ORIGINAL RESEARCH

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A Fight for Survival: Repeated and Single-Dose Corticosteroids in Preterm Births: A Systematic Review and Meta-Analysis of Neonatal and Maternal Health Outcomes

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This study was presented as a poster at the PIT POGI 27th (Annual Scientific Meeting Indonesian Society of Obstetricians and Gynecologists)-Symposium Culture, Tradition, and Digital Challenge in Maternal Care, July 22-24, 2024, Indonesia.

ABSTRACT Objective: The administration of corticosteroids, whether as a single or repeated dose, remains controversial due to its implications for reducing side effects in neonates and its impact on maternal morbidity and mortality. **Material and Methods:** We searched PubMed, ScienceDirect, WileyOnline, CENTRAL, and ClinicalTrials.gov for randomized controlled trials published between January 2000-March 2024. The studies assessed the neonatal and maternal outcomes of repeated corticosteroid administration (24 mg betamethasone or dexamethasone as rescue or weekly dose) after an initial 24 mg course in preterm pregnancies. A random effects model was used for statistical analysis. **Results:** A meta-analysis of 13 trials involving 5,246 pregnant women and 5,960 neonates found that repeated corticosteroid administration significantly reduced the risks of respiratory distress syndrome [relative risk (RR) 0.96, 95% confidence interval (CI) 0.78-0.95], oxygen supplementation (RR 0.93, 95% CI 0.87-0.99), mechanical ventilation (RR 0.80, 95% CI 0.72-0.89), and surfactant use (RR 0.76, 95% CI 0.68-0.86). However, it was associated with lower birth weights [mean birth weight (MD)-85.67 g, 95% CI -141.94 to -29.41] and increased maternal chorioamnionitis (RR 1.26, 95% CI 1.03-1.54). No significant differences were observed for maternal endometritis, hypertensive complications, adverse events, or latency intervals. **Conclusion:** Repeated corticosteroid administration reduces respiratory-related diseases in newborns but increases the risk of low birth weight and chorioamnionitis.

Keywords: Corticosteroid; repeated-dose; single-dose; preterm birth; side effects

Preterm birth, defined as delivery before 37 completed weeks of gestation, is a significant contributor to neonatal mortality, accounting for 24% of such deaths.[1,2] The etiology of preterm birth is multifactorial, encompassing maternal infections, uterine overdistension, and placental abnormalities.[3] Additionally, sociodemographic factors such as ethnicity, maternal age, smoking habits, educational attainment, nulliparity, and access to healthcare services also play a crucial role in the incidence of preterm birth.[4] The main reason that causes high morbidity in preterm neonates is respiratory distress syndrome and asphyxia neonatorum as the result of immature lung function. Other adverse events such

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as intraventricular hemorrhage and necrotizing enterocolitis sometimes occur.[5,6] The use of corticosteroids is then relied upon to prevent premature neonatal morbidity.

Corticosteroids are widely used in the management of preterm birth to accelerate fetal lung maturation and reduce the risk of neonatal complications. Administration of corticosteroids between 24-34 weeks of gestation significantly decreased the incidence of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death. The most commonly used corticosteroids for this purpose are betamethasone and dexamethasone, administered in 2 doses 24 hours apart.[7] The benefits of corticosteroid treatment have led to its recommendation as a standard practice in obstetric care for women at risk of preterm delivery, whether it is iatrogenic or spontaneous.[8] Respiratory distress in neonates is proven to be reduced with the use of corticosteroids in pregnant women who give birth at 24 hours until 7 days of administration [relative risk (RR) 0.46, 95% confidence interval (CI) 0.35-0.60, 9 studies, 1,110 infants]. Some studies revealed that there is no significant adverse effect like sepsis both in the maternal and neonatal groups after a single course administration of corticosteroids.[9]

A study in the United Kingdom (UK) elaborated that 74% of UK maternity units give repeated administration of corticosteroids every 7-10 days for women with preterm birth that remain undelivered since the comparison with the single course of corticosteroids showed that the infants still underwent a respiratory distress. Otherwise, adverse effects such as altered glycaemic control, fluid overload, neurological disturbances, and others are probably a concern.[10] Since it is still controversial, this study aimed to elaborate on the comparison of single and repeated administration of corticosteroids as a preventive treatment for preterm birth.

MATERIAL AND METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.

This study did not require ethics committee approval as it is a secondary analysis/systematic review and did not involve human or animal subjects.

ELIGIBILITY CRITERIA

Criteria of the eligible study were following (i) randomized control trial, (ii) women at risk of preterm birth, (iii) had received a single dose of prenatal corticosteroid at least 7 days before, (iv) following with either the 2nd or more dose of prenatal corticosteroid or placebo, (v) reported at least one of our outcomes of interest. We excluded (i) the quasirandom study and (ii) the animal study.

DATA SOURCES AND SEARCHES

We systematically searched PubMed, WileyOnline, ScienceDirect, Cochrane Register of Controlled Trials, and clinicaltrial.gov for articles published from January 2000 until March 2024. Search terms used specific keywords for each database (Table 1). Furthermore, we searched the reference list of other reviews and trials. We are restricted to English publication only.

STUDY SELECTION

Two review authors (ERSP and NLPYD) independently appraised the titles and abstracts of the retrieved articles. Full-text articles were evaluated for eligibility without considering their results. Any disagreements regarding eligibility were discussed with the 3rd author (RRW). There was no authorship blinding. We did not apply automation tools for the selection of studies.

DATA EXTRACTION AND MANAGEMENT

Data extraction was accomplished by 2 review authors (ERSP and NLPYD) using a pre-design data form on Google Sheets (Google Spreadsheet, Google LCC, California, US). The extracted data consisted of the study characteristics and study outcomes, including maternal and neonatal outcomes. Any discrepancies were resolved by discussion. The data were entered into the Review Manager Website (https://revman.cochrane.org/).

TABLE 1: Characteristic of studies

Trial	Participant	Interventions	Comparator	Outcome
Aghajafari 2002	12 pregnant women, 9 babies	Betamethasone (Celestone Soluspan; Schering Canada Inc.) 2x12 mg given every 24 hrs IM, repeated weekly in participants who remained at high risk of preterm birth.	Normal saline, 2 doses given every 24 hrs IM. Repeated weekly in participants who remained at high risk of preterm birth.	**Primary:** Mortality and morbidity in perinatal or neonatal patients [respiratory distress syndrome (RDS), IVH [gr 3 or 4], PVL, BPD, and NEC). **Secondary neonatal:** Birth anthropometry (weight, length, and head circumference), neonatal infection, ROP, stay period in NICU, ventilation with intubation usage, and PDA that require pharmacological or surgical treatment **Secondary maternal:** Chorioamnionitis and maternal infection after giving birth.
Crowther 2006,	982 pregnant women, 1,142 babies	Betamethasone 11.4 mg (Celestone Chronodose with 7.8 mg betamethasone sodium phosphate and 6 mg betamethasone acetate) repeated weekly to those remained at risk of preterm birth until <32 weeks	Saline placebo, repeated weekly	**Primary:** Frequency and severity of RDS, Severity of the respiratory disease showed, usage and duration of oxygen treatment, ventilation with endotracheal tube (including high frequency ventilation), birth and at discharge anthropometry (weight, length, and head circumference) **Secondary:** Intrapartum antibiotics administration due to clinical chorioamnionitis, maternal elevated temperature >38 °C after delivery, maternal side effect presented from injection (pain/discomfort, maternal distress, haematoma, rash, sleeplessness, lethargy, etc), and other neonatal morbidity (IVH, PVL, ROP, etc)
Church 2010	49 pregnant women, 60 babies	Betamethasone (Betamethasone phosphate 6 mg and Betamethasone acetate 6 mg) 2x12 mg given 24 hrs apart, IM. If remained high risk of preterm birth, betamethasone continued given weekly until 33 weeks 6 days of gestation or until delivery whichever comes 1st with maximum given 4 courses.	Normal saline, isovolumetric, weekly injection.	**Primary:** Neonatal auditory brainstem response **Secondary:** Neonatal anthropometry (weight, length, and head circumference), neonatal morbidity (NICU stay, oxygen therapy, RDS, NEC, etc)
Garite 2009	437 pregnant women, 577 babies	additional betamethasone 12 mg IM in 2 dose given 24 hours apart after 14 days of 1st course betamethasone	Placebo	Composite morbidity, RDS, BPD, surfactant, ventilator, ROP, IVH, NEC, Sepsis, perinatal death, pneumothorax, PVL, pneumonia, intrauterine growth restriction
Guinn 2001	502 pregnant women, 485 babies	additional betamethasone 12 mg IM in 2 dose given 24 hours apart after 7 days of first course betamethasone	Placebo	RDS, BPD, severe IVH, periventricular leukomalacia, proven sepsis, necrotizing enterocolitis, or perinatal death
Lee 2004, United States	161 pregnant women, 154 babies	Betamethasone 24 mg (12 mg IM every 24 hrs) within 48 hrs weekly until birth.	Saline placebo administered within 48 hrs weekly until birth.	Severe RDS, bronchopulmonary dysplasia, severe intraventricular hemorrhage, periventricular leukomalacia, proven NEC, proven sepsis, perinatal death Latency interval Infectious, antepartum antibiotic prophylaxis administration, clinical chorioamnionitis, endometritis, neonatal sepsis
Mazumder 2008	76 pregnant women, 83 babies	multiple dose of betamethasone (12 mg 24 hourly for 2 dose) after 7 days of first course of steroid until delivery or 34 weeks of gestation	Placebo	RDS, IVH, NEC, PDA, BPD, sepsis, and ROP, occipitofrontal circumference, weight, and length at birth
McEvoy 2002	37 pregnant women, 37 babies	Betamethasone 24 mg (12 mg IM every 24 hrs) weekly until delivery or 34 weeks of gestation	Placebo	Admission head circumference, oxygen therapy at the time of study, days on intermittent mandatory ventilation, days on oxygen, baseline cortisol, cortisol at 30 min
Murphy 2008	1858 pregnant women, 2304 babies	two dose of 12 mg betamethasone 24 hours apart	Placebo	Stillbirth or neonatal death, severe RDS, BPD, severe IVH, cystic PVL, NEC, birth weight, length at birth, mean head circumference , APGAR score, major life threatening anomaly, receiving supplementation oxygen after initial resuscitation, intubation and ventilator, surfactant given, neonatal infection (sepsis, meningitis, pneumonia), seizure before discharge, PDA, ROP, admitted to NICU
Peltoniemi 2007	249 pregnant women, 326 babies	1 additional dose of betamethasone 2x12 mg	Placebo	survival without RDS or severe IVH, birth weight, head circumference, length, apgar score at 1 minutes and 5 minutes, neonatal death. surfactant therapy, ventilator support, PDA, NEC, ROP, BPD
Porreco 2023 United States	194 pregnant women, 192 infants	2 dosage of 12 mg betamethasone for 24 hour apart or 4 dose of 6 mg dexamethasone 12 hours apart	Placebo	RDS, BPD, IVH grade 3-4, periventricular leukomalacia, sepsis, necrotizing enterocolitis, neonatal death, birth weight, head circumference, ventilator use, surfactant, O2 supplementation, ROP, PDA, ASD, 5-min APGAR score
Sawady 2007	194 pregnant women	2 dose of 12 mg betamethasone in 24 hours apart, weekly	Placebo	Latency to delivery. birth weight, PPROM, preterm delivery. clinical chorioamnionitis. preeclampsia/ gestational hypertension, postpartum endometritis
Wapner 2006	495 pregnant women, 591 infants	2 dose of 12 mg betamethasone (as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate), weekly	Placebo	Maternal side effect, latency from randomization to delivery, clinical chorioamnionitis, postpartum endometritis, PPROM, preterm birth, severe RDS, ventilator support, BPD, pneumothorax, IVH, seizure, ROP, PDA, sepsis, pneumonia, NEC

Complete course of Antenatal Corticosteroid: 2 doses of betamethasone 24 mg (12 mg IM every 24 hrs) or dexamethasone 24 mg (6 mg every 12 hrs) within 48 hrs; IM: Intramuscular; IVH: Intraventricular Hemorrhage; PVL: Periventricular Leukomalacia; BPD: Bronchopulmonary Dysplasia; NEC: Necrotizing Enterocolitis; PPROM: Preterm Premature Rupture of Membranes

RISK OF BIAS ASSESSMENT

Two review authors (ERSP and NLPYD) independently evaluated the risk of bias based on the risk of bias assessment by Cochrane Risk of Bias-1 (RoB1) for each study. The risk of bias was rated as low, unclear, or high for each study. Any discrepancies were discussed with the 3rd author (RRW).

SPECIFICATION OF THE OUTCOME AND EFFECT MEASUREMENT

The primary outcome for neonatal was respiratory aspect including respiratory distress, severe respiratory distress as defined per study, use of mechanical ventilation, using oxygen support, treatment with surfactant, and bronchopulmonary dysplasia. The secondary outcomes were for all stages of intraventricular hemorrhage, proven necrotizing enterocolitis, all stages of retinopathy of prematurity, proven patent ductus arteriosus, perinatal death, and birth weight.

The primary outcomes for the woman were chorioamnionitis and endometritis both clinically or definite. The secondary outcome was worsening of hypertension or preeclampsia and adverse events of corticosteroid use.

STATISTICAL ANALYSIS

The statistical analysis was conducted by using the Review Manager Website (Cochrane Review Manager, London). All the outcome data available were included in the analysis. Binary outcomes were analyzed using the random-effects model inverse variant and presented as relative risk (RR) with 95% CI and 2-sided p-value. Continuous outcomes are presented as mean differences with 95% CI and associated 2-sided p value. To evaluate the collective heterogeneity of each set of outcome data, we applied the chi-square and I2 test, whereby an I2 value of more than 50% and a p-value below 0.05 indicated substantial heterogeneity. Publication bias was assessed using a funnel plot, with pronounced asymmetry indicating significance.

RESULTS

STUDY SELECTION

A total of 274 studies from 5 databases were screened for the title. After removing the duplicate, non-randomized controlled trials (non-RCT) studies, and not human subjects, 55 studies were evaluated for eligibility based on the full text review. A total of 24 studies were excluded due to reporting secondary outcome of previous studies, not reporting outcome of interest, and not comparing repeated and single dose of corticosteroid. We also reviewed citation searching and found 3 potential studies. However, one of them did not report our outcome of interest. Therefore, 13 studies were eligible for our meta-analysis, as mentioned in Figure 1, Table 1.

RISK OF BIAS ASSESSMENT

Risk of bias was performed based on Risk of Bias-1 (RoB1), and the result is elaborated in Figure 2. Nine studies have adequate randomization processes that are implicitly written in the protocol. Four studies did not report computer-generated randomization. Thus, we declare it as unclear. All studies have an adequate allocation of concealment by using identical opaque, sealed envelopes for both placebo and intervention. All studies used a placebo for blind participants and caregivers, except for Mazumder 2006. Six studies did not provide details for blinding of outcome assessors. Three studies reported a loss of follow-up of more than 20%, stated at Peltoniemi, 2007, Wapner, 2006, and Mazumder, 2008. Only one study reported insufficient detail of selective outcome reporting. Three studies stopped recruitment due to "safety concern" stated at Guinn, 2002, Peltoniemi, 2007, and Wapner, 2006.

NEONATAL OUTCOME

Primary Outcome

Nine trials reported respiratory distress outcomes in newborns, with detailed results shown in Figure 3. There was a significant reduction of respiratory distress with the RR 0.68 (0.78-0.95), p=0.003. The heterogeneity was low, with an I^2 of 10% and a p value of 0.35, as shown in Figure 3.

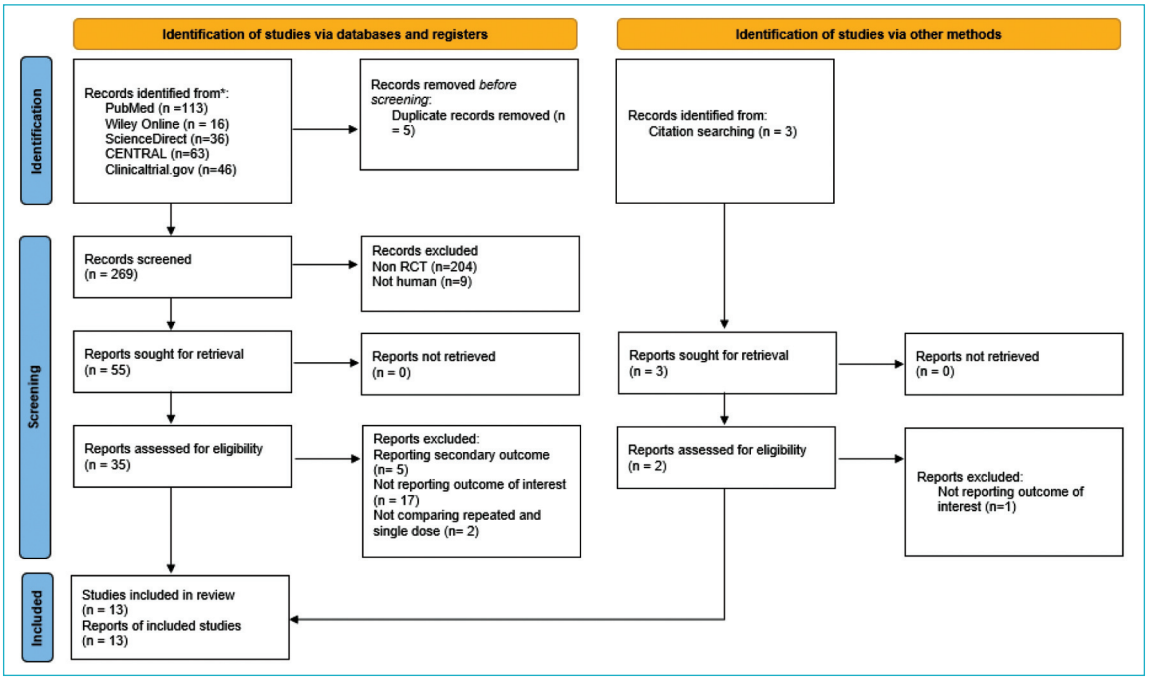

FIGURE 1: Flow diagram for the selection of included studies

There was no significant difference in severe respiratory distress reduction in newborns with the RR 0.75 (0.53-1.04), p =0.08, 7 trials. The heterogeneity was high, with I^2 of 76% and a p value of 0.0003, as shown in Figure 4.

There was a significant difference in oxygen supplementation in newborns with the RR 0.93 (0.87-0.99), p value=0.02, 4 trials. The heterogeneity was low, with I^2 0% and p value 0.73, as shown in Figure 5.

There was a significant difference in mechanical ventilator use in newborns with the RR 0.80 (0.72-0.89), p<0.0001, 4 trials. The heterogeneity was low, with an I^2 of 0% and a p value of 0.77, as shown in Figure 6.

There was a significant difference in surfactant treatment in newborns with the RR 0.76 (0.68-0.86), p<0.0001, 5 trials. The heterogeneity was low, with I^2 0% and a p value of 0.74, as shown in Figure 7.

There was no significant difference in bronchopulmonary dysplasia in newborns with the RR 0.96 (0.69-1.34), p value=0.82, eight trials. The heterogeneity was moderate, with an I^2 of 48% and a p value of 0.06, as shown in the supplementary page.

Secondary Outcome

There was a significant difference in birth weight with the MD 85.67 (-141.94 to -29.41), p=0.003, 5 trials. The heterogeneity was low, with an I^2 of 24% and a p value of 0.22, as shown in Figure 8.

There was no significant difference in the incidence of sepsis in newborns with the RR 1.18 (0.94-1.49), p=0.15, 10 trials. The heterogeneity was low, with an I^2 of 0% and a p value of 0.58, as shown in the supplementary page.

There was a significant difference in surfactant treatment in newborns with the RR 0.76 (0.68-0.86), p<0.0001, 5 trials. The heterogeneity was high, with an I^2 of 0% and a p value of 0.74, as shown in the supplementary page.

There was no significant difference in perinatal death with the RR 0.82 (0.59-1.13, p=0.22, 7 trials.

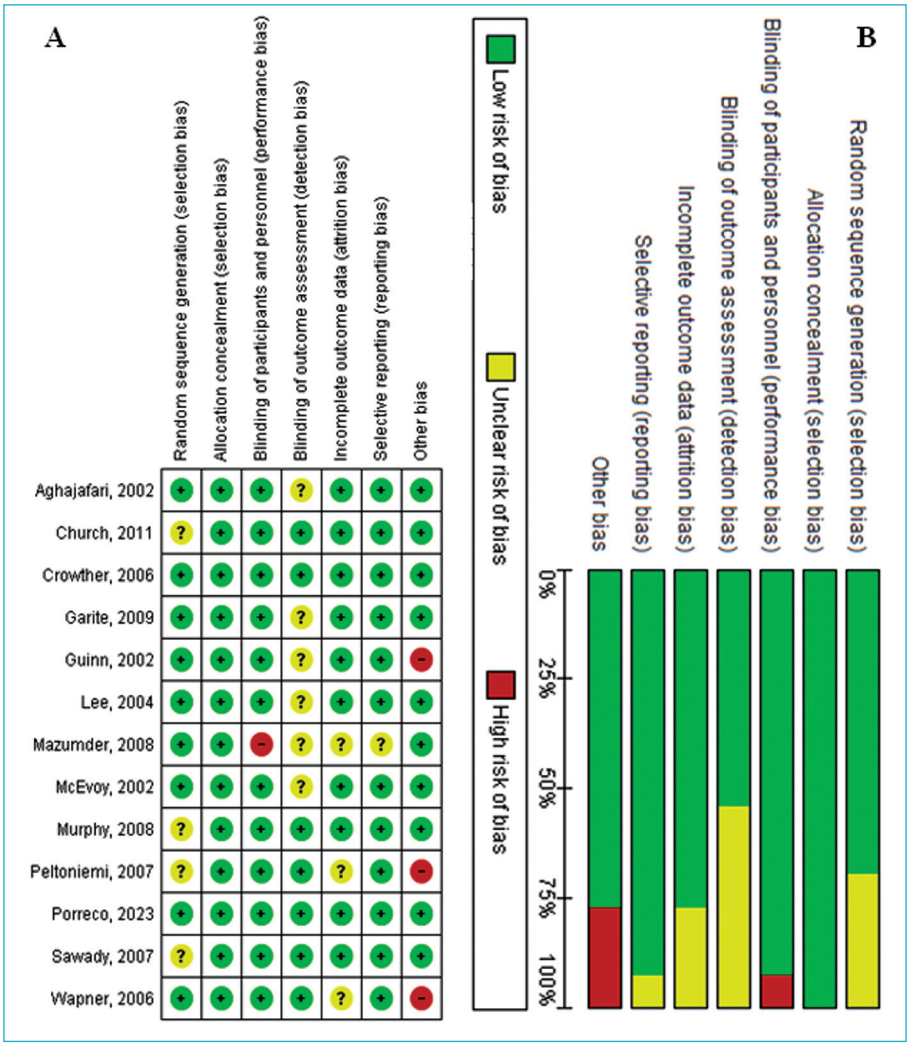

FIGURE 2: **(A)** Risk of bias summary; **(B)** Risk of bias graph

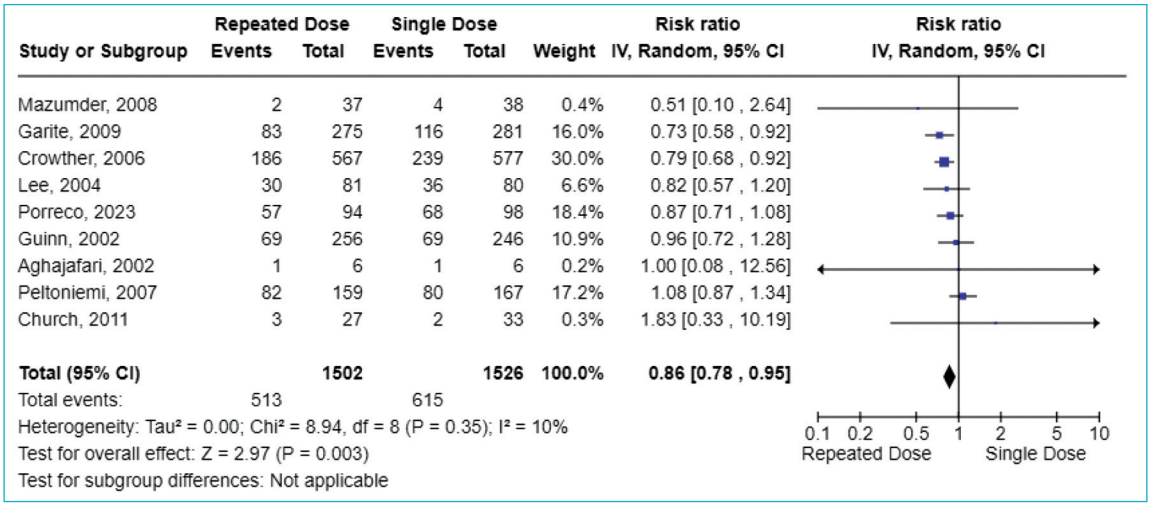

FIGURE 3: Respiratory distress
CI: Confidence interval

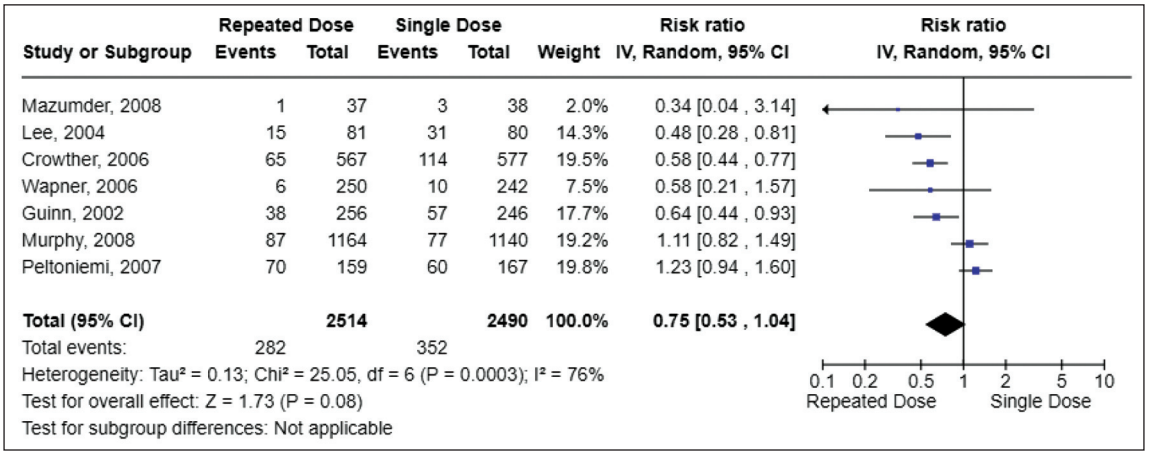

FIGURE 4: Severe respiratory distress
CI: Confidence interval

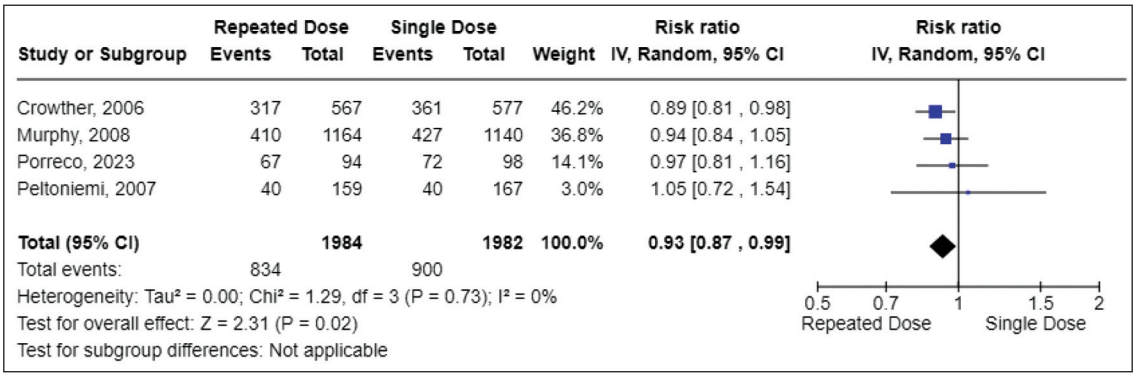

FIGURE 5: Oxygen supplementation
CI: Confidence interval

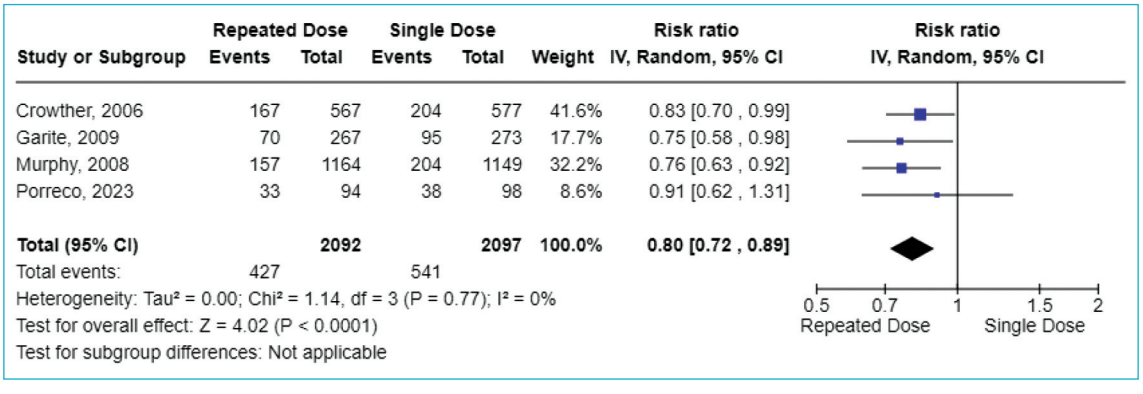

FIGURE 6: Mechanical ventilator
CI: Confidence interval

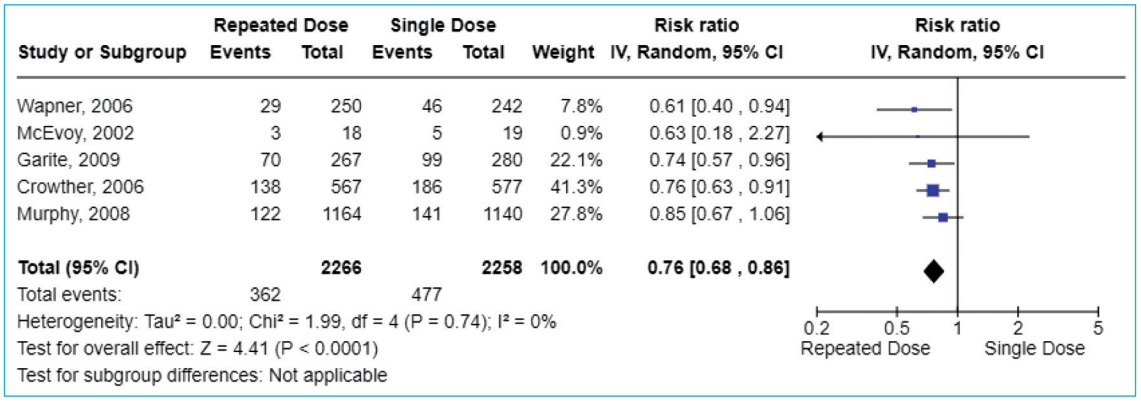

FIGURE 7: Surfactant treatment

CI: Confidence interval

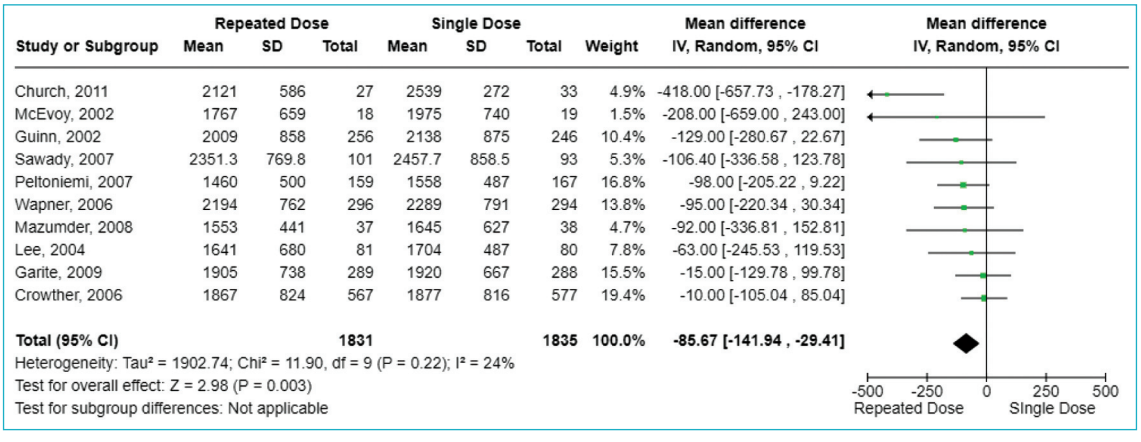

FIGURE 8: Birth weight

CI: Confidence interval

The heterogeneity was low, with an I^2 of 0% and a p value of 0.72, as shown in the supplementary page.

There was no significant difference in the patent ductus arteriosus with the RR 0.82 (0.63-1.07, p=0.15, 8 trials. The heterogeneity was low with I^2 of 21% and a p value of 0.26, as shown in the supplementary page.

There was no significant difference in retinopathy of prematurity with the RR 0.97 (0.77-1.21, p=0.77, 9 trials. The heterogeneity was low, with an I^2 of 0% and a p value of 0.78, as shown in the supplementary page.

There was no significant difference in intraventricular hemorrhage with the RR 0.89 (0.69-1.15, p=0.37, 7 trials. The heterogeneity was low, with an I^2 of 0% and a p value of 0.74, as shown in the supplementary page.

MATERNAL OUTCOME

Primary Outcome

There was a significant difference in chorioamnionitis with the RR 1.26 (1.03-1.54, p=0.02, 7 trials. The heterogeneity was low, with an I^2 of 0% and a p value of 0.83, as shown in Figure 9.

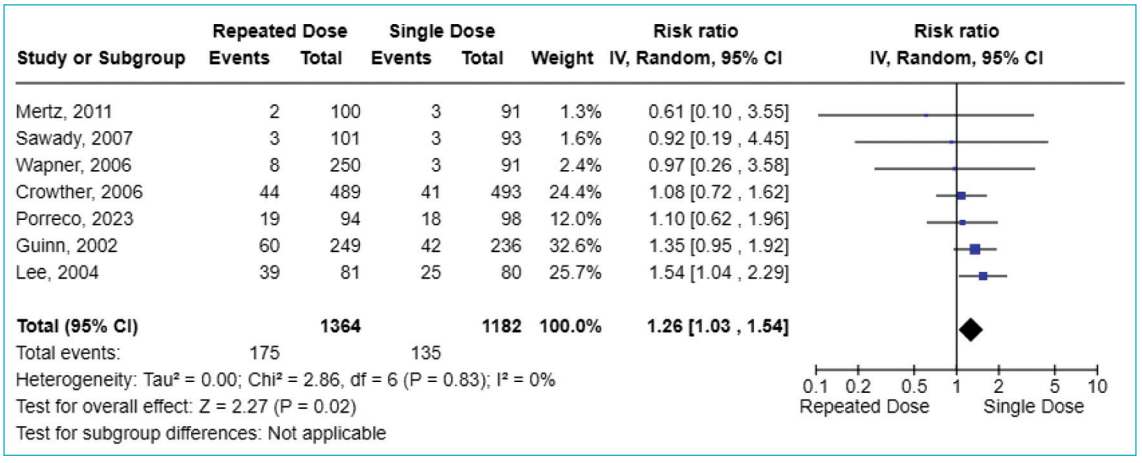

FIGURE 9: Chorioamnionitis

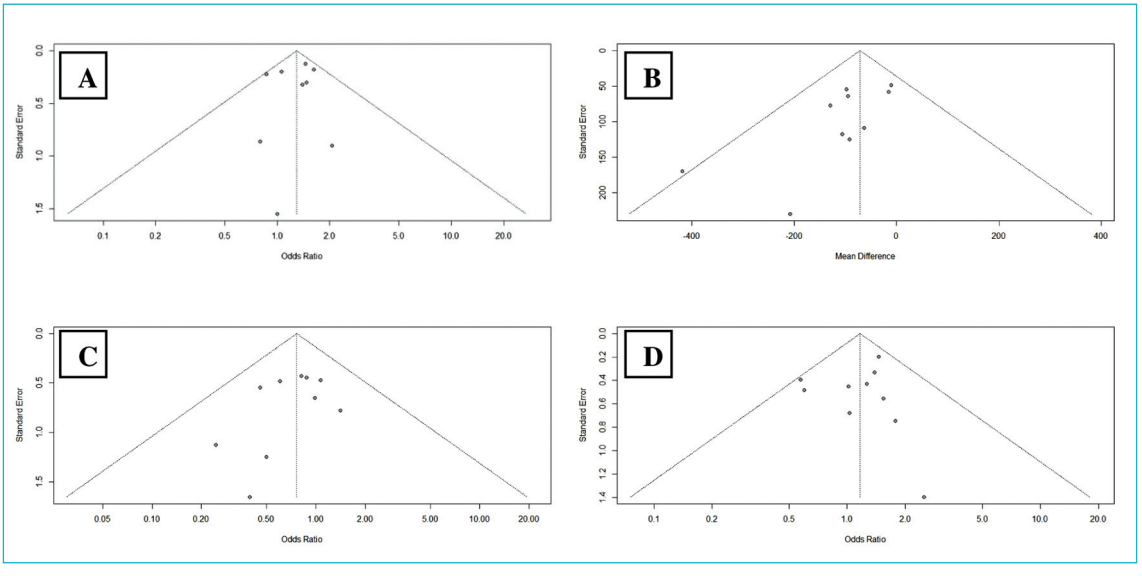

FIGURE 10: (**A**) Funnel plot of respiratory distress (Egger's test gave value of 0.631); (**B**) Funnel plot of birth weight (Egger's test gave p value of 0.035); (**C**) Funnel plot of necrotizing enterocolitis (Egger's test gave p value of 0.287); (**D**) Funnel plot of sepsis (Egger's test gave p value of 0.611)

There was no significant difference in endometritis with the RR 1.01 (0.57-1.77, p=0.98, 6 trials. The heterogeneity was moderate, with an I^2 of 34% and a p value of 0.18, as shown in the supplementary page.

Secondary Outcome

There was no significant difference in the latency interval with the mean difference -0.10 (-4.26 to 4.07), p=0.96, 2 trials. The heterogeneity was low, with an I^2 of 0% and a p value of 0.72, as shown in the supplementary page.

There was no significant difference in worsening hypertension or preeclampsia with the RR 1.18 (0.90-1.55) p=0.22 in 3 trials. The heterogeneity was low, with an I^2 of 0% and a p value of 0.22, as shown in the supplementary page.

There was no significant difference in adverse events with the RR 0.96 (0.25-3.70) p=0.95 in 3 trials. The heterogeneity was high, with an I^2 of 96% and p<0.0001, as shown in the supplementary page.

Publication Bias

Publication bias assessment was conducted by analysis of the funnel plot and Egger's test. There was no significant publication bias shown on respiratory distress, necrotizing enterocolitis, and sepsis parameters. However, there was a significant publication bias on birth weight outcomes, as mentioned in Figure 10.

DISCUSSION

The use of corticosteroids in preterm birth treatment presents a dilemma between single- and repeated-dose administration. While a single course of corticosteroids significantly reduces neonatal complications such as respiratory distress syndrome, intraventricular hemorrhage, and neonatal mortality, the benefits may diminish over time, raising the question of whether additional doses are necessary. Current guidelines recommend a single course of corticosteroids with repeat doses considered at approximately 3-week intervals if the risk of preterm birth persists, balancing efficacy and safety.[11] However, several studies have shown that repeated doses of corticosteroids can provide better outcomes in reducing respiratory distress syndrome, suggesting that ongoing benefits can be sustained with carefully monitored additional courses.[11] This ongoing debate highlights the need for individualized treatment plans based on the specific circumstances and risks faced by the mother and fetus. Several studies have been conducted to evaluate the efficacy and safety of repeated corticosteroid doses for preterm birth; however, ongoing RCTs necessitate updated meta-analyses to incorporate new data and provide more comprehensive and current evidence for clinical guidelines.

This study shows the reduced incidence of respiratory distress syndrome (RDS), oxygen supplementation, mechanical ventilation, and surfactant treatment, which all correlate with the lung functions of the preterm birth. This study aligned with Crowther et al. who stated a significant reduction of RDS after repeated administration of corticosteroids in preterm birth [Risk ratio (RR) 0.83, 95% confidence interval (CI) 0.75 to 0.91].[11] The use of corticosteroids is believed to reduce the evidence of respiratory distress in preterm birth. Antenatal corticosteroids facilitate fetal lung maturation by enhancing surfactant production and promoting fluid absorption in the fetal lungs through the upregulation of epithelial sodium channels and pulmonary beta-adrenergic receptors, which improves gas exchange and lung compliance.[12]

However, repeated corticosteroid administrations increase the risk of low birth weight as aligned with Crowther et al. which has a mean difference of mean birthweight-75.79 g, 95% CI -117.63 to -33.96.[11] Repeated doses of corticosteroids during preterm birth have been associated with low birth weight, primarily due to its impact on fetal growth. Corticosteroids, such as betamethasone and dexamethasone, are administered to accelerate fetal lung maturation and reduce the risk of neonatal respiratory distress syndrome. However, these corticosteroids also have catabolic effects, which can inhibit fetal growth by reducing cell proliferation and increasing apoptosis in developing tissues. This inhibition of cellular growth and differentiation can reduce overall fetal growth, resulting in lower birth weights. Additionally, corticosteroids can impact the regulation of the hypothalamic-pituitary-adrenal axis, further influencing fetal growth parameters and leading to intrauterine growth restriction.[13]

Our study also showed a significant correlation between repeated corticosteroid administration and chorioamnionitis. In contrast, Crowther et al. had no significant result in chorioamnionitis (RR 1.16, 95% CI 0.92-1.46).[11] Currently, the correlation between them is still debatable. It is argued that repeated corticosteroids might impair the inflammation response and alter the maternal immune system, leading to an infection. A premature ruptured membrane is also considered to increase the risk of chorioamnionitis.

LIMITATIONS

In this study, we cannot conduct a subgroup analysis due to the limited number of studies. Moreover, the sensitivity analysis was also not completed regarding not all variables consisting of a minimum of 10 journals. Publication bias also obtained at the birthweight variable where it is significantly tended to discuss the lower result.

CONCLUSION

Repeated administration of corticosteroids in preterm births is highly effective in reducing the incidence and severity of respiratory-related diseases in newborns, particularly neonatal respiratory distress syndrome, by promoting fetal lung maturation. However, this therapeutic strategy is not without risks; it has been associated with an increased likelihood of low birth weight and the development of chorioamnionitis. The immunosuppressive and anti-inflammatory properties of corticosteroids, while beneficial for respiratory outcomes, may contribute to these adverse effects by impairing the maternal immune response, altering the vaginal flora, and compromising the integrity of the fetal membranes, thereby increasing susceptibility to infection. These findings underscore the need for a balanced approach in the administration of corticosteroids, carefully weighing the benefits of respiratory disease prevention against the potential risks of infection and growth restriction.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Erlinda Rhestu Syah Putri, Ni Luh Putu Yunia Dewi, Robby Rinaldi Widodo;* ***Design:*** *Erlinda Rhestu Syah Putri, Ni Luh Putu Yunia Dewi;* ***Control/Supervision:*** *Erlinda Rhestu Syah Putri, Ni Luh Putu Yunia Dewi, Robby Rinaldi Widodo;* ***Data Collection and/or Processing:*** *Erlinda Rhestu Syah Putri, Ni Luh Putu Yunia Dewi;* ***Analysis and/or Interpretation:*** *Erlinda Rhestu Syah Putri, Ni Luh Putu Yunia Dewi;* ***Literature Review:*** *Erlinda Rhestu Syah Putri, Ni Luh Putu Yunia Dewi;* ***Writing the Article:*** *Erlinda Rhestu Syah Putri, Ni Luh Putu Yunia Dewi;* ***Critical Review:*** *Erlinda Rhestu Syah Putri, Ni Luh Putu Yunia Dewi, Robby Rinaldi Widodo.*

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