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Antenatal Corticosteroids for fetal lung maturation: proven benefits and adverse effects

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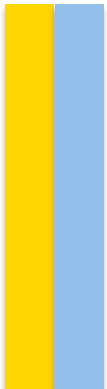

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**

Antenatal Corticosteroids for fetal lung maturation: proven benefits and adverse effects

REVISÃO SISTEMÁTICA

Dissertação de Candidatura ao grau de Mestre em Medicina submetida ao Instituto de Ciências Biomédicas de Abel Salazar, Universidade do Porto

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RESUMO

Enquadramento: Os recém-nascidos pré-termo apresentam um maior risco de desenvolver síndrome de dificuldade respiratória. A administração de corticóides durante a gestação é um tratamento de rotina nas ameaças de parto pré-termo. No entanto, tem sido descrito que a exposição excessiva a corticóides durante a gestação pode associar-se a restrição de crescimento fetal, ao desenvolvimento de doenças cardiovasculares e diabetes tipo 2, intolerância à glicose, dislipidemia e hipertensão, bem como a alterações do neurodesenvolvimento.

Objetivos: Reunir e sumariar a evidência científica publicada ao longo dos últimos 30 anos acerca dos benefícios comprovados dos corticóides na maturação pulmonar fetal, bem como sensibilizar para os possíveis efeitos adversos a curto e longo prazo desta abordagem. Propõe-se ainda um protocolo de administração de corticosteróides na gravidez.

Métodos: Foi realizada uma pesquisa na base de dados *Pubmed* utilizando palavras-chave relevantes em diferentes combinações. Os resultados foram filtrados, tendo sido incluídos os artigos publicados ao longo dos últimos 30 anos, bem como estudos realizados em animais. A pesquisa foi limitada a artigos escritos em Português e Inglês e com elevado nível de evidência científica. Recomendações internacionais e artigos selecionados por referenciação cruzada foram também considerados nesta revisão.

Resultados: Cinquenta e seis artigos foram incluídos: 8 recomendações internacionais, 29 ensaios randomizados, 2 ensaios clínicos, 10 meta-análises e 7 revisões sistemáticas. Tanto a dexametasona como a betametasona são corticóides seguros e eficazes e a dose total *standard* são 24mg. A via de administração preferencial é a intramuscular e deve ser administrada à mãe. Um único ciclo de corticóides reduz os efeitos adversos neonatais em recém-nascidos pré-termo antes das 34 semanas de gestação, bem como diminui o risco de alterações do neurodesenvolvimento. Uma repetição do ciclo de corticóides é aceitável e não aparenta ter implicações negativas para os recém-nascidos/crianças. Vários ciclos de corticóides estão contraindicados dada a associação a efeitos adversos como a restrição de crescimento, hipoglicemia neonatal e, a longo prazo, as crianças são mais suscetíveis de necessitar avaliação por défice de atenção.

Conclusão: Os benefícios dos corticóides são inegáveis na promoção da maturação pulmonar fetal, tendo-se demonstrado efeitos positivos no neurodesenvolvimento. Mais investigação é, no entanto, essencial para determinar o momento e a dose ideais em diferentes cenários. Estudos com enfoque em desfechos a longo prazo, além do neurodesenvolvimento, são essenciais para permitir uma compreensão mais abrangente do impacto da utilização antenatal dos corticóides.

Palavras-chave: *Antenatal corticosteroids, preterm birth, fetal lung maturation, respiratory distress syndrome, benefits, adverse effects.*

ABSTRACT

Background: Preterm infants are at a higher risk of respiratory distress syndrome (RDS). Antenatal corticosteroids (ACS) are considered standard of care for women at risk of preterm birth, in order to reduce the incidence of neonatal RDS. However, it has been proposed that the exposure to an excess of corticosteroids (CS) before birth may be associated with impaired fetal growth, cardiovascular disease and type 2 diabetes later in life, impaired glucose tolerance, dislipidemia, and hypertension, as well as neurodevelopmental disorders.

Objectives: To revise and summarize the relevant evidence published over the past 30 years on the proven benefits of ACS for fetal lung maturation, as well as raising awareness for its short and long-term adverse effects in infants. Also, to create a protocol on the use of ACS in preterm labour guiding clinicians on the optimal drug, dose, timing and route of administration.

Methods: A search through PubMed database was carried out in compliance with MeSH using relevant keywords in different combinations. The results were filtered to select papers published over the last 30 years, including the ones regarding animal studies. The search was also limited to papers written in Portuguese and English and with the highest level of scientific evidence. International guidelines and papers selected by cross-referencing that met the inclusion criteria were also considered in this review.

Results: Fifty-six articles were included: 8 international guidelines, 29 randomized controlled trials, 2 clinical trials, 10 meta-analysis and 7 systematic reviews. Either dexamethasone or betamethasone is safe to administer as ACS. The safest route of administration is the intramuscular and it should be administered to the mother. The standard dose is 24mg of either ACS. A single course of ACS is proven to reduce adverse neonatal outcomes in preterm infants before 34 weeks of gestation (but especially <28 weeks), as well as to decrease the risk of neurodevelopmental disorders. A single repeat course of ACS is acceptable and does not seem to impact negatively both short and long term the neonate/child. Multiple courses of ACS are not recommended as it is associated with adverse effects, incremental decrease in weight, neonatal hypoglycemia and, at long term, children are more likely to warrant assessment for neurodevelopment disorders.

Conclusion: In favour of ACS treatment, are the overall benefits on fetal lung maturity, especially considering the improved short-term outcomes and favourable long-term neurodevelopmental outcomes. Further investigation is needed to determine optimal timing and dosing in specific scenarios. Studies focusing on long-term outcomes beyond neurodevelopmental assessments are essential to gain a comprehensive understanding of the impact of ACS use.

Keywords: Antenatal corticosteroids, preterm birth, fetal lung maturation, respiratory distress syndrome, benefits, adverse effects.

LIST OF ABBREVIATIONS

ACOG: American College of Obstetricians and Gynecologists

ACS: antenatal corticosteroids

ACTORDS: Australasian Collaborative Trial of Repeat Doses of Steroids

aHR: adjusted hazard ratio

aOR: adjusted odds ratio

aRR: adjusted relative risk

BPD: bronchopulmonary dysplasia

BM: betamethasone

CI: confidence interval

CPAP: continuous positive airway pressure

Crs: Passive respiratory compliance

CS: corticosteroids

CTH: adrenocorticotropic hormone

DM: dexamethasone

FIGO: International Federation of Gynecology and Obstetrics

GA: gestational age

GRADE: Grading of Recommendations Assessment, Development and Evaluation

GMR: geometric mean ratio

HPA: hypothalamic-pituitary-adrenal

IGF-1: insulin-like growth factor 1

IQR: interquartile range

IUGR: intrauterine growth restriction

IVH: intraventricular haemorrhage

MACS: Multiple courses of antenatal corticosteroids for preterm birth

MC: multiple courses

MeSH: Medical Subject Heading of the Index Medicus

NEC: necrotizing enterocolitis

NICE: National Institute for Health and Care Excellence

NICU: neonatal intensive care unit

PPROM: Preterm prelabour rupture of membranes

PDA: patent ductus arteriosus

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PVL: periventricular leukomalacia

RCT: Randomized Controlled Trial

ROP: retinopathy of prematurity

SC: single course

SIGN: Scottish Intercollegiate Guideline Network

SOGC: Society of Obstetricians and Gynaecologists of Canada

TTN: transient tachypnoea of the neonate

uOR: unadjusted odds ratio

(w)MD: weighted mean difference

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BACKGROUND

The concept of “preterm birth” defines any birth occurring before 37 complete gestation weeks. It poses a significant global health burden with a great geographical variation and an incidence that ranges from 5% to 15%, worldwide.[1]

Preterm infants, particularly those born before 32 weeks' gestation, are at a higher risk of respiratory distress syndrome (RDS), a serious complication that remains one of the most common causes of early neonatal death and disability.[2,3]

Respiratory failure is the result of a combination of surfactant deficiency, poor lung anatomical development and immaturity in other organs, exposing the survivors to an increased risk of long-term neurological disability. Therefore, treatments that may reduce the incidence of RDS in infants born preterm, including ACS, have received substantial attention for a long time now.[3]

Antenatal corticosteroids are considered standard of care for women at risk of preterm birth, enhancing fetal lung maturation and thus improving neonatal outcomes in the event of preterm delivery. This approach has been shown to substantially reduce the risks of adverse neonatal complications, including death, RDS, intraventricular haemorrhage and sepsis.[1,2,4,5]

However, ACS may also cause harm. As a result of this treatment, all fetal organs are exposed to CS and the consequences of this exposure, particularly the long-term effects, are poorly described and understood.[1]

It has been proposed that the exposure to an excess of CS before birth may be associated with impaired fetal growth, cardiovascular disease and type 2 diabetes later in life, as well as with impaired glucose tolerance, dislipidemia, and hypertension. Regarding animal experimental work, impaired glucose tolerance and increased blood pressure is documented in adult animals after antenatal exposure to CS, as well as decreased brain growth in preterm and term infants exposed to single courses of CS.[2]

Despite the widespread use of ACS to prevent RDS in preterm infants, international guidelines lack consensus regarding the recommended type of corticosteroid and the gestational window of treatment administration. Moreover, little has been done to optimise the dose and formulation of antenatal corticosteroid treatment since the first clinical trial in 1972.[1,3] Further investigations are urgently needed to determine the safest and most effective treatment regimen for ACS, as well as to improve diagnostic tests that predict preterm birth.[1,3,6]

As recent findings indicate a trend towards more liberal use of ACS and given the potential implications of its overuse, researchers continue to investigate the possible associations between ACS and long-term outcomes in exposed children.[5]

The main purpose of this integrative systematic review is to revise, organize and summarize all the evidence published over the past 30 years not only on the proven benefits of ACS for fetal lung maturation, but mostly to raise awareness for the short and long-term adverse effects of this approach in infants. We also aim to create a standardised protocol on the use of ACS at gestational age (GA) ≥24 and ≤34 weeks guiding clinicians on the optimal drug, dose, timing and route of administration.

Antenatal corticosteroids for fetal lung maturation

Neonatal survival after preterm birth improves with gestation, which reflects the maturation of organ systems. Despite that, these infants are at higher risk for long-term neurological disability.[3]

To better understand how RDS occurs and why corticosteroids work, knowing lung development is essential, with emphasis over 28 to 35 weeks' gestation. It can be divided into five stages: embryonic, pseudoglandular, canalicular, terminal sac and alveolar. The embryonic phase is marked by the formation of the lung bud and initial branching of presumptive airways, which continues into the pseudoglandular stage. By the 16th week of gestation, the tracheobronchial tree has been formed, from the trachea up to and including the terminal bronchioles. During the canalicular phase, the basic structure of the gas-exchanging portion of the lung is formed and vascularized. The canalicular phase is marked by completion of the conducting airways and the development of the rudimentary gas exchange units and the timing between 22-24 weeks is marked by the initial differentiation of type II pneumocytes. During the saccular stage there is a rapid increase in the gas-exchange surface of the lung and thinning of the interstitium. During the period of 32-36 weeks, type II (surfactant producing) pneumocytes mature, completing the functional maturity of the lung. All the alveolar structures are uniformly present at 36 weeks of gestation, when the alveolar stage starts. However, it is not completed until 8 years of age, with the greatest increase in the number of alveoli occurring during the first 2 years of life. During this stage occurs further thinning of the blood-gas barrier, increase of surfactant production and progressive branching of the respiratory airways.[7,8,9]

As gestation progresses, there is also biochemical maturation of the fetal lung. Lamellar bodies, which store surfactant (a complex mixture of lipids and apoproteins), appear at 22-24 weeks. Surfactant is needed to maintain stability when breathing out as it prevents the collapse of the alveoli. Premature infants have not only a quantitative but also a qualitative deficiency of surfactant, predisposing to RDS. At the low lung volume associated with expiration, surface tension becomes very high, leading to atelectasis with subsequent intrapulmonary shunting, ventilation perfusion inequalities, and ultimately respiratory failure. Common problems of the preterm infant, like hypoxia, acidosis and hypothermia can reduce surfactant synthesis required to replenish surfactant loss from the system. [8,9]

In the fetal lung, the action of CS leads to an increase in protein production, biosynthesis of phospholipids and the appearance of surfactant. It was shown by Liggins in 1969 that lambs born preterm became functionally mature following antenatal CS administration. [8,9]

ACS therapy has been used liberally for more than thirty years to reduce the incidence of RDS and other complications of preterm birth. There is convincing evidence that normal maturation of fetal alveolar cells and their ability to produce surfactant is dependent on increased secretion of endogenous CS from the fetal adrenal cortex.[9] This physiologic mechanism is appropriated in the pharmacologic administration of CS to cause premature acceleration of fetal lung maturation.[10]

Nevertheless, studies in animals have found an association between exposure to ACS and harmful neurological outcomes, including alterations to the hypothalamic-pituitary-adrenal axis, diminished cortical surface, loss of essential synaptic proteins, and decreased blood flow in areas of the brain. In full-term animals, preterm exposure to ACS was associated with harmful neural outcomes, such as decreased hippocampal development. Moreover, in both preterm and full-term animals, there were implications for other organs, including reduced glomerular filtration rate; and in full-term animals, the use of ACS was associated with an increased insulin to glucose ratio. Therefore, it seems mandatory to explore the long-term implications of preterm exposure to ACS throughout life.[4]

METHODS

To guide and ensure the quality of this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations were used.

In this review, we aimed to include articles focusing on the advantages, adverse effects and drug selection on the administration of ACS for fetal lung maturation. Therefore, only Randomized Controlled Trials (RCTs), Meta-analyses, Systematic Reviews and Clinical Trials were included.

A search through PubMed database was conducted including the following MeSH terms "antenatal corticosteroids", "preterm birth", "benefits", "adverse effects" and "fetal lung maturation" in different combinations. International guidelines were also considered in this review. Papers selected by cross-referencing that met the inclusion criteria were also included.

All studies and guidelines identified were screened for the following inclusion criteria: papers related to the use of ACS for fetal lung maturation; published over the last 30 years (since 1993); papers regarding not only studies in humans, but also in animals; papers written in Portuguese or English. Firstly, papers were filtered by analysing titles and abstracts, using the same inclusion criteria. Secondly, the included articles were reviewed based on its full text.

The following were defined as exclusion criteria: full text not available; other types of study design; papers focusing on other medications; ACS for other purposes (not fetal lung maturation); postnatal corticosteroids; publications only with study design protocols; papers on methods to increase implementation of ACS; and papers withdrawn.

To assess the quality of evidence across studies, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used.[11] Evidence from all studies was rated as "high" quality of evidence, and then downgraded if a risk of bias, indirectness, inconsistency, imprecision or publication bias was detected. If the paper was already rated by its authors, this grade was kept, regardless of using GRADE[11] or SIGN[12] criteria for rating.

RESULTS

The summary of results from the articles included in this systematic review can be checked on tables I-VII, which contain the following information: Table I. Results - RCTs (Human); Table II. Results - RCTs (Animal); Table III. Results - Clinical Trials; Table IV. Results - Meta-analysis; Table V. Results - Systematic Review (Human); Table VI. Results - Systematic Review (Animal); Table VII. International guidelines on antenatal corticosteroids (ACS).

1. ACS – drug choice, dose regimens, including timing, frequency and mode of administration

A Cochrane meta-analysis[3] published in 2022 compared 9 trials of dexamethasone (DM) versus betamethasone (BM); all administered both drugs intramuscularly, and the total dose in the course was consistent (22.8 mg or 24 mg), but the regimen varied. This meta-analysis showed that it is unlikely that the choice of medicine makes a difference to the risk of any known death (p=0.88); the choice of medicine makes no difference to the risk of RDS (p=0.46), chronic lung disease (p=0.67) and intraventricular haemorrhage (IVH) (p=0.48). Only one trial consistently followed up children longer term (reporting at two years' adjusted age) and it showed no difference between DM and BM in the risk of neurodevelopmental disability at follow-up (p=0.82), visual impairment (p=0.50), hearing impairment (p=0.63), motor developmental delay (p=0.45) or intellectual impairment (p=0.78). However, the effect estimate for cerebral palsy is compatible with both an important increase in risk with DM, and no difference between interventions, as there were few events in the one study looking at this (p=0.06); information from more children is needed to accurately assess the differences between these medicines for this particular outcome. Also, according to this meta-analysis, three trials compared different ways of giving ACS. One trial compared two ways of giving DM (oral or intramuscular (IM)), another trial compared different preparations of BM and a third trial compared two ways of giving BM (different time intervals between doses). The only statistically significant result was the one comparing oral vs IM DM for the risk of neonatal sepsis (p=0.04), favouring IM route.[3] However, these are small trials with a moderate risk of bias, therefore, it's not clear whether their findings give a good indication of how best to give these medicines.

In 2021, Ninan et al.[13] systematic review aimed to evaluate neonatal and maternal effects of lower doses of ACS (<24 mg of BM or DM) compared with standard double doses (24 mg of BM or DM) administered to women at risk of preterm delivery. Only one trial was included which compared 16 mg of DM with 24 mg of BM, however, this trial had no data on major clinical outcomes of interest like perinatal death and severe RDS.

In 2018, Utama et al.[14] conducted a systematic review in order to assess if different routes of corticosteroid administration (maternal versus direct fetal) have effects on health outcomes for women and their babies. However, at that time, there were no completed RCTs that assessed the benefits and harms of direct injection of corticosteroid into the fetus compared with injection into the mother, for women who are at risk of preterm birth.

In a Cochrane systematic review by Brownfoot et al.[15] in 2013, which included 12 trials (1557 women and 1661 infants), dexamethasone was associated with a reduced risk of IVH compared with betamethasone (RR 0.44, 95% CI 0.21-0.92, p=0.029). No statistically significant differences were seen for other primary outcomes: RDS (RR 1.06, 95% CI 0.88-1.27, p=0.55) and neonatal death (RR 1.41, 95% CI 0.54-3.67, p=0.49). Similarly, very few differences were seen for secondary outcomes such as rate of admission to the neonatal intensive care unit (NICU) although in one trial, those infants exposed to DM, compared with BM, had a significantly shorter length of NICU admissions (MD -0.91 days, 95% CI -1.77 to -0.05; p value not shown). Compared with intramuscular (IM) dexamethasone, oral DM significantly increased the incidence of neonatal sepsis (RR 8.48, 95% CI 1.11-64.93, p=0.039) in one trial of 183 infants. Apart from a reduced maternal postpartum length of stay for women who received BM at 12-hourly intervals compared to 24-hourly intervals in one trial (MD -0.73 days, 95% CI -1.28 to -0.18, p=0.0095), no differences in maternal or neonatal outcomes were seen between the different BM dosing intervals assessed. Similarly, no significant differences were seen in outcomes like neonatal death (RR 0.32, 95% CI 0.01-7.69, p=0.49), RDS (RR 0.19, 95% CI 0.01-3.91, p=0.28) and birthweight (-0.10kg, 95% CI -0.44 to 0.24, p=0.56) when BM acetate plus phosphate was compared with BM phosphate in one trial.

In elective caesarean sections, it is known that infants born at term are more likely to develop respiratory morbidity than infants born vaginally. Prophylactic CS in singleton preterm pregnancies accelerate lung maturation and reduce the incidence of respiratory complications. However, it is unclear whether administration at term gestations, prior to caesarean section, improves the respiratory outcomes for these babies.[16] Bearing this in mind, in 2021, Sotiriadis et al.[16] assessed this issue on a systematic review. Only one trial was included (942 women and 942 neonates). Compared with usual care, it is uncertain if ACS reduce the risk of RDS (RR 0.34, 95% CI 0.07-1.65, p=0.18) or transient tachypnoea of the neonate (TTN) (RR 0.52, 95% CI 0.25-1.11, p=0.09) because the certainty of evidence is low and the 95% CIs are consistent with possible benefit and possible harm. ACS probably reduce the risk of admission to neonatal special care for respiratory complications, compared with usual care (RR 0.45, 95% CI 0.22-0.90, p=0.03). It is uncertain If ACS have any effect on the risk of needing mechanical ventilation, compared with usual care (RR 4.07, 95% CI 0.46-36.27, p-value not shown). The effect of ACS on the maternal development of

postpartum infection/pyrexia in the first 72 hours is unclear due to the very low certainty of the evidence; one study (942 women) reported zero cases.[16]

In the ASTEROID Trial[17] from 2019, 1346 pregnant women were randomly assigned to receive two IM injections of either 12 mg dexamethasone or 11.4 mg betamethasone, 24 hours apart. A similar incidence of death or neurosensory disability was found in the DM and BM groups (p=0.66). None of the birth-related secondary outcomes differed between groups, including the number of infants with RDS (p=0.72) or the number with IVH (p=0.72). It was also found that 29% of infants in the DM group and 30% of infants in the BM group died or had a neurosensory disability at age 2 years (p=0.46). In post-hoc analyses, the incidence of fetal distress (reported on cardiotocography) and the indications for the caesarean birth, did not differ between treatment groups. Moreover, 3% of women in the DM group and 4% of women in the BM group reported side-effects. Discomfort at the injection site, which was the most common side-effect, was reported less frequently in the DM group than in the BM group (p=0.02) (level of evidence – high).[17] In 2022, a secondary analysis[18] of the ASTEROID trial[17] was undertaken to determine the differences between the use of DM or BM as repeat ACS on maternal, infant, and childhood health outcomes - a repeat single dose of the same ACS could be given at weekly intervals up to a maximum of three repeat doses to 32 weeks'. The incidence of death or any neurosensory disability at age two years (corrected for prematurity) was similar in the DM group and the BM group (p=0.79). Infant secondary outcomes - RDS (p=0.45), IVH, severe IVH (grade 3 or 4), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), severity of neonatal lung disease, chronic lung disease, use of mechanical ventilation, confirmed infection, necrotizing enterocolitis (NEC), admission to the NICU before hospital discharge - were similar between treatment groups. Gestational age and body size (weight, length, and head circumference) at birth did not differ between the two treatment groups, as well as secondary child outcomes measured at two years' corrected age (level of evidence – moderate).[18]

The aim in the MACS trial[19] from 2008, was to see if a less frequent intervention (a course of ACS every 14 days in this trial vs every 7 days in other steroid trials) would show short-term respiratory benefits, and reduce to a minimum the risk of short-term and long-term adverse effects. Repeated courses of ACS, every 14 days, did not improve preterm-birth outcomes (p=0.83), and were associated with a decreased weight (p=0.0026), length (p<0.001), and head circumference at birth (p<0.001). Neonatal respiratory and other outcomes were comparable between the groups. It was concluded that multiple courses (MC) of ACS, given every 14 days, are associated with decreased growth in utero and has no neonatal benefits compared with a single course (SC) of ACS, so it should not be recommended. (level of evidence – high).[19]

The MACS-5 study[20], in 2013, determined the effects of single courses (SC) vs multiple courses (MC) (2 doses of 12 mg of BM IM 24 hours apart) of ACS therapy on death or neurodevelopmental disability at 5 years of age in children whose mothers participated in MACS. Neurodevelopmental disability was defined as disability in at least 1 of the following domains: neuromotor (nonambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual or hearing aids), or neurocognitive/neurobehavioral function (abnormal attention, memory, or behaviour). There was no significant difference between the groups in the primary outcome - risk of death or neurodevelopmental disability (p=0.84), and no association between type of pregnancy (single vs multiple) and the primary outcome. Preterm prelabour rupture of membranes (PPROM) at randomization was associated with an increased risk of the primary outcome (p<0.001). Among infants who were born at term (≥37 weeks' gestation), those on the multiple courses were at increased risk of the primary outcome (p=0.04). The mean weight, height, head circumference, and blood pressure for children at age 5 years in the multiple-courses group were not significantly different from those in the single-course group (level of evidence high).[20] On the following year, Asztalos et al.[21] work aimed to evaluate the association between GAs at birth in children exposed to SC versus MC of ACS therapy in utero and outcomes at 5 years of age. Gestational age at birth was strongly associated with death or survival with a disability (p<0.001). In the 2 preterm categories (<30 and 30–36 weeks gestation at birth), there was no difference in death or survival with disability between single vs. multiple ACS therapy. However, for infants born ≥37 weeks gestation, there was a statistically significant increase in the risk of death or survival with a disability in multiple ACS therapy, compared with the single ACS therapy (p=0.037) (level of evidence moderate).[21]

In 2009, Garite et al.[22] studied the option of a single rescue course of ACS on neonatal outcomes, its timing and the duration of effectiveness of this second rescue course of ACS. They stated that there was a significant reduction in the primary outcome of composite neonatal morbidity <34 weeks in the rescue steroid group versus placebo (43.9% versus 63.6%, respectively, p=0.002) and significantly decreased RDS (p=0.002), ventilator support (p=0.023), and surfactant use (p=0.004). The largest and most significant difference in composite morbidity was seen between 2 and 7 days after the first dose of the rescue course (p=0.035). There was no difference in outcome at ≥33 weeks (p=0.811). They concluded that the administration of a single rescue course of ACS before 33 weeks improves neonatal outcome without apparent increased short-term risk. (level of evidence: high).[22]

According to Guinn et al.[23] in 2001, who evaluated the efficacy of weekly administration of ACS compared with a single course, there were no significant differences between treatment groups in composite morbidity (p=0.16), neither in the following individual neonatal outcomes:

perinatal death (p=0.23); RDS (p=0.70), BPD (p=0.95), IVH (p=0.90), PVL (p=0.44), proven sepsis (p=0.60) and proven NEC (p=0.90). However, the weekly treatment with ACS was associated with a smaller prevalence of severe RDS alone, when compared to a single course (SC) (15% in MC vs. 24% in SC) (p=0.01). Additionally, this trial noted that, although not statistically significant, there was an adverse trend with MC treatment in the risk of severe IVH (7.6% in MC versus 2% in SC, p=0.06) and chorioamnionitis (24.1% in MC versus 17.8% in SC, p=0.09), conditions that may be related to the development of cerebral palsy (level of evidence: composite morbidity, individual neonatal outcomes: perinatal death, RDS, severe RDS: high; BPD, IVH, severe IVH, PVL, proven sepsis, proven NEC: moderate).[23]

About the mode of administration, Egerman et al.[24] compared the efficacies of oral and IM antenatal administration of DM in reducing neonatal RDS. No difference in the frequency of RDS was found between the oral and IM groups (p=0.53), even for the patients delivered at <34 weeks' gestation (p=0.29). Neonatal sepsis (p=0.01) and IVH (p=0.04) were significantly higher in the oral group. There were no statistical differences in the frequencies of NEC (p=0.13) or neonatal death (p=0.55) (level of evidence: very low).[24]

In 2022, using a sheep model of pregnancy, Usuda[25] tested whether a low-dose ACS regimen (total 8 mg: four IM doses of 2 mg of BM, 12 hours apart) would achieve preterm lung maturation equivalent to that of the existing WHO DM treatment regimen[26] (total 24 mg in divided doses: four doses of 6 mg DM (IM), 12 hours apart, or 2 doses of 12 mg BM (IM), 24 hours apart), but with reduced risk of adverse outcomes. Lambs from both steroid treated groups had significant and equivalent improvements in lung function relative to saline control ($p<0.05$). Maternal glucose was significantly higher in the DM group ($p<0.05$), when compared with BM, and in both ACS regimen when compared with saline ($p<0.01$); the exact same results were seen for fetal glucose. No significant differences were noted on fetal ACTH (adrenocorticotropic hormone) and cortisol when comparing DM and BM, but fetal plasma insulin-like growth factor 1 (IGF-1) was significantly reduced in the DM group (WHO-recommended dosing regimen) compared with the BM group (the low-dose regimen) ($p<0.05$). Fetal neutrophil percentage was significantly higher in the DM group when compared with both BM and saline ($p<0.01$), although no significant differences were observed on total white blood count. No significant difference between male and female lamb outcomes in any groups for any of the items evaluated. It was concluded that a low-dose treatment regimen of 8 mg BM achieves lung maturation equivalent to that of a 24 mg DM-based regimen, but with smaller perturbations to the maternofetal hypothalamic-pituitary-adrenal (HPA) axis (level of evidence: low).[25]

2. Effects of Antenatal Corticosteroids

a) Neonatal and perinatal effects

There are a few meta-analysis reporting on neonatal and perinatal outcomes. In regard to neonatal/ perinatal death, a Cochrane study by McGoldrick et al.[2] reported, in 2020, a reduction in the risk of neonatal death (RR 0.78, 95% CI 0.70 to 0.87, p<0.00001) and perinatal death (RR 0.85, 95% CI 0.77 to 0.93, p=0.0003) with the administration of ACS vs placebo. The same results were found by Amiya et al.[27] in 2016 (in the subgroup of women with chorioamnionitis: OR 0.49, 95% CI 0.34–0.73, p value not shown) and Roberge et al.[28] in 2011 (p=0.001). Bevilacqua et al.[29] reported that the risk of perinatal death was not significantly different between multiple and single courses of ACS (RR 0.86; 95% CI 0.61-1.20; p=0.37). According to Onland et al.[30], the overall meta-analysis revealed no significant differences in the combined fetal and neonatal mortality rates between the ACS arm and non-intervention arm. However, in trials with a mean GA >28 weeks, administration of CS did significantly reduce the risk for this outcome (RR 0.62, 95% CI 0.40-0.96, p<0.05); the meta-analyses of the two trials with a mean GA ≤28 weeks showed no evidence of a difference between the intervention and non-intervention arm regarding these outcomes. A clinical trial led by Gyamfi-Bannerman et al.[31], including only women in the late preterm period (34 weeks 0 days to 36 weeks 6 days), reported no relevant differences in neonatal death between treatment courses (BM vs placebo) (p=0.50). Also, no statistically significant differences were seen in the repeat CS group compared with the single CS group on fetal and neonatal mortality (RR 0.94, 95% CI 0.71-1.23, p=0.63) described in Crowther et al.[32] systematic review in 2015 (an updated version of McKinlay et al.[33] review from 2012 that included one more trial, with no significant changes in results or outcomes).

Relatively to RDS, according to McGoldrick et al.[2], there's a reduction in this risk with the administration of ACS (RR 0.71, 95% CI 0.65-0.78, p<0.00001), which was also verified on other meta-analysis by Amiya et al.[27] (in the subgroup of women with chorioamnionitis: OR 0.58, 95% CI 0.44–0.76), Peltoniemi et al.[34] (decreased RDS with repeat BM treatment: RR=0.85, 95% CI 0.77–0.93), Onland et al.[30] (RR 0.72, 95% CI 0.61-0.84, p<0.05), Roberge et al.[28] (RR 0.54, 95% CI 0.42-0.69, p<0.001) and Bevilacqua et al.[29] (decreased RDS with multiple courses of ACS: RR 0.80; 95% CI 0.71–0.89, p<0.0001). McGoldrick et al.[2] also reported on chronic lung disease, but no differences were seen when comparing treatment groups (RR 0.86, 95% CI 0.41-1.79, p=0.68).

Gyamfi-Bannerman et al.[31] clinical trial, which aimed to study the effects of administering BM in the late preterm period, showed a significantly reduced rate of neonatal respiratory complications with the administration of BM when compared with placebo (neonatal composite of treatment in the first 72 hours: RR 0.80, 95% CI 0.66-0.97, p=0.02; severe respiratory complications:

p<0.001, transient tachypnea of the newborn: p=0.002, surfactant use: p=0.03, and bronchopulmonary dysplasia: p=0.04). However, there were no significant between-group differences in the incidence of RDS or pneumonia.

A Cochrane systematic review by Crowther et al.[32] compared the effectiveness and safety of repeat doses of ACS with no repeat corticosteroid treatment, and it showed a reduced risk of RDS (RR 0.83, 95% CI 0.75-0.91, p=0) on the repeat corticosteroid arm; no significant differences on chronic lung disease were reported between treatment groups disease (RR 1.06, 95% CI 0.87-1.30, p=0.54), neither on severe lung disease (RR 0.80, 95% CI 0.56-1.14, p=0.22).

The following meta-analysis also reported on the effects of ACS on the occurrence of intraventricular haemorrhage. According to McGoldrick et al.[2], ACS probably reduce the risk of IVH (RR 0.58, 95% CI 0.45 to 0.75, p<0.0001); Amiya et al.[27] showed a reduction in IVH (OR: 0.41, 95% CI: 0.24–0.69) and severe IVH (OR: 0.40, 95% CI: 0.24–0.69) in women with chorioamnionitis; Peltoniemi et al.[34] stated that ACS treatments had no effect on the incidence of IVH, regardless of the severity of the disease (RR 0.97, 95% CI 0.77–1.23), which was also seen by Bevilacqua et al.[29] on IVH (RR 0.88; 95% CI 0.68-1.14, p=0.32) and severe IVH (RR 1,03; 95% CI 0.60-1.77, p=0.92); Onland et al.[30] only stated a significant reduction of severe IVH in favour of antenatal steroid treatment (RR 0.42, 95% CI 0.25- 0.70), defending no significant changes for all grades of IVH; for Roberge et al.[28], only severe IVH was analysed and it was also significantly reduced by the administration of ACS (RR 0.66, 95% CI 0.49-0.88, p=0.0004). The systematic review from Crowther in 2015[32] also reported on IVH, stating that no statistically significant differences were seen in infants in the repeat CS group compared with infants in the placebo group on this outcome (RR 0.94, 95% CI 0.75-1.18, p=0.61).

Bronchopulmonary dysplasia (BPD) was mentioned in 2 meta-analysis. According to Peltoniemi et al.[34], the risk of BPD was not influenced by the treatment (RR 1.01, 95% CI 0.83–1.23), neither in Bevilacqua et al.[29] analysis (RR 1.07, 95% CI 0.81-1.43, p=0.63).

The results about periventricular leukomalacia were reviewed in two meta-analysis and both reported no significant differences between treatment groups (Peltoniemi et al.[34] results: PVL, all grades: RR 0.71, 95% CI 0.43-1.18; Bevilacqua et al.[29] results: RR 0.64, 95% CI 0.36-1.15, p=0.14).

Another reported outcome was neonatal sepsis, which was addressed in two meta-analysis and one clinical trial. According to Onland et al.[30], no significant differences were noted on sepsis rates between the ACS arm and non-intervention arm (RR 0.60, 95% CI 0.28-1.29, p value not shown); the same was reported by Bevilacqua et al.[29], when comparing intervention groups (MC vs. SC of ACS) (RR 1.10; 95% CI 0.85-1.44, p=0.46). In the clinical trial led by Gyamfi-Bannerman et al.[31], the results also showed no significant between-group (BM vs. placebo) differences in the incidence of neonatal sepsis (RR 0.80, 95% CI 0.33-1.93, p=0.62).

One of the most reported outcomes across studies was birthweight. According to McGoldrick et al.[2], ACS probably have little to no effect on birthweight (mean difference (MD) -14.02g, 95% CI -33.79 to 5.76, p=0.16). However, as reported by Peltoniemi et al.[34], repeated BM had a negative influence on intrauterine growth, with significantly decreased birthweight, head circumference and length at birth (p=0.001, p=0.001, and p<0.0001, respectively). The infants exposed to weekly or biweekly repeated doses revealed a significant reduction in intrauterine growth, whereas single rescue courses of BM did not restrict it. The analysis published by Bevilacqua et al.[29] is concordant with the last, stating that the treatment with multiple courses of ACS is associated with a significant reduction in birthweight (weighted mean difference (WMD) -83.01, 95% CI -124.47 to -41.55, p<0.0001) and head circumference (WMD -0.35, 95% CI -0.52 to -0.17, p<0.0001). Gyamfi-Bannerman et al.[31] clinical trial reported no significant differences in mean birthweight between treatment courses (BM vs placebo) (p=0.32). The systematic review led by Crowther et al.[32] also showed that treatment with repeat dose(s) of CS was associated with a reduction in mean birthweight ((MD -75.79g, 95% CI -117.63 to -33.96, p=0). However, outcomes that adjusted birthweight for GA did not statistically differ between treatment groups (MD -0.11g, 95% CI -0.23-0.00, p=0.06).

As to the outcome of retinopathy of prematurity, Zeng et al.[35] analysis showed ACS exposure was not associated with ROP occurrence (uOR 0.92, 95% CI 0.80–1.07, I^2=71.4%, p=0.29); results from extremely preterm infants (GA < 28 weeks) revealed significant reduced risks of ROP occurrence in ACS-exposed infants (uOR 0.65, 95% CI 0.44–0.95, I2=74.7%, p=0.03), and the same results for extremely low birthweight infants (<1000g) (uOR 0.60, 95% CI 0.38–0.93, I2=77.8%, p=0.02). Bevilacqua et al.[29] results were similar, as the risks of ROP were not significantly different between multiple and single courses of ACS (RR 1.04, 95% CI 0.82-1.33, p=0.73).

Besides the previously reported outcomes, Bevilacqua et al.[29] also summed up and analysed studies reporting that multiple courses of ACS were associated with a significantly decreased risk of PDA (RR 0.74, 95% CI 0.57–0.95, p=0.02), the need for use of surfactant (RR 0.75, 95% CI 0.67–0.84, p<0.00001), and ventilation support (RR 0.84, 95% CI 0.77–0.91, p<0.0001); whereas for necrotizing enterocolitis and GA at delivery, the results were not significantly different between MC and SC of ACS (NEC: RR 0.58, 95% CI 0.53-1.15, p=0.20; GA at delivery: WMD -0,18, 95% CI -0.39-0.04, p=0.10).

Other than the outcomes already mentioned, the clinical trial by Gyamfi-Bannermal et al.[31], also reported that neonatal hypoglycemia was more common in the BM group than in the placebo group (p<0.001) (level of evidence: high).

Banks et al.[36] clinical trial examined outcomes for premature neonates after multiple courses of ACS compared with a single course. Neonates who received ≥3 courses of ACS had an increased risk of death (OR 2.8, 95% CI 1.3-5.9, p=0.008) as well as the combined adverse outcome

of chronic lung disease or death at 36 weeks' postmenstrual age (p=0.002) compared with neonates receiving less than 3 courses. Within each GA groups, no significant difference on RDS was seen for neonates receiving 1, 2, or ≥3 courses of ACS; number of courses of ACS also did not significantly affect the rate of surfactant administration (data not shown). Additionally, they compared the outcomes of neonates at 25 to 32 weeks' gestation delivered either 1-6 days or 7-13 days after the last dose of ACS was administered. No significant difference in mortality for neonates delivered 1-6 days after the last dose of ACS compared with those delivered within 7-13 days was reported (aOR 0.96; 95% CI 0.5-1.9, p=0.9). With respect to adrenal suppression, in neonates delivered 1-72 hours after treatment, those receiving ≥3 courses of ACS showed significantly decreased plasma cortisol levels compared with neonates receiving 1 course (p<0.001); in the latter time period, the changes were also significant and exacerbated (p<0.001). Growth was also affected, with an expected birthweight decreased by 39g in neonates of the same GA if received more than 1 course of ACS (p=0.016); expected birthweight after more than 2 courses was 80g less than that for the neonates receiving 1 course (p=0.09) (level of evidence: very low).

Apart from the results reported by Garite et al.[22] on drug choice, dose regimens and frequency of administration reported above, some other neonatal outcomes were described. Perinatal mortality and other morbidities alone like bronchopulmonary dysplasia (BPD), intrauterine growth restriction (IUGR), IVH, NEC, PVL and ROP were not significantly different between treatment groups (rescue course vs. placebo). Including all neonates in the analysis (regardless of GA at delivery) the results were similar, with a significant reduction in composite morbidity in the rescue course group (p=0.034) and improvement in respiratory morbidities. Regarding neonatal anthropomorphic measurements there was no statistically significant difference in birthweight, rates of IUGR, or head circumference. As lagging body or head growth due to repetitive CS may not be reflected in babies who deliver soon after treatment, these parameters were analysed in babies delivering after 36 weeks and >14 days after treatment. These sub-analyses demonstrated statistical similarity in mean head circumferences, mean birthweights, and rates of IUGR. In neither analysis was a trend toward reduced weight, body or head growth in rescue steroid–treated pregnancies (level of evidence: high).[22] These results are conflicting with the ones from Wapner et al.[37] study in 2007 which showed significant differences in birthweight (p=0.08) among treatment groups, although GA was not significantly different.

In 2006, the Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) Study Group[38] undertook a RCT that included 982 women (who were randomly assigned to receive a repeat IM dose of either 11.4 mg BM, or saline placebo, and the dose was repeated weekly if the mother was still considered to be at risk for preterm delivery up to 32 weeks' gestation) and produced clear evidence regarding the short-term benefit of MC of ACS. MC of ACS was associated

with significantly lower rates of RDS (33% in MC versus 41% in SC, p=0.01) and severe lung diseases (12% in MC versus 20% in SC, p=0.0003). Also, the reduction in RDS led to statistically significant reduction in the use of oxygen (p=0.03), and shorter duration of mechanical ventilation (p=0.01). Mean weight, length, and head circumference at birth and hospital discharge did not differ between treatment groups (level of evidence – high).

The Multiple Courses of Antenatal Corticosteroids for preterm birth (MACS) Collaborative Group led by Murphy[19] in 2008, aimed to find out whether MC of ACS would reduce neonatal morbidity and mortality without adversely affecting fetal growth. 1858 women at 25–32 weeks' gestation who remained undelivered 14–21 days after an initial course of ACS and continued to be at high risk of preterm birth were randomly assigned to multiple courses of ACS or placebo, every 14 days until week 33 or delivery, whichever came first. The composite primary outcome of perinatal or neonatal mortality, severe RDS, BPD, IVH (grade III or IV), PVL or NEC did not substantially differ between treatment and placebo groups (p=0.83). At birth, infants who received multiple courses of ACS weighed less than those who received placebo (p=0.0026), were shorter (p<0.001), and had a smaller head circumference (p<0.001). Neonatal respiratory and other outcomes were comparable between groups (level of evidence: high).[19] Wapner et al.[37] also reported similar neonatal outcomes when comparing repeat courses of ACS and placebo, such as IVH (p=0.64), RDS (p=0.26) and severe RDS (p=0.93).

A secondary analysis of the MACS trial[39] in 2012 intended to estimate the effect of multiple courses of ACS on neonatal size and to determine whether there was a dose–response relationship between number of courses of ACS and neonatal size. Neonates in the ACS group were born earlier as compared with those in the placebo group (p<0.001); after controlling for GA at birth, neonates in the ACS group weighed less (p=0.036), were shorter (p=0.016), and had smaller head circumferences (p<0.001). Lastly, controlling for GA at birth and other confounding factors, there was a general trend toward an incremental decrease in weight, length, and head circumference at birth for each additional course of ACS (level of evidence: head circumference: high; birthweight, length: moderate).

Another RCT by Oladapo et al.[40] in 2020 sought to assess the safety and efficacy of ACS in women in low-resource countries who are at risk for preterm birth through neonatal death and stillbirth. 2852 women (and their 3070 fetuses) underwent randomization. Neonatal death occurred in 19.6% of infants in the DM group and in 23.5% of infants in the placebo group (p=0.03). Stillbirth or neonatal death occurred in 25.7% and in 29.2% infants, respectively (p=0.04). As secondary neonatal outcomes, DM also showed a reduced incidence of: severe respiratory distress (RR 0.81, 95% CI 0.64-1.03), sepsis (RR 0.92, 95% CI 0.76-1.11) and hypoglycemia (RR 0.91, 95% CI

0.80-1.04). The trial was stopped for benefit at the second interim analysis (level of evidence: neonatal death alone, stillbirth or neonatal death: high).

A study by Jordan et al.[41] compared the pulmonary function, measured at birth and at hospital discharge, of infants whose mothers had been randomized to a single rescue course of ACS versus placebo. Rescue ACS significantly increased passive respiratory compliance (Crs) measured within 72 hours of birth, and this increase was sustained until hospital discharge. Infants in the placebo group demonstrated a decreased initial Crs compared with the rescue antenatal steroids group (p=0.043), but achieved a comparable Crs by the time of discharge (p not significant). No significant differences were observed in functional residual capacity between groups (level of evidence: low). In 2010, McEvoy et al.[42] also compared respiratory compliance and functional residual capacity in infants randomized to a rescue course of ACS vs placebo. Infants in the rescue group had an increased respiratory compliance (p=0.0433) compared with placebo and less required oxygen (p<0.05). Patients delivered at ≤34 weeks had greater pulmonary benefits. It also showed no significant difference in birthweight, or head circumference (level of evidence: respiratory compliance: high; functional residual capacity: moderate).

The effects of repeated ACS treatments on neonatal auditory brainstem response, a sensitive measure of neonatal brain maturity and auditory function, were assessed in 2010 by Church et al.[43] The majority of repeated ACS infants were exposed to ≥4 ACS treatments. Infant birthweight, length and head circumference were significantly smaller in the repeated ACS group (p<0.05). However, there were no significant group differences in the auditory brainstem response wave latencies or amplitudes (level of evidence: Very low).[43]

In a different analysis, Fonseca et al.[44] studied the effect of single and recurrent doses of ACS on fetal bone metabolism. Analysis was stratified according to the number of repeat antenatal courses of betamethasone or placebo (one to three compared with at least four courses, not including the initial course). When comparing the 251 umbilical cord serum samples, there was no difference in the serum marker for bone formation between treatment groups, but the serum marker for bone resorption was significantly lower in the BM group compared with placebo (p=0.01). There was no significant difference in serum levels of bone formation and resorption markers among those receiving one to three courses when comparing BM with placebo. Fetuses exposed to four or more repeat study courses had decreased serum levels of bone resorption compared with placebo (p=0.04).

Battin et al.[45] compared the effects of exposure to repeated courses of ACS with those of a single course on HPA axis function. In 86 infants, cortisol and ACTH levels did not differ between those exposed to single and repeated courses of ACS (p=0.53 and p=0.15, respectively) (level of evidence: low).

In 2007, Koivisto et al.[46] assessed the impact of ACS on neonatal glucose homeostasis between neonates who received a repeat dose of BM and a single course. Glucose levels were assessed 11 times in the first 3 days of life and there were no overall differences in mean glucose levels between groups. However, the long exposure time to ACS (>7 days) was associated with increased risk of hyperglycaemia ($p<0.001$). Also, one dose of ACS <24 hours before delivery, compared to full course, proved to be a risk factor for neonatal hypoglycaemia ($p=0.004$) (level of evidence: moderate). In the clinical trial by Gyamfi-Bannerman et al.[31], involving only women at high risk for delivery during the late preterm period, neonatal hypoglycemia was more common in the betamethasone group than in the placebo group (RR 1.60, 95% CI, 1.37 to 1.87, $p<0.001$).

A review on animal studies by Aghajafari et al.[47], which included 19 RCTs, had the purpose to assess the effects of repeated doses of ACS on lung and brain function and on growth restriction in animals. Eight studies assessed the effects of repeated doses of ACS on lung function and all studies reported improvement after repeated doses of ACS. Seven studies investigated the effects of repeated doses of ACS on brain/ nervous system function or growth, all showing adverse effects with repeated doses of ACS. Nine studies found evidence of fetal growth restriction with repeated doses of ACS. One study assessed long-term behavioural outcomes in mice and found no effect. Statistics on the group of these results were not obtained (level of evidence: low).

In order to compare the effects of single and repeated courses of CS on brain growth in fetal sheep, Huang et al.[48] performed a RCT which showed, in the single-injection group at preterm, no significant differences ($p=0.07$) in whole-brain weight between the corticosteroid-treated animals and controls. Cerebral length and depth were significantly reduced in the corticosteroid group ($p<0.05$); other measures were not significantly different. At term, whole-brain weight was significantly lower compared with controls ($p=0.022$). All other measures were significantly reduced ($p<0.05$) except cerebral and brain-stem weights and cerebral length. In the group that received repeated injections at preterm, whole-brain weight was significantly reduced ($p=0.005$) compared with controls. All other measures were significantly reduced ($p<0.05$) except cerebellar and brain-stem weights. At term, whole-brain weight was also significantly reduced ($p=0.001$) compared with controls as were all other measures ($p<0.05$) (level of evidence: low).

Another animal RCT[49] investigated the effect of repeated doses of CS on the maturation of the central nervous system through the myelination of the optic nerve and found a significant delay in the myelination of optic axons. No significant statistical differences were seen on the biometric measures of growth; however, brain weight and the cross-sectional area of the optic nerves area showed a strong trend ($p=0.07$) toward lower values in the corticosteroid group. Ultrastructurally, the nerves appeared less mature with a significantly lower percentage of axons having become fully myelinated in the corticosteroid group (52.4% vs. 32.7%) ($p<0.0001$) (level of evidence: very low).

b) Long-term effects

There are 4 meta-analysis[2,4,34,50] reporting on child and adult outcomes. Neurodevelopmental and/or psychological disorder was reported in 3 meta-analysis. Ninan et al.[4] (follow up at an average of 1 year of age) concluded that exposure to a single course of ACS for children with extremely preterm birth was associated with a significant reduction in risk of neurodevelopmental impairment (aOR 0.69, 95% CI 0.57-0.84, p<0.001). For children with late-preterm birth, exposure to ACS was associated with a higher risk of investigation for neurocognitive disorders (aHR 1.12, 95%CI 1.05-1.20). For children with full-term birth, exposure to ACS was associated with a higher risk of mental or behavioural disorders (adjusted hazard ratio (aHR) 1.47, 95%CI 1.36-1.60) as well as proven or suspected neurocognitive disorders (aHR 1.16, 95% CI 1.10-1.21). For McGoldrick et al.[2] (follow up at 2-12 years of age), ACS probably led to a slight reduction in developmental delay in childhood (RR 0.51, 95% CI 0.27 to 0.97, p=0.04), with no significant differences between treatment groups respecting intellectual, hearing and visual impairment. In Sotiriadis et al.[50] work (follow up at 1 year of age or later), a single course of ACS was associated with reduced risk for cerebral palsy (RR 0.678, 95% CI 0.564–0.815), psychomotor development index less than 70 (RR 0.829, 95% CI 0.737–0.933), and severe disability (RR 0.787, 95% CI 0.729–0.850). According to Peltoniemi et al.[34] (follow up at 2 years of age), the four follow-up studies did not reveal any disturbances in neurodevelopment at two years of corrected age (death or severe neurological impairment: RR 0.98, 95% CI 0.79–1.20; cerebral palsy: RR 0.99, 95% CI 0.68–1.45).

The systematic review from Crowther[32] gathered the results from four trials on child outcomes (from 18 months to two years' corrected age) that compared repeat doses of ACS with single doses. No statistically significant differences were seen for infants in the repeat CS group compared with infants in the placebo/ no treatment group for any of the primary outcomes for the child: total deaths up to early childhood follow-up (RR 1.06, 95% CI 0.80-1.41, p=0.66); survival free of any disability (RR 1.01, 95% CI 0.97-1.05, p=0.6); survival free of any major disability (RR 1.01, 95% CI 0.92-1.11, p=0.84); any disability at childhood follow-up (RR 0.98, 95% CI 0.83-1.16, p=0.8); major disability at childhood follow-up (RR 1.08, 95% CI 0.31-3.76, p=0.9); composite serious outcome at childhood follow-up (RR 0.99, 95% CI 0.87-1.12, p=0.86).

Respecting RCTs included in this systematic review, the data from the initial ACTORDS[38] was then used for subsequent studies, mostly to assess mid-childhood outcomes such as survival free of major neurosensory disability and body size, cardiometabolic disease, neurodevelopment and general health, and bone mass.

In 2007, Crowther et al.[51] reported the 2-year follow-up evaluation of the previously mentioned trial by Crowther et al. in 2006 and concluded that administration of MC of ACS reduced

neonatal morbidity without changing either survival free of major neurosensory disability (aRR 1.04, 95% CI 0.98 to 1.10; adjusted p=0.20), body size, blood pressure, use of health services, respiratory morbidity, or child behaviour scores, although children exposed to repeat doses of CS were more likely than those exposed to placebo to warrant assessment for attention problems (6.0% vs. 3.2%; aRR 1.87; 95% CI, 1.03 to 3.42; p=0.04) (level of evidence – high).

Later on, in 2016, Crowther et al.[52] aimed to evaluate if exposure to repeat dose(s) of ACS had beneficial effects on neurodevelopment and general health in mid-childhood, at 6 to 8 years' corrected age. The rate of survival free of neurosensory disability was similar in both groups (78.3% repeat betamethasone versus 77.3% placebo; RR 1.00, 95% CI, 0.94 to 1.08). Neurodevelopment - including cognitive function and behaviour, body size, blood pressure, spirometry, and health-related quality of life were similar in both groups (Level of evidence – high). Still concerning the influence of ACS in neurodevelopment, Peltoniemi et al.[53] analysed, in 2009, whether a single repeat dose of BM influences neurodevelopment and growth within 2 years. The rate of survival without severe neurodevelopment impairment was 98% in the BM group and 99% in the placebo group (OR 0.28, 95% CI 0.03-2.71). The risk of cerebral palsy, growth or re-hospitalisation rates did not differ between the groups (level of evidence: moderate).

In 2015, McKinlay et al.[54] studied whether exposure to repeat antenatal betamethasone increased risk factors for later cardiometabolic disease in children whose mothers participated in the ACTORDS[38]. In this follow-up study[54], children were assessed at 6 to 8 years' corrected age for body composition, insulin sensitivity, ambulatory blood pressure, and renal function. 258 of 320 survivors were studied (81%; 123 repeat betamethasone group; 135 placebo/single course group). Children exposed to repeat antenatal BM and those exposed to placebo had similar total fat mass (geometric mean ratio (GMR) 0.98, 95% CI 0.78-1.23), insulin sensitivity (geometric mean ratio 0.89, 95% CI 0.74-1.08), 24-hour ambulatory blood pressure (MD systolic 0 mmHg, 95% CI 22-2; diastolic 0 mmHg, 95% CI 21-1), and estimated glomerular filtration rate (MD 1.2 mL/min/1.73m2, 95% CI 23.2-5.6) (level of evidence: total fat mass, insulin sensitivity: moderate; 24-hour ambulatory blood pressure, estimated GFR: low). In 2017, McKinlay et al.[55] studied whether exposure to repeat antenatal BM alters bone mass in children (assessed by whole-body dual-energy radiograph absorptiometry at 6 to 8 years' corrected age). 185 children were studied (87%; 91 repeat BM group; 94 placebo/ single course group). Children had similar whole-body bone mineral content (geometric mean ratio 0.99; 95% CI 0.94–1.03, p=0.55) and bone area (GMR: 0.99, 95% CI: 0.92–1.07, p=0.75). The incidence of fractures was similar (p=0.65) (level of evidence – moderate).

Cartwright et al.[56] focused on the effects of repeat doses of ACS in a specific sub-group - neonates with fetal growth restriction (FGR). In 2018, a secondary analysis of the ACTORDS was undertaken to ascertain whether the use of repeat dose(s) in FGR neonates may increase the risk

of later cardiometabolic disease. 266 children were assessed at 6 to 8 years of age. FGR occurred in 34% exposed to repeat BM and 32% exposed to placebo. There was an interaction between FGR and repeat BM treatment for the effect on height: FGR: z-score mean difference 0.59, 95% CI 0.01 to 1.17; non-FGR: z-score MD −0.29, 95% CI −0.69 to 0.10; p=0.01. However, FGR did not influence the effect of repeat BM on cardiometabolic function, which was similar in treatment groups, both in FGR and non-FGR subgroups (level of evidence: glucose, insulin, insulin sensitivity: moderate; plasma creatinine, FGR, ambulatory blood pressure: low). In 2019[57], the aim was to determine the influence of FGR on the effects of repeated doses of antenatal betamethasone on neurocognitive function in mid-childhood (988 children were assessed at 6 to 8 years of age). FGR rate was 28.2% in the repeated BM treatment group and 24.6% in the placebo group (p=0.20). No evidence of an interaction effect for survival free of any disability: FGR group, 75.0% for repeated BM treatment vs 72.2% for placebo groups (OR 1.1, 95% CI 0.6-1.9); non-FGR group, 79.7% for repeated BM vs 79.0% for placebo groups (OR 1.0; 95% CI 0.7-1.5; p=0.77) and death or moderate to severe disability: FGR group, 14.6% for repeated BM treatment vs 15.9% for placebo groups (OR 0.9; 95% CI 0.4-1.9); non-FGR group, 8.6% for repeated BM vs 10.0% for placebo (OR, 0.8; 95%CI 0.4-1.3; p=0.84) (level of evidence: moderate).

Wapner et al.[37] reported long-term follow-up results of children enrolled in a randomized trial comparing single and repeat courses of ACS at follow-up examination, which also included Bayley testing to measure psychomotor and mental developmental. At 2 years of age, there was no difference in weight (p=0.19), height (p=0.26), head circumference (p=0.84), or Bayley scores (p=0.32) between infants exposed to SC versus MC of ACS. There were no significant differences between the groups in specific health outcomes like seizures (p=0.53), pneumonia (0.61), hospitalizations (p=0.3) and systolic and diastolic blood pressures (p=0.16 and p=0.32, respectively). Asthma was reported less frequently in the repeat-treatment group (p=0.05). Although not statistically significant, the rate of cerebral palsy in infants exposed to MC (p=0.12), especially more than four courses, was found to be of great concern. The authors suggested that the exposure to MC of ACS should be limited.

A 30-year follow up study was conducted by Dalziel et al.[58] in 2005 to assess whether antenatal exposure to BM for the prevention of neonatal RDS affects cardiovascular risk factors at 30 years of age. There were no significant differences between those exposed to BM and to placebo in body size (height: p=0.14; weight: p=0.13; head circumference: p=0.76), blood lipids (p=0.23), blood pressure (p=0.66), plasma cortisol (p=0.06), prevalence of diabetes or history of cardiovascular disease (results not shown). After a 75 grams oral glucose tolerance test, participants exposed to betamethasone had higher plasma insulin concentrations at 30 min (p=0.02) and lower

glucose concentrations at 120 min (p=0.05) than did those exposed to placebo (level of evidence: moderate).

c) Maternal effects

The previously mentioned meta-analysis by Williams et al.[3] published by Cochrane in 2022 suggests that although the rate of chorioamnionitis was lower with dexamethasone, no conclusive evidence of a difference between the two drugs was found (RR 0.71, 95% CI 0.48 to 1.06; moderate-certainty evidence). The proportion of women experiencing maternal adverse effects of therapy was lower with DM; however, there was not conclusive evidence of a difference between interventions (RR 0.63, 95% CI 0.35 to 1.13, p=0.12).

According to McGoldrick et al.[2], ACS probably result in little to no difference in maternal death (RR 1.19, 95% CI 0.36 to 3.89, p=0.77), chorioamnionitis (RR 0.86, 95% CI 0.69 to 1.08, p=0.19), and endometritis (RR 1.14, 95% CI 0.82 to 1.58, p=0.44).

For Bevilacqua et al.[29], the use of multiple vs. single courses of ACS was associated with a decreased risk of any maternal side effects (RR 0.79, 95% CI 0.66–0.96, p=0.02), a trend towards an increased risk of chorioamnionitis (RR, 1.20; 95% CI 0.94–1.51, p=0.14) and no significant differences on the effect on endometritis (RR 1.17, 95% CI 0.74-1.84, p=0.49).

In the clinical trial led by Gyamfi-Bannerman[31] et al., which only included women at high risk for delivery in the late preterm period, the results showed no statistically significant between-group (BM vs. placebo) differences in the incidence of chorioamnionitis (RR 0.61, 95% CI 0.35-1.07, p=0.08) or postpartum endometritis (RR 0.98, 95% CI 0.49-1.95, p=0.96); the need for caesarean delivery also seemed to be independent of the treatment course (RR 1.03, 95% CI 0.93-1.15, p=0.56).

The systematic review by Crowther[32] in 2015 showed similar results, reporting no increase in infectious morbidity of chorioamnionitis ((RR 1.16, 95% CI 0.92-1.46, p=0.22) or puerperal sepsis (RR 1.15, 95% CI 0.83-1.60, p=0.4), and the likelihood of a caesarean birth was unchanged (RR 1.05, 95% CI 0.99-1.1, p=0.09) when comparing repeat doses of CS versus a single course.

According to Hofer[18] et al., when comparing DM with BM as repeat ACS, for the women, no significant difference in the incidence of infectious morbidities between groups was found (p=0.18), neither regarding the need for induction of labour in DM vs. BM (p=0.83), postpartum haemorrhage (p=0.16), and caesarean section (p=0.47) (level of evidence – moderate).

The MACS Trial[19] from 2008 also reported on maternal outcomes, with no statistically significant difference between ACS administration and placebo: clinical chorioamnionitis (p=0.8) and maternal infection after delivery - defined as one or more of the following signs: endometritis,

pneumonia, wound infection or breakdown, pyelonephritis or maternal sepsis (p=0.26) (level of evidence – high).

The RCT led by Oladapo[40] in 2020 also evaluated the possibility of maternal infection and the incidence was 4.8% in the DM group and 6.3% in the placebo group (RR 0.76, 95% CI 0.56 to 1.03; p=0.002 for noninferiority) (level of evidence: maternal infection: moderate).

In 2007 Wapner et al.[37] also reported no significant differences in the incidence of maternal chorioamnionitis between the repeat ACS group and the placebo group (p=0.23). These results were similar to the ones found in the Clinical Trial by Gyamfi-Bannerman[31] in 2016, where no significant between-group differences were seen in the incidence of chorioamnionitis (level of evidence: high).

3. International Guidelines – summary and comparison

Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes. Therefore, international guidelines have been emerging on how to better approach preterm birth in order to improve fetal lung maturation and reduce neonatal/perinatal mortality and morbidity. The most recent guidelines included in this review are the "European guidelines on perinatal care: corticosteroids for women at risk of preterm birth"[59] published this year, 2023, and also guidelines from WHO[26], from 2022 ("WHO recommendations on antenatal corticosteroids for improving preterm birth outcomes"); the European Consensus Guidelines on the Management of RDS[60], from 2022; the Royal College of Obstetricians and Gynecologists (RCOG)[61] from 2022; the National Institute for Health and Care Excellence (NICE)[62] from 2022; the International Federation of Gynecology and Obstetrics (FIGO)[64] from 2021; the Society of Obstetricians and Gynaecologists of Canada (SOGC)[64] from 2018; and the American College of Obstetricians and Gynecologists (ACOG)[65] from 2017.

The guideline from WHO[26], published in 2022, was based in a review process that included: (i) identification of the priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations. The certainty of evidence for a given outcome was rated using the standard GRADE[11] approach based on consideration of study design limitations. This rating was also used on the European guidelines on perinatal care[59], European Consensus Guidelines[60] and by SOGC[64]. RCOG[61] rated the evidence using SIGN[12] criteria. The summary of guidelines and its level of recommendation is available on table VII. WHO[26] guideline also includes the approach to planned caesarean section, hypertensive disorders and gestational diabetes, as well as PPROM and maternal

infection, with very little variations from its previous version from 2015 – now emphasising on the administration of ACS in women with a high likelihood of preterm birth, whereas before the guidelines recommended this treatment whenever there was an increased risk of preterm birth.

The 2022 European Consensus Guidelines on the Management of RDS[60] contains guidance regarding not only the administration of ACS, but also other measures to prevent neonatal mortality and morbidity, like RDS. This is an update from a previous consensus from 2019, but with no fluctuations in relation to ACS administration recommendations. These guidelines emphasise the administration of ACS from a viable GA (in WHO's recommendation[26], the lower limit is defined at 24 weeks) up to 34 weeks' gestation, ideally more than 24 hours before birth. A repeat course can also be given if the risk of preterm birth remains, but should have an interval of 1-2 weeks from the first course, whereas WHO[26] recommendation specifies a minimum of 7 days interval between courses like stated in the European guidelines on perinatal care[59]. The WHO[26] recommendation specifies particular conditions that should be met prior to the administration of ACS, while the European Guidelines[60] are more permissive and generalist when it comes to ACS administration.

The European guidelines on perinatal care[59] complement the recent European Consensus Guideline on the Management of RDS[60] and is intended to assist practitioners in the optimal use of CS for women at risk of imminent spontaneous preterm birth, and those planned for iatrogenic preterm birth due to maternal or fetal pathology. According to these guidelines, the ACS administration should also be considered between 22^{+0} and 23^{+6} weeks when preterm birth is anticipated in the next seven days and active newborn life-support is indicated, taking into account parental wishes.

RCOG[61] guidelines are, in general, similar to the ones from WHO[26]. Still, RCOG[61] claims that ACS should be administered up to 34^{+6} weeks, like stated by SOGC[64], whereas WHO[26] recommendation is up to 34 completed weeks' gestation, as stated on the European Consensus Guidelines[60] and FIGO[63]; according to the European guidelines on perinatal care[59], ACOG[65] and NICE[62], the recommended upper limit is 33^{+6} weeks. NICE[62] goes further and suggests also considering offering ACS to women between 34 and 35^{+6} weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have PPROM. ACOG[65] is aligned with this recommendation, stating that a single course of BM is recommended for pregnant women between 34 weeks and 36^{+6} weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of ACS. European guidelines on perinatal care[59], FIGO[63] and SOGC[64] guidelines are more conservative in this matter, reporting that ACS should not be offered routinely to women in whom late preterm birth is anticipated, but a more individualized approach should be assumed. Within the respective window of administration

mentioned above, optimal benefits are found in infants delivered within 7 days of corticosteroid administration and benefits are also seen when the first dose is given within 24 hours of birth.[26,59,61]

Most guidelines recommend the administration of ACS to women with PPROM and no clinical signs of infection, but whether to administer a repeat or rescue course of CS with PPROM is controversial, and there is insufficient evidence to make a recommendation for or against.[26,60-62,64,65]

WHO[26] and ACOG[65] guidelines recommend against the use of ACS in women with chorioamnionitis.

European guidelines on perinatal care[59], WHO[26], FIGO[63] and RCOG[61] guidelines state that the ACS therapy is recommended for women with a high likelihood of preterm birth, irrespective of single or multiple pregnancy. The European guidelines on perinatal care[59] reinforces that ACS should be administered in twin pregnancies, with the same indication and doses as for singletons.

WHO[26] recommends against the administration of ACS for women undergoing planned caesarean section at 34 weeks to 36^{+6} weeks. Also, European guidelines on perinatal care[59], FIGO[63] and SOGC[64] recommend against ACS being routinely given before caesarean section at term (including at 37 and 38 weeks' gestation), whereas RCOG[61] is in favour of discussing it with the women.

The choice of drug, route of administration and the number and intervals of doses is reported on WHO guidelines[26]. Either IM DM or IM BM, total 24mg in divided doses, is recommended as the ACS of choice. RCOG[61] upholds this choice of drug, doses and route of administration and specifies: either (1) 24mg DM phosphate in two divided doses of 12mg, 24 hours apart or (2) 24mg DM in four divided doses of 6mg, 12 hours apart; an alternative is (3) 24 mg BM sodium phosphate/acetate mix in two divided doses of 12mg, 24 hours apart. European guidelines on perinatal care[59] provide the exact same regimens. FIGO guidelines[63] suggest options 1 and 3.

WHO[26] and FIGO[63] recommend only a single repeat dose of ACS for women who remain at high risk of preterm birth, with an interval of at least one week from the first course. For RCOG[61], there is currently limited evidence to recommend repeat courses of ACS; however, a further course may reduce the need for neonatal respiratory support. Bearing this in mind, RCOG[61] also affirms that the maximum number of corticosteroid courses given in any one pregnancy should not exceed three. NICE recommendations[62] are aligned with WHO[26] in this matter, and they recommend against the use of more than two courses of maternal corticosteroids for preterm birth, like ACOG[65]. SOGC[64] recommends against the routine use of repeat courses of ACS.

DISCUSSION

When considering antenatal corticosteroids in regard to the drug choice, according to the published evidence, when comparing betamethasone with dexamethasone, the risk of death, RDS, chronic lung disease and IVH is the same regardless of the drug chosen (level of evidence: low to high). [3,17] The same results are found for the incidence of neurosensory disability (level of evidence: high).[17] Discomfort at the injection site was reported less frequently in the DM group than in the BM group (level of evidence – high).[17]

The choice of the corticosteroid (DM vs. BM) did not impact on the risk of neurodevelopmental disability at follow-up, visual and hearing impairment, motor developmental delay or intellectual impairment (level of evidence: low to moderate). [3]

When choosing the drug for the repeat course of ACS, many outcomes both at birth and at two years' corrected age were similar between DM and BM (level of evidence: moderate).[18]

Concerning the mode of ACS administration it was concluded that the IM route is preferable regarding the risk of neonatal sepsis[3,15] (level of evidence: very low to moderate) and IVH[24] (level of evidence: very low), but with no significant changes on RDS[24], NEC[24] or neonatal death[24] (level of evidence: very low). Although it is notable that one of these studies was stopped early due to safety concerns relating to oral DM, the ability to draw conclusions is limited due to the studies' small sample size, concerns about risk of bias and limited number of outcomes reported.[3]

A systematic review[14] compared different routes of ACS administration - maternal versus direct fetal – but no completed RCTs that assessed the benefits and harms of direct injection of corticosteroid into the fetus compared with injection to the mother were available.

Relatively to the dose of ACS, only one trial[13] compared lower doses vs. standard doses of ACS in humans, but no major clinical outcomes of interest were reported (level of evidence – moderate). The lack of included studies with clinically relevant neonatal and maternal outcomes highlights the paucity of current available evidence in this matter. This is surprising given the benefits of lower doses of ACS found in animal studies[25] and the concerns about negative long-term effects of current dosing practices. This study[25] also showed significantly higher maternal glucose and higher fetal glucose in the higher dose regimen when compared with the reduced dose, as well as a significantly reduced fetal plasma IGF-1 in the high dose group (level of evidence: low).

Antenatal CS administration at term gestation (>37 weeks), prior to caesarean section, does not seem to reduce the risk of RDS or TTN (level of evidence: low).[16]

Multiple courses of ACS are associated with decreased growth in utero and have no neonatal benefits compared with a single course of ACS, so it should not be recommended (level of evidence – high).[19] Similar results seen in Guinn et al.[23], when comparing the efficacy of weekly

administration of ACS with a single course on most neonatal outcomes; however, the weekly treatment with ACS was associated with a smaller prevalence of severe RDS alone (level of evidence: moderate to high).[23] Nevertheless, it was demonstrated that a single rescue course of ACS (after a completed course of ACS) reduces significantly composite neonatal morbidity, RDS, ventilator support and surfactant use (level of evidence – high).[22] For patients born at term, those on the multiple courses were at increased risk of death or neurodevelopmental disability at 5 years of age (level of evidence: high).[20]

The mean weight, height, head circumference, and blood pressure for children at age 5 years in the MC group were not significantly different from those in the single-course group (Level of evidence: high).[20]

Considering neonatal and perinatal effects of ACS administration, the available evidence diverges regarding neonatal and perinatal death. Most studies showed a reduction in this outcome with the use of ACS[2,27-29,40], whereas a meta-analysis[30] only shows a reduction in this outcome for trials with a mean GA >28 weeks (level of evidence: high). In the late preterm period, no relevant differences were noted between BM vs placebo (level of evidence: high).[31] When comparing a repeat course of ACS with a single course, no differences were seen on fetal and neonatal mortality (level of evidence: high).[32] However, the number of courses of ACS seems to influence this outcome, as a RCT[36] showed an increased risk of death for neonates who received ≥3 courses of ACS (level of evidence: very low).

Studies reporting on the risk of RDS with ACS administration showed a decreased incidence of this outcome with this treatment (level of evidence: high).[2,27-30,34,38,40] No differences between groups were noted on the incidence of chronic lung disease (level of evidence: moderate)[2], except for more than 3 courses of ACS, which seemed associated with a poorer outcome (level of evidence: very low).[36] In the late preterm period, no differences between groups were seen on the risk of RDS and pneumonia, but significant changes were reported for severe respiratory complications, TTN, surfactant use and BPD, favouring the ACS treatment group (level of evidence: high)[31]. Relatively to repeat doses of ACS, it seems to decrease the incidence of RDS, with no impact on the incidence of chronic lung disease and severe lung disease, when compared with a single course of ACS (level of evidence: high).[22,32] However, two studies did not find a relevant difference between the administrations of MS and a SC of ACS in the incidence of severe RDS (level of evidence: moderate to high).[19,37] A review[47] of animal studies assessed the effects of repeated doses of ACS on lung function and all studies reported improvement after repeated doses of ACS (level of evidence: low).

Bronchopulmonary dysplasia was not influenced by treatment with ACS (level of incidence: moderate to high)[19,22,29,34], neither the incidence of PVL was affected by this treatment or repetition of ACS (level of evidence: high).[19,22,29,34]

The incidence of all grades of IVH seems to be decreased by ACS treatment, according to some studies[2,27](level of evidence: high), whereas on others, no differences were noted [19,29,34] at all (level of evidence: high), and for some[28,30], only severe IVH was decreased by ACS treatment (level of evidence: high). When comparing repeat with single ACS course, no differences were seen on the incidence of IVH (level of evidence: high).[22,32]

Incidence of neonatal sepsis did not seem to change when comparing ACS treatment with placebo and also when comparing MC vs. SC of ACS (level of evidence: high).[29-31] Although, a study reported a smaller incidence of neonatal sepsis with the administration of DM when compared to placebo (level of evidence: high).[40]

With respect to the impact on birthweight, it seems that the administration of a single course of ACS and placebo did not differ substantially (level of evidence: high).[2,31,34] However, it was shown throughout the studies that multiple courses had a negative influence on intrauterine growth, with significantly decreased birthweight, head circumference and length at birth; and there was a general trend toward an incremental decrease in weight, length, and head circumference at birth for each additional course of ACS (level of evidence: very low to high).[19,29,32,34,36,39,43] A review[47] of animal studies assessed the effects of repeated doses of ACS on growth restriction, and found evidence of a positive association with repeated doses of ACS (level of evidence: low). Interestingly, on the contrary, a RCT[38] showed that mean weight, length, and head circumference at birth and hospital discharge did not differ between MC and SC of ACS (level of evidence – high). It seems to be consensual that a single repeat course of ACS is not responsible for changes in birthweight, head circumference at birth or rates of IUGR (level of evidence: moderate to high).[22]

Neither a single course of ACS compared with placebo, or MC vs. SC were associated with ROP occurrence (level of evidence: high).[22,29,35] However, in 2 subgroups of extremely preterm (GA <28 weeks) and low birthweight infants (<1000g), there's a significantly reduced risk of ROP occurrence with ACS treatment when compared with placebo (level of evidence: high).[35]

Multiple courses of ACS seem to be associated with a significantly decreased risk of PDA[29], need for surfactant[29] use, ventilation support[29,38], shorter duration of mechanical ventilation[38] and severe lung disease[38] (level of evidence: moderate to high).[29] No differences were reported on the risk of NEC[22,29], and GA at delivery[29] when comparing MS with SC (level of evidence: high).

Neonatal hypoglycemia was more common among patients in the ACS treatment group when compared with placebo, although this study only regarded patients in the late preterm period (level of evidence: high).[31] This result was discrepant with the one found by Oladapo et al.[40], which showed, unexpectedly, a reduced incidence of hypoglycemia with ACS administration; however, this study did not provide p-values for assessing statistical significance (level of evidence: low). More different results were seen in another RCT[46], which showed no overall differences in mean

glucose levels between a repeat dose of ACS and a single course; although, one dose of ACS when administered <24 hours before delivery, compared to full course, proved to be a risk factor for neonatal hypoglycaemia (level of evidence: moderate).

In relation to the HPA axis, a study[36] showed that the administration of repeat courses of ACS (specially 3 or more) was associated with adrenal suppression and consequent significantly decreased plasma cortisol levels compared with neonates receiving 1 course (level of evidence: very low); on the contrary, another RCT[45] demonstrated that cortisol and ACTH levels did not differ between those exposed to SC and MC of ACS (level of evidence: low).

Pulmonary function, measured through passive respiratory compliance and functional residual capacity, increased with a repeat course of ACS within 72 hours of birth, but upon hospital discharge, no significant differences were seen between a repeat course of ACS and no rescue courses (level of evidence: low to high)[41,42].

When comparing MC with SC of ACS in the auditory brainstem response wave latencies or amplitudes, no significant group differences were seen (level of evidence: Very low).[43] A review[47] of animal studies assessed the effects of repeated doses of ACS on brain/ nervous system function, all showing adverse effects with repeated doses of ACS (level of evidence: low). Two animal RCTs reported on brain growth in fetal sheep and on the maturation of the central nervous system and one[48] showed that, in the preterm group, no significant differences in whole-brain weight between the CS-treated animals and controls; whereas both at term and preterm, whole-brain weight was significantly lower in the MC compared with SC of CS (level of evidence: low); the other RCT[49] found a significant delay in the myelination of optic axons on the MC group (level of evidence: very low).

Relatively to long-term effects (follow up between 1-12 years of age), the evidence shows that a single course of ACS is associated with a significant reduction in risk of neurodevelopmental impairment or delay[2,4] (level of evidence: low to moderate) and reduced risk of cerebral palsy, psychomotor development index less than 70 and severe disability[37,50] (level of evidence: moderate to high) when compared with placebo. However, a meta-analysis[34] reported that the rate of survival without severe neurodevelopmental impairment, the risk of cerebral palsy and growth or re-hospitalisation rates were similar in both groups (BM vs. placebo) (level of evidence: high). In the subgroup of late-preterm birth, exposure to ACS was associated with a higher risk of investigation for neurocognitive disorders (level of evidence: low).[4] For children with full-term birth, exposure to ACS was associated with a higher risk of mental or behavioural disorders (level of evidence: low).[4]

When comparing SC with MC of ACS on long-term effects, MC had no effect on survival free of major neurosensory disability, neurodevelopment - including cognitive function and behaviour, body size, blood pressure, respiratory morbidity, seizures and pneumonia, although children

exposed to repeat doses of CS were more likely than those exposed to placebo to warrant assessment for attention problems (level of evidence: moderate to high).[37,51-53]

When testing if exposure to MC of ACS increased risk factors for later cardiometabolic disease in children, it was shown that total fat mass, insulin sensitivity, ambulatory blood pressure, and estimated glomerular filtration rate were similar between groups (level of evidence: low to moderate).[54,58] It was also shown that repeat ACS does not alter bone mass in children (assessed by whole-body bone mineral content and bone area), and the incidence of fractures was similar between MC and SC of ACS (level of evidence: moderate).[55] In the subset of neonates with fetal growth restriction, the results were similar (level of evidence: low to moderate).[56]

Relatively to maternal effects of ACS treatment, it seems to be accepted that there are no significant differences between DM and BM in the rate of chorioamnionitis[3], in the incidence of infectious morbidities[18], neither regarding the need for induction of labour[18], postpartum haemorrhage[18], and caesarean section[18] (level of evidence: moderate). Although the proportion of women experiencing maternal adverse effects of therapy was lower with DM comparing with BM, this was not statistically significant (level of evidence: moderate).[3] Also, when comparing ACS treatment with placebo, it does not seem to influence the rates of maternal death[2], chorioamnionitis[2,19], endometritis[2,19], or a more overall outcome of maternal infection[19,40] (level of evidence: moderate to high). Regarding the comparison of maternal outcomes in SC vs MC of ACS, the use of MC seems to be associated with a decreased risk of any maternal side effects[29], a trend towards an increased risk of chorioamnionitis, although not statistically significant[29,31,32,37]; no significant differences on endometritis[29,31], puerperal sepsis[32], and the likelihood of a caesarean birth was unchanged[31,32] (level of evidence: low to high).

Considering all the included studies and international guidelines, a standardised protocol on the use of ACS was created by our group to guide clinicians on the optimal drug, dose, timing and route of administration, which is summarized below.

Recommendations

1 Women, with a GA between 24^{+0} and 33^{+6} weeks, at high risk for preterm birth in the following seven days, should be offered a course of ACS - even if it is anticipated that the full course of CS may not be completed, as a single dose is likely to improve neurodevelopmental outcome. The following should be cumulatively met: GA is accurately defined; there is no clinical evidence of maternal infection; adequate childbirth care is available; the preterm newborn can receive adequate care.

2 A total of 24mg of IM CS should be administered according to one of the 3 available options:

1. Betamethasone: 12mg, twice, 24 hours apart
2. Dexamethasone: 12mg, twice, 24 hours apart
3. Dexamethasone: 6mg, 4 doses, 12 hours apart.

3 ACS therapy is recommended for women with PPROM and no clinical signs of infection.

4 Administration of ACS before viability (<24 weeks GA) should be considered individually, in a shared decision-making process with parents, the obstetricians and neonatologists, as there is no formal indication.

5 Administration of ACS on late preterms (34 – 36^{+6} weeks) should be very restricted and considered with caution (between 34^{+0} and 34^{+6} weeks should only be offered to a few selected cases; between 35^{+0} and 36^{+6} weeks should be restricted to research).

6 Administration of ACS beyond 37^{+0} weeks is not recommended in any setting, including scheduled caesarean section.

7 ACS administration should follow the same indication and doses, irrespective of whether single or multiple birth is anticipated.

8 A single repeat course of ACS is recommended for women who have completed a single course of ACS at least 7 days prior and, on clinical assessment, have a high likelihood of giving birth preterm in the next 7 days, at less than 34^{+0} weeks gestation. More than 1 repeat course of ACS is not recommended.

CONCLUSION

In summary, either corticosteroid (dexamethasone or betamethasone) is safe to administer as ACS to promote lung maturation on preterm infants. The safest and preferable route of administration is the intramuscular and it should be administered to the mother. The standard total dose is 24mg of either ACS. This dosage has been considered standard protocol for many years, but concerns exist on the long-term effects of ACS; randomized controlled trials in humans are urgently needed to determine the lowest effective dose of ACS, as recent studies on animals have revealed encouraging results.

It seems that a course of ACS on preterm babies reduces neonatal and perinatal death, RDS, IVH and, for extremely preterm and low birthweight infants, also a decreased risk of ROP. Notwithstanding recent concerns, a single course of ACS does not seem to impact on birthweight. However, a single course of ACS was associated with neonatal hypoglycemia more often than placebo. All proven benefits of ACS seem to be less apparent after 34 weeks GA, and from this point forward, the greatest effect is a reduction in transient tachypnea of the newborn (which is generally a self-limitated condition); this benefit must be weighed against unanticipated outcomes. Despite the fact that multiple courses of ACS decrease the risk of PDA, IVH, need for surfactant, ventilation support and severe lung disease, it also tends to be associated with important adverse effects, such as an incremental decrease in weight, length, and head circumference at birth for each additional course of ACS; and adrenal suppression with decreased plasma cortisol levels. Nevertheless, a single repeat course of ACS does not seem to impact negatively on neonatal and long-term outcomes.

One of the major concerns nowadays regarding administration of ACS is the potential impact on long-term outcomes. A single course of ACS is associated with a significantly lower risk of neurodevelopmental impairment in children with extremely preterm birth (<28 weeks GA), but a higher risk of adverse neurocognitive and/or psychological outcomes in children with late preterm and fullterm birth, demanding increasing caution and ability to balance potential adverse effects when administering ACS as GA goes beyond 28 weeks. A normal cardiovascular function and psychological development at the age of 30 years was also reported, although with a trend on increasing insulin resistance, when a single course of ACS is administered up to 34 weeks GA.

Further investigation is needed to determine optimal timing and dosing in specific scenarios, such as preterm premature rupture of membranes.

It is crucial for healthcare providers to adhere to regional guidelines and consider individual patient circumstances when deciding on the administration of antenatal corticosteroids. Collaborative decision-making between healthcare professionals and parents is essential to ensure the best possible outcomes for both mother and baby.

Moreover, there is a growing interest in exploring alternative corticosteroids or adjunctive therapies that could potentially enhance the efficacy of ACS or mitigate their potential risks. These include investigating different corticosteroid preparations, studying the use of other medications in combination with corticosteroids, or identifying biomarkers that can predict individual fetal lung maturity and guide personalized treatment decisions.

APPENDIX

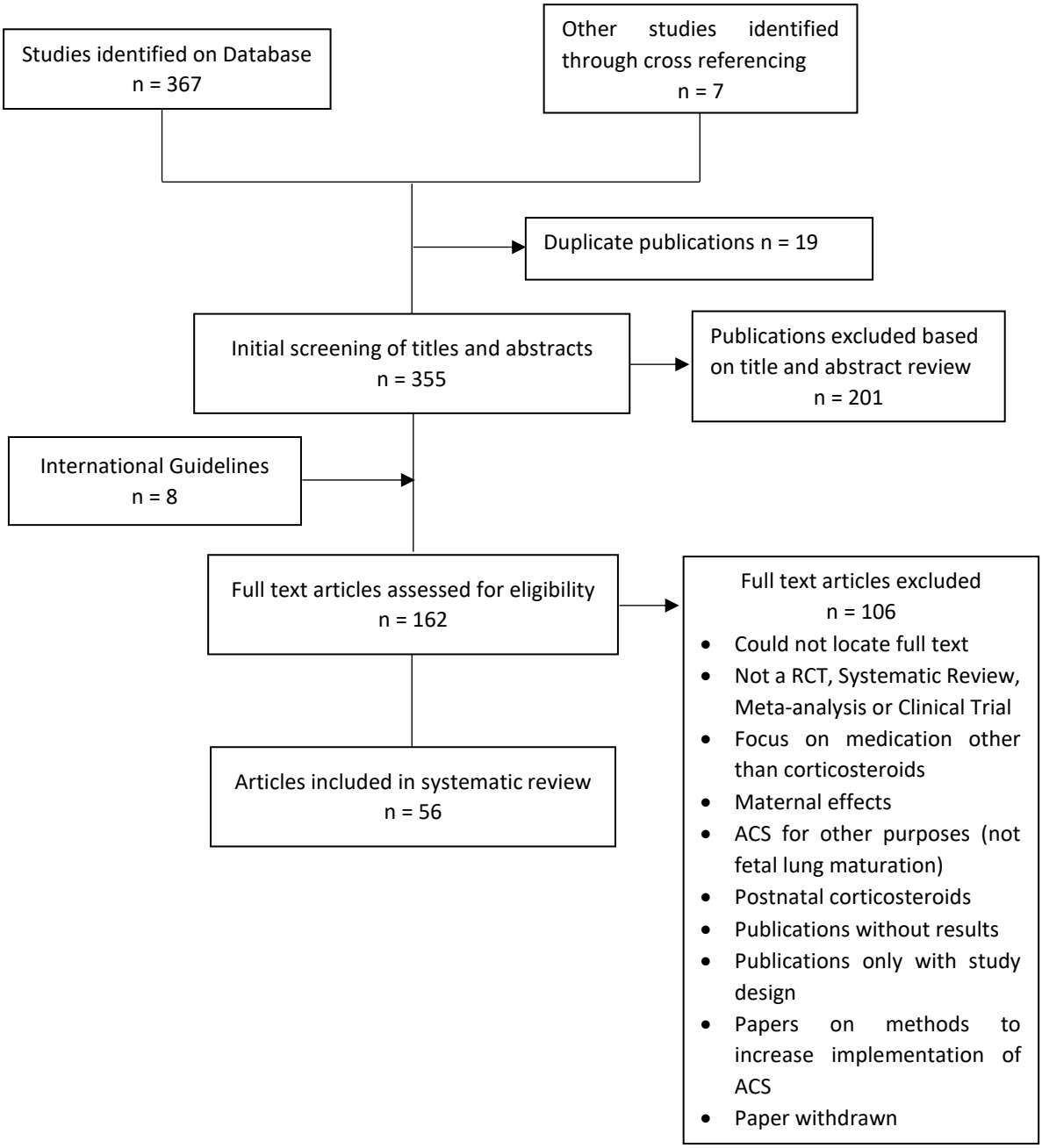

Figure 1. Flow diagram of study selection process for the systematic review on ACS for fetal lung maturation (PRISMA-P).

Table I. Results – Randomized Controlled Trials (Human)

Author (year, country)		Objectives	Primary Outcomes	Population	Results	Level of Evidence (GRADE)
Hofer[18] (2022, New Zealand)	ASTEROID Study Group	To determine the differences between the use of DM or BM as repeat ACS, in women who remain at risk of preterm birth after an initial course, on maternal, infant, and childhood health outcomes.	Death or any neurosensory disability at two years old	n=168 women + 168 infants	aOR: 0.89; adjusted treatment effect (95% CI) 0.39-2.06; adjusted p value: 0.79	Moderate
Crowther[17] (2019, New Zealand)		To assess whether administration of antenatal DM to women at risk of preterm birth reduced the risk of death or neurosensory disability in their children at age 2 years compared with BM. To assess whether DM reduced neonatal morbidity, had benefits for the mother, or affected childhood body size, blood pressure, behaviour, or general health compared with BM.	Death or neurosensory disability at the age of 2 years	n=1346 women + 1509 fetuses	aRR: 0.97; adjusted treatment effect (95% CI): 0.97 (0.83-1.13); adjusted p value: 0.66	High
Cartwright [57] (2019, New Zealand)	ACTORDS study group	To determine the influence of FGR on the effects of repeated doses of antenatal BM on neurocognitive function in mid-childhood.	Survival free of any neurosensory disability; death or moderate to severe disability	n=988	**Survival free of any neurosensory disability - FGR subgroup:** OR 1.1; 95% CI 0.6-1.9; **non-FGR subgroup:** OR 1.0; 95% CI 0.7-1.5; p=0.77; **death or moderate to severe disability - FGR subgroup:** OR 0.9; 95% CI 0.4-1.9; non-FGR subgroup: OR 0.8; 95% CI 0.4-1.3	Moderate
Cartwright [56] (2018, New Zealand)		To evaluate if exposure to repeat ACS, compared with a single dose, would have an adverse effect on growth, cardiometabolic risk factors, bone mass, and lung function at 6 to 8 years' corrected age in children with FGR but not children with normal prenatal growth.	Cardiometabolic function	n=290 woman + 352 live fetuses	No differences in glucose; insulin; insulin sensitivity; plasma creatinine; GFR; AMBP; FVC; FEV1: p>0.05 (NS)	Glucose, insulin, insulin sensitivity: moderate; plasma creatinine, GFR, AMBP: low
McKinlay[55] (2017, New Zealand)		To assess whether exposure to repeat antenatal BM alters bone mass in children whose mothers participated in the ACTORDS.	Whole-body bone mineral content; bone area	n=185	**Whole-body bone mineral content:** MD 0.99, 95% CI 0.94-1.03, p=0.55; **bone area:** MD 0.97, 95%CI 0.90-1.04, p=0.41	Moderate

Crowther[52] (2016, New Zealand)		To assess if exposure to repeat dose(s) of ACS has beneficial abstract effects on neurodevelopment and general health in mid-childhood, at 6 to 8 years' corrected age.	Survival free of neurosensory disability at 6 to 8 years	n=963	**Survival free of neurosensory disability at 6 to 8 years:** RR 1.00, 95% CI 0.94-1.08, p=0.89	High
McKinlay[54] (2015, New Zealand)		To assess whether exposure to repeat antenatal BM increased risk factors for later cardiometabolic disease in children whose mothers participated in the ACTORDS.	Body composition; insulin sensitivity; ambulatory blood pressure; renal function	n=258	**Total fat mass:** GMR 0.98, 95% CI 0.78-1.23; **insulin sensitivity:** GMR 0.89, 95% CI 0.74-1.08; **24-hour ambulatory blood pressure:** MD systolic 0 mmHg, 95% CI 22-2; diastolic 0 mmHg, 95% CI 21-1; **estimated GFR:** MD 1.2 mL/min/1.73m2, 95% CI 23.2-5.6	Total fat mass, insulin sensitivity: moderate; 24-hour ambulatory blood pressure, estimated GFR: low
Crowther[51] (2007, Australia)		To determine whether exposure to repeat doses of ACS affected the rate of survival free of major neurosensory disability; body size; general health, including respiratory health; blood pressure; or behaviour in later childhood.	Survival free of major neurosensory disability; body size at 2 years of age	n=1047	**Survival free of MND**: aRR 1.04, 95% CI 0.98-1.10, ap=0.20; **weight (kg):** aMD −0.1, 95% CI −0.3-0.2, ap=0.62; **height (cm)**: aMD −0.2, 95% CI −0.8-0.4, ap=0.45; **head circumference (cm)**: aMD 0.03, 95% CI −0.19-0.26, ap=0.78	High
Crowther[38] (2006, Australia)		To establish whether repeat ACS given to women at risk of preterm birth can reduce neonatal morbidity without harm.	Occurrence and severity of neonatal RDS; use of oxygen and mechanical ventilation	n= 982	**RDS**: aRR 0.82, 95% CI 0.71-0.95, p=0.01; **Severe lung disease**: aRR 0.60, 95% CI 0.46-0.79, p=0.0003; u**se of oxygen therapy**: aRR 0.90, 95% CI 0.81-0.99, p=0.03; **use of mechanical ventilation:** aRR 0.87, 95% CI 0.75-1.01, p=0.08	High
Asztalos[21] (2014, Canada)	MACS Collaborative Group	To evaluate the association between GA at birth in children exposed to single versus multiple courses of ACS therapy in utero and outcomes at 5 years of age.	Death or survival with a disability	n=1719	**Death or survival with a disability: Subgroup children born at term: multiple** ACS group compared to the single ACS group, 48/213 (22.5%) vs. 38/249 (15.3%); OR 1.69, 95% CI 1.04-2.77; p=0.037; **soubgroups children born preterm:** <u><30 weeks:</u> OR 0.85, 95% CI 0.35-2.11, p=0.608; <u>30-36 weeks:</u> OR 0.84, 95% CI 0.52-1.36, p=0.262	Moderate
Asztalos[20] (2013, Canada)		To determine the effects of single vs multiple courses of ACS therapy on death or neurodevelopmental disability at 5 years of age in children whose mothers participated in MACS.	Death or survival with a neurodevelop-mental disability	n=1719	**Death or neurodevelopmental disability:** 217 of 871 children (24.9%) in the multiple-courses group vs 210 of 848 children (24.8%) in the	High

					single-course group; OR 1.02, 95% CI 0.81-1.29; p=0.84	
Murphy[39] (2012, Canada)		To estimate the effect of multiple courses of ACS on neonatal size, controlling for at birth and other confounders, and to determine whether there was a dose–response relationship between number of courses of ACS and neonatal size.	Neonatal size	n=1853 woman + 2304 infants	**Birthweight**: ED 33.5g, CI 66.27-0.72, p=0.045; **length:** ED 0.339 cm, CI 0.62-0.056, p=0.019; **head circumference:** ED 0.296 cm, CI 0.45-0.13, p<0.001	Birthweight, length: moderate; head circumference: high
Oladapo[40] (2020, Geneva)		To assess the safety and efficacy of antenatal glucocorticoids in women in low-resource countries who are at risk for preterm birth.	Neonatal death alone; stillbirth or neonatal death; possible maternal bacterial infection	n=2852	**Neonatal death alone:** RR 0.84, 95% CI 0.72-0.97; p=0.03; **stillbirth or neonatal death:** RR 0.88; 95% CI 0.78-0.99; p=0.04; **possible maternal bacterial infection:** RR 0.76, 95% CI 0.56-1.03; p=0.002 for noninferiority	Neonatal death alone, stillbirth or neonatal death: high; possible maternal infection: moderate
Jordan[41] (2016, USA)		To compare the pulmonary function, measured at birth and at hospital discharge, of infants whose mothers had been randomized to a single rescue course of antenatal steroids versus those whose mothers had been randomized to placebo.	Passive respiratory compliance; functional residual capacity; passive respiratory resistance	n=85	**Mean Crs at birth:** 1.21 vs 1.01 mL/cm H2O/kg; p=0.043; **mean Crs at discharge:** 1.18 vs 1.22mL/cm H2O/kg, p not significant; **mean FRC at birth**: 24.8 vs 22.0mL/kg, p not significant; **mean FRC at discharge:** 24.9 vs 24.7mL/kg, p not significant; **mean Rrs at birth:** 0.075 vs 0.083cm H2O/mL/s, p not significant; **mean Rrs at discharge:** 0.063 vs 0.064cm H2O/mL/s, p not significant	Passive respiratory compliance, functional residual capacity, passive respiratory resistance: low
Church[43] (2010, USA)		To assess the effects of repeated ACS treatments on the neonatal auditory brainstem response, a sensitive measure of neonatal brain maturity and auditory function.	Neonatal brain maturity and auditory function	n=51	**Right ear wave I–V IPLs:** 5.29±0.44 and 5.31±0.52ms for the repeated (n=20) and single ACS (n=26) groups, p=0.89; **left ear wave I–V IPLs:** 5.43± 0.50 and 5.42±0.62ms for the repeated (n=25) and single ACS (n=26) groups, p=0.96	Very low
McEvoy[42] (2010, USA)		To compare respiratory compliance and functional residual capacity in infants randomized to a rescue course of ACS vs placebo.	Respiratory compliance; functional residual capacity	n=85	**Respiratory compliance:** 1.21 (rescue group) vs 1.01 (placebo) mL/cm H2O/kg, adjusted 95% CI 0.01-0.49, p=0.0433; **functional residual capacity:** 24.8 (rescue group) vs 22.0 (placebo) mL/kg, adjusted 95% CI -1.40-6.62, p=NS	Respiratory compliance: high; functional residual capacity: moderate

Peltoniemi[53] (2009, Finland)	To study prospectively whether a single repeat dose of BM influences neurodevelopment and growth within 2 years.	Neurodevelop-ment and growth within 2 years	n=259	**Survival without severe NDI:** 98% in the BM group and 99% in the placebo group, OR 0.28, 95% CI 0.03-2.71	Moderate
Fonseca[44] (2009, USA)	To estimate the effect of single and recurrent doses of ACS on fetal bone metabolism.	Fetal bone metabolism markers	n=285	**median PICP** (micrograms/L): 479.1 (placebo) vs. 480.2 (active), p=0.57; **median ICTP** µg/L): 57.9 (placebo) vs. 55.0 (active), p = 0.01	Moderate
Garite[22] (2009, USA)	To evaluate the option of a single rescue course of ACS on neonatal outcome.	Composite neonatal morbidity in babies delivering <34 weeks	n=437	**Composite morbidity:** ACS - 71/163 (43.9%), placebo - 105/165 (63.6%), OR 0.45, 95% CI 0.27-0.75; p=0.002	High
Murphy[19] (2008, Canada)	To find out whether multiple courses of ACS would reduce neonatal morbidity and mortality without adversely affecting fetal growth	Composite neonatal morbidity or perinatal death	n=502	Multiple courses of ACS vs placebo: similar **morbidity and mortality** (p=0.83); decreased **birthweight** (p=0.0026), **height** (p<0.001), and **head circumference** (p<0.001)	High
Wapner[37] (2007, USA)	To report long-term follow-up results of children enrolled in a randomized trial comparing single and repeat courses of ACS.	Neonatal outcomes in preterm infants	n=594	**Cerebral palsy:** RR 5.7, 95% CI 0.7-46.7, p=0.12; **asthma**: RR 0.6, 95% CI 0.3-1.0, p=0.05; **seizures**: RR 0.7, 95% CI 0.3-1.9, p=0.53;	Cerebral palsy, seizures: moderate; asthma: high
Battin[45] (2007, New Zealand)	To compare the effects of exposure to repeated courses of antenatal steroids with those of a single course HPA axis function.	Cortisol; ACTH	n=86	**Median Cortisol (ymol/L):** single course 204, repeat course 224, p=NS; **median ACTH (pmol/L):** single course 19.7, repeat course 23.0, p=NS	Low
Koivisto[46] (2007, Finland)	To determine the impact of ACS on neonatal glucose homeostasis.	Mean glucose levels	n=228	**Mean glucose levels:** OR 4.1, 95% CI 2.2–7.6	Moderate
Dalziel[58] (2005, New Zealand)	To assess whether antenatal exposure to BM for the prevention of neonatal RDS affects cardiovascular risk factors at 30 years of age	Height; weight; head circumference; systolic blood pressure; total cholesterol	n=534	**Height** (adjusted for sex): MD 0.9, 95% CI -0.1-2.3, p=0.14; **weight**: MD 2.6, 95% CI -0.7-5.9, p=0.13; **head circumference:** 0.1, 95% CI -0.3-0.5, p=0.76; **systolic blood pressure:** MD 1, 95% CI -2-3, p=0.66; **total cholesterol:** MD -0.1, 95% CI -0.3-0-1, p=0.23; **glucose concentration at 120 minutes:** adjusted MD –0·29, 95% CI –0.55-0.04, p=0.02; **insulin concentration at 120 minutes:** ratio of	Moderate

				geometric means 0.89, 95% CI 0.75-1.06, p=0.20	
Guinn[23] (2001, USA)	To evaluate the efficacy of weekly administration of ACS compared with a single course in reducing the incidence of neonatal morbidity and to evaluate potential complications of weekly treatment.	Composite neonatal morbidity	n=502	**Composite morbidity**: RR 0.80, 95% CI 0.65-0.98, p=0.16; **individual neonatal outcomes: perinatal death:** RR 0.53, 95% CI 0.18-1.55, p=0.23; **RDS:** RR 0.95, 95% CI 0.71-1.25), p=0.70; **severe RDS**: RR 0.63, 95% CI 0.44-0.91, p=0.01; **BPD**: RR 1.00, 95% CI 0.61-1.68, p=0.95; **IVH**: RR 1.03, 95% CI 0.65-1.63, p=0.90; **severe IVH:** RR 3.80, 95% CI 0.85-17.45, p=0.06; **PVL**: RR 0.60, 95% CI 0.09-3.40, p=0.44; **proven sepsis:** RR 1.20, 95% CI 0.55-2.80, p=0.60; **proven NEC**: RR 1.06, 95% CI 0.44-2.56, p=0.90	Composite morbidity, individual neonatal outcomes: perinatal death, RDS, severe RDS: high; BPD, IVH, severe IVH, PVL, proven sepsis, proven NEC: moderate
Egerman[24] (1998, USA)	To compare the efficacies of oral and IM antenatal administration of DM in reducing neonatal RDS.	RDS	n=170 woman + 188 fetuses	**RDS:** RR 1.2, 95% CI 0.7-23, p=0.53; **RDS when delivery < 34 weeks' gestation:** RR 1.24, 95% CI 0.84-1.82; p=0.29	Very low

ASTEROID: Maternal intramuscular dexamethasone versus betamethasone before preterm; DM: dexamethasone; BM: betamethasone; ACS: antenatal corticosteroids; aOR: adjusted odds ratio; CI: confidence interval; aRR: adjusted risk ratio; ACTORDS: Australasian Collaborative Trial of Repeat Doses of Steroids; FGR: fetal growth restriction; OR: odds ratio; GFR: glomerular filtration rate; AMBP: ambulatory blood pressure; FVC: forced vital capacity; FEV1: forced respiratory volume in 1 second; GMR: geometric mean ratio; MD: mean difference; MND: major neurosensory disability; aMD: adjusted mean difference; ap: adjusted p-value; RDS: respiratory distress syndrome; MACS: multiple courses of antenatal corticosteroids for preterm birth; ED: estimated difference; Crs: passive respiratory compliance; FRC: functional residual capacity ; Rrs: passive respiratory resistance; IPL: interpeak latency; NDI: neurodevelopmental impairment; PICP: carboxy-terminal propeptide of type I procollagen; ICTP: cross-linked carboxy-terminal telopeptide of type I collagen; HPA: Hypothalamic–pituitary–adrenal; ACTH: Adrenocorticotropic hormone; NS: not significant; FHR: fetal heart rate; BPD: bronchopulmonary dysplasia; IVH: : intraventricular haemorrhage; PVL: periventricular leukomalacia; NEC: necrotizing enterocolitis; IM: intramuscular.

Table II. Results - Randomized Controlled Trials (Animal)

Author (year, country)	Objectives	Primary outcomes	Population	Results	Level of Evidence (GRADE)
Usuda[25] (2022, Australia)	To test, using a sheep model of pregnancy, whether the low-dose antenatal steroid regimen proposed as part of the WHO ACTION trial would achieve preterm lung maturation equivalent to that of the existing WHO DM treatment regimen, but with reduced risk of adverse outcomes.	Lung maturation	n=59 ewes	Lambs from both steroid treated groups had significant and equivalent improvements in **lung function** relative to saline control ($p<0.05$); no significant difference in arterial blood pH, pO_2, pCO_2, lung compliance, ventilator efficiency index, or lung volume at necropsy; **fetal plasma insulin-like growth factor 1** was significantly reduced in the DM group compared with the BM group ($p<0.05$); **fetal adrenocorticotropic hormone** ($r=0.53$), **maternal glucose value** ($r=-0.52$), and **fetal glucose** values ($r=-0.42$) were correlated with maternal weight in the BM group ($p<0.05$), whereas fetal pCO_2 and pO_2 were not correlated; no significant difference between male and female lamb outcomes in any groups for any of the items evaluated	Low
Huang[48] (1999, Australia)	To compare the effects of single and repeated courses of CS on brain growth in fetal sheep.	Brain growth	n=36	**Single CS group at preterm: whole-brain weight (g)**: CS-treated animals (38.0±1.81g) vs. controls (42.5±1.65g), p=0.07; **at term: whole-brain weight (g)**: CS-treated animals (47.5±1.70g) vs. controls (53.4±1.73g), p=0.022; all other measures were significantly reduced ($p<0.05$) except cerebral and brain-stem weights and cerebral length. **Repeated CS group at preterm: whole-brain weight (g):** CS-treated animals (35.5±1.65g) vs. controls (42.5±1.65g), p=0.005; all other measures were significantly reduced ($p<0.05$) except cerebellar and brain-stem weights; **at term: whole-brain weight (g):** CS-treated animals (42.4±1.52g) vs. controls (53.4±1.73g), p=0.001, as were all other measures ($p<0.05$).	Low
Dunlop[49] (1997, Australia)	To investigate the effect of repeated doses of CS on the maturation of the central nervous system.	Myelination of the optic nerve	n=6	**Control group (mean %):** unmyelinated 36.7, fully myelinated 52.7, $p<0.0001$; **corticosteroid group (mean %):** unmyelinated 53.7, fully myelinated 32.6, $p<0.0001$	Very Low

WHO: world health organization; ACTION: antenatal corticosteroids for improving outcomes in preterm newborns; DM: dexamethasone; BM: betamethasone; CS: corticosteroids

Table III. Results - Clinical Trials

Author (year, country)	Objectives	Primary outcomes	Population	Results	Level of Evidence (GRADE)
Gyamfi-Bannerman[31] (2016, USA)	To study whether BM administered to women at risk for late preterm delivery decreases the risks of neonatal morbidities.	Neonatal composite of treatment in the first 72 hours; stillbirth; neonatal death within 72 hours after delivery	n=2827	**Composite PO: BM group vs placebo group**: 11.6% vs. 14.4%, RR 0.80, 95% CI 0.66–0.97; p=0.02; **CPAP or high-flow nasal cannula for ≥2 continuous hours:** RR 0.77, 95% CI 0.63–0.95, p=0.01; **fraction of inspired oxygen of ≥0.30 for ≥4 continuous hours:** RR 0.77, 95% CI 0.53–1.12, p=0.17; **mechanical ventilation:** RR 0.78, 95% CI 0.50–1.21, p=0.26; **ECMO + Stillbirth or neonatal death ≤72 hours after birth:** 0 patients	High
Banks[36] (1999, USA)	To examine outcome for premature neonates after multiple courses of ACS compared with a single course.	Growth; RDS; IVH; adverse outcome at 36 weeks' postmenstrual age (chronic lung disease or mortality); adrenal suppression	n=710	**Growth:** expected birthweight was decreased by 39g in neonates of the same GA if received >1 course of ACS: p=0.016; expected birthweight after ≥2 courses was 80g less than that for the neonates receiving 1 course: p=0.09; **RDS:** Within each GA group - no significant difference for neonates receiving 1, 2, or ≥3 courses of ACS. **Adverse outcome:** neonates who received ≥3 courses of ACS had an increased risk of death (OR 2.8, 95% CI 1.3-5.9; p=0.008); combined adverse outcome of chronic lung disease or death at 36 weeks' postmenstrual age (OR 2.0, 95% CI 1.3-3.2, p=0.002) compared with neonates receiving <3 courses. **Adrenal suppression: neonates delivered 1-72 hours after treatment:** plasma cortisol levels at age 2 hours for those receiving ≥3 courses of ACS (3.2 µg/dL) compared with neonates receiving 1 course (8.9 µg/dL, p<0.001); **latter time period:** mean plasma cortisol level 5.8 µg/dL in the group receiving ≥3 courses versus 20.1 µg/dL in the group receiving 1 course (p<0.001).	Very low

BM: betamethasone; CPAP: continuous positive airway pressure; RR: risk ratio; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; ACS: antenatal corticosteroids; RDS: respiratory distress syndrome; IVH: intraventricular haemorrhage; GA: gestational age; OR: odds ratio.

Table IV. Results - Meta-analysis

Author (year, country)	Objectives	Primary Outcomes	Population	Results	Level of Evidence (GRADE)
Zeng[35] (2022, China)	Assess the association between ACS exposure and the development of ROP in at-risk preterm infants.	ROP occurrence; ROP severity	n=196264 infants; 63 studies (40 RCTs, 23 cohorts)	**Any stage ROP development:** uOR 0.92, 95% CI 0.80–1.07, I^2=71.4%, p=0.29; extremely preterm infants (GA < 28 weeks): uOR 0.65, 95% CI 0.44–0.95, I2=74.7%, p=0.03; extremely low birthweight infants (<1,000g): uOR 0.60, 95% CI 0.38–0.93, I2=77.8%, p=0.02); **Severe ROP:** uOR 0.86, 95% CI 0.68–1.08, I^2=80.3%, p=0.19	High
Ninan[4] (2022, Canada)	Long-term outcomes associated with preterm exposure to ACS compared with no exposure in all children as well as children with preterm and full-term birth.	Author-defined composite of any adverse neurodevelopmental and/or psychological disorder	n>1.25 million children; 30 studies	**Extremely preterm birth group**: risk of NDI (aOR 0.69, 95% CI 0.57-0.84); **late-preterm birth group:** risk of investigation for neurocognitive disorders (aHR 1.12, 95% CI 1.05-1.20); **children with full-term birth group:** risk of mental or behavioural disorders (aHR 1.47, 95% CI 1.36-1.60); proven or suspected neurocognitive disorders (aHR 1.16, 95% CI 1.10-1.21).	Extremely preterm birth: risk of NDI: low; late-preterm birth: risk of investigation for neurocognitive disorders: low; full-term birth: risk of mental or behavioural disorders, proven or suspected neurocognitive disorders: low
Williams[3] (2022, United Kingdom)	To assess the effects on fetal and neonatal morbidity and mortality, on maternal morbidity and mortality, and on the child and adult in later life, of administering different types of CS (DM or BM), or different corticosteroid dose regimens, including timing, frequency and mode of administration.	**Maternal**: death; chorioamnionitis; puerperal sepsis. **Fetus/neonate:** any known death; RDS; IVH. **Child and child as an adult:** death; neurodevelopmental disability at follow-up	n=2494 women + 2762 infants; 11 trials	**Maternal outcomes:** chorioamnionitis: RR 0.71, 95% CI 0.48-1.06, p=0.09; adverse effects: RR 0.63, 95% CI 0.35-1.13, p=0.12; **Infant outcomes:** any known death RR 1.03, 95% CI 0.66-1.63, p=0.88; risk of RDS: RR 1.06, 95% CI 0.91-1.22, p=0.46; risk of IVH: RR 0.71, 95% CI 0.28-1.81, p=0.48; chronic lung disease: RR 0.92, 95% CI 0.64-1.34, p=0.67; NEC: RR 5.08, 95% CI 0.25-105.15, p=0.29; **Longer-term child outcomes:** neurodevelopmental disability at follow-up: RR 1.02, 95% CI 0.85-1.22, p=0.82; visual impairment: RR 0.33, 95% CI 0.01-8.15, p=0.50; hearing impairment: RR 1.16, 95% CI 0.63-2.16, p=0.63); motor developmental delay: RR 0.89, 95% CI 0.66-1.20, p=0.45; intellectual impairment: RR 0.97, 95% CI 0.79-1.20, p=0.78; cerebral palsy: RR 2.50, 95% CI 0.97- 6.39, p=0.06	Maternal outcomes: moderate Infant outcomes: any known death, chronic lung disease: moderate; risk of RDS: high; risk of IVH, NEC: low Longer-term child outcomes: neurodevelopmental disability at follow-up, motor developmental delay, intellectual impairment, hearing impairment: moderate; visual impairment, cerebral palsy: low

McGoldrick[2] (2020, United Kingdom)	To assess the effects of administering a course of CS to women prior to anticipated preterm birth (before 37 weeks of pregnancy) on fetal and neonatal morbidity and mortality, maternal mortality and morbidity, and on the child in later life.	Perinatal death; neonatal death; RDS; IVH; birthweight; developmental delay in childhood; maternal death	n=11272 women + 11925 neonates; 27 studies	**Neonatal/child outcomes:** perinatal death: RR 0.85, 95% CI 0.77-0.93, p=0.0003; neonatal death: RR 0.78, 95% CI 0.70-0.87, p<0.00001; RDS: RR 0.71, 95% CI 0.65-0.78, p<0.00001; chronic lung disease: RR 0.86, 95% CI 0.41-1.79, p=0.68; IVH: RR 0.58, 95% CI 0.45-0.75, p<0.0001; birthweight: MD -14.02g, 95% CI -33.79-5.76, p=0.16; developmental delay in childhood: RR 0.51, 95% CI 0.27-0.97, p=0.04; **Maternal outcomes:** maternal death: RR 1.19, 95% CI 0.36-3.89, p=0.77; chorioamnionitis: RR 0.86, 95% CI 0.69-1.08, p=0.19; endometritis: RR 1.14, 95% CI 0.82-1.58, p=0.44	Neonatal/child outcomes: perinatal death, neonatal death, RDS, birthweight: high; IVH, chronic lung disease, developmental delay in childhood: moderate Maternal outcomes: maternal death, chorioamnionitis, endometritis: moderate
Amiya[27] (2016, Japan)	To assess the effects on maternal and child outcomes of ACS administration in four important populations of pregnant women at risk of imminent preterm birth. All studies were conducted in high-income countries.	Women with chorioamnionitis: neonatal mortality; RDS; IVH; severe IVH; PVL	n=1424 mother/ newborn dyads; 8 meta-analysis	No eligible studies were identified for ACS use in diabetic pregnant women or those undergoing elective CS at late preterm. Effects of ACS use were inconclusive for cases with fetal growth restriction. **ACS administration in women with chorioamnionitis: neonatal mortality:** OR 0.49, 95% CI 0.34–0.73; **RDS:** OR 0.58, 95% CI 0.44–0.76; **IVH:** OR 0.41, 95% CI 0.24–0.69; **severe IVH:** OR 0.40, 95% CI 0.20–0.79; **PVL:** OR 0.74, 95% CI 0.26-2.09	Neonatal mortality, RDS, IVH: high; PVL: moderate
Sotiriadis[50] (2015, Greece)	To systematically review and integrate data on the neurodevelopmental outcome of children after administration of a single course of ACS for threatened preterm labour.	Severe disability; minor disability; cerebral palsy; mental development index <70; psychomotor development index <70	n=14 studies	**Cerebral palsy**: RR 0.678, 95% CI 0.564–0.815, I^2=0%; **mental development index <70:** RR 0.84, 95% CI 0.692-1.02, I^2=10%; **psychomotor development index <70:** RR 0.829, 95% CI 0.737–0.933, I^2=0%; **severe disability:** RR 0.787, 95% CI 0.729–0.85, I^2=0%; **intact survival:** RR 1.186, 95% CI 1.056–1.332, I^2=39%	High

Peltoniemi[34] (2011, Finland)	To systematically review the efficacy and safety of repeated antenatal corticosteroid on neonatal morbidity, growth and later development.	RDS; neurodevelopment; intrauterine growth	n=8 RCTs	**RDS:** RR 0.85, 95% CI 0.77–0.93; **severe RDS:** RR 0.87, 95% CI 0.75–1.0; **composite morbidity:** RR 0.95, 95% CI 0.85-1.07; **IVH, all grades:** RR 0.97, 95% CI 0.77–1.23; **BPD:** RR 1.01, 95% CI 0.83–1.23; **PVL, all grades**: RR 0.71, 95% CI 0.43-1.18; **follow up at two years of age: death or severe neurological impairment:** RR 0.98, 95% CI 0.79–1.20; **Cerebral palsy:** RR 0.99, 95% CI 0.68–1.45; **rehospitalization**: RR 1.02, 95% CI 0.94–1.11	High
Onland[30] (2011, Netherlands)	To determine the effects of ACS given to women at risk of preterm birth <26 weeks' gestation.	Fetal and neonatal mortality; RDS; neurodevelopment; short-term neonatal outcomes	n=1118 newborn patients; 9 RCTs	**Fetal and neonatal mortality:** RR 0.73, 95% CI 0.52-1.02; **RDS:** RR 0.72, 95% CI 0.61-0.84, p<0.05; **Short-term neonatal outcome: sepsis:** RR 0.60, 95% CI 0.28-1.29; **IVH all grades:** RR 0.74, 95% CI 0.51-1.07; **BPD at 28 days postnatal age**: RR 1.22, 95% CI 0.85-1.74	High
Roberge[28] (2011, Canada)	To review the available evidence regarding the effect of fetal sex in the prevention of RDS using ACS.	RDS	n=2077 (1109 male and 968 female infants)	**Total RDS:** RR 0.54, 95% CI 0.42-0.69, p<0.001; **RDS male:** RR 0.50, 95% CI 0.33-0.77, p=0.01; **RDS female:** RR 0.57, 95% CI 0.43-0.75, p<0.001), p between sexes = 0.99; **total IVH grade III-IV:** RR 0.66, 95% CI 0.49-0.88, p=0.0004; **IVH grade III-IV male:** 0.61, 95% CI 0.38-0.97; **IVH grade III-IV female:** 0.49, 95% CI 0.22-1.08; **total neonatal mortality:** RR 0.51, 95% CI 0.34-0.77, p=0.001; **neonatal mortality male:** RR 0.59, 95% CI 0.35-0.99; **neonatal mortality female**: RR 0.41, 95% CI 0.21-0.79	High

Bevilacqua[29] (2010, Italy)	To determine the risks and benefits of multiple courses of ACS compared with single courses.	**Infant outcomes:** RDS; severe RDS; BPD; IVH; severe IVH; PVL; PDA; neonatal sepsis; NEC; ROP; perinatal death; use of surfactant; ventilation support; composite neonatal morbidity; birthweight; head circumference; gestational age at delivery **Maternal outcomes:** any maternal side effect; chorioamnionitis; endometritis	n=4390 women; 5227 infants; 11 RCTs	**Multiple courses of ACS:** decreased risk of **RDS** (RR 0.80, 95% CI 0.71–0.89, p<0.0001), **PDA** (RR 0.74, 95% CI 0.57–0.95, p=0.02), **use of surfactant** (RR 0.75, 95% CI 0.67–0.84, p<0.00001), **ventilator support** (RR 0.84, 95% CI 0.77–0.91, p<0.0001), and **any maternal side effects** (RR 0.79, 95% CI 0.66–0.96, p=0.02); trend toward a decreased risk of **composite neonatal morbidity** (RR 0.88; 95% CI 0.77–1.01); significant reduction in **birthweight** (WMD -83.01, 95% CI -124.47 to -41.55, p<0.0001), **birth head circumference** (WMD -0.35, 95% CI -0.52 to -0.17, p<0.0001); a trend towards an increased risk of **chorioamnionitis** (RR, 1.20; 95% CI 0.94–1.51, p=0.14); the risks of **severe RDS** (RR 0.87, 95% CI 0.70-1.09, p=0.23), **BPD** (RR 1.07, 95% CI 0.81-1.43, p=0.63), **IVH** (RR 0.88, 95% CI 0.68-1.14, p=0.32), **severe IVH** (RR 1.03, 95% CI 0.60-1.77, p=0.92), **PVL** (RR 0.64, 95% CI 0.36-1.15, p=0.14), **neonatal sepsis** (RR 1.10, 95% CI 0.85-1.44, p=0.46), **NEC** (RR 0.58, 95% CI 0.53-1.15, p=0.20), **ROP** (RR 1.04, 95% CI 0.82-1.33, p=0.73), **perinatal death** (RR 0.86, 95% CI 0.61-1.20, p=0.37), **composite neonatal morbidity** stratified by GA at delivery (RR 0.91, 95% CI 0.78-1.06, p=0.23), **endometritis** (RR 1.17, 95% CI 0.74-1.84, p=0.49), **GA at delivery** (WMD -0,18, 95% CI -0.39-0.04, p=0.10) were not significantly different between multiple and single courses of ACS	Infant outcomes: RDS, severe RDS, IVH, PVL, PDA, neonatal sepsis, NEC, ROP, perinatal death, use of surfactant, GA at delivery: high; BPD, composite morbidity stratified by GA at delivery, birthweight, head circumference, ventilation support: moderate; severe IVH: low Maternal outcomes: chorioamnionitis: high; any maternal side effects: moderate; endometritis: low

ACS: antenatal corticosteroids; ROP: Retinopathy of prematurity; RCT: randomized controlled trial; CI: confidence interval; I^2: measure of heterogeneity; GA: gestational age; NDI: neurodevelopmental impairment; aHR: adjusted hazard ratio; DM: dexamethasone; BM: betamethasone; RDS: respiratory distress syndrome; IVH: intraventricular haemorrhage; CS: corticosteroids; RR: risk ratio; MD: mean difference; PVL: periventricular leukomalacia; CS: corticosteroid; BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; NEC: Necrotizing enterocolitis; ROP: retinopathy of prematurity; WMD: weighted mean difference.

Table V. Results - Systematic Review (Human)

Author (year, country)	Objectives	Primary Outcomes	Population	Results	Level of Evidence (GRADE)
Sotiriadis[16] (2021, Greece)	To assess the effect of prophylactic corticosteroid administration before elective caesarean section at term, as compared to usual care (which could be placebo or no treatment), on fetal, neonatal and maternal morbidity. To assess the impact of the treatment on the child in later life.	RDS, TTN, admission to neonatal special care for respiratory morbidity; need for mechanical ventilation	n=942 women + 942 neonates	**RDS**: RR 0.34, 95% CI 0.07-1.65, p=0.18; **TTN**: RR 0.52, 95% CI 0.25-1.11, p=0.09; **admission to neonatal special care:** RR 0.45, 95% CI 0.22-0.90, p=0.03; **need for mechanical ventilation:** RR 4.07, 95% CI 0.46-36.27	RDS, TTN: low; need for mechanical ventilation: very low; admission to neonatal special care for respiratory morbidity: moderate
Ninan[13] (2021, Canada)	To systematically review randomized and quasi-randomized trials on the neonatal and maternal effects of lower doses of ACS (<24 mg of BM or DM) compared with standard double doses of ACS (24 mg of BM or DM) administered to women at risk of preterm delivery.	Perinatal death; severe RDS	n=2 trials	**FHR:** DM group: mean 3.7, SD 8.8; BM group: mean−1.4, SD 8.8, p=0.01	Moderate
Utama[14] (2018, Australia)	To assess if different routes of corticosteroid administration (maternal versus direct fetal) have effects on health outcomes for women and their babies.	**Maternal:** maternal sepsis; **infant**: death; RDS; **child**: Survival free of any disability; Neurodevelopmental impairment	n=0	---	---
Crowther[32] (2015, New Zealand)	To assess the effectiveness and safety of repeat dose(s) of ACS.	**For the infant:** RDS; severe lung disease; composite serious outcome; birthweight; fetal, neonatal or later death; chronic lung disease; IVH **For the child:** total deaths; survival free of any disability; survival free of major disability; disability at childhood follow-up; composite serious outcome	n=4895 women + 5975 babies; 11 trials	**For the infant:** RDS (RR 0.83, 95% CI 0.75-0.91, p=0); composite for serious infant outcome (RR 0.84, 95% CI 0.75-0.94); birthweight (MD -75.79 g, 95% CI -117.63 to -33.96, p=0); severe lung disease (RR 0.80, 95% CI 0.56-1.14, I^2= 76%, p=0.22); fetal and neonatal mortality (RR 0.94, 95% CI 0.71-1.23, p=0.63); chronic lung disease (RR 1.06, 95% CI 0.87-1.30, p=0.54); IVH (RR 0.94, 95% CI 0.75-1.18, p=0.61); **for the child:** total deaths up to early childhood	High

		For the child as an adult: total deaths; survival free of any disability; survival free of major disability; disability at adult follow-up; major sensorineural disability; composite serious outcome **For the women:** chorioamnionitis; puerperal sepsis		follow-up (RR 1.06, 95% CI 0.80-1.41, p=0.66); survival free of any disability (RR 1.01, 95% CI 0.97-1.05, p=0.6); survival free of any major disability (RR 1.01, 95% CI 0.92-1.11, I^2= 88%, p=0.84); any disability at childhood follow-up (RR 0.98, 95% CI 0.83-1.16, p=0.8); major disability at childhood follow-up (RR 1.08, 95% CI 0.31-3.76, p=0.9); composite serious outcome at childhood follow-up (RR 0.99, 95% CI 0.87-1.12, p=0.86); **for the child as an adult:** no data available for inclusion; **for the women:** chorioamnionitis (RR 1.16, 95% CI 0.92-1.46, p=0.22); puerperal sepsis (RR 1.15, 95% CI 0.83-1.60, p=0.4)	
Brownfoot[15] (2013, Australia)	To assess the effects of different corticosteroid regimens for women at risk of preterm birth.	**Maternal**: death; chorioamnionitis; puerperal sepsis; **fetus/neonate**: death (fetal or neonatal); RDS; IVH; **child and child as adult:** death; neurodevelopmental disability at follow-up	n= 1557 women + 1661 infants; 12 trials	**For the infant:** neonatal death: RR 1.41, 95% CI 0.54-3.67, p=0.49; RDS: RR 1.06, 95% CI 0.88-1.27, p=0.55; IVH: RR 0.44, 95% CI 0.21-0.92, p=0.029; neonatal sepsis (RR 8.48, 95% CI 1.11-64.93, p=0.039) **for the child:** neurosensory disability: RR 1.67, 95% CI 0.08-33.75, p=0.74; **For the child as adult:** not included in trials	RDS: high; Neonatal death, neurosensory disability: moderate
McKinlay[33] (2012, New Zealand)	To determine the effectiveness and safety of 1 or more repeat doses of ACS, given to women at risk of preterm birth 7 or more days after an initial course of glucocorticoids, with the primary aim of reducing fetal, neonatal, and childhood morbidity and mortality.	Total deaths; survival free of any neurosensory disability; survival free of major neurosensory disability; composite serious outcome	n> 4730 women + 5700 infants; 12 trials	**Perinatal outcomes:** perinatal death: RR 0.94, 95% CI 0.71-1.23; RDS: RR 0.83, 95% CI 0.75-0.91; chronic lung disease: RR 1.06, 95% CI 0.87-1.30; IVH: 0.94, 95% CI 0.75-1.18; birthweight: MD -76g, 95% CI -118 to -34; composite serious infant outcome: RR 0.84, 95% CI 0.75-0.94; e**arly childhood outcomes:** total deaths: RR 1.06, 95% CI 0.80-1.41; survival free of any neurosensory	Survival free of major neurosensory disability: moderate; Total deaths, survival free of any neurosensory disability, composite serious outcome: high

				disability: RR 1.01, 95% CI 0.97-1.05; survival free of major neurosensory disability: RR 1.03, 95% CI 0.98-1.07, I^2=88%. composite serious outcome: RR 0.99, 95% CI 0.87-1.12; **maternal outcomes:** chorioamnionitis: RR 1.16, 95% CI 0.92-1.46; puerperal sepsis: RR 1.15, 95% CI 0.83-1.60	

RDS: respiratory distress syndrome; TTN: transient tachypnoea of the neonate; RR: risk ratio; CI: confidence interval; ACS: antenatal corticosteroids; BM: betamethasone; DM: dexamethasone; FHR: fetal heart rate; SD: standard deviation; IVH: intraventricular haemorrhage; MD: mean difference; I^2: measure of heterogeneity.

Table VI. Results - Systematic Review (Animal)

Author (year, country)	Objectives	Primary Outcome	Population	Results	Level of Evidence (GRADE)
Aghajafari[47] (2002, Canada)	To assess the effects of repeated doses of ACS on lung and brain function and on growth restriction in animals.	Lung function; fetal nervous system function; growth	n=19 studies	**Lung function:** 7/8 studies showed increased lung function/surfactant/antioxidant enzymes/breathing score and alveolar development with BM or DM; 1 showed no effect; **fetal nervous system function:** 6/7 studies showed delay in optic nerve myelination/ myelination in brain/ sciatic nerve growth/retinal maturation or decreased fetal brain growth/ neurons, degeneration with BM or DM; 1 showed no effect; **fetal growth**: 8/11 studies showed decreased birthweight/ organ weight/ lung weight/ body length / head width with BM or DM; 3 studies showed no effect	Low

ACS: antenatal corticosteroids; BM: betamethasone; DM: dexamethasone.

Table VII. International guidelines on antenatal corticosteroids. RCOG[61] rated the evidence using SIGN criteria[12]; European guidelines on perinatal care[59], WHO[26], European Consensus Guidelines[60] and SOGC[64] used GRADE[11] to rate the evidence.

	Guidelines	Level of evidence	
		Quality of evidence	Category/ Strenght of recommendati-on
European guidelines on perinatal care: corticosteroids for women at risk of preterm birth[59] 2023	**1.** Corticosteroids should be administered to women at a GA between 24^{+0} and 33^{+6} weeks, when preterm birth is anticipated in the next seven days. In selected cases, extension of this period up to 34^{+6} weeks may be considered.	Strong	Strong
	2. Optimal benefits are found in infants delivered within 7 days of CS administration. Even a single-dose administration should be given to women with imminent preterm birth, as this is likely to improve neurodevelopmental outcome.	Moderate	Conditional
	3. Either BM (12mg IM twice, 24-hours apart) or DM (6mg IM in four doses, 12-hours apart, or 12mg IM twice, 24-hours apart), may be used.	Moderate	Strong
	4. Administration between 22^{+0} and 23^{+6} weeks should be considered when preterm birth is anticipated in the next seven days and active newborn life-support is indicated, taking into account parental wishes.	Low/moderate	Weak
	5. Administration between 34^{+0} and 34^{+6} weeks should only be offered to a few selected cases. Administration between 35^{+0} and 36^{+6} weeks should be restricted to prospective randomized trials.	Moderate	Conditional
	6. Administration in pregnancies beyond 37+0 weeks is not indicated, even for scheduled caesarean delivery.	Low	Conditional
	7. Administration should be given in twin pregnancies, with the same indication and doses as for singletons. However, existing evidence suggests that it should be reserved for pregnancies at high-risk of delivering within a 7-day interval.	Low	Conditional
	8. Maternal diabetes mellitus is not a contraindication to the use of ACS.	Moderate	Strong
	9. A single repeat course of CS can be considered in pregnancies at less than 34^{+0} weeks gestation, if the previous course was completed more than seven days earlier, and there is a renewed risk of imminent delivery.	Low	Conditional

World Health Organization (WHO)[26] 2022	**1.** ACS therapy is recommended for women with a high likelihood of preterm birth from 24 weeks to 34 weeks of gestation when the following conditions are met: • Gestational age assessment can be accurately undertaken; • There is a high likelihood of preterm birth within 7 days of starting therapy; • There is no clinical evidence of maternal infection; • Adequate childbirth care is available (including the capacity to recognize and safely manage preterm labour and birth); • The preterm newborn can receive adequate care (including resuscitation, kangaroo mother care, thermal care, feeding support, infection treatment and respiratory support.	Moderate/ low *	Context-specific
	2. ACS therapy should be administered to women with a high likelihood of giving birth preterm in the next 7 days, even if it is anticipated that the full course of CS may not be completed.	Low	Context-specific
	3. ACS therapy is recommended for women with a high likelihood of preterm birth, irrespective of whether single or multiple birth is anticipated.	Low	Context-specific
	4. ACS therapy is recommended for women with PPROM and no clinical signs of infection.	Moderate/ low*	Context-specific
	5. ACS therapy is not recommended in women with chorioamnionitis who are likely to give birth preterm.	Very low	Not recommended
	6. ACS therapy is not recommended for women undergoing planned caesarean section at 34 weeks 0 days to 36 weeks 6 days.	Very low	Not recommended
	7. ACS therapy is recommended in women with hypertensive disorders in pregnancy who have a high likelihood of preterm birth.	Moderate/ low*	Context-specific
	8. ACS therapy is recommended for women with a high likelihood of preterm birth of a growth restricted fetus.	Very low	Context-specific
	9. ACS therapy is recommended for women with pre-gestational and gestational diabetes when there is a high likelihood of preterm birth, and this should be accompanied by interventions to optimize maternal blood glucose control.	Very low	Context-specific
	10. Either IM DM or IM BM (total 24 mg in divided doses) is recommended as the ACS of choice.	Low	Recommended
	11. A single repeat course of ACS is recommended for women who have received a single course of ACS at least 7 days prior and, on clinical assessment, have a high likelihood of giving birth preterm in the next 7 days.	Moderate/ low* * for newborn/ maternal outcomes, respectively	Recommended

European Consensus Guidelines on the Management of RDS[60] 2022	**1.** Clinicians should offer a single course of ACS to all women at high risk of preterm delivery, from when pregnancy is considered potentially viable up to 34 completed weeks of gestation, ideally at least 24 hours before birth. **2.** A single repeat course of steroids may be given in threatened preterm birth before 32 weeks of gestation if the first course was administered at least 1–2 weeks earlier.	High High	Strong Weak
Royal College of Obstetricians and Gynecologoists (RCOG)[61] 2022	**Benefits of ACS** **1.** A course of ACS given within the seven days prior to preterm birth reduces perinatal and neonatal death and RDS. **2.** For women undergoing planned caesarean birth between 37^{+0} and 38^{+6} weeks an informed discussion should take place with the woman about the potential risks and benefits of a course of ACS. Although ACS may reduce admission to the neonatal unit for respiratory morbidity, it is uncertain if there is any reduction in RDS, transient tachypnoea of the newborn (TTN) or neonatal unit admission overall, and ACS may result in harm to the neonate which includes hypoglycaemia and potential developmental delay. **Gestational age** **3.** Corticosteroids should be offered to women between 24^{+0} and 34^{+6} weeks' gestation in whom imminent preterm birth is anticipated (either due to established preterm labour, PPROM or planned preterm birth). **Particular circumstances – multiple pregnancy** **4.** Women with twins and triplets should be offered targeted ACS for early birth in line with recommendations for singletons. **Pregnancies complicated by fetal growth restriction, pre-eclampsia or antepartum haemorrhage** **5.** Birth should not be delayed for ACS if the indication for birth is impacting the health of the woman or her baby. **6.** A course of ACS should be offered if planned early birth is necessary for hypertension in pregnancy.	 1++ 2+ 1++ 3 4 1+	 A B A D GPP B

	7. If imminent preterm birth is likely, a course of ACS should be offered to women whose babies are thought to be either small for GA or to have fetal growth restriction, but women should be counselled about the lack of evidence to guide care	2++	C
	PPROM		
	8. ACS should be offered to women with PPROM, who are at increased risk of preterm birth.	1++	A
	Optimum dose and route of administration		
	9. In the UK it is recommended that 24mg dexamethasone (DM) phosphate is given IM in two divided doses of 12 mg 24 hours apart or four divided doses of 6 mg 12 hours apart.	2+	B
	10. An alternative is 24 mg betamethasone (BM) sodium phosphate/acetate mix given IM in two divided doses of 12 mg 24 hours apart.	2++	B
	Most effective timing for administration		
	11. ACS use reduces neonatal death when the first dose is given within the 48 hours prior to birth.	4	D
	12. Benefits are also seen when the first dose is given within 24 hours of birth and ACS should still be given if birth is expected within this time.	4	D

National Institute for Health and Care Excellence (NICE)[62] 2022	**1.** For women between 22^{+0} and 23^{+6} weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have PPROM, discuss with the woman (and her family members or carers, as appropriate) and the multidisciplinary team the use of maternal CS in the context of her individual circumstances. **2.** Offer maternal CS to women between 24^{+0} and 33^{+6} weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have PPROM. **3.** Consider maternal corticosteroids for women between 34^{+0} and 35^{+6} weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have PPROM. **4.** Consider a single repeat course of maternal CS for women less than 34^{+0} weeks of pregnancy who: • Have already had a course of CS more than 7 days before, and • Are at very high risk of giving birth in the next 48 hours. If the woman is less than 30^{+0} weeks pregnant or if there is suspected growth restriction, take into account the possible impact on fetal growth of a repeat course of maternal CS. **5.** Do not give more than 2 courses of maternal corticosteroids for preterm birth. **6.** When offering or considering maternal CS, discuss the benefits and risks with the woman (and her family members or carers, as appropriate).	
The International Federation of Gynecology and Obstetrics (FIGO)[63] 2021	**Clinical scenarios and drug administration** **1.** For women with singleton pregnancies where active neonatal care is appropriate, for whom preterm birth is anticipated between 24^{+0} and 34^{+0} weeks of gestation, ACS should be offered to improve outcomes for the baby. **2.** For women with multiple pregnancy where active neonatal care is appropriate, for whom preterm birth is anticipated between 24^{+0} and 34^{+0} weeks of gestation, ACS should be offered to improve outcomes for the baby. **3.** ACS should not be offered routinely to women in whom late preterm birth (34^{+0} and 36^{+6} weeks of gestation) is anticipated. Instead, the use of prenatal CS should be considered in light of the balance of risks and benefits for individual women. **Type and dose of prenatal corticosteroids**	

	Where ACS are given to improve fetal outcomes, appropriate regimens include two doses of BM acetate/phosphate 12 mg (=one course) IM 24h apart, or two doses of DM phosphate 12 mg (=one course) IM 24h apart. **Timing of administration** ACS should ideally be given 18–72h, and certainly no more than 1 week, before preterm birth is anticipated. However, if preterm birth is expected within 18h, ACS should still be administered. **Single or multiple courses of corticosteroids** In women in whom preterm birth is expected within 72 h and who have had one course of CS more than a week ago, one additional course of ACS could be given to improve outcomes for the baby. **Use of prenatal corticosteroids in low-resource settings** Prenatal steroids should be given to women with a singleton pregnancy where active neonatal care is appropriate and preterm birth is anticipated from 24–34 weeks of gestation, when ideally the following conditions are met: GA assessment can be accurately undertaken, preterm birth is considered imminent, there is no clinical evidence of maternal infection, adequate childbirth care is available (including the capacity to recognize and safely manage preterm labor and birth), the preterm newborn can receive adequate care if needed (including resuscitation, thermal care, feeding support, infection treatment, and safe oxygen use). **Babies born by caesarean at term** ACS should not be given routinely before cesarean section at term. **Prenatal corticosteroids as a "just in case" therapy** ACS should not be given "just in case". ACS administration should be reserved for women for whom preterm birth is expected within no more than 7 days, based on the woman's symptoms (including contractions or preterm prelabor membrane rupture) or an accurate predictive test.	

The Society of Obstetricians and Gynecologists of Canada (SOGC)[64] 2018	**Gestational Age Considerations**		
	1. One course of ACS therapy should be routinely administered to women at 24^{+0} to 34^{+6} weeks gestation who are at high risk for preterm delivery within the next 7 days.	Moderate	Strong
	2. Women between 22^{+0} weeks and 23^{+6} weeks gestation at high risk of preterm birth within the next 7 days should be provided with a multidisciplinary consultation regarding the high likelihood for severe perinatal morbidity and mortality and associated maternal morbidity. ACS therapy may be considered if early intensive care is requested and planned.	Low	Conditional
	3. The balance of risks and benefits does not support routine administration of ACS therapy for women at 35^{+0} to 35^{+6} weeks gestation who are at high risk for preterm birth in the next 7 days.	Moderate	Conditional
	4. ACS therapy should not be routinely administered to women at 36^{+0} to 36^{+6} weeks gestation who are at risk for preterm delivery.	Moderate	Conditional
	5. ACS therapy may be administered between 35^{+0} and 36^{+6} weeks gestation in select clinical situations after risks and benefits are discussed with the woman and the paediatric care provider(s).	Moderate	Conditional
	6. ACS therapy should not be routinely administered to women undergoing pre-labour caesarean section at term gestation (including at 37 weeks gestation).	Low	Strong
	<u>Agents, Dosage, Regimen, and Target Timing</u>		
	1. When ACS therapy is indicated, women should receive a course of ACS therapy (i.e., either 2 doses of BM 12 mg given by IM injection 24 hours apart or 4 doses of DM 6 mg given by IM injection 12 hours apart).	Moderate	Strong
	2. ACS therapy should be administered to women requiring medically indicated delivery only when the plan to proceed with delivery within 7 days has been finalized and GA criteria for ACS therapy are met.	Low	Strong
	3. ACS therapy should be routinely administered to women in spontaneous preterm labour characterized by regular uterine contractions associated with significant cervical dilation or significant cervical change on repeated examination when GA criteria for ACS therapy are met.	Low	Strong
	4. Regular contractions in the absence of cervical dilation/change, or a short cervical length in the absence of regular contractions, are not indications for ACS therapy.	Low	Strong
	5. ACS therapy should be routinely administered at the time of diagnosis to women with PPROM, when GA criteria are met.	Low	Strong
	6. ACS therapy should be administered to women with significant antepartum haemorrhage when the risk of delivery within 7 days is high and the GA criteria for such therapy are met.	Low	Strong

	7. ACS therapy should be administered to asymptomatic patients with vasa previa or placenta previa when the risk of delivery within 7 days is high and the GA criteria are met.	Low	Strong
	8. In cases where the diagnosis of preterm labour has not been firmly established (i.e., no documented cervical change and dilatation <3 cm), and the woman is being transferred to a higher level of care for further assessment, ACS therapy should not be administered prior to transfer.	Low	Strong
	9. If the risk of preterm delivery decreases significantly following administration of the first dose of ACS therapy, cancellation of the second dose of CS should be considered. If the second dose is cancelled and a high risk of preterm birth arises subsequently at less than 34^{+6} weeks gestation, 1 dose or 1 course of ACS therapy should be considered, depending on GA and timing since the first dose.	Low	Strong
	10. If the woman is still pregnant beyond 7 days after the first ACS course, the balance of risks and benefits does not support further routine administration of ACS therapy even if the risk of preterm delivery increases subsequently. The GA and the time interval since the first course of ACS therapy (at least 14 days) should be taken into account when considering a rescue course. A single rescue course of ACS therapy may be administered after risks and benefits are discussed.	Moderate	Conditional
	<u>Subpopulations and special considerations</u>		
	1. ACS therapy should be administered according to the same indications and in the same GA range to women with twins or higher-order multifetal pregnancies as for singleton pregnancies.	Low	Conditional
	2. ACS therapy should not be administered to women with multifetal pregnancies in the absence of a high risk of preterm birth within the next 7 days.	Low	Conditional
	3. ACS therapy should be administered to diabetic women at the same dosage, according to the same indications, and in the same GA range as that recommended for non-diabetic women.	Low	Conditional
	4. Close attention should be paid to control of maternal blood glucose among women with diabetes in the days following ACS therapy because of anticipated elevations in maternal blood glucose levels.	Low	Strong
	5. Because of the transient elevation of blood glucose levels induced by CS, gestational diabetes screening should be delayed for a minimum of 1 week following ACS therapy.	Low	Strong
	6. ACS therapy should be administered to women with obesity at the same dosage as that recommended for women without obesity (according to the same indications and in the same GA range) because there is insufficient evidence to guide dosage adjustments by maternal weight.	Low	Conditional

	7. There is insufficient evidence to withhold routine ACS therapy in cases of suspected fetal growth restriction with a high risk of preterm birth. Antenatal corticosteroid therapy should be administered according to the same indications and in the same GA range as in normal pregnancies after risks and benefits are discussed. **8.** ACS therapy should not be administered to women with suspected fetal growth restriction at the time of diagnosis unless there is a high risk of preterm birth within the next 7 days. **9.** Women should be informed of the potential for a transient reduction in fetal movements and advised to consult with their health care professional if this occurs.	Low Low Low	Conditional Conditional Strong
The American College of Obstetricians and Gynecologists (ACOG)[65] 2017	**1.** A single course of CS is recommended for pregnant women between 24^{+0} weeks and 33^{+6} weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations. It also may be considered for pregnant women starting at 23^{+0} weeks of gestation who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation, irrespective of membrane rupture status and regardless of fetal number. **2.** Administration of CS for pregnant women during the periviable period who are at risk of preterm delivery within 7 days is linked to a family's decision regarding resuscitation and should be considered in that context. **3.** A single course of BM 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 ACS.		

	4. Regularly scheduled repeat courses or serial courses (more than two) are not currently recommended. **5.** A single repeat course of ACS should be considered in women who are less than 34^{+0} weeks of gestation who are at risk of preterm delivery within 7 days, and whose prior course of ACS was administered more than 14 days previously. Rescue course CS could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. **6.** Whether to administer a repeat or rescue course of CS with PPROM is controversial, and there is insufficient evidence to make a recommendation for or against. Continued surveillance of long-term outcomes after in utero corticosteroid exposure should be supported.	

GRADE: Grading of Recommendations Assessment, Development and Evaluation; SIGN: Scottish Intercollegiate Guideline Network; ACS: antenatal corticosteroids; RDS: respiratory distress syndrome; RCOG: Royal College of Obstretricians and Gynaecologoists; GPP: considered good practice; PPROM: preterm prelabour rupture of membranes; TTN: transient tachypnoea of the newborn; DM: dexamethasone; BM: betamethasone; IM: intramuscular; NICE: National Institute for Health and Care Excellence; FIGO: The International Federation of Gynecology and Obstetrics; SOGC: The Society of Obstetricians and Gynaecologists of Canada; ACOG: The American College of Obstetricians and Gynecologists; WHO: World Health Organization

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