WHO recommendations on antenatal corticosteroids for improving preterm birth outcomes

Web annex. Evidence-to-decision framework

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Contents

Acronyms and abbreviations

ACS	Antenatal corticosteroid
ACT	Antenatal Corticosteroid Trial
ALPS	Antenatal Late Preterm Steroids [Trial]
aOR	Adjusted odds ratio
CI	Confidence interval
CPAP	Continuous positive airway pressure
FGR	Fetal growth-restriction
g	Gram
ICH	Intracerebral haemorrhage
IM	Intramuscular
IVH	Intraventricular haemorrhage
Kg	Kilogram
LMIC	Low- and middle-income country
LMP	Last menstrual period
MD	Mean difference
mg	Milligram
mL	Millilitre
PICO	Population, intervention, comparator, priority outcome
PVH	Periventricular haemorrhage
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
RR	Risk ratio
SGA	Small for gestational age
WHO	World Health Organization

Evidence-to-Decision framework 1.0

Antenatal corticosteroids compared to placebo or no treatment: **All women and babies**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of 5 years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- While there are interventions that can be directed at all women for primary reduction of risk of preterm birth or used to minimize the risk in women with known risk factors, the most beneficial set of maternal interventions are those that could improve survival chances and health outcomes of preterm infants when preterm birth is inevitable.
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.

2 Question

- Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)?

Problem: Adverse outcomes due to preterm birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[1]

Settings: Low- middle- and high-income settings

Subgroups:

- Population of women presenting at different gestational ages (≤35 weeks 0 days and ≥34 weeks 0 days)

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

[1] These outcomes reflect the prioritized outcomes used for this recommendation in the *WHO recommendations for interventions to improve preterm birth outcomes* (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

Summary of evidence

Evidence on the effects of antenatal corticosteroids versus placebo or no treatment for reducing adverse outcomes associated with prematurity was derived from an updated Cochrane systematic review, which included 27 trials (11 272 randomized women and 11 925 randomized infants) (12). Trials were published between 1972 and 2020. The included trials came from a range of health care systems and settings. Ten trials were conducted in the United States of America, two in Brazil, two in Finland and one each in Colombia, India, Iran, Jordan, New Zealand, the Netherlands, South Africa, Thailand, Tunisia, Turkey and the United Kingdom of Great Britain and Northern Ireland. One trial took place in the USA and Germany and another took place in Bangladesh, India, Kenya, Nigeria and Pakistan.

The trials recruited women with a wide range of preterm gestational ages (24 weeks 0 days to 36 weeks 6 days), with 20 trials recruiting women at ≤35 weeks 0 days and seven trials at ≥34 weeks 0 days. The indications for recruitment into the trials included premature rupture of membranes, spontaneous preterm labour and planned preterm delivery.

Most trials recruited only women with a singleton pregnancy. Twelve trials recruited women with singleton or multiple pregnancy. Exclusion criteria were variable but commonly included medical contraindications to steroid use, evidence of maternal infection, diabetes, lethal fetal anomalies, advanced first stage of labour, and any maternal or fetal indications requiring urgent delivery.

Antenatal corticosteroids used in the trials included betamethasone (15 trials; 5764 women, 5900 infants), dexamethasone (8 trials; 3930 women, 4962 infants) and hydrocortisone (1 trial; 196 women and infants). One trial used betamethasone or dexamethasone in the treatment arms (32 women and infants), one used betamethasone and methylprednisone in the treatment arms (155 women and infants) and one used betamethasone, methylprednisone and hydrocortisone in the treatment arms (92 women, 97 infants).

Summary of absolute effects per 1000 (95% confidence interval), antenatal corticosteroid therapy compared to placebo or no treatment: all women

Key:	High certainty (benefit)	Moderate certainty (probable benefit)	Low certainty (possible benefit)	High certainty (harm)	Moderate certainty (probable harm)	Low certainty (possible harm)	High certainty (no difference)	Moderate certainty (probable no difference)	Low certainty (possible no difference)	Very low certainty (uncertain)

MD: Mean difference. **CPAP**: Continuous positive airway pressure

Maternal outcomes		Neonatal outcomes				Child and adult outcomes	
Death	**Possibly no difference** 0 fewer (1 fewer to 5 more)	Perinatal death	**Reduced** 23 fewer (36 fewer to 11 fewer)	Surfactant use	**Reduced** 14 fewer (19 fewer to 6 fewer)	Death in childhood	**Probably no difference** 14 fewer (27 fewer to 11 more)
Admission to intensive care	**Possibly no difference** 13 fewer (37 fewer to 53 more)	Fetal death	**No difference** 0 fewer (7 fewer to 9 more)	Admission to neonatal intensive care	**Probably slightly reduced** 21 fewer (46 fewer to 0 fewer)	Cerebral palsy	**Possibly no difference** 27 fewer (45 fewer to 2 more)
Chorio-amnionitis	**Possibly no difference** 5 fewer (11 fewer to 3 more)	Neonatal death	**Probably reduced** 26 fewer (36 fewer to 15 fewer)	Mean duration hospitalisation	**Possibly no difference** MD 0.18 higher (0.51 lower to 0.87 higher)	Develop-mental delay	**Probably reduced** 38 fewer (57 fewer to 2 fewer)
Endometritis	**Probably no difference** 3 more (3 fewer to 11 more)	Respiratory distress syndrome (RDS)	**Probably reduced** 43 fewer (52 fewer to 32 fewer)	Mechanical ventilation/ CPAP	**Reduced** 56 fewer (from 77 fewer to 36 fewer)	Intellectual impairment	**Possibly no difference** 6 fewer (26 fewer to 32 more)
Postnatal fever	**Possibly no difference** 7 fewer (29 fewer to 27 more)	Moderate/ severe RDS	**Probably reduced** 35 fewer (47 fewer to 20 fewer)	Mean duration of mechanical ventilation/ CPAP	**Possibly no difference** MD 1.91 lower (4.59 lower to 0.76 higher)	Hearing impairment	**Uncertain**
Maternal side-effects	**Reduced** 63 fewer (83 fewer to 36 fewer)	Intra-ventricular haemorrhage	**Possibly reduced** 14 fewer (18 fewer to 8 fewer)	Mean birth weight	**Possibly no difference** MD 14.02 lower (33.79 lower to 5.76 higher)	Visual impairment	**Uncertain**
		Systemic infection in the first 48 hours	**Probably reduced** 30 fewer (44 fewer to 9 fewer)	Small for gestational age	**Probably no difference** 18 more (7 fewer to 47 more)	Behavioural difficulties	**Uncertain**
		Necrotizing enterocolitis	**Probably reduced** 11 fewer (16 fewer to 5 fewer)	Neonatal hypoglycaemia*	**Probably increased** 37 more (14 more to 60 more)		
		Chronic lung disease	**Uncertain**				

* Neonatal hypoglycaemia was not a prespecified outcome in the Cochrane review. The finding of increased neonatal hypoglycaemia was attributable to a trial conducted in the USA involving women in the late preterm period.

Effects of antenatal corticosteroid therapy versus placebo or no antenatal corticosteroid therapy: all women and babies

Maternal outcomes

- **Severe maternal morbidity or death**: Antenatal corticosteroid therapy may result in little or no difference in risk of maternal death (RR 1.19, 95% CI 0.36 to 3.89; 6 trials, 6244 women; *low certainty*) or maternal admission to intensive care (RR 0.74, 95% CI 0.26 to 2.05; 2 trials, 319 women; *low certainty*).
- **Maternal infectious morbidity**: Corticosteroid therapy probably results in little or no difference in the risk of endometritis (10 trials, 6764 women; RR 1.14, 95% CI 0.82 to 1.58; *moderate certainty*) and may result in little or no difference in risk of chorioamnionitis (RR 0.86, 95% CI 0.69 to 1.08; 15 trials, 8374 women; *low certainty*) or postnatal fever (RR 0.92, 95% CI 0.64 to 1.33; 5 trials, 1323 women; *low certainty*).
- **Maternal side-effects:** Corticosteroid therapy results in fewer cases of local reaction at the injection site after first dose than is found with placebo (RR 0.69, 95% CI 0.59 to 0.82; 1 trial, 2825 women; *high certainty*).[2]
- **Maternal well-being and maternal satisfaction**: No outcomes were reported in the review pertaining to maternal well-being or maternal satisfaction.

Infant outcomes

- **Fetal and neonatal death:** Antenatal corticosteroid therapy reduces the risk of perinatal death (composite of fetal and neonatal death) (RR 0.85, 95% CI 0.77 to 0.93; 14 trials, 9833 infants; *high certainty*). This is largely due to a probable reduction in the risk of neonatal death (RR 0.78, 95% CI 0.70 to 0.87; 22 trials, 10 609 infants; *moderate certainty*) but there is little or no difference in the risk of fetal death (RR 1.01, 95% CI 0.83 to 1.22; 14 trials, 9833 infants; *high certainty*).
- **Severe neonatal morbidity:** Antenatal corticosteroid therapy probably reduces the risk of respiratory distress syndrome (RR 0.71, 95% CI 0.65 to 0.78; 26 trials, 11 183 infants; *moderate certainty*), moderate or severe respiratory distress syndrome (RR 0.70, 95% CI 0.59 to 0.83; 7 trials, 4874 infants; *moderate certainty*), systemic infection in the first 48 hours of life (RR 0.60, 95% CI 0.41 to 0.88; 7 trials, 1708 infants; *moderate certainty*) and necrotizing enterocolitis (RR 0.50, 95% CI 0.32 to 0.78; 10 trials, 4702 infants; *moderate certainty*). Corticosteroid therapy may reduce the risk of intraventricular haemorrhage (RR 0.58, 95% CI 0.45 to 0.75*;* 12 trials, 8475 infants; *low certainty*) and the evidence on chronic lung disease is very uncertain. However, antenatal corticosteroid therapy probably increases the risk of neonatal hypoglycaemia[3] (RR 1.19, 95% CI 1.07 to 1.31; 4 trials, 5753 women; *moderate certainty*).

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[2] The high certainty assessment based on one trial reflects that this was a multicentre trial in 17 hospitals in the USA. This was a placebo-controlled trial of IM betamethasone in the late preterm period – the reduction in maternal side-effects at first dose were primarily driven by participants reporting fewer events of pain, bruising and swelling at the injection site.

[3] Neonatal hypoglycaemia was not reported in the 2020 Cochrane review. However, data from available trials in which this outcome was reported were pooled due to concerns about a possible increased risk among late preterm babies. In the trial providing most data for ≥34 weeks, hypoglycaemia was defined as blood glucose <40 mg/dL (2.2 mmol/L) at any time. In the trial providing data for ≤35 weeks, hypoglycaemia was defined as blood glucose <45 mg/dL (2.6 mmol/L) and measured at 6 and 36 hours after birth.

Antenatal corticosteroid therapy reduces surfactant use (RR 0.65, 95% CI 0.50 to 0.85; 6 trials, 6104 infants; *high certainty*) and the use of mechanical ventilation/CPAP (RR 0.75, 95% CI 0.66 to 0.84; 11 trials, 4519 infants; *high certainty*). It probably slightly reduces the risk of admission to neonatal intensive care (RR 0.96, 95% CI 0.91 to 1.00; 9 trials, 6667 infants; *moderate certainty*), although the confidence interval also includes the possibility of no effect. Corticosteroid therapy may result in little or no difference in duration of neonatal hospitalization (MD 0.18 days, 95% CI –0.51 to 0.87; 5 trials, 788 infants; *low certainty*) or duration of mechanical ventilation/CPAP (MD –1.91 days, 95% CI –4.59 to 0.76; 3 trials, 471 infants; *low certainty*).

- **Birth weight**: Antenatal corticosteroid therapy probably results in little or no difference in risk of small for gestational age (RR 1.11, 95% CI 0.96 to 1.28; 5 trials, 3478 infants; *moderate certainty*) and may result in little or no difference in mean birth weight (MD –14.02 g; 95% CI –33.79 g to 5.76 g; 19 trials, 9551 infants; *low certainty*).
- **Long-term morbidity**: Antenatal corticosteroid therapy probably results in little or no difference in the risk of childhood death (RR 0.68, 95% CI 0.36 to 1.27; 4 trials, 1010 children; *moderate certainty*) and may result in little or no difference in the risk of cerebral palsy (RR 0.60, 95% CI 0.34 to 1.03; 5 trials, 904 children; *low certainty*). It probably reduces the risk of developmental delay (RR 0.51, 95% CI 0.27 to 0.97; 3 trials, 600 children *moderate certainty*). There may be little or no difference in risk of intellectual impairment (RR 0.86, 95% CI 0.44 to 1.69; 3 trials, 778 children; *low certainty*). The evidence on hearing impairment, visual impairment and behavioural/learning difficulties in childhood is very uncertain.

Effects of antenatal corticosteroid therapy versus placebo or no antenatal corticosteroid therapy: subgroup of gestational age at therapy

In the same Cochrane systematic review (12), 26 trials were included in a subgroup analysis comparing results from trials recruiting women at gestational age of ≤35 weeks 0 days (20 trials, 7041 women) with those recruiting women ≥34 weeks 0 days (7 trials, 4142 women). With the exception of four trials, most fell on either side of this division. Data from one of these trials was available for women receiving their first dose at <35 weeks 0 days and from 35 to 37 weeks 0 days. Most women in the remaining three trials received their first dose before 34 weeks and were thus included in the earlier gestational age grouping for the subgroup analysis. One study did not report outcomes included in the subgroup analysis.

Maternal outcomes

- **Maternal infectious morbidity**: Antenatal corticosteroid therapy commenced at ≥34 weeks 0 days reduces the risk of chorioamnionitis (RR 0.58, 95% CI 0.34 to 0.99; 3 trials, 3242 women; *high certainty*) but therapy commenced at ≤35 weeks 0 days may have little to no effect (RR 0.94, 95% CI 0.73 to 1.20; 13 trials, 5132 women; *low certainty*).

  No data were available for other maternal outcomes (severe maternal morbidity or death, maternal side-effects, maternal well-being, maternal satisfaction).

Infant outcomes

- **Fetal and neonatal death:** Antenatal corticosteroid therapy reduces the risk of perinatal death when commenced at ≤35 weeks 0 days (RR 0.83, 95% CI 0.76 to 0.91; 11 trials, 6185 women; *high certainty*) but may have little or no effect when commenced at ≥34 weeks 0 days (RR 1.70, 95% CI 0.68 to 4.28; 4 trials, 3648 women; *low certainty*). Antenatal corticosteroid therapy commenced at ≤35 weeks 0 days probably reduces the risk of neonatal death (RR 0.77, 95% CI 0.69 to 0.86; 19 trials, 6961 women; *moderate certainty*) but has little or no effect on fetal death (RR 0.99, 95% CI 0.81 to 1.19; 11 trials, 6185 women; *high certainty*). For antenatal corticosteroid therapy commenced at ≥34 weeks 0 days, there were few trials and events (low certainty evidence) for fetal death (RR 1.92, 95% CI 0.42 to 8.82; 4 trials, 3648 women; *low certainty*) or neonatal death (RR 1.51, 95% CI 0.49 to 4.61; 4 trials, 3648 neonates; *low certainty*).
- **Severe neonatal morbidity:** The risk of neonatal hypoglycaemia is increased among babies born to women commencing therapy at ≥34 weeks (RR 1.61, 95% CI 1.38 to 1.87; 3 trials, 3294 infants; *high certainty*) but there is probably no difference in risk among babies born to women commencing therapy at ≤35 weeks 0 days (RR 0.85, 95% CI 0.60 to 1.21, 1 trial, 2459 infants; *moderate certainty).* There is probably a reduction in risk of respiratory distress syndrome[4] with antenatal corticosteroid therapy commenced at either ≤35 weeks 0 days (RR 0.70, 95% CI 0.63 to 0.78; 20 trials, 7041 neonates; *moderate certainty*) or ≥34 weeks 0 days (RR 0.75, 95% CI 0.60 to 0.95; 7 trials, 4142 neonates; *moderate certainty*). Antenatal corticosteroids commenced at ≤35 weeks 0 days may reduce the risk of intraventricular haemorrhage (RR 0.56, 95% CI 0.44 to 0.72; 11 trials, 5412 neonates; *low certainty*). The evidence on the effect of antenatal corticosteroid therapy commenced at ≥34 weeks 0 days on risk of intraventricular haemorrhage is very uncertain.

  No data were available for other severe neonatal morbidities (neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, retinopathy of prematurity).

- **Birth weight**: Antenatal corticosteroid therapy may have little or no effect on mean birth weight whether commenced at ≤35^0 weeks (MD –9.78, 95% CI –40.81 to 21.24; 13 trials, 5412 neonates; *low certainty*) or ≥34^0 weeks (MD –15.75, 95% CI –41.09 to 9.58; 7 trials, 4139 neonates; *low certainty*). No data were available for low birth weight or small for gestational age.

[4] The trial that provided most of the data for the ≥34 weeks group defined respiratory distress syndrome as the presence of clinical signs of respiratory distress (tachypnea, retractions, flaring, grunting, or cyanosis), with a requirement for supplemental oxygen with a fraction of inspired oxygen of >0.21 and a chest radiograph showing hypo-aeration and reticulogranular infiltrates. In the trial that provided most of the data for the ≤34 weeks group, severe respiratory distress was defined as the presence of fast breathing (respiratory rate ≥ 70 breaths per minute) AND at least one of the following clinical signs: marked nasal flaring during inspiration; expiratory grunting audible with naked ear; and severe chest in drawing AND oxygen saturation <90%, or use of supplemental oxygen.

Additional considerations

Subgroup analyses

While the Cochrane review subgroup analyses (≤35 weeks 0 days and ≥34 weeks 0 days) overlap slightly, the following needs to be considered with regards to the upper gestational age threshold for safe and effective use of antenatal corticosteroids:

- Evidence for ≤35 weeks 0 days indicates multiple, substantial benefits for the newborn. A careful examination of the available trials for this subgroup, as well as sensitivity analyses, indicate that the benefits of antenatal corticosteroids at <34 weeks' gestation are almost identical to ≤35 weeks 0 days. This is because the largest trial in this subgroup (2852 women across five low-middle income countries) randomized women from 26 weeks to <34 weeks' gestation, reporting mortality and respiratory morbidity benefits.
- The evidence for the period ≥34 weeks 0 days is almost entirely from trials in high-income country settings. Furthermore, there was insufficient evidence to determine whether antenatal corticosteroids have an effect on mortality outcomes (neonatal or perinatal death). While there appeared to be some benefit in respiratory distress syndrome reduction, the absolute effect was more modest, and attributable to a single multicentre trial conducted in the USA.
- The higher risk of neonatal hypoglycaemia observed in the main analysis was attributable to increased risk of this outcome at ≥34 weeks 0 days' gestation (there was no evidence of such an association in the ≤35 weeks 0 days subgroup).

Context of care

- Eleven trials took place in low- or middle-income countries – two trials in Brazil; one trial each in Colombia, India, Iran, Jordan, South Africa, Thailand and Turkey; and a multicountry trial in Bangladesh, India, Kenya, Nigeria and Pakistan. Trials were published between 1999 and 2020. Using the 2021 World Bank classifications, seven trials were in upper-middle-income countries and four trials were in lower-middle-income countries.
- Eight trials were single-centre studies, one trial was in two centres (Jordan), one trial was in six centres (South Africa) and the multicountry trial involved 29 hospitals. Aside from the 2020 multicountry trial, the context of care available was not well described in these trials: three self-described as tertiary, referral or teaching hospitals, and five trials reported outcomes related to mechanical ventilation and/or neonatal intensive care unit admission (implying that these newborn interventions were available). Five trials specified that gestational age was assessed using last menstrual period (LMP) and/or ultrasound, one trial specified ultrasound only, and four trials did not specify.
- The 2020 multicountry trial involved 29 hospitals were those that "could reasonably meet the antenatal corticosteroid administration criteria as defined in the 2015 WHO preterm birth guidelines" following a standardized assessment of facility capacity. This included comprehensive emergency obstetric care, as well as availability of newborn care interventions (access to resuscitation at birth, thermal care, breastmilk feeding support, parenteral infection treatment, safe oxygen use, access to hygiene, access to CPAP). The trial authors also stated that ultrasonographic systems, CPAP machines, pulse oximeters and glucometers were procured for all hospitals. In order to be eligible, gestational age was determined by the earliest ultrasonographic examination or an ultrasonographic examination performed at admission.

- The Cochrane review on antenatal corticosteroid efficacy did not conduct a subgroup analysis comparing effects of antenatal corticosteroids in trials in low- and middle-income countries versus high-income countries.
- A separate 2020 Cochrane review (13) aimed to determine the relative benefits and risks of strategies to optimize the use of antenatal corticosteroid therapy for anticipated preterm birth and included three studies. Two of the included trials assessed their use in high-resource hospital settings. The third trial, the Antenatal Corticosteroid Trial (ACT) was a multi-site trial conducted in rural and semi-urban settings of six low- and middle-income countries in South Asia, sub-Saharan Africa and Central and South America.
- In the ACT trial, providers were trained to assess gestational age using LMP and estimated delivery date, or uterine height if neither were known (a colour-coded tape was developed to assist this). In the ACT intervention cluster, deliveries occurred in 349 health facilities – 260 were clinics (health centres and other non-hospital facilities); the remainder were primary health centres, community health clinics, or dispensaries.
- The review found that in two trials, promoting the use of antenatal corticosteroids resulted in their increased use, whereas one trial did not find a difference in the rate of administration compared to usual care.
- It also found that, in low-resource settings, a strategy of actively promoting the use of antenatal corticosteroids in women at risk of preterm birth may increase antenatal corticosteroids use in the target population, but may also carry a substantial risk of unnecessary exposure of antenatal corticosteroids to women in whom antenatal corticosteroids is not indicated. At the population level, these effects were probably associated with increased risks of stillbirth (RR 1.11, 95% CI 1.02 to 1.21; 1 study, 100 705 women; *moderate certainty*), perinatal death (RR 1.11, 95% CI 1.04 to 1.19; 1 study, 100 705 women; *moderate certainty*), neonatal death before 28 days (RR 1.12, 95% CI 1.02 to 1.23; 1 study, 100 705 women; *moderate certainty*) and maternal infection (RR 1.49, 95% CI 1.32 to 1.68; 1 study, 99 742 women; *low certainty*).
- The findings of this review support a more conservative approach to clinical protocols and clinical decision-making, particularly in low-resource settings.

Additional evidence on antenatal corticosteroid efficacy at ≥34 weeks' gestation

- A 2016 systematic review assessed the effects of antenatal corticosteroids for maturity of term or near-term fetuses, identifying six trials (5698 women with singleton pregnancies) (14). Of these, three trials (3200 women) randomized women who were at 34 weeks 0 days to 36 weeks 6 days and at risk of imminent premature delivery at the time of hospital admission. The review reported that in two trials, antenatal corticosteroids reduced the risk of severe RDS (RR 0.60, 95% CI 0.33 to 0.94) but in three other trials had no effect on RDS (RR 0.98, 95% CI 0.77 to 1.24) or neonatal death (3 trials, RR 0.95 95% CI 0.20 to 4.58). The risk of neonatal hypoglycaemia was increased (2 trials, RR 1.61 95% CI 1.38 to 1.87).
- A randomized trial conducted in four hospitals in India included 782 women at risk of imminent preterm birth at 34 weeks 0 days to 36 weeks 0 days (15). The trial was stopped early due to lower than expected prevalence of primary outcomes and slow recruitment. No differences were reported, however, for neonatal death (RR 0.95; 95% CI 0.42 to 2.12), any baby death (RR 0.87; 95% CI 0.45 to1.67), severe respiratory distress of the newborn groups (RR 1.56; 95% CI 0.26 to 9.29) or neonatal hypoglycaemia (1.09 (0.65 to 1.81).

Additional evidence on effectiveness of antenatal corticosteroids prior to 24 weeks' gestation

Systematic reviews and observational studies have reported reduced mortality risk among infants exposed to corticosteroids born in the extremely preterm period (16). In three systematic reviews that included observational studies of infants who were born 22 weeks 0 days to 24 weeks 6 days of gestation, all reported significant reduction in mortality before discharge in neonates who received antenatal corticosteroids compared to those who did not.

- A 2016 systematic review (17 observational studies, 3626 neonates <24 weeks of gestation) found a significant reduction in mortality before discharge with antenatal corticosteroids receipt (aOR 0.48, 95% CI:0.38 to 0.61) (17). Similarly, a 2017 systematic review (8 studies, infants born at 22 0/7 weeks to 24 6/7 weeks) found a significant reduction in mortality (OR 0.47; 95% CI, 0.39 to 0.56) (18). This review also assessed neonatal mortality by gestational week and found a significant reduction in mortality for all weeks assessed, including 22 0/7 to 22 6/7 weeks (n=587; OR=0.58, 95% CI: 0.38 to 0.89), 23 0/7 to 23 6/7 weeks (n=3438; OR=0.50, 95% CI: 0.42 to 0.58), and 24 0/7 to 24 6/7 weeks (n=6084; OR=0.44, 95% CI: 0.29 to 0.67).
- A 2021 systematic review (31 observational studies, 2226 infants born at 22 0/7 weeks to 22 6/7 weeks of gestation) found that survival among infants who were provided comprehensive treatment (antenatal corticosteroid and neonatal treatment) was twice that of infants who were solely provided neonatal treatment (39% vs 19.5%, p<0.01) (19).
- More recent studies from the United States (6925 multiples, 22–28 weeks' gestation) (20), two studies from Sweden (707 infants, 22–26 weeks' gestation (21) and 1011 infants <26 weeks' gestation [22]), and one from South Korea (9142 very low birth weight infants 23–24 weeks gestation [23]) all reported a lower mortality rate with exposure to antenatal corticosteroids compared to no exposure.

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids?

Judgement

Overall	☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☒ Large
≤35 weeks	☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☒ Large
≥34 weeks	☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☒ Moderate	☐ Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids?

Judgement

Overall	☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☒ Trivial
≤35 weeks	☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☒ Trivial
≥34 weeks	☐ Don't know	☐ Varies	☐ Large	☒ Moderate	☐ Small	☐ Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids on maternal outcomes?

Overall	☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High
≤35 weeks	☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High
≥34 weeks	☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☒ High

What is the overall certainty of the evidence on effects of antenatal corticosteroids on infant outcomes?

Overall	☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High
≤35 weeks	☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High
≥34 weeks	☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids?

Research evidence

Findings from a mixed methods systematic review (24) on the appropriate use of interventions in the management of women experiencing preterm birth show that women commonly believed that administration of antenatal corticosteroids was beneficial, stressing the importance of using them only when necessary and receiving information about potential side-effects (*high confidence*). Likewise, most health care providers recognized the benefits of antenatal corticosteroids, believing they save lives and that the benefits mostly outweigh the risks (*high confidence*). Quantitative evidence from ten studies (four high-, one moderate- and five low-quality studies) from health care providers supported the qualitative findings regarding recognition of these benefits. However, quantitative evidence suggests that women may doubt the benefits of antenatal corticosteroids, which could be a barrier to their use.

While many health care providers believed that risks of antenatal corticosteroids were negligible, some had concerns about possible safety issues (particularly interactions with tocolytics, exacerbation of pulmonary oedema), long-term risks for women (maternal complications), whether use at earlier gestational ages (<28 weeks) is appropriate, and risk of maternal infection (*moderate confidence*). Quantitative evidence from four studies (one high-, one moderate-, two low-quality studies) supported the qualitative findings, with some providers expressing concern about possible risks in using steroids for women in certain situations.

Despite personal experiences of, and concerns about, potential side-effects of antenatal corticosteroids among women in high-income countries, women mostly felt that they would take antenatal corticosteroids in future pregnancies if indicated (*moderate confidence*).

Women highly valued time and space to have a two-way conversation and build trust with their health care providers to understand their condition and treatment options. While some women described positive relationships with health care providers, critical threats to building trust include insufficient health care provider time due to workload, lack of continuity of carers, and perceived invalidation of women's concerns about whether they were in labour or not (*moderate confidence*).

Women experiencing preterm labour placed high value on interventions that helped them to maintain autonomy and regain control over their bodies and premature labour, such as interventions that enabled them to stay out of hospital or regain mobility. These types of interventions helped to promote their freedom while giving them a sense of security regarding their baby's health (*low confidence*). During preterm birth management, women leaned on their families and partners for emotional and physical support, such as motivation for staying on bedrest, general advice about pregnancy and baby health, sharing experiences, and developing coping strategies. Several women and their partners described asking for support from families and friends as an important challenge during preterm birth management, as it is less common to ask for support during pregnancy compared to after the baby is born (*moderate confidence*).

The following evidence specific to gestational age at therapy was identified:

- Women and health providers reported that last menstrual period was the most common method in assessing gestational age in low- and middle-income countries, though providers acknowledged the limited accuracy. Some providers in these settings were aware of ultrasound assessments of gestational age, whereas community health workers were not aware of ultrasound dating (*moderate confidence)*.
- Beliefs about optimal gestational age for administration varied across providers, with mixed opinions about the earliest gestational age they would administer and agreement that these were difficult discussions to have with women and families. Beliefs about optimal gestational age were also balanced with other factors, including estimated time to birth, threatened versus imminent birth, and local standards of practice (*moderate confidence*). Quantitative evidence from 12 studies found that providers believed gestational age is one of the most important factors in administering antenatal corticosteroids, and that the preferred optimal gestational age and range varied across settings.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the survival of a preterm newborn without residual longer-term morbidity. The GDG is confident that there is no variation in this value among mothers, health care providers and policy-makers in low-, middle- and high-income settings.

Judgement

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids, or the comparator?

Judgement

	☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention
≤35 weeks	☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention
≥34 weeks	☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☒ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids?

Research evidence

Evidence on the resource implications of antenatal corticosteroid therapy was derived from a systematic review of studies evaluating the cost–effectiveness of antenatal corticosteroids when used in the management of preterm birth (25). The studies in the review evaluated cost–effectiveness according to the gestational age of antenatal corticosteroid therapy.

Early preterm birth (up to 34 weeks gestational age)

Eight studies conducted in Brazil, Canada, Netherlands, the United Kingdom and the United States examined cost–effectiveness in early preterm birth. Corticosteroid preparations studied included dexamethasone only (1 study) and either betamethasone or dexamethasone (1 study); six studies did not specify the corticosteroid preparation. Most studies used decision-modelling techniques (6 studies), while one study analysed costs alongside a randomized controlled trial, and one analysed costs alongside a retrospective cohort study for cost–effectiveness analysis. All studies used a short-time horizon for costs and outcomes (until neonatal discharge from hospital). Methodological quality was high for four studies, moderate for three studies and low for one study.

Five studies found antenatal corticosteroids both cost-saving and more effective than no treatment; three studies found antenatal corticosteroid therapy may increase costs but is likely to be cost–effective.

- A study in Brazil (2016) found that antenatal corticosteroids significantly reduced most neonatal morbidity outcomes and hospitalization costs in infants who survived hospitalization, except for late-onset sepsis where the probability increased by 2.5%.
- A study in Canada (2000) found that administration of antenatal corticosteroids was more effective in reducing respiratory distress syndrome and deaths and less costly than no intervention.
- A study from the UK (1991) found that antenatal corticosteroid therapy was cost-saving and reduced RDS and neonatal deaths; for women up to 31 weeks' gestation. Antenatal corticosteroids therapy increased total costs due to the greater cost of caring for surviving babies, but average cost per survivor still reduced compared with no antenatal corticosteroid therapy.
- A single-centre study from the USA (1986) found that antenatal corticosteroids conferred morbidity benefits in preterm newborns; hospital charges were thus reduced and the intervention was cost-saving.
- A 1995 study found that, in USA hospital settings, antenatal corticosteroids reduced hospital costs, deaths and index cases in all infants born <2 kg, as well as in premature infants at 28 to 31 weeks. In premature infants <28 weeks, the treatment group had fewer deaths but a greater number of index cases; however, antenatal corticosteroid use was still cost-saving in terms of hospital costs.
- One study in the Netherlands (1992) found antenatal corticosteroids reduced respiratory distress syndrome incidence but increased total hospitalisation time and costs due to greater neonatal survival compared to no intervention; antenatal corticosteroid therapy was considered cost–effective.

A cost–effectiveness analysis of a placebo-controlled trial of antenatal corticosteroid therapy (dexamethasone) for women at risk of early preterm birth in Bangladesh, India, Kenya, Nigeria and Pakistan has been conducted (WHO, unpublished) For all countries, 38 neonatal deaths were averted per 1000 woman-baby units. The intervention was cost saving in all countries, ranging from a saving of US$54 per woman-baby unit in Kenya to US$2 per woman-baby unit in Nigeria. In the probabilistic uncertainty analysis, the intervention was cost-saving for 100.0%, 99.9%, 97.2%, 63.9%, 95.3% of simulations in Bangladesh, India, Kenya, Nigeria, and Pakistan respectively. Across all five countries, the highest upper bound of the 95% uncertainty interval for cost per disability-adjusted life year (DALY) averted was US$11 in Nigeria.

Preterm birth (not specified)

Four studies conducted in Ethiopia, South Africa, and the United States examined cost–effectiveness for preterm births, though gestational age range was not always specified. One study studied betamethasone only, and the remaining three studies did not specify the corticosteroid preparation. Two studies used the LiST tool for cost–effectiveness analysis, one analysed costs alongside a retrospective cohort study, and one study used a decision-modelling technique. Two studies used a short-time horizon for costs and outcomes (seven days or until neonatal discharge from hospital), while two studies did not specify a time horizon. Methodological quality was high for two studies and moderate for two studies.

- One single-centre study from the USA (1981) found that antenatal corticosteroids reduced mortality in preterm newborns in the smallest birth weight categories, and reduced hospital charges for newborns in the larger birth weight categories; overall antenatal corticosteroid therapy was cost-saving.
- Two studies (Ethiopia and South Africa) used LiST models to assess the effects of increasing antenatal corticosteroids coverage. In Ethiopia, increasing antenatal corticosteroids coverage by 20% was cost–effective at $98 per disability-adjusted life year averted (26), while in South Africa, increasing coverage to 99% was cost–effective at $37 per life year gained.
- A modelling study from the USA (1997) found that a package comprising antenatal corticosteroids and tocolytics was cost-saving compared to no intervention if the baseline probability of respiratory distress syndrome was above 2%.

Late preterm birth (34 to <37 weeks gestational age)

Three studies conducted in the United States examined cost–effectiveness in late preterm birth. One of these studies used a literature review to construct a decision model considering antenatal corticosteroid use from a single payer perspective. The other two studies used outcomes related to betamethasone use from the Antenatal Late Preterm Steroids (ALPS) trial – one, conducted in 2019, used a third-party funder perspective while the other, conducted in 2020, used a health sector perspective. The decision model examined a lifetime horizon for costs and effects, while the two studies based on the ALPS trial used short time horizons – the first 72 hours or first 7.5 days of the neonatal period. Methodological quality of all three studies was high.

- The literature review-based decision model (2012) reported that the incremental cost–effectiveness ratio for a full course of antenatal corticosteroids (compared to no antenatal corticosteroids) favoured the full course at 34, 35 and 36 weeks using a threshold of $100 000/QALY; but a partial course was not cost–effective.
- The 2019 study concluded that compared to placebo, betamethasone decreased total mean costs for each woman–infant pair.

- Despite using the same data, the 2020 study reported that betamethasone was not cost–effective in the short term. This can be attributed to the 2019 study costing the primary trial outcome only (a composite of neonatal respiratory treatment in the first 72 hours representing neonatal respiratory morbidity), while the 2020 study included costs of additional outcomes (neonatal hypoglycaemia, which was increased with betamethasone) and derived utilities for each outcome from literature to calculate quality-adjusted life years. They reported late preterm antenatal corticosteroid use as being slightly more expensive and generating fewer quality-adjusted life years than placebo.

Additional considerations

Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing health structures and protocols that are designed to manage women at imminent risk of preterm birth with minimal cost. Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (27). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any neonatal side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (28) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (28) — In the systematic review of cost–effectiveness studies (25), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).

Resource	Description
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to accurately assess gestational age. • Administration of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, thermoregulatory support, infection control measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	• IM administration of a single dose takes 2 minutes. • Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	• Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☐ Don't know	☒ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (29). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (30). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (31).

Evidence from trials demonstrates that antenatal corticosteroid use is effective, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit from the protection offered by a relatively cheap and readily available medication in low-resource setting, thus increasing equity.

Judgement

☒	☐	☐	☐	☐	☐	☐
Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased

3.5 Acceptability

Is antenatal corticosteroid therapy of women at risk of imminent preterm birth acceptable to key stakeholders?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (24).

Health care providers had uncertainties and lacked confidence in prescribing and administering antenatal corticosteroids in certain circumstances, such as repeat dosing and use in specific clinical situations (diabetes, hypertension, fetal complications, infection or premature rupture of membranes) (*moderate confidence*). Quantitative evidence from six studies (two high-, two moderate- and two low-quality studies) supported these findings.

Some providers had concerns about the research evidence supporting antenatal corticosteroid therapy, which may act as a barrier to its use (*moderate confidence*). Quantitative evidence from five studies (one high-, one moderate-, three low-quality studies) similarly found provider scepticism due to fear of side-effects and birth defects. Providers perceived that more research is needed on administering antenatal corticosteroids to specific populations of women.

No findings specifically relevant to different gestational ages at time of therapy were identified.

Judgement

☐	☒	☐	☐	☐	☐
Don't know	Varies	No	Probably No	Probably Yes	Yes

3.6 Feasibility

Is antenatal corticosteroid therapy of women at risk of imminent preterm birth feasible to implement?

Research evidence

Findings from a mixed-methods systematic review which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth (24). Across different contexts there were substantial variations in the content of antenatal corticosteroid guidelines, typically around correct administration relating to appropriate gestational age, assessing imminent preterm birth, determining whether maternal infection is present, whether the childbirth and preterm newborn care environment is adequate, and its use in specific populations of women (*moderate confidence*). Quantitative evidence from four studies (three moderate-quality studies and one low-quality study) mirrored these findings.

Health care providers' knowledge about guidelines was variable. High knowledge and experience in administration was a facilitator, while lack of knowledge and outdated knowledge were barriers to appropriate use. Key knowledge gaps were differences between research evidence and clinical experience, and current clinical management standards related to courses, dosing and duration (*moderate confidence*). Quantitative evidence from 12 studies (two high-quality studies, four moderate-quality studies, five low-quality studies, and one very low-quality study) also found variable provider knowledge. Facilitators of knowledge and use included positive attitudes, improved knowledge, exposure to training, conferences, guidelines and research articles.

The unpredictability of preterm birth, including difficulty in diagnosing threatened versus imminent preterm birth, can lead to health care provider hesitation in administering antenatal corticosteroids *(moderate confidence)*, which may affect the duration of fetal exposure.

Maintaining a consistent stock of antenatal corticosteroids in the maternity ward and emergency department, and the availability of providers who are able to assess women in preterm labour, were seen as critical to ensuring women received prompt treatment (*high confidence*). In quantitative evidence from four studies (two high-quality studies, two moderate-quality studies, and one low-quality study), providers and policy-makers found that insufficient budgets resulted in sub-optimal procurement and distribution.

In some country guidelines and in clinical practice, administration of antenatal corticosteroids is allowed only at tertiary facilities where comprehensive emergency obstetric and newborn care services and essential preterm newborn care interventions are available. While some guidelines allow pre-referral first-dose administration at lower-level facilities, implementation of this is limited due to challenges around identifying preterm labour, lack of knowledge about importance of pre-referral dosing, and transportation issues (*high confidence*). Quantitative evidence from three studies (one high-, one moderate- and one low-quality study supported these qualitative findings.

Health care providers described time constraints as a critical overarching barrier, due to the acute nature and time pressures of imminent preterm birth, high workloads and competing tasks (*moderate confidence*). Quantitative evidence from four studies (two high-quality studies, two moderate-quality studies and one low-quality study) also found that insufficient time, difficulties in administering antenatal corticosteroids and high workloads were barriers.

No findings specifically relevant to different gestational ages at time of therapy were identified.

Additional considerations

Considering the findings from the Cochrane review on antenatal corticosteroid efficacy and the Cochrane review on strategies to optimize the use of antenatal corticosteroid therapy, it is important to ensure that antenatal corticosteroids are only administered to eligible women in a context in which adequate maternal and preterm newborn care are available.

A 2020 systematic review identified two studies assessing quality of dexamethasone (32). The prevalence of failed dexamethasone samples ranged from 3.14% to 32.2% due to inadequate Active Pharmacological Ingredient. A higher prevalence of failed dexamethasone samples was seen at point of care and in the public sector.

Judgement

☐	☐	☐	☐	☒	☐
Don’t know	Varies	No	Probably No	Probably Yes	Yes

4 Summary of judgements table

Desirable effects – overall	Don't know	Varies	Trivial	Small	Moderate	✓ **Large**
Desirable effects – ≤35 weeks	Don't know	Varies	Trivial	Small	Moderate	✓ **Large**
Desirable effects – ≥34 weeks	Don't know	Varies	Trivial	Small	✓ **Moderate**	Large
Undesirable effects – overall	Don't know	Varies	Large	Moderate	Small	✓ **Trivial**
Undesirable effects – ≤35 weeks	Don't know	Varies	Large	Moderate	Small	✓ **Trivial**
Undesirable effects – ≥34 weeks	Don't know	Varies	Large	✓ **Moderate**	Small	Trivial
Certainty of the evidence – maternal: overall	No included studies	Very low	✓ **Low**	Moderate	High	
Certainty of the evidence – maternal: ≤35 weeks	No included studies	Very low	✓ **Low**	Moderate	High	
Certainty of the evidence – maternal: ≥34 weeks	No included studies	Very low	Low	Moderate	✓ **High**	
Certainty of the evidence – neonatal: overall	No included studies	Very low	Low	✓ **Moderate**	High	
Certainty of the evidence – neonatal: ≤35 weeks	No included studies	Very low	Low	✓ **Moderate**	High	
Certainty of the evidence – neonatal: ≥34 weeks	No included studies	Very low	✓ **Low**	Moderate	High	
Values	Important uncertainty or variability	✓ **Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability		

Balance of effects – overall	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Balance of effects – ≤35 weeks	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Balance of effects – ≥34 weeks	Don't know	Varies	Favours comparator	Probably favours comparator	✓ **Does not favour either**	Probably favours intervention	Favours intervention
Resources required	Don't know	✓ **Varies**	Large costs	Moderate costs	Negligible costs or savings	Moderate savings	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High		
Cost–effectiveness	Don't know	✓ **Varies**	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Equity	✓ **Don't know**	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased
Acceptability	Don't know	✓ **Varies**	No	Probably No	Probably Yes	Yes	
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	

5 Summary of findings table

Source: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020;12:CD004454.

5.1 All randomized women

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Maternal death												
6	randomized trials	not serious	not serious	not serious	very serious [a]	none	6/3144 (0.2%)	5/3100 (0.2%)	**RR 1.19** (0.36 to 3.89)	**0 fewer per 1000** (from 1 fewer to 5 more)	⨁⨁◯◯ LOW	CRITICAL
Maternal admission into adult intensive care unit												
2	randomized trials	not serious	not serious	not serious	very serious [b]	none	6/160 (3.8%)	8/159 (5.0%)	**RR 0.74** (0.26 to 2.05)	**13 fewer per 1000** (from 37 fewer to 53 more)	⨁⨁◯◯ LOW	CRITICAL
Chorioamnionitis												
15	randomized trials	serious [c]	not serious	not serious	serious [d]	none	128/4195 (3.1%)	148/4179 (3.5%)	**RR 0.86** (0.69 to 1.08)	**5 fewer per 1000** (from 11 fewer to 3 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Endometritis												
10	randomized trials	not serious	not serious	not serious	serious [d]	none	71/3400 (2.1%)	62/3364 (1.8%)	**RR 01.14** (0.82 to 1.58)	**3 more per 1000** (from 3 fewer to 11 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Postnatal fever												
5	randomized trials	serious [c]	not serious	not serious	serious [d]	none	50/663 (7.5%)	54/660 (8.2%)	**RR 0.92** (0.64 to 1.33)	**7 fewer per 1000** (from 29 fewer to 27 more)	⨁⨁◯◯ LOW	CRITICAL
Maternal side-effects at first dose[5]												
1	randomized trial	not serious	not serious	not serious	not serious	none	201/1428 (14.1%)	283/1397 (20.3%)	**RR 0.69** (0.59 to 0.82)	**63 fewer per 1000** (from 83 fewer to 36 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Perinatal death (fetal and neonatal death)												
14	randomized trials	not serious	not serious	not serious	not serious	none	653/4963 (13.2%)	762/4870 (15.6%)	**RR 0.85** (0.77 to 0.93)	**23 fewer per 1000** (from 36 fewer to 11 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

[5] This was a placebo-controlled trial of IM betamethasone in the late preterm period conducted in 17 hospitals in the USA. The reduction in maternal side-effects at first dose were primarily driven by participants reporting less events of pain, bruising and swelling at injection site.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Fetal death												
14	randomized trials	not serious	not serious	not serious	not serious	none	201/4963 (4.0%)	198/4870 (4.1%)	**RR 1.01** (0.83 to 1.22)	**0 fewer per 1000** (from 7 fewer to 9 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Neonatal death												
22	randomized trials	serious [c]	not serious	not serious	not serious	none	497/5380 (9.2%)	621/5229 (11.9%)	**RR 0.78** (0.70 to 0.87)	**26 fewer per 1000** (from 36 fewer to 15 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Respiratory distress syndrome												
26	randomized trials	serious [c]	not serious	not serious	not serious	none	612/5664 (10.8%)	815/5519 (14.8%)	**RR 0.71** (0.65 to 0.78)	**43 fewer per 1000** (from 52 fewer to 32 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Moderate/severe respiratory distress syndrome												
7	randomized trials	serious [c]	not serious	not serious	not serious	none	203/2460 (8.3%)	278/2414 (11.5%)	**RR 0.70** (0.59 to 0.83)	**35 fewer per 1000** (from 47 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Intraventricular haemorrhage												
12	randomized trials	serious [c]	not serious	serious [e]	not serious	none	86/4258 (2.0%)	140/4217 (3.3%)	**RR 0.58** (0.45 to 0.75)	**14 fewer per 1000** (from 18 fewer to 8 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Systemic infection in the first 48 hours of life												
7	randomized trials	serious [c]	not serious	not serious	not serious	none	39/858 (4.5%)	64/850 (7.5%)	**RR 0.60** (0.41 to 0.88)	**30 fewer per 1000** (from 44 fewer to 9 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Necrotising enterocolitis												
10	randomized trials	serious [c]	not serious	not serious	not serious	none	27/2380 (1.1%)	53/2322 (2.3%)	**RR 0.50** (0.32 to 0.78)	**11 fewer per 1000** (from 16 fewer to 5 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Chronic lung disease												
5	randomized trials	serious [c]	serious [f]	not serious	serious [d]	none	48/382 (12.6%)	50/363 (13.8%)	**RR 0.86** (0.41 to 1.79)	**19 fewer per 1000** (from 81 fewer to 109 more)	⨁◯◯◯ VERY LOW	CRITICAL
Neonatal hypoglycaemia (not a pre-specified outcome in the Cochrane review)												
4	randomized trials	not serious	serious [f]	not serious	not serious	none	668/2908 (23.0%)	551/2845 (19.4%)	**RR 1.19** (1.07 to 1.31)	**37 more per 1000** (from 14 more to 60 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Surfactant use												
6	randomized trials	not serious	not serious	not serious	not serious	none	77/3083 (2.5%)	117/3021 (3.9%)	**RR 0.65** (0.50 to 0.85)	**14 fewer per 1000** (from 19 fewer to 6 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Admission to neonatal intensive care unit												
9	randomized trials	serious [c]	not serious	not serious	not serious	none	1647/3358 (49.0%)	1696/3309 (51.3%)	**RR 0.96** (0.91 to 1.00)	**21 fewer per 1000** (from 46 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Mean duration of neonatal hospitalization (days)												
5	randomized trials	serious [c]	not serious	not serious	serious [d]	none	399	389	–	MD **0.18 higher** (0.51 lower to 0.87 higher)	⨁⨁◯◯ LOW	CRITICAL
Use of mechanical ventilation/CPAP												
11	randomized trials	not serious	not serious	not serious	not serious	none	381/2271 (16.8%)	506/2248 (22.5%)	**RR 0.75** (0.66 to 0.84)	**56 fewer per 1000** (from 77 fewer to 36 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Mean duration of mechanical ventilation/CPAP (days)												
3	randomized trials	not serious	serious [f]	not serious	serious [d]	none	244	227	–	MD **1.91 lower** (4.59 lower to 0.76 higher)	⨁⨁◯◯ LOW	CRITICAL
Mean birth weight (g)												
19	randomized trials	serious [c]	not serious	not serious	serious [d]	none	4823	4728	–	MD **14.02 lower** (33.79 lower to 5.76 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Small-for-gestational age												
5	randomized trials	not serious	not serious	not serious	serious [d]	none	328/1774 (18.5%)	283/1704 (16.6%)	**RR 1.11** (0.96 to 1.28)	**18 more per 1000** (from 7 fewer to 47 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Death in childhood												
4	randomized trials	not serious	not serious	not serious	serious [d]	none	16/537 (3.0%)	20/473 (4.2%)	**RR 0.68** (0.36 to 1.27)	**14 fewer per 1000** (from 27 fewer to 11 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cerebral palsy in childhood												
5	randomized trials	serious [c]	not serious	not serious	serious [d]	none	20/490 (4.1%)	28/414 (6.8%)	**RR 0.60** (0.34 to 1.03)	**27 fewer per 1000** (from 45 fewer to 2 more)	⨁⨁◯◯ LOW	CRITICAL
Neurodevelopmental disability in childhood – Developmental delay												
3	randomized trials	serious [c]	not serious	not serious	not serious	none	14/316 (4.4%)	22/284 (7.7%)	**RR 0.51** (0.27 to 0.97)	**38 fewer per 1000** (from 57 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Neurodevelopmental disability in childhood – Intellectual impairment												
3	randomized trials	serious [c]	not serious	not serious	serious [d]	none	16/409 (3.9%)	17/369 (4.6%)	**RR 0.86** (0.44 to 1.69)	**6 fewer per 1000** (from 26 fewer to 32 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Neurodevelopmental disability in childhood – Hearing impairment												
2	randomized trials	serious [c]	not serious	not serious	very serious [b]	none	1/100 (1.0%)	1/66 (1.5%)	**RR 0.64** (0.04 to 9.87)	**5 fewer per 1000** (from 15 fewer to 134 more)	⨁◯◯◯ VERY LOW	CRITICAL
Neurodevelopmental disability in childhood – Visual impairment												
2	randomized trials	serious [c]	not serious	not serious	very serious [b]	none	9/100 (9.0%)	11/66 (16.7%)	**RR 0.55** (0.24 to 1.23)	**75 fewer per 1000** (from 127 fewer to 38 more)	⨁◯◯◯ VERY LOW	CRITICAL
Behavioural/learning difficulties in childhood												
1	randomized trial	serious [g]	not serious	not serious	very serious [b]	none	9/54 (16.7%)	7/36 (19.4%)	**RR 0.86** (0.35 to 2.09)	**27 fewer per 1000** (from 126 fewer to 212 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Wide confidence interval crossing line of no effect; effect estimate based on few events

b. Wide confidence interval crossing line of no effect; effect estimate based on small sample size and few events

c. Most studies contributing data had design limitations

d. Wide confidence interval crossing line of no effect

e. In some trials only a subset of infants was screened for intraventricular haemorrhage (IVH); some trials diagnosed IVH at postmortem only.

f. Statistical heterogeneity (I2>60%)

g. One study with design limitations

5.2 Gestational age at therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Maternal outcomes												
Chorioamnionitis – gestational age at therapy ≤35 weeks + 0 days												
13	randomized trials	serious [a]	not serious	not serious	serious [b]	none	108/2575 (4.2%)	113/2557 (4.4%)	**RR 0.94** (0.73 to 1.20)	**3 fewer per 1000** (from 12 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL
Chorioamnionitis – gestational age at therapy ≥34 weeks + 0 days												
3	randomized trials	not serious	not serious	not serious	not serious	none	20/1620 (1.2%)	35/1622 (2.2%)	**RR 0.58** (0.34 to 0.99)	**9 fewer per 1000** (from 14 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Infant outcomes												
Perinatal death – gestational age at therapy ≤35 weeks + 0 days												
11	randomized trials	not serious	not serious	not serious	not serious	none	643/3132 (20.5%)	756/3053 (24.8%)	**RR 0.83** (0.76 to 0.91)	**42 fewer per 1000** (from 59 fewer to 22 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Perinatal death – gestational age at therapy ≥34 weeks + 0 days												
4	randomized trials	not serious	not serious	not serious	very serious [c]	none	10/1831 (0.5%)	6/1817 (0.3%)	**RR 1.70** (0.68 to 4.28)	**2 more per 1000** (from 1 fewer to 11 more)	⨁⨁◯◯ LOW	CRITICAL
Fetal death – gestational age at therapy ≤35 weeks + 0 days												
11	randomized trials	not serious	not serious	not serious	not serious	none	197/3132 (6.3%)	196/3053 (6.4%)	**RR 0.99** (0.81 to 1.19)	**1 fewer per 1000** (from 12 fewer to 12 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Fetal death – gestational age at therapy ≥34 weeks + 0 days												
4	randomized trials	not serious	not serious	not serious	very serious [c]	none	4/1831 (0.2%)	2/1817 (0.1%)	**RR 1.92** (0.42 to 8.82)	**1 more per 1000** (from 1 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL
Neonatal death – gestational age at therapy ≤35 weeks + 0 days												
19	randomized trials	serious [a]	not serious	not serious	not serious	none	491/3549 (13.8%)	617/3412 (18.1%)	**RR 0.77** (0.69 to 0.86)	**42 fewer per 1000** (from 56 fewer to 25 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Neonatal death – gestational age at therapy ≥34 weeks + 0 days												
4	randomized trials	not serious	not serious	not serious	very serious [c]	none	6/1831 (0.3%)	4/1817 (0.2%)	**RR 1.51** (0.49 to 4.61)	**1 more per 1000** (from 1 fewer to 8 more)	⨁⨁◯◯ LOW	CRITICAL
Respiratory distress syndrome – gestational age at therapy ≤35 weeks + 0 days												
20	randomized trials	serious [a]	not serious	not serious	not serious	none	497/3587 (13.9%)	663/3454 (19.2%)	**RR 0.70** (0.63 to 0.78)	**58 fewer per 1000** (from 71 fewer to 42 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Respiratory distress syndrome – gestational age at therapy ≥34 weeks + 0 days												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	115/2077 (5.5%)	152/2065 (7.4%)	**RR 0.75** (0.60 to 0.95)	**18 fewer per 1000** (from 29 fewer to 4 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
IVH – gestational age at therapy ≤35 weeks + 0 days												
11	randomized trials	serious [a]	not serious	serious [d]	not serious	none	84/2726 (3.1%)	140/2686 (5.2%)	**RR 0.56** (0.44 to 0.72)	**23 fewer per 1000** (from 29 fewer to 15 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
IVH – gestational age at therapy ≥34 weeks + 0 days												
2	randomized trials	not serious [a]	not serious	serious [d]	very serious [c]	none	2/1532 (0.1%)	0/1531 (0.0%)	**RR 4.91** (0.24 to 102.09)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Hypoglycaemia – gestational age at therapy ≤35 weeks + 0 days												
1	randomized trials	not serious	not serious	not serious	serious [b]	none	301/1242 (24.2%)	328/1217 (27.0%)	**RR 0.85** (0.60 to 1.21)	**40 fewer per 1000** (from 108 fewer to 57 more)	⨁⨁⨁◯ MODERATE	
Hypoglycaemia – gestational age at therapy ≥34 weeks + 0 days												
3	randomized trials	not serious	not serious	not serious	Not serious	none	367/1666 (22.0%)	223/1628 (13.7%)	**RR 1.61** (1.38 to 1.87)	**84 more per 1000** (from 52 more to 9 more)	⨁⨁⨁⨁ HIGH	
Birth weight – gestational age at therapy ≤35 weeks + 0 days												
13	randomized trials	serious [a]	not serious	not serious	serious [b]	none	2748	2664	–	MD **9.78 lower** (40.81 lower to 21.24 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Birth weight – gestational age at therapy ≥34 weeks + 0 days												
7	randomized trials	serious [a]	not serious	not serious	serious [b]	none	2075	2064	–	MD **15.75 lower** (41.09 lower to 9.58 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Most studies contributing data had design limitations

b. Wide confidence interval crossing line of no effect

c. Wide confidence interval crossing line of no effect, estimate based on few events

d. In some trials only a subset of infants were screened for IVH; some trials diagnosed IVH at postmortem only

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Evidence-to-decision framework 1.1

Antenatal corticosteroids compared to placebo or no treatment: **Interval between corticosteroid therapy and birth**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human models have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.
- Questions remain as to what (if any) time interval between administration and birth is associated with most substantive improvement in outcomes, or if certain time intervals are associated with a reduction or lack of benefit, or harm.
- Animal studies suggest that longer time intervals favour fetal lung maturation. In addition, subgroup or secondary analyses of trials, as well as observational studies, have explored the associations between the administration-to-birth interval and maternal and newborn outcomes. It is not yet clear if an optimal administration-to-birth interval exists.

2 Question

Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)? If so:

- **Which population of pregnant women should be offered antenatal corticosteroids, considering the interval between corticosteroid administration and birth?**

Problem: Adverse outcomes due to preterm birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[6]

Settings: Low- middle- and high-income settings

Subgroups: Populations of women experiencing different corticosteroid administration-to-birth intervals (<24 hours, <48 hours, 1 to 7 days, >7 days)

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6 These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

Evidence on this question is derived from two sources:

1) a post-hoc subgroup analysis of the 2020 Cochrane systematic review on efficacy of antenatal corticosteroids conducted for the purpose of this guideline

2) a systematic review of studies reporting the effects of antenatal corticosteroids at different administration-to-birth intervals.

1) Summary of evidence – Post-hoc subgroup analysis of the 2020 Cochrane review

Evidence on the effects of antenatal corticosteroids versus placebo or no treatment for reducing adverse outcomes associated with prematurity was derived from a Cochrane systematic review updated in 2020 (12). In that review, interval between corticosteroid administration and birth was not a pre-specified subgroup analysis, on the basis that this interval is a post-randomization variable (i.e. it is not known at the time of randomization). Considering the clinical relevance of this question for this guideline, an additional, post-hoc analysis for this subgroup was prepared. However, this analysis should be interpreted with caution and certainty of the evidence has been downgraded accordingly.

The subgroup analysis comprised data from 10 trials (5723 women, 6163 infants). The included studies came from a range of health care systems and settings. Three studies were conducted in the United States of America, two in Finland and one each in the Netherlands, New Zealand, South Africa and the United Kingdom of Great Britain and Northern Ireland. One study took place in the USA and Germany and another study took place in Bangladesh, India, Kenya, Nigeria and Pakistan.

Obstetric indications for recruitment of women to these trials were premature rupture of membranes, spontaneous preterm labour and planned preterm delivery. The included studies recruited women with a wide range of gestational ages (24 weeks 0 days to 36 weeks 6 days). Three trials included women from 24 weeks, three from 26 weeks, two from 28 weeks and one at less than 34 weeks. Gestational age range was not stated in one study.

One trial recruited only women with singleton pregnancy and nine recruited women with singleton or multiple pregnancy.

Two trials specifically excluded women with premature rupture of membranes. Three trials reported outcome data for women with premature rupture of membranes. The remaining five trials reported data for a mixed population or the membrane status of included women was unclear.

Eight trials reported on outcomes associated with intervals between first dose and birth of <24 hours or 1–7 days. Six reported on an interval of >7 days and two reported on an interval of <48 hours.

Antenatal corticosteroids used in the studies included in the subgroup analysis were betamethasone (5 studies; 1647 women, 1770 infants) and dexamethasone (4 studies; 3909 women, 4224 infants). One study used betamethasone and methylprednisolone in the two treatment arms (167 women, 169 infants).

Table. 1 Summary of absolute effects per 1000 (95% confidence interval) by interval between antenatal corticosteroid therapy and birth

Key:	High certainty (benefit)	Moderate certainty (probable benefit)	Low certainty (possible benefit)	High certainty (harm)	Moderate certainty (probable harm)	Low certainty (possible harm)	High certainty (no difference)	Moderate certainty (probable no difference)	Low certainty (possible no difference)	Very low certainty (uncertain)

Outcome	Overall	<24 hours	<48 hours	1–7 days	>7 days	Subgroup differences
Chorioamnionitis	**Possibly no difference** 5 fewer (11 fewer to 3 more)	**Uncertain**	**Uncertain**	**Possibly no difference** 37 fewer (61 fewer to 9 more)	**Uncertain**	No suggested difference in effect (p=0.36; I^2=6.8%)
Perinatal death	**Reduced** 23 fewer (36 fewer to 11 fewer)	**Possibly no difference** 32 fewer (119 fewer to 93 more)	**Probably reduced** 130 fewer (187 fewer to 44 fewer)	**Possibly no difference** 30 fewer (106 fewer to 76 more)	**Uncertain**	No suggested difference in effect (p=0.30; I^2=17.8%)
Fetal death	**No difference** 0 fewer (7 fewer to 9 more)	**Uncertain**	**Possibly no difference** 22 fewer (61 fewer to 51 more)	**Possibly no difference** 44 more (50 fewer to 589 more)	**Possibly no difference** 22 more (14 fewer to 92 more)	No suggested difference in effect (p=0.36; I^2=6.4%)
Neonatal death	**Probably reduced** 26 fewer (36 fewer to 15 fewer)	**Possibly no difference** 3 fewer (47 fewer to 47 more)	**Probably reduced** 123 fewer (168 fewer to 46 fewer)	**Probably reduced** 54 fewer (87 fewer to 12 fewer)	**Uncertain**	**Difference in effect** **(p=0.04; I^2=63.7%)**
RDS	**Probably reduced** 43 fewer (52 fewer to 32 fewer)	**Possibly no difference** 19 fewer (91 fewer to 86 more)	**Possibly no difference** 79 fewer (226 fewer to 257 more)	**Uncertain**	**Uncertain**	No suggested difference in effect (p=0.28; I^2=22.5%)
Moderate/severe RDS	**Probably reduced** 35 fewer (47 fewer to 20 fewer)	**Uncertain**	**Probably reduced** 151 fewer (200 fewer to 74 fewer)	**Probably reduced** 123 fewer (153 fewer to 74 fewer)	**Uncertain**	**Difference in effect** **(p=0.03; I^2=67.4%)**
Intraventricular hemorrhage	**Possibly reduced** 14 fewer (18 fewer to 8 fewer)	**Uncertain**	**Possibly reduced** 75 fewer (92 fewer to 25 fewer)	**Uncertain**	**Uncertain**	No suggested difference in effect (p=0.25; I^2=27.7%)
Mean birth weight	**Possibly no difference** MD 14.02 lower (33.79 lower to 5.76 higher)	**Uncertain**	**Possibly no difference** MD 5.9 higher (131.95 lower to 120.15 higher)	**Possibly no difference** MD 105.92 lower (212.52 lower to 0.68 higher)	**Probably reduced** MD 147.01 lower (291.97 lower to 2.05 lower)	No suggested difference in effect (p=0.17; I^2=40.0%)

Maternal outcomes

- **Maternal infectious morbidity**: Antenatal corticosteroid therapy may result in little or no difference in risk of chorioamnionitis in women giving birth 1–7 days after first dose (RR 0.55, 95% CI 0.27 to 1.11; 1 trial, 482 women; *low certainty*). The evidence on the effect of antenatal corticosteroids on risk of chorioamnionitis in women giving birth at <24 hours, <48 hours and >7 days after first dose is very uncertain.
- No data were available for other maternal outcomes (severe maternal morbidity or death, maternal side effects, maternal well-being, maternal satisfaction).

Infant outcomes

- **Fetal and neonatal death**: Antenatal corticosteroid therapy probably reduces the risk of perinatal death in babies born <48 hours (RR 0.59, 95% CI 0.41 to 0.86; 1 trial, 373 infants; *moderate certainty*), largely because it probably reduces the risk of neonatal death in this group (RR 0.49, 95% CI 0.30 to 0.81; 1 trial, 339 infants; *moderate certainty*) as there may be no difference in risk of fetal death among babies born at <48 hours (RR 0.78, 95% CI 0.40 to 1.51; 1 trial, 373 infants; *low certainty*). Risk of neonatal death is also probably reduced among babies born 1–7 days after first dose (RR 0.77, 95% CI 0.63 to 0.95; 3 trials, 1387 infants; *moderate certainty*).

  Antenatal corticosteroid therapy may result in little or no difference in risk of: perinatal death among babies born <24 hours after first dose (RR 0.90, 95% CI 0.63 to 1.29; 3 trials, 1422 infants; *low certainty*) and at 1–7 days after first dose (RR 0.90, 95% CI 0.65 to 1.25; 3 trials, 1525 infants; *low certainty*); fetal death among babies born <48 hours (RR 0.78, 95% CI 0.40 to 1.51; 1 trial, 373 infants; *low certainty*), 1–7 days (RR 1.63, 95% CI 0.28 to 9.46; 2 trials, 553 infants; *low certainty*) and >7 days after first dose (RR 1.42, 95% CI 0.74 to 2.72; 2 trials, 539 infants; *low certainty*); and neonatal death among babies born <24 hours after first dose (RR 0.99, 95% CI 0.83 to 1.17; 4 trials, 1361 infants; *low certainty*).

  The evidence is very uncertain for the effect of antenatal corticosteroid therapy on risk of fetal death among babies born <24 hours after first dose and on the risk of perinatal and neonatal death among babies born >7 days after first dose.
- **Severe neonatal morbidity**: Antenatal corticosteroid therapy may result in little or no difference in risk of respiratory distress syndrome among babies born <48 hours after first dose (RR 0.77, 95% CI 0.34 to 1.75; 2 trials, 340 infants; *low certainty*) and <24 hours after first dose (RR 0.93, 95% CI 0.67 to 1.31; 7 trials, 473 infants; *low certainty*). The evidence on the effect of antenatal corticosteroid therapy on risk of respiratory distress syndrome among babies born 1–7 days and >7 days after first dose is very uncertain.

  Antenatal corticosteroid therapy probably reduces the risk of moderate/severe respiratory distress syndrome among babies born <48 hours (RR 0.45, 95% CI 0.27 to 0.73; 1 trial, 326 infants; *moderate certainty*) and 1–7 days after first dose (RR 0.37, 95% CI 0.22 to 0.62; 1 trial, 462 infants; *moderate certainty*). The evidence on the effect of antenatal corticosteroid therapy on risk among babies born <24 hours or >7 days after first dose is very uncertain.

  Antenatal corticosteroid therapy may reduce the risk of intraventricular haemorrhage among babies born <48 hours after first dose (RR 0.26, 95% CI 0.09 to 0.75; 1 trial, 339 infants; *low certainty*). The evidence on the effect of antenatal corticosteroids on risk of intravascular haemorrhage among babies born <24 hours, 1–7 days or >7 days after first dose is very uncertain.

- **Birth weight**: Antenatal corticosteroid therapy probably results in lower mean birth weight among babies born >7 days after first dose (MD –147.01 g, 95% CI –291.97 g to 2.05 g; 1 trial, 486 infants; *moderate certainty*). They may result in little or no difference in mean birth weight among babies born <48 hours (MD –5.9 g, 95% CI –131.95 g to 120.15 g; 1 trial, 373 infants; *low certainty*) or 1–7 days after first dose (MD –105.92 g, 95% CI –212.52 to 0.68 g; 1 trial, 520 infants; *low certainty*). The evidence on the effect of antenatal corticosteroids on mean birth weight among babies born <24 hours after first dose is very uncertain.
- **Long-term morbidity**: No data were available on childhood/long-term outcomes (infant or childhood death, cerebral palsy in childhood, developmental delay in childhood, intellectual impairment in childhood, hearing impairment in childhood, visual impairment in childhood, behavioural/learning difficulties in childhood).

2) Summary of evidence – systematic review of studies reporting the effects of antenatal corticosteroids at different administration-to-birth intervals

A systematic review of randomized trials and observational studies provided additional evidence on the effects of antenatal corticosteroids for different administration-to-birth intervals (13). The review identified 11 trials, 45 cohort studies and 3 case-control studies. The trials included the 10 trials already presented in the above subgroup analysis plus another small trial that compared betamethasone to ambroxol, but reported a sub-analysis comparing different intervals for the betamethasone arm. Findings from the 48 observational studies are presented below.

The cohort studies included at least 28 524 women (some studies did not report the total number of women) and 38 056 neonates. Participants were women with either singleton or multiple pregnancy (20 studies), women with singleton pregnancies only (19 studies) and women with twin pregnancies only (3 studies). Across studies, gestational age ranged from 20 to 37 weeks., Few studies, however, used the exact same range (gestational age range was not reported in two studies).

Antenatal corticosteroid (ACS) administration-to-birth interval and definition of the start time of ACS administration varied across studies, with 29 studies measuring the interval from first dose and the others using different starting points (such as end of first course), or not specifying. There were 65 unique time intervals reported, with the most commonly reported intervals being <24 hours, 1–7 days, 2–7 days and >7 days. Most of the cohort studies were conducted in high-income countries, with six from low- and middle-income countries (LMIC).

The three case-control studies included 469 women and 871 neonates. Gestational age range was 28 to 36 weeks in two studies and 26 to 32 weeks in the third. The three studies all used different administration-to-birth intervals. Two case-control studies were conducted in high-income countries (Israel and USA), and one was conducted in Iran (LMIC).

Maternal outcomes

- **Maternal infectious morbidity**: The evidence on corticosteroid administration-to-birth interval and chorioamnionitis was inconsistent for an interval of >7 days, with both increased risk and no difference compared to placebo or no treatment reported (*low to moderate risk of bias,* 3 studies, at least 3186 women[7]). Studies consistently reported no difference for an interval of <24 hours (*low to moderate risk of bias,* 3 studies, at least 2881 women) and an interval of 2–7 days (*moderate risk of bias*, 2 studies, 3017 women).

[7] One study did not report number of women

Infant outcomes

- **Fetal and neonatal death:** The evidence on corticosteroid administration-to-birth interval and perinatal death was limited. One study (*serious risk of bias,* 460 infants) found a decrease in odds of perinatal mortality with antenatal corticosteroids at an interval of >48 hours compared to no treatment, but not at <48 hours. Two other studies did not detect differences in perinatal mortality for <7 or ≥7 days.
- The evidence on corticosteroid administration-to-birth interval and neonatal death was inconsistent for most time intervals. When compared to no treatment, studies variably reported reduced or increased odds or no difference for <24 hours (*critical to low risk of bias,* 10 studies, 10 703 infants), and no difference or reduced odds for 2–7 days (*serious to moderate risk of bias,* 4 studies, 4058 infants) and >7 days (*serious to low risk of bias,* 4 studies, 6220 neonates). However, reduced odds of neonatal death were consistently reported for an interval of 1–7 days (*critical to low risk of bias,* 3 studies, 4989 women).
- **Severe neonatal morbidity:** The evidence on corticosteroid administration-to-birth interval and respiratory distress syndrome was inconsistent. Observational studies reported that, when compared to no treatment, there were no differences for intervals of <24 hours (*critical to moderate risk of bias,* 5 studies, 1664 infants), and reduced odds or no difference for intervals of 2–7 days (*serious to moderate risk of bias,* 3 studies, 1270 infants) and >7 days (*moderate risk of bias,* 2 studies, 1016 infants).

  The evidence on corticosteroid administration-to-birth interval and intraventricular haemorrhage was consistent for some time intervals. Observational studies reported that, when compared to no treatment, odds of intraventricular haemorrhage were reduced for 1–7 days (*critical to low risk of bias,* 4 studies, 1925 infants) and >7 days (*low to moderate risk of bias,* 4 studies, 4461 infants). However, studies reported reduced odds or no difference for <24 hours (*low to moderate risk of bias,* 5 studies, 4264 infants) or 2–7 days (*moderate risk of bias,* 2 studies, 3097 infants).

  The evidence on corticosteroid administration-to-birth interval and necrotizing enterocolitis was inconsistent. Four studies reported no differences for any time interval (*critical to moderate risk of bias,* 1577 infants). One study found increased odds compared to no treatment for >7 days (*low risk of bias,* 169 infants).

  The evidence on corticosteroid administration-to-birth interval and chronic lung disease was inconsistent for some time intervals, with reduced odds or no difference for 2–7 days (*moderate risk to serious of bias,* 2 studies, 2803 infants) and >7 days (*low to moderate risk of bias,* 2 studies, 919 infants). There was no difference for intervals of <24 hours (*low to moderate risk of bias,* 3 studies, 2881 infants) and 1–7 days (*low risk of bias,* 1 study, 169 infants).

  The evidence on corticosteroid administration-to-birth interval and **neonatal sepsis** was inconsistent – studies found both increased odds or no differences when compared to no treatment for intervals of 2–7 days (*serious to moderate risk of bias,* 4 studies, 3819 infants) and >7 days (*low to moderate risk of bias,* 4 studies, 3734 infants). There were no differences reported for intervals of <24 hours (*low to moderate risk of bias,* 3 studies, 3266 infants) or 1–7 days (*low risk of bias,* 1 study, 169 infants).

Additional data

Statistical modelling

In the aforementioned systematic review (13), an observational study used statistical modelling to further explore the effects of administration-to-birth interval on priority newborn outcomes. The study (14) (11 European countries, 4594 singleton infants with gestational ages between 24 and 31 weeks, without severe anomalies) showed that neonatal mortality immediately reduced within the first 24 hours after administration, including within the first 6 hours. A 50% risk reduction in neonatal death was observed at 18–36 hours. The benefits persisted up to 5 weeks post-administration, though the confidence interval crossed the line of no effect at approximately 24–25 days after administration.

Secondary analysis of the ACTION-1 trial

Data from a secondary analysis of an included trial (WHO, unpublished) also provided additional information. In this analysis, a multivariate logistic regression model was used to assess the association between administration-to-birth intervals (as a continuous variable) for dexamethasone and placebo, and newborn outcomes (neonatal death, baby death, severe respiratory distress at 24 hours and at 168 hours) among women at risk of imminent preterm birth who received a single course. The analysis found:

- the risk reduction for neonatal death was consistently at its lowest at 13–14 days after dexamethasone administration, regardless of gestational age at first dose
- for the outcomes severe respiratory distress at 24 hours or 168 hours, the risks continued to decrease with increasing intervals from 0 through 28 days (i.e. longer periods were always more beneficial, regardless of gestational age).

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids, considering interval between antenatal corticosteroid therapy and birth?

Judgement

☐	☒	☐	☐	☐	☐
Don't know	Varies	Trivial	Small	Moderate	Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids, considering interval between antenatal corticosteroid therapy and birth?

Judgement

☐	☒	☐	☐	☐	☐
Don't know	Varies	Large	Moderate	Small	Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids on outcomes, considering interval between antenatal corticosteroid therapy and birth?

☐	☐	☒	☐	☐
No included studies	Very low	Low	Moderate	High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids, considering interval between antenatal corticosteroid therapy and birth?

Research evidence

Findings from a mixed methods systematic review (15) on the appropriate use of interventions in the management of women experiencing preterm birth show the following:

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a health care provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most health care providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to different intervals between corticosteroid therapy and birth were identified.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the benefits of an intervention with the potential to reduce the risk of newborn death and serious morbidity even when given at short interval before birth. The GDG is confident that mothers, health care providers and policy-makers in any setting will invariably place a higher value on these benefits compared to any inconvenience that incomplete dosing of steroids might cause to the mother or the health system.

Judgement

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids or the comparator, considering interval between antenatal corticosteroid therapy and birth?

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids, considering interval between antenatal corticosteroid therapy and birth?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (16). Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed. The available studies did not explore differences in cost–effectiveness of antenatal corticosteroids for different intervals between therapy and birth.

Additional considerations

Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. A longer administration-to-birth interval (e.g. >7 days) may be associated with higher costs (e.g. longer hospital admission, use of repeat courses). Considering that benefit appears to vary for different administration-to-birth intervals, it is likely that cost–effectiveness also varies. Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (17). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.

Resource	Description
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (18) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (18) — In the systematic review of cost–effectiveness studies (16), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administration of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐	☒	☐	☐	☐	☐	☐
Don't know	Varies	Large costs	Moderate costs	Negligible costs or savings	Moderate savings	Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☐ Don't know	☒ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity, considering interval between antenatal corticosteroid therapy and birth?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (19). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (20). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (21).

Evidence from trials demonstrates that antenatal corticosteroid use is effective, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit from the protection offered by a relatively cheap and readily available medication in low-resource settings, thus increasing equity.

Judgement

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid treatment for women at risk of imminent preterm birth acceptable to key stakeholders, considering interval between therapy and birth?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (15).

In summary, the review found the following.

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.

No findings specific to different intervals between corticosteroid therapy and birth were identified.

Judgement

☐	☐	☐	☐	☒	☐
Don't know	Varies	No	Probably No	Probably Yes	Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth feasible to implement, considering interval between antenatal corticosteroid therapy and birth?

Research evidence

Findings from a mixed-methods systematic review (15) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following.

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well-stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and newborn care), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specific to different intervals between corticosteroid therapy and birth were identified.

Judgement

☐	☐	☐	☐	☒	☐
Don't know	Varies	No	Probably No	Probably Yes	Yes

4 Summary of judgements table

Desirable effects	Don't know	✓ **Varies**	Trivial	Small	Moderate	Large
Undesirable effects	Don't know	✓ **Varies**	Large	Moderate	Small	Trivial
Certainty of the evidence	No included studies	Very low	✓ **Low**	Moderate	High	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	No important uncertainty or variability		
Balance of effects	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Resources required	Don't know	✓ **Varies**	Large costs	Moderate costs	Negligible costs or savings	Moderate savings	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High		
Cost–effectiveness	Don't know	✓ **Varies**	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Equity	Don't know	Varies	Reduced	Probably reduced	Probably no impact	✓ **Probably increased**	Increased
Acceptability	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	

5 Summary of findings table

Source: Posthoc subgroup analysis of: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020;12:CD004454.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Chorioamnionitis – In women giving birth < 24 hours after 1st dose												
2	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	7/113 (6.2%)	10/126 (7.9%)	**RR 0.83** (0.33 to 2.09)	**13 fewer per 1000** (from 53 fewer to 87 more)	⨁◯◯◯ VERY LOW	CRITICAL
Chorioamnionitis – In women giving birth < 48 hours after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	very serious [c]	none	11/150 (7.3%)	18/191 (9.4%)	**RR 0.78** (0.38 to 1.60)	**21 fewer per 1000** (from 58 fewer to 57 more)	⨁◯◯◯ VERY LOW	CRITICAL
Chorioamnionitis – In women giving birth 1–7 days after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	serious [d]	none	11/242 (4.5%)	20/240 (8.3%)	**RR 0.55** (0.27 to 1.11)	**37 fewer per 1000** (from 61 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL
Chorioamnionitis – In women giving birth > 7 days after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	very serious [c]	none	11/229 (4.8%)	7/232 (3.0%)	**RR 1.59** (0.63 to 4.03)	**18 more per 1000** (from 11 fewer to 91 more)	⨁◯◯◯ VERY LOW	CRITICAL
Fetal and neonatal deaths – In babies born < 24 hours after 1st dose												
3	randomized trials	serious [a]	not serious	not serious	serious [d]	none	211/662 (31.9%)	247/760 (32.5%)	**RR 0.90** (0.63 to 1.29)	**32 fewer per 1000** (from 119 fewer to 93 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Fetal and neonatal deaths – In babies born < 48 hours after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	not serious	none	31/165 (18.8%)	66/208 (31.7%)	**RR 0.59** (0.41 to 0.86)	**130 fewer per 1000** (from 187 fewer to 44 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Fetal and neonatal deaths – In babies born 1–7 days after 1st dose												
3	randomized trials	serious [a]	not serious	not serious	serious [d]	none	209/810 (25.8%)	217/715 (30.3%)	**RR 0.90** (0.65 to 1.25)	**30 fewer per 1000** (from 106 fewer to 76 more)	⨁⨁◯◯ LOW	CRITICAL
Fetal and neonatal deaths – In babies born > 7 days after 1st dose												
3	randomized trials	serious [a]	serious [e]	not serious	serious [d]	none	95/738 (12.9%)	112/718 (15.6%)	**RR 0.99** (0.42 to 2.32)	**2 fewer per 1000** (from 90 fewer to 206 more)	⨁◯◯◯ VERY LOW	CRITICAL
Fetal deaths – In babies born < 24 hours after 1st dose												
2	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	9/122 (7.4%)	18/139 (12.9%)	**RR 0.65** (0.31 to 1.36)	**45 fewer per 1000** (from 89 fewer to 47 more)	⨁◯◯◯ VERY LOW	CRITICAL
Fetal deaths – In babies born < 48 hours after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	serious [d]	none	13/165 (7.9%)	21/208 (10.1%)	**RR 0.78** (0.40 to 1.51)	**22 fewer per 1000** (from 61 fewer to 51 more)	⨁⨁◯◯ LOW	CRITICAL
Fetal deaths – In babies born 1–7 days after 1st dose												
2	randomized trials	serious [a]	not serious	not serious	serious [d]	none	22/280 (7.9%)	19/273 (7.0%)	**RR 1.63** (0.28 to 9.46)	**44 more per 1000** (from 50 fewer to 589 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Fetal deaths – In babies born > 7 days after 1st dose												
2	randomized trials	serious [a]	not serious	not serious	serious [d]	none	22/277 (7.9%)	14/262 (5.3%)	**RR 1.42** (0.74 to 2.72)	**22 more per 1000** (from 14 fewer to 92 more)	⨁⨁◯◯ LOW	CRITICAL
Neonatal deaths – In babies born < 24 hours after 1st dose												
4	randomized trials	serious [a]	not serious	not serious	serious [d]	none	167/637 (26.2%)	202/724 (27.9%)	**RR 0.99** (0.83 to 1.17)	**3 fewer per 1000** (from 47 fewer to 47 more)	⨁⨁◯◯ LOW	CRITICAL
Neonatal deaths – In babies born < 48 hours after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	not serious	none	18/152 (11.8%)	45/187 (24.1%)	**RR 0.49** (0.30 to 0.81)	**123 fewer per 1000** (from 168 fewer to 46 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Neonatal deaths – In babies born 1–7 days after 1st dose												
3	randomized trials	serious [a]	not serious	not serious	not serious	none	135/736 (18.3%)	153/651 (23.5%)	**RR 0.77** (0.63 to 0.95)	**54 fewer per 1000** (from 87 fewer to 12 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Neonatal deaths – In babies born > 7 days after 1st dose												
3	randomized trials	serious [a]	serious [e]	not serious	serious [d]	none	46/689 (6.7%)	58/664 (8.7%)	**RR 1.09** (0.25 to 4.69)	**8 more per 1000** (from 65 fewer to 321 more)	⨁◯◯◯ VERY LOW	CRITICAL
Respiratory distress syndrome – In babies born < 24 hours after 1st dose												
7	randomized trials	serious [a]	not serious	not serious	serious [d]	none	63/236 (26.7%)	65/237 (27.4%)	**RR 0.93** (0.67 to 1.31)	**19 fewer per 1000** (from 91 fewer to 86 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Respiratory distress syndrome – In babies born < 48 hours after 1st dose												
2	randomized trials	serious [a]	serious [e]	not serious	not serious	none	33/153 (21.6%)	64/187 (34.2%)	**RR 0.77** (0.34 to 1.75)	**79 fewer per 1000** (from 226 fewer to 257 more)	⨁⨁◯◯ LOW	CRITICAL
Respiratory distress syndrome – In babies born 1–7 days after 1st dose												
7	randomized trials	very serious [a,f]	serious [d]	not serious	not serious	none	52/511 (10.2%)	119/503 (23.7%)	**RR 0.49** (0.28 to 0.87)	**119 fewer per 1000** (from 168 fewer to 30 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Respiratory distress syndrome – In babies born > 7 days after 1st dose												
6	randomized trials	very serious [a,f]	not serious	not serious	serious [d]	none	31/444 (7.0%)	29/429 (6.8%)	**RR 0.91** (0.57 to 1.47)	**7 fewer per 1000** (from 33 fewer to 37 more)	⨁◯◯◯ VERY LOW	CRITICAL
Moderate/severe respiratory distress syndrome – In babies born < 24 hours after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	very serious [g]	none	13/82 (15.9%)	23/100 (23.0%)	**RR 0.69** (0.37 to 1.27)	**71 fewer per 1000** (from 145 fewer to 62 more)	⨁◯◯◯ VERY LOW	CRITICAL
Moderate/severe respiratory distress syndrome – In babies born < 48 hours after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	not serious	none	18/147 (12.2%)	49/179 (27.4%)	**RR 0.45** (0.27 to 0.73)	**151 fewer per 1000** (from 200 fewer to 74 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Moderate/severe respiratory distress syndrome – In babies born 1–7 days after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	not serious	none	17/237 (7.2%)	44/225 (19.6%)	**RR 0.37** (0.22 to 0.62)	**123 fewer per 1000** (from 153 fewer to 74 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Moderate/severe respiratory distress syndrome – In babies born > 7 days after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	very serious [c]	none	11/223 (4.9%)	6/223 (2.7%)	**RR 1.83** (0.69 to 4.87)	**22 more per 1000** (from 8 fewer to 104 more)	⨁◯◯◯ VERY LOW	CRITICAL
Interventricular haemorrhage – In babies born < 24 hours after 1st dose												
3	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	7/133 (5.3%)	11/131 (8.4%)	**RR 0.56** (0.22 to 1.39)	**43 fewer per 1000** (from 76 fewer to 38 more)	⨁◯◯◯ VERY LOW	CRITICAL
Interventricular haemorrhage – In babies born < 48 hours after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	serious [h]	none	4/152 (2.6%)	19/187 (10.2%)	**RR 0.26** (0.09 to 0.75)	**75 fewer per 1000** (from 92 fewer to 25 fewer)	⨁⨁◯◯ LOW	CRITICAL
Interventricular haemorrhage – In babies born 1–7 days after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	very serious [c]	none	9/245 (3.7%)	17/237 (7.2%)	**RR 0.51** (0.23 to 1.13)	**35 fewer per 1000** (from 55 fewer to 9 more)	⨁◯◯◯ VERY LOW	CRITICAL
Interventricular haemorrhage – In babies born > 7 days after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	very serious [c]	none	4/226 (1.8%)	2/227 (0.9%)	**RR 2.01** (0.37 to 10.86)	**9 more per 1000** (from 6 fewer to 87 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mean birth weight (grams) – In babies born < 24 hours after 1st dose												
2	randomized trials	serious [a]	not serious	not serious	very serious [g]	none	112	130	–	MD **46.52 higher** (94.26 lower to 187.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Mean birth weight (grams) – In babies born < 48 hours after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	serious [d]	none	165	208	–	MD **5.9 lower** (131.95 lower to 120.15 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Mean birth weight (grams) – In babies born 1–7 days after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	serious [d]	none	264	256	–	MD **105.92 lower** (212.52 lower to 0.68 higher)	⨁⨁◯◯ LOW	CRITICAL
Mean birth weight (grams) - In babies born > 7 days after 1st dose												
1	randomized trial	serious [a]	not serious	not serious	not serious	none	245	241	–	MD **147.01 lower** (291.97 lower to 2.05 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Other bias; analysis is based on post-randomization variable

b. Wide confidence interval crossing line of no effect; estimate based on small sample and few events

c. Wide confidence interval crossing line of no effect, estimate based on few events

d. Wide confidence interval crossing line of no effect

e. Statistical heterogeneity (I^2>60%)

f. Most studies contributing data had design limitations

g. Wide confidence interval crossing line of no effect, estimate based on small sample size

h. Estimate based on few events

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Evidence-to-decision framework 1.2

Antenatal corticosteroids compared to placebo or no treatment: **Single or multiple birth**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.
- The risk of preterm birth is greater for women with multiple pregnancies than with singleton pregnancies – up to 60% of twins and >90% of higher-order multiples are born preterm (12). An estimated 20% of the 14.84 million preterm births occurring worldwide are attributable to women with a multiple pregnancy (1).

2 Question

Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)? If so:

- **Which population of pregnant women should be offered antenatal corticosteroids considering single and multiple birth?**

Problem: Adverse outcomes due to preterm birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[8]

Settings: Low- middle- and high-income settings

Subgroups: Population of women with singleton or multiple pregnancies.

[8] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome, intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

Summary of evidence

Evidence on the effects of antenatal corticosteroids versus placebo or no treatment for reducing adverse effects of prematurity was derived from an updated 2020 Cochrane review (13). A subgroup analysis was conducted in the published review, based on singleton or multiple pregnancy.

Eighteen trials contributed to the subgroup analysis. Thirteen recruited women with singleton pregnancy only. Twelve recruited women with singleton or multiple pregnancy, of which five reported some outcome data separately for women with singleton or multiple pregnancy. This subgroup analysis includes a total of 10 245 infants – 9240 in the singleton group and 1005 infants in the multiple pregnancy group.

The trials came from a range of health care systems and settings. Six studies were conducted in the United States of America, two in Brazil and one each in Colombia, India, Iran, Jordan, New Zealand, Thailand, Turkey and the United Kingdom of Great Britain and Northern Ireland. One trial took place in the USA and Germany and another study took place in Bangladesh, India, Kenya, Nigeria and Pakistan.

The trials recruited women with a wide range of preterm gestational ages, from 24 to <37 weeks. One trial recruited women at <29 weeks, eight trials recruited women at <34 weeks, one at <35 weeks, two at <36 weeks, five at 34 weeks and 0 days to 36 weeks and 5 days or 36 weeks and 6 days and one at <37 weeks.

Antenatal corticosteroids used in the trials included in the subgroup analysis were betamethasone (11 trials; 5392 women and 5485 infants), dexamethasone (6 trials; 4265 women and 4565 infants) and hydrocortisone (1 trial; 196 women and infants).

Antenatal corticosteroids versus placebo or no treatment: singleton and multiple births

Summary of absolute effects per 1000 (95% confidence interval) by plurality

Key:				
	High certainty (benefit)	Moderate certainty (probable benefit)	Low certainty (possible benefit)	Very low certainty (uncertain)
	High certainty (harm)	Moderate certainty (probable harm)	Low certainty (possible harm)	
	High certainty (no difference)	Moderate certainty (probable no difference)	Low certainty (possible no difference)	

Outcome	All pregnancies	Singleton	Multiple	Subgroup differences
Perinatal death	**Reduced** 23 fewer (36 fewer to 11 fewer)	**Reduced** 14 fewer (25 fewer to 1 more)	**Possibly no difference** 58 fewer (117 fewer to 44 more)	No suggested difference in effect (p=0.59; I^2=0%)
Fetal death	**No difference** 0 fewer (7 fewer to 9 more)	**Probably no difference** 1 more (6 fewer to 11 more)	**Possibly no difference** 39 fewer (66 fewer to 33 more)	No suggested difference in effect (p=0.19; I^2=41.8%)
Neonatal death	**Probably reduced** 26 fewer (36 fewer to 15 fewer)	**Probably reduced** 21 fewer (31 fewer to 10 fewer)	**Probably no difference** 50 fewer (90 fewer to 4 more)	No suggested difference in effect (p=0.75; I^2=0%)
Respiratory distress syndrome	**Probably reduced** 43 fewer (52 fewer to 32 fewer)	**Probably reduced** 49 fewer (61 fewer to 37 fewer)	**Possibly no difference** 38 fewer (100 fewer to 51 more)	No suggested difference in effect (p=0.14; I^2=53.3%)
Intraventricular haemorrhage	**Possibly reduced** 14 fewer (18 fewer to 8 fewer)	**Probably reduced** 16 fewer (21 fewer to 8 fewer)	**Uncertain**	No suggested difference in effect (p=0.83; I^2=0%)

Maternal outcomes

- No data were available for the pre-specified maternal outcomes (severe maternal morbidity or death, maternal infectious morbidity, maternal side effects, maternal well-being, maternal satisfaction).

Infant outcomes

- **Fetal and neonatal death:** In singleton pregnancies, antenatal corticosteroid therapy reduces the risk of perinatal death (RR 0.83, 95% CI 0.70 to 0.99; 7 trials, 5492 infants; *high certainty*). This is largely due to a probable reduction in neonatal deaths (RR 0.80,

95% CI 0.71 to 0.91; 13 trials, 8453 infants; *moderate certainty*) as they probably result in little or no difference in risk of fetal death (RR 1.06, 95% CI 0.76 to 1.46; 7 trials, 5492 infants; *moderate certainty*).

In multiple pregnancies, there is probably little or no difference in risk of neonatal death (RR 0.76, 95% CI 0.57 to 1.02; 3 trials, 813 infants; *moderate certainty*) and there may be little or no difference in risk of perinatal deaths (RR 0.71, 95% CI 0.41 to 1.22; 2 trials, 252 infants; *low certainty*) or fetal death (RR 0.53, 95% CI 0.20 to 1.40; 2 trials, 252 infants; *low certainty*).

- **Severe neonatal morbidity**: In singleton pregnancies, antenatal corticosteroid therapy probably reduces the risk of respiratory distress syndrome (RR 0.65, 0.57 to 0.74; 17 trials, 6731 infants; *moderate certainty*) and intraventricular haemorrhage (RR 0.51, 95% CI 0.35 to 0.75; 6 trials, 4494 infants; *moderate certainty*). In multiple pregnancies, there may be little or no difference in effect on respiratory distress syndrome (RR 0.85, 95% CI 0.61 to 1.20; 4 trials, 323 infants; *low certainty*) and the evidence on intraventricular haemorrhage is very uncertain.

  No data were available for moderate/severe respiratory distress syndrome, systemic infection in the first 48 hours of life, necrotising enterocolitis, chronic lung disease, patent ductus arteriosus, periventricular leukomalacia, retinopathy of prematurity, surfactant use, admission to neonatal intensive care, infection in neonatal intensive care, mean duration of hospitalization, use of mechanical duration, mean duration of mechanical duration or neonatal hypoglycaemia.

- **Birth weight**: No data were available for mean birth weight, low birth weight, small for gestational age.
- **Long-term morbidity**: No data were available for infant or childhood death, cerebral palsy, developmental delay, intellectual impairment, hearing impairment, visual impairment, behavioural/learning difficulties in childhood.

Additional considerations

Subgroup analyses

Subgroup analyses involve splitting available trials into different groups of participants. However, it should be acknowledged that subgroup analyses are not based on randomized comparisons, and are therefore susceptible to possible biases affecting observational studies (14). In this subgroup analysis, statistical tests for heterogeneity suggest that there are no differences in effect between singleton and multiples, for the available outcomes.

Observational evidence

A 2021 meta-analysis of observational studies investigated the effect of antenatal corticosteroids in women with multiple pregnancies (15). While available evidence was very low quality, the authors reported a reduced risk of neonatal death (RR 0.64, 95% CI 0.50 to 0.81; 11 studies), respiratory distress syndrome (OR 0.66, 95% CI 0.54 to 0.82; 14 studies), intraventricular haemorrhage (OR 0.67, 95% CI 0.54 to 0.83; 11 studies) and periventricular leukomalacia (OR 0.65, 95% CI 0.47 to 0.92; 8 studies). There was little or no difference in risk of necrotizing enterocolitis (OR 1.02, 95% CI 0.76 to 1.36; 7 studies), retinopathy of prematurity (OR 0.97, 95% CI 0.85 to 1.11; 7 studies) and bronchopulmonary dysplasia (OR 1.00, 95% CI 0.81 to 1.23; 8 studies). There was high heterogeneity in results for respiratory distress syndrome ($p<0.001$, $I^2=91.4\%$), mortality ($p<0.001$, $I^2=85.9\%$), intraventricular haemorrhage ($p<0.001$, $I^2=77.4\%$) and periventricular leukomalacia ($p<0.001$, $I^2=75.5\%$).

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids, considering single and multiple births?

Judgement

☐	☐	☐	☐	☐	☒
Don't know	Varies	Trivial	Small	Moderate	Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids, considering single and multiple births?

Judgement

☐	☐	☐	☐	☐	☒
Don't know	Varies	Large	Moderate	Small	Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids on maternal outcomes?

☒	☐	☐	☐	☐
No included studies	Very low	Low	Moderate	High

What is the overall certainty of the evidence on effects of antenatal corticosteroids on neonatal outcomes?

☐	☐	☒	☐	☐
No included studies	Very low	Low	Moderate	High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids, considering single and multiple births?

Research evidence

Findings from a mixed methods systematic review (16) on the appropriate use of antenatal corticosteroids in the management of women experiencing preterm birth show the following:

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally considered antenatal corticosteroids to be beneficial, and preferred that they are only used when necessary and in the context of a positive relationship with a health care provider. They preferred that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most health care providers believed that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some had concerns about safety in certain clinical situations.

No findings specific to plurality were identified.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the benefits of antenatal corticosteroids on the risk of newborn death and serious morbidities, particularly because of higher baseline risk of preterm birth in multiple pregnancy. It is likely that mothers, health care providers and policy-makers in any setting will place a higher value on these benefits, even if modest, and will choose to use the intervention.

Judgement

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids or the comparator, considering single and multiple birth?

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids, considering single and multiple births?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (17). Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed.

The available studies did not explore differences in cost–effectiveness of antenatal corticosteroids between singleton and multiple pregnancies.

Additional considerations

Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing health structures and protocols that are designed to manage women at imminent risk of preterm birth with minimal cost. Given the known health benefits of antenatal corticosteroids, it is highly likely that the intervention is cost–effective.

Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (18). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (19) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (19) — In the systematic review of cost–effectiveness studies (17), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administration of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☒ Moderate savings	☐ Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid treatment for women at risk of imminent preterm birth on health equity, considering single and multiple birth?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (20). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (21). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (22).

Evidence from trials demonstrates that antenatal corticosteroid use is effective, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit from the protection offered by a relatively cheap and readily available medication in low-resource settings, thus increasing equity.

Judgement

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid treatment for women at risk of imminent preterm birth acceptable to key stakeholders, considering single and multiple births?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid treatment among key stakeholders (16).

In summary, the review found:

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.

No findings specifically relevant to plurality were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid treatment for women at risk of imminent preterm birth feasible to implement, considering single and multiple births?

Research evidence

Findings from a mixed-methods systematic review (16) identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found:

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well-stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and newborn care), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to plurality were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

4 Summary of judgements table

Desirable effects	-Don't know	Varies	Trivial	Small	Moderate	✓ **Large**
Undesirable effects	Don't know	Varies	Large	Moderate	Small	✓ **Trivial**
Certainty of the evidence – maternal	✓ **No included studies**	Very low	Low	Moderate	High	
Certainty of the evidence – neonatal	No included studies	Very low	✓ **Low**	Moderate	High	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	No important uncertainty or variability		
Balance of effects	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Resources required	Don't know	Varies	Large costs	Moderate costs	Negligible costs or savings	✓ **Moderate savings**	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High	
Cost–effectiveness	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Equity	Don't know	Varies	Reduced	Probably reduced	Probably no impact	✓ **Probably increased**	Increased
Acceptability	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes

5 Summary of findings table

Source: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2020;12:CD004454.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Perinatal deaths – In babies born from singleton pregnancies												
7	randomized trials	not serious	not serious	not serious	not serious	none	185/2756 (6.7%)	225/2736 (8.2%)	**RR 0.83** (0.70 to 0.99)	**14 fewer per 1000** (from 25 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Perinatal deaths – In babies born from multiple pregnancies												
2	randomized trials	not serious	not serious	not serious	very serious [a]	none	19/131 (14.5%)	24/121 (19.8%)	**RR 0.71** (0.41 to 1.22)	**58 fewer per 1000** (from 117 fewer to 44 more)	⨁⨁◯◯ LOW	CRITICAL
Fetal death – In babies born from singleton pregnancies												
7	randomized trials	not serious	not serious	not serious	serious [b]	none	68/2756 (2.5%)	66/2736 (2.4%)	**RR 1.06** (0.76 to 1.46)	**1 more per 1000** (from 6 fewer to 11 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Fetal death – In babies born from multiple pregnancies												
2	randomized trials	not serious	not serious	not serious	very serious [c]	none	6/131 (4.6%)	10/121 (8.3%)	**RR 0.53** (0.20 to 1.40)	**39 fewer per 1000** (from 66 fewer to 33 more)	⨁⨁◯◯ LOW	CRITICAL
Neonatal death – In babies born from singleton pregnancies												
13	randomized trials	serious [d]	not serious	not serious	not serious	none	360/4250 (8.5%)	444/4203 (10.6%)	**RR 0.80** (0.71 to 0.91)	**21 fewer per 1000** (from 31 fewer to 10 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Neonatal death – In babies born from multiple pregnancies												
3	randomized trials	not serious	not serious	not serious	serious [b]	none	66/415 (15.9%)	83/398 (20.9%)	**RR 0.76** (0.57 to 1.02)	**50 fewer per 1000** (from 90 fewer to 4 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Respiratory distress syndrome – In babies born from singleton pregnancies												
17	randomized trials	serious [d]	not serious	not serious	not serious	none	310/3385 (9.2%)	472/3346 (14.1%)	**RR 0.65** (0.57 to 0.74)	**49 fewer per 1000** (from 61 fewer to 37 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Respiratory distress syndrome – single or multiple pregnancy – In babies born from multiple pregnancies												
4	randomized trials	serious [d]	not serious	not serious	serious [b]	none	44/167 (26.3%)	40/156 (25.6%)	**RR 0.85** (0.61 to 1.20)	**38 fewer per 1000** (from 100 fewer to 51 more)	⨁⨁◯◯ LOW	CRITICAL
Intraventricular haemorrhage – In babies born from singleton pregnancies												
6	randomized trials	not serious	not serious	serious [e]	not serious	none	37/2254 (1.6%)	71/2240 (3.2%)	**RR 0.51** (0.35 to 0.75)	**16 fewer per 1000** (from 21 fewer to 8 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Intraventricular haemorrhage – In babies born from multiple pregnancies												
1	randomized trial	not serious	not serious	serious [e]	very serious [c]	none	2/81 (2.5%)	4/69 (5.8%)	**RR 0.43** (0.08 to 2.26)	**33 fewer per 1000** (from 53 fewer to 73 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Wide confidence interval crossing line of no effect; estimate based on small sample

b. Wide confidence interval crossing line of no effect

c. Wide confidence interval crossing line of no effect; estimate based on small sample and few events

d. Most studies contributing data had design limitations

e. In some trials only a subset of infants were screened for intravascular haemorrhage; some trials diagnosed intravascular haemorrhage at postmortem only

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Evidence-to-decision framework 1.3

Antenatal corticosteroids compared to placebo or no treatment: **Preterm premature rupture of membranes**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of 5 years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.
- Preterm birth can be classified as: 1) provider-initiated preterm birth, through induction or antepartum caesarean section (30–35% of preterm births); or 2) spontaneous preterm birth, comprising women in spontaneous preterm labour with intact membranes (40–45%) and women with preterm premature rupture of the membranes (PPROM) (25–30%).

2 Question

Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)? If so:

- **Which population of pregnant women should be offered antenatal corticosteroids considering preterm premature of the membranes?**

Problem: Adverse outcomes due to preterm birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[9]

Settings: Low- middle- and high-income settings

Subgroups: Populations of women with intact or ruptured amniotic membranes.

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

[9] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

Summary of evidence

Evidence on the effects of antenatal corticosteroids versus placebo or no treatment for reducing adverse effects of prematurity was derived from an updated Cochrane systematic review (12). The review included a subgroup analysis based on membrane status at first dose.

Five trials specifically excluded women with premature rupture of membranes. Discrete outcome data from women with intact membranes at the first dose of study medication were available from eight studies, discrete outcome data from women with ruptured membranes at the first dose of trial medication were available from ten studies, with the remainder of the studies not reporting rupture of membrane status or reporting combined data from women with intact and ruptured membranes. This subgroup analysis included 15 trials (3424 women and 3624 infants).

The 15 trials included in the subgroup analysis came from a range of healthcare systems and settings. Seven studies were conducted in the United States of America and one each in Brazil, Colombia, Finland, Jordan, the Netherlands, New Zealand, South Africa and Thailand.

The included trials were conducted over a wide range of gestational ages, including those of extreme prematurity and late prematurity. Obstetric indications for women's recruitment to these trials were premature rupture of membranes, spontaneous preterm labour and planned preterm delivery.

Five trials included women with prolonged rupture of the membranes (≥24 hours to nearly 40 days); duration of membrane rupture was not stated in the other trials. Eight trials included singleton pregnancies only and seven included both singleton and multiple pregnancies. Gestational age at trial entry ranged from 24 to 37 weeks.

Antenatal corticosteroids used in the trials included in the subgroup analysis were betamethasone (9 trials; 1962 women and 2064 infants), dexamethasone (5 trials; 1390

women and 1487 infants), methylprednisone (2 trials; 57 women and 58 infants) and hydrocortisone (1 study; 15 women and infants).

Summary of absolute effects per 1000 (95% confidence interval) by membrane status

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	All women	Intact membranes	Ruptured membranes	Subgroup differences
Chorioamnionitis	**Possibly no difference** 5 fewer (11 fewer to 3 more)	**Probably no difference** 8 fewer (24 fewer to 19 more)	**Possibly no difference** 3 more (24 fewer to 19 more)	No suggested difference in effect ($p=0.51$; $I^2=0\%$)
Perinatal death	**Reduced** 23 fewer (36 fewer to 11 fewer)	**Probably no difference** 25 fewer (59 fewer to 21 more)	**Reduced** 96 fewer (134 fewer to 43 fewer)	**Suggested difference in effect ($p=0.05$; $I^2=72.9\%$)**
Fetal death	**No difference** 0 fewer (7 fewer to 9 more)	**Probably no difference** 6 more (17 fewer to 40 more)	**Probably no difference** 8 fewer (30 fewer to 34 more)	No suggested difference in effect ($p=0.52$; $I^2=0\%$)
Neonatal death	**Probably reduced** 26 fewer (36 fewer to 15 fewer)	**Probably no difference** 30 fewer (from 57 fewer to 7 more)	**Probably reduced** 64 fewer (from 90 fewer to 27 fewer)	No suggested difference in effect ($p=0.25$; $I^2=24.9\%$)
Respiratory distress syndrome	**Probably reduced** 43 fewer (52 fewer to 32 fewer)	**Reduced** 101 fewer (126 fewer to 73 fewer)	**Probably reduced** 86 fewer (from 123 fewer to 40 fewer)	No suggested difference in effect ($p=0.14$; $I^2=55.1\%$)
Intraventricular haemorrhage	**Possibly reduced** 14 fewer (18 fewer to 8 fewer)	**Probably reduced** 54 fewer (68 fewer to 32 fewer)	**Possibly reduced** 56 fewer (77 fewer to 22 fewer)	No suggested difference in effect ($p=0.77$; $I^2=0\%$)
Mean birth weight	**Possibly no difference** MD 14.02 lower (33.79 lower to 5.76 higher)	**Probably no difference** MD 30.27 lower (100.43 lower to 39.89 higher)	**Possibly no difference** MD 49.72 lower (113.91 lower to 14.46 higher)	No suggested difference in effect ($p=0.69$; $I^2=0\%$)

Antenatal corticosteroids versus placebo or no treatment, by subgroups of membrane status

Maternal outcomes

- **Maternal infectious morbidity**: Antenatal corticosteroid therapy in women with intact membranes at first dose probably has little or no effect on risk of chorioamnionitis (RR 0.83, 95% CI 0.50 to 1.40; 4 trials, 1243 women; *moderate certainty*). They may also have little or no effect in women with ruptured membranes at first dose (RR 1.03, 95% CI 0.72 to 1.48; 7 trials, 1129 women; *low certainty*).

  No data were available for other maternal outcomes (severe maternal morbidity or death, maternal side-effects, maternal wellbeing, maternal satisfaction).

infant outcomes

- **Fetal and neonatal death**: Among women with intact membranes at first dose, antenatal corticosteroid therapy probably results in little or no difference in perinatal death (RR 0.88, 95% CI 0.71 to 1.10; 4 trials, 1332 infants; *moderate certainty*), fetal death (RR 1.09, 95% CI 0.73 to 1.64; 4 trials, 1332 women; *moderate certainty*) or neonatal death (RR 0.79, 95% CI 0.60 to 1.05; 4 trials, 1332 women; *moderate certainty*). However, among women with ruptured membranes at first dose, antenatal corticosteroid therapy reduces the risk of perinatal death (RR 0.62, 95% CI 0.47 to 0.83; 3 trials, 688 infants; *high certainty*), due to a probable reduction in neonatal death (RR 0.62, 95% CI 0.46 to 0.84; 7 trials, 1014 women; *moderate certainty*). There is probably little or no difference in risk of fetal death in this group (RR 0.86, 95% CI 0.46 to 1.61; 3 trials, 688 women; *moderate certainty*).
- **Severe neonatal morbidity**: Among babies of women with intact membranes at first dose, antenatal corticosteroid therapy reduces the risk of respiratory distress syndrome (RR 0.60, 95% CI 0.50 to 0.71; 8 trials, 1924 infants; *high certainty*) and probably reduces the risk of intraventricular haemorrhage (RR 0.43, 95% CI 0.28 to 0.66; 4 trials, 1332 infants; *moderate certainty*). Among babies of women with ruptured membranes at first dose, the risk of respiratory distress syndrome is probably reduced (RR 0.72, 95% CI 0.60 to 0.87; 10 trials, 1202 infants; *moderate certainty*) and the risk of intraventricular haemorrhage may also be reduced (4 trials, 722 infants; RR 0.47, 95% CI 0.28 to 0.79; *low certainty*)

  No data were available for moderate/severe respiratory distress syndrome, neonatal infection, necrotising enterocolitis, chronic lung disease, patent ductus arteriosus, periventricular leukomalacia, retinopathy of prematurity, surfactant use, admission to neonatal intensive care, infection in neonatal intensive care, mean duration of hospitalization, use of mechanical duration, mean duration of mechanical duration.
- **Birth weight**: Antenatal corticosteroids probably result in little or no difference in mean birth weight among women with intact membranes at first dose (4 trials, 1301 infants; –30.27 g, 95% CI –100.43 g to 39.89 g; *moderate certainty*) and may have little or no effect among babies women with ruptured membranes at first dose (5 trials, 835 infants; MD –49.72 g, 95% CI –113.91 g to 14.46 g; *low certainty*). No data were available for low birth weight or small for gestational age.
- **Long-term morbidity:** No data were available for childhood death, cerebral palsy, developmental delay, intellectual impairment, hearing impairment, visual impairment, behavioural/learning difficulties in childhood.

Additional considerations

There are insufficient data to enable a systematic assessment of the effect of antenatal corticosteroids on maternal and infant outcomes for different durations of time since membrane rupture (i.e. prolonged rupture of membranes).

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids, considering membrane status?

Judgement

Intact membranes	☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☒ Moderate	☐ Large
Ruptured membranes	☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☒ Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids, considering membrane status?

Judgement

Intact membranes	☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☒ Trivial
Ruptured membranes	☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☒ Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids among women with intact membranes?

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

What is the overall certainty of the evidence on effects of antenatal corticosteroids among women with ruptured membranes?

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids, considering membrane status?

Research evidence

Findings from a mixed methods systematic review (13) on the appropriate use of interventions in the management of women experiencing preterm birth show the following:

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a healthcare provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most healthcare providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to membrane status were identified.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the reduction in the risk of newborn death and serious morbidity and less value on the potential for increased risk of maternal infection. It is likely that mothers, health care providers and policy-makers in any setting will invariably place a higher value on these benefits, and will chose to use the intervention.

Judgement

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids or the comparator, considering membrane status?

Judgement

Intact membranes	☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention
Ruptured membranes	☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☒ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids, considering membrane status?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (14). Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed.

The available studies did not explore differences in cost–effectiveness of antenatal corticosteroids between women with different membrane status.

Additional considerations

Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing health structures and protocols that are designed to manage women at imminent risk of preterm birth with minimal cost. Given the known health benefits of antenatal corticosteroids, it is highly likely that the intervention is cost–effective. Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (15). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.

Resource	Description
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (16) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (16) — In the systematic review of cost–effectiveness studies (14), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administration of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐	☐	☐	☐	☐	☒	☐
Don’t know	Varies	Large costs	Moderate costs	Negligible costs or savings	Moderate savings	Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity, considering membrane status?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (17). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality healthcare services during pregnancy, childbirth and the postnatal period (18). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (19).

Evidence from trials demonstrates that antenatal corticosteroid use is effective, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit from the protection offered by a relatively cheap and readily available medication in low-resource settings, thus increasing equity.

Judgement

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth acceptable to key stakeholders, considering membrane status?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (13).

In summary, the review found the following.

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.

No findings specifically relevant to membrane status were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth feasible to implement, considering membrane status?

Research evidence

Findings from a mixed-methods systematic review (13) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following.

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well-stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and newborn care), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to membrane status were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

4 Summary of judgements table

Desirable effects – intact membranes	Don't know	Varies	Trivial	Small	✓ **Moderate**	Large	
Desirable effects – ruptured membranes	Don't know	Varies	Trivial	Small	Moderate	✓ **Large**	
Undesirable effects – intact membranes	Don't know	Varies	Large	Moderate	Small	✓ **Trivial**	
Undesirable effects – ruptured membranes	Don't know	Varies	Large	Moderate	Small	✓ **Trivial**	
Certainty of the evidence – intact membranes	No included studies	Very low	✓ **Low**	Moderate	High		
Certainty of the evidence – ruptured membranes	No included studies	Very low	✓ **Low**	Moderate	High		
Values	Important uncertainty or variability	Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects – intact membranes	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Balance of effects – ruptured membranes	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	✓ **Favours intervention**
Resources required	Don't know	Varies	Large costs	Moderate costs	Negligible costs or savings	✓ **Moderate savings**	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High		
Cost–effectiveness	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Equity	Don't know	Varies	Reduced	Probably reduced	Probably no impact	✓ **Probably increased**	Increased
Acceptability	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	

5 Summary of findings table

Source: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2020;12:CD004454.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Chorioamnionitis – intact or ruptured membranes – In women with intact membranes at 1st dose												
4	randomized trials	not serious	not serious	not serious	serious [a]	none	24/611 (3.9%)	30/632 (4.7%)	**RR 0.83** (0.50 to 1.40)	**8 fewer per 1000** (from 24 fewer to 19 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Chorioamnionitis – intact or ruptured membranes – In women with ruptured membranes at 1st dose												
7	randomized trials	serious [b]	not serious	not serious	serious [a]	none	52/565 (9.2%)	50/564 (8.9%)	**RR 1.03** (0.72 to 1.48)	**3 more per 1000** (from 25 fewer to 43 more)	⨁⨁◯◯ LOW	CRITICAL
Perinatal death – intact or ruptured membranes – In babies born from pregnancies with intact membranes at 1st dose												
4	randomized trials	not serious	not serious	not serious	serious [a]	none	119/659 (18.1%)	138/673 (20.5%)	**RR 0.88** (0.71 to 1.10)	**25 fewer per 1000** (from 59 fewer to 21 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Perinatal death – intact or ruptured membranes – In babies born from pregnancies with ruptured membranes at 1st dose												
3	randomized trials	not serious	not serious	not serious	not serious	none	55/345 (15.9%)	87/343 (25.4%)	**RR 0.62** (0.47 to 0.83)	**96 fewer per 1000** (from 134 fewer to 43 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Fetal death – intact or ruptured membranes – In babies born from pregnancies with intact membranes at 1st dose												
4	randomized trials	not serious	not serious	not serious	serious [a]	none	45/659 (6.8%)	42/673 (6.2%)	**RR 1.09** (0.73 to 1.64)	**6 more per 1000** (from 17 fewer to 40 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Fetal death – intact or ruptured membranes – In babies born from pregnancies with ruptured membranes at 1st dose												
3	randomized trials	not serious	not serious	not serious	serious [a]	none	16/345 (4.6%)	19/343 (5.5%)	**RR 0.86** (0.46 to 1.61)	**8 fewer per 1000** (from 30 fewer to 34 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Neonatal deaths – intact or ruptured membranes – In babies born from pregnancies with intact membranes at 1st dose												
4	randomized trials	not serious	not serious	not serious	serious [a]	none	74/659 (11.2%)	96/673 (14.3%)	**RR 0.79** (0.60 to 1.05)	**30 fewer per 1000** (from 57 fewer to 7 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Neonatal deaths – intact or ruptured membranes – In babies born from pregnancies with ruptured membranes at 1st dose												
7	randomized trials	serious [b]	not serious	not serious	not serious	none	54/512 (10.5%)	84/502 (16.7%)	**RR 0.62** (0.46 to 0.84)	**64 fewer per 1000** (from 90 fewer to 27 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
RDS – intact or ruptured membranes – In babies born from pregnancies with intact membranes at 1st dose												
8	randomized trials	not serious	not serious	not serious	not serious	none	145/961 (15.1%)	242/963 (25.1%)	**RR 0.60** (0.50 to 0.71)	**101 fewer per 1000** (from 126 fewer to 73 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
RDS – intact or ruptured membranes – In babies born from pregnancies with ruptured membranes at 1st dose												
10	randomized trials	serious [b]	not serious	not serious	not serious	none	144/630 (22.9%)	176/572 (30.8%)	**RR 0.72** (0.60 to 0.87)	**86 fewer per 1000** (from 123 fewer to 40 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
IVH – intact or ruptured membranes – In babies born from pregnancies with intact membranes at 1st dose												
4	randomized trials	not serious	not serious	serious [c]	not serious	none	27/659 (4.1%)	64/673 (9.5%)	**RR 0.43** (0.28 to 0.66)	**54 fewer per 1000** (from 68 fewer to 32 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
IVH – intact or ruptured membranes – In babies born from pregnancies with ruptured membranes at 1st dose												
4	randomized trials	serious [b]	not serious	serious [c]	not serious	none	19/365 (5.2%)	38/357 (10.6%)	**RR 0.47** (0.28 to 0.79)	**56 fewer per 1000** (from 77 fewer to 22 fewer)	⨁⨁◯◯ LOW	CRITICAL
Mean birth weight – intact or ruptured membranes – In babies born from pregnancies with intact membranes at 1st dose												
4	randomized trials	not serious	not serious	not serious	serious [a]	none	641	660	–	MD **30.27 lower** (100.43 lower to 39.89 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Mean birth weight – intact or ruptured membranes – In babies born from pregnancies with ruptured membranes at 1st dose												
5	randomized trials	serious [b]	not serious	not serious	serious [a]	none	420	415	–	MD **49.72 lower** (113.91 lower to 14.46 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Wide confidence interval crossing line of no effect

b. Most studies contributing data had design limitations

c. In some trials only a subset of infants was screened for IVH; some trials diagnosed IVH at postmortem only

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Evidence-to-decision framework 1.4

Antenatal corticosteroids compared to placebo or no treatment: **Women with chorioamnionitis**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.
- Chorioamnionitis is acute inflammation of the membranes and chorion of the placenta, a complication of pregnancy that can occur in women whose membranes have ruptured. It is estimated to affect 3.9% of women giving birth (12). Treatment typically involves antibiotics and prompt delivery of the fetus.

2 Question

Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)? If so:

- **Which population of pregnant women should be offered antenatal corticosteroids considering presence of chorioamnionitis?**

Problem: Adverse outcomes due to preterm birth (PTB)

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[10]

Settings: Low- middle- and high-income settings

Subgroups: Populations of women with or without chorioamnionitis.

[10] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

It was not possible to use trial evidence to assess the effects of antenatal corticosteroids in women with chorioamnionitis, as the 2020 Cochrane review on antenatal corticosteroid efficacy did not conduct a subgroup analysis in women with and without chorioamnionitis. Any such subgroup analysis is unlikely to be informative, as chorioamnionitis was generally an exclusion criterion in these trials.

Summary of evidence

Evidence supporting the WHO 2015 recommendation was derived from a systematic review of maternal and child outcomes following antenatal corticosteroid therapy for women in special populations at risk of imminent preterm birth, which was published in 2016 (13). The review was updated in 2021 (14), identifying a total of eight studies relevant to outcomes among women with histological or clinical chorioamnionitis receiving antenatal corticosteroids were included (1461 women and infants). Two were prospective cohort studies and six were retrospective cohort studies.

Studies were conducted exclusively in high-income settings: two in France, two in the Republic of Korea, two in the United States of America, and one each in Canada and the Netherlands.

All women recruited into the studies were expected to deliver preterm (≤35 weeks) due to spontaneous preterm labour, preterm prelabour rupture of the membranes or where a health care provider initiated preterm birth for fetal or maternal indications.

Chorioamnionitis among women in these studies was diagnosed either clinically or histologically. Four studies provided data on the effects of antenatal corticosteroids when used in women with histological chorioamnionitis, two studies provided data on antenatal corticosteroids when used in women with clinical chorioamnionitis only, and two studies provided data on antenatal corticosteroid therapy in women with either histological or clinical chorioamnionitis.

Four studies used betamethasone in the treatment arm (996 women and neonates), one study used dexamethasone (89 women and neonates) and three studies used either betamethasone or dexamethasone (376 women and neonates).

The eight cohort studies all evaluated the use of a corticosteroid compared with no exposure to antenatal corticosteroids.

Antenatal corticosteroids versus placebo or no treatment

Table 1: Summary of absolute effects per 1000 (95% confidence interval), among babies of women with clinical and histological chorioamnionitis

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	Clinical chorioamnionitis	Histological chorioamnionitis
Neonatal death	**Uncertain**	**Possibly reduced** 78 fewer (106 fewer to 38 fewer)
Respiratory distress syndrome (RDS)and moderate/severe RDS	**Uncertain**	**Uncertain**
Intraventricular haemorrhage (IVH)	**Possibly reduced** 74 fewer (107 fewer to 1 fewer)	**Possibly reduced** 91 fewer (123 fewer to 41 fewer)
Severe IVH (grade 3–4)	**Uncertain**	**Possibly reduced** 64 fewer (90 fewer to 13 fewer)
Necrotizing enterocolitis	**Uncertain**	**Uncertain**
Chronic lung disease	**Uncertain**	**Uncertain**
Patent ductus arteriosus	**Uncertain**	**Uncertain**
Periventricular leukomalacia	**Possibly reduced** 103 fewer (135 fewer to 19 fewer)	**Uncertain**
Retinopathy of prematurity	**Not reported**	**Uncertain**
Surfactant use	**Not reported**	**Uncertain**
Use of mechanical ventilation	**Uncertain**	**Uncertain**
Mean duration of mechanical ventilation	**Not reported**	**Uncertain**
Duration of oxygen therapy	**Not reported**	**Uncertain**

Maternal outcomes

- No data were available for pre-specified maternal outcomes (maternal severe morbidity or death, infectious morbidity, side-effects, maternal well-being, maternal satisfaction).

Infant outcomes

- **Fetal and neonatal death:** Among babies of women with histological chorioamnionitis, antenatal corticosteroid therapy may reduce neonatal death (OR 0.49, 95% CI 0.33 to 0.74; 6 studies, 1193 infants; *low certainty*). The evidence on risk of neonatal death among women with clinical chorioamnionitis is very uncertain.
- **Severe neonatal morbidity**: Among babies of women with clinical chorioamnionitis, antenatal corticosteroid therapy may reduce the risk of intraventricular haemorrhage (OR 0.39, 95% CI 0.15 to 0.99; *low certainty*) and periventricular leukomalacia (OR 0.30, 95% CI 0.11 to 0.86; 3 studies, 318 infants; *low certainty*). The evidence on the risk RDS and moderate/severe RDS, severe intraventricular haemorrhage (grade 3–4), necrotizing enterocolitis, chronic lung disease, patent ductus arteriosus and use of mechanical ventilation among babies of women with clinical chorioamnionitis who received antenatal corticosteroid therapy is very uncertain. No data were available for retinopathy of prematurity, surfactant use, mean duration of mechanical ventilation or duration of oxygen therapy.

  Among babies of women with histological chorioamnionitis, antenatal corticosteroid therapy may reduce intraventricular haemorrhage (OR 0.41, 95% CI 0.23 to 0.72; 5 studies, 658 infants; *low certainty*) and severe intraventricular haemorrhage (grade 3–4) (OR 0.41, 95% CI 0.19 to 0.87; 4 studies, 528 infants; *low certainty*). The evidence on RDS and moderate/severe RDS, necrotizing enterocolitis, chronic lung disease, patent ductus arteriosus, periventricular leukomalacia, retinopathy of prematurity, surfactant use, use of mechanical ventilation, mean duration of mechanical ventilation and duration of oxygen therapy among babies of women with histological chorioamnionitis who received antenatal corticosteroids was very uncertain.
- **Birth weight**: No data were available on mean birth weight, low birth weight, small for gestational age.
- **Long-term morbidity:** No data were available for childhood death, cerebral palsy, developmental delay, intellectual impairment, hearing impairment, visual impairment, behavioural/learning difficulties in childhood.

Additional considerations

- Corticosteroids are known to suppress the immune system, and so the concern that their use may activate latent infections is reasonable. In a pregnant woman with ongoing infection, it may theoretically suppress the natural immune response and exacerbate infectious morbidities.
- There is no direct evidence, however, from randomized and observational studies on the effects of corticosteroid therapy on mothers with chorioamnionitis who are at risk of giving birth to preterm neonates to either confirm or refute this theory. Evidence from the reviewed observational studies from high-income countries suggests that in women with histological chorioamnionitis, there are some benefits for the preterm neonates without increasing potential harm of steroid therapy, particularly neonatal sepsis. However, insufficient evidence of benefits was shown for neonatal mortality and RDS in women with clinical chorioamnionitis.

- A 2020 Cochrane review (15) aimed to determine the relative benefits and risks of strategies to optimize the use of antenatal corticosteroid therapy for anticipated preterm birth and included three studies. Two of the included trials assessed their use in high-resource hospital settings. The third trial, the Antenatal Corticosteroid Trial (ACT) was a multi-site trial conducted in rural and semi-urban settings of six low- and middle-income countries in South Asia, sub-Saharan Africa and Central and South America.
- In the ACT trial, in low-resource settings (where baseline risk of maternal infectious morbidity may be higher), a strategy of actively promoting the use of antenatal corticosteroids in women at risk of preterm birth may increase antenatal corticosteroids use in the target population, but may also carry a substantial risk of unnecessary exposure of antenatal corticosteroids to women in whom antenatal corticosteroids is not indicated. At the population level, these effects were probably associated with increased maternal infection (a 67% increase in odds of suspected maternal infection for mothers of preterm newborns), as well as newborn harms.

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids, considering presence of chorioamnionitis?

Judgement

☒ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☐ Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids, considering presence of chorioamnionitis?

Judgement

☒ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☐ Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids, considering presence of chorioamnionitis?

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids, considering presence of chorioamnionitis?

Research evidence

Findings from a mixed methods systematic review (16) on the appropriate use of interventions in the management of women experiencing preterm birth show the following:

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a health care provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most health care providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to presence of chorioamnionitis were identified.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in high-income settings might place a higher value on the potential benefits of antenatal steroids in terms of reduction in RDS and neonatal mortality (regardless of the limited evidence on benefits in this context) over concerns about exacerbation of maternal infections, and therefore chose not to adhere to the recommendation in all women; whereas those in low- and middle-income settings might put a higher value on the potential risk of increasing maternal infectious morbidity over unclear benefits for clinical chorioamnionitis and thus chose to adhere to the recommendation in the majority of women.

Judgement

☐	☒	☐	☐
Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids, considering presence of chorioamnionitis?

Judgement

☐	☐	☐	☒	☐	☐	☐
Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids, considering presence of chorioamnionitis?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (17). Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed.

The available studies did not explore differences in cost–effectiveness of antenatal corticosteroids between women with or without chorioamnionitis.

Additional considerations

Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing health structures and protocols that are designed to manage women at imminent risk of preterm birth with minimal cost. Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (18). Injectable betamethasone preparations are not listed.

There is evidence of some possible benefits of antenatal corticosteroids in women with histological chorioamnionitis, though there is a lack of clear evidence of benefit and harms in women with clinical chorioamnionitis. In light of the uncertainty, it cannot be assumed that the intervention is cost–effective when used in women with chorioamnionitis. In addition, it might not be cost–effective if it has adverse impact on maternal infectious morbidity.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.

Resource	Description
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (19) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (19) — In the systematic review of cost–effectiveness studies (17), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administering of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☒ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity, considering presence of chorioamnionitis?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (20). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (21). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (22). In addition, women in these circumstances may be more likely to experience infectious morbidity during pregnancy (such as chorioamnionitis), or for such morbidities to remain undetected or untreated.

There is also lack of evidence on the benefits and possible harms of antenatal corticosteroids when used in women with clinical chorioamnionitis.

Judgement

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth acceptable to key stakeholders, considering presence of chorioamnionitis?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (16).

In summary, the review found the following.

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.
- Providers were reluctant to administer antenatal corticosteroids to women who had signs of infection. Some providers perceived that administration could disguise early signs of infections, or may increase the risks of maternal infection. Some providers reported looking for signs of infections before administration.
- Guidelines regarding the presence of infection as a contraindication to antenatal corticosteroid use were not uniform across countries.

Judgement

☐ Don't know	☐ Varies	☐ No	☒ Probably No	☐ Probably Yes	☐ Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth feasible to implement, considering presence of chorioamnionitis?

Research evidence

Findings from a mixed-methods systematic review (16) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following.

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well-stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and neonatal care), implementation may be limited due to challenges around identifying

preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to presence of chorioamnionitis were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

4 Summary of judgements table

Desirable effects	✓ **Don't know**	Varies	Trivial	Small	Moderate	Large	
Undesirable effects	✓ **Don't know**	Varies	Large	Moderate	Small	Trivial	
Certainty of the evidence	No included studies	✓ **Very low**	Low	Moderate	High		
Values	Important uncertainty or variability	✓ **Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Don't know	Varies	Favours comparator	✓ **Probably favours comparator**	Does not favour either	Probably favours intervention	Favours interventio n
Resources required	✓ **Don't know**	Varies	Large costs	Moderate costs	Negligible costs or savings	Moderate savings	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low		✓ Moderate	High	
Cost–effectiveness	✓ **Don't know**	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Equity	✓ **Don't know**	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased
Acceptability	Don't know	Varies	No	✓ **Probably No**	Probably Yes	Yes	
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	

5 Summary of findings table

Source: Saito K, Nishimura E, Swa T, Cao J, Ramson JA, Namba F, et al. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. Under review.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
Neonatal death (Histological chorioamnionitis)												
6	observational studies	serious [a]	not serious	not serious	not serious	strong association	63/677 (9.3%)	87/516 (16.9%)	**OR 0.49** (0.33 to 0.74)	**78 fewer per 1000** (from 106 fewer to 38 fewer)	⨁⨁◯◯ LOW	CRITICAL
Neonatal death (Clinical chorioamnionitis)												
2	observational studies	serious [a]	not serious	not serious	very serious [b]	none	14/109 (12.8%)	14/81 (17.3%)	**OR 0.71** (0.32 to 1.60)	**44 fewer per 1000** (from 110 fewer to 78 more)	⨁◯◯◯ VERY LOW	CRITICAL
Respiratory distress syndrome (RDS) and moderate/severe RDS (Histological chorioamnionitis)												
6	observational studies	serious [a]	not serious	not serious	not serious	none	305/677 (45.1%)	289/516 (56.0%)	**OR 0.59** (0.45 to 0.77)	**131 fewer per 1000** (from 196 fewer to 65 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Respiratory distress syndrome (RDS) and moderate/severe RDS (Clinical chorioamnionitis)												
4	observational studies	serious [a]	not serious	not serious	serious [c]	none	99/209 (47.4%)	99/208 (47.6%)	**OR 0.74** (0.48 to 1.12)	**74 fewer per 1000** (from 172 fewer to 28 more)	⨁◯◯◯ VERY LOW	CRITICAL
Intraventricular haemorrhage (Histological chorioamnionitis)												
5	observational studies	serious [a]	not serious	not serious	not serious	strong association	42/502 (8.4%)	26/156 (16.7%)	**OR 0.41** (0.23 to 0.72)	**91 fewer per 1000** (from 123 fewer to 41 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
Intraventricular haemorrhage (Clinical chorioamnionitis)												
3	observational studies	serious [a]	not serious	not serious	not serious	strong association	13/163 (8.0%)	20/155 (12.9%)	**OR 0.39** (0.15 to 0.99)	**74 fewer per 1000** (from 107 fewer to 1 fewer)	⨁⨁◯◯ LOW	CRITICAL
Severe intraventricular haemorrhage (grade 3–4) (Histological chorioamnionitis)												
4	observational studies	serious [a]	not serious	not serious	not serious	strong association	25/414 (6.0%)	13/114 (11.4%)	**OR 0.41** (0.19 to 0.87)	**64 fewer per 1000** (from 90 fewer to 13 fewer)	⨁⨁◯◯ LOW	CRITICAL
Severe intraventricular haemorrhage (grade 3–4) (Clinical chorioamnionitis)												
3	observational studies	serious [a]	not serious	not serious	serious [d]	none	5/163 (3.1%)	14/155 (9.0%)	**OR 0.28** (0.06 to 1.31)	**63 fewer per 1000** (from 84 fewer to 25 more)	⨁◯◯◯ VERY LOW	CRITICAL
Necrotizing enterocolitis (Histological chorioamnionitis)												
5	observational studies	serious [a]	not serious	not serious	serious [c]	none	64/625 (10.2%)	31/480 (6.5%)	**OR 1.23** (0.72 to 2.10)	**14 more per 1000** (from 17 fewer to 62 more)	⨁◯◯◯ VERY LOW	CRITICAL
Necrotizing enterocolitis (Clinical chorioamnionitis)												
2	observational studies	serious [a]	not serious	not serious	very serious [b]	none	16/104 (15.4%)	3/46 (6.5%)	**OR 2.58** (0.70 to 9.55)	**87 more per 1000** (from 19 fewer to 335 more)	⨁◯◯◯ VERY LOW	CRITICAL
Chronic lung disease / Bronchopulmonary dysplasia (Histological chorioamnionitis)												
4	observational studies	serious [a]	not serious	not serious	not serious	none	75/420 (17.9%)	30/116 (25.9%)	**OR 0.55** (0.32 to 0.93)	**98 fewer per 1000** (from 158 fewer to 14 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Chronic lung disease / Bronchopulmonary dysplasia (Clinical chorioamnionitis)												
3	observational studies	serious [a]	not serious	not serious	very serious [e]	none	25/142 (17.6%)	16/90 (17.8%)	**OR 0.91** (0.44 to 1.86)	**13 fewer per 1000** (from 91 fewer to 109 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
Patent ductus arteriosus (Histological chorioamnionitis)												
4	observational studies	serious [a]	not serious	not serious	not serious	none	109/407 (26.8%)	112/438 (25.6%)	**OR 0.67** (0.47 to 0.98)	**69 fewer per 1000** (from 117 fewer to 4 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Patent ductus arteriosus (Clinical chorioamnionitis)												
1	observational study	serious [a]	not serious	not serious	very serious [e]	none	22/64 (34.4%)	13/29 (44.8%)	**OR 0.64** (0.26 to 1.58)	**106 fewer per 1000** (from 274 fewer to 114 more)	⨁◯◯◯ VERY LOW	CRITICAL
Periventricular leukomalacia (Histological chorioamnionitis)												
4	observational studies	serious [a]	not serious	not serious	serious [d]	none	18/414 (4.3%)	6/114 (5.3%)	**OR 0.76** (0.27 to 2.12)	**12 fewer per 1000** (from 38 fewer to 53 more)	⨁◯◯◯ VERY LOW	CRITICAL
Periventricular leukomalacia (Clinical chorioamnionitis)												
3	observational studies	serious [a]	not serious	not serious	not serious	strong association	8/163 (4.9%)	24/155 (15.5%)	**OR 0.30** (0.11 to 0.86)	**103 fewer per 1000** (from 135 fewer to 19 fewer)	⨁⨁◯◯ LOW	CRITICAL
Retinopathy of prematurity requiring treatment (Histological chorioamnionitis)												
1	observational study	not serious	not serious	not serious	very serious [b]	none	9/97 (9.3%)	2/12 (16.7%)	**OR 0.51** (0.10 to 2.71)	**74 fewer per 1000** (from 147 fewer to 185 more)	⨁◯◯◯ VERY LOW	CRITICAL
Surfactant use (Histological chorioamnionitis)												
3	observational studies	serious [a]	serious [f]	not serious	serious [c]	none	176/355 (49.6%)	236/402 (58.7%)	**OR 0.73** (0.32 to 1.65)	**78 fewer per 1000** (from 274 fewer to 114 more)	⨁◯◯◯ VERY LOW	CRITICAL
Use of mechanical ventilation (Histological chorioamnionitis)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational study	serious [a]	not serious	not serious	very serious [e]	none	66/89 (74.2%)	29/32 (90.6%)	**OR 0.30** (0.08 to 1.07)	**163 fewer per 1000** (from 470 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL
Use of mechanical ventilation (Clinical chorioamnionitis)												
1	observational study	serious [a]	not serious	not serious	serious [g]	none	49/64 (76.6%)	29/29 (100.0%)	**OR 0.05** (0.00 to 0.94)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Mean duration of mechanical ventilation, days (Histological chorioamnionitis)												
1	observational study	serious [a]	not serious	not serious	very serious [e]	none	52	36	–	MD **2 days lower** (4.23 lower to 0.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Duration of oxygen use, days (Histological chorioamnionitis)												
1	observational study	serious [a]	not serious	not serious	serious [g]	none	52	36	–	MD **9 days higher** (5.66 higher to 12.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Most studies contributing data had design limitations.
b. Wide confidence interval crossing interval of no effect; estimate based on small sample size and few events.
c. Wide confidence interval crossing the line of no effect.
d. Wide confidence interval crossing interval of no effect; estimate based on few events.
e. Wide confidence interval crossing the line of no effect; estimate based on small sample size.
f. Heterogeneity is high ($I^2 \geq 60\%$.)
g. Estimate based on small sample size.

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Evidence-to-decision framework 1.5

Antenatal corticosteroids compared to placebo or no treatment: **Women undergoing planned caesarean section at 34 weeks and 6 days to 36 weeks and 6 days**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Approximately three-quarters of all preterm births occur in the late preterm period (i.e. 34 – <37 weeks' gestation) – while these babies generally have lower risks of mortality and morbidity compared to those born in the early preterm period, they have higher risks of adverse outcomes compared to babies born at term. In many countries, the rate of provider-initiated late preterm birth appears to be rising, which has been linked to the more generalised increases in planned caesarean section rates (11).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (12). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns, though the balance of benefits and possible harms of this treatment in the late preterm period are less clear.
- Babies born via caesarean section do not receive the normal physical and hormonal stimuli of passage through the birth canal; these processes can enhance fluid reabsorption in fetal lung tissue. Hence babies born via caesarean section tend to have higher rates of respiratory morbidity. Some studies have suggested that the risk of neonatal hypoglycaemia may be increased following caesarean section, though this may be confounded by the underlying indication for caesarean section.

2 Question

Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)? If so:

- **Which population of pregnant women should be offered antenatal corticosteroids considering women undergoing planned caesarean section at 34 weeks and 0 days to 36 weeks and 6 days?**

Problem: Adverse outcomes due to preterm birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth at 34 weeks and 0 days to 36 weeks and 6 days

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[11]

Settings: Low- middle- and high-income settings

Subgroups: Populations of women undergoing caesarean section.

[11] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Evidence on this question is derived from two systematic reviews:

1. Direct and indirect evidence from a systematic review of observational studies of women giving birth by planned caesarean section at late preterm or term (34 weeks and 0 days to 38 weeks and 6 days) (13)
2. Indirect evidence from a Cochrane review on the effectiveness of antenatal corticosteroids among women undergoing planned caesarean section at ≥37 weeks' gestation (14)

Research evidence

1) Summary of evidence: Systematic review of observational studies of women giving birth by planned caesarean section at 34 weeks and 0 days to 38 weeks and 6 days

Evidence on the effectiveness and safety of antenatal corticosteroid therapy for reducing adverse maternal and neonatal outcomes in women undergoing planned caesarean section was sought through a systematic review of randomized and non-randomized studies (13). Two primary studies were identified; a retrospective cohort study and a case-control study (373 women). The studies were conducted in high-income settings only; one in Israel and one in Spain.

Women recruited into both studies had planned caesarean births that were either late preterm or term (34 weeks and 0 days to 38 weeks and 6 days).

Both studies evaluated outcomes among women who received betamethasone compared to women who did not receive betamethasone.

Antenatal corticosteroids versus placebo or no treatment among women giving birth by planned caesarean section at late preterm or term (34 weeks and 0 days to 38 weeks and 6 days)

Table 1: Summary of absolute effects per 1000 (95% confidence interval), among women giving birth by planned caesarean section at late preterm or term

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	**Planned caesarean section at 34 weeks and 0 days to 38 weeks and 6 days**
Neonatal death	**No data**
Fetal death	**No data**
Respiratory distress syndrome	**Uncertain**
Intraventricular haemorrhage	**Uncertain**
Necrotizing enterocolitis	**Uncertain**
Neonatal hypoglycaemia	**Uncertain**
Neonatal intensive care unit admission	**Uncertain**
Mechanical ventilation	**Uncertain**
Mean duration of mechanical ventilation	**Uncertain**
Oxygen for 4 hours	**Uncertain**

Maternal outcomes

- No data were available for maternal outcomes (severe maternal morbidity or death, maternal infectious morbidity, maternal side-effects, maternal well-being, maternal satisfaction).

infant outcomes

- **Fetal and neonatal death**: Fetal and/or neonatal deaths among babies of women giving birth by planned caesarean section at late preterm or term (34 weeks and 0 days to 38 weeks and 6 days) who received antenatal corticosteroids were not reported.
- **Severe neonatal morbidity**: The evidence on the risk of respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, neonatal hypoglycaemia, admission to neonatal intensive care, mechanical ventilation, mean duration of mechanical ventilation and oxygen therapy for 4 hours among babies of women giving

birth by planned caesarean section at late preterm or term who received antenatal corticosteroid therapy was very uncertain.

Evidence on chronic lung disease, patent ductus arteriosus, periventricular leukomalacia, retinopathy of prematurity, surfactant use and mean duration of hospitalization in this group was not reported.

- **Birth weight:** Mean birth weight, low birth weight, small for gestational age were not reported.
- **Long-term morbidity:** No data were available for childhood death, cerebral palsy, developmental delay, intellectual impairment, hearing impairment, visual impairment, behavioural/learning difficulties in childhood.

2) Summary of evidence: Women undergoing planned caesarean section at ≥37 weeks

Indirect evidence on the effects of antenatal corticosteroids versus placebo or no treatment for accelerating fetal lung maturation for women at risk of imminent preterm birth was derived from an updated Cochrane systematic review on their use in women undergoing planned caesarean section after 37 weeks' gestation (14). The review is considered indirect evidence as it is derived from women receiving antenatal corticosteroids at term, rather than late preterm.

Since the version upon which the WHO 2015 recommendation was based (15), the Cochrane review has been updated twice: once in August 2018 (16) and again in 2021 (14). The 2018 update included an additional three studies, all of which were subsequently excluded from the 2021 review based on trustworthiness criteria. Therefore, the most recent update has not contributed any additional data.

The review included one trial, which was conducted at 10 hospitals in the United Kingdom (942 women).

Women were recruited to the trial if they had a singleton pregnancy and were undergoing a planned caesarean after 37 weeks' gestation.

The trial compared betamethasone with treatment as usual (no antenatal corticosteroids).

Antenatal corticosteroids versus placebo or no treatment among women undergoing planned caesarean section at ≥37 weeks

Table 2: Summary of absolute effects per 1000 (95% confidence interval), among women undergoing planned caesarean section at ≥37 weeks

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	**Planned caesarean section at ≥37 weeks**
Perinatal death	**Uncertain**
RDS	**Uncertain**
Transient tachypnoea of the newborn	**Uncertain**
Neonatal infection	**Uncertain**
Admission to neonatal intensive care (all levels) for any indication	**Uncertain**
Admission to neonatal intensive care for respiratory morbidity	**Uncertain**
NICU admission (all levels) for respiratory morbidity	**Possibly reduced** 28 fewer (39 fewer to 5 fewer)
NICU length of stay	**Possibly lower** MD 2.14 days (2.5 lower to 1.78 lower)
Use of mechanical ventilation	**Uncertain**
Cognitive impairment	**Possibly increased** 92 more (13 more to 234 more)
Learning difficulty	**Uncertain**

Maternal outcomes

- No data were available for maternal outcomes (severe maternal morbidity or death, maternal infectious morbidity, maternal adverse effects, maternal well-being, maternal satisfaction).

Infant outcomes

- **Fetal and neonatal death**: The evidence on the risk of perinatal death among babies of women undergoing planned caesarean at ≥37 weeks is very uncertain. Fetal death and neonatal death were not reported separately.

- **Severe neonatal morbidity**: The evidence on the effect of antenatal corticosteroids on the risk of respiratory distress syndrome, neonatal infection and transient tachypnoea of the newborn among babies of women undergoing planned caesarean at ≥37 weeks who received antenatal corticosteroid therapy is very uncertain. Among babies of women undergoing planned caesarean section at ≥37 weeks, antenatal corticosteroid therapy may reduce admission to neonatal special care (all levels) for respiratory morbidity (RR 0.45, 95% CI 0.22 to 0.90; 1 trial, 942 infants; *low certainty*) and length of stay in neonatal intensive care (MD –2.14 days, 95% CI –2.5 days to –1.78 days; 1 trial, 942 infants; *low certainty*).

  The evidence on the risk of admission to neonatal intensive care unit for respiratory morbidity, risk of admission to neonatal special care (all levels) for any indication and use of mechanical ventilation among babies of women undergoing planned caesarean section at ≥37 weeks is very uncertain. No data were available for moderate/severe respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, chronic lung disease, patent ductus arteriosus, periventricular leukomalacia, retinopathy of prematurity surfactant use or mean duration of neonatal hospitalisation.

- **Long-term morbidity:** Antenatal corticosteroids may increase the risk of lower quarter of academic ability at childhood follow-up among babies of women undergoing planned caesarean section at ≥37 weeks (RR 2.08, 95% CI 1.15 to 3.74; 1 trial, 350 children; *low certainty*). The evidence on learning difficulty at childhood follow-up is very uncertain. No data were available for childhood death, cerebral palsy, developmental delay, hearing impairment, visual impairment or behavioural difficulties in childhood.

Additional considerations

Post hoc subgroup analysis based on gestational age at birth[12]

A post hoc subgroup analysis of data from six trials (2554 women, 2728 neonates) from the 2020 Cochrane review (18), provided indirect evidence on the effectiveness of antenatal corticosteroids among women giving birth in the late preterm period (≥34 weeks; ≥36 weeks).

The analysis suggested that antenatal corticosteroid therapy among babies born at ≥34 weeks may reduce the risk of respiratory distress syndrome (RR 0.59, 95% CI 0.37 to 0.95; 5 trials, 1393 infants; *low certainty*) and may result in little or no difference in risk of perinatal death (RR 1.13, 95% CI 0.66 to 1.96; 1 trial, 770 infants; *low certainty*), while evidence on these outcomes among babies born at ≥36 weeks was very uncertain. There was little or no difference in mean birth weight among babies born at ≥34 weeks (MD –12.0, 95% CI –107.48 to 83.48; 1 trial, 770 infants; *low certainty*) or ≥36 weeks (MD –34.84, 95% CI –117.23 to 47.55; 1 trial, 757 infants; *low certainty*). The evidence on other outcomes (chorioamnionitis, fetal death, neonatal death and intraventricular haemorrhage) was very uncertain or inestimable for both groups.

While neonatal hypoglycaemia is not a WHO priority outcome and was not reported in the 2020 Cochrane review, data from those trials in the Cochrane review in which it was reported were pooled due to concerns about a possible increased risk among late preterm babies. The results showed an increased risk of neonatal hypoglycaemia with antenatal corticosteroids compared to placebo among babies born to women commencing therapy at ≥34 weeks (RR 1.61, 95% CI 1.38 to 1.87, 3 trials, 3294 infants).

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[12] Note that subgroup analyses are not based on randomized comparisons and are therefore susceptible to possible biases affecting observational studies.

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids, considering women undergoing planned caesarean section in the late preterm period (34 weeks and 0 days to 36 weeks and 6 days)?

Judgement

☒ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☐ Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids, considering women undergoing planned caesarean section in the late preterm period (34 weeks and 0 days to 36 weeks and 6 days)?

Judgement

☒ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☐ Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids on maternal outcomes?

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

What is the overall certainty of the evidence on effects of antenatal corticosteroids on neonatal outcomes?

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids, considering women undergoing planned caesarean section in the late preterm period (34 weeks and 0 days to 36 weeks and 6 days)?

Research evidence

Findings from a mixed methods systematic review (19) on the appropriate use of interventions in the management of women experiencing preterm birth show the following:

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a health care provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.

- Most health care providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to caesarean section were identified.

Additional considerations

Health-care providers, policy-makers, and pregnant women and their families in high-income settings might place a higher value on the potential cost saving of antenatal steroids in terms of a possible (but not confirmed) reduction in RDS or neonatal intensive care unit (NICU) admission, and may therefore choose the intervention regardless of the lack of evidence on mortality outcomes; whereas those in low- and middle-income settings might put a higher value on the potential maternal harm related to caesarean section and lower value on modest reduction in NICU admission – which may not be available in such settings. As a result of variability in these values and preferences across settings, clinical practice and choice made by women and their families are likely to vary across settings.

Judgement

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids or the comparator, considering women undergoing planned caesarean section in the late preterm period (34 weeks and 0 days to 36 weeks and 6 days)?

Judgement

☒ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (20). Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed.

The available studies did not explore differences in cost–effectiveness of antenatal corticosteroids between women with different mode of birth.

Additional considerations

Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (21). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (22) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (22) — In the systematic review of cost–effectiveness studies (20), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administering of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☒ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity, considering women undergoing planned caesarean section in the late preterm period (34 weeks and 0 days to 36 weeks and 6 days)?

Research evidence

The mixed-methods systematic review on appropriate use of maternal interventions in managing preterm birth did not identify any direct evidence on health equity (19).

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (23). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (24). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (25).

Evidence from trials demonstrates that antenatal corticosteroid use is effective in all settings, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit to the protection offered by a relatively cheap and readily available medication in low-resource setting, thus increasing equity.

Judgement

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth acceptable to key stakeholders, considering women undergoing planned caesarean section in the late preterm period (34 weeks and 0 days to 36 weeks and 6 days)?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (19).

In summary, the review found the following.

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.

No findings specifically relevant to birth by caesarean section were identified.

Additional considerations

None.

Judgement

☒	☐	☐	☐	☐	☐
Don't know	Varies	No	Probably No	Probably Yes	Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth feasible to implement, considering women undergoing planned caesarean section in the late preterm period (34 weeks and 0 days to 36 weeks and 6 days)?

Research evidence

Findings from a mixed-methods systematic review (19) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following.

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well-stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and neonatal care), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to birth by caesarean section were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

4 Summary of judgements table

Desirable effects	✓ **Don't** know	Varies	Trivial	Small	Moderate	Large
Undesirable effects	✓ **Don't know**	Varies	Large	Moderate	Small	Trivial
Certainty of the evidence: maternal outcomes	No included studies	✓ **Very low**	Low	Moderate	High	
Certainty of the evidence: neonatal outcomes	No included studies	✓ **Very low**	Low	Moderate	High	
Values	Important uncertainty or variability	✓ **Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability		
Balance of effects	✓ **Don't know**	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Resources required	✓ **Don't know**	Varies	Large costs	Moderate costs	Negligible costs or savings	Moderate savings	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High		
Cost–effectiveness	✓ **Don't know**	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Equity	✓ **Don't know**	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased
Acceptability	✓ **Don't know**	Varies	No	Probably No	Probably Yes	Yes	
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	

5 Summary of findings tables

5.1 Women giving birth by planned caesarean section at 34 weeks and 0 days to 38 weeks and 6 days

Source: Saito K, Nishimura E, Swa T, Cao J, Ramson JA, Namba F, et al. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. Under review.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with planned CS in the late preterm period	Placebo	Relative (95% CI)	Absolute (95% CI)		
Respiratory distress syndrome (RDS) and moderate/severe RDS												
2	observational studies	not serious	not serious	not serious	very serious [a]	none	12/88 (13.6%)	11/117 (9.4%)	**OR 0.80** (0.29 to 2.24)	**17 fewer per 1000** (from 65 fewer to 95 more)	⨁◯◯◯ VERY LOW	CRITICAL
Interventricular haemorrhage												
1	observational studies	not serious	not serious	not serious	very serious [b]	none	0/58 (0.0%)	1/107 (0.9%)	**OR 0.61** (0.02 to 15.13)	**4 fewer per 1000** (from 9 fewer to 116 more)	⨁◯◯◯ VERY LOW	CRITICAL
Necrotizing enterocolitis												
1	observational studies	not serious	not serious	not serious	very serious [b]	none	0/58 (0.0%)	1/107 (0.9%)	**OR 0.61** (0.02 to 15.13)	**4 fewer per 1000** (from 9 fewer to 116 more)	⨁◯◯◯ VERY LOW	CRITICAL
Neonatal hypoglycaemia												
2	observational studies	not serious	not serious	not serious	very serious [a]	none	30/88 (34.1%)	37/117 (31.6%)	**OR 1.50** (0.81 to 2.78)	**93 more per 1000** (from 44 fewer to 246 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with planned CS in the late preterm period	Placebo	Relative (95% CI)	Absolute (95% CI)		
Use of mechanical ventilation												
2	observational studies	not serious	not serious	not serious	very serious [b]	none	12/88 (13.6%)	11/117 (9.4%)	**OR 0.80** (0.30 to 2.12)	**17 fewer per 1000** (from 64 fewer to 86 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mean duration of mechanical ventilation, days												
1	observational studies	serious [c]	not serious	not serious	very serious [a]	none	30	10	–	MD **0.2 lower** (1.35 lower to 0.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Oxygen requirement for at least 4 hours												
1	observational studies	not serious	not serious	not serious	very serious [a]	none	13/58 (22.4%)	25/107 (23.4%)	**OR 0.95** (0.44 to 2.03)	**9 fewer per 1000** (from 115 fewer to 149 more)	⨁◯◯◯ VERY LOW	CRITICAL
Admission to neonatal intensive care unit												
2	observational studies	not serious	not serious	not serious	very serious [b]	none	10/88 (11.4%)	14/117 (12.0%)	**OR 0.73** (0.26 to 2.05)	**29 fewer per 1000** (from 86 fewer to 98 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Wide confidence interval crossing line of no effect; estimate based on small sample size.

b. Wide confidence interval crossing line of no effect; estimate based on small sample size and few events.

c. The study contributing data had design limitations.

5.2 Women giving birth by planned caesarean section at term (≥37 weeks)

Source: Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP, McGoldrick E. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. *Cochrane Database Syst Rev*. 2021:CD006614.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Perinatal death												
1	randomized trial	serious [a]	not serious	serious [b]	serious [c]	none	0/467 (0.0%)	0/475 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Neonatal infection												
1	randomized trial	serious [a]	not serious	serious [b]	serious [c]	none	0/467 (0.0%)	0/475 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Respiratory distress syndrome												
1	randomized trial	serious [a]	not serious	serious [b]	very serious [d]	none	1/467 (0.2%)	5/475 (1.1%)	**RR 0.34** (0.07 to 1.65)	**7 fewer per 1000** (from 10 fewer to 7 more)	⨁◯◯◯ VERY LOW	CRITICAL
Transient tachypnoea of the newborn												
1	randomized trial	serious [a]	serious [e]	serious [b]	very serious [d]	none	10/467 (2.1%)	19/475 (4.0%)	**RR 0.52** (0.25 to 1.11)	**19 fewer per 1000** (from 30 fewer to 4 more)	⨁◯◯◯ VERY LOW	CRITICAL
Length of stay in neonatal intensive care unit (days)												
1	randomized trial	serious [a]	not serious	serious [b]	not serious	none	467	475	–	MD **2.14 lower** (2.5 lower to 1.78 lower)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Admission to neonatal intensive care unit for respiratory morbidity												
1	randomized trial	serious [a]	not serious	serious [b]	serious [f]	none	2/467 (0.4%)	14/475 (2.9%)	**RR 0.15** (0.03 to 0.64)	**25 fewer per 1000** (from 29 fewer to 11 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Admission to neonatal special care (all levels) for respiratory morbidity												
1	randomized trial	serious [a]	not serious	serious [b]	not serious	none	11/467 (2.4%)	24/475 (5.1%)	**RR 0.45** (0.22 to 0.90)	**28 fewer per 1000** (from 39 fewer to 5 fewer)	⨁⨁◯◯ LOW	CRITICAL
Admission to neonatal special care (all levels) for any indication												
1	randomized trial	serious [a]	not serious	serious [b]	serious [g]	none	26/467 (5.6%)	32/475 (6.7%)	**RR 0.81** (0.49 to 1.33)	**13 fewer per 1000** (from 34 fewer to 22 more)	⨁◯◯◯ VERY LOW	CRITICAL
Use of mechanical ventilation												
1	randomized trial	serious [a]	not serious	serious [b]	very serious [d]	none	4/467 (0.9%)	1/475 (0.2%)	**RR 4.07** (0.46 to 36.27)	**6 more per 1000** (from 1 fewer to 74 more)	⨁◯◯◯ VERY LOW	CRITICAL
Lower quarter of academic ability at childhood follow-up												
1	randomized trial	serious [a]	not serious	serious [b]	not serious	none	33/186 (17.7%)	14/164 (8.5%)	**RR 2.08** (1.15 to 3.74)	**92 more per 1000** (from 13 more to 234 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antenatal corticosteroids	placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Reported learning difficulty at childhood follow-up												
1	randomized trial	serious [a]	not serious	serious [b]	serious [g]	none	25/217 (11.5%)	27/190 (14.2%)	**RR 0.81** (0.49 to 1.35)	**27 fewer per 1000** (from 72 fewer to 50 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Most studies contributing data had design limitations.

b. Evidence was derived from a population that does not correspond to the population of interest (i.e. women undergoing planned caesarean section at term rather than in late preterm).

c. No events reported for outcome.

d. Wide confidence interval crossing the line of no effect; effect estimate based on few events.

e Statistical heterogeneity (I^2>60%)

f. Effect estimate based on few events.

g. Wide confidence interval crossing the line of no effect.

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Evidence-to-decision framework 1.6

Antenatal corticosteroids compared to placebo or no treatment: **Women with hypertensive disorders**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.

2 Question

Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)? If so:

- **Which population of pregnant women should be offered antenatal corticosteroids considering hypertensive disorders in pregnancy?**

Problem: Adverse outcomes due to preterm birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[13]

Settings: Low- middle- and high-income settings

Subgroups: Populations of women with or without hypertensive disorders.

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

[13] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

Summary of evidence

Evidence on the effects of antenatal corticosteroids versus placebo or no treatment for accelerating fetal lung maturation for women at risk of imminent preterm birth was derived from an updated Cochrane systematic review (12). Subgroup analysis was conducted based on presence of hypertensive disorders.

Eight trials were included in the subgroup analysis. They were conducted in a range of health care systems and settings. One study each was conducted in Brazil, Finland, New Zealand, Thailand, Tunisia, Turkey, the United Kingdom of Great Britain and Northern Ireland and the United States of America.

Obstetric indications for recruitment to trials were premature rupture of membranes, spontaneous preterm labour and planned preterm delivery. The trials included 2685 women and 2858 infants.

Three trials excluded women with pre-eclampsia (2 trials; 174 women) or pregnancy-induced hypertension (1 trial; 194 women) and one trial included only women with severe pre-eclampsia (220 women). The remaining four trials reported on pregnancies affected or not affected by hypertension.

Three trials included singleton pregnancies only and five included singleton and multiple pregnancies. Three trials excluded participants with ruptured membranes, one included only women with ruptured membranes and four included women of mixed membrane status.

Antenatal corticosteroids used in the trials included in the subgroup analysis were betamethasone (6 trials; 1795 women, 1907 infants) and dexamethasone (2 trials; 890 women, 951 infants).

Summary of absolute effects per 1000 (95% confidence interval) by presence of hypertensive disorders

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	All women	Hypertensive disorders	No hypertensive disorders	Subgroup differences
Perinatal death	**Reduced** 23 fewer (36 fewer to 11 fewer)	**Possibly no difference** 50 fewer (from 126 fewer to 59 more)	**Probably no difference** 28 fewer (from 65 fewer to 20 more)	No suggested difference in effect (p=0.88; I^2=0%)
Fetal death	**No difference** 0 fewer (7 fewer to 9 more)	**Probably no difference** 58 more (from 7 fewer to 182 more)	**Probably no difference** 19 fewer (from 36 fewer to 9 more)	**Suggested difference in effect (p=0.03; I^2=78.7%)**
Neonatal death	**Probably reduced** 26 fewer (36 fewer to 15 fewer)	**Reduced** 109 fewer (from 151 fewer to 36 more)	**Probably no difference** 12 fewer (from 41 fewer to 29 more)	**Suggested difference in effect (p=0.05; I^2=72.8%)**
Respiratory distress syndrome	**Probably reduced** 43 fewer (52 fewer to 32 fewer)	**Probably reduced** 173 fewer (from 220 fewer to 103 fewer)	**Probably reduced** 61 fewer (from 80 fewer to 40 more)	No suggested difference in effect (p=0.31; I^2=1.7%)

Antenatal corticosteroids versus placebo or no treatment among women with and without hypertensive disorders

Maternal outcomes

No data were available for maternal outcomes (severe maternal morbidity or death, maternal infectious morbidity, maternal side-effects, maternal well-being, maternal satisfaction).

Infant outcomes

- **Fetal and neonatal death**: Among babies of women with hypertensive disorders, antenatal corticosteroid therapy reduces the risk of neonatal death (RR 0.48, 95% CI 0.28 to 0.83; 2 trials, 313 infants; *high certainty*) but may result in little or no difference in risk of perinatal death (RR 0.83, 95% CI 0.57 to 1.20; 2 trials, 313 infants; *low certainty*) and probably results in little or no difference in risk of fetal death (RR 1.73, 95% CI 0.91 to 3.28; 3 trials, 331 infants; *moderate certainty*).

  Among babies of women without hypertensive disorders, antenatal corticosteroid therapy probably has little or no effect on the risk of perinatal death (RR 0.86, 95% CI 0.67 to 1.10; 1 trial, 1123 infants; *moderate certainty*), fetal death (RR 0.74, 95% CI 0.49 to 1.12; 2 trials, 1373 infants; *moderate certainty*) or neonatal death (RR 0.90, 95% CI 0.65 to 1.25; 1 trial, 1123 infants; *moderate certainty*).

- **Severe neonatal morbidity**: Antenatal corticosteroid therapy probably reduces the risk of respiratory distress syndrome among babies of women with hypertensive syndrome (RR 0.48, 0.34 to 0.69; 5 trials, 418 infants; *moderate certainty*) and babies of women without hypertensive syndrome (RR 0.60, 95% CI 0.48 to 0.74; 7 trials, 2511 infants; *moderate certainty*). Data were not available for any other severe neonatal morbidities
- **Birth weight:** No data were available for mean birth weight, low birth weight or small-for-gestation age.
- **Long-term morbidity:** No data were available for childhood death, cerebral palsy, developmental delay, intellectual impairment, hearing impairment, visual impairment, behavioural/learning difficulties in childhood.

Additional considerations

Subgroup analyses involve splitting available trials into different groups of participants. However, it should be acknowledged that subgroup analyses are not based on randomized comparisons, and are therefore susceptible to possible biases affecting observational studies (13).

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids, considering hypertensive disorders in pregnancy?

Judgement

☐	☐	☐	☐	☐	☒
Don't know	Varies	Trivial	Small	Moderate	Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids, considering hypertensive disorders in pregnancy?

Judgement

☒	☐	☐	☐	☐	☐
Don't know	Varies	Large	Moderate	Small	Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids on maternal outcomes?

☒	☐	☐	☐	☐
No included studies	Very low	Low	Moderate	High

What is the overall certainty of the evidence on effects of antenatal corticosteroids on neonatal outcomes?

☐	☐	☐	☒	☐
No included studies	Very low	Low	Moderate	High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids, considering hypertensive disorders in pregnancy?

Research evidence

Findings from a mixed methods systematic review (14) on the appropriate use of interventions in the management of women experiencing preterm birth show the following:

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a health care provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most health care providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to presence of hypertensive disorders were identified.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the survival of a preterm baby born to a mother with a hypertensive disorder during pregnancy. It is likely that there is little or no variation of this value among mothers, health care providers and policy-makers in low-, middle- and high-income settings, particularly because hypertensive disorders can pose further risk of morbidity and mortality for the preterm newborn.

Judgement

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids or the comparator, considering hypertensive disorders in pregnancy?

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (15). Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed.

The available studies did not explore differences in cost–effectiveness of antenatal corticosteroids between women with or without hypertensive disorders.

Additional considerations

Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (16). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (17) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (17) — In the systematic review of cost–effectiveness studies (15), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).

Resource	Description
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administering of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☒ Moderate savings	☐ Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (18). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (19). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (20).

Evidence from trials demonstrates that antenatal corticosteroid use is effective in all settings, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit to the protection offered by a relatively cheap and readily available medication in low-resource setting, thus increasing equity.

Judgement

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth acceptable to key stakeholders, considering hypertensive disorders in pregnancy?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (14).

In summary, the review found the following.

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and.

No findings specifically relevant to presence of hypertensive disorders were identified.

Additional considerations

None.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth feasible to implement, considering hypertensive disorders in pregnancy?

Research evidence

Findings from a mixed-methods systematic review (14) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following.

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well-stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and neonatal care), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to presence of hypertensive disorders were identified.

Judgement

☐	☐	☐	☐	☒	☐
Don’t know	Varies	No	Probably No	Probably Yes	Yes

4 Summary of judgements table

Desirable effects	Don't know	Varies	Trivial	Small	Moderate	✓ **Large**
Undesirable effects	✓ **Don't know**	Varies	Large	Moderate	Small	Trivial
Certainty of the evidence – maternal	✓ **No included studies**	Very low	Low	Moderate	High	
Certainty of the evidence – neonatal	No included studies	Very low	Low	✓ **Moderate**	High	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	No important uncertainty or variability		
Balance of effects	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Resources required	Don't know	Varies	Large costs	Moderate costs	Negligible costs or savings	✓ **Moderate savings**	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High	
Cost–effectiveness	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Equity	Don't know	Varies	Reduced	Probably reduced	Probably no impact	✓ **Probably increased**	Increased
Acceptability	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes

5 Summary of findings table

Source: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020;12:CD004454.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Perinatal deaths – hypertension syndrome vs other trials – Hypertension syndrome												
2	randomized trials	not serious	serious [a]	not serious	serious [b]	none	38/156 (24.4%)	46/157 (29.3%)	**RR 0.83** (0.57 to 1.20)	**50 fewer per 1000** (from 126 fewer to 59 more)	⨁⨁◯◯ LOW	CRITICAL
Perinatal deaths – hypertension syndrome vs other trials – No hypertension syndrome or hypertension syndromes excluded												
1	randomized trial	not serious	not serious	not serious	serious [b]	none	94/555 (16.9%)	112/568 (19.7%)	**RR 0.86** (0.67 to 1.10)	**28 fewer per 1000** (from 65 fewer to 20 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Fetal deaths – hypertension syndrome vs other trials – Women with hypertension syndrome												
3	randomized trials	not serious	not serious	not serious	serious [b]	none	22/168 (13.1%)	13/163 (8.0%)	**RR 1.73** (0.91 to 3.28)	**58 more per 1000** (from 7 fewer to 182 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Fetal deaths – hypertension syndrome vs other trials – No hypertension syndrome or hypertension syndromes excluded												
2	randomized trials	not serious	not serious	not serious	serious [b]	none	36/674 (5.3%)	50/699 (7.2%)	**RR 0.74** (0.49 to 1.12)	**19 fewer per 1000** (from 36 fewer to 9 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Neonatal deaths – hypertension syndrome vs other trials – Hypertension syndrome												
2	randomized trials	not serious	not serious	not serious	not serious	none	16/156 (10.3%)	33/157 (21.0%)	**RR 0.48** (0.28 to 0.83)	**109 fewer per 1000** (from 151 fewer to 36 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Neonatal deaths – hypertension syndrome vs other trials – No hypertension syndrome or hypertension syndromes excluded												
1	randomized trial	not serious	not serious	not serious	serious [b]	none	59/555 (10.6%)	67/568 (11.8%)	**RR 0.90** (0.65 to 1.25)	**12 fewer per 1000** (from 41 fewer to 29 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Respiratory distress syndrome – hypertension syndrome vs other trials – Hypertension syndrome												
5	randomized trials	serious [c]	not serious	not serious	not serious	none	33/214 (15.4%)	68/204 (33.3%)	**RR 0.48** (0.34 to 0.69)	**173 fewer per 1000** (from 220 fewer to 103 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Respiratory distress syndrome – hypertension syndrome vs other trials – No hypertension syndrome or hypertension syndromes excluded												
7	randomized trials	serious [c]	not serious	not serious	not serious	none	113/1236 (9.1%)	195/1275 (15.3%)	**RR 0.60** (0.48 to 0.74)	**61 fewer per 1000** (from 80 fewer to 40 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Statistical heterogeneity (I^2>60%)

b. Wide confidence interval crossing line of no effect

c. Most studies contributing data had design limitations

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Evidence-to-decision framework 1.7

Antenatal corticosteroids compared to placebo or no treatment: **Fetal growth restriction**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.
- Fetal growth restriction is a pathological process that prevents the fetus from attaining its growth potential (12). The incidence is difficult to estimate, varying between populations, settings and definitions used (13). However, the prevalence of small-for-gestational-age (SGA) – many of whom are growth restricted – is nearly 20% in low- and middle-income countries (14). Despite the high prevalence, it is often not detected during routine antenatal care (14–17).

2 Question

Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)? If so:

- **Which population of pregnant women should be offered antenatal corticosteroids considering fetal growth restriction?**

Problem: Adverse outcomes due to preterm birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[14]

Settings: Low- middle- and high-income settings

Subgroups: Populations of women with babies with fetal growth restriction or small-for-gestational-age babies, growth-restricted babies or small-for-gestational age babies

[14] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia (PVL), and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

It was not possible to use trial evidence to assess the effects of antenatal corticosteroids in women with growth-restricted fetuses, as the 2020 Cochrane review on antenatal corticosteroid efficacy did not conduct a subgroup analysis in this group. Any such subgroup analysis is unlikely to be informative as fetal growth restriction is often an exclusion criterion in many of these trials, but it is noteworthy that fetal growth restriction was not an exclusion criterion in the largest trial of this meta-analysis.

Evidence supporting the WHO 2015 recommendation was derived from a non-Cochrane systematic review of maternal and child outcomes following antenatal corticosteroid therapy of women in specific populations at risk of imminent preterm birth, which was subsequently published in 2016 (18). The review was updated in 2021 (19).

The updated review included a total of 18 cohort studies (8464 women and neonates) involving women with babies that were small for gestational age (SGA) and/or had fetal growth-restriction (FGR), who received antenatal corticosteroids compared to those who did not receive them. Additional unpublished data on one of the studies was obtained from a previous review paper identified through the search strategy.

Studies were conducted exclusively in high-income settings – three in the Netherlands, two each in Israel, Italy, the Republic of Korea and the United States of America; one each in Canada, China, France, Japan and Sweden; one study in Australia and New Zealand; and one study in Canada and the United States of America.

All women recruited into the studies were expected to give birth preterm (≤35 weeks) due to either spontaneous preterm labour, preterm prelabour rupture of the membranes or provider-initiated preterm birth due to fetal or maternal indications.

Three studies included babies with fetal growth restriction ***or*** who were small for gestational age (see Table 2), 12 studies included only small-for-gestational-age babies (see Table 3) and two included only babies with fetal growth restriction (see Table 4). One study reported fetal growth restriction and small-for-gestational-age separately. Where heterogeneity between the three sub-groups (i.e. SGA/FGR, SGA only, FGR only) was low, sub-group data were combined and total odds ratios calculated (see Table 1).

The studies all evaluated the use of a corticosteroid compared with no treatment. Eight studies used betamethasone in the treatment arm (1366 infants), one used dexamethasone (82 infants) and three studies used either betamethasone or dexamethasone (789 infants). The remaining six studies did not specify the type of corticosteroid used (6127 infants).

Sixteen studies specified that the comparison group comprised women who did not receive antenatal corticosteroids, one study compared antenatal corticosteroids to saline placebo and one compared to 'no treatment', without further explanation.

Antenatal corticosteroids versus placebo or no treatment — all growth-restricted babies (i.e. 18 studies: fetal growth restriction, small-for-gestational-age, and fetal growth restriction or small-for-gestational-age)

Table 1: Summary of absolute effects per 1000 (95% confidence interval), among all growth-restricted babies

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	Effect
Maternal outcomes	
Chorioamnionitis	**Uncertain**
Neonatal outcomes	
Neonatal death before discharge	**Uncertain**
Intraventricular haemorrhage (IVH)	**Uncertain**
Severe IVH (grade 3–4)	**Possibly reduced** 46 fewer (from 57 fewer to 31 fewer)
Neonatal infection	**Uncertain**
Necrotizing enterocolitis	**Uncertain**
Chronic lung disease	**Uncertain**
Patent ductus arteriosus	**Uncertain**
Retinopathy of prematurity	**Uncertain**
Neonatal hypoglycaemia	**Possibly increased** 155 more (47 more to 273 more)
Major brain lesion	**Uncertain**
Duration of hospital stay	**Possibly reduced** MD 2.32 lower (3.81 lower to 0.83 lower)
Cerebral palsy	**Uncertain**

Maternal outcomes

- **Maternal infectious morbidity**: The evidence on the effect of antenatal corticosteroids on risk of chorioamnionitis among women with growth restricted babies is very uncertain

  No data were available for other maternal outcomes (maternal severe morbidity or death, adverse effects, well-being, satisfaction).

Infant outcomes

- ***Fetal and neonatal death:*** The evidence on the effect of antenatal corticosteroids on risk of neonatal death before discharge among growth-restricted babies is very uncertain. No data were available on fetal death or perinatal death.
- ***Severe neonatal morbidity:*** Among growth-restricted babies, antenatal corticosteroid therapy may increase the risk of neonatal hypoglycaemia[15] (OR 2.06 95% CI 1.27 to 3.32; 2 studies; *low certainty*) and may reduce the risk of severe intraventricular haemorrhage (OR 0.54 95% CI 0.43 to 0.68; 9 studies; *low certainty*) and duration of hospital stay (MD –2.32 95% CI –3.81 to –0.83; 2 studies; *low certainty*).

  The evidence on the effect of antenatal corticosteroid therapy on risk of intraventricular haemorrhage, neonatal infection, necrotizing enterocolitis, chronic lung disease/bronchopulmonary dysplasia, patent ductus arteriosus, retinopathy of prematurity and major brain lesion (IVH, Intracerebral haemorrhage [ICH] or PVL) among growth-restricted babies is very uncertain. No data were available on respiratory distress syndrome, moderate/severe respiratory distress syndrome, periventricular leukomalacia, surfactant use, admission to neonatal intensive care, use of mechanical ventilation, mean duration of mechanical ventilation.
- **Birth weight**: No data were available for mean birth weight or low birth weight.
- **Long-term morbidity**: The evidence on the effect of antenatal corticosteroid therapy and risk of cerebral palsy among growth-restricted babies is very uncertain. No data were available for other childhood or long-term outcomes (infant, child or adult death, developmental delay, intellectual, hearing or visual impairment, behavioural/learning difficulties).

[15] Neonatal hypoglycaemia is not a WHO priority outcome and was not reported in the 2020 Cochrane review. However, it is included here due to concerns about a possible increased risk among late preterm babies.

Antenatal corticosteroids versus placebo or no treatment – babies with fetal growth restriction *or* small-for-gestational-age babies[16] (i.e. three studies)

Table 2: Summary of absolute effects per 1000 (95% confidence interval), among babies with fetal growth restriction or small-for-gestational-age babies

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	Effect
Maternal outcomes	
Chorioamnionitis	**Uncertain**
Neonatal outcomes	
Neonatal death	**Uncertain**
RDS and moderate/severe RDS	**Uncertain**
IVH	**Uncertain**
Severe IVH (grade 3–4)	**Uncertain**
Neonatal infection	**Uncertain**
Necrotizing enterocolitis	**Uncertain**
Chronic lung disease	**Uncertain**
Patent ductus arteriosus	**Uncertain**
Retinopathy of prematurity	**Uncertain**
Neonatal hypoglycaemia	**Uncertain**
Surfactant use	**Possibly reduced** 133 fewer (173 fewer to 76 fewer)
Use of mechanical ventilation	**Possibly reduced** 182 fewer (254 fewer to 95 fewer)
Oxygen therapy	**Possibly reduced** 158 fewer (235 fewer to 61 fewer)
Admission to neonatal care	**Uncertain**
Duration of hospital stay	**Possibly reduced** MD 2.3 days lower (3.8 lower to 0.8 lower)
Mean birth weight	**Uncertain**
Survival free from disability	**Uncertain**
Cerebral palsy	**Uncertain**

[16] Only those studies that recruited "fetal growth restriction or small-for-gestational-age infants"

Maternal outcomes

- **Maternal infectious morbidity**: The evidence on the effect of antenatal corticosteroids on risk of chorioamnionitis among women with FGR or SGA babies is very uncertain.

  No data were available on other maternal outcomes (severe maternal morbidity or death, adverse effects, maternal well-being, maternal satisfaction).

Infant outcomes

- ***Fetal and neonatal death**:* The evidence on the effect of antenatal corticosteroids on risk of neonatal death among FGR or SGA babies is very uncertain. No data on perinatal death and fetal death were available.
- ***Severe neonatal morbidity:*** Among FGR or SGA babies, antenatal corticosteroid therapy may reduce use of surfactant (OR 0.38 95% CI 0.23 to 0.62; 3 studies; *low certainty*), mechanical ventilation (OR 0.42 95% CI 0.26 to 0.66; 2 studies; *low certainty*) and use of oxygen therapy (OR 0.48 95% CI 0.30 to 0.77; 2 studies; *low certainty*) and duration of hospital stay (MD –2.32 95% CI –3.81 to –0.83; 1 study; *low certainty*).

  The evidence on the effect of antenatal corticosteroids on risk of respiratory distress syndrome, intraventricular haemorrhage, severe intraventricular haemorrhage, neonatal infection, necrotizing enterocolitis, chronic lung disease/bronchopulmonary dysplasia, patent ductus arteriosus, retinopathy of prematurity, neonatal hypoglycaemia and admission to neonatal intensive care among FGR or SGA babies is very uncertain. No data were available for moderate/severe RDS or periventricular leukomalacia, admission to neonatal intensive care or mean duration of hospitalisation.
- **Birth weight**: The evidence on the effect of antenatal corticosteroid therapy on mean birth weight among FGR or SGA babies is very uncertain. No data were available for low birth weight or small-for-gestational age.
- **Long-term morbidity**: The evidence on the effect of antenatal corticosteroids therapy on survival free from disability and cerebral palsy among FGR or SGA babies is very uncertain. No data were available for other childhood or long-term outcomes (infant or child death, developmental delay, intellectual, hearing or visual impairment, behavioural/learning difficulties).

Antenatal corticosteroids versus placebo or no treatment – small-for-gestational-age babies only (i.e. 13 studies)

Table 3: Summary of absolute effects per 1000 (95% confidence interval), among small-for-gestational-age babies

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	Effect
Maternal outcomes	
Chorioamnionitis	**Uncertain**
Neonatal outcomes	
Neonatal death	**Possibly reduced** 0 fewer (0 fewer to 0 fewer)
Neonatal death before discharge	**Uncertain**
RDS and moderate/severe RDS	**Uncertain**
IVH	**Uncertain**
Severe IVH (grade 3–4)	**Possibly reduced** 47 fewer (59 fewer to 33 fewer)
Neonatal infection	**Uncertain**
Necrotizing enterocolitis	**Uncertain**
Chronic lung disease	**Uncertain**
Periventricular leukomalacia	**Uncertain**
Patent ductus arteriosus	**Uncertain**
Retinopathy of prematurity	**Uncertain**
Neonatal hypoglycaemia	**Uncertain**
Major brain lesion	**Uncertain**
Surfactant use	**Uncertain**
Use of mechanical ventilation	**Uncertain**
Duration of hospital stay	**Uncertain**
Birth weight	**Uncertain**
Cerebral palsy	**Uncertain**
Severe hearing impairment	**Uncertain**
Visual impairment	**Uncertain**

Maternal outcomes

- **Maternal infectious morbidity**: The evidence on the effect of antenatal corticosteroid therapy on risk of chorioamnionitis among women with SGA babies is very uncertain.

  No data were available on other maternal outcomes (severe maternal morbidity or death, adverse effects, maternal well-being, maternal satisfaction).

Infant outcomes

- ***Fetal and neonatal death:*** Antenatal corticosteroid therapy may reduce the risk of neonatal death among SGA babies (OR 0.61 95% CI 0.49 to 0.78; 8 studies; *low certainty*). The evidence on the effect of antenatal corticosteroids on risk of death before discharge among SGA babies is very uncertain. No data were available on fetal death or perinatal death.
- ***Severe neonatal morbidity:*** Antenatal corticosteroid therapy may reduce the risk of severe intraventricular haemorrhage among SGA babies (OR 0.52 95% CI 0.41 to 0.66; 7 studies; *low certainty*). The evidence on the effect of antenatal corticosteroid therapy on risk of respiratory distress syndrome, intraventricular haemorrhage, neonatal infection, necrotizing enterocolitis, chronic lung disease/bronchopulmonary dysplasia, patent ductus arteriosus, periventricular leukomalacia, retinopathy of prematurity, neonatal hypoglycaemia, major brain lesion (IVH, ICH or PVL), surfactant use, use of mechanical ventilation and duration of hospital stay among SGA babies is very uncertain. No data were available on moderate/severe respiratory distress syndrome, admission to neonatal intensive care or mean duration of mechanical ventilation.
- **Birth weight**: The evidence on the effect of antenatal corticosteroids on mean birth weight among SGA babies is very uncertain. No data were available for low birth weight or small-for-gestational-age.
- **Long-term morbidity**: The evidence on the effect of antenatal corticosteroids on risk of cerebral palsy, severe hearing impairment and visual impairment among SGA babies is very uncertain. No data were available on other childhood or long-term outcomes (infant or childhood death, developmental delay, intellectual impairment, behavioural/learning difficulties).

Antenatal corticosteroids versus placebo or no treatment – babies with fetal growth restriction only (i.e. three studies only)

Table 4: Summary of absolute effects per 1000 (95% confidence interval), babies with fetal growth restriction

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	Effect
Neonatal outcomes	
Neonatal death	**Uncertain**
Neonatal death before discharge	**Uncertain**
RDS or moderate/severe RDS	**Uncertain**
IVH	**Uncertain**
Severe IVH (grade 3–4)	**Uncertain**
Neonatal infection	**Uncertain**
Necrotizing enterocolitis	**Uncertain**
Chronic lung disease	**Uncertain**
Patent ductus arteriosus	**Uncertain**
Major brain lesion	**Uncertain**
Surfactant use	**Uncertain**
Use of mechanical ventilation	**Uncertain**
Duration of mechanical ventilation	**Uncertain**
Small-for-gestational-age	**Uncertain**
Abnormal behaviour at long-term follow-up at school age	**Uncertain**

Maternal outcomes

- No data were available on maternal outcomes (severe maternal morbidity or death, maternal infectious morbidity, adverse effects, maternal well-being, maternal satisfaction).

Infant outcomes

- ***Fetal and neonatal death:*** The evidence on the effect of antenatal corticosteroids on risk of neonatal death and risk of death before discharge among FGR babies is very uncertain. No data were available for fetal death or neonatal death.
- ***Severe neonatal morbidity:*** The evidence on the effect of antenatal corticosteroids on risk of respiratory distress syndrome, intraventricular haemorrhage, severe intraventricular haemorrhage, neonatal sepsis, necrotizing enterocolitis, chronic lung disease/bronchopulmonary dysplasia, patent ductus arteriosus and major brain lesion (IVH, ICH or PVL), surfactant use and mean duration of mechanical ventilation among babies with fetal growth restriction is very uncertain. No data were available for moderate/severe respiratory distress syndrome, periventricular leukomalacia, retinopathy of prematurity, admission to neonatal intensive care, mean duration of hospitalization or use of mechanical ventilation.

- **Birth weight**: The evidence on the effect of antenatal corticosteroids on small-for-gestational-age (<2.3rd percentile for gestational age) among FGR babies is very uncertain. No data were available for mean birth weight or low birth weight.
- **Long-term morbidity**: The evidence on abnormal behaviour at long-term follow-up at school age among FGR babies is very uncertain. No data were available for other childhood or long-term outcomes (child death, cerebral palsy, developmental delay, intellectual, hearing or visual impairment, learning difficulties).

Additional considerations

Subgroup analyses involve splitting available trials into different groups of participants. However, it should be acknowledged that subgroup analyses are not based on randomized comparisons and are therefore susceptible to possible biases affecting observational studies (20).

The largest efficacy trial of antenatal corticosteroids in low-resource countries (WHO ACTION-I Trial) enrolled 2852 women, including 189 women with known or suspected fetal growth restriction (21).

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids, considering fetal growth restriction?

Judgement

☐	☐	☐	☒	☐	☐
Don't know	Varies	Trivial	Small	Moderate	Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids, considering fetal growth restriction?

Judgement

☒	☐	☐	☐	☐	☐
Don't know	Varies	Large	Moderate	Small	Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids on maternal outcomes?

☐	☒	☐	☐	☐
No included studies	Very low	Low	Moderate	High

What is the overall certainty of the evidence on effects of antenatal corticosteroids on neonatal outcomes?

☐	☒	☐	☐	☐
No included studies	Very low	Low	Moderate	High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids, considering fetal growth restriction?

Research evidence

Findings from a mixed methods systematic review (22) on the appropriate use of interventions in the management of women experiencing preterm birth show the following.

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a health care provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most health care providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to presence of fetal growth restriction were identified.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the potential benefits of antenatal steroids on babies' survival without handicap and less value on potential effect on physical growth. It is likely that mothers, health care providers and policy-makers in any setting will invariably place a higher value on these benefits in the light of overall benefits of antenatal steroids for preterm population, and will chose to use the intervention.

Judgement

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids or the comparator, considering fetal growth restriction?

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (23). Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed.

The available studies did not explore differences in cost–effectiveness of antenatal corticosteroids for presence or absence of fetal growth restriction.

Additional considerations

Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (24). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (25) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (25) — In the systematic review of cost–effectiveness studies (23), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester).

Resource	Description
	• Administering of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☒ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity, considering fetal growth restriction?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (26). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (27). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (28).

Evidence from trials demonstrates that antenatal corticosteroid use is effective in all settings, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit to the protection offered by a relatively cheap and readily available medication in low-resource setting, thus increasing equity.

Judgement

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth acceptable to key stakeholders, considering fetal growth restriction?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (22).

In summary, the review found the following:

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.

No findings specifically relevant to presence of fetal growth restriction were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth feasible to implement, considering fetal growth restriction?

Research evidence

Findings from a mixed-methods systematic review (22) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following.

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well-stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and

neonatal care), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to presence of fetal growth restriction were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

4 Summary of judgements table

Desirable effects	Don't know	Varies	Trivial	✓ **Small**	Moderate	Large	
Undesirable effects	✓ **Don't know**	Varies	Large	Moderate	Small	Trivial	
Certainty of the evidence: maternal outcomes	No included studies	✓ **Very low**	Low	Moderate	High		
Certainty of the evidence: neonatal outcomes	No included studies	✓ **Very low**	Low	Moderate	High		
Values	Important uncertainty or variability	Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Resources required	Don't know	Varies	Large costs	Moderate costs	✓ **Negligible costs or savings**	Moderate savings	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High		
Cost–effectiveness	✓ **Don't know**	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Equity	✓ **Don't know**	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased
Acceptability	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	

5 Summary of findings table

Source: Saito K, Nishimura E, Swa T, Cao J, Ramson JA, Namba F, et al. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. Under review.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Chorioamnionitis (histologic and /or clinical)												
5	observational studies	serious [a]	not serious	not serious	serious [b]	none	82/785 (10.4%)	85/1102 (7.7%)	**OR 1.39** (0.98 to 1.97)	**27 more per 1000** (from 1 fewer to 64 more)	⨁◯◯◯ VERY LOW	
Chorioamnionitis (histologic and /or clinical) (SGA)												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	63/702 (9.0%)	83/1094 (7.6%)	**OR 1.42** (0.99 to 2.03)	**29 more per 1000** (from 1 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Chorioamnionitis (histologic and /or clinical) (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	19/83 (22.9%)	2/8 (25.0%)	**OR 0.89** (0.17 to 4.78)	**21 fewer per 1000** (from 196 fewer to 364 more)	⨁◯◯◯ VERY LOW	
Neonatal death (FGR)												
2	observational studies	serious [a]	not serious	not serious	very serious [d]	none	15/199 (7.5%)	20/53 (37.7%)	**OR 0.69** (0.26 to 1.81)	**82 fewer per 1000** (from 241 fewer to 146 more)	⨁◯◯◯ VERY LOW	
Neonatal death (SGA)												
8	observational studies	not serious	not serious	not serious	not serious	none	[e]	[e]	**OR 0.61** (0.49 to 0.78)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Neonatal death (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	9/83 (10.8%)	2/8 (25.0%)	**OR 0.36** (0.06 to 2.09)	**143 fewer per 1000** (from 230 fewer to 161 more)	⨁◯◯◯ VERY LOW	
Death before discharge home												
5	observational studies	serious [a]	serious [e]	not serious	not serious	none	399/2808 (14.2%)	401/2406 (16.7%)	**OR 0.61** (0.44 to 0.85)	**58 fewer per 1000** (from 86 fewer to 21 more)	⨁◯◯◯ VERY LOW	
Death before discharge home (FGR)												
1	observational study	not serious	not serious	not serious	very serious [c]	none	9/62 (14.5%)	15/62 (24.2%)	**OR 0.53** (0.21 to 1.33)	**97 fewer per 1000** (from 179 fewer to 56 more)	⨁◯◯◯ VERY LOW	
Death before discharge home (SGA)												
4	observational studies	serious [a]	serious [e]	not serious	serious	none	390/2746 (14.2%)	386/2344 (16.5%)	**OR 0.62** (0.43 to 0.90)	**56 fewer per 1000** (from 87 fewer to 14 more)	⨁◯◯◯ VERY LOW	
Respiratory distress syndrome (RDS) and moderate / severe RDS (FGR)												
3	observational studies	serious [a]	not serious	not serious	very serious [d]	none	[f]	[f]	**OR 0.85** (0.57 to 1.26)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Respiratory distress syndrome (RDS) and moderate / severe RDS (SGA)												
13	observational studies	serious [a]	not serious	not serious	not serious	none	[f]	[f]	**OR 0.90** (0.81 to 1.00)	**1 fewer per 1000** (from 1 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Respiratory distress syndrome (RDS) and moderate / severe RDS (FGR or SGA)												
3	observational studies	not serious	not serious	not serious	serious [b]	none	77/358 (21.5%)	74/241 (30.7%)	**OR 0.74** (0.51 to 1.07)	**60 fewer per 1000** (from 123 fewer to 15 more)	⨁◯◯◯ VERY LOW	
Interventricular haemorrhage												
10	observational studies	not serious	not serious	not serious	serious [b]	none	397/3737 (10.6%)	387/2828 (13.7%)	**OR 0.76** (0.56 to 1.04)	**29 fewer per 1000** (from 55 fewer to 5 more)	⨁◯◯◯ VERY LOW	
Interventricular haemorrhage (FGR)												
1	observational study	not serious	not serious	not serious	very serious [c]	none	8/62 (12.9%)	9/62 (14.5%)	**OR 0.87** (0.31 to 2.43)	**16 fewer per 1000** (from 95 fewer to 147 more)	⨁◯◯◯ VERY LOW	
Interventricular haemorrhage (SGA)												
8	observational studies	not serious	serious [e]	not serious	serious [b]	none	384/3592 (10.7%)	378/2758 (13.7%)	**OR 0.75** (0.53 to 1.06)	**31 fewer per 1000** (from 59 fewer to 7 more)	⨁◯◯◯ VERY LOW	
Interventricular haemorrhage (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	5/83 (6.0%)	0/8 (0.0%)	**OR 1.19** (0.06 to 23.46)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Severe interventricular haemorrhage (grade 3–4)												
9	observational studies	not serious	not serious	not serious	not serious	none	190/3018 (6.3%)	171/1618 (10.6%)	**OR 0.54** (0.43 to 0.68)	**46 fewer per 1000** (from 57 fewer to 31 fewer)	⨁⨁◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Severe interventricular haemorrhage (grade 3–4) (FGR)												
1	observational study	not serious	not serious	not serious	very serious [c]	none	8/62 (12.9%)	9/62 (14.5%)	**OR 0.87** (0.31 to 2.43)	**16 fewer per 1000** (from 95 fewer to 147 more)	⨁◯◯◯ VERY LOW	
Severe interventricular haemorrhage (grade 3–4) (SGA)												
7	observational studies	not serious	not serious	not serious	not serious	none	177/2873 (6.2%)	162/1543 (10.5%)	**OR 0.52** (0.41 to 0.66)	**47 fewer per 1000** (from 59 fewer to 33 fewer)	⨁⨁◯◯ LOW	
Severe interventricular haemorrhage (grade 3–4) (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	5/83 (6.0%)	0/8 (0.0%)	**OR 1.19** (0.06 to 23.46)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Neonatal infection												
8	observational studies	serious [a]	not serious	not serious	serious [b]	none	191/1437 (13.3%)	165/1847 (8.9%)	**OR 1.17** (0.92 to 1.50)	**14 more per 1000** (from 7 fewer to 39 more)	⨁◯◯◯ VERY LOW	
Neonatal infection (FGR)												
2	observational studies	not serious	not serious	not serious	very serious [d]	none	45/115 (39.1%)	36/96 (37.5%)	**OR 0.83** (0.44 to 1.58)	**43 fewer per 1000** (from 166 fewer to 112 more)	⨁◯◯◯ VERY LOW	
Neonatal infection (SGA)												
5	observational studies	serious [a]	not serious	not serious	serious [b]	none	128/1239 (10.3%)	126/1743 (7.2%)	**OR 1.28** (0.98 to 1.68)	**18 more per 1000** (from 1 fewer to 43 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Neonatal infection (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	18/83 (21.7%)	3/8 (37.5%)	**OR 0.46** (0.10 to 2.12)	**159 fewer per 1000** (from 318 fewer to 185 more)	⨁◯◯◯ VERY LOW	
Necrotizing enterocolitis												
10	observational studies	serious [a]	not serious	not serious	serious [b]	none	246/3889 (6.3%)	165/3003 (5.5%)	**OR 0.82** (0.67 to 1.01)	**9 fewer per 1000** (from 17 fewer to 1 more)	⨁◯◯◯ VERY LOW	
Necrotizing enterocolitis (FGR)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	3/53 (5.7%)	2/34 (5.9%)	**OR 0.96** (0.15 to 6.07)	**2 fewer per 1000** (from 50 fewer to 216 more)	⨁◯◯◯ VERY LOW	
Necrotizing enterocolitis (SGA)												
8	observational studies	serious [a]	not serious	not serious	serious [b]	none	238/3753 (6.3%)	162/2961 (5.5%)	**OR 0.83** (0.67 to 1.02)	**9 fewer per 1000** (from 17 fewer to 1 more)	⨁◯◯◯ VERY LOW	
Necrotizing enterocolitis (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	5/83 (6.0%)	1/8 (12.5%)	**OR 0.45** (0.05 to 4.40)	**65 fewer per 1000** (from 118 fewer to 261 more)	⨁◯◯◯ VERY LOW	
Chronic lung disease / bronchopulmonary dysplasia												
10	observational studies	serious [a]	not serious	not serious	not serious	none	641/3033 (21.1%)	415/2216 (18.7%)	**OR 1.22** (1.05 to 1.41)	**32 more per 1000** (from 8 more to 58 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Chronic lung disease / bronchopulmonary dysplasia (FGR)												
2	observational studies	not serious	not serious	not serious	very serious [d]	none	22/115 (19.1%)	23/96 (24.0%)	**OR 0.83** (0.42 to 1.63)	**32 fewer per 1000** (from 123 fewer to 100 more)	⨁◯◯◯ VERY LOW	
Chronic lung disease / bronchopulmonary dysplasia (SGA)												
7	observational studies	serious [a]	not serious	not serious	not serious	none	596/2835 (21.0%)	389/2112 (18.4%)	**OR 1.25** (1.07 to 1.46)	**36 more per 1000** (from 10 more to 64 more)	⨁◯◯◯ VERY LOW	
Chronic lung disease / bronchopulmonary dysplasia (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	23/83 (27.7%)	3/8 (37.5%)	**OR 0.64** (0.14 to 2.89)	**98 fewer per 1000** (from 298 fewer to 259 more)	⨁◯◯◯ VERY LOW	
Periventricular leukomalacia (SGA)												
4	observational studies	serious [a]	not serious	not serious	not serious	none	74/2219 (3.3%)	68/1736 (3.9%)	**OR 0.54** (0.38 to 0.77)	**18 fewer per 1000** (from 24 fewer to 9 fewer)	⨁◯◯◯ VERY LOW	
Patent ductus arteriosus												
6	observational studies	serious [a]	not serious	not serious	serious [b]	none	367/1330 (27.6%)	378/1748 (21.6%)	**OR 1.19** (1.00 to 1.42)	**31 more per 1000** (from 0 fewer to 65 more)	⨁◯◯◯ VERY LOW	
Patent ductus arteriosus (FGR)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	10/53 (18.9%)	6/34 (17.6%)	**OR 1.09** (0.35 to 3.32)	**13 more per 1000** (from 107 fewer to 239 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Patent ductus arteriosus (SGA)												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	315/1194 (26.4%)	368/1706 (21.6%)	**OR 1.20** (1.00 to 1.43)	**32 more per 1000** (from 0 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Patent ductus arteriosus (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [d]	none	42/83 (50.6%)	4/8 (50.0%)	**OR 1.02** (0.24 to 4.37)	**5 more per 1000** (from 306 fewer to 314 more)	⨁◯◯◯ VERY LOW	
Retinopathy of prematurity												
5	observational studies	serious [a]	not serious	not serious	serious [b]	none	135/1978 (6.8%)	44/832 (5.3%)	**OR 1.13** (0.79 to 1.61)	**6 more per 1000** (from 11 fewer to 30 more)	⨁◯◯◯ VERY LOW	
Retinopathy of prematurity (SGA)												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	130/1895 (6.9%)	44/824 (5.3%)	**OR 1.13** (0.79 to 1.62)	**7 more per 1000** (from 11 fewer to 30 more)	⨁◯◯◯ VERY LOW	
Retinopathy of prematurity (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	5/83 (6.0%)	0/8 (0.0%)	**OR 1.19** (0.06 to 23.46)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Neonatal hypoglycaemia[17]												
2	observational studies	not serious	not serious	not serious	not serious	none	72/181 (39.8%)	36/148 (24.3%)	**OR 2.06** (1.27 to 3.32)	**155 more per 1000** (from 47 more to 273 more)	⨁⨁◯◯ LOW	
Neonatal hypoglycaemia (SGA)												
1	observational study	not serious	not serious	not serious	very serious [c]	none	17/45 (37.8%)	8/37 (21.6%)	**OR 2.20** (0.82 to 5.91)	**161 more per 1000** (from 32 fewer to 404 more)	⨁◯◯◯ VERY LOW	
Neonatal hypoglycaemia (FGR or SGA)												
1	observational study	serious [a]	not serious	not serious	serious [f]	none	55/136 (40.4%)	28/111 (25.2%)	**OR 2.01** (1.16 to 3.48)	**152 more per 1000** (from 29 more to 288 more)	⨁◯◯◯ VERY LOW	
Major brain lesion (IVH, ICH, PVH, or PVL)												
5	observational studies	not serious	not serious	not serious	very serious [d]	none	[f]	[f]	**OR 0.66** (0.37 to 1.16)	**1 fewer per 1000** (from 1 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Major brain lesion (IVH, ICH, PVH, or PVL) (FGR)												
2	observational studies	not serious	not serious	not serious	very serious [c]	none	12/116 (10.3%)	10/96 (10.4%)	**OR 0.86** (0.35 to 2.10)	**13 fewer per 1000** (from 65 fewer to 92 more)	⨁◯◯◯ VERY LOW	

[17] While the OR for this outcome exceeded 2, the lower bound of the confidence interval is more modest and there were few studies and women.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Major brain lesion (IVH, ICH, PVH, or PVL) (SGA)												
3	observational studies	not serious	not serious	not serious	very serious [c]	none	[f]	[f]	**OR 0.55** (0.27 to 1.14)	**1 fewer per 1000** (from 1 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Surfactant use (FGR)												
1	observational study	serious [a]	not serious	not serious	very serious [c]	none	19/53 (35.8%)	13/34 (38.2%)	**OR 0.90** (0.37 to 2.20)	**25 fewer per 1000** (from 196 fewer to 194 more)	⨁◯◯◯ VERY LOW	
Surfactant use (SGA)												
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	62/209 (29.7%)	34/176 (19.3%)	**OR 1.66** (0.91 to 3.03)	**91 more per 1000** (from 14 fewer to 227 more)	⨁◯◯◯ VERY LOW	
Surfactant use (FGR or SGA)[18]												
3	observational studies	not serious	not serious	not serious	not serious	none	61/358 (17.0%)	58/241 (24.1%)	**OR 0.38** (0.23 to 0.62)	**133 fewer per 1000** (from 173 fewer to 76 fewer)	⨁⨁⨁◯ MODERATE	
Use of mechanical ventilation (FGR)												
2	observational studies	not serious	not serious	not serious	very serious [d]	none	61/115 (53.0%)	45/96 (46.9%)	**OR 1.24** (0.72 to 2.14)	**54 more per 1000** (from 80 fewer to 185 more)	⨁◯◯◯ VERY LOW	

[18] While the OR for this outcome is lower than 0.5 (i.e. risk is more than halved), data were available from few studies and women.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Use of mechanical ventilation (SGA)												
2	observational studies	not serious	serious [e]	not serious	very serious [d]	none	89/191 (46.6%)	25/56 (44.6%)	**OR 1.03** (0.37 to 2.90)	**7 more per 1000** (from 217 fewer to 254 more)	⨁◯◯◯ VERY LOW	
Use of mechanical ventilation (FGR or SGA)[6]												
2	observational studies	not serious	not serious	not serious	not serious	none	73/275 (26.5%)	94/233 (40.3%)	**OR 0.42** (0.26 to 0.66)	**182 fewer per 1000** (from 254 fewer to 95 fewer)	⨁⨁◯◯ LOW	
Duration of mechanical ventilation (FGR)												
2	observational studies	not serious	not serious	not serious	very serious [d]	none	115	96	–	MD **1.09 higher** (0.86 lower to 3.05 higher)	⨁◯◯◯ VERY LOW	
Oxygen therapy (FGR or SGA)[19]												
2	observational studies	not serious	not serious	not serious	not serious	none	79/275 (28.7%)	94/233 (40.3%)	**OR 0.48** (0.30 to 0.77)	**158 fewer per 1000** (from 235 fewer to 61 fewer)	⨁⨁◯◯ LOW	
Admission to neonatal intensive care unit (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious [d]	none	131/136 (96.3%)	107/111 (96.4%)	**OR 0.98** (0.26 to 3.74)	**1 fewer per 1000** (from 90 fewer to 26 more)	⨁◯◯◯ VERY LOW	

[19] While the OR for this outcome is lower than 0.5 (i.e. risk is more than halved), data were available from few studies and women.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Duration of hospital stay												
2	observational studies	not serious	not serious	not serious	not serious	none	223	173	–	MD **2.32 lower** (3.81 lower to 0.83 lower)	⨁⨁◯◯ LOW	
Duration of hospital stay (SGA)												
1	observational studies	serious [a]	not serious	not serious	very serious [d]	none	87	62	–	MD **4 lower** (17.43 lower to 9.43 higher)	⨁◯◯◯ VERY LOW	
Duration of hospital stay (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	serious [f]	none	136	111	–	MD **2.3 lower** (3.8 lower to 0.8 lower)	⨁⨁◯◯ LOW	
Small for gestational age (< 2.3rd percentile for gestational age) (FGR)												
1	observational studies	serious [a]	not serious	not serious	very serious [d]	none	63/146 (43.2%)	12/19 (63.2%)	**OR 0.44** (0.16 to 1.19)	**202 fewer per 1000** (from 416 fewer to 39 more)	⨁◯◯◯ VERY LOW	
Birth weight (g) (SGA)												
2	observational studies	serious [a]	serious [e]	not serious	serious [b]	none	806	1272	–	MD **49.1 lower** (110.53 lower to 12.32 higher)	⨁◯◯◯ VERY LOW	
Birth weight (g) (FGR or SGA)												
2	observational studies	not serious	not serious	not serious	serious [b]	none	275	233	–	MD **80.97 higher** (20.48 lower to 182.41 higher)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Survival free from disability (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious [d]	none	108/144 (75.0%)	91/126 (72.2%)	**OR 1.15** (0.67 to 1.98)	**27 more per 1000** (from 87 fewer to 115 more)	⨁◯◯◯ VERY LOW	
Cerebral palsy												
2	observational studies	not serious	not serious	not serious	serious [b]	none	25/417 (6.0%)	30/620 (4.8%)	**OR 1.31** (0.76 to 2.27)	**14 more per 1000** (from 11 fewer to 55 more)	⨁◯◯◯ VERY LOW	
Cerebral palsy (SGA)												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	19/278 (6.8%)	25/498 (5.0%)	**OR 1.39** (0.75 to 2.57)	**18 more per 1000** (from 12 fewer to 69 more)	⨁◯◯◯ VERY LOW	
Cerebral palsy (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious [c]	none	6/139 (4.3%)	5/122 (4.1%)	**OR 1.06** (0.31 to 3.55)	**2 more per 1000** (from 28 fewer to 91 more)	⨁◯◯◯ VERY LOW	
Abnormal behaviour at long-term follow-up at school age (FGR)												
1	observational studies	not serious	not serious	not serious	very serious [d]	none	21/49 (42.9%)	19/42 (45.2%)	**OR 0.91** (0.40 to 2.08)	**23 fewer per 1000** (from 204 fewer to 180 more)	⨁◯◯◯ VERY LOW	
Severe hearing impairment (SGA)												
1	observational studies	serious [a]	not serious	not serious	very serious [g]	none	0/277 (0.0%)	5/502 (1.0%)	**OR 0.16** (0.01 to 2.96)	**8 fewer per 1000** (from 10 fewer to 19 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Visual impairment (SGA												
1	observational studies	serious [a]	not serious	not serious	very serious [g]	none	1/275 (0.4%)	3/490 (0.6%)	**OR 0.59** (0.06 to 5.72)	**3 fewer per 1000** (from 6 fewer to 28 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Most studies contributing data had design limitations.

b. Wide confidence interval crossing the line of no effect.

d. Wide confidence interval crossing line of no effect; estimate based on small sample size.

c. Wide confidence interval crossing line of no effect; estimate based on small sample size and few events.

e. Statistical heterogeneity (I^2 ≥60%.).

f. Estimate based on small sample size.

g. Wide confidence interval crossing line of no effect; estimate based on few events.

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Evidence-to-decision framework 1.8

Antenatal corticosteroids compared to placebo or no treatment: **Women with pregestational and gestational diabetes**

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.
- Pregnant women with diabetes are at an increased risk of several perinatal complications, including macrosomia, perinatal mortality and preterm birth. Furthermore, respiratory morbidities affecting preterm newborns may be exacerbated in the setting of poor maternal glycaemic control. While pregnant women with diabetes may require antenatal corticosteroids for imminent preterm birth, this may have hyperglycaemic effects in the woman. These hyperglycaemic effects may be greater in women with insulin-treated diabetes. Maternal hyperglycaemic episodes may also adversely affect fetal lung maturity.

2 Question

Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)? If so:

- **Which population of pregnant women should be offered antenatal corticosteroids considering pregestational and gestational diabetes?**

Problem: Adverse outcomes due to preterm birth (PTB)

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): No antenatal corticosteroid therapy or placebo

Priority outcomes (O)[20]

Settings: Low- middle- and high-income settings

Subgroups: Populations of women with pregestational diabetes or gestational diabetes

[20] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

It was not possible to use trial evidence to assess the effects of antenatal corticosteroids in women with pregestational or gestational diabetes, as the 2020 Cochrane review on antenatal corticosteroid efficacy did not conduct a subgroup analysis in this group. Any such subgroup analysis is unlikely to be informative, as gestational diabetes is often an exclusion criterion in these trials.

Summary of evidence

Evidence supporting the WHO 2015 recommendation was derived from a systematic review of maternal and child outcomes following antenatal corticosteroid therapy for women in special populations at risk of imminent preterm birth, which was subsequently published in 2016 (12). The review did not identify any studies reporting on outcomes among women with pregestational or gestational diabetes.

The review was updated in 2021 (13) and a total of five studies relevant to outcomes among women with pregestational or gestational diabetes receiving antenatal corticosteroids were identified. The studies included data from 10 273 women and infants. The studies were all retrospective cohort studies.

The studies were all conducted in high-income countries with advanced maternal and newborn care including neonatal intensive care units. Two of the studies were conducted in in New Zealand, two in the United States of America and one in Israel.

Women recruited into three studies were expected to give birth preterm (≤36 weeks) due to spontaneous preterm labour, preterm pre-labour rupture of the membranes, or fetal or maternal indications for birth, while two studies included women expected to proceed to term birth. One study included women with pregestational diabetes, one study included women with pregestational diabetes and diabetes in pregnancy and the other three studies included women with gestational diabetes.

Three studies used betamethasone in the treatment arm (2376 women), one study used either betamethasone or dexamethasone (7282 women) and one study did not specify the type of corticosteroid (615 women).

All studies evaluated the use of a corticosteroid compared with no exposure to corticosteroids.

Antenatal corticosteroids versus placebo or no treatment among women with pregestational or gestational diabetes

Summary of absolute effects per 1000 (95% confidence interval)

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	
Neonatal death within 48 hours of birth	**Uncertain**
Respiratory distress syndrome	**Uncertain**
Neonatal hypoglycaemia	**Uncertain**
Admission to neonatal intensive care	**Possibly increased** 314 more (227 more to 409 more)

Maternal outcomes

No data were available for maternal outcomes (severe maternal morbidity or death, maternal infectious morbidity, maternal side-effects, maternal well-being, maternal satisfaction).

Infant outcomes

- **Fetal and neonatal death:** The evidence on the effect of antenatal corticosteroid therapy neonatal death within 48 hours of birth is very uncertain. No data were available on perinatal or fetal death.

- **Severe neonatal morbidity**: There may be an increased risk of admission to neonatal intensive care units among babies born to women with pregestational or gestational diabetes who received antenatal corticosteroid therapy (OR 7.41, 95% CI 5.04 to 10.89; 1 study; 2262 infants; *low certainty*).

  The evidence on the risk of respiratory distress syndrome (RDS) and moderate/severe RDS, neonatal hypoglycaemia and admission to neonatal intensive care unit among babies born to women with pregestational or gestational diabetes who received antenatal corticosteroid therapy is very uncertain.

  No data were available for other neonatal outcomes or for childhood/long-term outcomes.

Infant outcomes

The Guideline Development Group acknowledged the paucity of evidence on the benefits of antenatal corticosteroids in this subgroup of women. However, the group placed emphasis on the overall benefits of antenatal steroids in women at risk of imminent preterm birth, the potential benefits in terms of reducing the higher risk of newborn respiratory morbidity posed by maternal diabetes, and potential impact on the overall newborn survival.

Desirable effects

How substantial are the desirable anticipated effects of antenatal corticosteroids, considering pregestational and gestational diabetes?

Judgement

☒ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☐ Large

Undesirable effects

How substantial are the undesirable anticipated effects of antenatal corticosteroids, considering pregestational and gestational diabetes?

Judgement

☒ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☐ Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids on maternal outcomes?

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

What is the overall certainty of the evidence on effects of antenatal corticosteroids on neonatal outcomes?

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids, considering pregestational and gestational diabetes?

Research evidence

Findings from a mixed methods systematic review (14) on the appropriate use of interventions in the management of women experiencing preterm birth show the following:

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a health care provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most health care providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to presence of pregestational diabetes or gestational diabetes were identified.

Additional considerations

Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the survival of preterm newborns who are at higher risk of respiratory morbidities from maternal diabetes. It is likely that there is little or no variation of this value among mothers, health-care providers and policy-makers in low-, middle- and high-income settings.

Some trials do not describe whether women with diabetes were excluded so it is not possible to rule out women with diabetes being included. The largest trial providing evidence on corticosteroids compared to placebo did not consider gestational diabetes as an exclusion criteria and it was present in 1.5% and 1.1% of participants in the intervention and placebo groups, respectively.

Judgement

☐	☐	☒	☐
Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour antenatal corticosteroids or the comparator, considering pregestational and gestational diabetes?

Judgement

☒ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (15). Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed.

The available studies did not explore differences in cost–effectiveness of antenatal corticosteroids between women with or without diabetes.

Additional considerations

Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing health structures and protocols, including for the management of women with diabetes, that are designed to manage women at imminent risk of preterm birth with minimal cost. Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (16). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.

Resource	Description
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (17) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (17) — In the systematic review of cost–effectiveness studies (15), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administering of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☒ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity, considering pregestational and gestational diabetes?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (18). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (19). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (20).

Evidence from trials demonstrates that antenatal corticosteroid use is effective in all settings, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit to the protection offered by a relatively cheap and readily available medication in low-resource setting, thus increasing equity.

Judgement

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth acceptable to key stakeholders, considering pregestational and gestational diabetes?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (14).

In summary, the review found the following:

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.

No findings specifically relevant to presence of pregestational diabetes or gestational diabetes were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth feasible to implement, considering pregestational and gestational diabetes?

Research evidence

Findings from a mixed-methods systematic review (14) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following:

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well-stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and neonatal car), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to presence of pregestational diabetes or gestational diabetes were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

4 Summary of judgements table

Desirable effects	✓ **Don't know**	Varies	Trivial	Small	Moderate	Large
Undesirable effects	✓ **Don't know**	Varies	Large	Moderate	Small	Trivial
Certainty of the evidence: maternal outcomes	No included studies	✓ **Very low**	Low	Moderate	High	

Certainty of the evidence: neonatal outcomes	No included studies	✓ **Very low**	Low	Moderate	High		
Values	Important uncertainty or variability	Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	✓ **Don't know**	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Resources required	Don't know	Varies	Large costs	Moderate costs	✓ **Negligible costs or savings**	Moderate savings	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High		
Cost–effectiveness	✓ **Don't know**	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Equity	✓ **Don't know**	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased
Acceptability	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	

5 Summary of findings table

Source: Saito K, Nishimura E, Swa T, Cao J, Ramson JA, Namba F, et al. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. Under review.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with PGDM	Placebo	Relative (95% CI)	Absolute (95% CI)		
Neonatal death within 48 hours of birth												
1	observational study	not serious	not serious	not serious	very serious [c]	none	6/536 (1.1%)	2/79 (2.5%)	**OR 0.44** (0.09 to 2.20)	**14 fewer per 1000** (from 23 fewer to 29 more)	⨁◯◯◯ VERY LOW	CRITICAL
Respiratory distress syndrome (RDS) and moderate/severe RDS												
3	observational studies	not serious	serious [a]	not serious	serious [b]	none	179/695 (25.8%)	39/2242 (1.7%)	**OR 2.03** (0.60 to 6.85)	**17 more per 1000** (from 7 fewer to 91 more)	⨁◯◯◯ VERY LOW	CRITICAL
Neonatal hypoglycaemia												
3	observational studies	serious [d]	not serious	not serious	serious [b]	none	32/177 (18.1%)	77/2199 (3.5%)	**OR 1.74** (0.96 to 3.16)	**24 more per 1000** (from 1 fewer to 68 more)	⨁◯◯◯ VERY LOW	CRITICAL
Admission to neonatal intensive care unit												
1	observational study	not serious	not serious	not serious	not serious	none	51/129 (39.5%)	173/2133 (8.1%)	**OR 7.41** (5.04 to 10.89)	**314 more per 1000** (from 227 more to 409 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Statistical heterogeneity ($I^2 \geq 60\%$).
b. Wide confidence interval crossing line of no effect.
c. Wide confidence interval crossing line of no effect; estimate based on few events.
d. Most studies contributing data had design limitations.

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Evidence-to-decision framework 1.9

Type and regimen of antenatal corticosteroids

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.
- Different types and regimens of corticosteroids have been evaluated for their effects on women at risk of imminent preterm birth, the main options include injectable dexamethasone phosphate, betamethasone phosphate and betamethasone acetate.

2 Question

Which corticosteroids (and regimens) should be used for eligible women?

Problem: Adverse outcomes due to preterm birth (PTB)

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Antenatal corticosteroid therapy

Comparator (C): Any other antenatal corticosteroid therapy

Priority outcomes (O)[21]

Settings: Low- middle- and high-income settings

Critical outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse events of treatment
- Maternal well-being
- Maternal satisfaction

[21] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

Summary of evidence

Evidence on the effectiveness of different corticosteroids and regimens for women at risk of imminent preterm birth was derived from an updated Cochrane systematic review, which included 11 trials (2494 women and 2762 infants) (12).

The included studies came from a range of health care systems. All trials were conducted in high-income countries (three in the United States of America, two in France and Israel and one each in Australia/New Zealand, the Netherlands, Poland and the United Kingdom of Great Britain and Northern Ireland).

The gestational age at trial entry varied between trials (from 23 to 35 weeks of gestation). All women were at increased risk of preterm birth or had a medical indication for preterm birth.

Nine trials compared intramuscular dexamethasone to intramuscular betamethasone (2096 women and 2319 infants):

- 24 mg dexamethasone phosphate (6 mg, 12 hourly, four doses) versus 24 mg betamethasone phosphate, acetate/phosphate or dipropionate (12 mg, 24 hourly, two doses) (four trials, 517 women and 577 infants)
- 24 mg dexamethasone (unspecified) (12 mg, 12 hourly, two doses) and 24 mg betamethasone (unspecified) (12 mg, 12 hourly, two doses) (two trials, 91 women and infants)
- 16 mg dexamethasone phosphate (4 mg, 12 hourly, four doses) and 24 mg betamethasone phosphate or acetate/phosphate (6 mg, 12 hourly, four doses) (one trial, 82 women and infants)
- 24 mg dexamethasone phosphate (12 mg, 12 hourly, two doses) and 24 mg betamethasone acetate/phosphate (12 mg, 24 hourly, two doses) (one trial, 60 women and 60 infants)

- 24 mg dexamethasone phosphate (12 mg, 24 hourly, 2 doses) versus 22.8 mg betamethasone acetate/phosphate (11.4 mg, 24 hourly, two doses) (one trial, 1346 women and 1509 infants).

One trial compared different dexamethasone regimens: 32 mg oral dexamethasone phosphate (8 mg, 12 hourly, four doses) versus 24 mg intramuscular dexamethasone phosphate (6 mg, 12 hourly, four doses) (170 women and 183 infants).

One trial compared dosing intervals of betamethasone acetate and phosphate (12 mg, 2 doses, 12 hourly versus 24 hourly) (228 mothers and 260 infants).

One trial compared two forms of betamethasone (acetate and phosphate versus phosphate alone) (69 women and infants).

Table 1: Summary of absolute effects per 1000 (95% confidence interval), IM dexamethasone versus IM betamethasone

Key:	High certainty (benefit)	Moderate certainty (probable benefit)	Low certainty (possible benefit)	High certainty (harm)	Moderate certainty (probable harm)	Low certainty (possible harm)	High certainty (no difference)	Moderate certainty (probable no difference)	Low certainty (possible no difference)	Very low certainty (uncertain)

Maternal outcomes		Neonatal outcomes			
Chorioamnionitis	**Probably no difference** 24 fewer (43 fewer to 5 more)	Any death after randomization	**Probably no difference** 1 more (11 fewer to 20 more)	Chronic lung disease	**Probably no difference** 6 fewer (26 fewer to 25 more)
Maternal infection	**No difference** 7 fewer (40 fewer to 38 more)	Fetal death	**Possibly no difference** 2 more 6 fewer to 23 more	Bronchopulmonary dysplasia	**Possibly no difference** 162 more (97 fewer to 1000 more)
Adverse effects	**Probably no difference** 16 fewer (27 fewer to 5 more)	Neonatal death	**Possibly no difference** 0 fewer (9 fewer to 17 more)	Periventricular leukomalacia	**Possibly no difference** 2 fewer (5 fewer to 8 more)
		Respiratory distress syndrome	**No difference** 14 more (21 fewer to 52 fewer)	Patent ductus arteriosus	**Probably no difference** 10 more (9 fewer to 38 more)
		Moderate/severe Respiratory distress syndrome	**Probably no difference** 7 more (24 fewer to 46 more)	Retinopathy of prematurity	**Possibly no difference** 26 fewer (38 fewer to 175 more)
		Intraventricular haemorrhage	**Possibly no difference** 15 fewer (38 fewer to 42 more)	Neonatal sepsis	**Probably no difference** 12 more (35 fewer to 103 more)
		Necrotising enterocolitis	**Possibly no difference** 0 fewer (0 fewer to 0 fewer)	Neonatal infection in 1st 48 hours	**Possibly no difference** 4 fewer (6 fewer to 7 more)

Neonatal interventions	
Admission to neonatal intensive care	**Possibly no difference** 240 more (163 fewer to 1000 more)
Mean intensive care unit stay	**Probably no difference** 1.5 days lower (3.61 lower to 0.61 higher)
Use of mechanical ventilation	**Probably no difference** 9 fewer (41 fewer to 30 more)
Mean duration of mechanical ventilation	**Probably no difference** 9.2 hours lower (26.69 lower to 8.29 higher)

Birth weight	
Mean birth weight	**Possibly no difference** MD g 0.03 higher (0.05 lower to 0.11 higher)
Low birth weight	**Uncertain**

Childhood outcomes	
Cerebral palsy	**Possibly no difference** 15 more (0 fewer to 53 more)
Neurosensory disability	**Probably no difference** 6 more (43 fewer to 64 more)
Cognitive or language delay	**Probably no difference** 7 fewer (49 fewer to 47 more)
Motor developmental delay	**Probably no difference** 15 fewer (46 fewer to 27 fewer)
Visual impairment	**Possibly no difference** 1 fewer (2 fewer to 12 more)
Hearing impairment	**Probably no difference** 5 more (11 fewer to 34 more)

Comparison 1: Intramuscular dexamethasone versus intramuscular betamethasone

Maternal outcomes

- **Maternal infectious morbidity**: Compared to betamethasone, there is no difference in risk of maternal infection (RR 0.96, 95% CI 0.76 to 1.23; 1 trial, 1346 women; *high certainty*[22]) with dexamethasone. There is probably no difference in risk of chorioamnionitis (RR 0.71, 95% CI 0.48 to 1.06; 1 trial, 1346 women; *moderate certainty*)
- **Maternal adverse effects**: Compared to betamethasone, there is probably no difference in risk of maternal adverse effects with dexamethasone (RR 0.63, 95% CI 0.35 to 1.13; 1 trial, 1346 women; *moderate certainty*).
- No data were available for other maternal outcomes (severe maternal morbidity or death, maternal well-being, maternal satisfaction).

Infant outcomes

- ***Fetal and neonatal death:*** Compared to betamethasone, there is probably no difference in risk of any death after randomization (RR 1.03, 95% CI 0.66 to 1.63; 5 trials, 2105 infants; *moderate certainty*), and possibly no difference in risk of fetal death (RR 1.19, 95% CI 0.50 to 2.87; 1 trial, 1509 infants; *low certainty*) or neonatal death (RR 1.02, 95% CI 0.58 to 1.80; 5 trials, 2105 infants; *low certainty*) with dexamethasone.
- ***Severe neonatal morbidity:*** Compared to betamethasone, with dexamethasone there is no difference in risk of: respiratory distress syndrome (RR 1.06, 95% CI 0.91 to 1.22; 5 trials, 2105 infants; *high certainty*); probably no difference in risk of moderate/severe respiratory distress syndrome (RR 1.06, 95% CI 0.80 to 1.39; 1 trial, 1509 infants; *moderate certainty*); chronic lung disease (RR 0.92, 95% CI 0.64 to 1.34; 1 trial, 1509 infants; *moderate certainty*); patent ductus arteriosus (RR 1.20, 95% CI 0.82 to 1.76; 2 trials, 1868 infants; *moderate certainty*) or neonatal sepsis (RR 1.14, 95% CI 0.60 to 2.17; 1 trial, 359 infants; *moderate certainty*); and possibly no difference in risk of bronchopulmonary dysplasia (RR 2.50, 95% CI 0.10 to 61.34; 2 trials, 464 infants; *low certainty*).

  Compared to betamethasone, with dexamethasone there is possibly no difference in risk of: intraventricular haemorrhage (RR 0.71, 95% CI 0.28 to 1.81; 4 trials, 1901 infants; *low certainty*); necrotizing enterocolitis (RR 5.08, 95% CI 0.25 to 105.15; 2 trials, 441 infants; *low certainty*); periventricular leukomalacia (RR 0.64, 95% CI 0.18 to 2.25; 4 trials, 1901 infants; *low certainty*); retinopathy of prematurity (RR 0.32, 95% CI 0.02 to 5.50; 2 trials, 1868 infants; *low certainty*) and neonatal infection in the first 48 hours of life (RR 0.39, 95% CI 0.08 to 2.01; 1 trial, 1509 infants; *low certainty*)

  Compared to betamethasone, with dexamethasone there is probably no difference in risk of: mean intensive care unit stay (MD –1.5 days, 95% CI –3.61 to 0.61; 1 trial, 1489 infants; *moderate certainty*); use of mechanical ventilation (RR 0.94, 95% CI 0.74 to 1.19; 1 trial, 1509 infants; *moderate certainty*); and mean duration of mechanical ventilation (MD –9.2 days, 95% CI –26.69 to 8.29; 1 trial, 1489 infants; *moderate certainty*). Compared to betamethasone, with dexamethasone there is possibly no difference in risk of neonatal intensive care unit admission (2 trials, 1614 infants; RR 1.75, 95% CI 0.49 to 6.25; *low certainty*).
- **Birth weight**: Compared to betamethasone, with dexamethasone there is possibly no difference in mean birth weight (MD 0.03 kg, 95% CI –0.05 to 0.11; 5 trials, 2066 infants;

[22] The high certainty assessment based on one trial reflects that this was a multi-centre trial in 14 hospitals in Australia and New Zealand.

low certainty). The evidence on the effects of dexamethasone compared to betamethasone on risk of low birth weight is very uncertain.

- **Long-term morbidity**: Compared to betamethasone, with dexamethasone there is probably no difference in risk of: neurosensory disability as a child (RR 1.02, 95% CI 0.85 to 1.22; 1 trial, 1151 infants; *moderate certainty*) and developmental delay (cognitive or language) (RR 0.97, 95% CI 0.79 to 1.20; 1 trial, 1161 infants; *moderate certainty*).

  Compared to betamethasone, with dexamethasone there is probably no difference in risk of: developmental delay (motor) (RR 0.89, 95% CI 0.66 to 1.20; 1 trial, 1166 infants; *moderate certainty*) and hearing impairment (RR 1.16, 95% CI 0.63 to 2.16; 1 trial, 1227 infants; *moderate certainty*).

  Compared to betamethasone, with dexamethasone there is possibly no difference in risk of: cerebral palsy (RR 2.50, 95% CI 0.97 to 6.39; 1 trial, 1223 infants; *low certainty*) and visual impairment (RR 0.33, 95% CI 0.01 to 8.15; 1 trial, 1227 infants; *low certainty*).

Comparison 2: Oral dexamethasone compared to intramuscular dexamethasone

Table 2: Summary of absolute effects per 1000 (95% confidence interval), oral dexamethasone versus intramuscular dexamethasone

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	Effect
Neonatal death	**Uncertain**
Respiratory distress syndrome	**Uncertain**
Intraventricular haemorrhage	**Uncertain**
Necrotizing enterocolitis	**Uncertain**
Neonatal sepsis	**Uncertain**
Mean birth weight	**Uncertain**

Maternal outcomes

- No data were available for maternal outcomes (severe maternal morbidity or death, maternal infectious morbidity, maternal side-effects, maternal well-being, maternal satisfaction).

infant outcomes

- The evidence on all reported outcomes — neonatal death, respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, neonatal sepsis and mean birth weight — is very uncertain. No other neonatal outcomes were reported.

Comparison 3: Betamethasone at 12-hour intervals versus betamethasone at 24-hour intervals

Table 3: Summary of absolute effects per 1000 (95% confidence interval), betamethasone at 12-hour intervals versus betamethasone at 24-hour intervals

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	Effect
Maternal fever	**Uncertain**
Perinatal death	**Uncertain**
Respiratory distress syndrome	**Uncertain**
Interventricular haemorrhage	**Uncertain**
Necrotizing enterocolitis	**Uncertain**
Chronic lung disease	**Uncertain**
Retinopathy of prematurity	**Uncertain**
Neonatal sepsis	**Uncertain**
Neonatal intensive care unit admission	**Possibly reduced** 152 fewer (233 fewer to 63 fewer)
Mean birth weight	**Uncertain**
Small for gestational age	**Uncertain**

Maternal outcomes

- **Maternal infectious morbidity**: The evidence of the effect of betamethasone 12 hourly or 24 hourly on maternal fever is very uncertain.
- No data were available for other maternal outcomes (severe maternal morbidity or death, maternal adverse effects, maternal well-being, maternal satisfaction).

Infant outcomes

- **Fetal and neonatal death:** The evidence on perinatal death is very uncertain. Fetal and neonatal death were not reported separately.
- **Severe neonatal morbidity**: Compared to betamethasone 24 hourly, betamethasone 12 hourly may reduce the risk of admission to neonatal intensive care unit (RR 0.83, 95% CI 0.74 to 0.93; 1 trial, 253 infants; *low certainty*). The evidence on all other outcomes — respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, chronic lung disease, retinopathy of prematurity and neonatal sepsis — is very uncertain. No other neonatal outcomes were reported.
- **Birth weight**: The evidence on mean birth weight and small-for-gestational age is very uncertain.

Comparison 4: Intramuscular betamethasone acetate plus phosphate versus intramuscular betamethasone phosphate

Table 4: Summary of absolute effects per 1000 (95% confidence interval), betamethasone acetate plus phosphate versus betamethasone phosphate

Key:			
	High certainty (benefit)	**Moderate certainty (probable benefit)**	**Low certainty (possible benefit)**
	High certainty (harm)	**Moderate certainty (probable harm)**	**Low certainty (possible harm)**
	High certainty (no difference)	**Moderate certainty (probable no difference)**	**Low certainty (possible no difference)**
	Very low certainty (uncertain)		

Outcome	Effect
Neonatal death	**Uncertain**
Respiratory distress syndrome	**Uncertain**
Interventricular haemorrhage	**Uncertain**
Bronchopulmonary dysplasia	**Uncertain**
Periventricular leukomalacia	**Uncertain**
Neonatal intensive care unit admission	**Uncertain**
Mean birth weight	**Uncertain**
Low birth weight	**Uncertain**
Neurosensory disability as a child	**Uncertain**

Maternal outcomes

- No maternal outcomes were reported.

Infant outcomes

- **Fetal and neonatal death:** The evidence on neonatal death is very uncertain. Perinatal and fetal death were not reported separately.
- **Severe neonatal morbidity**: The evidence on respiratory distress syndrome, intraventricular haemorrhage, bronchopulmonary dysplasia, periventricular leukomalacia and neonatal intensive care unit admission is very uncertain. No other neonatal outcomes were reported.
- **Birth weight**: The evidence on mean birth weight and low birth weight is very uncertain.
- **Long-term morbidity:** The evidence on neurosensory disability as a child is very uncertain. No other long-term outcomes were reported.

Desirable effects

How substantial are the differences in desirable anticipated effects of different antenatal corticosteroid regimens?

Judgement

☐ Don't know	☐ Varies	☒ Trivial	☐ Small	☐ Moderate	☐ Large

Undesirable effects

How substantial are the undesirable anticipated effects of different antenatal corticosteroid regimens?

Judgement

☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☒ Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of different antenatal corticosteroid regimens?

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with antenatal corticosteroids?

Research evidence

Findings from a mixed methods systematic review (13) on the appropriate use of interventions in the management of women experiencing preterm birth show the following:

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a health care provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most health care providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to antenatal corticosteroid regimen were identified.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in all settings are likely to place a higher value on the overall clinical benefits of either drug as well-tested corticosteroids (in terms of reduction preterm morbidity and mortality) over subtle pharmacological differences that might exist, and therefore chose to adhere to the

recommendation. It is likely that there is no variation of this value among mothers, health care providers and policy-makers in low-, middle- and high-income settings.

Judgement

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour one type or regimen of antenatal corticosteroids?

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☒ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (14). Studies in the early preterm period included dexamethasone only (1 study), betamethasone only (2 studies), either betamethasone or dexamethasone (1 study) or the antenatal corticosteroid regimen wasn't specified (3 studies). Studies in the late preterm period all used betamethasone. Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed.

Additional considerations

Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (15). Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	**Description**
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.

Resource	Description
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (16) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (16) — In the systematic review of cost–effectiveness studies (14), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administration of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☒ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of different antenatal corticosteroid regimens on health equity?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (17). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (18). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (19).

Evidence from trials demonstrates that antenatal corticosteroid use is effective in all settings, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit to the protection offered by a relatively cheap and readily available medication in low-resource setting, thus increasing equity.

Judgement

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of different antenatal corticosteroid regimens for women at risk of imminent preterm birth acceptable to key stakeholders?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (13).

In summary, the review found the following:

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.

No findings specifically relevant to antenatal corticosteroid regimen were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

3.6 Feasibility

Are different antenatal corticosteroid regimens feasible to implement?

Research evidence

Findings from a mixed-methods systematic review (13) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following:

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and neonatal care), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to antenatal corticosteroid regimen were identified.

Additional considerations

Dexamethasone is listed on the WHO Essential Medicines List and is more widely available than betamethasone.

Judgement

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

4 Summary of judgements table

Desirable effects	Don't know	Varies	✓ **Trivial**	Small	Moderate	Large
Undesirable effects	Don't know	Varies	Large	Moderate	Small	✓ **Trivial**
Certainty of the evidence	No included studies	Very low	✓ **Low**	Moderate	High	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	No important uncertainty or variability		
Balance of effects	Don't know	Varies	Favours comparator	Probably favours comparator	✓ **Does not favour either**	Probably favours intervention	Favours intervention
Resources required	Don't know	Varies	Large costs	Moderate costs	✓ **Negligible costs or savings**	Moderate savings	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High	
Cost–effectiveness	Don't know	Varies	Favours comparator	Probably favours comparator	✓ **Does not favour either**	Probably favours intervention	Favours intervention
Equity	Don't know	Varies	Reduced	Probably reduced	Probably no impact	✓ **Probably increased**	Increased
Acceptability	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes
Feasibility	Don't know	✓ **Varies**	No	Probably No	Probably Yes	Yes

5 Summary of findings table

Source: McGoldrick, E, Williams, M, Ramson J et al. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. Under review.

5.1 Dexamethasone versus betamethasone

Maternal outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Betamethasone	Relative (95% CI)	Absolute (95% CI)		
Chorioamnionitis												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	40/679 (5.9%)	55/667 (8.2%)	**RR 0.71** (0.48 to 1.06)	**24 fewer per 1000** (from 43 fewer to 5 more)	⨁⨁⨁◯ Moderate	CRITICAL
Maternal infection requiring use of antibiotics												
1	randomized trial	not serious	not serious	not serious	not serious	none	109/679 (16.1%)	111/667 (16.6%)	**RR 0.96** (0.76 to 1.23)	**7 fewer per 1000** (from 40 fewer to 38 more)	⨁⨁⨁⨁ High	CRITICAL
Maternal adverse effects												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	18/679 (2.7%)	28/667 (4.2%)	**RR 0.63** (0.35 to 1.13)	**16 fewer per 1000** (from 27 fewer to 5 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.

Fetal and neonatal outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	betamethasone – subgrouped by regimen, all outcomes	Relative (95% CI)	Absolute (95% CI)		
Any known death after randomization												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	35/1041 (3.4%)	34/1064 (3.2%)	**RR 1.03** (0.66 to 1.63)	**1 more per 1000** (from 11 fewer to 20 more)	⨁⨁⨁◯ Moderate	CRITICAL
Fetal death												
1	randomized trial	not serious	not serious	not serious	very serious[b]	none	11/763 (1.4%)	9/746 (1.2%)	**RR 1.19** (0.50 to 2.87)	**2 more per 1000** (from 6 fewer to 23 more)	⨁⨁◯◯ Low	CRITICAL
Neonatal death												
5	randomized trials	serious[c]	not serious	not serious	serious[a]	none	22/1041 (2.1%)	22/1064 (2.1%)	**RR 1.02** (0.58 to 1.80)	**0 fewer per 1000** (from 9 fewer to 17 more)	⨁⨁◯◯ Low	CRITICAL
Respiratory distress syndrome												
5	randomized trials	not serious	not serious	not serious	not serious	none	266/1041 (25.6%)	251/1064 (23.6%)	**RR 1.06** (0.91 to 1.22)	**14 more per 1000** (from 21 fewer to 52 more)	⨁⨁⨁⨁ High	CRITICAL
Moderate/severe respiratory distress syndrome												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	95/763 (12.5%)	88/746 (11.8%)	**RR 1.06** (0.80 to 1.39)	**7 more per 1000** (from 24 fewer to 46 more)	⨁⨁⨁◯ Moderate	CRITICAL
Intraventricular haemorrhage												
4	randomized trials	not serious	serious[d]	not serious	serious[a]	none	41/944 (4.3%)	50/957 (5.2%)	**RR 0.71** (0.28 to 1.81)	**15 fewer per 1000** (from 38 fewer to 42 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	betamethasone – subgrouped by regimen, all outcomes	Relative (95% CI)	Absolute (95% CI)		
Necrotising enterocolitis												
2	randomized trials	not serious	not serious	not serious	very serious[b]	none	2/218 (0.9%)	0/223 (0.0%)	**RR 5.08** (0.25 to 105.15)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Chronic lung disease												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	51/763 (6.7%)	54/746 (7.2%)	**RR 0.92** (0.64 to 1.34)	**6 fewer per 1000** (from 26 fewer to 25 more)	⨁⨁⨁◯ Moderate	CRITICAL
Bronchopulmonary dysplasia												
2	randomized trials	not serious	serious[d]	not serious	serious[a]	none	22/214 (10.3%)	27/250 (10.8%)	**RR 2.50** (0.10 to 61.34)	**162 more per 1000** (from 97 fewer to 1000 more)	⨁⨁◯◯ Low	CRITICAL
Periventricular leukomalacia												
4	randomized trials	not serious	not serious	not serious	very serious[b]	none	4/944 (0.4%)	6/957 (0.6%)	**RR 0.64** (0.18 to 2.25)	**2 fewer per 1000** (from 5 fewer to 8 more)	⨁⨁◯◯ Low	CRITICAL
Patent ductus arteriosus												
2	randomized trials	not serious	not serious	not serious	serious[a]	none	56/941 (6.0%)	46/927 (5.0%)	**RR 1.20** (0.82 to 1.76)	**10 more per 1000** (from 9 fewer to 38 more)	⨁⨁⨁◯ Moderate	CRITICAL
Retinopathy of prematurity												
2	randomized trials	not serious	serious[d]	not serious	serious[a]	none	26/941 (2.8%)	36/927 (3.9%)	**RR 0.32** (0.02 to 5.50)	**26 fewer per 1000** (from 38 fewer to 175 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	betamethasone – subgrouped by regimen, all outcomes	Relative (95% CI)	Absolute (95% CI)		
Neonatal sepsis												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	18/178 (10.1%)	16/181 (8.8%)	**RR 1.14** (0.60 to 2.17)	**12 more per 1000** (from 35 fewer to 103 more)	⨁⨁⨁◯ Moderate	CRITICAL
Neonatal infection in first 48 hours												
1	randomized trials	not serious	not serious	not serious	very serious[b]	none	2/763 (0.3%)	5/746 (0.7%)	**RR 0.39** (0.08 to 2.01)	**4 fewer per 1000** (from 6 fewer to 7 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.

b. Wide confidence interval crossing line of no effect; estimate based on few events.

c. Most studies contributing data had design limitations.

d. Statistical heterogeneity (I2≥60%).

Neonatal interventions

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	betamethasone – subgrouped by regimen, all outcomes	Relative (95% CI)	Absolute (95% CI)		
Neonatal intensive care unit admission												
2	randomized trials	not serious	serious[b]	not serious	serious[a]	none	277/799 (34.7%)	261/815 (32.0%)	**RR 1.75** (0.49 to 6.25)	**240 more per 1000** (from 163 fewer to 1000 more)	⨁⨁◯◯ Low	CRITICAL
Neonatal intensive care unit stay (mean; days)												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	752	737	–	MD **1.50 lower** (3.61 lower to 0.61 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Use of mechanical ventilation												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	113/763 (14.8%)	118/746 (15.8%)	**RR 0.94** (0.74 to 1.19)	**9 fewer per 1000** (from 41 fewer to 30 more)	⨁⨁⨁◯ Moderate	CRITICAL
Duration of mechanical ventilation (hours, mean)												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	752	757	–	MD **9.2 lower** (26.69 lower to 8.29 higher)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.

b. Statistical heterogeneity (I2≥60%).

Birth weight

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	betamethasone – subgrouped by regimen, all outcomes	Relative (95% CI)	Absolute (95% CI)		
Birth weight (mean; kg)												
5	randomized trials	serious[b]	not serious	not serious	serious[a]	none	1024	1042	–	MD **0.03 higher** (0.05 lower to 0.11 higher)	⨁⨁◯◯ Low	CRITICAL
Low birth weight												
1	randomized trial	serious[b]	not serious	not serious	very serious[c]	none	21/36 (58.3%)	45/69 (65.2%)	**RR 0.89** (0.65 to 1.24)	**72 fewer per 1000** (from 228 fewer to 157 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.

b. Most studies contributing data had design limitations.

c. Wide confidence interval crossing line of no effect; estimate based on small sample size.

d. Wide confidence interval crossing line of no effect; estimate based on small sample size and few events.

Long-term outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Betamethasone	Relative (95% CI)	Absolute (95% CI)		
Cerebral palsy												
1	randomized trial	not serious	not serious	not serious	very serious[a]	none	15/612 (2.5%)	6/611 (1.0%)	**RR 2.50** (0.97 to 6.39)	**15 more per 1000** (from 0 fewer to 53 more)	⨁⨁◯◯ Low	CRITICAL
Neurosensory disability as a child												
2	randomized trials	serious[b]	not serious	not serious	not serious	none	172/584 (29.5%)	164/567 (28.9%)	**RR 1.02** (0.85 to 1.22)	**6 more per 1000** (from 43 fewer to 64 more)	⨁⨁⨁◯ Moderate	CRITICAL
Developmental delay - cognitive or language												
1	randomized trial	serious[b]	not serious	not serious	not serious	none	134/589 (22.8%)	134/572 (23.4%)	**RR 0.97** (0.79 to 1.20)	**7 fewer per 1000** (from 49 fewer to 47 more)	⨁⨁⨁◯ Moderate	CRITICAL
Motor developmental delay												
1	randomized trial	not serious	not serious	not serious	serious[c]	none	71/589 (12.1%)	78/577 (13.5%)	**RR 0.89** (0.66 to 1.20)	**15 fewer per 1000** (from 46 fewer to 27 more)	⨁⨁⨁◯ Moderate	CRITICAL
Visual impairment												
1	randomized trial	not serious	not serious	not serious	very serious[b]	none	0/614 (0.0%)	1/613 (0.2%)	**RR 0.33** (0.01 to 8.15)	**1 fewer per 1000** (from 2 fewer to 12 more)	⨁⨁◯◯ Low	CRITICAL
Hearing impairment												
1	randomized trial	not serious	not serious	not serious	serious[c]	none	21/614 (3.4%)	18/613 (2.9%)	**RR 1.16** (0.63 to 2.16)	**5 more per 1000** (from 11 fewer to 34 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect; estimate based on few events.

b. Loss to follow-up >20% in both groups.

c. Wide confidence interval crossing line of no effect.

5.2 Oral dexamethasone versus intramuscular dexamethasone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone: oral	intramuscular	Relative (95% CI)	Absolute (95% CI)		
Neonatal death												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	7/99 (7.1%)	4/84 (4.8%)	**RR 1.48** (0.45 to 4.90)	**23 more per 1000** (from 26 fewer to 186 more)	⨁◯◯◯ Very low	CRITICAL
Respiratory distress syndrome												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	34/99 (34.3%)	25/84 (29.8%)	**RR 1.15** (0.75 to 1.77)	**45 more per 1000** (from 74 fewer to 229 more)	⨁◯◯◯ Very low	CRITICAL
Intraventricular haemorrhage												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	10/99 (10.1%)	2/84 (2.4%)	**RR 4.24** (0.96 to 18.83)	**77 more per 1000** (from 1 fewer to 425 more)	⨁◯◯◯ Very low	CRITICAL
Necrotising enterocolitis												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	6/99 (6.1%)	1/84 (1.2%)	**RR 5.09** (0.63 to 41.45)	**49 more per 1000** (from 4 fewer to 482 more)	⨁◯◯◯ Very low	CRITICAL
Neonatal sepsis												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	10/99 (10.1%)	1/84 (1.2%)	**RR 8.48** (1.11 to 64.93)	**89 more per 1000** (from 1 more to 761 more)	⨁◯◯◯ Very low	CRITICAL
Birth weight (kg, mean)												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	99	84	–	MD **0.05 higher** (0.17 lower to 0.27 higher)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Most studies contributing data had design limitations.

b. Wide confidence interval crossing line of no effect; estimate based on small sample and few events.

5.3 12 hourly betamethasone versus 24 hourly betamethasone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betamethasone 12 hourly	Betamethasone 24 hourly	Relative (95% CI)	Absolute (95% CI)		
Maternal fever												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	9/176 (5.1%)	5/77 (6.5%)	**RR 0.71** (0.25 to 2.02)	**14 fewer per 1000** (from 47 fewer to 82 more)	⨁◯◯◯ Very low	CRITICAL
Perinatal death												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	21/177 (11.9%)	10/78 (12.8%)	**RR 0.93** (0.46 to 1.87)	**9 fewer per 1000** (from 69 fewer to 112 more)	⨁◯◯◯ Very low	CRITICAL
Respiratory distress syndrome												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	61/176 (34.7%)	28/77 (36.4%)	**RR 0.95** (0.67 to 1.36)	**18 fewer per 1000** (from 120 fewer to 131 more)	⨁◯◯◯ Very low	CRITICAL
Intraventricular haemorrhage												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	32/176 (18.2%)	10/77 (13.0%)	**RR 1.40** (0.73 to 2.70)	**52 more per 1000** (from 35 fewer to 221 more)	⨁◯◯◯ Very low	CRITICAL
Necrotising enterocolitis												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	10/177 (5.6%)	0/76 (0.0%)	**RR 9.08** (0.54 to 153.08)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betamethasone 12 hourly	Betamethasone 24 hourly	Relative (95% CI)	Absolute (95% CI)		
Chronic lung disease												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	36/177 (20.3%)	20/76 (26.3%)	**RR 0.77** (0.48 to 1.24)	**61 fewer per 1000** (from 137 fewer to 63 more)	⨁◯◯◯ Very low	CRITICAL
Retinopathy of prematurity												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	26/177 (14.7%)	11/76 (14.5%)	**RR 1.01** (0.53 to 1.95)	**1 more per 1000** (from 68 fewer to 138 more)	⨁◯◯◯ Very low	CRITICAL
Neonatal sepsis												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	16/177 (9.0%)	6/76 (7.9%)	**RR 1.15** (0.47 to 2.81)	**12 more per 1000** (from 42 fewer to 143 more)	⨁◯◯◯ Very low	CRITICAL
Neonatal intensive care unit admission												
1	randomized trial	serious[a]	not serious	not serious	serious[d]	none	131/177 (74.0%)	68/76 (89.5%)	**RR 0.83** (0.74 to 0.93)	**152 fewer per 1000** (from 233 fewer to 63 fewer)	⨁⨁◯◯ Low	CRITICAL
Birth weight (mean, kg)												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	177	78	–	MD **0.08 higher** (0.15 lower to 0.31 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betamethasone 12 hourly	Betamethasone 24 hourly	Relative (95% CI)	Absolute (95% CI)		
Small-for-gestational age												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	25/177 (14.1%)	18/78 (23.1%)	**RR 0.61** (0.36 to 1.05)	**90 fewer per 1000** (from 148 fewer to 12 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data from a single study with design limitations.

b. Wide confidence interval crossing line of no effect; estimate based on small sample size and few events.

c. Wide confidence interval crossing line of no effect; estimate based on small sample size.

d. Estimate based on small sample size.

5.4 Betamethasone acetate and phosphate versus betamethasone phosphate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betamethasone acetate + phosphate	betamethasone phosphate	Relative (95% CI)	Absolute (95% CI)		
Neonatal death												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	0/35 (0.0%)	1/34 (2.9%)	**RR 0.32** (0.01 to 7.69)	**20 fewer per 1000** (from 29 fewer to 197 more)	⨁◯◯◯ Very low	CRITICAL
Respiratory distress syndrome												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	0/35 (0.0%)	2/34 (5.9%)	**RR 0.19** (0.01 to 3.91)	**48 fewer per 1000** (from 58 fewer to 171 more)	⨁◯◯◯ Very low	CRITICAL
Intraventricular haemorrhage												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/35 (0.0%)	1/34 (2.9%)	**RR 0.32** (0.01 to 7.69)	**20 fewer per 1000** (from 29 fewer to 197 more)	⨁◯◯◯ Very low	CRITICAL
Bronchopulmonary dysplasia												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	0/35 (0.0%)	0/34 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Periventricular leukomalacia												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	0/35 (0.0%)	0/34 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betamethasone acetate + phosphate	betamethasone phosphate	Relative (95% CI)	Absolute (95% CI)		
Neonatal intensive care unit admission												
1	randomized trial	serious[a]	not serious	not serious	very serious[b]	none	0/35 (0.0%)	4/34 (11.8%)	**RR 0.11** (0.01 to 1.93)	**105 fewer per 1000** (from 116 fewer to 109 more)	⨁◯◯◯ Very low	CRITICAL
Mean birth weight (kg)												
1	randomized trial	serious[a]	not serious	not serious	very serious[d]	none	34	35	–	MD **0.1 lower** (0.44 lower to 0.24 higher)	⨁◯◯◯ Very low	CRITICAL
Low birth weight												
1	randomized trial	serious[a]	not serious	not serious	very serious[d]	none	25/35 (71.4%)	20/34 (58.8%)	**RR 1.21** (0.86 to 1.72)	**124 more per 1000** (from 82 fewer to 424 more)	⨁◯◯◯ Very low	CRITICAL
Neurodevelopmental disability												
1	randomized trial	serious[a]	not serious	not serious	very serious[c]	none	0/35 (0.0%)	0/34 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Most studies contributing data had design limitations.

b. Wide confidence interval crossing line of no effect; estimate based on small sample size and few events.

c. Effect not estimable.

d. Wide confidence interval crossing line of no effect; estimate based on small sample size.

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Evidence-to-decision framework 1.10

Repeat course compared to a single course of antenatal corticosteroids

Contents

1 Background

- Complications of preterm birth (<37 weeks' gestation) are the leading cause of neonatal death and deaths among children under the age of five years (1). Preterm newborns who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities (2–10).
- Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women at risk of preterm birth, they can cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (11). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.
- Efficacy evidence has shown that a single course of antenatal corticosteroids can reduce preterm-associated newborn mortality and several morbidities. Further trials have been conducted to evaluate whether the use of additional courses (sometimes called repeat or rescue courses) of antenatal corticosteroids also provide additional benefit.

2 Question

Should repeat course(s) of corticosteroids be offered to a woman who has completed a course of corticosteroid but remains at risk of preterm birth 7 days or more after the initial treatment?

Problem: Adverse outcomes due to preterm birth

Perspective: Clinical practice recommendation – population perspective

Population (P): Pregnant women at risk of imminent preterm birth

Intervention (I): Repeat course/s of antenatal corticosteroid therapy

Comparator (C): Single course of antenatal corticosteroid therapy

Priority outcomes (O)[23]

Settings: Low- middle- and high-income settings

Subgroups: Populations receiving only one repeat course or more than one repeat course

Populations receiving antenatal corticosteroid therapy at ≤7 days or ≥14 days

[23] These outcomes reflect the prioritized outcomes used for this recommendation in the WHO recommendations for interventions to improve preterm birth outcomes (2015). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Critical outcomes

Critical maternal outcomes considered were:

- Pregnancy prolongation (preterm birth <28 weeks, <34 weeks, <37 weeks, ≥37 weeks, mean gestational age at birth)
- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death
- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome, intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

3 Assessment

3.1 Effects of interventions

Research evidence

Summary of evidence

Evidence on repeat courses versus a single course of antenatal corticosteroids for improving health outcomes among women at risk of imminent preterm birth was derived from an updated 2021 Cochrane review, which included 11 trials (4895 women and 5975 infants) (12). All trials started recruitment between 1996 and 2004 and completed recruitment between 1999 and 2008.

Trials were mainly conducted in high-resource settings: five in the United States of America; one each in Canada, Finland, India, the United Kingdom of Great Britain and Northern Ireland; one in Australia and New Zealand; and one involved 20 countries (including a number of middle-income countries): Argentina, Bolivia (Plurinational State of), Brazil, Canada, Chile, China, Columbia, Denmark, Germany, Hungary, Israel, Jordan, the Netherlands, Peru, Poland, Russian Federation, Spain, Switzerland, the United Kingdom and the USA.

Additional subgroup analyses based on planned interval between treatments and planned number of repeats were conducted.

All women in the trials were at increased risk of preterm birth and had received a single course of antenatal corticosteroids one week or more before trial entry.

The gestational age at trial entry varied between the trials: 24 to 30 weeks in one study; 25 to 32 weeks in one study; 25 to less than 33 weeks in two studies; 26 to 33 weeks in two studies; 25 to 33 weeks in one study; 23 to less than 32 weeks in one study; less than 32 weeks in two studies; and less than 34 weeks in one study.

All trials used betamethasone as the repeat corticosteroid. The type, amount and timing regimen for administration of the corticosteroid given for the pre-trial course of antenatal corticosteroids varied between the trials.

The repeat course regimen differed between trials: a single repeat course (versus no repeat) was given in three trials and planned multiple repeat courses (versus no repeat) were given in eight trials.

Table 1: Summary of absolute effects per 1000 (95% confidence interval), repeat dose versus single dose of corticosteroids

Key:	High certainty (benefit)	Moderate certainty (probable benefit)	Low certainty (possible benefit)	High certainty (harm)	Moderate certainty (probable harm)	Low certainty (possible harm)	High certainty (no difference)	Moderate certainty (probable no difference)	Low certainty (possible no difference)	Very low certainty (uncertain)

Maternal outcomes		Neonatal outcomes				Child and adult outcomes	
Maternal death	**Possibly no difference** 3 fewer (5 fewer to 32 more)	Perinatal death	**Probably no difference** 2 fewer (10 fewer to 9 more)	Peri ventricular leukomalacia	**Probably no difference** 3 fewer (6 fewer to 3 more)	Survival free of neuro-developmental impairment	**No difference** 8 more (16 fewer to 31 more)
Chorio-amnionitis	**Probably no difference** 7 more (6 fewer to 23 more)	Fetal death	**Possibly no difference** 1 fewer (3 fewer to 7 more)	Patent ductus arteriosus	**Possibly reduced** 17 fewer (28 fewer to 3 fewer)	Neurodevelopmental impairment	**No difference** 6 fewer (28 fewer to 19 more)
Maternal sepsis	**Probably no difference** 9 more (5 fewer to 26 more)	Neonatal death	**Probably no difference** 3 fewer (14 fewer to 13 more)	Retinopathy of prematurity	**Probably no difference** 1 more (10 fewer to 14 more)	Developmental delay	**No difference** 9 fewer (30 fewer to 17 more)
Adverse effects	**No meta-analysis conducted**	Composite of serious outcomes*	**Reduced** 25 fewer (42 fewer to 6 fewer)	Admission to neonatal intensive care	**No difference** 5 more (25 fewer to 35 more)	Cerebral palsy	**Probably no difference** 1 more (8 fewer to 13 more)
		Respiratory distress syndrome	**Reduced** 61 fewer (88 fewer to 34 fewer)	Surfactant use	**Probably reduced** 45 fewer (61 fewer to 25 fewer)	Visual impairment	**Probably no difference** 2 more (4 fewer to 14 more)
		Severe respiratory distress syndrome	**Possibly no difference** 3 fewer (20 fewer to 18 more)	Use of respiratory support	**Reduced** 51 fewer (85 fewer to 13 fewer)	Hearing impairment	**Probably no difference** 0 fewer (6 fewer to 10 more)
		Chronic lung disease	**No difference** 0 fewer (11 fewer to 14 more)	Use of oxygen supplementation	**Reduced** 41 fewer (69 fewer to 9 fewer)		
		Intraventricular haemorrhage	**No difference** 4 fewer (21 fewer to 16 more)	Mean duration of oxygen supple-mentation	**Probably no difference** MD 0.32 lower (0.94 lower to 0.3 higher)		
		Severe intraventricular haemorrhage	**Probably no difference** 1 more (3 fewer to 10 more)	Small for gestational age	**Increased** 35 more (11 more to 61 more)		
		Early systemic infection	**No difference** 16 fewer (47 fewer to 24 more)	Mean birth weight	**Reduced** MD 74.49 (115.8 lower to 33.18 lower)		
		Necrotising enterocolitis	**Probably no difference** 3 fewer (9 fewer to 5 more)				

* Composite of serious outcomes was variously defined by trial authors but generally included one or more of perinatal death, respiratory distress syndrome, intraventricular haemorrhage, bronchopulmonary disorder, necrotizing enterocolitis, periventricular leukomalacia and/or neonatal sepsis.

Antenatal corticosteroids: single course versus repeat courses

Maternal outcomes

- **Maternal mortality**: There may be no difference in risk of maternal death between women receiving repeat antenatal corticosteroids and women receiving a single course (RR 0.32, 95% CI 0.01 to 7.81; 1 trial, 437 women; *low certainty*).
- **Maternal infectious morbidity**: There is probably no difference between women receiving repeat antenatal corticosteroids compared to women receiving a single course in risk of: chorioamnionitis (RR 1.13, 95% CI 0.90 to 1.42; 7 trials, 4417 women; *moderate certainty*); and maternal sepsis (RR 1.13, 95% CI 0.93 to 1.39; 8 trials, 4666 women; *moderate certainty*).
- **Maternal adverse effects**: The evidence on risk of adverse effects of antenatal corticosteroids was not pooled due to high heterogeneity and opposite directions of effect from the two trials contributing data.
- **Maternal well-being and satisfaction**: No data were available on maternal well-being or satisfaction.

Infant outcomes

- **Fetal and neonatal death:** There is probably no difference between babies of women receiving repeat antenatal corticosteroids compared to women receiving a single course in risk of: perinatal death (composite of fetal or neonatal death or infant death <1 year of age) (RR 0.95, 95% CI 0.73 to 1.24; 10 trials, 5849 infants; *moderate certainty*[24]); and neonatal death (RR 0.91, 95% CI 0.62 to 1.34; 7 trials, 2758 infants; *moderate certainty*). There may be no difference between babies of women receiving repeat antenatal corticosteroids and those of women receiving a single course in risk of fetal death (RR 0.82, 95% CI 0.24 to 2.84; 7 trials, 2758 infants; *low certainty*[25]).
- **Severe neonatal morbidity:** Compared to a single course of antenatal corticosteroids, repeat doses reduce the risk of: composite of serious outcomes[26] (RR 0.88, 0.80 to 0.97; 9 trials, 5736 infants; *high certainty*[27]); respiratory distress syndrome (RR 0.82, 95% CI 0.74 to 0.90; 9 trials, 3540 infants; *high certainty*); and possibly reduce the risk of patent ductus arteriosus (RR 0.78, 95% CI 0.63 to 0.96; 7 trials, 4657; *low certainty*).

  Compared to a single course of antenatal corticosteroids, repeat doses result in no difference in risk of: chronic lung disease (RR 1.00, 95% CI 0.83 to 1.22; 9 trials, 5661 infants; *high certainty*); intraventricular haemorrhage (RR 0.95, 95% CI 0.75 to 1.19; 6 trials, 3223 infants; *high certainty*); and early systemic infection (RR 0.93, 95% CI 0.79 to 1.11; 4 trials, 1738 infants; *high certainty*).

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24 In the Cochrane review, certainty for the outcome *perinatal death* was considered high. As the World Health Organization (WHO) approach downgrades –1 when the confidence interval is imprecise (i.e. it crosses the line of no effect and the lower and upper bounds are <0.75 and >1.25, respectively), certainty has been downgraded for imprecision and is considered moderate.

25 In the Cochrane review, certainty for the outcome *fetal death* was downgraded once for imprecision and was considered moderate. As the WHO approach downgrades –1 for an imprecise confidence interval and –1 for small sample size and/or few events, the certainty for this outcome has been downgraded twice and is considered low.

26 Composite of serious outcomes was variously defined by trial authors but generally included one or more of perinatal death, respiratory distress syndrome, intraventricular haemorrhage, bronchopulmonary disorder, necrotizing enterocolitis, periventricular leukomalacia and neonatal sepsis.

27 In the Cochrane review, certainty for the outcome *composite of serious outcomes* was downgraded due to inconsistency (I^2=42%) and was considered moderate. As the WHO approach does not downgrade for inconsistency until I^2≥60%, the certainty for this outcome has not been not downgraded for inconsistency and is considered high.

Compared to a single course of antenatal corticosteroids, repeat doses probably result in no difference in risk of: severe intraventricular haemorrhage (RR 1.13, 95% CI 0.69 to 1.86; 7 trials, 5066 infants; *moderate certainty*); necrotising enterocolitis (RR 0.84, 95% CI 0.59 to 1.22; 9 trials, 5736 infants; *moderate certainty*); periventricular leukomalacia (RR 0.75, 95% CI 0.43 to 1.31; 8 trials, 5142 infants; *moderate certainty*); and retinopathy of prematurity (RR 1.01, 95% CI 0.81 to 1.27; 8 trials, 5234 infants; *moderate certainty* [28]).

Compared to a single course of antenatal corticosteroids, repeat doses may result in no difference in risk of severe respiratory distress syndrome (5 trials, 3809 infants; RR 0.97, 95% CI 0.82 to 1.16; *low certainty*[29]).

Compared to babies of women who received a single course of antenatal corticosteroids, babies of women who received repeat doses have a reduced risk of use of respiratory support (RR 0.88, 95% CI 0.80 to 0.97; 2 trials, 2497 infants; *high certainty*) and oxygen supplementation (RR 0.91, 95% CI 0.85 to 0.98; 3 trials, 3643 infants; *high certainty*) and probably have reduced surfactant use (RR 0.80, 95% CI 0.73 to 0.89; 10 trials, 5870 infants; *moderate certainty*). There is no difference between groups in risk of admission to neonatal intensive care (RR 1.01, 95% CI 0.95 to 1.07; 2 trials, 3455 infants; *high certainty*) and probably no difference in mean duration of oxygen supplementation (MD –0.32, 95% CI –0.94 to 0.3; 4 trials, 1619 infants; *moderate certainty*).

- **Birth weight**: Compared to babies of women who receive a single course of antenatal corticosteroids, babies of women who receive repeat doses have an increased risk of small-for-gestational age (RR 1.25, 95% CI 1.08 to 1.44; 7 trials, 4013 infants; *high certainty*) and lower mean birth weight (MD –74.49 grams, 95% CI –115.8 to –33.18 grams; 10 trials, 5808 infants; *high certainty*).
- **Long-term morbidity**: Among children of women who received repeat antenatal corticosteroids compared to those of women who received a single course, there is no difference in risk of: survival free of neurodevelopmental impairment (RR 1.01, 95% CI 0.98 to 1.04; 4 trials, 3845 children; *high certainty*); neurodevelopmental impairment (RR 0.97, 95% CI 0.85 to 1.10; 4 trials, 3616 children; *high certainty*); and developmental delay (RR 0.95, 95% CI 0.84 to 1.09; 4 trials, 3581 children; *high certainty*). There is probably no difference in risk of cerebral palsy (RR 1.03, 95% CI 0.71 to 1.49; 5 trials, 3923 children; *moderate certainty*), blindness or visual impairment (RR 1.17, 95% CI 0.65 to 2.10; 3 trials, 3274 children; *moderate certainty*) or deafness or hearing impairment (RR 0.97, 95% CI 0.56 to 1.71; 4 trials, 3528 children; *moderate certainty*) between groups. No data were available on infant or child death or behavioural/learning difficulties.

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[28] In the Cochrane review, certainty for the outcome *retinopathy of prematurity* was not downgraded for imprecision and was considered high. As the WHO approach downgrades –1 when the confidence interval is imprecise (i.e. it crosses the line of no effect and the lower and upper bounds are <0.75 and >1.25, respectively), certainty has been downgraded for imprecision and is considered moderate.

[29] In the Cochrane review, certainty for the outcome *severe respiratory distress syndrome* was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings and the certainty of the evidence was considered moderate. As the WHO approach downgrades for risk of bias when >50% of studies are rated 'B' (which was the case in this instance), certainty is considered low.

Subgroup analyses

Subgroup analyses were conducted for planned number of repeat courses of corticosteroids and planned interval between corticosteroid courses.

Subgroup analysis by number of repeats

Maternal outcomes

- **Maternal infectious morbidity**: Among women planned for one or more repeat courses of corticosteroids, there is probably no difference in risk of maternal sepsis among women (RR 1.10, 95% CI 0.89 to 1.36; 87 trials, 4448 women; *moderate certainty*) compared to women who receive a single course. The evidence among women planned for only one repeat dose is very uncertain.

Infant outcomes

- **Fetal and neonatal death**: Among babies of women who receive one or more repeat courses, there is probably little or no difference in risk of perinatal death (RR 0.90, 95% CI 0.68 to 1.19; 7 trials, 4831 women; *moderate certainty*) or neonatal death (RR 0.80, 95% CI 0.51 to 1.23; 4 trials, 1740 infants; *moderate certainty*) and possibly no difference in risk of fetal death (RR 0.71, 95% CI 0.14 to 3.57; 4 trials, 1740 infants; *low certainty*) compared to babies of women who receive a single course of corticosteroids.

  Among babies of women who receive only one repeat course, there is probably no difference in risk of perinatal death (RR 1.38, 95% CI 0.65 to 2.92; 3 trials, 1018 infants; *moderate certainty*) and possibly no difference in risk of fetal (RR 1.02, 95% CI 0.14 to 7.23; 3 trials, 1018 infants; *low certainty*) or neonatal death (RR 1.36, 95% CI 0.58 to 3.19; 3 trials, 1018 infants; *low certainty*) compared to babies who receive a single course.
- **Severe neonatal morbidity**: Among babies of women who receive one or more repeat courses, risk of composite serious outcome (RR 0.88, 95% CI 0.78 to 1.00; 4831 infants; 7 trials; *high certainty*) and respiratory distress syndrome (RR 0.80, 95% CI 0.71 to 0.91; 6 trials, 2522 women; *high certainty*) is reduced compared to babies of women who receive a single course of corticosteroids. There is probably no difference in risk of chronic lung disease (RR 0.95, 95% CI 0.77 to 1.19; 6 trials, 4643 infants; *moderate certainty*), severe intraventricular haemorrhage (RR 0.98, 95% CI 0.53 to 1.79; 5 trials, 4161 infants; *moderate certainty*), intraventricular haemorrhage (RR 0.92, 95% CI 0.69 to 1.24; 4 trials, 2318 infants; *moderate certainty*) or necrotising enterocolitis (RR 0.92, 95% CI 0.61 to 1.39; 7 trials, 4831 infants; *moderate certainty*) and there may be little or no difference in risk of severe respiratory distress syndrome (RR 0.87, 95% CI 0.70 to 1.09; 4 trials, 3481 infants; *low certainty*).

  Among babies of women who receive only one repeat course, risk of respiratory distress syndrome is probably reduced (RR 0.84, 95% CI 0.72 to 0.98; 3 trials, 1018 infants; *moderate certainty*) compared to babies of women who receive a single course. There is probably no difference in risk of chronic lung disease (RR 1.20, 95% CI 0.80 to 1.82; 3 trials, 1018 infants; *moderate certainty*) and intraventricular haemorrhage (RR 0.99, 95% CI 0.69 to 1.42; 2 trials, 905 infants; *moderate certainty*) and possibly no difference in risk of composite serious outcome (RR 0.87, 95% CI 0.75 to 1.02; 2 trials, 905 infants; *low certainty*), severe respiratory distress syndrome (RR 1.23, 95% CI 0.94 to 1.60; 1 trial, 328 infants; *low certainty*), severe intraventricular haemorrhage (RR 1.53, 95% CI 0.63 to 3.71; 2 trials, 905 infants; *low certainty*) and necrotizing enterocolitis (RR 0.60, 95% CI 0.27 to 1.37; 2 trials, 905 infants; *low certainty*).

Subgroup analysis by interval between repeat doses

Maternal outcomes

- **Maternal infectious morbidity**: Compared to women who receive a single course of corticosteroids, there is probably no difference in risk of maternal sepsis among women who receive a repeat dose at ≤7 days (RR 0.97, 95% CI 0.78 to 1.20; 6 trials, 3172 women), 95% CI 0.90 to 1.42; 6 trials, 2376 women; *moderate certainty*) or ≥14 days (RR 1.01, 95% CI 0.83 to 1.22; 2 trials, 2295 women; *moderate certainty*).

Infant outcomes

- **Fetal and neonatal death**: Compared to babies of women who receive a single course of corticosteroids, babies of women who receive a repeat dose at an interval of ≤7 days probably have no difference in risk of perinatal death (RR 0.89, 95% CI 0.62 to 1.28; 7 trials, 2850 infants; *moderate certainty*) or neonatal death (RR 0.92, 95% CI 0.61 to 1.39; 5 trials, 2068 infants; *moderate certainty*) and possibly no difference in risk of fetal death (RR 0.78, 95% CI 0.19 to 3.15; 5 trials, 2068 infants; *low certainty*).

  Among babies of women who receive a repeat dose at an interval of ≥14 days, there is probably no difference in risk of perinatal death (RR 1.02, 95% CI 0.69 to 1.52; 3 trials, 2999 infants; *moderate certainty*) and possibly no difference in risk of fetal (RR 1.00, 95% CI 0.06 to 15.86; 2 trials, 690 infants; *low certainty*) or neonatal death (RR 0.85, 95% CI 0.27 to 2.61; 2 trials, 690 infants; *low certainty*).
- **Severe neonatal morbidity**: Compared to babies of women who receive a single course of corticosteroids, babies of women who receive a repeat dose at an interval of ≤7 days have a reduced risk of composite serious outcome (RR 0.87, 95% CI 0.76 to 0.99; 7 trials, 2850 infants; *high certainty*) and respiratory distress syndrome (RR 0.85, 95% CI 0.76 to 0.95; 7 trials, 2850 infants; *high certainty*). They probably had no difference in risk of chronic lung disease (RR 0.91, 95% CI 0.74 to 1.14; 6 trials, 2662 infants; *moderate certainty*), intraventricular haemorrhage (RR 0.99, 95% CI 0.77 to 1.27; 5 trials, 2646 infants; *moderate certainty*), severe intraventricular haemorrhage (RR 1.32, 95% CI 0.69 to 2.53; 5 trials, 2180 infants; *moderate certainty*) or necrotising enterocolitis (RR 0.89, 95% CI 0.56 to 1.40; 7 trials, 2850 infants; *moderate certainty*) and possibly no difference in risk of severe respiratory distress syndrome (RR 0.89, 95% CI 0.72 to 1.10; 4 trials, 1500 infants; *low certainty*).

  Compared to babies of women who receive a single course of corticosteroids, babies of women who receive a repeat dose at an interval of ≥14 days have a reduced risk of respiratory distress syndrome (RR 0.70, 95% CI 0.57 to 0.87; 2 trials, 690 infants; *high certainty*) and probably have a reduced risk of composite serious outcome (RR 0.89, 95% CI 0.76 to 1.04; 2 trials, 2886 infants; *moderate certainty*) and intraventricular haemorrhage (RR 0.76, 95% CI 0.43 to 1.34; 1 trial, 577 infants; *moderate certainty*). There is probably no difference in risk of chronic lung disease (RR 1.39, 95% CI 0.91 to 2.12; 3 trials, 2999 infants; *moderate certainty*) and possibly no difference in risk of severe respiratory distress syndrome (RR 1.11, 95% CI 0.82 to 1.49; 1 trial, 2309 infants; *low certainty*) and severe intraventricular haemorrhage (RR 0.91, 95% CI 0.42 to 1.99; 2 trials, 2886; *low certainty*). The evidence on necrotising enterocolitis is very uncertain.

- **Long-term morbidity**: Compared to children of women who receive a single course of corticosteroids, children of women who receive a repeat dose at an interval of ≤7 days have no difference in risk of survival free of neurodevelopmental impairment (RR 1.02, 95% CI 0.96 to 1.09; 3 trials, 1741 children; *high certainty*) and developmental delay (RR 0.94, 95% CI 0.81 to 1.09; 3 trials, 1680 children; *high certainty*) and probably have no

difference in risk of neurodevelopmental impairment (RR 0.95, 95% CI 0.82 to 1.10; 3 trials, 1608 children; *moderate certainty*) and cerebral palsy (RR 1.12, 95% CI 0.68 to 1.85; 4 trials, 1915 children; *moderate certainty*).

Compared to babies of women who receive a single course of corticosteroids, children of women who receive a repeat dose at an interval of ≥14 days probably have no difference in risk of survival free of neurodevelopmental impairment (RR 1.00, 95% CI 0.97 to 1.03; 1 trial, 2104 children; *moderate certainty*) and there is possibly no difference in risk of neurodevelopmental impairment (RR 1.01, 95% CI 0.77 to 1.32; 1 trial, 2008 children; *low certainty*), developmental delay (RR 0.99, 95% CI 0.75 to 1.32; 1 trial, 1901 children; *low certainty*) and cerebral palsy (RR 0.93, 95% CI 0.53 to 1.62; 1 trial, 2008; *low certainty*).

Additional considerations

- Based on the above review, there are short-term benefits for infants exposed to repeat course(s) of corticosteroids in terms of less respiratory distress, use of oxygen supplementation, use of surfactant, and fewer serious morbidities (when considered as a composite) compared to infants exposed to a single course. However, these short-term benefits do not translate into a reduction in neonatal death. The downside of repeat course is a reduction in mean birth weight, and increased risk of small-for-gestational age. While there seems to be no apparent long-term benefits, available data did not show any increase in harm during childhood.
- Available evidence supports the concern about restriction of growth of the preterm infants with repeat corticosteroid from animal studies, though it neither confirms nor refutes the concern regarding brain developmental delay and behavioural abnormalities.

Desirable effects

How substantial are the desirable anticipated effects of a repeat course of antenatal corticosteroids compared to a single course?

Judgement

☐	☐	☐	☐	☒	☐
Don't know	Varies	Trivial	Small	Moderate	Large

Undesirable effects

How substantial are the undesirable anticipated effects of a repeat course of antenatal corticosteroids compared to a single course?

Judgement

☐	☐	☐	☐	☒	☐
Don't know	Varies	Large	Moderate	Small	Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of antenatal corticosteroids on maternal outcomes?

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

What is the overall certainty of the evidence on effects of antenatal corticosteroids on neonatal outcomes?

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

3.2 Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with repeated courses of antenatal corticosteroids?

Research evidence

Findings from a mixed methods systematic review (13) on the appropriate use of interventions in the management of women experiencing preterm birth show the following.

- Women and partners' knowledge about antenatal corticosteroids varies across settings, with higher levels of knowledge in high-income countries than in low- and middle-income countries. Women generally consider antenatal corticosteroids to be beneficial, and prefer that they are only used when necessary and in the context of a positive relationship with a health care provider. They prefer that clear information is provided about treatment options, with adequate time to make shared decisions and ask questions.
- Most health care providers believe that the benefits of antenatal corticosteroids for women experiencing preterm birth mostly outweigh the risks, although some have concerns about safety in certain clinical situations.

No findings specific to antenatal corticosteroid regimen or use of repeat courses were identified.

Additional considerations

Health care providers, policy-makers, and pregnant women and their families in high-income settings might place a higher value on the potential cost saving of antenatal corticosteroids in terms of further reduction in newborn respiratory distress syndrome and surfactant use, and therefore chose the intervention regardless of the lack of further benefits on newborn mortality outcomes; whereas those in low- and middle-income settings might place a higher value on the concern about potential harm to the mother and lower value on reducing surfactant use – which is often not part of standard care in such settings.

Judgement

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour repeat course of antenatal corticosteroids, or single course?

Judgement

☐ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☒ Probably favours intervention	☐ Favours intervention

3.3 Resources

How large are the resource requirements (costs) of antenatal corticosteroids?

Research evidence

The available evidence on the cost–effectiveness of antenatal corticosteroids for improving preterm birth outcomes was synthesized in a systematic review (14) Evidence suggests antenatal corticosteroid use in early preterm period is cost–effective, but evidence for cost–effectiveness in the late preterm period is mixed. Studies did not explore differences for repeated versus single course.

Additional considerations

Dexamethasone sodium phosphate (4 mg per mL) is available on the WHO Essential Medicines List (15) Injectable betamethasone preparations are not listed.

Main resource requirements

Resource	Description
Staffing	• Identifying women at risk of preterm birth requires skilled health personnel who can identify and diagnose preterm labour, excluding contraindications (such as maternal infection), prescribe and administer intramuscular (IM) antenatal corticosteroids and monitor women's care. • Accurate estimation of gestational age also requires personnel trained in the use of obstetric ultrasound. • Preterm babies may require additional specialist care.
Training	• Training for skilled health personnel to administer injections, and to monitor and manage any side-effects, is part of standard maternity staff training. • Additional training would be required if antenatal corticosteroids were introduced in settings where they have not previously been available.

Resource	Description
Supplies	Antenatal corticosteroids that are readily available in the maternity ward and emergency department. Antenatal corticosteroid indicative costs: • Injectable dexamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2358 per mL (16) — In the ACTION-1 cost–effectiveness analysis, price of 1 mL (4mg/mL) ampoule of dexamethasone ranged from USD$0.05 to USD$2.26. • Injectable betamethasone (4mg/mL) — Median unitary price (2015) was USD$0.2950 per mL (16) — In the systematic review of cost–effectiveness studies (14), betamethasone unitary price ranged from USD$0.2503 for 4mg/1mL dose to USD$29.36 for 12mg dose. Other costs: • IM administration: needle, syringe, antiseptic solution, swab, gloves, sharps disposal • Women in preterm labour may require tocolysis with an effective agent (such as nifedipine) • Women who are admitted for antenatal corticosteroid administration often require special investigations (such as blood tests, urinalysis or fetal heart monitoring).
Equipment and infrastructure	• Obstetric ultrasound system, probes and ultrasound gel to assess gestational age (preferably in first trimester). • Administration of antenatal corticosteroids requires inpatient admission of the woman. • Babies born preterm often require additional care, including oxygen or respiratory support, feeding support, warmth, hygiene measures, diagnosis and treatment of infection, or admission to neonatal intensive care.
Time	IM administration of a single dose takes 2 minutes. Time for consultation between skilled health personnel and women about the risks and benefits of antenatal corticosteroids.
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

☐	☐	☐	☐	☐	☒	☐
Don’t know	Varies	Large costs	Moderate costs	Negligible costs or savings	Moderate savings	Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Cost–effectiveness

Judgement

☒ Don't know	☐ Varies	☐ Favours comparator	☐ Probably favours comparator	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.4 Equity

What would be the impact of a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth on health equity?

Research evidence

No direct evidence was identified.

Additional considerations

Preterm birth affects an estimated 10.6% of births worldwide, though rates are higher in many low- and middle-income countries (17). Similarly, preterm-associated newborn morbidity and mortality are generally higher in low- and middle-income countries due to the lack of good-quality health care services during pregnancy, childbirth and the postnatal period (18). It is likely that risks of preterm birth and its adverse consequences are worse for women and newborns living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal and intrapartum care (19).

Evidence from trials demonstrates that antenatal corticosteroid use is effective in all settings, provided that a minimum level of maternal and preterm newborn care is available. Some women – such as women living in rural or remote areas, women with limited educational or employment opportunities, or women without access to higher levels of care – would be more likely to benefit to the protection offered by a relatively cheap and readily available medication in low-resource setting, thus increasing equity.

Judgement

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

3.5 Acceptability

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth acceptable to key stakeholders?

Research evidence

A mixed-methods systematic review including 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the acceptability of antenatal corticosteroid therapy among key stakeholders (13).

In summary, the review found the following.

- Providers may be uncertain about the benefits and risks of antenatal corticosteroids, and when to use them. Acceptability may be improved by providing high-quality evidence on effectiveness and safety (including in specific clinical situations), guidance on who can prescribe and administer them, training to improve administration skills, and promoting a multidisciplinary approach with clear role definitions and responsibilities.
- Quantitative evidence from one moderate-quality study suggests that health care providers' lack of knowledge on doses and frequency of antenatal corticosteroids were a concern, for example, in one survey in Ecuador, El Salvador, Mexico and Uruguay, 40–80% of health care providers could not recall the correct regimen and 21–90% of health care providers reported following the recommended regimen.
- There is limited evidence on repeat doses (three qualitative studies from Australia, New Zealand and the United States, and one multicountry quantitative study from Ecuador, El Salvador, Mexico and Uruguay). Overall, there were mixed beliefs about the benefits and risks of repeat doses – some providers feel these improve outcomes of the baby, though some feel that it has negative side effects for the baby. Many providers reported uncertainties on the evidence that support the use of repeat antenatal corticosteroids. This uncertainty is greater in women with certain clinical conditions, such as women with diabetes. One quantitative study reported that 60% of providers said they would repeat the administration of antenatal corticosteroids. Providers hoped to have simplified and easy access to evidence on the benefits and risks of repeat doses.
- Similarly, women reported difficulty in deciding to use antenatal corticosteroids, especially after providers inform them of the uncertainty of evidence around repeat doses.

Judgement

☐	☒	☐	☐	☐	☐
Don't know	Varies	No	Probably No	Probably Yes	Yes

3.6 Feasibility

Is a strategy of antenatal corticosteroid therapy for women at risk of imminent preterm birth feasible to implement?

Research evidence

Findings from a mixed-methods systematic review (13) which included 45 studies on appropriate use of maternal interventions in managing preterm birth identified some evidence on the feasibility of implementing antenatal corticosteroid therapy for women at risk of imminent preterm birth.

In summary, the review found the following:

- Evidence suggests that there is variation in current clinical guidance on when and how antenatal corticosteroids should be used. Feasibility may be impacted by varying levels of provider knowledge on safe and correct use, the unpredictability of preterm birth, and high staff workloads. Correct use of antenatal corticosteroids could be improved through provider education and training, clear guidelines and clinical protocols on when to use them, and ensuring facilities are well stocked. Where pre-referral first dose administration is allowed in lower-level facilities (with basic emergency obstetric and neonatal care), implementation may be limited due to challenges around identifying preterm labour, limited knowledge about the importance of pre-referral dosing, and transportation issues.

No findings specifically relevant to antenatal corticosteroid regimen or use of repeat courses were identified.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

4 Summary of judgements table

Desirable effects	Don't know	Varies	Trivial	Small	✓ **Moderate**	Large
Undesirable effects	Don't know	Varies	Large	Moderate	✓ **Small**	Trivial
Certainty of the evidence: maternal outcomes	No included studies	Very low	✓ **Low**	Moderate	High	
Certainty of the evidence: neonatal outcomes	No included studies	Very low	Low	✓ **Moderate**	High	
Values	Important uncertainty or variability	✓ **Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability		
Balance of effects	Don't know	Varies	Favours comparator	Probably favours comparator	Does not favour either	✓ **Probably favours intervention**	Favours intervention
Resources required	Don't know	Varies	Large costs	Moderate costs	Negligible costs or savings	✓ **Moderate savings**	Large savings
Certainty of the evidence on required resources	No included studies	Very low	Low	✓ **Moderate**	High	
Cost–effectiveness	✓ **Don't know**	Varies	Favours comparator	Probably favours comparator	Does not favour either	Probably favours intervention	Favours intervention
Equity	✓ **Don't know**	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased
Acceptability	Don't know	✓ **Varies**	No	Probably No	Probably Yes	Yes	
Feasibility	Don't know	Varies	No	Probably No	✓ **Probably Yes**	Yes	

5 Summary of findings tables

5.1 All women and babies

Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. Under review.

Maternal outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Preterm birth <28 weeks' gestation												
5	randomized trials	not serious	not serious	serious[a]	serious[b]	none	175/2015 (8.7%)	156/2007 (7.8%)	**RR 1.13** (0.92 to 1.38)	**10 more per 1,000** (from 6 fewer to 30 more)	⨁⨁◯◯ LOW	CRITICAL
Preterm birth <34 weeks' gestation												
6	randomized trials	not serious	not serious	serious[a]	not serious	none	862/1338 (64.4%)	850/1344 (63.2%)	**RR 1.02** (0.97 to 1.08)	**13 more per 1,000** (from 19 fewer to 51 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Preterm birth <37 weeks												
7	randomized trials	not serious	serious[c]	serious[a]	not serious	none	1520/2038 (74.6%)	1495/2030 (73.6%)	**RR 1.02** (0.98 to 1.05)	**15 more per 1,000** (from 15 fewer to 37 more)	⨁⨁◯◯ LOW	CRITICAL
Term birth ≥ 37 weeks												
7	randomized trials	not serious	not serious	serious[a]	not serious	none	509/2038 (25.0%)	525/2030 (25.9%)	**RR 0.96** (0.86 to 1.06)	**10 fewer per 1,000** (from 36 fewer to 16 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mean gestational age at birth (weeks)												
10	randomized trials	not serious	not serious	serious[a]	not serious	none	2626	2609	–	MD **0.18 lower** (0.37 lower to 0.01 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Maternal death												
1	randomized trial	not serious	not serious	not serious	very serious[d]	none	0/223 (0.0%)	1/214 (0.5%)	**RR 0.32** (0.01 to 7.81)	**3 fewer per 1,000** (from 5 fewer to 32 more)	⨁⨁◯◯ LOW	CRITICAL
Chorioamnionitis												
7	randomized trials	not serious	not serious	not serious	serious[b]	none	142/2231 (6.4%)	122/2186 (5.6%)	**RR 1.13** (0.90 to 1.42)	**7 more per 1,000** (from 6 fewer to 23 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Maternal sepsis												
8	randomized trials	not serious	not serious	not serious	serious[b]	none	180/2356 (7.6%)	155/2310 (6.7%)	**RR 1.13** (0.93 to 1.39)	**9 more per 1,000** (from 5 fewer to 26 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse effects of corticosteroid												
2	randomized trials	not serious	serious[c]	not serious	not serious	none	115/739 (15.6%)	159/735 (21.6%)		**Not pooled**		IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Participants in the trials varied markedly in their gestational age at entry, limiting the generalizability of this finding.

b. Wide confidence interval crossing line of no effect.

c. Statistical heterogeneity ($I^2 \geq 60\%$).

d. Wide confidence interval crossing line of no effect; effect not estimable due to few events.

Fetal and neonatal outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Fetal or neonatal or infant death (<1year of age)												
10	randomized trials	not serious	not serious	not serious	serious[a]	none	102/2935 (3.5%)	107/2914 (3.7%)	**RR 0.95** (0.73 to 1.24)	**2 fewer per 1,000** (from 10 fewer to 9 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Fetal death												
7	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	4/1376 (0.3%)	5/1382 (0.4%)	**RR 0.82** (0.24 to 2.84)	**1 fewer per 1,000** (from 3 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL
Neonatal death												
7	randomized trials	not serious	not serious	not serious	serious[a]	none	47/1376 (3.4%)	52/1382 (3.8%)	**RR 0.91** (0.62 to 1.34)	**3 fewer per 1,000** (from 14 fewer to 13 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Composite of serious outcomes												
9	randomized trials	not serious	not serious	not serious	not serious	none	530/2879 (18.4%)	602/2857 (21.1%)	**RR 0.88** (0.80 to 0.97)	**25 fewer per 1,000** (from 42 fewer to 6 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Respiratory distress syndrome												
9	randomized trials	not serious	not serious	not serious	not serious	none	488/1769 (27.6%)	602/1771 (34.0%)	**RR 0.82** (0.74 to 0.90)	**61 fewer per 1,000** (from 88 fewer to 34 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Severe respiratory distress syndrome												
5	randomized trials	serious[c]	serious[d]	not serious	not serious	none	202/1919 (10.5%)	207/1890 (11.0%)	**RR 0.97** (0.82 to 1.16)	**3 fewer per 1,000** (from 20 fewer to 18 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Chronic lung disease												
9	randomized trials	not serious	not serious	not serious	not serious	none	186/2841 (6.5%)	185/2820 (6.6%)	**RR 1.00** (0.83 to 1.22)	**0 fewer per 1,000** (from 11 fewer to 14 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Intraventricular haemorrhage												
6	randomized trials	not serious	not serious	not serious	not serious	none	129/1610 (8.0%)	137/1613 (8.5%)	**RR 0.95** (0.75 to 1.19)	**4 fewer per 1,000** (from 21 fewer to 16 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Severe Intraventricular haemorrhage (grade 3/4)												
7	randomized trials	not serious	not serious	not serious	serious[a]	none	32/2542 (1.3%)	28/2524 (1.1%)	**RR 1.13** (0.69 to 1.86)	**1 more per 1,000** (from 3 fewer to 10 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Early systemic neonatal infection												
4	randomized trials	not serious	not serious	not serious	not serious	none	179/860 (20.8%)	195/878 (22.2%)	**RR 0.93** (0.79 to 1.11)	**16 fewer per 1,000** (from 47 fewer to 24 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Necrotising enterocolitis												
9	randomized trials	not serious	not serious	not serious	serious[a]	none	52/2879 (1.8%)	61/2857 (2.1%)	**RR 0.84** (0.59 to 1.22)	**3 fewer per 1,000** (from 9 fewer to 5 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Periventricular leukomalacia												
8	randomized trials	not serious	not serious	not serious	serious[a]	none	21/2580 (0.8%)	28/2562 (1.1%)	**RR 0.75** (0.43 to 1.31)	**3 fewer per 1,000** (from 6 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Patent ductus arteriosus												
7	randomized trials	very serious [e]	not serious	not serious	not serious	none	135/2334 (5.8%)	175/2323 (7.5%)	**RR 0.78** (0.63 to 0.96)	**17 fewer per 1,000** (from 28 fewer to 3 fewer)	⨁◯◯◯ LOW	CRITICAL
Retinopathy of prematurity												
8	randomized trials	not serious	not serious	not serious	serious[a]	none	140/2623 (5.3%)	138/2611 (5.3%)	**RR 1.01** (0.81 to 1.27)	**1 more per 1,000** (from 10 fewer to 14 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Admission to the neonatal intensive care unit												
2	randomized trials	not serious	not serious	not serious	not serious	none	872/1734 (50.3%)	863/1721 (50.1%)	**RR 1.01** (0.95 to 1.07)	**5 more per 1,000** (from 25 fewer to 35 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Surfactant use												
10	randomized trials	not serious	serious[d]	not serious	not serious	none	529/2944 (18.0%)	661/2926 (22.6%)	**RR 0.80** (0.73 to 0.89)	**45 fewer per 1,000** (from 61 fewer to 25 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Use of respiratory support												
2	randomized trials	not serious	not serious	not serious	not serious	none	468/1260 (37.1%)	523/1237 (42.3%)	**RR 0.88** (0.80 to 0.97)	**51 fewer per 1,000** (from 85 fewer to 13 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Use of oxygen supplementation												
3	randomized trials	not serious	not serious	not serious	not serious	none	756/1828 (41.4%)	829/1815 (45.7%)	**RR 0.91** (0.85 to 0.98)	**41 fewer per 1,000** (from 69 fewer to 9 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mean duration of oxygen supplementation (days)												
4	randomized trials	not serious	not serious	not serious	serious[a]	none	800	819	–	MD **0.32 lower** (0.94 lower to 0.3 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Small-for-gestational age at birth												
7	randomized trials	not serious	not serious	not serious	not serious	none	350/2017 (17.4%)	278/1996 (13.9%)	**RR 1.25** (1.08 to 1.44)	**35 more per 1,000** (from 11 more to 61 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Mean birthweight (g)												
10	randomized trials	not serious	not serious	not serious	not serious	none	2911	2897	–	MD **74.49 lower** (115.8 lower to 33.18 lower)	⨁⨁⨁⨁ HIGH	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **g**: gram

Explanations

a. Wide confidence interval crossing line of no effect.

b. Estimate based on few events.

c. Most studies contributing data had design limitations.

d. Statistical heterogeneity ($I^2 \geq 60\%$).

e. Limiting the analysis to findings at low risk of bias changed the effect

Childhood outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Survival free of neurodevelopmental impairment at early childhood follow up												
4	randomized trials	not serious	not serious	not serious	not serious	none	1523/1939 (78.5%)	1481/1906 (77.7%)	**RR 1.01** (0.98 to 1.04)	**8 more per 1,000** (from 16 fewer to 31 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Neurodevelopmental impairment at early childhood follow-up												
4	randomized trials	not serious	not serious	not serious	not serious	none	326/1822 (17.9%)	335/1794 (18.7%)	**RR 0.97** (0.85 to 1.10)	**6 fewer per 1,000** (from 28 fewer to 19 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Developmental delay or intellectual impairment at early childhood follow-up (any)												
4	randomized trials	not serious	not serious	not serious	not serious	none	322/1796 (17.9%)	337/1785 (18.9%)	**RR 0.95** (0.84 to 1.09)	**9 fewer per 1,000** (from 30 fewer to 17 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Cerebral palsy at early childhood follow-up												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	55/1968 (2.8%)	53/1955 (2.7%)	**RR 1.03** (0.71 to 1.49)	**1 more per 1,000** (from 8 fewer to 13 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Blindness or visual impairment at early childhood follow-up												
3	randomized trials	not serious	not serious	not serious	serious[a]	none	24/1649 (1.5%)	20/1625 (1.2%)	**RR 1.17** (0.65 to 2.10)	**2 more per 1,000** (from 4 fewer to 14 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Deafness or hearing impairment at early childhood follow-up												
4	randomized trials	not serious	not serious	not serious	serious[a]	none	24/1769 (1.4%)	24/1759 (1.4%)	**RR 0.97** (0.56 to 1.71)	**0 fewer per 1,000** (from 6 fewer to 10 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.

5.2 Subgroup analysis: number of repeats

Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. Under review.

Maternal outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Maternal sepsis – For women planned for one or more repeat course of antenatal corticosteroids												
7	randomized trials	not serious	not serious	not serious	serious[a]	none	161/2245 (7.2%)	143/2203 (6.5%)	**RR 1.10** (0.89 to 1.36)	**7 more per 1,000** (from 7 fewer to 24 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Maternal sepsis – For women planned for only one repeat course of antenatal corticosteroids												
1	randomized trial	serious[b]	not serious	not serious	very serious[c]	none	19/125 (15.2%)	12/124 (9.7%)	**RR 1.57** (0.80 to 3.10)	**55 more per 1,000** (from 19 fewer to 203 more)	⨁◯◯◯ VERY LOW	CRITICAL

Neonatal outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Fetal or neonatal or infant death (<1year of age) – In babies planned for one or more repeat course of antenatal corticosteroids												
7	randomized trials	not serious	not serious	not serious	serious[a]	none	87/2430 (3.6%)	96/2401 (4.0%)	**RR 0.90** (0.68 to 1.19)	**4 fewer per 1,000** (from 13 fewer to 8 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Fetal or neonatal or infant death (<1year of age) – In babies planned for only one repeat course of antenatal corticosteroids												
3	randomized trials	not serious	not serious	not serious	serious[a]	none	15/505 (3.0%)	11/513 (2.1%)	**RR 1.38** (0.65 to 2.92)	**8 more per 1,000** (from 8 fewer to 41 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Fetal death – In babies planned for one or more repeat course of antenatal corticosteroids												
4	randomized trials	not serious	not serious	not serious	very serious[c]	none	2/871 (0.2%)	3/869 (0.3%)	**RR 0.71** (0.14 to 3.57)	**1 fewer per 1,000** (from 3 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL
Fetal death – In babies planned for only one repeat course of antenatal corticosteroids												
3	randomized trials	not serious	not serious	not serious	very serious[c]	none	2/505 (0.4%)	2/513 (0.4%)	**RR 1.02** (0.14 to 7.23)	**0 fewer per 1,000** (from 3 fewer to 24 more)	⨁⨁◯◯ LOW	CRITICAL
Neonatal death – In babies planned for one or more repeat course of antenatal corticosteroids												
4	randomized trials	not serious	not serious	not serious	serious[a]	none	34/871 (3.9%)	43/869 (5.0%)	**RR 0.80** (0.51 to 1.23)	**10 fewer per 1,000** (from 24 fewer to 11 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Neonatal death – In babies planned for only one repeat course of antenatal corticosteroids												
3	randomized trials	not serious	not serious	not serious	very serious[c]	none	12/505 (2.4%)	9/513 (1.8%)	**RR 1.36** (0.58 to 3.19)	**6 more per 1,000** (from 7 fewer to 38 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Respiratory distress syndrome – In babies planned for one or more repeat course of antenatal corticosteroids												
6	randomized trials	not serious	not serious	not serious	not serious	none	308/1264 (24.4%)	383/1258 (30.4%)	**RR 0.80** (0.71 to 0.91)	**61 fewer per 1,000** (from 88 fewer to 27 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Respiratory distress syndrome – In babies planned for only one repeat course of antenatal corticosteroids												
3	randomized trials	not serious	serious[b]	not serious	not serious	none	180/505 (35.6%)	219/513 (42.7%)	**RR 0.84** (0.72 to 0.98)	**68 fewer per 1,000** (from 120 fewer to 9 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Severe respiratory distress syndrome – In babies planned for one or more repeat course of antenatal corticosteroids												
4	randomized trials	serious[d]	serious[b]	not serious	serious	none	132/1759 (7.5%)	147/1722 (8.5%)	**RR 0.87** (0.70 to 1.09)	**11 fewer per 1,000** (from 26 fewer to 8 more)	⨁⨁◯◯ LOW	CRITICAL
Severe respiratory distress syndrome – In babies planned for only one repeat course of antenatal corticosteroids												
1	randomized trial	serious[d]	not serious	not serious	serious[a]	none	70/160 (43.8%)	60/168 (35.7%)	**RR 1.23** (0.94 to 1.60)	**82 more per 1,000** (from 21 fewer to 214 more)	⨁⨁◯◯ LOW	CRITICAL
Chronic lung disease – In babies planned for one or more repeat course of antenatal corticosteroids												
6	randomized trials	not serious	not serious	not serious	serious[a]	none	141/2336 (6.0%)	147/2307 (6.4%)	**RR 0.95** (0.77 to 1.19)	**3 fewer per 1,000** (from 15 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Chronic lung disease – In babies planned for only one repeat course of antenatal corticosteroids												
3	randomized trials	not serious	not serious	not serious	serious[a]	none	45/505 (8.9%)	38/513 (7.4%)	**RR 1.20** (0.80 to 1.82)	**15 more per 1,000** (from 15 fewer to 61 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Severe Intraventricular haemorrhage (grade 3/4) – In babies planned for one or more repeat course of antenatal corticosteroids												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	20/2093 (1.0%)	20/2068 (1.0%)	**RR 0.98** (0.53 to 1.79)	**0 fewer per 1,000** (from 5 fewer to 8 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Severe Intraventricular haemorrhage (grade 3/4) – In babies planned for only one repeat course of antenatal corticosteroids												
2	randomized trials	not serious	not serious	not serious	very serious[c]	none	12/449 (2.7%)	8/456 (1.8%)	**RR 1.53** (0.63 to 3.71)	**9 more per 1,000** (from 6 fewer to 48 more)	⨁⨁◯◯ LOW	CRITICAL
Intraventricular haemorrhage – In babies planned for one or more repeat course of antenatal corticosteroids												
4	randomized trials	not serious	not serious	not serious	serious[a]	none	79/1161 (6.8%)	85/1157 (7.3%)	**RR 0.92** (0.69 to 1.24)	**6 fewer per 1,000** (from 23 fewer to 18 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Intraventricular haemorrhage – In babies planned for only one repeat course of antenatal corticosteroids												
2	randomized trials	not serious	not serious	not serious	serious[a]	none	50/449 (11.1%)	52/456 (11.4%)	**RR 0.99** (0.69 to 1.42)	**1 fewer per 1,000** (from 35 fewer to 48 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Necrotising enterocolitis – In babies planned for one or more repeat course of antenatal corticosteroids												
7	randomized trials	not serious	not serious	not serious	serious[a]	none	43/2430 (1.8%)	46/2401 (1.9%)	**RR 0.92** (0.61 to 1.39)	**2 fewer per 1,000** (from 7 fewer to 7 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Necrotising enterocolitis – In babies planned for only one repeat course of antenatal corticosteroids												
2	randomized trials	not serious	not serious	not serious	very serious[c]	none	9/449 (2.0%)	15/456 (3.3%)	**RR 0.60** (0.27 to 1.37)	**13 fewer per 1,000** (from 24 fewer to 12 more)	⨁⨁◯◯ LOW	CRITICAL
Composite serious outcome (variously defined) – In babies planned for one or more repeat course of antenatal corticosteroids												
7	randomized trials	not serious	not serious	not serious	not serious	none	359/2430 (14.8%)	402/2401 (16.7%)	**RR 0.88** (0.78 to 1.00)	**20 fewer per 1,000** (from 37 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Composite serious outcome (variously defined) – In babies planned for only one repeat course of antenatal corticosteroids												
2	randomized trials	not serious	serious[b]	not serious	serious[a]	none	171/449 (38.1%)	200/456 (43.9%)	**RR 0.87** (0.75 to 1.02)	**57 fewer per 1,000** (from 110 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.

b. Statistical heterogeneity (I2≥60%)

c. Wide confidence interval crossing line of no effect; estimate based on few events

d. Most studies contributing data had design limitations

5.3 Subgroup analysis: interval between repeat doses

Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. Under review.

Maternal outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Maternal sepsis – For women treated with repeat corticosteroids at a minimum interval of 7 days or less												
6	randomized trials	not serious	not serious	not serious	serious[a]	none	140/1980 (7.0%)	121/1192 (10.2%)	**RR 0.97** (0.78 to 1.20)	**3 fewer per 1,000** (from 20 fewer to 22 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Maternal sepsis – For women treated with repeat corticosteroids at a minimum interval of 14 days or more												
2	randomized trials	not serious	not serious	not serious	serious[a]	none	40/1160 (3.5%)	34/1135 (3.0%)	**RR 1.01** (0.83 to 1.22)	**0 more per 1,000** (from 5 fewer to 7 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.

Neonatal outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Fetal or neonatal or infant death (<1year of age) – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
7	randomized trials	not serious	not serious	not serious	serious[a]	none	53/1424 (3.7%)	60/1426 (4.2%)	**RR 0.89** (0.62 to 1.28)	**5 fewer per 1,000** (from 16 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Fetal or neonatal or infant death (<1year of age) – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
3	randomized trials	not serious	not serious	not serious	serious[a]	none	49/1511 (3.2%)	47/1488 (3.2%)	**RR 1.02** (0.69 to 1.52)	**1 more per 1,000** (from 10 fewer to 16 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Fetal death – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
5	randomized trials	not serious	not serious	not serious	very serious[c]	none	3/1031 (0.3%)	4/1037 (0.4%)	**RR 0.78** (0.19 to 3.15)	**1 fewer per 1,000** (from 3 fewer to 8 more)	⨁⨁◯◯ LOW	CRITICAL
Fetal death – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
2	randomized trials	not serious	not serious	not serious	very serious[c]	none	1/345 (0.3%)	1/345 (0.3%)	**RR 1.00** (0.06 to 15.86)	**0 fewer per 1,000** (from 3 fewer to 43 more)	⨁⨁◯◯ LOW	CRITICAL
Neonatal death – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	42/1031 (4.1%)	46/1037 (4.5%)	**RR 0.92** (0.62 to 1.39)	**4 fewer per 1,000** (from 17 fewer to 17 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Neonatal death – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
2	randomized trials	not serious	not serious	not serious	very serious[c]	none	5/345 (1.4%)	6/345 (1.7%)	**RR 0.85** (0.27 to 2.61)	**3 fewer per 1,000** (from 13 fewer to 28 more)	⨁⨁◯◯ LOW	CRITICAL
Respiratory distress syndrome – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
7	randomized trials	not serious	not serious	not serious	not serious	none	390/1424 (27.4%)	463/1426 (32.5%)	**RR 0.85** (0.76 to 0.95)	**49 fewer per 1,000** (from 78 fewer to 16 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Respiratory distress syndrome – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
2	randomized trials	not serious	not serious	not serious	not serious	none	98/345 (28.4%)	139/345 (40.3%)	**RR 0.70** (0.57 to 0.87)	**121 fewer per 1,000** (from 173 fewer to 52 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Severe respiratory distress syndrome – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
4	randomized trials	not serious	serious[b]	not serious	serious[a]	none	115/753 (15.3%)	130/747 (17.4%)	**RR 0.89** (0.72 to 1.10)	**19 fewer per 1,000** (from 49 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL
Severe respiratory distress syndrome – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
1	randomized trial	serious[d]	not serious	not serious	serious[a]	none	87/1166 (7.5%)	77/1143 (6.7%)	**RR 1.11** (0.82 to 1.49)	**7 more per 1,000** (from 12 fewer to 33 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Chronic lung disease – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
6	randomized trials	not serious	not serious	not serious	serious[a]	none	137/1330 (10.3%)	150/1332 (11.3%)	**RR 0.91** (0.74 to 1.14)	**10 fewer per 1,000** (from 29 fewer to 16 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Chronic lung disease – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
3	randomized trials	not serious	not serious	not serious	serious[a]	none	49/1511 (3.2%)	35/1488 (2.4%)	**RR 1.39** (0.91 to 2.12)	**9 more per 1,000** (from 2 fewer to 26 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Severe Intraventricular haemorrhage (grade 3/4) – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	20/1087 (1.8%)	15/1093 (1.4%)	**RR 1.32** (0.69 to 2.53)	**4 more per 1,000** (from 4 fewer to 21 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Severe Intraventricular haemorrhage (grade 3/4) – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
2	randomized trials	not serious	not serious	not serious	very serious[c]	none	12/1455 (0.8%)	13/1431 (0.9%)	**RR 0.91** (0.42 to 1.99)	**1 fewer per 1,000** (from 5 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL
Intraventricular haemorrhage – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	110/1321 (8.3%)	112/1325 (8.5%)	**RR 0.99** (0.77 to 1.27)	**1 fewer per 1,000** (from 19 fewer to 23 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Intraventricular haemorrhage – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	19/289 (6.6%)	25/288 (8.7%)	**RR 0.76** (0.43 to 1.34)	**21 fewer per 1,000** (from 49 fewer to 30 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Necrotising enterocolitis – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
7	randomized trials	not serious	not serious	not serious	serious[a]	none	34/1424 (2.4%)	38/1426 (2.7%)	**RR 0.89** (0.56 to 1.40)	**3 fewer per 1,000** (from 12 fewer to 11 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Necrotising enterocolitis – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
2	randomized trials	not serious	serious[b]	not serious	very serious[c]	none	9/1455 (0.6%)	23/1431 (1.6%)	**RR 0.39** (0.18 to 0.83)	**10 fewer per 1,000** (from 13 fewer to 3 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Composite serious outcome (variously defined) – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
7	randomized trials	not serious	not serious	not serious	not serious	none	292/1424 (20.5%)	339/1426 (23.8%)	**RR 0.87** (0.76 to 0.99)	**31 fewer per 1,000** (from 57 fewer to 2 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Composite serious outcome (variously defined) – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
2	randomized trials	not serious	serious[b]	not serious	not serious[a]	none	238/1455 (16.4%)	263/1431 (18.4%)	**RR 0.89** (0.76 to 1.04)	**20 fewer per 1,000** (from 44 fewer to 7 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.
b. Statistical heterogeneity (I2≥60%)
c. Wide confidence interval crossing line of no effect; estimate based on few events
d. Most studies contributing data had design limitations

Childhood outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Neurodevelopmental impairment at early childhood follow-up – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
3	randomized trials	not serious	not serious	not serious	serious[a]	none	227/802 (28.3%)	240/806 (29.8%)	**RR 0.95** (0.82 to 1.10)	**15 fewer per 1,000** (from 54 fewer to 30 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Neurodevelopmental impairment at early childhood follow-up – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
1	randomized trial	serious[b]	not serious	not serious	serious[a]	none	99/1020 (9.7%)	95/988 (9.6%)	**RR 1.01** (0.77 to 1.32)	**1 more per 1,000** (from 22 fewer to 31 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Survival free of neurodevelopmental impairment at early childhood follow up – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
3	randomized trials	not serious	not serious	not serious	not serious[a]	none	602/870 (69.2%)	588/871 (67.5%)	**RR 1.02** (0.96 to 1.09)	**14 more per 1,000** (from 27 fewer to 61 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Survival free of neurodevelopmental impairment at early childhood follow up – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
1	randomized trial	serious[b]	not serious	not serious	not serious[a]	none	921/1069 (86.2%)	893/1035 (86.3%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1,000** (from 26 fewer to 26 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cerebral palsy at early childhood follow-up – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
4	randomized trials	not serious	not serious	not serious	serious[a]	none	31/948 (3.3%)	28/967 (2.9%)	**RR 1.12** (0.68 to 1.85)	**3 more per 1,000** (from 9 fewer to 25 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cerebral palsy at early childhood follow-up – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
1	randomized trial	serious[b]	not serious	not serious	serious[a]	none	24/1020 (2.4%)	25/988 (2.5%)	**RR 0.93** (0.53 to 1.62)	**2 fewer per 1,000** (from 12 fewer to 16 more)	⨁⨁◯◯ LOW	CRITICAL
Developmental delay or intellectual impairment at early childhood follow-up (any) – In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less												
3	randomized trials	not serious	not serious	not serious	not serious[a]	none	236/831 (28.4%)	253/849 (29.8%)	**RR 0.94** (0.81 to 1.09)	**18 fewer per 1,000** (from 57 fewer to 27 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat corticosteroids	Single course of corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Developmental delay or intellectual impairment at early childhood follow-up (any) – In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more												
1	randomized trial	serious[b]	not serious	not serious	serious[a]	none	86/965 (8.9%)	84/936 (9.0%)	**RR 0.99** (0.75 to 1.32)	**1 fewer per 1,000** (from 22 fewer to 29 more)	⨁⨁◯◯ LOW	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence interval crossing line of no effect.

b. Most studies contributing data had design limitations

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