

# EVALUATION OF LONG TERM OUTCOMES ASSOCIATED WITH PRETERM EXPOSURE TO ANTENATAL CORTICOSTEROIDS: A SYSTEMATIC REVIEW

Rio Martin Rajagukguk\*

\*PELNI General Hospital, Petamburan, Jakarta, Indonesia

\*Corresponding Author:  
ryoorio94@gmail.com

---

## Abstract

**Background:** Each year, approximately, 15 million infants are born prematurely (<37 week gestation), and nearly, 1 million infants die due to complications of preterm birth. The use of antenatal corticosteroids (ACS) has been proven to be one of the most effective interventions to reduce mortality and major morbidities of premature infants, especially for those at gestational age (GA) <32 weeks. So far, ACSs have been recommended by several guidelines to be used for pregnant women at risk of preterm delivery.

**The aim:** This study aims to show about evaluation of long term outcomes associated with preterm exposure to antenatal corticosteroids.

**Methods:** By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

**Result:** In the PubMed database, the results of our search brought up 117 articles, whereas the results of our search on SagePub brought up 112 articles. The results of the search conducted for the last year of 2013 yielded a total 91 articles for PubMed and 66 articles for SagePub. The result from title screening, a total 2 articles for PubMed and 11 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.

**Conclusion:** Numerous studies have shown no evidence of long-term harm (and in fact showed improved survival and neurodevelopmental outcomes with long-term pulmonary and others benefit), particularly as it relates to a single course of corticosteroids administered at less than 34 0/7 weeks of gestation.

**Keyword:** Preterm, antenatal, corticosteroid

## INTRODUCTION

Antenatal corticosteroids (ACS) are part of standard therapy in women with anticipated preterm birth to improve outcomes following delivery. Although there is a potential for long-term neurodevelopmental harm especially in the extremely preterm infant, the reduction in respiratory distress syndrome from accelerated fetal lung maturation and perinatal and neonatal death, favor treatment.<sup>1</sup>

Late preterm (LPT) infants (born at 34 to 36 weeks' gestation) are at-risk for postnatal respiratory distress, short and long-term morbidities and mortality when compared to term infants. We reported that the rates of mechanical ventilation (MV) and mortality was 4.2 and 3.9-fold higher, respectively, compared to term infants during an observational period of no ACS during LPT gestation. Following the ALPS trial, ACS use increased substantially in mothers at-risk for LPT delivery. Despite the preferential recommendation for antenatal betamethasone, dexamethasone is currently used with the same total dose of 24 mg for any LPT pregnancy where delivery is anticipated within 7 days.<sup>1,2</sup>

Betamethasone and dexamethasone are the most widely studied corticosteroids, and they generally have been preferred for antenatal treatment to accelerate fetal organ maturation. Both cross the placenta in their active form and have nearly identical biologic activity. Both lack mineralocorticoid activity and have relatively weak immunosuppressive activity with short-term use. Although betamethasone and dexamethasone differ only by a single methyl group, betamethasone has a longer half-life because of its decreased clearance and larger volume of distribution. Betamethasone and dexamethasone are the most widely studied corticosteroids, and they generally have been preferred for antenatal treatment to accelerate fetal organ maturation. Both cross the placenta in their active form and have nearly identical biologic activity. Both lack mineralocorticoid activity and have relatively weak immunosuppressive activity with short-term use. Although betamethasone and dexamethasone differ only by a single methyl group, betamethasone has a longer half-life because of its decreased clearance and larger volume of distribution.<sup>3</sup>

Fetal lung development can be divided into five stages: embryonic, pseudoglandular, canalicular, terminal sac and alveolar. From 28 to 35 weeks of gestation, the alveoli increase in number and mature. Lamellar bodies, which store surfactant, appear at 22–24 weeks. Surfactant is needed to stabilize alveoli and is a complex mixture of lipids and apoproteins.<sup>4</sup>

ACS accelerate the development of type 1 and type 2 pneumocytes, induce pulmonary beta receptors and subsequently are responsible for modifications on alveolar structure, vascularization, surfactant production and airspace fluid clearance. The increase of surfactant production will be achieved through both transcription and post-transcriptional mechanisms, enhancing the rate of phosphatidylcholine and fatty acid biosynthesis in the fetal lung. Animal and human studies have shown that ACS also increase lung compliance and volume and increase response to exogenous surfactant treatment.<sup>4</sup>

## METHODS

### Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

### Criteria for Eligibility

For the purpose of this literature review, we show evaluation of long term outcomes associated with preterm exposure to antenatal corticosteroids. It is possible to accomplish this by researching or investigating the risk factor for physical disability in patients with leprosy. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine the best time to perform emergency surgery for congenital diaphragmatic hernia. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

### Search Strategy

We used "evaluation of long term outcomes associated with preterm exposure to antenatal corticosteroids" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: (*"Longterm outcomes of corticosteroid"*[MeSH Subheading] OR *"preterm exposure to antenatal corticosteroids"*[All Fields] OR *"Antenatal corticosteroids"*[All Fields]) AND (*"corticosteroid in preterm exposure"*[All Fields] OR *"longterm outcomes of corticosteroid exposure"*[All Fields]) AND (*"corticosteroid exposure"*[MeSH Terms] OR (*"incident of preterm"*[All Fields]) OR (*"incident of antenatal corticosteroid exposure"*[All Fields]) AND *"corticosteroid exposure in preterm"*[All Fields])) used in searching the literature.

### Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to

the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

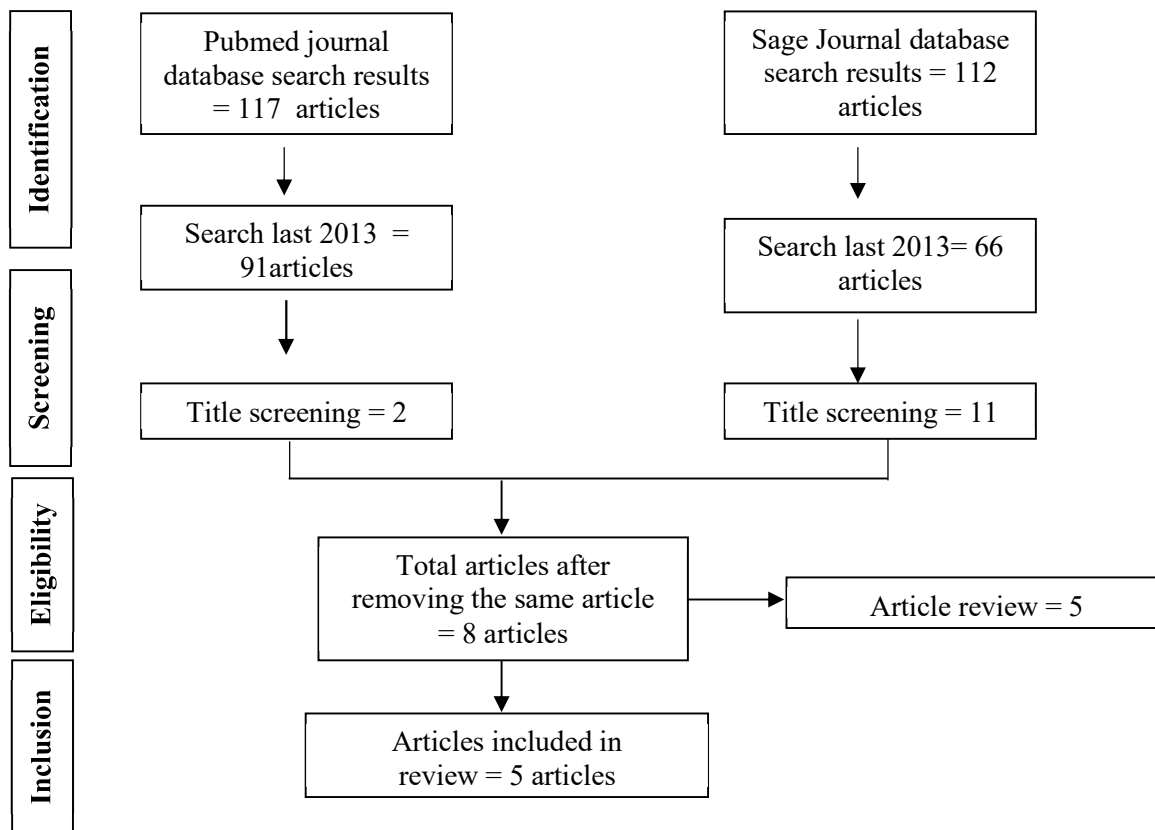


Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

**RESULT**

In the PubMed database, the results of our search brought up 117 articles, whereas the results of our search on SagePub brought up 112 articles. The results of the search conducted for the last year of 2013 yielded a total 91 articles for PubMed and 66 articles for SagePub. The result from title screening, a total 2 articles for PubMed and 11 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.

Yao, TC *et al* (2023)<sup>5</sup> showed the nationwide cohort study found that children exposed to one course of antenatal corticosteroids were significantly more likely to have an increased risk of serious infection during the first 12 months of life. These findings suggest that before starting treatment, the long term risks of rare but serious infection associated with antenatal corticosteroids should be carefully weighed against the benefits in the perinatal period.

Ushida, T *et al* (2020)<sup>6</sup> showed that administration of ACS to women with HDP resulted in a beneficial effect on major short-term neonatal outcomes. This benefit was similar in magnitude to the benefit observed among mothers without HDP. We could not find any additional effects of ACS treatment in the HDP group on offspring outcomes such as severe brain injury in the short-term or neurodevelopmental disorders at 3 years of age, including CP and neurodevelopmental delay. However, these results must be interpreted with caution; our results did not suggest that ACS treatment should be withheld from mothers with HDP. In addition, further investigation is required to verify our findings in different populations.

**Table 1. The literature include in this study**

Author	Origin	Method	Sample Size	Result
<b>Yao, TC et al., 2023<sup>5</sup></b>	Taiwan	Nationwide cohort study	1 960 545 pairs of pregnant individuals and their singleton offspring. 45 232 children were exposed and 1 915 313 were not exposed to antenatal corticosteroids.	The study cohort was 1 960 545 singleton children: 45 232 children were exposed to one course of antenatal corticosteroids and 1 915 313 children were not exposed to antenatal corticosteroids. The adjusted hazard ratios for overall serious infection, sepsis, pneumonia, and acute gastroenteritis among children exposed to antenatal corticosteroids were significantly higher than those not exposed to antenatal corticosteroids during the first six months of life (adjusted hazard ratio 1.32, 95% confidence interval 1.18 to 1.47, P<0.001, for overall serious infection; 1.74, 1.16 to 2.61, P=0.01, for sepsis; 1.39, 1.17 to 1.65, P<0.001, for pneumonia; and 1.35, 1.10 to 1.65, P<0.001, for acute gastroenteritis). Similarly, the adjusted hazard ratios for overall serious infection (P<0.001), sepsis (P=0.02), pneumonia (P<0.001), and acute gastroenteritis (P<0.001) were significantly higher from birth to 12 months of life. In the sibling matched cohort, the results were comparable with those observed in the whole cohort, with a significantly increased risk of sepsis in the first six (P=0.01) and 12 (P=0.04) months of life.
<b>Ushida, T et al., 2020<sup>6</sup></b>	Japan	Cohort study	48569 neonates	Neonates born to mothers receiving ACS in both the HDP and non-HDP groups had lower rates of mortality and RDS, but higher rate of CLD compared with neonates born to mothers not receiving ACS. ACS treatment in the HDP group did not significantly decrease the rates of severe IVH (grade III/IV), PVL, sepsis, and short-term composite adverse outcomes, which was in contrast to the non-HDP group. With respect to long-term outcomes, ACS treatment was associated with a significant decrease in CP, DQ < 85, and composite adverse outcomes at 3 years of age in the non-HDP group. Conversely, in the HDP group, no significant differences were observed with respect to the rates of mortality, severe disabilities, CP, and neurodevelopmental delay between the offspring with and without ACS treatment. In the non-HDP group, short-term outcomes without follow-up tended to be worse compared to those with 3-year follow-up.
<b>Bae, SP et al., 2023<sup>7</sup></b>	Korea	Nationwide prospective cohort study	9531 preterm infants	Antenatal corticosteroids significantly decreased the risk of surfactant use (adjusted relative risk (aRR): 0.972 (95% CI: 0.961 to 0.984)), high-grade intraventricular haemorrhage (aRR: 0.621 (95% CI: 0.487 to 0.794)), periventricular leucomalacia (aRR: 0.728 (95% CI: 0.556 to 0.954)) and mortality (aRR: 0.758 (95% CI: 0.679 to 0.846)) in the gestational age group of 23–28 weeks. In the gestational age group of 29–33 weeks, antenatal corticosteroids significantly decreased the risk of surfactant use (aRR: 0.914 (95% CI: 0.862 to 0.970)) and mortality (aRR: 0.409 (95% CI: 0.269 to 0.624)) but increased the risk of sepsis (aRR: 1.416 (95% CI: 1.018 to 1.969)).
<b>Diguisto, C et al., 2020<sup>8</sup></b>	French	Cohort study	667.567 participants	he rate of head circumference below the 5th percentile was 5.8% (n=3388) among children exposed to antenatal corticosteroids and 4.3% (n=7077) and 4.6% (n=198462), respectively, for the two unexposed groups. After adjustment, the risk of having a head circumference below the 5th percentile did not differ between the exposed group and the two control groups (aRR 1.28, 95% confidence interval [CI] 0.97-1.69) and aRR 0.91, 95% CI 0.74-1.13). We did not find an association between antenatal corticosteroids and the rate of birthweight below the 5th percent-tile. Children exposed to antenatal corticosteroids had a higher risk of a birth length below the 5th percentile when compared with those not exposed to threatened pre-term labor or corticosteroids
<b>Raikkonen, K et al., 2022<sup>9</sup></b>	Finland	Retrospective register-linkage study	670.097 participants	Compared with nonexposure in the entire population, treatment exposure was significantly associated with higher adjusted hazard ratios (aHRs) for specific developmental disorders of speech and language (aHR, 1.38 [95% CI, 1.27-1.50]; P < .001), specific developmental disorders of scholastic skills (aHR, 1.32 [95% CI, 1.13-1.54]; P = .004), specific developmental disorder of motor function (aHR, 1.32 [95% CI, 1.18-1.49]; P < .001), pervasive developmental disorder (aHR, 1.35 [95% CI, 1.17-1.56]; P < .001), other or unspecified disorder of psychological development (aHR, 1.88 [95% CI, 1.58-2.25]; P < .001), and vision or hearing loss (aHR, 1.22 [95% CI, 1.04-1.43]; P = .02).

Bae, SP *et al* (2023)<sup>7</sup> showed This study demonstrates that effect of antenatal corticosteroids on neonatal outcomes of preterm infants with very low birth weight does not differ significantly by plurality (twin or singleton pregnancy). Despite differences in demographic and clinical characteristics according to plurality, ACS therapy administered before birth had comparable positive effects on neonatal outcomes of preterm infants with VLBW regardless of plurality.

Diguisto, C *et al* (2020)<sup>8</sup> showed that they did not find an association between antenatal corticosteroids and the rates of head circumference or birthweight below under the 5th percentile but did find a higher rate of birth length below this cutoff among children born at term who received antenatal corticosteroids when compared with those whose mother had neither threatened preterm labor nor corticosteroids. Clinicians should continue to give corticosteroids whenever there is a risk of preterm birth but further studies need to be conducted to eluci-date the potential effects of antenatal corticosteroids on children born at term.

Raikkonen, K *et al* (2022)<sup>9</sup> showed Compared with nonexposure in the term-born group, treatment exposure was significantly associated with higher aHRs for specific developmental disorders of speech and language (aHR, 1.47 [95% CI, 1.31-1.66];  $P < .001$ ), specific developmental disorders of scholastic skills (aHR, 1.28 [95% CI, 1.01-1.63];  $P = .04$ ), specific developmental disorder of motor function (aHR, 1.38 [95% CI, 1.12-1.70];  $P < .001$ ), pervasive developmental disorder (aHR, 1.42 [95% CI, 1.16-1.75];  $P < .001$ ), other or unspecified disorder of psychological development (aHR, 1.92 [95% CI, 1.51-2.43];  $P < .001$ ), epilepsy (aHR, 1.57 [95% CI, 1.22-2.01];  $P < .001$ ), and cerebral palsy (aHR, 2.18 [95% CI, 1.47-3.23];  $P < .001$ ). The hazard for any psychological developmental and neurosensory disorder was significantly higher for the treatment-exposed sibling compared with the nonexposed cosibling (absolute difference, 1.2% [95% CI, 0.03%-2.4%];  $P < .001$ ; aHR, 1.22 [95% CI, 1.04-1.42];  $P = .01$ ). Antenatal corticosteroids were not associated with either significant benefit or risk in the preterm group.

## DISCUSSION

Premature birth is one of the main causes of neonatal mortality and morbidity. Even though the number of children who die before the age of 5 has reached a new minimum — 5.6 million in 2016, in comparison to almost 9.9 million in 2000 —, the proportion of these deaths in the neonatal period raised from 41 to 46% during the same period, globally.<sup>1</sup> In countries of Sub-Saharan Africa and the South of Asia, the death rates of newborns (NB) is not decreasing fast, especially regarding children aged from 1 to 5 years. As a result, newborns respond for the growing proportion of children dying every year.<sup>10</sup>

Epidemiological studies suggest that the prevalence of preterm birth is increasing, and the survival of vulnerable infants has also increased owing to recent advances in perinatal and neonatal medicine. The implementation of treatment with antenatal corticosteroids (ACS) in preterm infants as recommended in the American College of Obstetricians and Gynecologists (ACOG) guidelines has contributed to improved outcomes. ACS has become the gold standard in pregnancies at high risk of imminent preterm birth.<sup>11,12</sup>

Although the immediate benefits of antenatal corticosteroids for preterm infants are not disputed, the data on their long-term neurodevelopmental effects are inconsistent. Animal studies suggest that in utero exposure to single doses of exogenous corticosteroids may affect fetal brain development and neurologic outcomes. Theoretically, these effects could be more pronounced after 34 weeks of gestation when rapid brain growth occurs.<sup>13</sup>

Antenatal corticosteroids (ACS) are an effective intervention for improving outcomes for neonates born to women at risk of early preterm birth. They confer benefits by crossing the placenta and accelerating structural maturation of fetal lung tissue and other organs.<sup>5,6</sup> The 2020 update of the Cochrane review on ACS efficacy found that ACS use significantly reduces the risk of moderate/severe respiratory distress, perinatal death and neonatal death, and probably reduces the risk of intraventricular haemorrhage (IVH) and developmental delay in childhood.<sup>7</sup> WHO currently recommends that ACS should be administered to women between 24 and 34 weeks' gestation who are at risk of imminent preterm birth, provided that certain criteria related to a minimum level of maternal and preterm newborn care can be met.<sup>14,15</sup>

## CONCLUSION

Numerous studies have shown no evidence of long-term harm (and in fact showed improved survival and neurodevelopmental outcomes with long-term pulmonary and others benefit), particularly as it relates to a single course of corticosteroids administered at less than 34 0/7 weeks of gestation.

## REFERENCES

- [1]. Amawat J, Wirayannawat W, Boonyanunt P, Paes B, Kitsommart R. Effects of antenatal dexamethasone on postnatal serum cortisol levels in late preterm infants. *J Matern Neonatal Med* [Internet]. 2023;36(2). Available from: <https://doi.org/10.1080/14767058.2023.2224491>
- [2]. Zhao J, Feng Z, Dai Y, Zhang W, Jiang S, Wang Y, et al. Use of antenatal corticosteroids among infants with gestational age at 24 to 31 weeks in 57 neonatal intensive care units of China: a cross-sectional study. *Chin Med J (Engl)*. 2023;136(7):822–9.
- [3]. El-Sayed YY, Borders AEB, Gyamfi-Bannerman C. Antenatal Corticosteroid Therapy for Fetal Maturation. Vol. 130, *Obstetrics and Gynecology*. 2017. p. E102–9.
- [4]. Dagklis T, Sen C, Tsakiridis I, Villalaín C, Karel Allegaert, Wellmann S, et al. The use of antenatal corticosteroids for fetal maturation: Clinical practice guideline by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine foundation. *J Perinat Med*. 2022;50(4):375–85.
- [5]. Yao TC, Chang SM, Wu CS, Tsai YF, Sheen KH, Hong X, et al. Association between antenatal corticosteroids and risk of serious infection in children: nationwide cohort study. *BMJ*. 2023;382:e075835.

- [6]. Ushida T, Kotani T, Hayakawa M, Hirakawa A, Sadachi R, Nakamura N, et al. Antenatal corticosteroids and preterm offspring outcomes in hypertensive disorders of pregnancy: A Japanese cohort study. *Sci Rep.* 2020;10(1):1–10.
- [7]. Bae SP, Hahn WH, Park S, Jung YH, Park JY, Oh KJ, et al. Effects of antenatal corticosteroids on neonatal outcomes in twin and singleton pregnancies: A Korean national cohort study. *BMJ Paediatr Open.* 2023;7(1):1–9.
- [8]. Diguisto C, Arthuis C, Couderchet J, Morgan AS, Perrotin F, Rivière O, et al. Impact of antenatal corticosteroids on head circumference of full-term newborns: A French multicenter cohort study. *Acta Obstet Gynecol Scand.* 2020;99(9):1147–54.
- [9]. Räikkönen K, Gissler M, Tapiainen T, Kajantie E. Associations between Maternal Antenatal Corticosteroid Treatment and Psychological Developmental and Neurosensory Disorders in Children. *JAMA Netw Open.* 2022;5(8):E2228518.
- [10]. da Cunha AJLA, Rezende KB de C, Moreira MEL, da Gama SGN, Leal M do C. Use of antenatal corticosteroids in Brazil: Data analysis from the National Survey Nascer no Brasil. *Rev Paul Pediatr.* 2022;40.
- [11]. Yum SK, Lee JH. Dose completion of antenatal corticosteroids and neonatal outcomes in non-small-for-gestational age or small-for-gestational age very-low-birthweight infants: A Korean population-based cohort study. *Pediatr Neonatol [Internet].* 2022;63(2):165–71. Available from: <https://doi.org/10.1016/j.pedneo.2021.08.020>
- [12]. Frier EM, Lin C, Reynolds RM, Allegaert K, Been J V., Fraser A, et al. Consortium for the Study of Pregnancy Treatments (Co-OPT): An international birth cohort to study the effects of antenatal corticosteroids. *PLoS One.* 2023;18(3 March):1–27.
- [13]. Reddy UM, Deshmukh U, Dude A, Harper L, Osmundson SS. Society for Maternal-Fetal Medicine Consult Series #58: Use of antenatal corticosteroids for individuals at risk for late preterm delivery: Replaces SMFM Statement #4, Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery, August 2016. *Am J Obstet Gynecol [Internet].* 2021;225(5):B36–42. Available from: <https://doi.org/10.1016/j.ajog.2021.07.023>
- [14]. McDougall ARA, Aboud L, Lavin T, Cao J, Dore G, Ramson J, et al. Effect of antenatal corticosteroid administration-to-birth interval on maternal and newborn outcomes: a systematic review. *eClinicalMedicine [Internet].* 2023;58:101916. Available from: <https://doi.org/10.1016/j.eclinm.2023.101916>
- [15]. Razaz N, Allen VM, Fahey J, Joseph KS. Antenatal Corticosteroid Prophylaxis at Late Preterm Gestation: Clinical Guidelines Versus Clinical Practice. *J Obstet Gynaecol Canada [Internet].* 2023;45(5):319–26. Available from: <https://doi.org/10.1016/j.jogc.2023.03.003>