When to induce for overweight? – a randomised controlled trial

Acronym: WINDOW

Statistical Analysis Plan

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Note: This is a detailed Statistical Analysis Plan. The content was initially presented with less detail in the original Study Protocol. While the statistical plans remain unchanged, some sections are now outlined more comprehensively.

Content

Abbreviations

BMI:	Body mass index
CI:	Confidence Interval
CPAP:	Continuous Positive Airway Pressure
CTG:	Cardiotocography
CS:	Caesarean Section
DMEC:	Data Monitoring and Ethics Committee
eCRF:	electronic Case Record Form
IOL:	Induction of Labour
GDM:	Gestational Diabetes Mellitus
HNFC:	High-Flow Nasal Cannula
NICU:	Neonatal Intensive Care Unit
OR:	Odds Ratio
RCT:	Randomised Controlled trial
REDCap:	Research Electronic Data Capture
sBE:	Standard Base Excess
TSC:	Trial Steering Committee
WHO:	World Health Organisation

1. Trial objective

1.1 Primary objective

To compare the risk of caesarean section with induction of labour (IOL) versus expectant management of pregnancy in women with a pre- or early pregnancy BMI ≥ 30 kg/m^2.

P – Pre- or early pregnancy BMI ≥ 30 kg/m^2
I – Induction of labour at 39 gestational weeks and 0 to 3 days
C – Expectant management until induction from 41 gestational weeks
O – Caesarean section

1.2 Secondary objectives

- To compare the effect of IOL at 39 gestational weeks and expectant management on maternal and neonatal morbidity and mortality.
- To compare the effect of IOL at 39 gestational weeks and expectant management on women's birth experience.
- To compare the effect of IOL at 39 gestational weeks and expectant management on women's mental health in the postpartum period.
- To compare the effect of IOL at 39 gestational weeks and expectant management on breast feeding.
- To compare the effect of IOL at 39 gestational weeks and expectant management on health resource utilization.

Maternal and neonatal outcomes will be included in the main paper, whereas the reamaining secondary objectives will be reported in the main or in secondary papers.

2. Trial methods

2.1 Trial design

Multicentre randomised controlled trial parallel group with an allocation ratio of 1:1. The study will recruit participants from sites with an in-house neonatal care unit in Denmark.

2.2 Trial interventions

Management strategies:

- *Intervention arm; induction of labour in pregnancy at 39 gestational week and 0 to 3 days*
  Induction is performed according to local policy for IOL (Prostaglandin E1, E2, Foley catheter, cervical ripening balloon catheter, artificial rupture of membranes (AROM), or oxytocin infusion when applicable). All medications are approved for IOL.
- *Comparison arm; expectant management*
  Waiting for spontaneous onset of labour unless a situation develops necessitating either IOL or caesarean section. All women with prolonged pregnancy can be offered IOL from 41 gestational weeks and 0 days in accordance to local policy.

2.3 Outcome measures

2.3.1 Primary outcome

The primary outcome is caesarean section.

2.3.2 Secondary maternal outcomes

- Mode of delivery if not by caesarean
  - vaginal delivery
  - vaginal assisted delivery
- Vaginal assisted delivery
  - Forceps
  - Ventouse
- Indication for caesarean section (more than one is possible):
  - Labour dystocia
  - Fetal distress
  - Maternal request
  - Suspected macrosomia
  - Non-cephalic presentation
  - Extensive vaginal bleeding
  - Suspected uterine rupture
  - Maternal or fetal complication/condition
  - Other
- Indication for vaginal assisted delivery (more than one is possible):
  - Labour dystocia
  - Fetal distress
  - Maternal request
  - Other indication for assisted vaginal delivery
- Use of epidural

<u>Complications:</u>

- Minor shoulder dystocia defined as the need McRoberts maneuver
- Major shoulder dystocia defined as the need for procedures other than McRoberts maneuver
- Clinical suspicion of abruption of the placenta leading to an intervention in labour
- Cord prolapse
- Maternal fever defined as temperature >38,2 / >38,0 °C with / without epidural
- Perineal 3rd degree laceration
- Perineal 4th degree laceration
- Episiotomy
- Damage to internal organs defined as bladder, bowel or ureters

<u>Postpartum morbidity:</u>

- Postpartum hemorrhage in milliliters defined as vaginal bleeding in the time frame 0-2 hours postpartum
- Blood loss >500ml from a vaginal bleeding in the time frame 0-2 hours postpartum.

- Blood loss >1000ml from a vaginal bleeding in the time frame 0-2 hours postpartum.
- Blood transfusion within 2 days postpartum.
- Hysterectomy caused by delivery complications.
- Puerperal infection treated in hospital.
- Admission to Intensive Care Unit.
- Maternal cardiopulmonary arrest.
- Maternal death.

2.3.3 Neonatal outcomes

- Neonatal composite including any of the following; perinatal death (stillbirth and neonatal), the need for respiratory support (intubation and mechanical ventilation, oxygen, continuous positive airway pressure (CPAP), or high-flow nasal cannula (HNFC)) within 72 hours after birth if admitted to a neonatal department, Apgar score <4 at 5 minutes, hypoxic–ischemic encephalopathy (defined as the need for therapeutic hypothermia), seizures, infection (defined as antibiotic treatment continuously for 7 days minimum) meconium aspiration syndrome, birth trauma (bone fracture, Duchenne-Erbs palsy, or retinal hemorrhage), intracranial or subgaleal hemorrhage, or hypotension requiring vasopressor support.
  Time frame: From randomisation during delivery hospitalisation until 28 days of life
  All components of the neonatal composite will additionally be reported separately.
- Neonatal trauma composite including any of the following; birth trauma (bone fracture, Duchenne-Erbs palsy, or retinal hemorrhage), intracranial or subgaleal hemorrhage.
  Time frame: From birth during delivery hospitalization until 28 days of life
- Neonatal asphyxia composite including any of the following; seizures, Apgar score < 4 at 5 minutes, umbilical cord pH < 7.0, umbilical cord sBE < -15.0 mmol/l, or hypoxic–ischemic encephalopathy (defined as the need for therapeutic hypothermia).
  Time frame: From birth during delivery hospitalisation until 28 days of life
- Apgar score at 5 minutes (absolute number)
  - <4
  - 4-7
  Time frame: At birth
- Umbilical cord arterial pH and standard base excess value
  - pH < 7.0
  - sBE < -15.0 mmol/l
  Time frame: At birth
- Umbilical cord venous pH and standard base excess value
  - pH < 7.0
  - sBE < -15.0 mmol/l
  Time frame: At birth
- Neonatal admission.
  Time frame: 0-72 hours from delivery
  - Treatment during admission.
    - CPAP

- HNFC
- Oxygen supplement treatment
- Ventilator treatment
- Therapeutic hypothermia
- Vasopressor support
- Antibiotic treatment continuously for 7 days' minimum

Time frame: From admission during delivery hospitalisation until 28 days of life

2.3.4 Maternal demographics and pregnancy characteristics

- Age
- Pre- or early gestational BMI
- Pre- or early gestational weight
- Height
- Parity
- Marital or cohabitant status
- Occupation
- Level of education
- Smoking during pregnancy,
- Origin of nationality Conceived by Assisted Reproductive Technologies (y/n)
- 120 minutes value from Oral Glucose Tolerance Test (OGTT) in mmol/L
- Gestational diabetes mellitus treated by diet alone (y/n)

2.3.5 Neonatal characteristics

- Birthweight (continuous; in grams)

  Birthweight > 4500 grams
- Sex (boy/girl)

2.3.6 Labour characteristics

- Gestational age at delivery
- Onset of labour:
  - Spontaneous
  - Induction
  - Casarean before spontaneous onset or induction of labour
- If induction of labour; Indications for induction of labour (more than one category possible):
  - Randomised to induction
  - Prolonged pregnancy
  - Maternal request
  - Pre- or early pregnancy BMI ≥ 35
  - Maternal or fetal complication/condition (free text)
- If induction of labour; Method of induction of labour (more than one category possible):
  - Prostaglandin tablet
  - Prostaglandin vaginal pad

  - Foley catheter
  - Cervical ripening catheter
  - Oxytocin infusion for induction
  - Artificial rupture of membranes and not augmentation of labour
  - Other (free text)
- If induction of labour; Number of whole days (24 h) without induction interventions and reasons for pause
- If induction of labour; Time from induction of labour until delivery (days)
- Cervical dilation at delivery ward admission
- Fetal head station at delivery ward admission
- Cervix length at delivery ward admission
- If caesarean; urgency of caesarean
  - Emergency caesarean before labour onset
  - Scheduled caesarean before labour onset
  - Emergency caesarean during labour before a previously scheduled caesarean
  - Emergency caesarean during labour
- If caesarean; Cervical dilation at caesarean section
- If caesarean; Fetal head station at caesarean section
- If caesarean; Cervix length at caesarean section
- Use of oxytocin augmentation during labour

2.3.7 Postpartum characteristics

- Surgical removal of placenta.
  Time frame: 0-2 hours postpartum
- Puerperal complications other than infections treated in hospital (free text).
  Time frame: 0-30 days postpartum
- Thromboembolic event (deep venous thrombosis or venous pulmonary embolism).
  Time frame: 0-30 days postpartum
- Acute colonic pseudo-obstruction.
  Time frame: 0-30 days postpartum
- Surgical procedures in the puerperal period and their indication.
  Time frame: 0-30 days postpartum

2.3.8 Maternal experience on birth, breastfeeding and mental health

- Birth experience (Childbirth Experience Questionnaire, CEQ1)[1].
  Time frame: 4-6 weeks postpartum
- Breastfeeding indicators.
  Time frame: 4-6 weeks postpartum
- Mental health as assessed by Major Depression Inventory (MDI)[2] and Edinburgh Postnatal Depression Score [3].

Time frame: 4-6 weeks postpartum

2.3.9 Characteristics on health resource utilization

- Telephone consultations from randomisation to delivery admission (n)
- Outpatient visits from randomisation to delivery admission (n)
- Hospital admissions from randomisation to delivery admission (n)
- Time on the delivery unit (hours)
- Maternal postpartum length of hospital stay (days)
- Neonatal length of hospital stay (days)
- Telephone consultations from delivery till 30 days postpartum (n)
- Outpatient visits from delivery till 30 days postpartum (n)
- Hospital admissions from delivery till 30 days postpartum (n)

2.3.10 Long-term follow-up

A follow-up on long-term maternal and pediatric outcomes will be reported. An additional study-specific protocol and statistical analysis plan on the long-term outcomes will be completed when time for follow-up is approaching. Long-term outcomes will be presented in a separate paper.

2.4 Timing of outcome measures

Maternal outcomes are measured from randomisation to 30 days after delivery. Neonatal outcomes are measured from randomisation to 28 days after delivery. Exceptions are made for individual outcomes.
Outcomes on birth experience, breastfeeding indicators, and mental health are collected from four to six weeks after delivery in a combined survey.

2.5 Timing of final analysis

The final analysis will occur after the data collection is completed.

2.6 Data collection and data management

Data will be collected and managed using REDCap electronic data capture tools hosted at Aarhus University. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Except from some of the baseline data and data from the post-partum questionnaires, all data will be obtained from the in-hospital electronical medical record.

- Data collection methods; Data will be collected in electronic case record forms (eCRFs) on which almost every response is pre-coded. The forms are generated using REDCap.

- If participants discontinue or deviate from the intervention protocol, we will continue to collect data, unless the woman specifically state that we cannot collect or store her data.

2.7 Randomisation

- Sequence generation and concealment; Eligible women will be randomised using an Internet-based randomisation programme in a 1:1 ratio using permuted and random block-sizes of 2, 4, and 6. There will be stratification on delivery site. The randomisation programme will automatically transfer the entry data to eCRFs in REDCap.
- Implementation; The allocation sequence is pre-coded and generated from the randomisation programme.

2.8 Criteria for discontinuation

Withdrawal of consent.

2.9 Blinding

The trial is open label.

2.10 Sample size

The planned sample size is 1,900 (950 per group).

For the primary outcome, the sample size is based on an assumption of a caesarean section rate in the non-intervention group (based on the caesarean section rate among women with a pre- or early pregnancy BMI ≥30 kg/m^2 who delivered at Aarhus University Hospital in 2018) is 25%. Assuming that the caesarean rate in the intervention group is 19%, then 854 participants are needed in each group to provide evidence for a difference of caesarean risk in the two groups with a power of 85% (alpha 0.05).

2.11 Frame work

The objective of this trial is to test the superiority of one intervention to another. The null hypothesis is that there is no difference in the rate of caesarean delivery between women allocated to IOL at 39 gestational weeks versus expectant management.

2.12 Interim analysis and stopping rules

No interim analysis is planned for, and there will be no formal stopping criteria.

An independent data monitoring and ethics committee (DMEC) are appointed prior to initiation of the trial. The DMEC will review de-identified data for safety at two predetermined milestones (600 and 1300 enrolled participants) but can – at any time – require extra reviews. The trial will continue while the DMEC reviews data. After the review, the DMEC will create a short report to the independent trial steering

committee (TSC) with recommendations for continuation with or without modifications or termination of the trial. Recommending termination will be at the discretion of the DMEC, and there will be no formal statistical criteria for termination due to safety.

3. Statistical principles

3.1 Analysis population

All statistical analyses will be based upon the total cohort of participants randomized into the trial. Data will be analysed according to intention-to-treat.

3.2 Definition of adherence

Adherence in the intervention group includes spontanous births or IOL from randomization to 39 gestational weeks and 4 days. All participants randomised to the expectant management group will be considered adherent.

3.3 Loss to follow-up

Loss to follow-up is defined as no information on mode of delivery.

4. Trial population

4.1 Recruitment

Participant flow will be presented in a CONSORT flow diagram including reasons for exclusion (Figure 1).

4.2 Baseline characteristics

Baseline characteristics will be tabulated as presented in Table 1 at the end of this document with counts and percentages for categorical variables, mean and standard deviation for continuous Gaussian distributed variables, and median and interquartile range for continuous non-Gaussian variables. Tests for statistical significance in baseline characteristics between the groups will not be undertaken, nor confidence intervals presented.

5. Analysis methods

5.1 Analysis of the primary outcome

The primary outcome variable will be assessed by comparing the event rates in the two groups using a two-sided chi-squared test, and presented as absolute and relative risks with 95% confidence intervals (CI) and numbers needed to treat (if applicable).

5.2 Analysis of secondary outcomes

Categorical secondary outcomes will be assessed in the same way as the primary outcome. For continuous secondary outcomes we will assess differences between groups using the Student t-test or a non-parametric Mann-Whitney U test as appropriate. For composite outcomes, the individual outcomes are also examined.

For all analyses, P-values of 0.05 will be interpreted as statistically significant.

5.3 Planned subgroup analysis and secondary analysis

We will conduct the following subgroup analyses:

- BMI ≤ or ≥ 35 kg/m^2
- Parity 0 versus 1+
- No gestational diabetes mellitus (GDM) versus GDM

A secondary analysis will be performed to evaluate the effect of site (stratification variable) by comparing the result of a random effect logistic regression model with site at random effect to an odds ratio without adjustment for site.

5.4 Missing data

Analysis will be completed on received data only with every effort made to follow-up participants to minimise any potential for bias. No imputation of missing data will be performed.

5.5 Sensitivity analysis/supportive analysis

Sensitivity analyses will consist of

A per-protocol analysis (adherent, see section 3.2) for the primary outcome only.

An as-treated analysis (see section 2.2) for the primary outcome only.

5.6 Statistical software

We will use STATA version 18.0 or higher for data management and analyses.

References

1. Dencker, A., et al., *Childbirth experience questionnaire (CEQ): development and evaluation of a multidimensional instrument.* BMC Pregnancy Childbirth, 2010. **10**: p. 81.
2. Bech, P., et al., *The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity.* J Affect Disord, 2001. **66**(2-3): p. 159-64.
3. Cox, J.L., J.M. Holden, and R. Sagovsky, *Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale.* Br J Psychiatry, 1987. **150**: p. 782-6.

Figure 1. CONSORT flow diagram

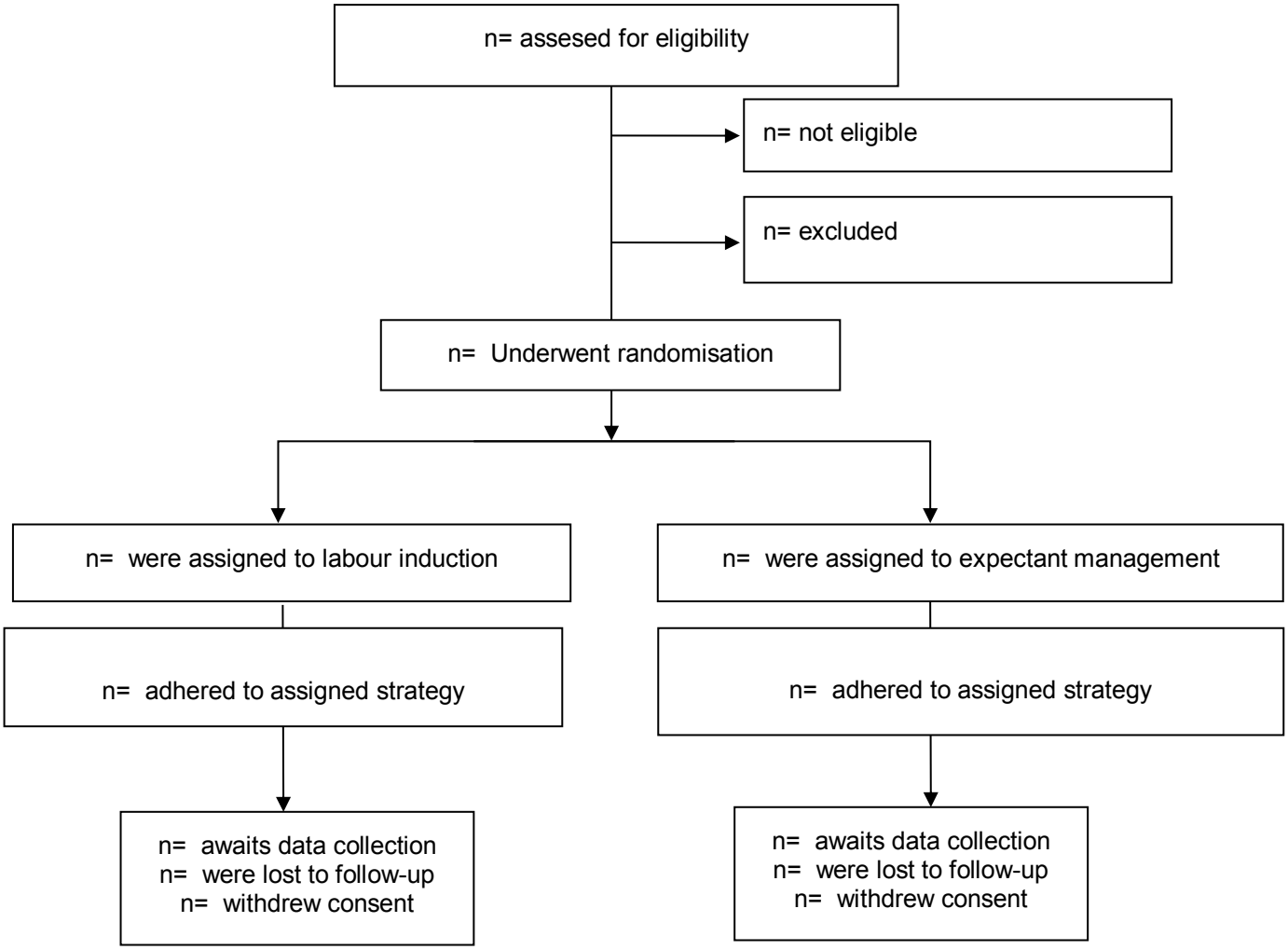

Table 1. Maternal characteristics at baseline.

Characteristic	IOL Group (n=)	Expectant management group (n=)
Pre- or early gestational BMI*		
Median	-	-
Interquartile range	-	-
30 to 34 – no. (%)	-	-
35 to 39 – no. (%)	-	-
40 or more – no. (%)	-	-
Parity		
P0 – no. (%)	-	-
P1 – no. (%)	-	-
P more than 1 – no. (%)	-	-
Age – yr		
Mean (SD)	-	-
Origin of nationality		
Danish national origin – no. (%)	-	-
Other national origin – no. (%)	-	-
Married or living with a partner – no. (%)	-	-
Employment status		
Studying – no. (%)	-	-
Employed– no. (%)	-	-
Not employed – no. (%)	-	-
Employment status unknown – no. (%)	-	-
Level of education**		
State school – no. (%)	-	-
High school – no. (%)	-	-
Vocational education – no. (%)	-	-
Short further education (≤2 yr) – no. (%)	-	-
Medium further education (2-4 yr) – no. (%)	-	-
Long further education (>4 yr) – no. (%)	-	-
Length of gestation at randomization – days		
Mean (SD)	-	-
Assisted conception – no. (%)	-	-
Current smoking status – no. (%)	-	-
GDM*** – no. (%)	-	-

**BMI is the weight in kilograms divided by the square of the height in meters; **Level of education is self-reported; ***Only GDM treated by diet alone is registered hence GDM treated by insulin is excluded. Induction of labor (IOL), Body-mass index (BMI), Gestational diabetes mellitus (GDM), Year (yr)*

Table of Characteristics of labor onset.

Characteristics	IOL Group (n=)	Expectant Management Group (n=)
Onset of labor		
Spontaneous labor – no. (%)	-	-
Induced labor – no. (%)	-	-
Cesarean delivery before labor onset – no. (%)	-	-
Gestational age at onset of labor - wk		
Median	-	-
Interquartile range	-	-
Indication for IOL*		
Randomized to induction – no. (%)	-	-
Prolonged pregnancy – no. (%)	-	-
BMI of 35 kg/m^2 or more – no. (%)**	-	-
Hypertensive disorder of pregnancy – no. (%)	-	-
Suspicion of fetus magnus – no. (%)	-	-
Maternal request – no. (%)	-	-
Other – no. (%)	-	-

**More than one indication per participant possible; **BMI is the weight in kilograms divided by the square of the height in meters. Induction of labor (IOL); Body mass index (BMI); Week (wk)*

Table of Maternal outcomes.				
Outcome	**IOL group (n=)**	**Expectant management group (n=)**	**RR (95%CI)**	**P Value**
Method of delivery – no. (%)				
Cesarean delivery	-	-	-	-
Assisted vaginal delivery	-	-	-	-
Indication for cesarean delivery – no. (%)				
Labor dystocia	-	-	-	-
Fetal distress	-	-	-	-
Maternal request	-	-	-	-
Suspected macrosomia	-	-	-	-
Non-cephalic presentation	-	-	-	-
Extensive vaginal bleeding	-	-	-	-
Suspected uterine rupture	-	-	-	-
Maternal medical complication	-	-	-	-
Other	-	-	-	-
Indication for assisted vaginal delivery – no. (%)				
Labor dystocia	-	-	-	-
Fetal distress	-	-	-	-
Maternal request	-	-	-	-
Other	-	-	-	-
Use of epidural – no. (%)	-	-	-	-
Intrapartum fever* – no. (%)	-	-	-	-
Minor shoulder dystocia** – no. (%)	-	-	-	-
Major shoulder dystocia*** – no. (%)	-	-	-	-
Abruption of the placenta**** – no. (%)	-	-	-	-
Cord prolapse – no. (%)	-	-	-	-
Perineal laceration – no. (%)				
3rd degree laceration	-	-	-	-
4th degree laceration	-	-	-	-
Episiotomy – no. (%)	-	-	-	-
Postpartum hemorrhage^ – no. (%)				
Blood loss >500ml	-	-	-	-
Blood loss >1000ml	-	-	-	-
Blood transfusion	-	-	-	-
Uterine scar dehiscence or rupture – no. (%)	-	-	-	-
Damage to internal organs^^ – no. (%)	-	-	-	-
Hysterectomy – no. (%)	-	-	-	-
Admission to ICU – no. (%)	-	-	-	-
Cardiopulmonary arrest – no. (%)	-	-	-	-
Death – no. (%)	-	-	-	-
Puerperal infection^^^ – no. (%)	-	-	-	-
Severe postpartum conditions^^^^ – no. (%)	-	-	-	-

**Defined as temperature >38.2°C with epidural, without epidural: >38.0°C; **Defined as the need McRoberts maneuver; ***Defined as the need for procedures other than McRoberts maneuver; ****Defined as clinical suspicion leading to an intervention in labor; ^Estimated postpartum hemorrhage within the first 48 hours from birth; ^^Defined as bladder, bowel and ureters; ^^^Defined as puerperal infection treated in hospital; ^^^^Severe postpartum conditions treated in hospital besides puerperal infections, including any thromboembolic event. Induction of labor (IOL), Relative risk (RR), Confidence interval (CI), Intensive Care Unit (ICU).*

Table of Neonatal characteristics and outcomes.

Characteristics	IOL group (n=)	Expectant management group (n=)	RR (95%CI)	P Value
Female sex – no. (%)	-	-	-	-
Mean birth weight (± SD)	-	-	-	-
Birth weight > 4500g – no. (%)	-	-	-	-
Median Apgar scores at 5 min	-	-	-	-
Apgar scores from 4 to 7 at 5 min	-	-	-	-
Primary composite outcome – no. (%)	-	-	-	-
Perinatal death (stillbirth or neonatal)	-	-	-	-
Respiratory support*	-	-	-	-
Apgar scores <4 at 5 min	-	-	-	-
Moderate to severe hypoxic ischemic encephalopathy**	-	-	-	-
Seizures	-	-	-	-
Meconium aspiration syndrome	-	-	-	-
Infection***	-	-	-	-
Birth trauma****	-	-	-	-
Intracranial or subgaleal hemorrhage	-	-	-	-
Hypotension ^	-	-	-	-
Trauma composite outcome – no. (%)	-	-	-	-
Hypoxia composite outcome – no. (%)	-	-	-	-
Umbilical cord – no. (%)				
Arterial pH <7.0	-	-	-	-
Arterial base excess <-15.0 mmol/L	-	-	-	-
Venous pH <7.0	-	-	-	-
Venous base excess <-15.0 mmol/L	-	-	-	-
NICU admission^^ – no. (%)	-	-	-	-
Treatment if NICU admission – no. (%)	-	-	-	-
CPAP	-	-	-	-
HNFC	-	-	-	-
Oxygen supplement treatment	-	-	-	-
Ventilator treatment	-	-	-	-
Therapeutic hypothermia	-	-	-	-
Vasopressor support	-	-	-	-
Antibiotic treatment^^^	-	-	-	-

**Defined as the need for respiratory support (intubation and mechanical ventilation, oxygen, continuous positive airway pressure (CPAP), or high-flow nasal cannula (HNFC)) within 72 hours after birth if admitted to Neonatal Intensive Care Unit (NICU); **Defined as the need for therapeutic hypothermia; ***Defined as antibiotic treatment continuously for 7 days minimum; ****Defined as any fracture, Duchenne-Erbs palsy, or retinal hemorrhage; ^Defined as hypotension requiring vasopressor support; ^^Defined as NICU admission within 72 hours from birth; ^^^Defined as antibiotic treatment administered continuously for 7 days minimum. Induction of labor (IOL), Relative risk (RR), Confidence interval (CI), Minutes (min), Grams (g).*

Table of sub-group analyses for the primary outcome cesarean section.

Subgroup	No. of participants	No. with outcome	RR (95%CI)	P Value
Overall	-	-	-	-
BMI				
Below 35 kg/m^2	-	-	-	-
35 kg/m^2 or more	-	-	-	-
Parity				
Nulliparous	-	-	-	-
Parous	-	-	-	-
Presence of GDM*				
No GDM	-	-	-	-
GDM	-	-	-	-

**Only GDM treated by diet alone is registered hence GDM treated by insulin is excluded. Relative risk (RR),Confidence interval (CI), Body mass index (BMI), Gestational diabetes mellitus (GDM).*