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Antenatal corticosteroids for women at risk of birth in the late preterm period to improve newborn outcomes

Submission date
04/03/2021

Recruitment status
Recruiting

Registration date
07/06/2021

Overall study status
Ongoing

Last Edited
16/10/2025

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Preterm birth (when a baby is born early in pregnancy, i.e earlier than 37 weeks) is a common condition. It affects around 10% of pregnancies. When a woman is likely to give birth too early in pregnancy, it is common practice for the doctors to give her an injection of steroids. This injection can speed up the development of the baby's lungs so that when they are born, they have a better chance of survival. While the benefits of steroid on the newborn are clear in the early preterm period (26-34 weeks), the benefits of steroid injection given to women who are likely to deliver a preterm baby later in pregnancy (34 to 37 weeks) are not clear, especially in low resource settings. This study will aim to establish whether steroid injections given to mothers at risk of a late preterm birth improve outcomes compared to placebo (dummy injection). It will also look into the effect of a lower dose of steroid, as there is recent evidence that the dose of steroid used conventionally is higher than necessary and may mediate some of the side effects seen in the newborn.

Who can participate?
Women with a single or multiple pregnancy at 34+0 weeks to 36+5 weeks and a high probability of late preterm birth (up to 36+6 weeks)

What does the study involve?
Participants are randomly allocated to three groups. Participants in one group will be given dexamethasone phosphate 6 mg for a maximum of four doses, participants in the second group will be given betamethasone phosphate 2 mg for a maximum of four doses while participants in the third group will be given a placebo (dummy treatment). Participants will be followed up from recruitment to 28 days after birth. During that time, it will be necessary to contact participants by phone telephone, and for a researcher to visit 28 days after the birth.
A substudy will be done in a subset of participants (300 women in the Indian and Nigerian sites) to measure the levels of the steroid in the maternal blood and the fraction that crosses the placenta (cord blood). The effects of the steroid on the body in terms of changes in white blood cell counts, cortisol levels and blood sugar will also be studied.

After Dec 2025 interim analysis, only the two active arms are being continued, therefore the participants are now being allocated to one of the two active groups.

What are the possible benefits and risks of participating?
Two-thirds of the participants will receive up to four injections of steroids over 36 hours. This drug can very rarely cause side effects. Any side effects are temporary and will end when the treatment is finished. Participants may experience difficulty sleeping or headache due to the treatment, but these symptoms can occur often during pregnancy and childbirth. The injection can cause some temporary swelling or soreness around the place where the injection goes into the arm.

Where is the study run from?
World Health Organization (Switzerland)

When is the study starting and how long is it expected to run for?
July 2020 to May 2026

Who is funding the study?
Bill & Melinda Gates Foundation (USA)

Who is the main contact?
Dr Ayesha De Costa
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Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
1.13

Study information

Scientific Title
ACTION III: A multi-country, multi-centre, three-arm, parallel group, double-blind, placebo-controlled, randomized trial of two doses of antenatal corticosteroids for women with a high probability of birth in the late preterm period in hospitals in low-resource countries to improve newborn outcomes

Acronym
ACTION III

Study objectives
Current study hypothesis as of 10/04/2025:
1. It is hypothesised that the use of a regimen of dexamethasone phosphate 4 x 6 mg q 12 h will result in clinical benefits for the baby (a reduction in stillbirth and/or neonatal death, and/or need for respiratory support) compared to placebo (superiority hypothesis)
2. It is hypothesised that the use of a regimen of betamethasone phosphate 4 x 2 mg q 12 h will result in clinical benefits for the baby (a reduction in stillbirth and/or neonatal death, and/or need for respiratory support) compared to placebo (superiority hypothesis)
3. In the event of there being a similar benefit-risk of the dexamethasone phosphate 4 x 6mg q12h regimen and betamethasone phosphate 4 x 2 mg q 12h regimen when compared separately against placebo, it is hypothesised that use of the latter regimen will result in clinical benefits that are non-inferior to the dexamethasone phosphate 4 x 6 mg q 12 h regimen

In addition, a sub-study is embedded into the trial with the following objective:
To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) effects of two different ACS dosing regimens in pregnant women, and to ascertain the fetal-maternal ratio of dexamethasone and betamethasone, respectively, with the dosage regimens used in the trial at birth.

Previous study hypothesis:
1. It is hypothesised that the use of a regimen of dexamethasone phosphate 4 x 6 mg q 12 h will result in clinical benefits for the baby (a reduction in stillbirth and/or neonatal death, and/or need for respiratory support) compared to placebo (superiority hypothesis)
2. It is hypothesised that the use of a regimen of betamethasone phosphate 4 x 2 mg q 12 h will result in clinical benefits for the baby (a reduction in stillbirth and/or neonatal death, and/or

need for respiratory support) compared to placebo (superiority hypothesis)
3. In the event of there being a similar benefit-risk of the dexamethasone phosphate 4 x 6mg q12h regimen and betamethasone phosphate 4 x 2 mg q 12h regimen when compared separately against placebo, it is hypothesised that use of the latter regimen will result in clinical benefits that are non-inferior to the dexamethasone phosphate 4 x 6 mg q 12 h regimen

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/03/2021, WHO Ethics Review Committee (20, Avenue Appia, Ch-1211, Geneva 27, Switzerland; +41 (0)22 791 1479; ercsec@who.int), ref: 0003488

Study design
Multi-country multi-centre three-arm parallel-group double-blind placebo-controlled randomized trial

(added 16/10/2025) Following the November 2024 interim analysis, the study is now randomizing participants into two active arms and is continuing as a two-arm non-inferiority trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Preterm birth

Interventions
Site-stratified individual randomization with permuted blocks of 12 will be used. The computer-generated randomization sequence will be prepared centrally at WHO by staff not involved in the trial. Allocation concealment will be through the use of pre-labeled treatment packs (prelabeled by participant number). All treatment packs are identical, therefore participants, care providers, and investigators are blind to randomized group assignment.

The intervention regimens will be:
1. Dexamethasone phosphate 4 x 6 mg q 12 h (Dexa-4 x 6 mg) regimen: A single course of 6 mg IM dexamethasone sodium phosphate administered every 12 hours, to a total of four doses (starting immediately after randomisation at time points 0 hours, 12 hours, 24 hours and 36 hours) or until birth occurs, whichever comes first. If the full regimen is completed, the woman would have received a total of 24 mg of dexamethasone in divided doses
2. Betamethasone phosphate 4 x 2 mg IM q 12 h (Beta-4 x 2 mg) regimen: A single course of 2 mg IM betamethasone phosphate administered every 12 hours, to a total of four doses (starting immediately after randomisation at time points 0 hours, 12 hours, 24 hours and 36 hours) or until birth occurs, whichever comes first. If the full regimen is completed, the woman would have received a total of 8 mg betamethasone phosphate in divided doses

Comparison:
Identical placebo, given in exactly the same schedule as above, i.e. administered every 12 hours, to a total of four doses (time points 0 hours, 12 hours, 24 hours and 36 hours) or until birth

occurs, whichever comes first.
Packaging, appearance, labelling and volumes administered allow complete blinding of the three arms.

Updated 18/12/2024:
The ACTION trial DSMB convened for an interim analysis at 60% recruitment, and as per pre-specified rules, recommended that the placebo arm be halted and the trial continue as a non-inferiority comparison.

Updated 10/04/2025:
From January 2025, the trial is implemented as a two-arm non-inferiority trial.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Dexamethasone phosphate, betamethasone phosphate

Primary outcome(s)
Stillbirth (post randomization) OR neonatal death within 72 hours of birth OR use of respiratory support within 72 hours of birth or until discharge from hospital, whichever is earlier. Use of respiratory support defined as any one of the following: (i) mechanical ventilation (ii) continuous use of CPAP for 12 hours or more with an FiO_2 ≥0.4 at any time (iii) continuous use of supplementary oxygen for 24 hours or more with an FiO_2 ≥0.4 at any time

Key secondary outcome(s))
Newborn:
Efficacy outcomes:
1. Neonatal death, defined as the death of a live birth by 28 completed days of life
2. Early neonatal death, defined as the death of a live birth by 7 completed days of life
3. Need for resuscitation at birth, defined as the use of positive pressure ventilation for >1 min at birth
4. Severe respiratory distress (SRD) within 72 hours after birth or until discharge from hospital, whichever is earlier, defined as any of the following clinical signs for at least 12 h: respiratory rate ≥70/min, chest indrawing, grunting, or SpO_2 <90%
5. Death or high settings for CPAP or mechanical ventilation: stillbirth OR neonatal death in 72h OR mechanical ventilation in 72 h OR need for very high CPAP settings (≥8 cm water pressure and ≥0.7 FiO_2) in 72 h
6. Cause-specific mortality, ascertained by two physicians with dissenting opinions settled by a third

Safety outcomes:
1. Clinically suspected neonatal sepsis (≤7 days), defined as new onset of at least two (or more) of the following signs at the same time between birth and 7 days:
1.1. Stopped feeding well
1.2. Severe chest in-drawing (or rise in respiratory support after 24 hours)
1.3. Fever (body temperature of 38 °C or greater)
1.4. Hypothermia (body temperature less than 35.5 °C)

1.5. Movement only when stimulated or no movement at all
1.6. Convulsions
2. Neonatal hypoglycaemia, defined as blood glucose by point of care glucometer or lab value < 45 mg% at 2, 6, 12, 24 or 36 h, or detected anytime < 36 h based on a test because of clinical suspicion requiring correction by IV fluids

Health service utilization outcomes:
1. Admission to special newborn care unit, defined as any admission in the special newborn care unit during the first 3 days
2. Total days of hospital stay during birth hospitalization
3. Any parenteral antibiotic use, defined as parenteral antibiotics administered to the newborn before 7 days of life

Maternal
Safety outcomes:
1. Possible maternal bacterial infection during hospital admission (women with maternal fever (≥38.0 °C) or clinical signs of infection (obstetric or non-obstetric) AND therapeutic antibiotics were used. Assessment must be made by the obstetric care provider. Randomization to 28 days postpartum (during hospital admission only)
2. Chorioamnionitis suspected or confirmed by the obstetric care physician from randomization to 28 days postpartum (during postpartum admission/s only)
3. Postpartum endometritis suspected or confirmed by the obstetric care physician from delivery to 28 days postpartum (during postpartum admission/s only)
4. Maternal death, defined as any maternal death in a trial participant from time of randomization to 28 completed days after birth

Health service utilization outcomes:
1. Total number of days post-randomization which women are hospitalized for delivery (initial hospitalization for delivery)
2. Any therapeutic antibiotic use, defined as any use of therapeutic antibiotic in response to sepsis from randomization to 28 completed days postpartum
3. Any use of antibiotic (therapeutic or prophylactic) from randomization to 28 completed days postpartum

Completion date
31/05/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 10/04/2025:
The population of interest is women with singleton or multiple pregnancy at 34+0 weeks to 36+5 weeks and a high probability of late preterm birth (which extends up to 36 weeks 6 days). High probability of late preterm birth is defined as birth expected between 12 hours and 7 days

Inclusion criteria (all to be met):
1. Gestational age from 34 weeks 0 days to 36 weeks 5 days
2. High probability of late preterm birth (up to 36+6 weeks) defined as birth expected between 12 hours and 7 days after randomization as a result of:
2.1. Membrane rupture without preterm labour (where preterm labour is defined as at least 6 regular uterine contractions/ hr and at least one of the following: cervical dilatation of ≥3 cm or

effacement ≥75%). OR
2.2. Preterm labour with intact membranes, defined as at least 6 regular contractions/hr and at least one of the following: (i) cervix ≥3cm dilated or (ii) 75% effaced; OR
2.3. Planned delivery by induction of labour or caesarean section between 24 hours and 7 days, as deemed necessary by the provider. An induction must be scheduled to start by 36+5 weeks at the latest, whereas a caesarean delivery must be scheduled by 36+6 weeks at the latest
3. Singleton or multiple pregnancies, where the foetus/es (or at least one foetus in a multiple pregnancy) is/are confirmed alive by doppler or ultrasonography
4. Women with no clinical signs of severe infection (as per obstetric care physician's assessment)
5. Women willing and able to provide consent (or if a minor, provides assent and guardian provides consent)

Women recruited to the main trial will be invited to participate in the substudy on the pharmacokinetics and pharmacodynamics. Therefore, inclusion and exclusion criteria will be the same for the sub-study. However, women with severe anemia (Hb <7 mg/dL) or having received blood/blood product transfusion in <=7d before enrolment in the ACTION-III trial will be excluded.

Previous participant inclusion criteria:
The population of interest is women with singleton or multiple pregnancy at 34+0 weeks to 36+5 weeks and a high probability of late preterm birth (which extends up to 36 weeks 6 days). High probability of late preterm birth is defined as birth expected between 12 hours and 7 days

Inclusion criteria (all to be met):
1. Gestational age from 34 weeks 0 days to 36 weeks 5 days
2. High probability of late preterm birth (up to 36+6 weeks) defined as birth expected between 12 hours and 7 days after randomization as a result of:
2.1. Membrane rupture without preterm labour (where preterm labour is defined as at least 6 regular uterine contractions/ hr and at least one of the following: cervical dilatation of ≥3 cm or effacement ≥75%). OR
2.2. Preterm labour with intact membranes, defined as at least 6 regular contractions/hr and at least one of the following: (i) cervix ≥3cm dilated or (ii) 75% effaced; OR
2.3. Planned delivery by induction of labour or caesarean section between 24 hours and 7 days, as deemed necessary by the provider. An induction must be scheduled to start by 36+5 weeks at the latest, whereas a caesarean delivery must be scheduled by 36+6 weeks at the latest
3. Singleton or multiple pregnancies, where the foetus/es (or at least one foetus in a multiple pregnancy) is/are confirmed alive by doppler or ultrasonography
4. Women with no clinical signs of severe infection (as per obstetric care physician's assessment)
5. Women willing and able to provide consent (or if a minor, provides assent and guardian provides consent)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex

Female

Key exclusion criteria
1. Ruptured membranes with cervix dilated ≥3 cm or effaced ≥75%, or with more than 6 contractions per hour (or both)
2. Cervical dilation ≥8 cm with intact membranes
3. Clinical suspicion or evidence of clinical chorioamnionitis or severe infection, as per obstetric care physician assessment
4. Evidence of non-reassuring foetal status requiring immediate delivery
5. Major or lethal congenital foetal anomaly identified
6. No prior ultrasound-based estimate of gestational age available and immediate ultrasound examination is not possible
7. Any systemic corticosteroid use during the current pregnancy (outside of trial)
8. Unwilling or unable to provide consent or assent (including due to active labour)
9. Currently a participant in another clinical trial related to maternal and neonatal health, or previously participated in any ACTION trial
10. Any other clinical indication where the treating clinician considers corticosteroids to be contraindicated

Date of first enrolment
15/07/2022

Date of final enrolment
30/04/2026

Locations

Countries of recruitment
Bangladesh

India

Kenya

Nigeria

Pakistan

Study participating centre
Projahnmo Research Foundation
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Study participating centre

Safdarjung Hospital
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Study participating centre
Obafemi Awolowo University
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Study participating centre
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Sponsor information

Organisation
World Health Organization

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, Gates Learning Foundation, William H. Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Ayesha De Costa (Deay@who.int)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		12/04/2024	15/04/2024	Yes	No
Participant information sheet		15/02/2021	07/06/2021	No	Yes

Protocol (other)	Population pharmacokinetics and pharmacodynamics of two dosing regimens of antenatal corticosteroids: protocol for a prospective nested study in a randomised controlled trial	08/06/2025	09/06/2025	No	No
Statistical Analysis Plan	version 1.3	01/04/2022	18/12/2023	No	No
Statistical Analysis Plan	version 2.1	01/03/2025	16/10/2025	No	No