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Antenatal corticosteroids after 34 weeks' gestation: Do we have the evidence?

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ABSTRACT

There is evidence to support the use of antenatal corticosteroids prior to late preterm birth at 35^{+0} to 36^{+6} weeks' gestation and for specific 'at-risk' populations, such as planned cesarean section birth and infants of women with diabetes in pregnancy, to reduce short-term neonatal respiratory morbidity. However, the overall size of effect at late preterm and term gestational ages is less than for early and moderate preterm birth and should be countered against the potential harms. Evidence from randomized trials suggest an increase in the incidence of neonatal hypoglycemia after corticosteroid use prior to late preterm birth; any effect of antenatal corticosteroids on neonatal glycemic control after planned cesarean section birth or for infants born to mothers with diabetes in pregnancy is unknown. Accumulating evidence suggests neonatal hypoglycemia may adversely affect childhood development. To date, no trials of antenatal corticosteroids after 34 weeks' gestation have reliably assessed outcomes beyond the neonatal period.

1. Introduction

There is no doubt that the administration of antenatal corticosteroids (ACS) to mothers prior to preterm birth is seen as one of the single greatest advances in perinatal medicine. A large body of evidence from multiple randomized controlled trials (RCTs) supports the administration of ACS prior to early preterm birth to reduce perinatal death, respiratory distress syndrome (RDS) and other measures of neonatal adverse outcome [1] with little or no evidence of later harm [2–6]. Clinical practice guidelines recommend their use as standard, where possible, for all women deemed to be at imminent and very high risk of early preterm birth regardless of the reason or indication for birth or the planned mode of birth [7–11].

What is less clear is if their use at late preterm gestational ages (35^{+0} to 36^{+6} weeks) and for specific 'at-risk' populations, such as planned cesarean section birth and infants of women with diabetes in pregnancy, provides benefit without harm; simply extrapolating evidence from early preterm birth is not sufficient. The individual risk of harm as a consequence of these scenarios is significantly lower than for early preterm birth and hence the balance of benefit versus risk of ACS needs to be carefully reconsidered for each scenario. The absolute number of women giving birth at late preterm gestational ages and in these at-risk groups represent a significant proportion of the population and hence a significant proportion of infants born have the potential to gain benefit from, or be harmed by, this intervention.

ACS are likely to provide benefit to infants by reducing short-term respiratory morbidity often reported as RDS and transient tachypnoea of the newborn (TTN). Late preterm and term babies rarely die from this respiratory morbidity [12] but do require admission to the neonatal unit for respiratory support resulting in separation of the mother and her baby and the subsequent potential impact on bonding and breastfeeding [13]. However, ACS may also cause harm, highlighted by the recent unanticipated finding of an increased risk of neonatal hypoglycemia in a large RCT of ACS prior to late preterm birth [14]. An effect of ACS exposure on neonatal glycemic control is physiologically plausible. It has been shown that antenatal betamethasone results in elevated concentrations of betamethasone and decreased concentrations of cortisol in cord blood at birth, suggesting suppression of fetal hypothalamic-pituitary-adrenal function, and this persists for up to seven days [15,16]. In addition, higher cord blood glucose and C-peptide levels suggests these fetuses are at risk of hyperinsulinemia at birth and consequent hypoglycemia in the early newborn period [17], with the potential need for admission to the neonatal unit for treatment and possible longer-term adverse effects on neurodevelopment.

1.1. Neonatal respiratory morbidity and hypoglycemia after 34 weeks' gestation

1.1.1. Late preterm birth

Preterm birth accounts for approximately 11% of all births

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worldwide and almost 9% of all births in developed countries [18]. Approximately three quarters of these will occur at 34–37 weeks' gestation due to both spontaneous and medically indicated preterm birth. Respiratory morbidity as a consequence of immature alveolar type II pneumocyte cells and a lack of surfactant production is a well-recognised complication of prematurity. Although this is usually less severe after late preterm birth it continues to pose a risk [19–23]. In the prospective UK population based Late and Moderately Preterm Birth Study (LAMBS), neonatal outcomes of infants born at 34^{+0} to 36^{+6} weeks' gestation were compared to infants born at term [22]. Of those infants born at late preterm gestations, 8.4% (66/785) required some form of ventilation and/or non-invasive respiratory support compared to only 0.9% (9/972) after a term birth. Those that required support at late preterm gestations were not solely at the mild end of the spectrum; indeed 73% (48/66) required some mechanical ventilation and 29% (19/66) required endotracheal intubation at birth [22].

Estimating an accurate risk of hypoglycemia is difficult due to variations in its definition; the populations in which it is reported; and the reliability in the methods used and frequency of blood glucose concentration testing after birth. Rates of hypoglycemia in the term population have been reported to be 10% (hypoglycemia defined by a blood glucose concentration < 2.2 mmol/L [< 40 mg/dL]) in a general population within the first 12 h of life [24] and 14% (hypoglycemia defined by a blood glucose concentration < 2.6 mmol/L [< 47 mg/dL]) in appropriately grown babies born to mothers without diabetes within the first four days of life [25]. Babies born preterm are at increased risk of hypoglycemia compared to their term counterparts and recent evidence shows this remains true for those born at late preterm gestations. The Sugar Babies Study [26] included 193 babies born at 35–37 weeks' gestation who underwent standard blood glucose concentration measurements using a glucose oxidase method of testing with samples taken one hour after birth and then 3 to 4 hourly in the first 24 h and 3 to 8 hourly for the next 24 h. Hypoglycemia was defined as a blood glucose concentration < 2.6 mmol/L and occurred in 54% (103/193) of infants; there were a total of 155 hypoglycaemic events and 80% (124) of these occurred within the first 24 h of life [26]. These findings are further supported by the LAMBS study in which blood glucose concentrations were only performed and reported as part of standard clinical care but a significant increase was seen in the incidence of more severe hypoglycemia (defined by blood glucose concentration < 2.2 mmol/L [< 40 mg/dL]) in those born at 34^{+0} to 36^{+6} weeks' gestation compared to term births, 5.7% (45/785) and 0.9% (9/972) respectively [22].

1.1.2. Planned cesarean section birth

The rate of birth by cesarean section continues to increase globally with an average annual increase of 3.7% from 2000 to 2015 [27]. By 2015 almost 30 million babies (21% of all births) worldwide were born by cesarean section. Increases have predominantly been driven by rising rates of planned or elective cesarean section rather than an increase in emergency cesarean section after the onset of labour [27,28]. In most developed countries more than half of all cesarean section births are now planned prior to labour. Previous cesarean section is a major indication for planned cesarean section birth, and so although there may be some stabilisation or even a slight decrease in cesarean section rates in some countries, future reductions will take time to impact on overall rates due to the majority of women with a previous cesarean section opting for a repeat procedure. Hence, we currently face approximately one in ten births in developed countries being by planned cesarean section at or close to term.

Birth by planned cesarean section provides some protection for the infant but also poses additional risk. Labour provides both mechanical and hormonal stimuli to enhance fluid reabsorption in the infant lung. When birth is by cesarean section prior to the onset of labour, infants do not receive these stimuli and this results in an increase in respiratory morbidity, most commonly as TTN [29].

Table 1
Neonatal respiratory morbidity in term babies after planned cesarean section compared to intended vaginal birth [32].

Gestational age	Respiratory morbidity[a]		Adjusted odds ratio[b] (95% confidence interval)
	Planned cesarean section	Intended vaginal delivery	
37 weeks	26 (10.0%)	49 (2.8%)	3.7 (2.2–6.1)
38 weeks	60 (5.1%)	68 (1.7%)	3.0 (2.1–4.4)
39 weeks	23 (2.1%)	89 (1.1%)	1.9 (1.2–3.0)
40 weeks	2 (1.5%)	180 (1.6%)	0.9 (0.2–3.7)

Data are number (percentage).
[a] Respiratory morbidity includes transient tachypnea of the newborn, respiratory distress syndrome and persistent pulmonary hypertension of the newborn.
[b] Adjusted for smoking, alcohol intake, parity, body mass index, marital status, maternal age and years of schooling.

Neonatal respiratory morbidity after birth by prelabour planned cesarean section is increased seven-fold compared with infants born vaginally and three-fold compared with infants born by cesarean section once labour has established [30,31]. This increased risk remains present at early term gestations (Table 1) and increases with decreasing gestational age [31–33]. Hence national clinical practice guidelines recommend that elective cesarean section, where possible, should be planned at $\geq 39^{+0}$ weeks [8,9,34]. However, there are indications when late preterm or early term planned cesarean section is required on maternal and/or fetal grounds and, planned cesarean section at 39^{+0} to 39^{+6} weeks still imposes an almost two-fold increase in neonatal respiratory morbidity [32].

There are very limited data regarding the effect of cesarean section on the incidence of hypoglycemia and whether cesarean section imposes additional risk. Only two small studies have made comparisons of the incidence of hypoglycemia after cesarean section and vaginal birth (n = 60 [35] and n = 100[36]). Mean blood glucose concentrations were lower in babies born by cesarean section and rates of hypoglycemia were higher, 20% versus 14% (hypoglycemia defined by a blood glucose concentration < 2.2 mmol/L [< 40 mg/dL]) [36]. There are a number of reasons that infants born by planned cesarean section may be at risk of lower blood glucose concentration including confounding factors such as higher rates of large for gestational age in those undergoing cesarean section and delay in first feed after operative delivery, but it is also possible that the activation of catecholamines stimulated by labour and vaginal birth is absent and hence gluconeogenesis is delayed after cesarean section.

1.1.3. Infants of women with diabetes in pregnancy

Over recent years the rates of diabetes in pregnancy, both pre-gestational and gestational, have risen significantly [37,38]. This is likely to reflect the changing demographic and risk profile of the pregnant population with increasing maternal age and body mass index, as well as shifts in the criteria to define diabetes in pregnancy. Rates of diabetes in pregnancy vary across hospitals, regions and countries reflecting the risk profile of the population. Within Europe, reported prevalence rates are approximately 5% [39] but are now up to 10% in countries such as the United States and Australia [40,41].

It has long been known that neonatal respiratory morbidity is more common in infants born to mothers with diabetes. There are a number of potential confounding factors including the need for earlier birth due to other risks associated with diabetes and co-morbidities such as pre-eclampsia and higher rates of cesarean section birth for women with diabetes that may explain this association. However, it is also likely that maternal diabetes directly affects newborn respiratory function. There is evidence to suggest that poor control of diabetes with fetal hyperglycemia and hyperinsulinemia delays maturation of alveolar type II pneumocyte cells and hence reduces surfactant production, effectively

Table 2
Neonatal hypoglycemia and later neurodevelopmental outcome [51].

Outcome	Number of studies/ infants	Rate for exposed vs unexposed to neonatal hypoglycemia	Exposure effect odds ratio (95% confidence interval)
Early childhood (2–5 years)			
Neurodevelopmental impairment	6/1657	25.8% vs 16.6%	1.16 (0.86–1.57)
Visual-motor impairment	2/508	4.6% vs 1.5%	***3.46 (1.13–10.57)***
Executive dysfunction	1/463	10.6% vs 4.7%	***2.50 (1.20–5.22)***
Any cognitive impairment	3/746	15.4% vs 15.9%	1.11 (0.73–1.69)
Mild cognitive impairment	3/746	12.8% vs 13.7%	0.86 (0.55–1.35)
Moderate/severe cognitive impairment	3/746	2.6% vs 2.1%	1.57 (0.55–4.48)
Epilepsy	4/772	4.2% vs 2.1%	1.93 (0.76–4.85)
Emotional behavioural difficulties	3/587	18.9% vs 19.0%	1.00 (0.66–1.53)
Visual impairment	2/616	5.0% vs 1.7%	2.14 (0.70–6.53)
Hearing impairment	1/477	0% vs 0.5%	0.23 (0.01–5.76)
Motor impairment	4/777	17.5% vs 17.8%	1.06 (0.70–1.60
Cerebral palsy	1/401	0.9% vs 1.1%	0.81 (0.11–6.07)
Mid-childhood (6–11 years)			
Neurodevelopmental impairment	2/54	47.8% vs 22.6%	***3.62 (1.05–12.42)***
Emotional behavioural difficulties	1/28	30.8% vs 6.7%	6.22 (0.60–64.97)
Motor impairment	1/28	15.4% vs 13.3%	1.18 (0.14–9.83)
Low language/literacy	1/1395	67.4% vs 43.0%	***2.04 (1.20–3.47)***
Low numeracy	1/1395	53.9% vs 34.0%	***2.04 (1.21–3.44)***

All studies included in this systematic review and meta-analysis were graded as low/very low quality evidence.

mimicking the preterm lung [42,43]. In addition hyperinsulinemia may cause relative fetal cardiac hypertrophy [44,45] leading to a degree of left ventricular outflow obstruction, poor cardiac output, congestive cardiac failure and respiratory morbidity after birth. Several retrospective series have reported increased rates of neonatal respiratory morbidity for infants of mothers with pre-gestational and gestational diabetes in comparison to women without diabetes [46,47]. The largest of these studies to date reports on pregnancy outcomes from a French cohort of over 18,000 singleton births at or after 34 weeks, of which 11.1% had diet-controlled diabetes and 3.4% had insulin-treated diabetes [44]. The rates of respiratory morbidity were 2.2%, 2.1% and 5.7% for those without diabetes, with diet-controlled diabetes and with insulin-treated diabetes respectively. Insulin-treated diabetes significantly increased the risk of respiratory distress at late preterm and term gestational ages, independent of gestational age and mode of birth, adjusted incidence rate ratio (RR) 1.44 (95% confidence interval [CI] 1.00, 2.08) [44].

Diabetes and maternal hyperglycemia results in an increased transfer of glucose across the placenta with subsequent fetal hyperglycemia and fetal hyperinsulinemia. At the time of birth and occlusion of the umbilical cord the newborn is no longer exposed to the maternal glucose supply but hyperinsulinemia persists causing a transient but sometimes profound fall in blood glucose concentration. Neonatal hypoglycemia is thus a common complication for infants born to mothers with diabetes. Systematic testing within the Sugar Babies Study including 199 babies born to mothers with diabetes at ≥35 weeks quantified the incidence of hypoglycemia (defined by a blood glucose concentration < 2.6 mmol/L [< 47 mg/dL]) as 48% and of severe hypoglycemia (defined by a blood glucose concentration ≤2.0 mmol/L [≤36 mg/dL]) as 19% within the first 48 h of life [26].

1.1.4. Consequences of neonatal hypoglycemia

Birth at late preterm gestational age, by prelabour planned cesarean section or after pregnancy complicated by maternal diabetes significantly increases the risk of neonatal respiratory morbidity and hence researchers and clinicians have proposed the potential benefit of ACS, known to be effective at early preterm gestational ages. However, it also seems clear that these clinical scenarios increase the risk of neonatal hypoglycemia which may be further exacerbated by the use of ACS, thus creating two opposing effects where the balance of risk and benefit needs to be closely considered.

Despite neonatal hypoglycemia being the most common newborn metabolic condition there has been much debate not only on its threshold for definition, but also on the appropriate level of monitoring and treatment [48]. This seems to be predominantly due to a lack of knowledge on the long-term adverse effects and whether indeed there are any. However, neonatal hypoglycemia results in neuroglycopenia at a time when metabolic activity is high in the developing brain and so risk of injury and long-term effect is real. Hypoglycemia has been associated with a variety of brain abnormalities seen on ultrasound and MRI [49] and accumulating evidence now suggests that even transient and treated neonatal hypoglycemia may be associated with adverse childhood outcomes. It was the only common neonatal morbidity, including comparison with respiratory morbidity, in the Dutch Longitudinal Preterm Outcome Project (LOLLIPOP) of moderate preterm children (born at 32^{+0} to 35^{+6} weeks) to be associated with developmental delay at four years of age [50]. A recent systematic review and meta-analysis by Shah and colleagues has identified this cohort and a further nine cohort studies comparing the outcomes of 'at-risk' infants (preterm, late preterm, small for gestational age, large for gestational age, mothers with diabetes) for those exposed and unexposed to neonatal hypoglycemia [51]. Conclusions are limited due to the variety of inclusions; degree of glucose monitoring; definition of hypoglycemia (ranging from ≤1.11 mmol/L [≤20 mg/dL]to < 2.6 mmol/L [< 47 mg/dL]); and quality and timing of follow-up. Although neonatal hypoglycemia was not associated with impaired neurodevelopment at 2–5 years or 6–11 years, significant effects on visual-motor function and executive function in early childhood and on language/literacy in mid-childhood [51] (Table 2) warrant on-going attention and consideration.

The Children with Hypoglycaemia and their Later Development (CHYLD) study is the only prospective cohort study of infants born after 32 weeks and at risk of hypoglycemia to include routine gold standard blood glucose concentration measurements with standardised treatment for hypoglycemia (blood glucose concentration < 2.6 mmol/L [< 47 mg/dL]) and standardised developmental assessments at two [52] and 4.5 years of age [53]. At both time-points hypoglycemia had no effect on a composite outcome of neurosensory impairment. However by 4.5 years in assessment of 473 children (78.7% of initial study group), children in the lowest quintile for mean and maximum interstitial blood glucose concentrations in the first 12 h had an increased risk of neurosensory impairment and all exposed to hypoglycemia had a greater risk of low executive function (executive function z-score below −1.5: 10.6% (29/273) after hypoglycemia and 4.7% (9/190) in

Table 3
Primary and selected secondary outcomes reported in 2016 systematic review of all trials of corticosteroid use in women at risk of imminent preterm birth at 34^{+0} to 36^{+6} weeks' gestation [63].

Outcomes	Balci 2010 [65]		Porto 2011 [64]		Gyamfi-Bannerman 2016 [14]		All trials		Relative risk (95% confidence interval)
	Corticosteroid group n = 50	Control group* n = 50	Corticosteroid group n = 143	Control group† n = 130	Corticosteroid group n = 1427	Control group† n = 1400	Corticosteroid group	Control group	
RDS	8 (16%)	2 (4%)	36 (25.1%)	30 (23.1%)	79 (5.5%)	89 (6.3%)	123/1620 (7.6%)	121/1580 (7.7%)	0.98 (0.44–1.32)
Severe RDS	NR	NR	2 (1.4%)	1 (0.8%)	20 (1.4%)	34 (2.4%)	22/1570 (1.4%)	35/1530 (2.3%)	***0.60 (0.33 – 0.94)***
TTN	NR	NR	34 (23.7%)	29 (22.3%)	95 (6.6%)	138 (9.9%)	129/1570 (8.2%)	167/1530 (10.9%)	***0.72 (0.56 – 0.92)***
Surfactant use	NR	NR	1 (0.7%)	0	26 (1.8%)	43 (3.1%)	27/1570 (1.7%)	43/1530 (2.8%)	0.61 (0.21–1.03)
Mechanical ventilation use	NR	NR	2 (1.4%)	1 (0.8%)	34 (2.4%)	43 (3.1%)	36/1570 (2.3%)	44/1530 (2.9%)	0.80 (0.42–1.30)
NICU admission	8 (16%)	2 (4%)	47 (32.9%)	43 (33.1%)	593 (41.6%)	627 (44.8%)	648/1620 (40.0%)	672/1580 (42.5%)	0.94 (0.73–1.15)
Neonatal hypoglycemia	NR	NR	15 (10.5%)	9 (6.9%)	343 (24.0%)	209 (14.9%)	358/1570 (22.8%)	218/1530 (14.2%)	***1.61 (1.16 – 2.12)***
Neonatal death	0	0	0	2 (1.6%)	2 (0.1%)	0	2/1620 (0.1%)	2/1530 (0.1%)	0.95 (0.15–5.87)

Data are number (percentage). Control comparator: *no treatment or † placebo. RDS, respiratory distress syndrome; TTN, transient tachypnoea of the newborn; NICU, neonatal intensive care unit; NR, not reported.

those with no hypoglycemia (adjusted RR 2.32, 95% CI 1.17, 4.59) and low visual-motor function (visual motor integration score < 85: 4.7% (13/277) after hypoglycemia and 1.5% (3/194) in those with no hypoglycemia (adjusted RR 3.67, 95% CI 1.15, 11.69) with a dose dependent effect by severity and number of episodes of hypoglycemia [53]. Ongoing assessment of this cohort will continue to provide further insight into later childhood and adolescent effects of neonatal hypoglycemia.

1.2. The role of antenatal corticosteroids after 34 weeks' gestation

In his attempts to describe the physiology of parturition in Auckland in the 1960s Sir Graham "Mont" Liggins serendipitously observed partial aeration of the lungs in lambs born at the equivalent of 32 weeks' gestation after receiving treatment with dexamethasone [54]. He theorised that this may have occurred as the result of accelerated surfactant activity. This has since been confirmed in further studies suggesting corticosteroids enhance alveolar type II pneumocyte cell maturation to increase surfactant production and in addition improve anti-oxidant activity and reduce pro-inflammatory cytokine production to promote lung maturity [55].

By the early 1970s Liggins and Howie had confirmed the clinical significance of this finding in the first in human placebo-controlled clinical trial [56] but sadly it was many years later and many more clinical trials confirming the findings of this original trial until there was a significant global change in practice for early preterm birth. We now have clear and accepted evidence that ACS prior to preterm birth, regardless of mode of birth, reduces perinatal death and neonatal death; and the most serious adverse outcomes related to prematurity including RDS, intraventricular hemorrhage, necrotizing enterocolitis, and early systemic infection [1] with no evidence of later harm to the infant or to the mother [2–6]. The majority of trials included in the latest Cochrane review included women at risk of preterm birth prior to 32–34 weeks' [1], and, until recently, all international and leading national clinical practice guidelines included an upper limit of gestation for recommendation for use between 33^{+6} and 34^{+6} weeks' gestation [7,8,11,57–59].

Recent evidence from a single large trial in the United States suggesting respiratory benefit following ACS at late preterm gestations (34^{+0} to 36^{+6} weeks [14]) very quickly lead to recommendations for practice change, such that the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion now states that 'a single course of betamethasone is recommended for pregnant women between 34^{+0} weeks and 36^{+6} weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.' [10] Subsequently several expert commentaries and reviews have highlighted concerns over this rapid adoption of practice change where realistic concerns over the risk/benefit ratio remain unresolved [60–62].

1.3. Benefits and risks of antenatal corticosteroid use

1.3.1. Late preterm birth

The evidence for benefit of ACS at late preterm gestations (up to 36^{+6} weeks) has predominantly been established by the Antenatal Betamethasone for Women at Risk for Late Preterm Delivery (ALPS) trial [14]. This trial included 2827 women with a singleton pregnancy deemed to be at high risk of imminent birth by all modes of birth at 34^{+0} to 36^{+6} weeks, 73% (2063) of whom were recruited $\geq 35^{+0}$ weeks. Participants were randomized to receive two injections of betamethasone or a matching placebo 24 h apart. Betamethasone was associated with a 20% reduction in the primary outcome, a composite of death and significant respiratory support; occurring in 11.6% (165/1427) of infants in the betamethasone group and 14.4% (202/1400) of infants in the placebo group (RR 0.80, 95% CI 0.66, 0.97). Similar effects were seen on other measures of respiratory morbidity including

TTN, use of continuous positive airway pressure ventilation, bronchopulmonary dysplasia and surfactant use but with no significant reduction in the incidence of RDS. RDS occurred in 5.5% (79/1427) of infants in the betamethasone group and 6.4% (89/1400) of infants in the placebo group (RR 0.87, 95% CI 0.65, 1.17). These findings of significant improvement in some measures of respiratory morbidity have been further supported by a 2016 systematic review by Saccone and Berghella [63] that included the ALPS trial and two other much smaller trials (Table 3) [64,65].

An unanticipated finding of the ALPS trial [14] was an increased rate of neonatal hypoglycemia (defined as blood glucose concentration < 2.2 mmol/L [< 40 mg/dL]) in babies exposed to corticosteroids compared to those exposed to placebo (24.0% [343/1427] vs 15.0% [210/1400], RR 1.6, 95% CI 1.4, 1.9, p < 0.001). This finding was confirmed in meta-analysis of data from the ALPS trial and the trial reported by Porto et al. of 273 infants exposed to ACS at 34^{+0} to 36^{+6} weeks (Table 3) [64]. Measurement of blood glucose concentration in the newborn period was not mandated in the protocol in either of these trials, suggesting that the overall rates of hypoglycemia and potential effect size may be an underestimate.

1.3.2. Planned cesarean section birth

To date only four randomized trials of ACS specific to planned cesarean section at term, $\geq 37^{+0}$ weeks, have been reported [66–69]. Only one of these trials [67] included a placebo comparator, with the remaining three comparing ACS to usual care [66,68,69]. Saccone and Berghella included three trials in their 2016 systematic review [63]. As may be expected with term birth, the overall rates of respiratory morbidity were lower but the benefit of ACS remained consistent; RDS occurred in 2.7% (33/1217) of infants in the corticosteroid group and 6.7% (86/1281) of infants in the placebo/no treatment group (RR 0.40, 95% CI 0.27, 0.59). A similar size of effect was seen on mild and moderate RDS, TTN, and use of mechanical ventilation (Table 4) [63]. Corticosteroid use was not associated with a reduction in admission to neonatal intensive care (3% [38/1217] in the corticosteroid group and 5.3% [68/1281] in the placebo/no treatment group, RR 0.48, 95% CI 0.19, 1.20) but did reduce the duration of neonatal intensive care stay (mean difference −7.44 days) [63].

An additional trial not included in the systematic review is a French multi-center open label trial published in 2017. A total of 200 pregnancies were included in the *per-protocol* analysis comparing antenatal betamethasone and planned cesarean section at 38 weeks with planned cesarean section at 39 weeks with no betamethasone. There was no difference in the primary outcome of neonatal unit admission for respiratory distress (2.1% [2/95] after delivery at 38 weeks with betamethasone group and 3.8% [4/105] after delivery at 39 weeks, RR 0.54, 95% CI 0.1, 2.9) but fewer women required emergency cesarean section when birth was planned at 38 weeks after betamethasone (12.7% [12/95] vs 26.7% [28/105], p = 0.01) [69].

These trials demonstrate that corticosteroid use prior to planned cesarean section at term reduces the incidence of short-term respiratory morbidity which may lead to less time in neonatal intensive care, and so potentially improved maternal bonding and higher breastfeeding rates. However, none of these four randomized trials included routine measurement of newborn blood glucose concentrations nor reported rates of neonatal hypoglycemia. Hence no conclusions of benefit over harm can be reliably made.

1.3.3. Infants of women with diabetes in pregnancy

Pregnancies complicated by diabetes are at higher risk of neonatal respiratory morbidity, where ACS may provide benefit, and neonatal hypoglycemia, where ACS may cause harm; however we have even less evidence to guide practice on their use in these situations. No trials have specifically addressed this question. Only 10.8% (306/2831) of the ALPS trial population had gestational diabetes (women with pre-existing diabetes were excluded) [14] and a further 22 women in three

Table 4
Primary and selected secondary outcomes reported in 2016 systematic review of all trials of corticosteroid use in women prior to planned cesarean birth ≥37 weeks' gestation [63].

Outcomes	Stutchfield 2005 [68]		Ahmed 2015 [66]		Nada 2016 [67]		All trials		Relative risk (95% confidence interval)
	Corticosteroid group n = 373	Control group* n = 446	Corticosteroid group n = 228	Control group * n = 224	Corticosteroid group n = 616	Control group†n = 611	Corticosteroid group	Control group	
RDS	11 (2.9%)	24 (5.4%)	18 (7.9%)	52 (23.25)	4 (0.6%)	10 (1.6%)	33/1217 (2.7%)	86/1281 (6.7%)	***0.40 (0.27 – 0.59)***
Severe RDS	1 (0.3%)	5 (1.1%)	0	2 (0.9%)	NR	NR	3/601 (0.5%)	7/672 (1.0%)	0.22 (0.02–1.31)
TTN	10 (2.7%)	19 (4.3%)	18 (7.9%)	50 (22.3%)	8 (1.3%)	21 (3.4%)	36/1217 (3.0%)	90/1281 (7.0%)	***0.38 (0.25 – 0.57)***
Mechanical ventilation use	2 (0.5%)	17 (3.8%)	NR	NR	5 (0.8%)	21 (3.4%)	7/989 (0.7%)	38/1057 (3.5%)	***0.19 (0.08 – 0.43)***
NICU admission	26 (7.0%)	32 (7.1%)	2 (0.9%)	12 (0.4%)	10 (1.6%)	24 (3.9%)	38/1217 (3.0%)	68/1281 (5.3%)	0.48 (0.19–1.20)
Neonatal hypoglycemia	NR	NR	NR	NR	NR	NR	–	–	–
Neonatal death	0	0	0	0	1 (0.4)	2 (0.3)	1/616 (0.4%)	2/611 (0.4%)	0.50 (0.02–8.49)

Data are number (percentage). Control comparator *no treatment or † placebo. RDS, respiratory distress syndrome; TTN, transient tachypnoea of the newborn; NICU, neonatal intensive care unit; NR, not reported.

of the other trials had pre-gestational or gestational diabetes [64,68,69]. Although maternal diabetes was not an exclusion in the remaining trials, the number of women with diabetes was not reported [65–67]. Hence, subgroup meta-analyses of existing trials will not significantly further our knowledge.

1.3.4. Longer-term effects

Evidence suggests that the use of ACS after 34 weeks' gestation provides benefit for respiratory morbidity for those infants in specific 'at-risk' groups. The majority of this respiratory disease is likely to be short-term, although this often requires admission of the infant to the neonatal unit which may have longer-term consequences due to early separation of baby from his or her mother. However, emerging evidence now suggests that any advantage on respiratory morbidity gained by ACS may have a consequent negative effect on neonatal glycemic control, which may in turn have more significant longer-term adverse effects. There are no high quality data on longer-term benefit or harm associated with ACS at term and late preterm gestations. None of the trials in late preterm birth have, as yet, reported outcomes beyond primary hospital discharge [14,64,65]. Only one trial with limited follow-up has reported childhood outcomes after ACS prior to planned cesarean section $\geq 37^{+0}$ weeks.

The Antenatal Steroids for Term Elective Cesarean Section (ASTECS) trial [68], an open trial of betamethasone versus standard care, assessed 352 children from the original trial cohort of 942 (37%) by use of parental and school questionnaires completed at 8–15 years of age [70]. The majority of the results were reassuring with no differences reported in childhood asthma or wheeze; hyperactivity, emotional or peer difficulties; or in parent-reported learning difficulties (requiring additional help in school) or national education achievement tests. However, a higher proportion of children whose mothers had received ACS were judged by their teachers to be in the lower quartile for ability compared to those whose mothers had not received them (17.7% [33/217] vs 8.5% [14/190], p = 0.03) [70]. This is a finding of concern which requires further evaluation, particularly as neonatal hypoglycemia has been identified as a possible underlying mechanism leading to this difference.

1.4. Current clinical practice guidance

Advice from national and international guidelines regarding ACS after 34 weeks' gestation is limited and conflicting. The World Health Organisation makes a strong recommendation for use of ACS in women at imminent risk of birth at 24–34 weeks', but no recommendation is made for preterm birth after 34 weeks' gestation. Their guidelines include a conditional recommendation based on 'very low-quality evidence' that ACS are not recommended in women undergoing planned cesarean section at 34^{+0} to 36^{+6} weeks. ACS are recommended for women with pre-gestational and gestational diabetes at risk of imminent preterm birth (24–34 weeks), and that this should be accompanied by interventions to optimise maternal blood glucose concentrations; but again no comment is made for women with diabetes > 34 weeks' gestation [7].

The British National Institute for Health and Care Excellence Preterm Labour and Birth guideline recommends that all women in suspected or established preterm labour, with planned preterm birth or preterm prelabour rupture of membranes up to 33^{+6} weeks should be offered ACS. It also recommends that there should be 'consideration' of their use at 34^{+0} to 35^{+6} weeks [59]. British guidelines for the care of women with diabetes in pregnancy suggests that ACS are not contraindicated in women with diabetes [71]. However they provide no guidance on any variation in indications for use in women with diabetes but do recommend adjustment of maternal insulin dose and monitoring in women with insulin-treated diabetes around the time of ACS administration [71]. Until recently the British Royal College of Obstetricians and Gynaecologists guideline recommended ACS for all planned cesarean sections $\leq 38^{+6}$ weeks [58]. This guideline has now been archived and replaced by the National Institute for Health and Care Excellence guideline on Cesarean Section which provides no guidance on their use [9].

The American College of Obstetricians and Gynecologists have recently been updated to provide guidance for ACS at late preterm gestations, recommending their use for all births at 34^{+0} to 36^{+6} weeks in women who have not received a previous course. These guidelines provide no specific advice for women with diabetes or for planned cesarean section > 36^{+6} weeks [10].

New Zealand and Australian guidelines make a strong recommendation for ACS up to 34^{+6} weeks but no advice is given for late preterm birth [8]. These guidelines conclude there is insufficient evidence to make a recommendation for planned cesarean section at term or for women with diabetes at term but provide practice points recommending their use if there is known fetal lung immaturity prior to planned cesarean section and for maternal glucose monitoring and treatment when used in women with diabetes [8].

2. Conclusion

There is increasing evidence that the use of ACS given to mothers after 34 weeks' gestation prior to late preterm birth, birth by planned cesarean section and for infants born to mothers with diabetes reduces the risk of short-term respiratory morbidity. For many this evidence has been sufficient for practice change. However, the lack of data to refute or confirm the potential harm of this therapy including on neonatal glycemic control and any potential long-term effects should limit this practice change to their use only in the context of large RCTs. Future research of this therapy must focus on specific and clearly defined 'at-risk' populations and include outcomes that are easily measured and defined focussing on both the benefits and risks of treatment. Wherever possible they should plan and be funded to include assessment of meaningful long-term outcomes that include measurement of respiratory, metabolic and neurodevelopmental outcomes.

Conflict of interest statement

No conflict of interest.

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Practice points

The use of ACS therapy prior to late preterm birth and planned cesarean section at term reduces short-term neonatal respiratory morbidity.

The use of ACS therapy prior to late preterm birth and possibly prior to planned cesarean section at term increases the risk of neonatal hypoglycemia.

We have insufficient evidence regarding the effect of ACS use on neonatal respiratory morbidity and neonatal hypoglycemia in infants born to mothers with diabetes in pregnancy.

The longer-term effects of ACS use prior to late preterm birth, planned cesarean section at term and for infants born to mothers with diabetes in pregnancy on childhood outcomes are unknown.

If using ACS therapy after 34^{+6} weeks' to improve infant outcomes, consider routine newborn blood glucose concentration monitoring in the first 24–48 h of life.

Research directions

The effect of ACS therapy on neonatal respiratory morbidity AND hypoglycemia when given prior to late preterm birth.

The effect of ACS therapy on neonatal respiratory morbidity AND hypoglycemia when given prior to planned cesarean section at term.

The effect of ACS therapy on neonatal respiratory morbidity AND hypoglycemia when given prior to birth of infants born to mothers with diabetes in pregnancy after 34^{+6} weeks.

The effect of ACS therapy (and neonatal hypoglycemia) after late preterm birth, planned cesarean section at term and for infants born to mothers with diabetes in pregnancy on childhood respiratory, metabolic and neurodevelopmental outcomes.

References

[1] Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017;3:CD004454.

[2] Cartwright RD, Harding JE, Crowther CA, et al. Repeat antenatal betamethasone and cardiometabolic outcomes. Pediatrics 2018;142(1).

[3] McKinlay CJD, Cutfield WS, Battin MR, et al. Mid-childhood bone mass after exposure to repeat doses of antenatal glucocorticoids: a randomized trial. Pediatrics 2017;139(5).

[4] Dalziel SR, Rea HH, Walker NK, et al. Long term effects of antenatal betamethasone on lung function: 30 year follow up of a randomised controlled trial. Thorax 2006;61(8):678–83.

[5] Dalziel SR, Lim VK, Lambert A, et al. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. BMJ 2005;331(7518):665.

[6] Dalziel SR, Walker NK, Parag V, et al. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. Lancet 2005;365(9474):1856–62.

[7] World Health Organisation. WHO recommendations on interventions to improve preterm birth outcomes Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/preterm-birthguideline/en/; 2015.

[8] Crowther C, Brown J, Alsweiler J, Middleton P, Groom K. Antenatal corticosteroids clinical practice guidelines panel. Liggins Institute. The University of Auckland. Antenatal corticosteroids given to women prior to birth to improve fetal, infant, child and adult health: Clinical practice guidelines; 2015 Available from: http://www.ligginstrials.org/ANC_CPG.

[9] NICE. National Institute for Health and care excellence. Caesarean section clinical guideline (CG 132). 2011 Available from: URL: https://www.nice.org.uk/guidance/cg132.

[10] ACOG. American College of Obstetricians and Gynecologists. ACOG committee opinion No. 713: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol 2017;130(2):e102–9.

[11] Crane J, Armson A, Brunner M, et al. Antenatal corticosteroid therapy for fetal maturation. J Obstet Gynaecol Can 2003;25(1):45–52.

[12] PMMRC. Eleventh annual report of the perinatal and maternal mortality review committee - reporting mortality and morbidity 2015 2017 Available from: https://www.hqsc.govt.nz/assets/PMMRC/Publications/2017_PMMRC_Eleventh_Annual_Report.pdf.

[13] Northrup TF, Wootton SH, Evans PW, Stotts AL. Breastfeeding practices in mothers of high-respiratory-risk NICU infants: impact of depressive symptoms and smoking. J Matern Fetal Neonatal Med 2013;26(18):1838–43.

[14] Gyamfi-Bannerman C, Thom EA. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 2016;375(5):486–7.

[15] Ballard PL, Gluckman PD, Liggins GC, Kaplan SL, Grumbach MM. Steroid and growth hormone levels in premature infants after prenatal betamethasone therapy to prevent respiratory distress syndrome. Pediatr Res 1980;14(2):122–7.

[16] Padbury JF, Ervin MG, Polk DH. Extrapulmonary effects of antenatally administered steroids. J Pediatr 1996;128(2):167–72.

[17] Sifianou P, Thanou V, Karga H. Metabolic and hormonal effects of antenatal betamethasone after 35 weeks of gestation. J Pediatr Pharmacol Ther.: JPPT: Off J PPAG 2015;20(2):138–43.

[18] Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379(9832):2162–72.

[19] Consortium on Safe L, JU Hibbard, Wilkins I, et al. Respiratory morbidity in late preterm births. J Am Med Assoc 2010;304(4):419–25.

[20] Cheng YW, Kaimal AJ, Bruckner TA, Halloran DR, Caughey AB. Perinatal morbidity associated with late preterm deliveries compared with deliveries between 37 and 40 weeks of gestation. BJOG 2011;118(12):1446–54.

[21] Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. Int J Epidemiol 2014;43(3):802–14.

[22] Boyle EM, Johnson S, Manktelow B, et al. Neonatal outcomes and delivery of care for infants born late preterm or moderately preterm: a prospective population-based study. Arch Dis Child Fetal Neonatal Ed 2015;100(6):F479–85.

[23] Ruth CA, Roos N, Hildes-Ripstein E, Brownell M. The influence of gestational age and socioeconomic status on neonatal outcomes in late preterm and early term gestation: a population based study. BMC Pregnancy Childbirth 2012;12:62.

[24] Samayam P, Ranganathan PK, Kotari UD, Balasundaram R. Study of asymptomatic hypoglycemia in full term exclusively breastfed neonates in first 48 hours of life. J Clin Diagn Res 2015;9(9). SC07-10.

[25] Hoseth E, Joergensen A, Ebbesen F, Moeller M. Blood glucose levels in a population of healthy, breast fed, term infants of appropriate size for gestational age. Arch Dis Child Fetal Neonatal Ed 2000;83(2):F117–9.

[26] Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr 2012;161(5):787–91.

[27] Boerma T, Ronsmans C, Melesse DY, et al. Global epidemiology of use of and disparities in caesarean sections. Lancet 2018;392(10155):1341–8.

[28] Ministry of Health. Report on maternity 2015. Wellington: Ministry of Health; 2017.

[29] Tutdibi E, Gries K, Bucheler M, Misselwitz B, Schlosser RL, Gortner L. Impact of labor on outcomes in transient tachypnea of the newborn: population-based study. Pediatrics 2010;125(3):e577–83.

[30] Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Elective caesarean section and respiratory morbidity in the term and near-term neonate. Acta Obstet Gynecol Scand 2007;86(4):389–94.

[31] Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. Br J Obstet Gynaecol 1995;102(2):101–6.

[32] Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. BMJ 2008;336(7635):85–7.

[33] Tita AT, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. N Engl J Med 2009;360(2):111–20.

[34] ACOG. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 559: cesarean delivery on maternal request. Obstet Gynecol 2013;121(4):904–7.

[35] Cole MD, Peevy K. Hypoglycemia in normal neonates appropriate for gestational age. J Perinatol 1994;14(2):118–20.

[36] Dias E, Gada S. Glucose levels in newborns with special reference to hypoglycemia: a study from rural India. J Clin Neonatol 2014;3(1):35–8.

[37] Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin N Am 2007;34(2):173–99. [vii].

[38] Lavery JA, Friedman AM, Keyes KM, Wright JD, Ananth CV. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. Bjog 2017;124(5):804–13.

[39] Buckley BS, Harreiter J, Damm P, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med 2012;29(7):844–54.

[40] AICHW. Australian Institute of Health and Welfare. Australia's mothers and babies 2015 - in brief. Perinatal Statistics series no. 33. Canberra: AIHW; 2017.

[41] CDC. Centers for disease control and prevention Gestational Diabetes https://www.cdc.gov/diabetes/basics/gestational.html.

[42] Piper JM, Xenakis EM, Langer O. Delayed appearance of pulmonary maturation markers is associated with poor glucose control in diabetic pregnancies. J Matern Fetal Med 1998;7(3):148–53.

[43] McGillick EV, Morrison JL, McMillen IC, Orgeig S. Intrafetal glucose infusion alters glucocorticoid signaling and reduces surfactant protein mRNA expression in the lung of the late-gestation sheep fetus. Am J Physiol Regul Integr Comp Physiol 2014;307(5):R538–45.

[44] Becquet O, El Khabbaz F, Alberti C, et al. Insulin treatment of maternal diabetes mellitus and respiratory outcome in late-preterm and term singletons. BMJ Open 2015;5(6):e008192.

[45] Elmekkawi SF, Mansour GM, Elsafty MS, Hassanin AS, Laban M, Elsayed HM. Prediction of fetal hypertrophic cardiomyopathy in diabetic pregnancies compared with postnatal outcome. Clin Med Insights Women's Health 2015;8:39–43.

[46] Fung GP, Chan LM, Ho YC, To WK, Chan HB, Lao TT. Does gestational diabetes mellitus affect respiratory outcome in late-preterm infants? Early Hum Dev 2014;90(9):527–30.

[47] Vignoles P, Gire C, Mancini J, et al. Gestational diabetes: a strong independent risk factor for severe neonatal respiratory failure after 34 weeks. Arch Gynecol Obstet 2011;284(5):1099–104.

[48] Harding JE, Harris DL, Hegarty JE, Alsweiler JM, McKinlay CJ. An emerging evidence base for the management of neonatal hypoglycaemia. Early Hum Dev 2017;104:51–6.

[49] Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics 2008;122(1):65–74.

[50] Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, Reijneveld SA, Bos AF. Neonatal morbidities and developmental delay in moderately preterm-born children. Pediatrics 2012;130(2):e265–72.

[51] Shah R, Harding J, Brown J, McKinlay C. Neonatal Glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. Neonatology 2018;115(2):116–26.

[52] McKinlay CJ, Alsweiler JM, Ansell JM, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015;373(16):1507–18.

[53] McKinlay CJD, Alsweiler JM, Anstice NS, et al. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. JAMA Pediatr 2017;171(10):972–83.

[54] Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol 1969;45(4):515–23.

[55] Vyas J, Kotecha S. Effects of antenatal and postnatal corticosteroids on the preterm lung. Arch Dis Child Fetal Neonatal Ed 1997;77(2):F147–50.

[56] Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50(4):515–25.

[57] ACOG. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 475: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol 2011;117(2 Pt 1):422–4.
[58] Royal College of Obstetricians and Gynaecologists. Antenatal corticosteroids to reduce neonatal morbidity (Green-top guideline No. 7). 2010 Available from: https://www.rcog.org.uk/en/guidelinesresearch-services/guidelines/gtg7/. (updated 2014).
[59] NICE. National Institute for health and care excellence. Preterm labour and birth guideline (NG25) Available from: https://www.nice.org.uk/guidance/ng25; 2015.
[60] Crowther CA, Harding JE. Antenatal glucocorticoids for late preterm birth? N Engl J Med 2016;374(14):1376–7.
[61] Kamath-Rayne BD, Rozance PJ, Goldenberg RL, Jobe AH. Antenatal corticosteroids beyond 34 weeks gestation: what do we do now? Am J Obstet Gynecol 2016;215(4):423–30.
[62] Smith GC, Rowitch D, Mol BW. The role of prenatal steroids at 34-36 weeks of gestation. Arch dis child fetal neonatal, vol. 102. 2017. p. F284–5. (4).
[63] Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ 2016;355:i5044.
[64] Porto AM, Coutinho IC, Correia JB, Amorim MM. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. BMJ 2011;342:d1696.
[65] Balci O, Ozdemir S, Mahmoud AS, Acar A, Colakoglu MC. The effect of antenatal steroids on fetal lung maturation between the 34th and 36th week of pregnancy. Gynecol Obstet Investig 2010;70(2):95–9.
[66] Ahmed MR, Sayed Ahmed WA, Mohammed TY. Antenatal steroids at 37 weeks, does it reduce neonatal respiratory morbidity? A randomized trial. J Matern Fetal Neonatal Med 2015;28(12):1486–90.
[67] Nada AM, Shafeek MM, El Maraghy MA, Nageeb AH, Salah El Din AS, Awad MH. Antenatal corticosteroid administration before elective caesarean section at term to prevent neonatal respiratory morbidity: a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2016;199:88–91.
[68] Stutchfield P, Whitaker R, Russell I. Antenatal Steroids for Term Elective Caesarean Section Research T. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. BMJ 2005;331(7518):662.
[69] Sananes N, Koch A, Escande B, et al. Pilot randomised controlled trial comparing the risk of neonatal respiratory distress in elective caesarean section at 38 weeks' gestation following a course of corticosteroids versus caesarean at 39 weeks. Eur J Obstet Gynecol Reprod Biol 2017;212:54–9.
[70] Stutchfield PR, Whitaker R, Gliddon AE, Hobson L, Kotecha S, Doull IJ. Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed 2013;98(3):F195–200.
[71] NICE. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period (NG3). 2015 Available from: nice.org.uk/guidance/ng3.