Labor Induction in Low-risk Women at 39 Weeks of Gestation to Reduce Cesarean Rate: A Pilot Randomized Trial in China

Protocol

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CONTENTS

1 Background

1.1 Expectant Management Until 41 Weeks is Currently Recommended for Low-risk Pregnancies

Labor induction is a critical component of obstetric clinical management. Globally, the number of labor induction is substantial. In 2022–2023, the induction rate in the United States reached 31.9% (1), while in the UK, it was 33.3% (2). Although official statistics are unavailable in China, a study covering 96 hospitals revealed that the induction rate among nulliparous women was 18.4% in 2015–2016 (3), and this figure is likely increasing as understanding of optimal delivery timing improves.

Gestational duration directly impacts fetal maturity, but prolonged pregnancy may increase perinatal risks for both mother and child, including higher perinatal mortality (4). Large-scale, multicenter randomized controlled trials (RCTs) have provided evidence-based guidance on the optimal timing of delivery for low-risk pregnancies. The INDEX and SWEPIS studies, published in 2019, demonstrated that induction at 41 weeks, compared with expectant management until 42 weeks, significantly reduces neonatal mortality and other adverse perinatal outcomes without increasing maternal complications (5, 6).

In 2020, the WHO updated its guidelines on labor induction, recommending induction at 41 weeks of gestation (7). China's latest Guidelines for Cervical Ripening and Labor Induction in Late Pregnancy (2024) align with WHO recommendations, advising induction at 41 weeks for low-risk pregnancies. While expectant management until 41 weeks is widely accepted in clinical practice, the potential benefits of lowering this threshold are under debate, prompting ongoing research worldwide to evaluate the risks and benefits of earlier induction.

1.2 Preliminary Evidence Supports Induction at 39 Weeks for Low-risk Pregnancies

1.2.1 The ARRIVE Trial: Induction at 39 Weeks Reduces Cesarean Rates

The ARRIVE trial is the only large-scale RCT to date evaluating induction at 39 weeks, with significant influence in obstetrics (8). It included 6,106 low-risk nulliparous women randomized to either induction at 39 weeks or expectant management until 41 weeks. After adjusting for covariates, no significant differences were observed in the primary outcomes (including perinatal death, respiratory support, low Apgar scores, hypoxic-ischemic encephalopathy, seizures, infections, meconium aspiration syndrome, birth trauma, intracranial or subgaleal hemorrhage, and hypotension requiring vasopressor support). Secondary outcomes showed that induction at 39 weeks significantly reduced cesarean rates, self-reported maternal pain during labor, and did not increase other adverse outcomes (8).

Inspired by the ARRIVE trial, the FRENCH-ARRIVE study is currently underway at Bordeaux University Hospital, aiming to enroll 4,200 pregnant women, with completion expected by 2027. To date, no large-scale RCT has been conducted in Asia on induction at 39 weeks.

1.2.2 Meta-analysis: Induction at 39 Weeks May Improve Maternal and Neonatal Outcomes

In 2020, the Cochrane Library updated its review on labor induction at term, with a meta-analysis indicating that induction between 37 and 41 weeks reduces perinatal deaths, absolute mortality rates, and cesarean rates. The review highlighted the need for future research to focus on long-term child health outcomes (9). In 2023, Hong et al. conducted a meta-analysis of 12 retrospective cohort studies, 1 cross-sectional study, and 1 RCT involving 86,555 pregnant women. The results showed that elective induction at 39 weeks reduced the risks of third- or fourth-degree perineal lacerations, macrosomia, and emergency cesarean delivery (10).

1.2.3 Long-term Effects of Induction at 39 Weeks on Offspring

Since the publication of the ARRIVE trial, three retrospective cohort studies have examined the long-term effects of induction at 39 weeks on offspring. These studies focused on academic performance or teacher-assessed composite scores during school-age years, with inconsistent results: two studies reported no significant effects, while one found

an association between induction and lower academic performance in middle school (11-13). To date, no studies have explored the impact of induction at 39 weeks on early childhood growth or other health outcomes.

1.2.4 Further Research Needed on Induction at 39 Weeks for Low-risk Pregnancies

Given the limited evidence supporting the safety and potential benefits of induction at 39 weeks for low-risk pregnancies, the WHO's 2020 guidelines adjusted their stance from "not recommending induction" to "not recommending routine induction" between 39 and 41 weeks. The WHO noted that in middle- and high-income countries, induction at 39 weeks may offer perinatal benefits but requires more evidence to support widespread adoption. China's 2022 Expert Consensus on Timing of Delivery for Pregnancy Complications and Comorbidities states that the earliest timing for elective induction or cesarean delivery without medical indication should be 39 weeks. However, the 2024 Guidelines for Cervical Ripening and Labor Induction in Late Pregnancy emphasize balancing the risks of adverse outcomes with potential neonatal complications due to prematurity, recommending induction at 39 weeks for suspected macrosomia (Grade 1B).

1.3 Balloon Catheters as a Primary Method for Cervical Ripening

In recent years, clinical methods for labor induction have evolved, introducing challenges in directly applying past evidence.

1.3.1 RCT Meta-analysis Evidence: Balloon Catheters Are Safer

For women requiring induction, if cervical conditions are unfavorable (Bishop score < 6), cervical ripening is typically performed before oxytocin induction. Common methods include vaginal prostaglandins and cervical balloon catheters. A 2023 meta-analysis by Jones et al. (CPI Collaborative) involving 12 RCTs found that balloon catheters significantly reduced composite adverse neonatal outcomes, uterine hyperstimulation, and improved neonatal acid-base balance compared to vaginal prostaglandins, demonstrating greater safety (14).

1.3.2 Early Artificial Rupture of Membranes Combined with Balloon Catheters

In current clinical practice, balloon catheter induction is often combined with active artificial rupture of membranes (ARM). Most prior RCTs did not standardize the use of ARM. A 2024 meta-analysis by Yara et al. compared early versus delayed ARM in women undergoing balloon catheter induction, including five trials with 849 participants. The results showed that early ARM did not increase cesarean rates, chorioamnionitis, or other adverse perinatal outcomes but significantly improved the probability of vaginal delivery within 24 hours (15).

1.4 Rationale for This Study

1.4.1 Establishing a Cohort Based on the Chinese Population

Given existing evidence supporting the perinatal benefits of induction at 39 weeks for low-risk pregnancies, more clinicians may consider this approach. However, as the WHO guidelines indicate, broader adoption requires further evidence. Currently, the only cohorts studying induction at 39 weeks are the ARRIVE and FRENCH-ARRIVE trials, both conducted in Western populations. Research on East Asian populations, including Chinese women, is lacking. Notably, elective induction at 39 weeks is already common in Chinese clinical practice, underscoring the urgent need for localized studies to establish evidence-based guidelines for this population.

Additionally, the ARRIVE trial was published seven years ago, with expectant management continuing until 42 weeks and no strict control over induction methods. Current guidelines recommend terminating expectant management at 41 weeks, and induction methods have evolved. Thus, replicating the ARRIVE findings requires an optimized study design incorporating the latest guidelines and advancements.

1.4.2 Exploring Early Biological Changes in Offspring Using Multi-omics

Early-life influences may not immediately manifest as disease. For example, the effects of cesarean delivery on offspring health often emerge during childhood or adulthood (16). However, the biological foundations of disease may already be present in early life, making precise early detection and intervention critical.

Advances in omics technologies provide powerful tools for early disease prediction. For instance, infants who later develop asthma, autism, or attention deficit disorders exhibit specific metabolic and gut microbiota profiles (17, 18). Similarly, early differences in umbilical cord blood metabolomics and proteomics may serve as potential biomarkers for future diseases.

Previous induction studies have not collected neonatal or infant biological samples, leaving the long-term effects of induction at 39 weeks uncertain. This study will collect early-life biological samples and perform multi-omics analyses to explore the potential impact of induction at 39 weeks on offspring biology, enabling early predictions of long-term health outcomes.

1.4.3 Providing Decision-making Evidence for Large-scale RCTs

Comprehensive evaluation of perinatal outcomes requires large sample sizes. However, China lacks prior cohort studies on term induction and systematic follow-up data, making large-scale RCTs currently unfeasible. This pilot study aims to assess the impact of induction at 39 weeks versus expectant management or induction at 41 weeks on cesarean rates in low-risk pregnancies, while evaluating the feasibility of a large-scale RCT and providing decision-making evidence for future research.

2 Study Design

2.1 Primary Research Question

For low-risk parturient, can elective induction of labor at 39 weeks reduce the cesarean section rate compared with expectant management until 41 weeks?

2.2 Secondary Research Question

- For low-risk parturient, can elective induction of labor at 39 weeks reduce perinatal maternal risks compared with expectant management until 41 weeks?
- Reduce perinatal offspring risks ?
- Affect the early physical and neurodevelopment of offspring?
- Affect the early intestinal flora development and metabolomic changes of offspring?
- Affect the changes in cord blood metabolome and proteome?

2.3 Design Overview

This is an open-label, single-center, randomized controlled superiority trial. A total of 1,074 low-risk women will be randomized into two groups:

- Intervention group: Induction at 39 weeks 0 days to 39 weeks 4 days.
- Control group: Expectant management until spontaneous labor or induction at 41 weeks.

2.4 Eligibility Criteria

2.4.1 Inclusion Criteria

1. Age ⩾18 years.
2. Singleton pregnancy or twin pregnancy reduced to singleton before 14 weeks.
3. Gestational age of 38 weeks 6 days or 39 weeks 0 days at randomization.
4. Eligible for vaginal delivery with a desire for vaginal birth.
5. Reliable gestational age determination (confirmed by methods in Section 2.4.2).
6. Maternal and fetal conditions assessed as favorable by at least two senior obstetricians, with no indications requiring delivery before 41 weeks.
7. Ability to understand study information and provide informed consent.

2.4.2 Gestational Age Determination

Gestational age ("project gestational age") is determined as follows:

- For pregnancies via in vitro fertilization (IVF-ET), gestational age is calculated based on the embryo transfer date and embryo age at transfer.
- For natural conceptions (including ovulation induction and intrauterine insemination), gestational age is determined by the first ultrasound estimate and last menstrual period (LMP):
    1. If LMP is reliable and regular, and the ultrasound estimate matches (±5 days), LMP is used.
    2. If LMP is unreliable, gestational age is determined by the first ultrasound crown-rump length (CRL) measurement before 14 weeks 0 days.

2.4.3 Exclusion Criteria

1. First ultrasound estimate >13 weeks 6 days.
2. Planned induction before 41 weeks.
3. Planned cesarean delivery or contraindications to vaginal delivery.
4. Already delivered, in labor, or ruptured membranes at enrollment.
5. Placenta previa, vasa previa, placenta accreta, or placental abruption.

6. Contraindications to induction (e.g., cervical cancer, history of uterine rupture, genital tract malformations, abnormal fetal position, cord prolapse).
7. Active vaginal bleeding exceeding spotting.
8. History of cesarean delivery or uterine/cervical surgery.
9. Cervical cerclage during this pregnancy.
10. Maternal conditions not suitable for expectant management beyond 39 weeks (e.g., pregestational diabetes, gestational diabetes requiring insulin, hypertensive disorders, intrahepatic cholestasis of pregnancy).
11. Fetal conditions not suitable for expectant management beyond 39 weeks (e.g., fetal death, major anomalies, growth restriction, macrosomia, anemia, oligohydramnios, polyhydramnios).
12. Maternal infections or positive screenings for sexually transmitted pathogens or group B Streptococcus.
13. Planned delivery at a non-study facility.
14. Participation in another intervention study affecting delivery management.

2.5 Informed Consent

The informed consent form will be developed based on the template provided by the Ethics Committee of Women's Hospital, Zhejiang University School of Medicine. A signed copy of the consent form will be provided to the patient. For non-Chinese-speaking participants, interpreters will assist, and verbal/written consent will be documented.

2.6 Randomization and Blinding

Stratified block randomization (1:1) will be used, with dynamic block sizes (2–4), stratified by maternal age (<35/ ≥35 years) and parity (nulliparous/parous). An independent statistician will generate the randomization sequence using R Studio. Due to clinical practicality, blinding is not feasible; this is an open-label study.

3 Study Procedures

3.1 Screening and Consent

All singleton pregnant women who have reached 37 weeks and came to our obstetric outpatient clinic are eligible for screening. After preliminary medical record review, researchers will introduce this study to potentially eligible participants. Upon obtaining consent, researchers will assign a screening number, conduct eligible assessments, and confirm the project gestational age. For women who meet the screening criteria, contact information will be retained to remind them to attend follow-up visits as scheduled.

3.2 Randomization

Prior to randomization, patient eligibility will be reconfirmed. Eligible participants who have provided informed consent will undergo randomization via the Electronic Data Capture (EDC) platform by certified researchers between 38 weeks 6 days and 39 weeks 0 days of gestation. Patients will be randomly assigned to either the intervention group or the control group. Once randomization is completed, the allocation will be locked in the EDC system, and the result may be communicated to the patient on-site or by phone.

The randomization sequence will be generated in advance by an independent statistician using R Studio and stored in the EDC system. This sequence will not be visible to researchers, healthcare providers, or patients.

3.3 Data Collection

3.3.1 Maternal Baseline Data

The following maternal information will be collected from the hospital electronic medical records (EMR) system:

- Demographics: Age, ethnicity
- Obstetric history: Gravidity, parity, past medical history
- Personal history: Marital status, smoking/alcohol use
- Pregnancy details: Prenatal care records, current pregnancy complications
- Anthropometrics: Current height, weight, gestational weight gain
- Medication use: Medications taken during pregnancy
- Cervical status: Bishop score at randomization

3.3.2 Paternal Baseline Data

The following paternal information will be collected via electronic questionnaires:

- Demographics: Age, ethnicity, education level
- Medical history: Past illnesses, personal habits
- Preconception medication use

3.3.3 Maternal Follow-up Data

The following intrapartum and postpartum data will be recorded:

- Timing: Randomization time, admission time, delivery time
- Labor progression: Duration of first, second, and third stages of labor
- Cervical status: Bishop score at admission and after cervical ripening (if applicable)
- Delivery details: Mode of delivery (vaginal/cesarean), artificial rupture of membranes (method and time from rupture to delivery)
- Medications: Intrapartum drugs (name, dosage, administration), antibiotic use (intrapartum/postpartum), analgesia method
- Pain assessment: Self-reported labor pain (Likert scale)
- Surgical records: Operative notes (if applicable), estimated blood loss

- Postpartum medications

3.3.4 Offspring Follow-up Data

Infant data will be collected at multiple follow-up time points (in-hospital, 7 days, 6 weeks, and 6 months) via electronic questionnaires:

- Feeding history:
  1. Initial feeding: Breastfeeding within 1 hour after birth (yes/no)
  2. Current feeding mode: Breast milk, formula, cow's milk, complementary foods, mixed feeding
  3. Breastfeeding frequency: Daily breastfeeding sessions
  4. Supplement use: Probiotics, complementary foods (type)
  5. Medication use
- Growth and development assessments (at 6 weeks and 6 months):
  1. Anthropometrics: Weight, length, head circumference, chest circumference, sitting height, mid-upper arm circumference, subcutaneous fat, height-to-chest circumference ratio, crown-rump length/body length ratio
  2. Growth indices: Length-for-age, weight-for-age, weight-for-length Z-scores (calculated using WHO Anthro Survey Analyser)
  3. Stunting (defined as length-for-age Z-score < -2SD or below the 3rd percentile)
  4. Neurological examination: Hearing development, reflexes,
  5. Bayley Scales of Infant and Toddler Development (Bayley-3): Total score and domain scores (cognitive, language, motor, social-emotional, adaptive behavior);
  6. Ages & Stages Questionnaires (ASQ-3): Total score and subdomain scores (communication, gross motor, fine motor, problem-solving, personal-social)

3.4 Interventions

Based on national clinical guidelines and expert consensus, and taking into account the practical context of clinical work in the hospital, the following management approaches for the intervention and control groups have been developed. All care will be provided by attending obstetricians, and other medical decisions during labor will be made by the attending physician according to the clinical situation.

3.4.1 Intervention Group: Induction at 39 Weeks

Women assigned to the intervention group will be admitted between 39 weeks +0 days to 39 weeks +4 days of gestation as Figure 1.

- If Bishop score ＜6: Cervical ripening will be performed first, followed by oxytocin induction if needed (19).
- If Bishop score ≥6: Direct oxytocin induction will be initiated.

Table 1. Scoring System for the Bishop Score

Score	0	1	2	3
Cervical Dilation (cm)	Unopened	1-2	3-4	>4
Cervical Effacement (%)	0-30	40-50	60-70	≥ 80
Station of Presenting Part (in relation to ischial spines)	-3	-2	-1/0	+1/+2
Cervical Consistency	Hard	Medium	Soft	
Cervical Position	Posterior	Mid - position	Anterior	

Given the superior perinatal safety profile of balloon catheters compared to vaginal prostaglandins (14), and

consistent with our institutional protocol of performing immediate cervical assessment post-balloon removal, this study adopts balloon catheter + early ARM as the primary cervical ripening strategy (see Figure 2 for procedure): After thorough vaginal and cervical disinfection, a single/double balloon catheter is inserted. The catheter is removed upon spontaneous expulsion or after 12 hours, with Bishop reassessment within 1 hour:

- If Bishop score ⩾6, ARM is performed after consent. Oxytocin infusion follows if inadequate contractions occur (19, 20). If ARM consent is not obtained but contractions are inadequate, perform oxytocin infusion.
- If ripening proves ineffective (Bishop score < 6), the medical team will conduct a thorough reassessment of maternal and fetal conditions. Taking into account the patient's preferences, cervical ripening may be reattempted, or the criteria for cesarean delivery may be reconsidered. The method for reinitiating cervical ripening will be determined by the attending physician, either through reinsertion of the balloon after a 24-hour interval or by a 10 mg dinoprostone vaginal insertion (see Figure 3 for guidelines).

The initial oxytocin solution should be prepared as a 0.5% concentration (2.5 IU oxytocin in 500 mL lactated Ringer's or normal saline). Infusion should begin at 8 drops/min, with subsequent adjustments made based on uterine contraction patterns. The drip rate is typically increased incrementally every 20 minutes until effective contractions are achieved. Effective contractions are defined as 3 contractions per 10 minutes, each lasting 30–60 seconds, accompanied by cervical shortening and dilation. Maximum infusion rate is 40 drops/min (13.2 mIU/min) for the 0.5% solution. If effective contractions are not achieved at the maximum rate, the oxytocin concentration may be increased to 1% (5 IU in 500 mL lactated Ringer's solution). In this case, the drip rate should first be halved before gradual re-titration, with a new maximum of 40 drops/min (26.4 mIU/min). Neither the drip rate nor the concentration should be further increased beyond these limits (21).

3.4.2 Control Group: Expectant Management or Induction at 41 weeks

Women assigned to the control group will be followed up by their attending physicians at least once a week. Unless there is a newly developed medical indication after randomization—such as fetal distress, oligohydramnios, or preeclampsia—no artificial intervention will be initiated to induce labor. Participants will be admitted to the hospital upon the spontaneous onset of labor.

If spontaneous labor has not occurred by 41 weeks + 2 days, labor induction will be initiated using oxytocin (19). For women with a Bishop score < 6, cervical ripening will be performed prior to induction, with a preference for the use of a balloon catheter combined with early amniotomy. The induction procedures will be the same as those used in the intervention group.

3.5 Study Management

3.5.1 Standardized Guidelines for Cesarean Delivery Not Requested by the Participant (22, 23)

- Failed induction: If the woman fails to enter active labor or remains in the latent phase after 18 hours of adequate uterine contractions (more than 3 contractions per 10 minutes accompanied by pain) following amniotomy and intravenous oxytocin administration, cesarean delivery may be considered for "failed induction."
- Failed cervical ripening: If the cervix remains unfavorable (Bishop score < 6) after balloon removal, a comprehensive maternal-fetal assessment should be performed. If maternal and fetal conditions allow, cervical ripening may be repeated under close monitoring. If continued waiting is not advisable, cesarean delivery should be performed. If the woman no longer wishes to attempt vaginal delivery, indications for cesarean section may be appropriately broadened.
- Fetal distress: Cesarean delivery is recommended if Category III fetal heart rate tracings are present, or if Category II tracings are assessed as threatening fetal well-being and vaginal delivery is not feasible.

- Labor arrest: If labor fails to progress due to uterine dysfunction or other causes despite adequate trial of labor, and vaginal delivery is not indicated, cesarean delivery is recommended.
- Other emergencies: Cesarean delivery may also be indicated in confirmed cases of umbilical cord prolapse, uterine rupture, placental abruption, preeclampsia/eclampsia, or acute maternal complications (e.g., infectious shock, severe cardiopulmonary failure) that preclude the continuation of labor.

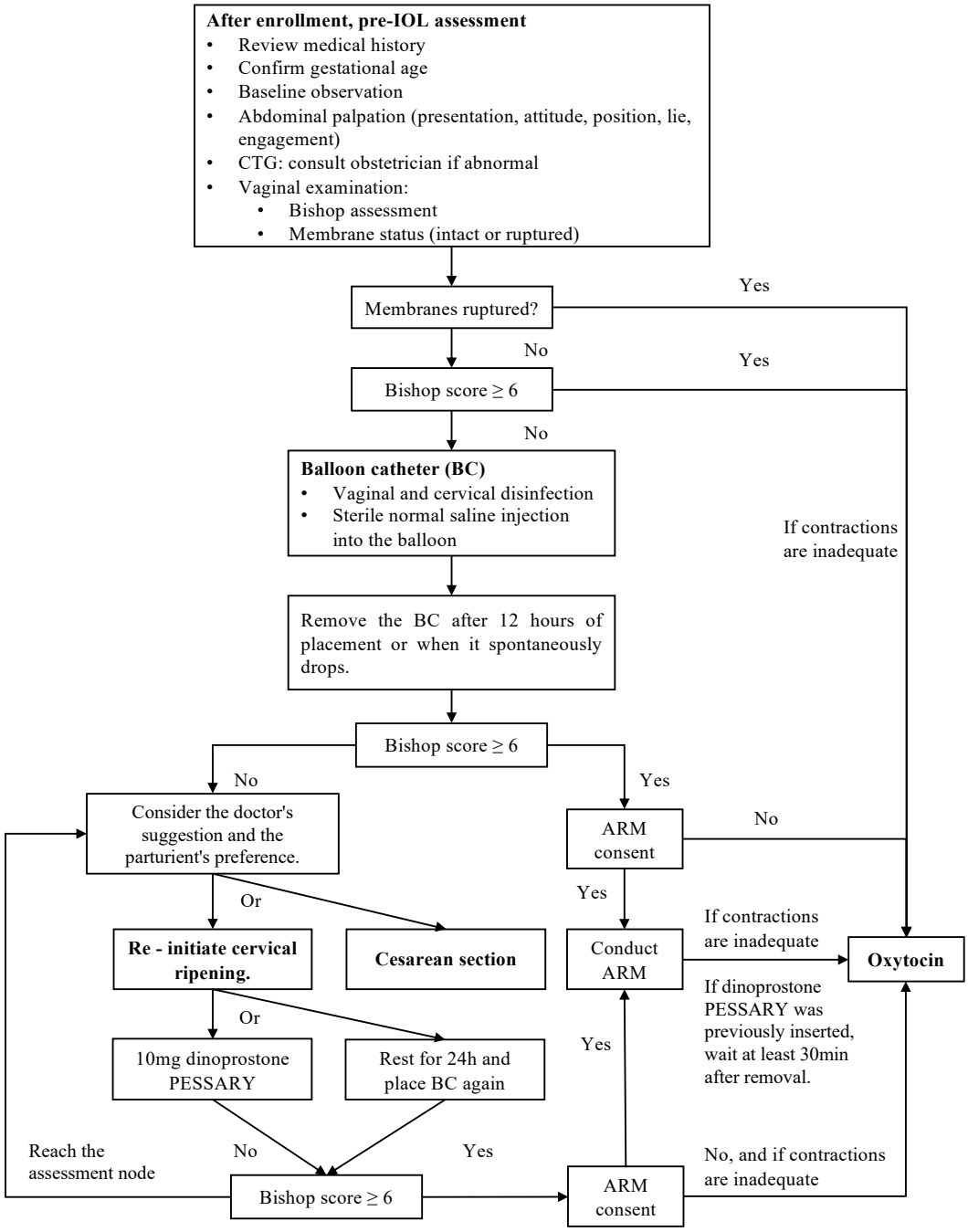

Figure 1. Flow chart of induction of labor methods (post - randomization).

Abbreviations: IOL, induction of labor; CTG, cardiotocography; BC, balloon catheter; ARM, artificial rupture of membrane.

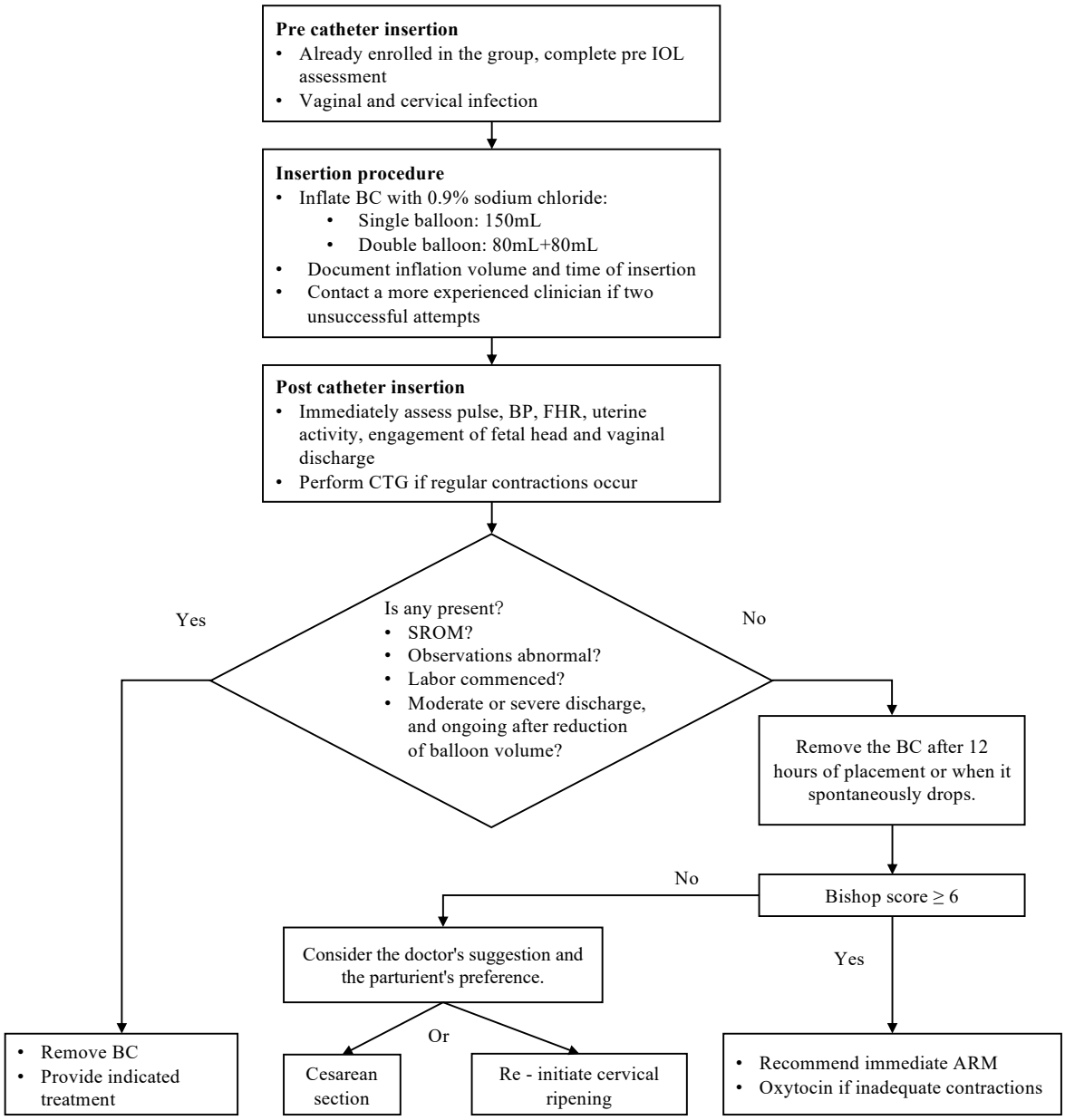

Figure 2. Flow chart of balloon catheter.

Abbreviations: IOL, induction of labor; CTG, cardiotocography; BC, balloon catheter; BP, blood pressure; FHR, fetal heart rate; SROM, spontaneous rupture of membranes; ARM, artificial rupture of membrane.

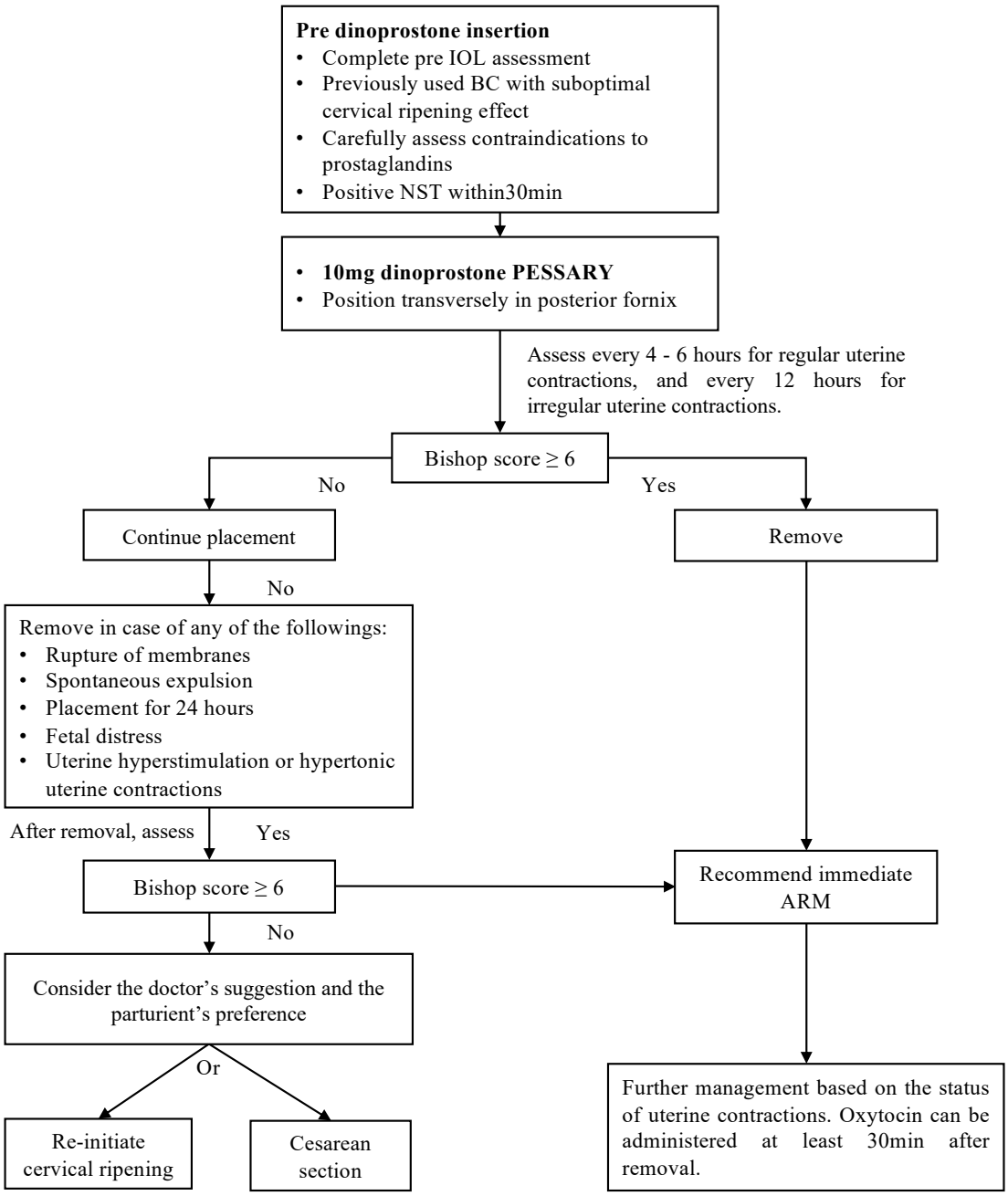

Figure 3. Flow chart of dinoprostone insertion.

Abbreviations: IOL, induction of labor; NST, Non-stress test; BC, balloon catheter; ARM, artificial rupture of membrane.

3.5.2 Guidelines for Intrapartum Antibiotic Use

- Antibiotics should be administered promptly in cases of clinical or suspected chorioamnionitis. Diagnostic criteria include maternal fever (⩾37.8°C or ⩾38.0°C) and at least two of the following:
    1. Maternal tachycardia (>100 bpm);
    2. Fetal tachycardia (>160 bpm);
    3. Uterine tenderness;
    4. Purulent or foul-smelling amniotic fluid or vaginal discharge;
    5. Maternal leukocytosis (white blood cell count >15,000/mm^3) (23, 24).

- Prophylactic antibiotics should be considered if the duration of membrane rupture exceeds 12 hours and the fetus has not been delivered.

3.5.3 Criteria for discontinuing or modifying allocated intervention/comparator

Participants can withdraw at any time on their own initiative, or the research institution will terminate their participation or modify the intervention/comparator in the following circumstances:

- The doctors think they need other treatments, or they do not comply with the research plan;
- The study is terminated early;
- Other special circumstances required by the ethics committee, such as the occurrence of serious adverse events.

3.6 Biological Sample Collection

3.6.1 Maternal Samples

- Late-pregnancy vaginal secretions: Collected at 39 weeks during outpatient visit after informed consent is obtained. Samples will be frozen at −80°C as soon as possible.
- Maternal stool: Collected at any time between 39 weeks and 3 days postpartum during hospitalization. Samples are snap-frozen on dry ice and stored at −80°C.

3.6.2 Offspring Samples

- Cord blood: Collected by midwives using anticoagulant tubes at the time of delivery. Samples are stored overnight at 4°C. The next day, 1/3 of the whole blood is stored directly at −80°C, and 2/3 is centrifuged to isolate plasma, which is then frozen at −80°C.
- Meconium: Collected by midwives or obstetric nurses, snap-frozen on dry ice, and stored at −80°C.
- Neonatal stool: Collected twice — once between 24–48 hours after birth (in hospital or at home), and once at 1 week of age.
- Infant stool: Collected twice — once at 6 weeks and once at 6 months postpartum. Samples are collected at home, placed in a cold box by caregivers, and delivered to the hospital within 1 hour for −80°C storage.

3.7 Outcome Measures

3.7.1 Primary outcome

Outcome Measure	Measure Description	Time Frame
Incidence of cesarean section	The proportion of deliveries completed by cesarean section	Delivery day

3.7.2 Primary Secondary Outcome

Outcome Measure	Measure Description	Time Frame
Composite incidence of severe neonatal morbidity and perinatal mortality	The composite incidence of any of the following: 1. Antepartum, intrapartum, or neonatal death 2. Intubation, continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) for ventilation or cardiorespiratory support within first 72 hours 3. Apgar ⩽ 3 at 5 minutes 4. Neonatal encephalopathy 5. Seizures 6. Sepsis (presence of a clinically ill infant in whom systemic infection is suspected with a positive blood, cerebral spinal fluid (CSF), or	Hospital discharge

	catheterized/suprapubic urine culture; or, in the absence of positive cultures, clinical evidence of cardiovascular collapse or an unequivocal X-ray confirming infection). 7. Pneumonia confirmed by X-ray or positive blood culture. 8. Meconium aspiration syndrome 9. Birth trauma (bone fractures, brachial plexus palsy, other neurologic injury, retinal hemorrhage, facial nerve injury) 10. Intracranial hemorrhage or subgaleal hemorrhage 11. Hypotension requiring pressor support	

3.7.3 Maternal Secondary Outcomes

Outcome Measure	Measure Description	Time Frame
Emergency Cesarean Rate	Cesarean delivery performed immediately or shortly after clinical decision due to imminent threat to the life of the mother or fetus	Delivery day
Category 1 Emergency Cesarean Rate	Cesarean performed within approximately 30 minutes due to immediate life-threatening conditions (e.g., uterine rupture, severe fetal distress)	Delivery day
Category 2 Emergency Cesarean Rate	Cesarean performed within 60–75 minutes due to urgent but not immediately life-threatening indications (e.g., progressive fetal distress, labor arrest)	Delivery day
Elective Cesarean Rate	Planned cesarean performed at or after 39 weeks in the absence of emergency conditions, meeting all of the following: 1. Surgery scheduled ⩾24 hours before onset of labor; 2. No spontaneous contractions or rupture of membranes; 3. Clear medical indications (e.g., placenta previa, breech presentation) or maternal request.	Delivery day
Operative Vaginal Delivery	The rate of vaginal deliveries assisted with instruments such as forceps or vacuum.	Delivery day
Gestational Age at Delivery	Expressed in weeks and decimal days (e.g., 39 weeks + 5 days = 39.7 weeks).	Delivery day
Chorioamnionitis	Incidence of chorioamnionitis, defined as a clinical diagnosis before delivery as: maternal body temperature rises (>38°C) with 1 or more of the following symptoms: 1. Maternal tachycardia (>100 beats/min); 2. Fetal tachycardia (>160 beats/min) 3. Uterine tenderness and irritability 4. Purulent or malodorous amniotic fluid or vaginal discharge 5. Maternal leukocytosis (white blood cell count > 15000/mm3)	Delivery day
Third-or fourth-degree perineal laceration	The incidence of third-or fourth-degree perineal laceration	Delivery day

Time from Randomization to Delivery	Measured in hours	Delivery day
Postpartum hemorrhage	Refer to the ARRIVE cohort, defined as any of the following situations: 1. Transfusion 2. Non-elective hysterectomy 3. Use of two or more uterotonics other than oxytocin 4. Other surgical interventions such as uterine compression sutures, uterine artery ligation, embolization and hypogastric ligation, balloon tamponade 5. Curettage	Hospital discharge
Postpartum infection	Refer to the ARRIVE cohort, defined as any of the following situations: 1. Clinical diagnosis of endometritis 2. Wound reopened for hematoma, seroma, infection or other reasons 3. Cellulitis requiring antibiotics 4. Pneumonia 5. Pyelonephritis 6. Bacteremia unknown source 7. Septic pelvic thrombosis	Hospital discharge
ICU admission	The proportion of admission to the ICU	Hospital discharge
Maternal death	The incidence of maternal death	Hospital discharge
Preeclampsia/gestational hypertension	The incidence of preeclampsia or gestational hypertension diagnosed during labor	Hospital discharge
Maternal venous thromboembolism	Deep vein thrombosis or pulmonary embolism	Hospital discharge
Maternal pain	Median patient-reported pain outcomes with a 10-point Likert scale	Hospital discharge

3.7.4 Fetal and neonatal secondary outcomes

Outcome Measure	Measure Description	Time Frame
Birth weight	The mean birth weight	Delivery day
Female gender	The proportion of female offspring in terms of physiological gender	Delivery day
Macrosomia	Birth weight > 4000g	Delivery day
Incidence of large for gestational age	According to the infant's gender and gestational age, the birth weight exceeds the 90th percentile of infants of the same gestational age	Delivery day
Incidence of small for gestational age	According to the infant's gender and gestational age, the birth weight is less than the 10th percentile of infants of the same gestational age	Delivery day

Apgar scores at 5 min	Apgar score at 5 minutes after birth	Delivery day
Neonatal acidosis	The incidence of neonatal acidosis defined as umbilical artery blood pH < 7.00	Delivery day
Shoulder dystocia	The incidence of shoulder dystocia	Delivery day
Hyperbilirubinemia	The incidence of hyperbilirubinemia requiring phototherapy or exchange transfusion	Hospital discharge
Transfusion of blood products or blood	The incidence of neonatal transfusion of blood products or blood	Hospital discharge
Hypoglycemia incidence	The incidence of hypoglycemia (blood glucose < 35mg/L) requiring intravenous treatment	Hospital discharge
Neonatal intensive care unit (NICU) admission	The incidence of admission to the NICU	Hospital discharge

3.7.5 Infant early-development outcomes

Outcome Measure	Measure Description	Time Frame
Physical measurement indicators	Infant weight, length, head circumference, chest circumference, sitting height, upper arm circumference, subcutaneous fat, height-chest circumference index, crown-rump length/length	42 days and 6 months
Growth balance indicators	Weight-for-length, length-for-age, weight-for-age z scores of infants, calculated using the WHO tool WHO Anthro Survey Analyser	42 days and 6 months
Growth retardation	Height standard deviation for age < mean-2S or percentile method < P3	42 days and 6 months
Abnormal neurological examination	The proportion of abnormal results in neurological examinations (hearing development, nerve reflexes)	42 days and 6 months
Bayley-3 scores of the Infant Development Scale	Total score, cognitive scale score, language scale score, motor scale score, social-emotional scale score, adaptive behavior scale score	42 days and 6 months
ASQ-3 scores of the Ages and Stages Questionnaires	Total score, communication domain score, gross motor domain score, fine motor domain score, problem-solving domain score, personal-social domain score	42 days and 6 months

3.7.6 Multi-omics outcomes

Outcome Measure	Measure Description	Time Frame
Gut microbiota development	Microbiota richness, dominant species, species transferred from mother to child, sub-group functional trajectory changes of the dominant species in offspring, and the transmissibility of species number and function	Meconium, first 48h, 7 days, 6 weeks and 6 months
Fecal metabolomic characteristics	Non-targeted metabolomic macroscopic differences, core metabolomic differences (including tryptophan, fatty acids), and differences in gut microbiota metabolites	Meconium, first 48h, 7 days, 6 weeks and 6 months
Cord blood metabolomic characteristics	Assessment of non-targeted metabolomic macroscopic differences and core metabolomic differences (including	Delivery day

	tryptophan, fatty acids) in cord blood plasma	
Cord blood proteomic characteristics	Analysis of the proteomic characteristics of cord blood whole blood to trace back the health status during the fetal period	Delivery day

3.7.7 Utilization of Medical Resources

Outcome Measure	Measure Description	Time Frame
Time from randomization to delivery	Median time from randomization to birth of the fetus, measured in hours	Delivery day
Use of epidural analgesia	Rate of epidural analgesia use	Delivery day
Time spent in the delivery room	Median time spent in the delivery room, measured in hours	Delivery day
Length of postpartum hospital stay	Median postpartum length of stay, measured in hours	Delivery day
Neonatal length of hospital stays	Median neonatal hospital stays, measured in hours	Delivery day
Pre-insurance hospitalization cost	Total hospitalization cost during delivery, before insurance reimbursement	Delivery day
Out-of-pocket hospitalization cost	Out-of-pocket cost incurred during delivery hospitalization	Delivery day

3.8 Adverse Event Reporting

Throughout the implementation of the study protocol, detailed information on adverse events will be collected and evaluated. Serious adverse events (SAEs) include maternal death, perinatal death, and life-threatening maternal complications occurring in the study hospital (e.g., uterine rupture, cervical laceration, amniotic fluid embolism syndrome). For all SAEs, a case report must be submitted to the hospital's Ethics Committee and Biostatistics Coordinating Center within 72 hours. The Coordinating Center will forward the information to the Data and Safety Monitoring Committee (DSMC) within 24 hours. In the event of a death, a copy of the patient's medical record must also be submitted.

Adverse events not meeting the above criteria for severity will be summarized along with other safety data and included in the DSMC's annual safety review report.

4 Statistical Considerations

4.1 Calculation of sample size based on the primary outcome

This is a superiority trial. Considering the potentially low incidence of the primary outcome, we calculated the sample size using the Fleiss correction based on normal approximation (25). For a 1:1 allocation, the formula for comparing two proportions is:

$$n_{per\_group} = \frac{\left[Z_{1-\alpha/2}\sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2)^2},\ \bar{p} = \frac{p_1+p_2}{2}$$

This calculation was implemented using the stats package in R. The assumptions were a two-sided alpha of 5% ($\alpha = 0.05$) and a power of 80% ($1-\beta = 0.80$).

In our hospital, approximately 30% of women initially planning vaginal delivery ultimately undergo cesarean section. After excluding cesarean deliveries performed upon maternal request and assuming stricter control over cesarean indications in this interventional trial, we estimate the cesarean rate in the expectant management group (p_1) to be between 13% and 18%. Preliminary observational pilot results suggest a cesarean rate of 9.5% in the 39-week induction group (p_2), so we consider p_2 to range from 8% to 11% (Table 2).

Additionally, some participants in the induction group may go into spontaneous labor before the planned intervention, while some in the expectant management group may undergo elective induction without medical indication. These protocol deviations can reduce the observed effect size. In the ARRIVE trial, the protocol deviation rate was approximately 5%; here, we consider a deviation range of 0–7.5%.

For example, assuming a cesarean rate of 16% in the expectant group and 9.5% in the induction group, with a 5% protocol deviation rate, each group would require 510 participants. Accounting for a 5% loss to follow-up, the final estimated sample size is n = 537 per group.

Table 2. Sample Sizes per Group for Different Primary Outcome Rates

Nominal Primary Outcome Rate in Induction Group	Nominal Primary Outcome Rate in Expectant Management Group					
	13%	14%	15%	16%	17%	18%
0% not delivering per protocol						
8%	589	426	325	258	211	177
9.50%	1279	803	557	413	320	257
11%	4144	1907	1109	733	524	396
2.5% not delivering per protocol						
8%	653	472	361	286	234	196
9.50%	1417	890	617	457	355	285
11%	4591	2113	1229	812	581	439
5% not delivering per protocol						
8%	728	526	402	319	261	219
9.50%	1579	992	688	510	395	317
11%	5116	2355	1369	905	647	490
7.5% not delivering per protocol						
8%	816	590	451	358	293	245
9.50%	1770	1112	771	571	443	356
11%	5735	2640	1535	1014	726	549

4.2 Interim Analysis

4.2.1 Interim Analysis Plan

To account for potential challenges in participant recruitment and biospecimen collection, two pre-specified interim analyses will be conducted:

- First Interim Analysis
  - Timing: Upon enrollment and follow-up of the first 200 participants through the primary outcome.
  - Content:
  1. Preliminary trends in the primary outcome (cesarean rate);
  2. Biospecimen collection rate and quality;
  3. Preliminary assessment of multi-omics data (and whether biospecimen targets need to be revised);
  4. Feasibility review (e.g., need for protocol adjustments, inclusion criteria, or sample handling procedures).
- Second Interim Analysis
  - Timing: Upon enrollment and follow-up of 500 participants through the primary outcome.
  - Content:
  1. Effect sizes of primary and secondary outcomes;
  2. Reassessment of sample size (based on observed effect size and variability);
  3. Safety data (serious adverse event rate).

4.2.2 Statistical Methods and Early Termination Criteria

- Statistical Methods:
  - Two-sided significance testing will be used; the Haybittle-Peto alpha-spending function will be applied to control the overall type I error rate (total $\alpha = 5\%$).
  - The significance threshold for interim analyses is set at $p < 0.002$ ($Z \geqslant 3.0$), to minimize false positives.
- The trial may be recommended for early termination if:
  - In interim analysis:
  1. There is clear evidence of efficacy ($p < 0.002$ and favorable risk-benefit profile) ;
  2. There are safety concerns (e.g., a significantly higher SAE rate in the intervention group);
  3. Futility is determined (the primary endpoint is unlikely to be achieved).
  - Final decisions regarding early termination must be proposed by the DSMB and approved by the Ethics Committee.

4.2.3 Data and Safety Monitoring Board (DSMB)

- Composition and Responsibilities:

The DSMB will consist of three members, including experts in clinical medicine, biostatistics, and ethics. Responsibilities include:

  - Periodic review of safety data and efficacy trends (at least annually or more frequently depending on recruitment pace);
  - Providing recommendations regarding continuation, modification, or termination of the trial based on interim results.
- Reporting Requirements:

Prior to each DSMB meeting, the Biostatistics Coordinating Center will submit a detailed report including:

  - Baseline characteristics: participant demographics and clinical features;
  - Protocol adherence: deviations and corrective actions;
  - Safety data: summary of adverse events categorized by SOC/PT codes;
  - Site performance: recruitment progress, data quality, loss to follow-up, biospecimen collection rate.

4.3 Data Analysis

Statistical analysis will follow the intention-to-treat (ITT) principle. All randomized participants who have not withdrawn informed consent will be included in the primary comparisons. Per-protocol (PP) analysis may also be performed to account for protocol deviations, but will be considered exploratory.

All statistical tests will be two-sided, and $p < 0.05$ will be considered statistically significant. A detailed statistical analysis plan (SAP) will be developed prior to the enrollment of the final participant. This protocol outlines only the general principles of analysis.

4.3.1 Baseline Analysis

Baseline characteristics will be described using descriptive statistics to assess balance between groups. Categorical variables will be presented as counts (percentages) and compared using chi-square tests or Fisher's exact tests (if expected cell counts <5). Continuous variables will be assessed for normality (Shapiro-Wilk test + histogram).

Normally distributed variables: mean ± SD, compared using t-tests;

Non-normally distributed variables: median and interquartile range (IQR), compared using the Mann-Whitney U test.

Recruitment numbers, loss to follow-up, and protocol deviation rates will also be reported.

4.3.2 Primary Outcome Analysis

The cesarean delivery rate will be compared using modified Poisson regression or log-binomial regression to estimate the relative risk (RR), risk difference (RD), and 95% confidence intervals (CIs), adjusting for stratification factors (maternal age and parity). In cases of baseline imbalance in potential confounders, multivariable adjusted models with robust variance estimation will be applied.

4.3.3 Secondary Outcome Analysis

- Binary variables: analyzed as for the primary outcome;
- Continuous variables: t-test for normally distributed variables; non-parametric tests for skewed data (as per baseline analysis);
- Time-to-event data: analyzed using Kaplan-Meier curves and log-rank tests.

4.3.4 Handling of Missing Data

- Baseline data: complete case analysis followed by multiple imputation.
- Loss to follow-up and protocol deviations: sensitivity analysis will be conducted using worst-/best-case imputation. Per-protocol analysis will be used for protocol deviations. In cases where pregnancy is terminated (e.g., stillbirth), competing risk analysis will be used in place of traditional methods. If the rate of loss to follow-up is high, inverse probability of censoring weighting (IPCW) may be applied to correct for selection bias.

4.3.5 Subgroup Analyses

Subgroup analyses for the primary outcome will be performed by stratifying participants according to: parity (nulliparous vs. multiparous), maternal age (<35 vs. ≥35 years), bishop score at randomization (<6 vs. ≥6), BMI (<30 vs. ≥30 kg/m^2).

Subgroup-specific effects will be estimated using the same methods as for the main analysis. Interaction terms between subgroup variables and treatment assignment will be tested. All subgroup analyses will be considered exploratory.

5 Ethical Considerations

The expectant management arm will follow current WHO and Chinese national guidelines. Elective induction at 39 weeks in low-risk pregnancies is not prohibited by current international or domestic guidelines. Existing evidence suggests that the enrolled population may derive certain perinatal benefits. Therefore, both treatment arms align with current clinical practice and pose no harm to participants.

Before initiation of the study, the final version of the protocol—including the informed consent form and all participant-facing materials—must receive written approval from the appropriate ethics committee. The investigators are responsible for submitting all documents and obtaining formal approval. All ethics committee decisions must be documented in writing and archived.

This study will collect basic maternal data while maintaining strict confidentiality. All patient information and data will be handled securely throughout the study and during manuscript preparation and publication.

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