Reproductive Health

STUDY PROTOCOL

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Double-blind, non-inferiority, randomized controlled trial of dexamethasone 4, 5 and 6 mg for preventing adverse neonatal and maternal outcomes in very preterm to late preterm pregnancies between 29^{0} and 36^{6} weeks of gestation: study protocol

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Abstract

Background Premature birth poses significant health challenges, including respiratory distress syndrome (RDS). Corticosteroids reduce the incidence of RDS, but higher dexamethasone doses may lead to adverse neonatal outcomes, such as growth restriction and neurodevelopmental issues. Determining the appropriate dose is crucial to balance efficacy and safety. Dexamethasone is inexpensive and widely available in most low- and middle-income countries. This study aims to compare the efficacy and safety of 4-mg, 5-mg and 6-mg dexamethasone in preventing RDS among preterm infants. This trial aims to determine whether lower dexamethasone doses are as effective as the standard dose in preventing RDS in preterm infants. By assessing efficacy and potential adverse outcomes, this study will provide critical insights for optimizing treatment protocols and improving neonatal care.

Methods This randomized controlled trial will include pregnant women with gestational ages between 29^{0} and 36^{6} weeks admitted to Siriraj Hospital and three secondary centres in Thailand. The participants will be randomly assigned to receive intramuscular dexamethasone at 4 mg, 5 mg or 6 mg, which will be administered every 12 h for a total of four doses over 48 h. The same dose will be used for rescue or repeat courses. The primary outcome will be the incidence of RDS, defined by clinical criteria and confirmed by a neonatologist. The secondary outcomes will include other adverse neonatal and maternal outcomes.

Results The study requires 1,560 participants, accounting for a 15% loss to follow-up. The data will be analysed via descriptive statistics, chi-squared tests for categorical data, and one-way ANOVA or Kruskal–Wallis tests for continuous data. An independent Data Safety Monitoring Board will conduct interim analyses every 3 months to ensure participant safety and study integrity.

Discussion This trial addresses the gap in research regarding optimal dexamethasone dosing for preventing RDS in preterm infants. The study will provide evidence on whether lower doses of dexamethasone (4 and 5 mg) are

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as effective as the standard 6-mg dose and will examine their potential adverse outcomes. The results will guide adjustments to medical practice guidelines, aiming to align them with clinical practices while ensuring safety and efficacy.

Trial registration page https://www.thaiclinicaltrials.org/export/pdf/TCTR20220511003 10/05/2022.

Keywords 4-mg dose, 5-mg dose, 6-mg dose, Antenatal corticosteroids, Apnoea, Dexamethasone, Dose–response, Hypoglycaemia, Late preterm, Moderately preterm, Prematurity, Preterm birth, Respiratory distress syndrome, Transient tachypnoea

Background

The importance of antenatal corticosteroids

Steroids or glucocorticoids have been widely used to prevent respiratory distress syndrome (RDS) in neonates at high risk of preterm birth. These agents have demonstrated effectiveness in reducing morbidity and mortality in premature infants [1]. Glucocorticoids cross the placenta and induce surfactant formation, which has been shown to reduce RDS and prevent intraventricular haemorrhage and necrotizing enterocolitis in premature infants [2].

Currently, institutions worldwide, including the National Institutes of Health, the Royal College of Medicine, the American College of Obstetricians and Gynecologists [3] and others [4–6], recommend steroid administration for the prevention of RDS in neonates at high risk of preterm birth. Two steroids are commonly used: betamethasone and dexamethasone. Dosing is based on the infant's glucocorticoid concentration. Compared with the physiological stress dose of cortisol observed in premature infants with RDS, the recommended steroid dosage results in 75–80% glucocorticoid receptor occupancy, which is sufficient to stimulate lung function [7].

Higher doses or increased frequencies of glucocorticoid administration have not shown additional benefits in stimulating lung function. Moreover, they may cause potential adverse effects, including adrenal insufficiency, foetal growth restriction and increased risk of infection due to excessive immunosuppression [8].

The impact of preterm birth on health and quality of life

Caring for preterm babies poses significant public health and financial challenges, and preterm birth adversely affects the quality of life for both newborns and their families [9–13]. Each year, approximately 15 million infants are born prematurely worldwide, with prematurity defined as birth before 37 weeks of gestation [14]. In 2020, an estimated 2.4 million newborns died, with 0.88 million of these deaths due to complications arising from premature birth [4, 15, 16].

The complications include respiratory distress syndrome (RDS), necrotizing enterocolitis, intraventricular haemorrhage, sepsis, bronchopulmonary dysplasia and retinopathy of prematurity [17–19]. RDS, a frequent short-term complication in preterm infants, results from underdeveloped foetal lungs and insufficient surfactant production [20, 21]. As gestational age increases, lung development and surfactant production improve, leading to a decreased incidence of RDS [22, 23].

Benefits of corticosteroids in preventing preterm complications

Corticosteroids are frequently administered to mothers at risk of preterm delivery to prevent RDS. These drugs significantly reduce mortality and morbidity in preterm newborns, lowering foetal morbidity by 15%, neonatal morbidity by 21%, neonatal RDS by 28% and intraventricular haemorrhage by 42% [24]. Importantly, the use of corticosteroids does not increase maternal morbidity, chorioamnionitis or postpartum endometritis [24].

Corticosteroids enhance neonatal outcomes through various mechanisms, particularly by promoting surfactant production [8, 25–33] and the maturation of multiple organ systems, including the respiratory, gastrointestinal and central nervous systems [29, 30]. Additionally, corticosteroids help reduce the incidence of intraventricular haemorrhage [24, 30, 34–37] and necrotizing enterocolitis [38–40].

Use of dexamethasone and betamethasone to prevent neonatal RDS and other adverse outcomes

Many international organizations recommend the use of dexamethasone and betamethasone to accelerate foetal lung development in women at risk for preterm birth, thereby preventing neonatal RDS [4, 5, 41–46]. These organizations include the American College of Obstetricians and Gynecologists, the Royal College of

Obstetricians and Gynaecologists and the Society for Maternal–Fetal Medicine. Both dexamethasone and betamethasone can cross the placenta [30, 44, 47, 48].

Two intramuscular injection regimens are currently recommended: 24 mg of dexamethasone (4 doses of 6 mg, 12 h apart) or 24 mg of betamethasone (2 doses of 12 mg, 24 h apart). The efficacy and safety of these drugs are comparable [17, 48–51]. However, the WHO recommendations on interventions to improve preterm birth outcomes [4] suggest that dexamethasone be preferred over betamethasone owing to its lower cost, broader availability and use for various other medical indications. Additionally, dexamethasone is included in the WHO Model List of Essential Medicines 2021 and most national essential medicine lists, including Thailand's National List of Essential Medicines 2021 [49, 50].

In Thailand, dexamethasone has been used to prevent RDS in women at risk for preterm birth for at least 50 years because of its affordability and effectiveness.

Short- and long-term effects of antenatal corticosteroid exposure

While corticosteroids have been used to reduce complications in preterm neonates for more than 50 years, few studies have investigated the long-term effects of antenatal corticosteroid exposure. Research in humans has indicated that preterm neonates whose mothers receive antenatal corticosteroid therapy tend to have lower birth weights and reduced head circumference and body length [51–53]. Additionally, rodent studies have shown that in utero corticosteroid exposure is linked to low birth weight, changes in foetal programming, alterations in hypothalamic–pituitary–adrenal axis function, cardiovascular and blood pressure effects, and disruptions in glucose homeostasis and metabolism [54].

Several retrospective studies and animal experiments have suggested that repeated corticosteroid administration can lead to foetal growth restriction and neuronal damage, with some reports indicating behavioural disorders later in life [55–58]. Higher doses or frequencies of antenatal corticosteroids do not enhance lung maturation in preterm newborns. Instead, these drugs have adverse effects, such as prolonged adrenal suppression [8, 59], foetal growth restriction [60–62] and an increased risk of infection due to excessive immune suppression [63].

Moreover, high doses of antenatal corticosteroids negatively impact foetal programming and metabolism [64] and increase the risk of neurodevelopmental and neuropsychological impairments [65]. There is also evidence suggesting a trend towards higher rates of cerebral palsy in children born after 34 weeks of gestation who receive four or more full courses of betamethasone. However, this trend is not observed with half courses [66, 67]. Rodent studies imply that lower doses of antenatal betamethasone may be less harmful to brain development, indicating a potential benefit in dose reduction [68, 69].

Study objectives

Dexamethasone is widely used to prevent RDS in premature infants because of its cost-effectiveness and broad application across various medical fields, particularly obstetrics and gynaecology. The standard recommended regimen involves administering four 6-mg injections of dexamethasone to mothers at risk of preterm birth, given 12 h apart. However, most hospitals use dexamethasone ampoules containing 4 or 5 mg, as the 6-mg form is not available. Consequently, at the Department of Obstetrics and Gynaecology at the Faculty of Medicine Siriraj Hospital, a 5-mg dose is administered intramuscularly four times, 12 h apart, which deviates from international guidelines recommending a 6-mg dose.

Despite the long-standing use of the 5-mg dose at Siriraj Hospital for more than 50 years, no studies have evaluated its effectiveness compared with the standard 6-mg dose in preventing RDS. A previous study reported that the 5-mg dose is comparable to the 6-mg dose, with a lower incidence of neonatal hypoglycaemia [70]. Therefore, a 4-mg dose of dexamethasone is also of interest for investigation. Our research team aims to conduct a comparative study on the use of 4-mg and 5-mg doses of dexamethasone versus the standard 6-mg dose. This study seeks to determine whether there is a significant difference in the occurrence of RDS, short- and long-term adverse outcomes in neonates, and adverse outcomes in mothers. The goal is to align medical practice guidelines with actual practice, ensuring the safe and appropriate administration of steroid doses to mothers at risk of premature birth without causing harm to the infants.

Methods and study design

This study will be conducted as a double-blind, randomized, controlled, non-inferiority trial across multiple centres. The principal investigation centre will be Siriraj Hospital, Bangkok, Thailand, with three secondary investigation centres as follows:

1. Pranangklao Hospital, Nonthaburi, Thailand
2. Chonburi Hospital, Chonburi, Thailand
3. Vajira Hospital, Bangkok, Thailand

The study protocol has been approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Si-1796/2022). The trial has been registered with the Thai Clinical Trials Registry (TCTR20220511003).

Objectives

Primary objective

The primary objective is to compare the effects of dexamethasone at doses of 4, 5 and 6 mg on the incidence of RDS in premature infants between 29^0 and 36^6 weeks of gestation.

RDS is defined as infants exhibiting respiratory distress, which is characterized by clinical signs such as rapid breathing (> 60 breaths per minute), nasal flaring, grunting sounds, and chest retractions. Additionally, the infants may be receiving non-invasive positive pressure ventilation or intubation, and/or surfactant replacement therapy [13, 46]. Diagnoses of RDS will be confirmed by a neonatologist.

Secondary objectives

The secondary objectives are as follows:

1. To compare the effects of dexamethasone on infants with RDS between 29^0 and 36^6 weeks of gestation, as defined in the primary objective.
2. To assess the effects of various doses of dexamethasone on adverse outcomes other than RDS in preterm infants with gestational ages of 29^0–31^6 weeks (very preterm), 32^0–33^6 weeks (moderately preterm) and 34^0–36^6 weeks (late preterm) and their mothers during the postpartum period. The adverse events include the following:

- Apgar score < 7.
- Infants requiring positive pressure ventilation.
- Infants transferred to the neonatal intensive care unit within 72 h of birth.
- Infants requiring respiratory support (non-invasive respiratory support or intubation using maximum respiratory support within 72 h of life).
- Other neonatal outcomes:
- Transient tachypnoea of the newborn.
- Congenital pneumonia.
- Intraventricular haemorrhage ≥ Grade 2 according to the Papile classification [71].
- Necrotizing enterocolitis ≥ grade 2 according to modified Bell's staging criteria [72, 73].
- Early-onset sepsis (blood culture positive within 72 h of life).
- Patent ductus arteriosus.
- Hypoglycaemia within the first 48 h after birth.
- Maternal infections after birth, including chorioamnionitis and postpartum endomyometritis (fever ≥ 38 °C, abdominal pain, parametrial tenderness, foul-smelling lochia, white blood cell count > 15,000).
- The lengths of hospital stays for infants and mothers after birth.

3. To follow up infant development (neurodevelopmental assessment) at:

- Corrected age 12–18 months (using the Bayley Scales of Infant and Toddler Development, Fourth Edition).
- Corrected age 2 years (using the Mullen Scales of Early Learning).

Definitions

1. Bronchopulmonary dysplasia [74]

- For infants born at ≤ 32 weeks gestation
- A chest X-ray image that demonstrates findings consistent with persistent lung parenchymal disease.
- The need for oxygen or respiratory support at 36 weeks postmenstrual age to maintain oxygen saturation in the range of 90–95% for ≥ 3 consecutive days.
- Infants requiring mechanical ventilation due to central hypoventilation or airway disease will be excluded.
- The severity of bronchopulmonary dysplasia will be classified according to an infant's fraction of inspired oxygen and the degree of respiratory support needed, as shown in Table 1.

2. Pulmonary hypertension in bronchopulmonary dysplasia [75]

- Screening criteria:
- Newborns with a gestational age of less than 29 weeks.
- A birth weight of less than 1,000 g.
- Diagnosis of bronchopulmonary dysplasia at 36 weeks post-birth.
- Infants meeting these criteria will be screened for pulmonary hypertension in bronchopulmonary dysplasia by echocardiography at 34–36 weeks post-birth by an expert neonatal cardiologist. The diagnosis of pulmonary hypertension in patients with bronchopulmonary dysplasia will be made according

Table 1 Severity of bronchopulmonary dysplasia based on the fraction of inspired oxygen and degree of respiratory support needed

	Ventilator	CPAP/BiPAP/NIPPV/NC > 3 LPM	NC 1–3 LPM	NC < 1 LPM	O_2 hood
I	–	0.21	0.22–0.29	0.22–0.70	0.22–0.29
II	0.21	0.22–0.29	≤ 0.3	> 0.70	≤ 0.3
III	> 0.21	≥ 0.3	–	–	–
IIIa	The infant dies between DOL 14 and PMA 36 weeks due to persistent lung parenchymal disease				

BiPAP bilevel positive airway pressure, *CPAP* continuous positive airway pressure, *DOL* day of life, *LPM* litres per minute, *NC* nasal cannula, *NIPPV* non-invasive positive pressure ventilation, *O_2 hood* oxygen hood, *PMA* postmenstrual age

to the guidelines of the Pediatric Pulmonary Hypertension Network, as detailed in Table 2.

Sample-size calculation

Our comparative study aims to investigate the effects of different dexamethasone doses on the incidence of RDS in premature infants between 29^0 and 36^6 weeks of gestation. Data from the Medical Statistics Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, indicate that premature infants whose mothers received a 5-mg dose of dexamethasone before birth had an RDS rate of 10%.

Assuming non-inferiority in the incidence of RDS for dexamethasone doses of 4, 5 and 6 mg, we have set a non-inferiority margin of 10%. With a statistical significance level of 0.05 and a test power of 80%, we have calculated a sample size of 446 individuals per group using the nQuery Advisor programme.

Accounting for an estimated loss to follow-up of approximately 15%, we require a sample size of 520 individuals per group. As the study comprises three groups, the total sample size needed is 1,560 participants.

Inclusion criteria

1. Pregnant women delivering between 29^0 and 36^6 weeks of gestation (calculated from menstrual history and first-trimester ultrasound).
2. Singleton pregnancies.
3. Pregnant women with preterm labour (defined as having regular uterine contractions and changes in cervical dilation and/or effacement) or regular uterine contractions and cervical dilation of at least 2 cm at first admission.
4. Pregnant women providing informed consent to participate in the research.

Exclusion criteria

1. Pregnant women under 18 years of age.
2. Pregnant women administered steroids before 29 weeks of gestation.
3. Pregnant women allergic to steroids.
4. Pregnant women with infections or other contraindications.
5. Pregnant women with gestational diabetes requiring treatment with hypoglycaemic drugs.

Withdrawal or termination criteria

Volunteers will be withdrawn from the research immediately if they receive dexamethasone and experience an allergic reaction or severe side effects from the drug.

Study design and participant allocation

Blind allocation and stratified randomization

After obtaining maternal consent, participants will be randomly allocated into three groups to receive dexamethasone doses of 4, 5 or 6 mg. This allocation process will be blinded to ensure unbiased results. Only one researcher will be responsible for the randomization code and hence aware of the group assignments. All other research team members and the physicians, nurses and patients will remain blind to the allocations.

The randomization will be performed via a computer-generated list and a web-based application with secure access. Stratified randomization will be employed to ensure a balanced distribution across different gestational age groups: 28^0–31^6 weeks, 32^0–33^6 weeks and 34^0–36^6 weeks, in a ratio of 1:1:8. This stratification is crucial for addressing the varying risks and outcomes associated with different stages of prematurity.

The randomization sequence will be centrally generated and concealed until the completion and locking of the database. Each participant will be assigned a study number corresponding to a treatment pack containing identical, opaque and study-labelled vials to maintain blinding throughout the study.

Table 2 Criteria for diagnosing pulmonary hypertension in bronchopulmonary dysplasia per the Pediatric Pulmonary Hypertension Network guidelines

Level of severity	Echocardiography findings
No PHT	RVSP < 1/3 SBP by TR gradient; septal position rounded at end-systole of LV; no RVH; normal RV size and function; if present, large VSD or PDA gradients suggesting < 1/3 systemic RV pressures
Mild PHT	RVSP 1/3–1/2 SBP; flattening of IVS at end-systole of LV; mild RVH and RV dilatation; RV function may be normal
Moderate PHT	RVSP ½–2/3 SBP; flattening of IVS at end-systole of LV or with late systolic posterior bowing; moderate RVH or dilatation; RV may have reduced function
Severe PHT	RVSP > 2/3 SBP; if present, shunt with predominant R-L gradient; pansystolic posterior septal bowing; severe RVH; RV dilatation; low velocity shunting across PDA or VSD

IVS interventricular septum, *LV* left ventricle, *PDA* patent ductus arteriosus, *PHT* pulmonary hypertension, *R-L* right to left, *RV* right ventricle, *RVH* right ventricular hypertrophy, *RVSP* right ventricular systolic pressure, *SBP* systolic blood pressure, *TR* tricuspid regurgitation, *VSD* ventricular septal defect

This approach ensures that the allocation process is both concealed and unbiased, thereby maintaining the integrity of the study and the validity of the outcomes. Figure 1 illustrates the stratified randomization process and group allocation.

Participant recruitment

Pregnant women with a gestational age between 29^0 and 36^6 weeks who present with labour pains or ruptured membranes and are admitted to Siriraj Hospital will be informed about the study and asked to provide signed consent to participate.

Randomization and group assignment

Doctors and research assistants will identify eligible women requiring dexamethasone and will randomly assign them to one of three study groups via a statistically generated randomization table. A total of 1,560 participants will be recruited, with 520 women in each group.

- Group A will receive dexamethasone in doses of 4 mg.
- Group B will receive dexamethasone in doses of 5 mg.
- Group C will receive dexamethasone in doses of 6 mg.

Gestational age distribution (stratified randomization)

Participants will be stratified on the basis of gestational age as follows:

- Early preterm (gestational age 28^0–31^6 weeks): 10%.
- Moderately preterm birth (gestational age 32^0–33^6 weeks): 10%.
- Late preterm birth (gestational age 34^0–36^6 weeks): 80%.

The sample collection ratio within each group will be 1:1:8.

Dexamethasone administration

1. Participants in Groups A, B and C will receive intramuscular dexamethasone at doses of 4 mg, 5 mg and 6 mg, respectively, every 12 h for a total of four doses over 48 h.

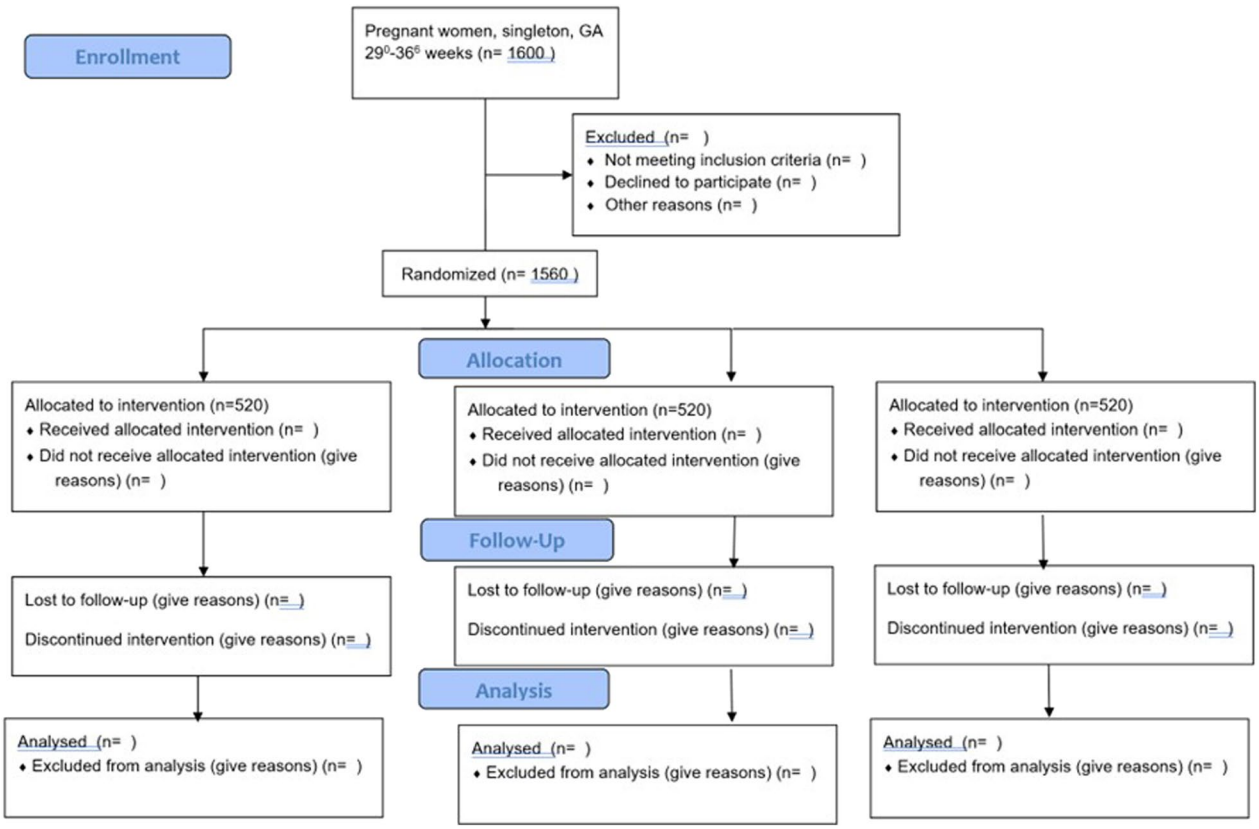

Fig. 1 Study design and participate allocation (CONSORT 2010 Flow Diagram)

2. If a participant delivers before completing the 48-h regimen, the number of doses received will be documented.

Re-admission and rescue versus repeat courses

1. If a participant is discharged without having delivered but is later re-admitted with preterm labour and requires another course of dexamethasone, she will receive the same dose as initially assigned.
2. The study coder, who is the only person with knowledge of the dexamethasone doses, will be contacted to disclose the dose previously received.

Data recording post-delivery

The following data will be recorded after delivery:

1. Newborn characteristics: Information will be collected on the newborn's sex, weight, Apgar score and need for positive pressure ventilation. Additionally, the respiratory rate and any transfer to the neonatal intensive care unit or nursery will be documented.
2. Neonatal complications: The need for respiratory support and the occurrence of various complications will be recorded. These include RDS, transient tachypnoea of the newborn, apnoea, intraventricular haemorrhage, necrotizing enterocolitis, early-onset sepsis and pneumonia.
3. Maternal outcomes: Post-delivery infections, including chorioamnionitis and postpartum endomyometritis, will be recorded. Endomyometritis is characterized by fever ≥ 38 °C, abdominal pain, parametrial tenderness, foul-smelling lochia and a white blood cell count > 15,000. Additionally, the lengths of hospital stays for both mothers and infants will be documented.

Neonatal follow-up

Neonatologists will conduct neonatal follow-up assessments as follows:

1. Preterm neonates:
- Daily visits will be undertaken from Day 1 to Day 7 and again on Day 28.
- Assessments will be made of vital and ventilation parameters, along with primary and secondary outcome measures.
2. Full-term neonates:
- Visits will be conducted on Day 1 and 48 h after birth in the postpartum units.
3. Final research visit:
- Preterm neonates: evaluations will be performed in neonatology units.
- Full-term neonates: assessments will be undertaken in the postpartum units on the day of hospital discharge.
- During the final research visits, neonatologists will review the secondary outcome measures to ensure comprehensive monitoring and evaluation of the infants' health and development.

Long-term follow-up

Certified neuropsychologists will conduct neurodevelopmental assessments when the children reach 2 years of age. However, these evaluations are not included in the current protocol.

Safety monitoring

An independent Data Safety Monitoring Board (DSMB), appointed by the Deputy Dean of Research at Siriraj Hospital, will oversee the trial's safety. The DSMB, comprising experts in obstetrics, neonatology and clinical trial methodology, will conduct evaluations during each interim analysis or when requested by the sponsor or steering committee.

At its initial meeting, the DSMB will ensure that the study's methodology aligns with participants' safety. Prior to each subsequent meeting, the DSMB will receive:

1. A comprehensive list of all adverse events.
2. A statistical report detailing the study population and interim analysis results.

The DSMB may recommend halting the trial temporarily or permanently if unexpected or unacceptable risks to the women or newborns are identified, or if the interim analysis indicates non-inferiority or futility.

Data monitoring and analysis

1. The DSMB will analyse data every 3 months.
2. The study will be terminated immediately if the analysis reveals statistically significant complications in mothers or newborns, such as RDS.

Initial data review

1. The preliminary analysis will focus on the 29^0–31^6-week gestational age group, with 20 cases per dose group.
2. The results will be reported to the DSMB, and subsequent meetings will be organized to review the findings.
3. The following data will be documented:

- The need for respiratory support.
- Occurrences of RDS, transient tachypnoea of the newborn, apnoea, intraventricular haemorrhage, necrotizing enterocolitis, early-onset sepsis and pneumonia.
- Instances of maternal post-delivery infections, such as chorioamnionitis and postpartum endomyometritis. Endomyometritis is characterized by fever ≥ 38 °C, abdominal pain, parametrial tenderness, foul-smelling lochia and white blood cell count > 15,000.
- Lengths of hospital stays for both mothers and infants.

Statistical methods for data analysis

General patient data analysis

Continuous data will be presented as means and standard deviations or as medians and ranges. Categorical data will be expressed as counts and percentages.

Comparative analysis between groups

Categorical data will be analysed via the chi-squared test. Continuous data will be assessed using one-way ANOVA for normally distributed data or the Kruskal–Wallis test for non-normally distributed data.

Analysis population

The primary non-inferiority statistical analysis and interim analyses will be conducted using both the intention-to-treat and per-protocol principles.

- Intention-to-treat analysis. This will include all randomized patients, who will be analysed in the treatment group to which they were originally assigned, regardless of the treatment received.
- Per-protocol analysis. This will include only those participants who strictly adhere to the protocol in terms of eligibility, interventions and outcome assessment. Participants will be excluded from this analysis if they:
- Do not meet the eligibility criteria.
- Do not receive any intervention after randomization.
- Receive the intervention intended for the opposite arm as their first or rescue course.
- Receive an overdose of the intervention or if it is administered intravenously.

In both analyses, participants will be reviewed in their original randomization arm if they receive the first course as randomized but are subsequently administered an incomplete rescue course.

Interim analyses

Interim analyses will be conducted after every 300 cases from the total of 1,560 cases. These analyses will follow the same intention-to-treat and per-protocol principles detailed above.

Final analyses

Data analysis and reporting will adhere to the CONSORT guidelines for non-inferiority randomized controlled trials. We will compare both groups based on the characteristics of the women and neonates. Qualitative variables will be summarized via numbers and percentages for each treatment group.

The final primary non-inferiority statistical analyses will include all neonates enrolled in the trial, including those not covered in the interim analyses. We will estimate the difference between the failure rates observed across all groups, along with the two-sided confidence intervals. This difference will be compared to the critical value corresponding to the number of women included to determine non-inferiority. A figure displaying the confidence intervals and the non-inferiority margin will summarize the primary outcome.

Primary outcome analysis

The primary outcome will be the incidence of RDS in premature infants (gestational age 28^0–36^6 weeks).

Secondary clinical outcome analyses

The continuous variables will include Apgar scores < 7, infants requiring positive pressure ventilation, infants transferred to the neonatal intensive care unit, maternal postpartum infection and lengths of hospital stays. The data for these variables will be compared between groups via one-way ANOVA for normally distributed data or the Kruskal–Wallis test for non-normally distributed data, with differences between groups reported with 95% confidence intervals.

Categorical data will be compared using the chi-squared test or Fisher's exact test.

Analyses of other pre-specified secondary outcomes will involve estimations and comparisons among the

4-mg, 5-mg and 6-mg dosage groups. The 95% confidence intervals for the differences between groups will be constructed. All the statistical tests will be two-sided, with the level of statistical significance set at 5%.

Discussion

Administering antenatal dexamethasone to women at risk of preterm delivery is associated with significant benefits for preterm infants, particularly in reducing the incidence of RDS. However, the optimal dose of dexamethasone remains unclear, with high doses potentially leading to adverse short-term and long-term neonatal outcomes. Therefore, determining the appropriate dosage is crucial for balancing efficacy and safety.

Our study aims to compare the effects of 4-mg, 5-mg and 6-mg doses of dexamethasone on the incidence of RDS in premature infants born between 29^0 and 36^6 weeks of gestation. By evaluating these different doses, we seek to identify a regimen that is non-inferior to the higher dose while minimizing adverse outcomes. This research is critical because the currently recommended doses are based on studies conducted decades ago. There is a pressing need for updated, evidence-based guidelines.

Our randomized controlled trial is meticulously designed, utilizing stratified randomization to ensure balanced allocation across the different gestational age groups (28–31, 32–34 and 34 weeks onwards) in a 1:1:8 ratio. This approach ensures that our findings will be robust and applicable to a diverse population of preterm infants. Except for the researcher who manages the coding, all research team members will be blind to the allocations. This blinding methodology will minimize bias and enhance the validity of our results.

Neonatal follow-up will be conducted daily until discharge to monitor vital and ventilation parameters and primary and secondary outcomes. Long-term neurodevelopmental assessments are planned at 3 years of age to evaluate the lasting impact of the different doses, although this is not part of the present protocol.

Interim analyses will be conducted every 300 cases to ensure the ongoing safety of the participants. The primary non-inferiority analysis will follow both the intention-to-treat and per-protocol principles, ensuring a comprehensive data evaluation.

If our study demonstrates that lower doses of dexamethasone are non-inferior to higher doses in preventing RDS and associated complications, it could lead to a significant shift in clinical practice. Reducing the dose could minimize potential adverse effects, improving short- and long-term outcomes for preterm infants. This research could provide critical evidence to support revised dosing guidelines, ultimately benefiting countless women and their children at risk of preterm delivery.

Conclusions

This study aims to evaluate the efficacy and safety of different doses of dexamethasone (4, 5 and 6 mg) in preventing RDS in preterm infants. By comparing these doses, we seek to identify a regimen that is as effective as the standard higher dose but with potentially reduced adverse effects. Our rigorous trial design, which includes stratified randomization and blind allocation, ensures robust and unbiased results. Regular interim analyses and comprehensive neonatal follow-up will help safeguard participants' well-being and provide insights into immediate and long-term outcomes. If successful, this research could lead to updated dosing guidelines that better balance efficacy and safety, ultimately improving the management of preterm labour and neonatal health.

Abbreviations

DSMB Data safety monitoring board
RDS Respiratory distress syndrome

Acknowledgements

Not applicable.

Principal investigation centre

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Author contributions

S.C., P.W., S.A., and S.S. conceptualized and designed the study. S.C. was responsible for data collection and management. S.C. conducted the statistical analysis, wrote the main manuscript text and prepared the figures and tables. All authors reviewed and provided critical revisions to the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethics approval has been granted by the Faculty of Medicine Siriraj Hospital (Si 480/2019). All the authors have completed the International Committee of Medical Journal Editors' Form for Uniform Disclosure of Potential Conflicts of Interest and declare that they have nothing to disclose. All procedures involving human participants will be conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate
Written informed consent will be obtained from all study participants.

Competing interests
The authors declare no competing interests.

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