THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

Taylor & Francis
Taylor & Francis Group

The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijmf20

European guidelines on perinatal care: corticosteroids for women at risk of preterm birth

George Daskalakis, Vasilios Pergialiotis, Magnus Domellöf, Harald Ehrhardt, Gian Carlo Di Renzo, Esin Koç, Ariadne Malamitsi-Puchner, Marian Kacerovsky, Neena Modi, Andrew Shennan, Diogo Ayres-de-Campos, Elko Gliozheni, Kristiina Rull, Thorsten Braun, Artur Beke, Katarzyna Kosińska-Kaczyńska, Ana Luisa Areia, Simona Vladareanu, Tanja Premru Sršen, Thomas Schmitz & Bo Jacobsson

To cite this article: George Daskalakis, Vasilios Pergialiotis, Magnus Domellöf, Harald Ehrhardt, Gian Carlo Di Renzo, Esin Koç, Ariadne Malamitsi-Puchner, Marian Kacerovsky, Neena Modi, Andrew Shennan, Diogo Ayres-de-Campos, Elko Gliozheni, Kristiina Rull, Thorsten Braun, Artur Beke, Katarzyna Kosińska-Kaczyńska, Ana Luisa Areia, Simona Vladareanu, Tanja Premru Sršen, Thomas Schmitz & Bo Jacobsson (2023) European guidelines on perinatal care: corticosteroids for women at risk of preterm birth, The Journal of Maternal-Fetal & Neonatal Medicine, 36:1, 2160628, DOI: 10.1080/14767058.2022.2160628

To link to this article: https://doi.org/10.1080/14767058.2022.2160628

Published online: 23 Jan 2023.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2023, VOL. 36, NO. 1, 2160628
https://doi.org/10.1080/14767058.2022.2160628

Taylor & Francis
Taylor & Francis Group

OTHER

OPEN ACCESS Check for updates

European guidelines on perinatal care: corticosteroids for women at risk of preterm birth

George Daskalakis[a], Vasilios Pergialiotis[a], Magnus Domellöf[b], Harald Ehrhardt[c,d]*, Gian Carlo Di Renzo[e,f,g], Esin Koç[h], Ariadne Malamitsi-Puchner[i], Marian Kacerovsky[j], Neena Modi[k,l], Andrew Shennan[m], Diogo Ayres-de-Campos[n,o], Elko Gliozheni[p], Kristiina Rull[q,r,s], Thorsten Braun[t], Artur Beke[u], Katarzyna Kosińska-Kaczyńska[v], Ana Luisa Areia[w,x,y], Simona Vladareanu[z], Tanja Premru Sršen[A,B], Thomas Schmitz[C,D] and Bo Jacobsson[E,F,G]

[a]1st department of Obstetrics and Gynecology, Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece; [b]Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden; [c]Department of General Pediatrics and Neonatology, Justus-Liebig-University and Universities of Giessen and Marburg Lung Center (UGMLC), Giessen, Germany; [d]German Lung Research Center (DZL), Giessen, Germany; [e]Center for Perinatal and Reproductive Medicine, University of Perugia, Perugia, Italy; [f]PREIS International and European School of Perinatal, Neonatal and Reproductive Medicine, Florence, Italy; [g]Department of Obstetrics and Gynecology, I.M. Sechenov First State University of Moscow, Moscow, Russia; [h]Department of Neonatology, Gazi University, Faculty of Medicine, Ankara, Turkey; [i]Neonatal Intensive Care Unit, 3rd Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece; [j]Department of Obstetrics and Gynecology, University Hospital Hradec Kralove, Charles University, Faculty of Medicine in Hradec Králové, Hradec Kralove, Czech Republic; [k]Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, London, UK; [l]Chelsea and Westminster NHS Foundation Trust, London, UK; [m]Department of Women and Children's Health, King's College London, London, UK; [n]Medical School, Santa Maria University Hospital, Lisbon, Portugal; [o]European Board and College of Obstetrics and Gynaecology, Brussels, Belgium; [p]Department of Obstetrics and Gynaecology, Maternity Koco Gliozheni Hospital, Tirana, Albania; [q]Women's Clinic of Tartu University Hospital, Tartu, Estonia; [r]Department of Obstetrics and Gynaecology, University of Tartu, Tartu Estonia; [s]Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia; [t]Department of Obstetrics and Division of 'Experimental Obstetrics', Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [u]Department of Obstetrics and Gynecology, Semmelweis University, Budapest, Hungary; [v]Department of Obstetrics, Perinatology and Neonatology, Center of Postgraduate Medical Education, Warsaw, Poland; [w]Obstetrics Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [x]Faculty of Medicine; Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [y]Centre of Investigation in Environment, Genetics and Oncobiology (CIMAGO), Coimbra, Portugal; [z]Neonatology Clinic, Department of Obstetrics and Gynecology, Faculty of General Medicine, Elias University Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [A]Department of Perinatology, Division of Obstetrics and Gynecology, University Medical Centre Ljubljana, Ljubljana, Slovenia; [B]Medical Faculty, University of Ljubljana, Ljubljana, Slovenia; [C]Department of Obstetrics and Gynecology, Robert Debré Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [D]Service de gynécologie-obstétrique, hôpital Robert-Debré, Université Paris Cité, Paris, France; [E]Department of Obstetrics and Gynecology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [F]Department of Obstetrics and Gynecology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden; [G]Department of Genetics and Bioinformatics, Domain of Health Data and Digitalization, Institute of Public Health, Oslo, Norway

ABSTRACT

Summary of recommendations

1. Corticosteroids should be administered to women at a gestational age between 24^{+0} and 33^{+6} weeks, when preterm birth is anticipated in the next seven days, as these have been consistently shown to reduce neonatal mortality and morbidity. (Strong-quality evidence; strong recommendation). In selected cases, extension of this period up to 34^{+6} weeks may be considered (Expert opinion). Optimal benefits are found in infants delivered within 7 days of corticosteroid administration. Even a single-dose administration should be given to women with imminent preterm birth, as this is likely to improve neurodevelopmental outcome (Moderate-quality evidence; conditional recommendation).
2. Either betamethasone (12 mg administered intramuscularly twice, 24-hours apart) or dexamethasone (6 mg administered intramuscularly in four doses, 12-hours apart, or 12 mg administered intramuscularly twice, 24-hours apart), may be used (Moderate-quality evidence; Strong recommendation). Administration of two "all" doses is named a "course of corticosteroids".

ARTICLE HISTORY
Received 30 September 2022
Revised 6 December 2022
Accepted 13 December 2022

KEYWORDS
Corticosteroids; guideline; preterm birth; antenatal

CONTACT Bo Jacobsson bo.jacobsson@obgyn.gu.se Department of Obstetrics and Gynecology, Goteborgs Universitet Sahlgrenska Akademin, Goteborg 405 30, Sweden
*Division of Neonatology and Pediatric Intensive Care Medicine, Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm, Germany.

3. Administration between 22^{+0} and 23^{+6} weeks should be considered when preterm birth is anticipated in the next seven days and active newborn life-support is indicated, taking into account parental wishes. Clear survival benefit has been observed in these cases, but the impact on short-term neurological and respiratory function, as well as long-term neurodevelopmental outcome is still unclear (Low/moderate-quality evidence; Weak recommendation).
4. Administration between 34 + 0 and 34 + 6 weeks should only be offered to a few selected cases (Expert opinion). Administration between 35^{+0} and 36^{+6} weeks should be restricted to prospective randomized trials. Current evidence suggests that although corticosteroids reduce the incidence of transient tachypnea of the newborn, they do not affect the incidence of respiratory distress syndrome, and they increase neonatal hypoglycemia. Long-term safety data are lacking (Moderate quality evidence; Conditional recommendation).
5. Administration in pregnancies beyond 37^{+0} weeks is not indicated, even for scheduled cesarean delivery, as current evidence does not suggest benefit and the long-term effects remain unknown (Low-quality evidence; Conditional recommendation).
6. Administration should be given in twin pregnancies, with the same indication and doses as for singletons. However, existing evidence suggests that it should be reserved for pregnancies at high-risk of delivering within a 7-day interval (Low-quality evidence; Conditional recommendation). Maternal diabetes mellitus is not a contraindication to the use of antenatal corticosteroids (Moderate quality evidence; Strong recommendation).
7. A single repeat course of corticosteroids can be considered in pregnancies at less than 34^{+0} weeks gestation, if the previous course was completed more than seven days earlier, and there is a renewed risk of imminent delivery (Low-quality evidence; Conditional recommendation).

Introduction

Preterm birth is associated with significant newborn mortality and morbidity, as well as a large economic burden, estimated to account for billions of euros annually in high-resource countries.

In normal pregnancies, fetal exposure to maternal cortisol is restricted by the enzyme 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2), which is abundantly expressed in the placenta very early during human pregnancy [1]. Synthetic glucocorticosteroids are also metabolized by the placental 11β-HSD2 [2].

Parenteral administration of corticosteroids to pregnant women at risk of preterm birth has been shown for decades to reduce respiratory and neurological newborn complications caused by the immaturity of these systems [3–5], becoming a part of routine obstetric care.

Nevertheless, several studies suggest that antenatally-administered corticosteroids may delay myelination and reduce brain growth [6]. An association has also been shown between corticosteroid use and higher diastolic pressure in adolescence, as well as with neurodevelopmental disability, mental and behavioral disorders [7,8]. More research is needed to establish the long-term effects of corticosteroids and their possible impact on cardiometabolic syndromes, as moderate links have been found with coronary heart disease, stroke, hypertension, and type 2 diabetes in adulthood [9].

For all these reasons, corticosteroid use in pregnancy must be tempered by caution. Optimal selection of cases benefiting from its use, optimal drug selection, dose and timing are paramount to provide maximum value and reduce unnecessary use. Current evidence suggests that less than half of women with symptoms of preterm birth receive antenatal corticosteroids at an optimal timing [10–12]. In asymptomatic women at risk for preterm delivery, this proportion may be as low as 10% [11].

This evidence-based guideline is intended to assist practitioners in the optimal use of corticosteroids for women at risk of imminent spontaneous preterm birth, and those planned for iatrogenic preterm birth due to maternal or fetal pathology. It complements the recent European consensus guideline on the management of respiratory distress syndrome [13] and EAPM′s guidelines that refer to the management of preterm labor [14,15].

Recommendations

1. Corticosteroids should be administered to women at a gestational age between 24^{+0} and 33^{+6} weeks, when preterm birth is anticipated in the next seven days, as they have been consistently shown to reduce neonatal mortality and morbidity (Strong-quality evidence; strong recommendation). In selected cases, extension of this period up to 34^{+6} weeks may be considered (Expert opinion). Optimal benefits are found in infants delivered within 7 days of corticosteroid administration; even single-dose administrations should be given in women with imminent preterm birth, as it is likely to improve neurodevelopmental outcome (Moderate-quality evidence; conditional recommendation).

The benefits of antenatal corticosteroids in reducing neonatal mortality and morbidity have been shown in

numerous randomized controlled trials. A Cochrane meta-analysis from 2020, evaluating 30 trials, concluded that, compared to placebo or no treatment, corticosteroids reduce perinatal and neonatal death by approximately 20%, neonatal respiratory distress syndrome by approximately 30%, and probably also decrease the risk of intraventricular hemorrhage [16]. Limited evidence suggests that they may also reduce long-term neurodevelopmental impairment. They have no significant impact on maternal outcomes, such as puerperal sepsis, endometritis, and maternal death. The actual period for use of corticosteroids seems to be based on optimally defined intervals, rather than predefined ones. Hence, it is difficult to determine the actual upper limit [16], but most seem to favor the intake of corticosteroids up until $34+6$ weeks. On the other hand, the most recent randomized trial, commissioned by the World Health Organization (ACTION-I) which was included in the Cochrane review mentioned above, used $33+6$ weeks as the upper limit interval [16]. Therefore, in selected cases, extension of this period up to 34^{+6} weeks may be considered. In this same trial, researchers observed that the use of dexamethasone significantly decreased perinatal death (RR 0.88, 95%CI 0.78–0.99], without increasing the risk of maternal infection or other adverse events [17].

The maximum benefit of corticosteroids seems to occur within the first week following administration. An observational study reported benefits on mortality and intraventricular hemorrhage/periventricular leukomalacia even when interval-to-birth was less than six hours, and becoming less when exceeding seven days [18]. A recent secondary analysis from two observational studies confirmed the optimal benefit for respiratory distress in infants delivered between two and seven days after treatment [19]. In women with iatrogenic preterm delivery, timing is usually easier to achieve. For spontaneous preterm birth timing relies on clinical evaluation, including biochemical markers and cervical length measurement.

A meta-analysis of 14 studies indicated that a complete or incomplete course of corticosteroids, in women at high-risk of imminent delivery, improves neurodevelopmental outcome, although information is mainly limited to the use of betamethasone [20]. A recent meta-analysis that combined data from observational and case-control studies, conducted in small-for-gestational-age preterm fetuses also observed a reduction in neonatal mortality rate (OR 0.63, 95%CI 0.46–0.86), although the incidence of respiratory distress syndrome was not affected (OR 0.89, 95%CI 0.69–1.15) [21].

2. Either betamethasone (12 mg administered intramuscularly twice, 24-h apart) or dexamethasone (6 mg administered intramuscularly in four doses, 12-h apart, or 12 mg administered intramuscularly twice, 24-h apart), may be used (Moderate-quality evidence; Strong recommendation). Administration of two "all" doses is termed a "course of corticosteroids".

The most widely studied corticosteroids for use in this setting are betamethasone (12 mg administered intramuscularly twice, 24-h apart) and dexamethasone (6 mg administered intramuscularly in four doses, 12-h apart) [22]. The preparation used in most betamethasone trials was a mixture of betamethasone phosphate (a short-acting form) and betamethasone acetate (a long-acting form) [23]. The largest randomized trial comparing the two corticosteroids recruited 1346 women from 14 centers and allocated them to receive two intramuscular injections of either 12 mg dexamethasone or 11.4 mg betamethasone, 24-h apart. Similar results were found for betamethasone and dexamethasone, regarding survival without neurosensory disability at two-years of age [24]. A recent network meta-analysis also concluded that both corticosteroids are equally effective in preventing neonatal death, neurodevelopmental disability, and intraventricular hemorrhage [25]. On the other hand, dexamethasone has a lesser effect on the incidence of respiratory distress syndrome. The same study concludes that dexamethasone may reduce chorioamnionitis and fetal death but may increase endometritis/puerperal sepsis.

In conclusion, currently existing evidence suggests that both betamethasone and dexamethasone have similar effects on survival and long-term neurodevelopmental disability, and that minor differences are seen in short-term morbidity and mortality. These are insufficient to judge the superiority of either regimen, or of alternative doses.

3. Administration between 22^{+0} and 23^{+6} weeks should be considered when preterm birth is anticipated within the next seven days and active newborn life-support is indicated, taking into account parental wishes. A clear survival benefit has been observed in these cases, but the impact on short-term neurological and respiratory function, as well as long-term neurodevelopmental outcome is still unclear (Low/moderate-quality evidence; Weak recommendation).

Whereas the improvement in newborn morbidity given by antenatal corticosteroids during the period

24^{+0} and 33^{+6} weeks has been established in randomized trials, their impact on offspring delivered at the threshold of viability (between 22^{+0} and 23^{+6} weeks) has only been investigated in observational studies. A meta-analysis including nine observational studies of deliveries in gestational weeks 22–24 ($n = 13{,}443$), showed that antenatal corticosteroid exposure was associated with a significant reduction in mortality (OR 0.48; 95%CI 0.42–0.55), and a decreased incidence of intraventricular hemorrhage or periventricular leukomalacia (OR 0.70; 95%CI 0.63–0.79). Mortality remained significantly lower when analyzing weeks 22 and 23 separately, but statistical significance was loess for intraventricular hemorrhage or periventricular leukomalacia in week 22. The most recent Cochrane review [26], also concluded that there is moderate-certainty evidence that antenatal corticosteroids reduce perinatal mortality when administered before 24–25 weeks.

Active life support in newborns with less than 24 weeks gestational age varies between countries. Varying obstetric and newborn practices are directly related to the percentage of live newborns, survival, and prevalence of long-term morbidities [27]. A recent case-control study from the United States, evaluating clinical practice in 24,379 pregnancies delivered during weeks 22–23, reported that antenatal corticosteroids were administered in 7.7% of pregnancies at risk of imminent delivery during week 22, and in 9.4% of pregnancies during week 23 [28]. In contrast, the most recent national population-based study from Sweden ($n = 1009$) reports that 64% of liveborn infants at week 22 and 92% of infants at week 23 had received antenatal steroids [29].

The recommendation for administration of corticosteroids in these gestational ages needs to be consistent with the decision to provide active life-support to the child after birth, and this needs to be based on a detailed and sensitive discussion between parents and the perinatal team.

4. Administration between $34 + 0$ and $34 + 6$ weeks should only be offered to a few selected cases (Expert opinion). Administration between 35^{+0} and 36^{+6} weeks should be restricted to prospective randomized trials. Current evidence suggests that, although corticosteroids reduce the incidence of transient tachypnea of the newborn, they do not affect the incidence of respiratory distress syndrome, and increase neonatal hypoglycemia. Long-term safety data are lacking (Moderate quality evidence; Conditional recommendation).

Several studies have addressed the impact of antenatal corticosteroids in late preterm deliveries, between 34^{+0} and 36^{+6} weeks of gestation. These account for approximately 10% of all births worldwide (about 75% of preterm births). Despite the relatively low incidence of neonatal morbidity among preterm births at these gestational ages, the overall size of this population has an important impact on neonatal care [30–32]. Late preterm cesarean deliveries impose an increased risk of neonatal morbidity and mortality [33]. A large randomized trial that recruited 2,831 women at risk of late preterm delivery and allocated women to an intervention group that received two injections of 12 mg betamethasone, 24-h apart, documented a significant reduction in a composite of respiratory complications, when compared to a placebo group. However, these differences were driven mainly by the need for continuous positive airway pressure (CPAP) or high-flow nasal cannula for more than two hours [34]. The corticosteroid group also had a reduction in demand of CPAP/high flow cannula for more than 12 h and in transient tachypnea of the newborn. However, no differences were observed in the incidences of respiratory distress syndrome, mortality, or length of hospital stay, and there was a significant increase in the incidence of neonatal hypoglycemia. A meta-analysis involving women from six trials indicated that antenatal steroids in late preterm pregnancies reduced neonatal respiratory morbidity, including reduced incidence of transient tachypnea of the newborn (0.38, 95%CI 0.25–0.57), RDS (0.40, 95%CI 0.27, 0.59), and use of mechanical ventilation (0.19, 95%CI 0.08–0.43) [35]. Taking this information into consideration the authors suggested that a single course of corticosteroids should be considered in women at risk of preterm birth between $34 + 0$ and $36 + 6$ weeks.

A recent meta-analysis suggests that offspring exposed to antenatal corticosteroids during the early preterm period have decreased incidence of neurodevelopmental impairment (OR 0.69, 95%CI 0.57, 0.84) [36]. The long-term benefit, however, for children with late preterm exposure seems to be negative as neurocognitive disorders increase (OR 1.12, 95%CI 1.05, 1.20). This effect becomes more prominent for offspring exposed at term as they seem to have more behavioral and mental disorders (OR 1.47, 95%CI 1.36, 1.60) [36].

Considering this information, counterbalancing of the benefits and adverse effects of antenatal corticosteroids should be investigated prior to their introduction in clinical practice. For these reasons, antenatal corticosteroid use in women at risk of preterm delivery between 34^{+0} weeks and 36^{+6} weeks, should be limited to prospective randomized trials only.

5. Administration in pregnancies beyond 37^{+0} weeks should not be considered, even before scheduled cesarean delivery, as current evidence does not suggest a clear indication of benefit and the long-term effects of treatment remain unknown (Low-quality evidence; Conditional recommendation).

A recent Cochrane review suggests that corticosteroid treatment for elective cesarean section at term decreases the risk of respiratory distress syndrome (RR 0.48, 95%CI 0.27–0.87) [37], a result that was also found in a large individual trial [38], but was not consistent across all trials. In contrast, a recent observational study found that corticosteroids for planned early-term ceasarean delivery increases the risk of neonatal hypoglycemia without affecting the incidence of respiratory distress syndrome [39]. A decisive factor in deciding whether to administer corticosteroids in this population is the low prevalence of respiratory distress syndrome, limiting the overall effect of any treatment.

Therefore, given the low prevalence of respiratory distress syndrome in this group of patients and the unknown long-term effects of corticosteroids, they should not be administered routinely, even before scheduled cesarean delivery.

6. Administration should be given in twin pregnancies, with the same indication and doses as for singletons. However, existing evidence suggests that it should only be administered for pregnancies at high-risk of delivering within seven days as in the case of singletons (Low-quality evidence; Conditional recommendation). Maternal diabetes mellitus is not a contraindication to the use of antenatal corticosteroids (Moderate quality evidence; Strong recommendation).

Several retrospective cohort studies indicate that antenatal corticosteroids improve neonatal outcomes in twin pregnancies delivered before 34 weeks [12, 40–42], reducing severe neurological and respiratory morbidity, as well as the need for mechanical ventilation by approximately 50%. Most of these cases seem to have been delivered within a seven-day interval from corticosteroid administration. A sub-analysis of the EPIPAGE-2 study revealed that the beneficial effect of corticosteroids does not seem to extend beyond one week [12]. In a population-based study of 6546 preterm twins under 32 weeks, the beneficial effect of corticosteroids involved only short-term neurologic outcomes, whereas no difference was found in the incidence of respiratory distress syndrome or neonatal death [43]. Severe morbidity in preterm twins does not appear to be different from that of singletons [44], therefore it is reasonable to assume corticosteroid use should be the same.

Given the large proportion of twin pregnancies delivered in the late preterm period, there is need for robust evidence on the effect of corticosteroid use in these situations. No randomized controlled trials have so far been published on this subject, but a large trial is ongoing [45].

The beneficial effect of corticosteroids in diabetic pregnancies appears to be similar to the non-diabetic population before 34 weeks [46]. However, late preterm pregnancies are less prone to serious respiratory complications [47], and current evidence suggests that administration of corticosteroids during this period increases the rate of neonatal hypoglycemia [19, 48]. Diabetes should not be considered a contraindication to corticosteroid administration, but close follow-up of glycemic values is required to adjust insulin infusion rates [49]. The optimal regimen and dose remain to be defined as a recent randomized controlled trial suggested that dexamethasone (12 mg administered intramuscularly twice, 12-h apart) may be superior to dexamethasone (6 mg administered intramuscularly four times, 12-h apart) in terms of reducing maternal hyperglycemic episodes [50]. Offspring of diabetic mothers are at an increased risk of developing hypoglycemia and respiratory morbidity beyond that attributed to prematurity [51].

7. A single repeat course of corticosteroids can be considered in pregnancies below 34^{+0} weeks gestation, if the previous course was administered more than 7 days earlier and there is renewed high-risk of imminent delivery (Low-quality evidence; Conditional recommendation).

The majority of the available evidence concerning the safety of antenatal corticosteroids is retrieved from cohort studies. Given that potential confounders may partially skew the findings of several studies, it is important to evaluate current evidence based on large series which are designed on a post-market setting and which complement the efficacy data that emanate from pre-market randomized trials, using real-world data. A Cochrane review analyzing data from 10 randomized trials concluded that repeat courses of corticosteroids in pregnancies at risk of being born seven or more days after the initial course reduces severe short-term neonatal morbidity [18]. A slight reduction in birth weight was also found, but no significant harm was observed in childhood. A recent individual patient data meta-analysis reported that repeat courses of corticosteroids, at a total dose of 24–48 mg reduced the likelihood of respiratory support after birth, but neonatal deaths and neurosensory

disability were not influenced [52]. Similar results are reported in the latest Cochrane review [18]. Evidence from two large multicentre cohorts failed to find a difference in the risk of death or disability at five years of age, between offspring that received single or multiple courses of corticosteroids, questioning the long-term benefits of a second course [53,54]. Children born at term following multiple courses of corticosteroids had a 70% higher risk of death or neurodevelopmental disability at five years of age than those exposed to a single course [55]. The gestational age threshold at which the benefits of repeated courses outweigh the risks remains unknown. Large cohort studies indicate that multiple courses of corticosteroids initiated before 29 weeks may have increased benefits than risks.

Among this balance of conflicting evidence, it is recommended to consider one single repeat course of corticosteroids in pregnancies below 34^{+0} weeks gestation if the previous course was administered more than 7 days earlier, and there is renewed high-risk of preterm birth [51]. Concerning their impact on the prevalence of cardiometabolic disease, no adverse effect was found when assessing children at school age exposed antenatally to repeated doses of corticosteroids [56].

Methodology used in the development of this guideline

The writing group conducted searches in PubMed, EMBASE, Cochrane Library, Ovid, UpToDate for articles related to this topic. These were limited to studies involving humans and articles published in English between January 1988 and April 2022. Randomized trials and observational studies were considered eligible. The searches were completed manually by consulting the reference list in the identified publications and other guidelines related to the topic. The search terms used were corticosteroids, betamethasone, dexamethasone, antenatal, pregnancy, preterm birth, prematurity, twin pregnancies, cesarean section, diabetes mellitus, intrauterine growth restriction, repeat doses, interval to delivery. The writing group synthesized the evidence and elaborated the first draft of the manuscript, proposing recommendations according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The guideline panel members were asked to comment and modify the text in three successive interactions until a final version of the manuscript was reached. All panel members who agreed with the final version and gave their consent for co-authorship are listed in the document.

Disclosure statement

George Daskalakis, Vasilios Pergialiotis, Ariadne Malamitsi-Puchner, Elko Gliozheni, Artur Beke, Katarzyna Kosińska-Kaczyńska, Ana Luisa Areia, and Simona Vladareanu have no conflicts of interest. No lectures, presentations, travel or personal reimbursement has been financed by any company. Magnus Domellöf received Consultation honoraria or speaker fees from Baxter AB, Baxter Deutschland GmbH, Danone Nutricia, Elgan Pharma, BioQuest Solutions Pvt. Ltd., Medscape Education/WebMD, Nestec Ltd. (Nestlé) and Nestlé Nutrition Institute. Grants/research supports from Arla Foods Ingredients. CEO of Nutrium AB. Harald Ehrhardt received Research grants from the German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), von Behring-Röntgen-Foundation and Chiesi Foundation. Member European Neonatal Research Consortium of the European Society for Paediatric Research (ESPR) and member EAPM special interest group of preterm delivery. Ehrhardt is the Member of the expert commission perinatal medicine (QS PM) of the federal quality assurance office of Hesse (LAGQH). No lectures, presentations, travel or personal reimbursement has been financed by any company. Gian Carlo Di Renzo received Research grants from Kedrion, Italy, Diabetomics Inc USA and from Italian Ministry of Health. Renzo is the Director of the PREIS School in Florence which receives unrestricted educational grants from several companies. No conflicts of interest. No lectures, presentations, travel or personal reimbursement has been financed by any company. Esin Koç received Clinical trial grants from Turkish Neonatal Society and Gazi University and also an ongoing clinical trial, products provided by Chiesi company. Koç is the President of Turkish Neonatal Society, board member of UENPS and WAPM. Marian Kacerovsky received Research grants from the Czech Research Foundation, Czehc Health Research Foundation, Ministry of Health of the Czech Republic Ministry of Education, Youth and Sports of the Czech Republic, and Ministry of Regional Development of the Czech Republic. Chairman of the Czech Society of Perinatal and Maternal-Fetal Medicine. No lectures, presentations, travel or personal reimbursement has been financed by any company. Neena Modi NM reports grants outside the submitted work from the National Institute for Health Research, Medical Research Council, British Heart Foundation, Health Data Research UK, HCA International, Nestle, Takeda Pharmaceuticals, Prolacta Life Sciences, Chiesi Pharmaceuticals and March of Dimes. NM reports a lecture fee from Nestle International and Chiesi Pharmaceuticals, and reimbursement of travel and accommodation expenses from Nestle International, Chiesi Pharmaceuticals and Prolacta Life Sciences. NM is a member of the Nestle Scientific Advisory Board, president of the UK Medical Women's Federation, vice-chair of the Strategy and Advocacy Committee of the Medical Women's International Association, past-president of the UK Royal College of Paediatrics and Child Health, president-elect of the British Medical Association, president-elect of the European Association of Perinatal Medicine, patron of the charities

Keep Our NHS Public and HealthProm, trustee of the charities TheirWorld, Action Cerebral Palsy and David Harvey Trust, and trustee and council member of the UK Academy of Medical Sciences. Andrew Shennan AS has a number of research grants in the last three years related to the prediction of preterm birth, from Guys and St Thomas's Charity and government UK funding agencies. He has given online talks organised by Hologic, expences paid to instiitue. Other funding is unrelated to the subject atter of this review. Diego Ayres-de-Campos received Consultation honoraria and speaker fees for Philips Medical, Boeblingen, Germany. No conflicts of interest to declare related to the topic of this guideline. Kristiina Rull has no conflicts of interest to declare. Rull is the Member of board of Estonian Perinatology Society (2019–2022) and Member of board of Estonian Gynecologists' Society (since 2022) Research project financed by the Clinical Medicine Institute, University of Tartu, Estonia "Fetal malformations and genetic defects: prevalence, prenatal detection rate, prognosis and treatment in Estonia 2019–2023. Thorsten Braun received Research grants from the German Research Foundation (DFG), Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Developmental Origins of Health and Disease (DOHaD), Stiftung für das behinderte Kind, Haackert Stiftung. No lectures, presentations, travel or personal reimbursement has been financed by any company. Tanja Premru-Sršen received Research grants from Slovenian Research Agency and University Medical Centre Ljubljana, Slovenia. No lectures, presentations, travel, or personal reimbursement has been financed by any company. Dr. Thomas Schmitz reports receiving consulting fees from Dilafor. Bo Jacobsson received Research grants from Swedish Research Council, Norwegian Research Council, March of Dimes, Burroughs Wellcome Fund and the US National Institute of Health. During the last years performed clinical diagnostic trials on NIPT with Ariosa (completed), Natera (ongoing), Vanadis (completed) and Hologic (ongoing) with expenditures reimbursed per patient. Jacobsson also performed clinical probiotic studies with the probiotic product provided by FukoPharma (ongoing, no funding) and BioGaia (ongoing; also provided a research grant for the specific study) Previously (2018–2020) he was a collaborator in IMPACT study where Roche, Perkin Elmer and Thermo Fisher provided reagenses to PLGF analyses. No lectures, presentations, travel or personal reimbursement has been financed by any company. He is the Division Director of Maternal and Neonatal Health of the International Federation of Gynecology and Obstetrics (FIGO), Board member of the European Association of Perinatal Medicine and chair the EAPM special interest group of preterm delivery. He is the Steering group member of Genomic Medicine Sweden and is in charge of the Genomic Medicine Sweden complexe diseases group. Jacobsson is the Swedish representative in Nordic Society of Precision Medicine.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

George Daskalakis http://orcid.org/0000-0001-7108-211X
Marian Kacerovsky http://orcid.org/0000-0001-9858-7900
Andrew Shennan http://orcid.org/0000-0001-5273-3132
Diogo Ayres-de-Campos http://orcid.org/0000-0002-7136-6240
Bo Jacobsson http://orcid.org/0000-0001-5079-2374

References

[1] Salvante KG, Milano K, Kliman HJ, et al. Placental 11 beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2) expression very early during human pregnancy. J Dev Orig Health Dis. 2017;8(2):149–154.
[2] Murphy VE, Fittock RJ, Zarzycki PK, et al. Metabolism of synthetic steroids by the human placenta. Placenta. 2007;28(1):39–46.
[3] Committee Opinion No.677: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2016; 128:e187-94.
[4] Boutin A, Skoll A, Bujold E, et al. Antenatal corticosteroid therapy for improving neonatal outcomes: balancing benefits and risks. J Obstet Gynaecol Can. 2018;40(9):1193–1197.
[5] Good clinical practice advice. Antenatal corticosteroids for fetal lung maturation. Int J Gynaecol Obstet. 2019;144:352–355.
[6] Modi N, Lewis H, Al-Naqeeb N, et al. The effects of repeated antenatal glucocorticoid therapy on the developing brain. Pediatr Res. 2001;50(5):581–585.
[7] Melamed N, Asztalos E, Murphy K, et al. Neurodevelopmental disorders among term infants exposed to antenatal corticosteroids during pregnancy: a population-based study. BMJ Open. 2019; 9(9):e031197.
[8] Raikkonen K, Gissler M, Kajantie E. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children. JAMA. 2020;323(19):1924–1933.
[9] Asztalos E. Antenatal corticosteroids: a risk factor for the development of chronic disease. J Nutr Metab. 2012;2012:930591.
[10] Grzeskowiak LE, Grivell RM, Mol BW. Trends in receipt of single and repeat courses of antenatal corticosteroid administration among preterm and term births: a retrospective cohort study. Aust N Z J Obstet Gynaecol. 2017;57(6):643–650.
[11] Levin HI, Ananth CV, Benjamin-Boamah C, et al. Clinical indication and timing of antenatal corticosteroid administration at a single Centre. BJOG. 2016; 123(3):409–414.
[12] Palas D, Ehlinger V, Alberge C, et al. Efficacy of antenatal corticosteroids in preterm twins: the EPIPAGE-2 cohort study. BJOG. 2018;125(9):1164–1170.
[13] Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome - 2019 update. Neonatology. 2019; 115(4):432–450.
[14] Di Renzo GC, Roura LC, Facchinetti F, et al. Guidelines for the management of spontaneous preterm labor: identification of spontaneous preterm labor, diagnosis

of preterm premature rupture of membranes, and preventive tools for preterm birth. J Matern Fetal Neonatal Med. 2011;24(5):659–667.
[15] Di Renzo GC, Cabero Roura L, Facchinetti F, et al. Preterm labor and birth management: recommendations from the european association of perinatal medicine. J Matern Fetal Neonatal Med. 2017;30(17): 2011–2030.
[16] McGoldrick E, Stewart F, Parker R, et al. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020;12: CD004454.
[17] Antenatal dexamethasone for early preterm birth in Low-Resource countries. N Eng J Med. 2020;383: 2514–2525.
[18] Crowther CA, McKinlay CJ, Middleton P, et al. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. 2015;Cd003935.
[19] Battarbee AN, Ros ST, Esplin MS, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Genomics and Proteomics Network for Preterm Birth Research (GPN-PBR), et al. Optimal timing of antenatal corticosteroid administration and preterm neonatal and early childhood outcomes. Am J Obstet Gynecol MFM. 2020;2(1):100077.
[20] Sotiriadis A, Tsiami A, Papatheodorou S, et al. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. Obstet Gynecol. 2015; 125(6):1385–1396.
[21] Blankenship SA, Brown KE, Simon LE, et al. Antenatal corticosteroids in preterm small-for-gestational age infants: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2(4):100215.
[22] Committee Opinion No. 713: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2017; 130:e102–e9.
[23] UN Commission/Born Too soon Care Antenatal Corticosteroids Working Group. Dexamethasone versus betamethasone as an antenatal corticosteroid (ACS). 20 August 2013. Retrieved: July 2021.
[24] Crowther CA, Ashwood P, Andersen CC, ASTEROID Study Group, et al. Maternal intramuscular dexamethasone versus betamethasone before preterm birth (ASTEROID): a multicentre, double-blind, randomised controlled trial. Lancet Child Adolesc Health. 2019;3(11):769–780.
[25] Ciapponi A, Klein K, Colaci D, et al. Dexamethasone vs. betamethasone for preterm birth: a systematic review and network meta-analysis. Am J Obstet Gynecol MFM. 2021;3(3):100312.
[26] Deshmukh M, Patole S. Antenatal corticosteroids in impending preterm deliveries before 25 weeks' gestation. Arch Dis Child Fetal Neonatal Ed. 2018;103(2): F173–F176.
[27] Dixon CL, Too G, Saade GR, et al. Past and present: a review of antenatal corticosteroids and recommendations for late preterm birth steroids. Am J Perinatol. 2018;35(13):1241–1250.
[28] Hajdu SA, Rossi RM, DeFranco EA. Factors associated with maternal and neonatal interventions at the threshold of viability. Obstet Gynecol. 2020;135(6): 1398–1408.
[29] Norman M, Hallberg B, Abrahamsson T, et al. Association between year of birth and 1-Year survival among extremely preterm infants in Sweden during 2004–2007 and 2014–2016. JAMA. 2019;321(12): 1188–1199.
[30] Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832): 2162–2172.
[31] Hibbard JU, Wilkins I, Sun L, Consortium on Safe Labor, et al. Respiratory morbidity in late preterm births. JAMA. 2010;304(4):419–425.
[32] Cheng YW, Kaimal AJ, Bruckner TA, et al. Perinatal morbidity associated with late preterm deliveries compared with deliveries between 37 and 40 weeks of gestation. BJOG. 2011;118(12):1446–1454.
[33] Malloy MH. Impact of cesarean section on intermediate and late preterm births: United States, 2000-2003. Birth. 2009;36(1):26–33.
[34] Gyamfi-Bannerman C, Thom EA, Blackwell SC, NICHD Maternal–Fetal Medicine Units Network, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016;374(14): 1311–1320.
[35] Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ. 2016;355:i5044–i.
[36] Ninan K, Liyanage SK, Murphy KE, et al. Evaluation of long-term outcomes associated with preterm exposure to antenatal corticosteroids: a systematic review and meta-analysis. JAMA Pediatr. 2022;176(6): e220483.
[37] Sotiriadis A, Makrydimas G, Papatheodorou S, et al. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. Cochrane Database Syst Rev. 2018;8(8):CD006614.
[38] Stutchfield P, Whitaker R, Russell I, Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. BMJ. 2005;331(7518):662.
[39] Gupta K, Rajagopal R, King F, et al. Complications of antenatal corticosteroids in infants born by early term scheduled cesarean section. Diabetes Care. 2020;43(4): 906–908.
[40] Melamed N, Shah J, Yoon EW, et al. The role of antenatal corticosteroids in twin pregnancies complicated by preterm birth. Am J Obstet Gynecol. 2016;215(4): 482.e1–e1482.e9.
[41] Bibbo C, Deluca L, Gibbs KA, et al. Rescue corticosteroids in twin pregnancies and short-term neonatal outcomes. BJOG. 2013;120(1):58–63.
[42] Kong X, Xu F, Wang Z, et al. Antenatal corticosteroids administration on mortality and morbidity in premature twins born at 25～34 gestational weeks: a

retrospective multicenter study. Eur J Obstet Gynecol Reprod Biol. 2020;253:259–265.

[43] Ushida T, Kotani T, Sadachi R, et al. Antenatal corticosteroids and outcomes in preterm twins. Obstet Gynecol. 2020;135:1387–1397.

[44] Dudenhausen JW, Misselwitz B, Piedvache A, EPICE Research Group, et al. Characteristics, management and outcomes of very preterm triplets in 19 European regions. Int J Gynaecol Obstet. 2019;147(3):397–403.

[45] Hong S, Lee SM, Kwak DW, et al. Effects of antenatal corticosteroids in twin neonates with late preterm birth (ACTWIN [antenatal corticosteroids in TWIN late preterm neonates] trial): study protocol for a randomized controlled trial. BMC Pregnancy Childhood. 2019; 19:114.

[46] Battarbee AN, Sandoval G, Grobman WA, for the Eunice Kennedy Shriver National Institute of Child Health Human Development Maternal-Fetal Medicine Units (MFMU) Network, et al. Antenatal corticosteroids and preterm neonatal morbidity and mortality among women with and without diabetes in pregnancy. Am J Perinatol. 2022;39(01):067–074.

[47] Werner EF, Romano ME, Rouse DJ, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU)*, et al. Association of gestational diabetes mellitus with neonatal respiratory morbidity. Obstet Gynecol. 2019;133(2):349–353.

[48] Ali H, Salama H, Robertson N, et al. Antenatal corticosteroids and short-term neonatal outcomes in term and near-term infants of diabetic mothers. Analysis of the Qatar PEARL-peristat registry. J Perinat Med. 2020; 49:377–382.

[49] National Institute for Health and Care Excellence (NICE). NICE Guidance. Diabetes in pregnancy: management from preconception to the postnatal period [NG3]. Retrieved 22 January 2021. Available from: https://www.nice.org.uk/guidance/NG3.

[50] Sukarna N, Tan PC, Hong JGS, et al. Glycemic control following two regimens of antenatal corticosteroids in mild gestational diabetes: a randomized controlled trial. Arch Gynecol Obstet. 2021;304(2):345–353.

[51] Kawakita T, Bowers K, Hazrati S, et al. Increased neonatal respiratory morbidity associated with gestational and pregestational diabetes: a retrospective study. Am J Perinatol. 2017;34(11):1160–1168.

[52] Crowther CA, Middleton PF, Voysey M, PRECISE Group, et al. Effects of repeat prenatal corticosteroids given to women at risk of preterm birth: an individual participant data meta-analysis. PLoS Med. 2019;16(4): e1002771-e.

[53] Asztalos EV, Murphy KE, Willan AR, MACS-5 Collaborative Group, et al. Multiple courses of antenatal corticosteroids for preterm birth study: outcomes in children at 5 years of age (MACS-5). JAMA Pediatr. 2013;167(12):1102–1110.

[54] Crowther CA, Anderson PJ, McKinlay CJ, for the ACTORDS Follow-up Group, et al. Mid-Childhood outcomes of repeat antenatal corticosteroids: a randomized controlled trial. Pediatrics. 2016;138(4): e20160947.

[55] Zephyrin LC, Hong KN, Wapner RJ, Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units (MFMU) Network, et al. Gestational age-specific risks vs benefits of multicourse antenatal corticosteroids for preterm labor. Am J Obstet Gynecol. 2013;209(4): 330.e1–7.

[56] McKinlay CJ, Cutfield WS, Battin MR, ACTORDS Study Group, et al. Cardiovascular risk factors in children after repeat doses of antenatal glucocorticoids: an RCT. Pediatrics. 2015;135(2):e405-15–e415.