetes n=5 • Type 2 diabetes n=7 • GDM n= 35 • 22 randomized to ACS	Pregnant women with a singleton or twin pregnancy who have PGDM or GDM and who planned to give birth by elective CS between 35^{+0} and 38^{+6} weeks of gestation	Participants were randomized to receive 2 injections of either betamethasone 11.4 mg in 2 mL, or 2 mL normal saline placebo, 24 hours apart.	Primary outcomes were measures of feasibility. Secondary outcomes included neonatal respiratory morbidity defined as the need for respiratory support for ≥ 4 hours; neonatal hypoglycemia <2.6mmol/L; maternal hyperglycemia defined as the highest maternal blood glucose in the interval between randomization and birth as well as the need for additional insulin
Thevathasan et al. 2022[33]	Retrospective cohort study	• 306 women with PGDM • 65 exposed to ACS ≤7 days prior to delivery	Consecutive women with PGDM who gave birth by elective CS between 36^{+0} and 38^{+6} weeks gestation.	Two doses of Betamethasone 11.4 mg given 24 h apart within 7 days of cesarean birth	Neonatal RDS defined as requirement for respiratory support of any type for >60 min. Secondary outcomes included neonatal hypoglycemia requiring parenteral therapy.
Tuohy et al. 2021[34]	Retrospective cohort study	• 7317 women with diabetes • Type 1 diabetes – 13% • Type 2 diabetes 21% • GDM 65% • 647 (8.8%) received ACS but glycaemic data were only available for 579 others and 714 babies	Women with a singleton or multiple pregnancy giving birth at < 37^{+0} weeks' gestation; admitted to hospital for > 2 hours for any reason during pregnancy between 22^{+0}–36^{+6} weeks' gestation; birthing by elective CS at any gestation; or birthing by emergency CS at < 39 weeks' gestation.	ACS was betamethasone 11.4mg in 97% of patients with 85% receiving 2 doses at a 24 hour interval. Most patients (72%) received a single course of ACS while 18% received a repeat course which comprised a single dose in 92% of those who received a repeat course. The first dose of ACS was given prior to 34 weeks in the majority but 17% received their first dose after 34 weeks' gestation.	Maternal hyperglycemia: Blood glucose above a threshold of 7,8,10 or 11mmol/L, peak hyperglycemia, time to onset of hyperglycemia, time between administration of the first dose of ANC and first blood glucose above the threshold. Neonatal hypoglycaemia <2.6mmol/L, severe hypoglycaemia ≤2.0mmol/L.
Uquillas et al. 2020[35]	Retrospective cohort study	• 233 total • 39 women with GDM • 11 received ACS • Women with PGDM excluded	Women with a singleton pregnancy birthing at 34^{+0} to 36^{+6} weeks of gestation who had not received ACS prior to 34^{+0} weeks gestation.	Betamethasone administration at 34^{+0} to 36^{+6} weeks of gestation compared to no betamethasone administration (dose not stated)	Neonatal hypoglycaemia, defined as glucose < 40 mg/dl (2.2mmol/L) within 72 h of birth.
Weydig HM et al. 2022[36]	Retrospective and prospective single centre cohort study between 2011 -2018.	• 1813 total • 284 born to mothers with diabetes (type not specified) • 133 received ACS	Preterm neonates delivered at 29^{+0}–33^{+6} weeks gestation	Two doses of 12 mg betamethasone acetate/betamethasone sodium phosphate [Celestone] 24 hours apart	Primary outcome was surfactant administration after ACS exposure. RDS defined as clinical features, FiO2 >0.40 and compatible radiologic features.

ACS, antenatal corticosteroids; DM, diabetes mellitus; GA, gestational ag; GDM, gestational diabetes; ICD, International Classification of Diseases; NICU, neonatal intensive care unit; PGDM, pre-gestational diabetes; RDS, respiratory distress syndrome; TTN, transient tachypnoea of the newborn.

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TABLE 2
Summary of maternal and neonatal outcomes after ACS exposure

Authors	Neonatal respiratory morbidity	Neonatal hypoglycaemia	Maternal Hyperglycemia
Ali H, et al 2020[18]	ACS was associated with an increased risk of RDS/ TTN after adjusting for diabetes status aOR= 4.57 (3.14−6.64). However, ACS exposure did not alter the incidence of RDS / TTN after adjusting for diabetes, hypertension, prematurity, maternal age, mode of delivery and macrosomia. aOR=1.10 (0.72 −1.69, *p*=.65)	ACS was associated with an increased risk of NICU admission for hypoglycaemia after univariate analysis adjusting for diabetes status alone. aOR=3.25 (1.57− 5.87). However, ACS exposure did not alter the incidence of NICU admission for hypoglycaemia after adjusting for diabetes, hypertension, prematurity, maternal age, mode of delivery and macrosomia. aOR=1.10 (0.54-12.26, *p*=.78)	Not reported
Battarbee AN, et al 2022[19]	In the entire cohort (including women without diabetes), ACS exposure did not reduce the risk of respiratory distress syndrome or early death (aRR = 0.94, 95% CI: 0.85−1.04) or mechanical ventilation (aRR=0.95, 95% CI: 0.86−1.05). Maternal diabetes did not significantly modify the association between antenatal corticosteroids and respiratory distress syndrome or early death (*p*=.42) or mechanical ventilation (*p*=.83)	Not reported	Not reported
Cassimatis IR et al. 2020[20]	The composite neonatal respiratory morbidity was more frequent in the betamethasone group than in the control group but was not statistically significant (50 vs 25%, *p*=.066).	Neonatal hypoglycemia did not differ between the 2 groups (50% vs 47%, *P*=.8)	Not reported
Dude AM et al. 2021[21]	No differences were observed in the pre-ACS protocol group compared to the post-protocol group for respiratory morbidity. RDS: 3/58 (5.2%) pre-ACS protocol period vs 4/65 (6.2%) post-ACS protocol period (aOR 1.03, 0.22 −4.97) TTN: 7/58 (12.1%) pre-ACS protocol period vs 8/65 (12.3%) post-ACS protocol period (aOR 1.04, 0.31−3.33) Surfactant administration 2/58 (3.5%) pre-ACS protocol period vs 2/65 (3.1%) post-ACS protocol period aOR 0.73, 0.10−5.54)	Neonates born in the post- ACS protocol period experienced hypoglycemia in the first 24 h of life at the level of ≤60 mg/dL (3.3mmol/L) significantly more frequently than neonates born in the pre-ACS protocol period (81.5% post-ACS protocol vs 59.7% pre-ACS protocol; aOR 2.96, 1.29 −6.82, *p*=.008). There was no significant difference in the frequencies of hypoglycemia ≤40 mg/dL (2.2mmol/L) (44.6% post-ACS protocol vs 29.3% pre- ACS protocol; aOR 1.76, 0.81−3.79, *p*=.08) or in IV dextrose administration (35.4% post-ACS protocol vs 24.1% pre-ACS protocol; aOR 1.62 0.71−3.72) *p*=.18)	Not reported
Gupta K et al. 2020[22]	Neonates of women administered corticosteroids were more likely to be admitted to the NICU with RDS/TTN (12/33 (15.2%) in the ACS exposed group vs 4/69 (7.2%) in the unexposed group) but this was not statistically significant, *p*=.209	Neonates of women administered corticosteroids were significantly more likely to have hypoglycemia (8/33 (24.2% in the ACS exposed group vs 3/ 69 (4.4%) in the unexposed group, *p*=.003.	Not reported
Gyamfi-Bannerman C et al. 2023[23]	Not reported	In the betamethasone group, gestational diabetes (OR: 1.80, 95% CI: 1.25−2.59), and cesarean delivery (OR: 1.72, 95% CI: 1.34−2.22) were associated with neonatal hypoglycemia. Of the 108 women with both gestational diabetes and an infant with hypoglycemia, the frequency of treatment for hypoglycemia was similar between betamethasone (58; 41.1%) and placebo (50; 35.2%) groups, RR of 1.17 (95% CI: 0.87−1.57)	Not reported
Jolley JA et al. 2016[24]	Not reported	Not reported	The mean maximum blood glucose in those with diabetes was significantly different from those without diabetes (205.9 ± 23.42 mg/dL vs. 171.0 ± 18.67 mg/dL, p < 0.01). All patients with diabetes had at least one episode of hyperglycemia ≥140mg/dL and 10/ 11 (91 had at least one episode of hyperglycemia ≥160mg/dL)

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TABLE 2
Summary of maternal and neonatal outcomes after ACS exposure *(continued)*

Authors	Neonatal respiratory morbidity	Neonatal hypoglycaemia	Maternal Hyperglycemia
Kakoulidis I et al. 2019[25]	Not reported	Not reported	In insulin-treated women the mean increase in total daily dose of insulin was of 61.4%. The increase in insulin dose was significantly linked to betamethasone dosage (p = 0.014), especially in women that received two 12 mg betamethasone doses (33/52 women; total daily insulin dose needed to be increased by 23.8 ± 3.5 units on average), versus a single 12 mg betamethasone dose (19/52 women; with an average increase of 5.3 ± 6.2 units of insulin).
Krispin E et al. 2018[26]	Neonatal composite respiratory morbidity was not seen more frequently in infants born preterm following ACS exposure prior to 34^{+0} weeks: ACS exposed 11/47 (23.4%) vs ACS unexposed 25/114 (121.9%) *p*=.84. Neonatal composite respiratory morbidity was not seen more frequently in infants born at term following ACS exposure prior to 34^{+0} weeks: ACS exposed 9/82 (10.9%) vs ACS unexposed 123/2019 (6.1%) *p*=.763.	Neonatal hypoglycemia was not seen more frequently in infants born preterm following ACS exposure prior to 34^{+0} weeks: ACS exposed 3/47 (6.3%) vs ACS unexposed 13/114 (11.4%) *p*=.29. Neonatal hypoglycemia was not seen more frequently in infants born at term following ACS exposure prior to 34^{+0} weeks: ACS exposed 2/82 (2.4%) vs ACS unexposed 36/2019 (1.8%) *p*=.662. Corticosteroid treatment was not associated with neonatal adverse composite outcome (including neonatal hypoglycemia) when delivery occurred at the late preterm, nor at term (aOR = 0.708, 95% CI 0.2-2.3, *p*=.572), and aOR = 1.6, 95% CI 0.2 −12.7, *p*=.635, respectively).	Not reported
Langen ES et al. 2014[27]	Not reported	Not reported	The trend of glucose control among women with diet controlled GDM appears similar to the pattern seen in non-diabetic women. There was no period when the gestational diabetic women spent significantly more time with elevated blood glucose compared with nondiabetic women. The mean percentage of time spent above 110mg/dL in the first 24 hours after administration was 62% for women without diabetes compared with 75% for women with diabetes. In the 24-48 hour period after administration, the mean percentage of time above 110mg/dL was 73% for women without diabetes and 79% for women with diabetes.
Li J et al. 2022[28]	No difference in RDS rates following ACS exposure <2days and >7 days prior to birth (no RDS events in those exposed 2-7 days so unable to estimate odds ratio) <2 days after ACS aOR 1.308 (0.410,4.170) *p*=.650 >7 days after ACS aOR 0.943 (0.565, 1.575) *p*=.823 *adjusted for hypertensive disorders, gestational age, birth weight, small for gestational age	There was an increased likelihood of neonatal hypoglycaemia among neonates born within 2 days of ACS administration (22.6% in the 2 day group vs 8.4% in the no ACS group p<0.001). This was no longer statistically significant for exposure 2-7 days prior to birth or >7 days prior to birth. <2 days after ACS aOR 2.684 (1.647, 4.374) *p*<.001 2-7 days after ACS aOR 1.128 (0.822, 1.548) *p*=.455 >7 days after ACS aOR 0.986 (0.791, 1.229) *p*=.902 *adjusted for hypertensive disorders, gestational age, birth weight, small for gestational age	Not reported

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TABLE 2
Summary of maternal and neonatal outcomes after ACS exposure *(continued)*

Authors	Neonatal respiratory morbidity	Neonatal hypoglycaemia	Maternal Hyperglycemia
Liang FW et al. 2021[29]	There were no differences in the incidence of neonatal respiratory distress, CPAP, mechanical ventilation or oxygen use following ACS exposure Respiratory Distress: aOR 0.76 (0.52-1.12) CPAP: aOR 1.01 (0.58-1.76) Mechanical ventilation: aOR 0.89 (0.30-2.68) Oxygen use: aOR 1.15 (0.78-1.69) *Adjusted for nulliparity, sex, hypertensive disorders and CS	In the subgroups that underwent caesarean section, or had gestational hypertension or GDM, the adjusted risks of subgroups were consistent with comprehensive results where glucose levels in the ACS group were lower than the control group (640 (11.1) compared to 3648 (13.0) $p<.0002$) Neonatal hypoglycaemia was not increased overall for women with GDM who were included in an adjusted OR for neonatal outcomes in women administered and not administered ACS - aOR 0.70 (0.46, 1.08) *Adjusted for nulliparity, sex, hypertensive disorders and CS	Not reported
Paul R et al. 2019[30]	Fewer NICU admission for respiratory disease in the ACS exposed group compared to the control group (3.3% vs 20%, $p=.046$)	The mean nadir glucose level in babies was significantly lower in the corticosteroid group compared to those in the control group (2.37 mmol/L vs 2.79 mmol/L; $P=.014$). The incidence of neonatal hypoglycemia was greater in the corticosteroid group than in the control group but this was not statistically significant (60.0% vs 36.7%, $P=.07$).	Not reported
Raj-Derouin et al. 2023[31]	The prevalence of RDS and TTN as well as the rates of CPAP use were similar between the 2 groups (21% ACS exposed vs 24% non-exposed, p=0.907, aOR= 1.11 CI: 0.56−2.19). No neonates required intubation.	The proportion of neonatal hypoglycaemia in the ACS group was significantly higher compared to those without ACS exposure (40.2% vs.23.2%, p-value $<.05$). This relationship remained adjusting for predefined covariates (OR=2.23, CI: 1.14, 4.35). Of the neonates who experience hypoglycemia, those exposed to ACS were more likely to require treatment for hypoglycemia (40.3% vs.22.4%, $p<.05$; OR=2.34, CI: 1.10, 4.97).	Not reported
Said JM et al. 2023[32]	All 4 infants (7.8%) who required respiratory support for greater than 4 hours were in the placebo group. One infant allocated to betamethasone (4.2%) and 5 infants allocated to placebo (18.5%) had respiratory morbidity requiring respiratory support for at least 60 minutes. (No statistical tests were applied as this was a feasibility study)	Hypoglycaemia (any blood glucose <2.6mmol/L) occurred in 9/24 in the Betamethasone group (37.5%) and 12/27 in the placebo group (44.4%)	Women who received betamethasone were more likely to require additional insulin to manage hyperglycemia 12/22, 54.5%) compared with women who received the placebo (4/25, 16.0%). The highest median blood glucose between study drug administration and caesarean section was greater in women exposed to betamethasone (8.5, IQR 8.30 - 10.70) compared to those who received placebo (7.60, IQR 6.70-8.60)
Thevathasan I et al. 2022[33]	There were no differences in the proportion of infants requiring respiratory support; however, there was a non-statistically significant reduction in the requirement for nursery admission and respiratory support in ACS-exposed infants born prior to 38+0 weeks compared to those who were not exposed. 1. Respiratory distress requiring respiratory support at 36+0 to 36+6 weeks ACS exposed: 3/21 (14.3%) vs ACS unexposed 7/30 (23.3%) OR 0.55; 95% CI 0.12−2.42 $p=.427$ 2. Respiratory distress requiring respiratory support at 37+0 to 37+6 weeks ACS exposed: 2/36 (5.5%) vs ACS unexposed 9/92 (9.8%) OR 0.54; 95% CI 0.11−2.64 $p=.449$	Neonates exposed to ACS who were born prior to 37+0 weeks were less likely to require parenteral treatment for neonatal hypoglycaemia; however, those born after 37+0 weeks were more likely to require parenteral treatment for neonatal hypoglycaemia, but these findings were not statistically significant 1. Hypoglycaemia requiring parenteral therapy at 36+0 to 36+6 weeks ACS exposed: 11/21 (52.4%) vs ACS unexposed 22/30 (73.3%) OR 0.40; 95% CI 0.12-1.30 $p=.127$ 2. Hypoglycaemia requiring parenteral therapy at 37+0 to 37+6 weeks ACS exposed: 17/36 (47.2%) vs ACS unexposed 39/92 (42.4%) OR 1.22; 95% CI 0.56 -2.64 $p=.621$ 3. Hypoglycaemia requiring parenteral therapy at 38+0 to 38+6 weeks ACS exposed: 3/8 (37.5%) vs ACS unexposed 23/119 (19.3%) OR 2.50; 95% CI 0.56 -11.25 $p=.231$	Not reported

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TABLE 2
Summary of maternal and neonatal outcomes after ACS exposure *(continued)*

Authors	Neonatal respiratory morbidity	Neonatal hypoglycaemia	Maternal Hyperglycemia
Tuohy et al. 2021[34]	Not reported	Hypoglycaemia occurred in 46% (331/713) of babies, and was severe in 27% (193/713) and recurrent in 11% (77/713), while 6% (43/713) developed hyperglycemia. The majority of babies who developed hypoglycemia did so within 2 h of birth (75%).	Following an initial course of ACS, 92% of women were hyperglycaemic at a threshold of 7 mmol/L, 83% at a threshold of 8 mmol/L, 52% at a threshold of 10 mmol/L and 35% at a threshold of 11 mmol/L
Uquillas et al. 2020[35]	Not reported	Neonatal hypoglycaemia in the pregnancies that received betamethasone was not increased if the mother was diagnosed with gestational diabetes (a OR 0.39, 95% CI 0.09−1.61, p=.19) or was taking insulin (aOR 1.22, 95% CI 0.09 −16.12, p=.88). * Adjusted for birth weight and gestational age	Not reported
Weydig HM et al. 2022[36]	In women with diabetes without hypertension, surfactant administration was not less frequent following ACS exposure (P=.67). However, the sample size was insufficient to rule out an association with ACS. In the group of patients with diabetes and hypertensive disorders), surfactant administration was independently associated with ACS exposure (aOR 0.29, CI 0.12−0.71, P=.007)	Not reported	Not reported

ACS, antenatal corticosteroids; DM, diabetes mellitus; GA, gestational age; GDM, gestational diabetes; NICU, neonatal intensive care unit; PGDM, pregestational diabetes; RDS, respiratory distress syndrome; TTN, transient tachypnoea of the newborn.

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observational studies. There was considerable heterogeneity in the clinical settings, study populations, type of corticosteroid and timing between administration and delivery.

Neonatal respiratory morbidity

Neonatal respiratory morbidity was reported in 13 studies.[18-22,26,28-33,36] Of these 13 studies, 2 investigated the impact of ACS on respiratory morbidity in neonates born prior to 33^{+6} weeks' gestation[19,36] and the remaining 11 studies included gestations beyond 34 weeks.[18,20-22,26,28-33] Table 2 presents a summary of the findings of these studies.

Both studies investigating the association between ACS administration and respiratory morbidity in the early preterm period presented results from a wider cohort of women with and without diabetes in pregnancy but also presented sub-group analysis of this association in those with diabetes.[19,36] Notably, both studies investigating the effects of ACS in this early gestational period, consistently reported no statistically significant reduction in neonatal respiratory morbidity following ACS exposure in sub-groups of women with diabetes in pregnancy.[19,36]

None of the studies that investigated ACS administration during the late preterm and term periods reported a significant reduction in the prevalence of neonatal respiratory morbidity. Thevathasan et al.[33] reported no differences in the proportion of infants born by planned cesarean section to women with PGDM requiring respiratory support in those who were exposed to ACS compared to those who were not exposed at 36^{+0}-36^{+6} weeks (OR 0.55; 95% CI 0.12 − 2.42) or 37^{+0}-37^{+6} weeks (OR 0.54: 95% CI 0.11-2.64). Cassimatis et al. reported a non-significant increase in composite respiratory morbidity in ACS-exposed neonates born to women with PGDM (50% vs 25%; p=.066) who were not exposed to ACS.[20]

Neonatal hypoglycemia

This review identified 14 studies that reported on neonatal hypoglycemia after ACS exposure in women with diabetes (Table 2).[18,20-23,26,28-35] Of these 14 studies, 6 studies observed an increased incidence of neonatal hypoglycemia in pregnancies complicated by diabetes following administration of ACS.[21,22,28-31,35] The extent of this increase varied between these studies with Raj-Derouin et al. reporting that neonatal hypoglycemia was significantly higher in ACS exposed neonates compared to those unexposed (40.2% vs 23.2% p<.05)[31] whereas Gyamfi-Bannerman et al. reported that while GDM was associated with hypoglycemia (OR: 1.80, 95% CI: 1.25−2.59), the frequency of treatment for hypoglycemia was similar between the ACS and placebo groups (41.1% vs 35.2%, RR 1.17, 0.87 −1.57).[23] Although the retrospective cohort study by Uquillas et al. reported a significant increase in neonatal hypoglycemia in ACS-exposed neonates, sensitivity analysis identified that maternal GDM did not increase the likelihood of this outcome.[35]

There were 4 studies that reported similar incidences in hypoglycemia between ACS exposed and unexposed groups with diabetes.[20,23,26,32]

Maternal hyperglycemia

Maternal hyperglycemia was described as a key outcome in 5 of the included studies (Table 2).[24,25,27,32,34] These studies unanimously reported increases in maternal hyperglycemia amongst ACS exposed women with resulting increases in insulin requirements. Notably, Kakoulidis et al.[25] reported that increased insulin requirements correlated with dosage of ACS (p=.014).

This review identified 12 studies[18,20-22,26,28-34] that reported on more than one of the outcomes outlined above. There were 11 studies[18,20-22,26,28-33] that reported on both neonatal respiratory morbidity and neonatal hypoglycemia. Of these, 4 studies[18,20,26,33] reported no significant difference in either outcome in ACS exposed neonates. Conversely, there were 5 studies[21,22,28,29,31] that reported no difference in respiratory morbidity but demonstrated an increased in neonatal hypoglycemia after ACS exposure. There was one study that reported a decrease in respiratory morbidity and an increase in neonatal hypoglycemia in exposed neonates.[30]

Other neonatal outcomes

This review identified other neonatal outcomes that were reported in tandem with neonatal hypoglycemia and respiratory morbidity. Of the 19 included studies, 11 studies[18,21,22,26,28-33,35]reported on neonatal intensive care unit (NICU) admission with 2 of these studies reporting on admissions specifically for neonatal hypoglycemia[22,35] and 2 studies reporting on NICU admission for respiratory disease.[26,30] The majority of studies that reported on NICU admission regardless of the indication found no significant difference between the proportion of ACS exposed and unexposed neonates who were admitted.[21,29,31-33] Conversely, 2 studies reported an increase in the risk of NICU admission after ACS exposure.[18,28] Ali et al. [18] reported a slight increase in this risk (OR 1.46 (1.04−2.03)) whilst Li et al. [28] reported a significant increase in this risk regardless of the timing between ACS administration and birth (p=.023).

Similarly, there were studies that reported on the length of neonatal hospital stay.[20,21,23,28,30,32,35] Notably, 5 out of the 7 studies reported no significant difference in length of stay between ACS exposed and unexposed neonates.[20,21,28,32,35] Gyamfi-Bannerman and colleagues[23] reported that median length of nursery stay was shorter for neonates who were exposed to betamethasone (7 days, interquartile range [IQR: 3−11] vs 8 days, [IQR: 4 −12], p=.01). However, this outcome was reported based on pregnancies with and without diabetes and data for women with diabetes was not separated for this outcome.

Discussion

This review aimed to summarise the literature surrounding maternal and neonatal outcomes of ACS administration in women with diabetes. The systematic search identified 19 publications that provided relevant data pertaining to neonatal and maternal outcomes following ACS administration to women with diabetes in pregnancy. While we have summarised the observations from multiple published sources, the significant heterogeneity across the included study settings meant that robust conclusions could not be made due to the paucity of available data.

Neonatal respiratory morbidity

Randomized controlled trials in pregnancies not complicated by diabetes have demonstrated a reduction in the prevalence of RDS in neonates born preterm following ACS.[1] As such, clinical guidelines unanimously recommend ACS administration to women at risk of delivering pre-term, extrapolating this recommendation to include women with diabetes[14,17] However, it is evident from this review, that there is a paucity of randomized controlled trials investigating the outcomes of neonates born to mothers with diabetes. Of the 2 randomized trials included in this review, including just 283[23] and, 47[32] participants with diabetes, only one reported on neonatal respiratory outcomes[32] and was underpowered to identify a reduction in neonatal respiratory morbidity in ACS exposed infants. It is noteworthy that while not all randomized controlled trials of ACS excluded participants with diabetes, this subgroup usually comprised only a small proportion of participants and subgroup analysis was often not provided (see Supplementary Table 2).

The majority of retrospective studies reported no statistically significant reduction in neonatal respiratory morbidity following ACS in infants born to women with diabetes[18,19,26,28,31,33] however, Cassimatis et al. reported that babies born to women exposed to betamethasone in the late preterm period (n=18) experienced greater incidence of composite respiratory morbidity (50 vs 25%, P=.066) compared to babies born to women with diabetes who were not exposed (n=36).[20] This was the only study in our review to suggest an increase in neonatal respiratory morbidity amongst babies born to women with diabetes who were exposed to ACS. It is notable that the majority of studies reporting on neonatal respiratory morbidity in this review are retrospective (12/13, 92%), and (8/12, 66%) have small sample sizes (fewer than 150) of women with diabetes who were exposed to ACS[18,20-22,30,31,33,36] thereby limiting the conclusions regarding the efficacy of ACS in preventing neonatal respiratory morbidity.

Studies reporting neonatal respiratory morbidity rates included in this review may be influenced by several confounding factors. Notably, the incidence of respiratory morbidity decreases with advancing gestation.[37] The benefit of corticosteroids for respiratory outcomes, particularly in the late preterm and term periods remains contentious and is the subject of ongoing randomized trials.

Neonatal hypoglycemia

Overall, this review found that of the 14 studies that reported on neonatal glycaemic outcomes, only 5 (36%) supported the notion that neonates born to women exposed to ACS have an increased incidence of hypoglycemia.[21,22,29-31] Gyamfi-Bannerman reported that neonatal

hypoglycemia was more likely to occur in infants born to ACS exposed mothers in a population of more than 2800 women including 306 women with GDM (RR: 1.60; 95% CI, 1.37 to 1.87; P<0.001).[4] These findings incited further studies of ACS to explore neonatal hypoglycemia as an outcome. Notably, the findings of this review align with the results from studies investigating neonatal hypoglycemia after ACS in pregnancies not complicated by diabetes.[38,39]

Considering the well-established association between maternal diabetes and neonatal hypoglycemia,[40,41] the findings that maternal diabetes increased the risk of neonatal hypoglycemia in ACS exposed neonates are not surprising. However, it is important to note that the results from these studies may be influenced by the severity of maternal diabetes and by the heterogeneity of maternal glycaemic management both prior to and following ACS administration.

Notably, the study by Uquillas et al.[35] was the only study that found that babies born to women with diabetes were less likely to experience hypoglycemia after ACS exposure. It is important to note that there were only 39 women with GDM in this subgroup and only 11 of these women received ACS. Moreover, only 3 of the included women with GDM who received ACS managed their diabetes with insulin. As a result of this small sample size and the milder nature of diabetes included, extreme caution must be exercised in interpreting these data.

Importantly, given the serious sequelae associated with neonatal hypoglycemia including neurodevelopmental consequences[42] these findings highlight an urgent need for further research evaluating this risk with consideration to the underlying severity and management of maternal diabetes following ACS administration.

Maternal Hyperglycemia

The small number of studies included in this review that investigated maternal hyperglycemia as an outcome following ACS exposure identifies a significant gap in the published literature. The studies that did explore this outcome unanimously reported that hyperglycemia was common amongst women receiving ACS, regardless of diabetes status.[24,25,27,32,34] These findings align with current guidelines which recommend glucose monitoring after ACS exposure for women with diabetes;[17] however, these guidelines are limited in their recommendations for the management of diabetes after administration of ACS due to the paucity of data surrounding glycaemic changes in diabetic women when receiving ACS.

The PRECeDe Pilot Trial was a triple-blind placebo-controlled, randomized controlled trial that reported on the effect of ACS exclusively in women with diabetes and investigated both neonatal and maternal glycaemic outcomes. Notably, 12 out of the 22 participants exposed to betamethasone required additional insulin after exposure and the highest maternal blood glucose reported was higher in the ACS exposed group (8.95mmol/L (IQR 8.30-10.70)) compared to the placebo exposed group (7.60mmol/L (IQR 6.70-8.60)).[32]

Several protocols for management of maternal glycaemia following administration of ACS have been published but these are not used consistently and exhibit considerable heterogeneity. Kaushal et al.[43] and Rowe et al.[44] established protocols for the administration of intravenous insulin to manage the onset of hyperglycemia, yet many protocols describing the use of subcutaneous insulin have also been described.[45] Importantly, none of these protocols have been incorporated into national or international guidelines regarding ACS administration in women with diabetes.[14-17] This lack of consensus regarding management protocols coupled with the paucity of studies specifically investigating the impact of ACS on maternal glycaemia in women with diabetes reinforces the need for the collection of comprehensive glucose data from ACS exposed women in this population.

Strengths and limitations

This review addresses a significant gap in the published literature, calling to attention the urgent need for high quality randomized controlled trials designed to explore the impact of ACS specifically on women with diabetes and their babies. The findings of this review are consistent with the findings from the 2020 Cochrane review which noted the limited data available regarding the risks and benefits of ACS in high-risk obstetric groups such as women with diabetes in pregnancy.[1] A key strength of this review is the use of a thorough systematic search of 2 databases to ensure the literature screened provided a holistic representation of the published literature in this field. Additionally, the specific inclusion and exclusion criteria used, particularly the exclusion of studies that did not conduct specific subgroup analysis on those with diabetes, ensured that bias in the results was reduced.

This review was limited by the paucity of literature investigating ACS in women with diabetes (and their babies) and hence, many studies included only a very small number of participants with diabetes and therefore lacked sufficient power to make robust conclusions. Moreover, with only 2 randomized trials included in this review, the majority of studies are influenced by confounding due to their retrospective nature. Notably, the nature of the reporting of in the results of many of the included studies did not provide sufficient data for further analysis, particularly pertaining to included sub-groups with diabetes. As a result, it is difficult to generalise these findings to all women with diabetes in pregnancy. This underlines the importance of making data for all studies of corticosteroids in diabetes publicly available to allow for further analysis in future reviews.

Conclusion

This review ultimately concludes that there are insufficient data regarding the risks and benefits of ACS administration in pregnancies complicated by diabetes. Whilst the neonatal outcomes pertaining to respiratory morbidity and hypoglycemia have been reported to some extent by the published literature, with varying conclusions, there is

evident discrepancy between studies and no clear evidence of benefit – in contrast to the overwhelming evidence in pregnancies without diabetes. Notably, this review identified a specific gap in the reporting of maternal hyperglycemia following ACS which appears to have been under-investigated in the published literature. Overall, this paucity of comprehensive data pertaining to neonatal and maternal outcomes after ACS in pregnancies complicated by diabetes highlights the urgent need for high quality randomized controlled trials to ensure well informed clinical practice for these women and their infants. The PRECeDe Trial (ACTRN12623000015640) has been designed to address the knowledge gap in relation to ACS for women with diabetes undergoing planned caesarean section during the late preterm and term period. Given the rising rates of diabetes in pregnancy, further studies are required to investigate the efficacy of ACS in the early preterm period to ensure that the benefits of this therapy do outweigh the risks in women with diabetes. ■

CRediT authorship contribution statement

Klea Atallah: Writing – original draft, Methodology, Investigation, Conceptualization. **Serena Moon:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **I-Lynn Lee:** Writing – review & editing. **Rosalynn Pszczola:** Writing – review & editing. **Joanne M. Said:** Writing – review & editing, Supervision, Methodology, Conceptualization. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2024.100416.

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