When to induce for overweight? – a randomised controlled trial

Acronym: WINDOW

TRIAL PROTOCOL

Version: 1.6
August 15, 2023

ClinicalTrials.gov number: NCT04603859

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Content

Abbreviations

AROM:	Artificial Rupture of Membranes
BMI:	Body Mass Index
CI:	Confidence Interval
CPAP:	Continuos Positive Airway Pressure
CTG:	Cardiotocografia
CS:	Caesarean Section
DMEC:	Data Monitoring and Ethics Committee
eCRF:	electronic Case Record Form
eIOL:	elective Induction of Labour
GCP:	Good Clinical Practice
GDM:	Gestational Diabetes Mellitus
GDPR:	General Data Protection Regulation
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
SOP:	Standard Operating Procedure
TSC:	Trial Steering Committee
WHO:	World Health Organisation

Roles and responsibilities

WINDOW study group

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Conflicts of interest

The members of the WINDOW study group have no conflicts of interest to declare. The trial sponsor has no ultimate authority over any aspects of the trial design, conduct, or reporting.

Recruiting Trial sites

Aarhus University Hospital
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Responsible physician investigator: Lise Qvirin Krogh, Consultant, PhD-student

Regional Hospital Gødstrup
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Preliminary list, more trial sites could follow.

Protocol amendments

In case of significant protocol amendments is added to the original protocol, a new version number will be assigned to the protocol. Simultaneously, we will add the amendments to the clinicaltrials.gov registration, and we will submit a supplementary protocol to the Central Denmark Region Committee on Biomedical Research Ethics.

Trial registration

The trial will be registered at clinicaltrials.gov using the administrative authorities of Aarhus University (UAarhus).

Funding

Funding for the trial is provided by the Novo Nordic Foundation (DKK 6,500,000), the Health Research Foundation of Central Region Denmark (DKK 512,000), and Department of Clinical Medicine, Aarhus University (DKK 120,000). Additional funding will be applied from private and public funds. The funding agencies will have no role in any of the aspects of the trial.

1. Introduction

The World Health Organisation [1] defines overweight as a body mass index (BMI) of ≥25 kg/m^2 and obesity as a BMI of ≥30 kg/m^2 [1]. More than 650 million adults were obese in 2016, which corresponds to 13% of the adult population in the world [1]. In fertile women, the prevalence of obesity is one third in the United States, 20% in the UK, and 12-13% in Denmark [2, 3].

The risk of gestational complications increases with increasing BMI [2]. Obesity in pregnancy is associated with a number of complications including gestational diabetes, preeclampsia, fetal macrosomia, stillbirth, postpartum haemorrhage, neonatal death, and caesarean delivery [4-8]. Delivery by caesarean section further adds significant risks of wound infection or other infectious morbidity in obese women as compared to normal weight women [8-10].

The longer duration of pregnancy, the longer the pregnant woman is at risk of pregnancy complications. In an otherwise low-risk pregnant woman at full term (39+ weeks of gestation), it is an on-going clinical dilemma, whether the benefits of elective induction of labour (eIOL) and termination of the pregnancy will outweigh the potential harms from the induction and delivery process [11, 12]. With regard to delivery complications, based on data from historical cohorts, eIOL has been associated with an increased risk of caesarean section and instrumental delivery [11]. Therefore, expectant management has been the preferred clinical option.

This interpretation has been challenged by two randomised trials [13, 14] of which the largest, the ARRIVE trial, with >6000 low-risk pregnant women found that eIOL at 39 gestational week was associated with lower caesarean delivery rates [14]. There are no randomised studies concerning timing of eIOL in obese women, but three observational studies found lower odds of caesarean delivery in obese women with eIOL as compared to awaiting labour onset [15-17]. Furthermore, guidelines such as the guideline on "Care of women with obesity in pregnancy" from the Royal College of Obstetricians in the UK advocates that the option of induction of labour should be discussed with the pregnant women [18].

Current practice in Denmark is to offer eIOL at 41 gestational week and 3 to 5 days to all low-risk pregnant women including women with BMI of ≥30 kg/m^2, whereas women with BMI of ≥35 kg/m^2 are offered eIOL at 41 gestational week and 0 days. Danish obstetrical practice differs significantly from that used in other parts of the world (e.g. the United States), in particular with regard to much better prenatal care, but also with regard to demographic factors in the obstetric population (i.e. fewer obese and multiparous women) and in an overall much lower caesarean delivery rate (20% vs. 30-35% in the United States). Results from the United States may therefore not be immediately transferable to a Danish or a Scandinavian setting. Hence, a randomised trial that would compare the incidence of caesarean delivery among obese women whose labour is induced compared with those who are managed expectantly is warranted. Such a randomised study will provide new and important knowledge into the area of induction of labour among overweight and obese women. The results will be expected to have international attention and to have a large impact to the increasing number of obese pregnant women worldwide.

2. Objective

To compare the risk of caesarean section with eIOL versus expectant management of pregnancy in women with a pre- or early pregnancy BMI ≥ 30.

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

3. Trial design

Multicentre randomised controlled trial parallel group with an allocation ratio of 1:1.

4. Allocation

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. Stratification will be on, site. The randomisation programme will automatically transfer the entry data to electronic case record forms (eCRF) in REDCap.
Implementation; The allocation sequence is pre-coded and generated from the randomisation programme.

5. Intervention

5.1 Management strategies

5.1.1 Intervention arm/elective induction of labour in pregnancy at 39 gestational week and 0 to 3 days

Induction is performed according to local policy for induction of labour (Prostaglandin E1, E2, Foley catheter, cervical ripening balloon catheter, artificial rupture of membranes (AROM), or oxytocin infusion when applicable). All medications are approved for induction of labour.

5.1.2 Comparison arm/expectant management

Waiting for spontaneous onset of labour unless a situation develops necessitating either induction of labour or caesarean section. All women with prolonged pregnancy can be offered induction of labour from 41 gestational weeks and 0 days in accordance to local policy.

5.2 Existing pharmaceutical or non-pharmaceutical strategies

Any existing pharmaceutical or non-pharmaceutical strategies used for emotional support, labour support, or for pain relief prior to or during labour are permitted.

5.3 Criteria for discontinuation

Withdrawal of consent.

6. Study setting

Danish delivery wards with an in-house neonatal care unit.
In each delivery site, a responsible physician investigator will be appointed. The responsible physician investigator will be formally educated about the trial and relevant procedures. Data on the individual study sites including the responsible physician investigators can be obtained from clinicaltrials.gov. We will initiate the study in three sites (Aarhus University Hospital, Regional Hospital of Randers and Regional Hospital of Gødstrup), followed by the remaining sites when appropriate.

7. Blinding

The trial is open label.

8. Eligibility criteria

8.1 Inclusion criteria

Pregnant women with pre- or early pregnancy BMI ≥ 30 kg/m^2.

Pre- or early pregnancy BMI is defined as the pre-pregnancy BMI stated in the patient's medical record or the early pregnancy BMI obtained by the general practitioner in early pregnancy.

8.2 Exclusion criteria

- Legal or ethical considerations: maternal age <18 years, language difficulties requiring an interpreter or translator
- Multiple pregnancy
- Previous caesarean section
- Uncertain gestational age, defined as gestational age not determined by Crown-Rump-Length
- Planned elective caesarean section at time of randomisation
- Known fetal contraindications to IOL at time of randomisation: e.g. non-cephalic presentation, or other fetal conditions contraindicating vaginal delivery
- Known fetal contraindications to expectant management at time of randomisation: e.g. fetal conditions*
- Known maternal contraindications to IOL at time of randomisation: e.g. placenta previa/accreta, vasa previa
- Maternal contraindications to expectant management at time of randomisation: e.g. maternal medical conditions**, ultrasonically diagnosed oligohydramnios (DVP< 2 cm), signs of labour including pre-labour rupture of membranes (PROM)

*Fetal conditions: Fetal demise, history of continuously abnormal or pathologic CTG, FGR or macrosomia diagnosed by ultrasound, or major malformations. All conditions are considered from an individual clinical perspective.
**Maternal medical conditions: Insulin treated diabetes mellitus, any hypertensive disorder with blood pressure >140/90, cardiac disease, renal insufficiency, other medical or psychological conditions with indicated delivery < 41 gestational week and 0 days.

9. Screening for participation

9.1 The screening process

There will be a three-step screening to optimise recruitment and at the same time taking the use of resources into consideration.
In the first step screening, the women are screened for the inclusion criteria. Optimally, this screening will take place when the women are referred from the general practitioner. If this screening does not occur at this time of pregnancy it can take place later during pregnancy e.g. when attending the midwifery outpatient clinic, the ultrasound unit, or the outpatient clinic for pregnant women. The screening will be

performed by a trained member of the local clinical team. If the woman meets the inclusion criteria, she will be registered in a screening log. A screening log is essential to avoid duplicate entries in the study. Duplicate entries can occur because a woman can be pregnant more than once during the inclusion period, and she can attend to more than one of the inclusions sites within the same pregnancy, and from one pregnancy to the next.
In the second step screening, women listed in the screening log will be screened for exclusion criterions for the first time. Optimally, this screening will take placed at approximal gestational week 32. The screening will be performed by a trained member of the local clinical team. This screening step is performed to identify to whom it will be relevant to receive written information on the study.
In the third step screening, women in the screening log will be screened for exclusion criterions for the second time to identify any new circumstances leading to exclusion. This screening step is performed to narrow the population eligible to receive verbal information. Optimally, this screening is performed as close to gestational week 38 as possible trying to ensure a minimum of exclusions after randomisation, and still leave time for securing the informed consent, the randomisation, and the planning of the intervention. This screening will be performed by the responsible physician investigator at each site or from another assigned research staff member from the local clinical team.
When introducing a new trial site, all women meeting the inclusion criterion at that trial site and at gestational week 37 or less will be registered in the screenings log at once. The second and third step screening of these women will take place as described in the above.

9.2 The information process

Written information on the trial will be sent electronically to women found eligible after the second step screening. Women found eligible after the third step screening will be given verbal information on the trial from the responsible physician investigator or from another assigned research staff member at each site. Verbal information will include information on the background of the study, inclusion criteria, potential risks and benefits, as well as practical aspects and purpose of the study.
Depending on availability and safety circumstances the verbal information will be given per telephone, per video consultation, or at a consultation at the midwifery outpatient clinic, or outpatient clinic for pregnant women. The eligible women will have the opportunity to request an assessor. Between the verbal information and the consent request, the eligible woman will be offered time for consideration (an appropriate amount of time will be agreed individually allowing a minimum of 24 hours if needed), and further time can be requested as needed.
Prior to the beginning of patient enrolment, and continuously throughout the enrolment period, members of the local clinical team, the responsible physician investigator, and other assigned research staff members will be formally introduced to the trial. This include information on the trials background, objectives, inclusion/exclusion criteria, intervention, and the procedures they are involved in.

10. Consent or assent

The responsible physician investigator takes responsibility that the eligibility criteria are fulfilled prior to randomisation and will also ensure to obtain the written consent. Consent from eligible participants is obtained by the responsible physician investigator or an appointed research staff member at approximately 38 weeks of gestation and no later than the time of randomisation. The consent form will

be digital, and all signatures will be written on a smart phone, a tablet or a computer using REDCap which has dedicated functionalities for written consent.

11. Variables

11.1 Maternal demographics and pregnancy characteristics

1. Age
2. Pre- or early gestational BMI
3. Pre- or early gestational weight
4. Height
5. Parity
6. Marital or cohabitant status
7. Occupation
8. Level of education
9. Smoking during pregnancy,
10. Origin of nationality Conceived by Assisted Reproductive Technologies (y/n)
11. 120 minutes value from Oral Glucose Tolerance Test (OGTT) in mmol/L - allow missing data
12. Gestational diabetes mellitus treated by diet alone (y/n)

11.2 Neonatal characteristics

1. Birthweight (continuous; in grams)
   - Birthweight > 4500 grams
2. Sex (boy/girl)

11.3 Labour characteristics

1. Gestational age at delivery
2. Onset of labour:
   - Spontaneous
   - Induction
   - Casarean before spontaneous onset or induction of labour
3. If induction of labour; Indications for induction of labour (more than one category possible):
   - Randomised to induction
   - Prolonged pregnancy,
   - Maternal request
   - Maternal or fetal complication/condition (free text)
4. 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)
5. If induction of labour; Number of days (>24 h) without induction interventions and reasons for pause

6. If induction of labour; Time from induction of labour until delivery (days)
7. Cervical dilation at admission time on delivery ward
8. Caput station at admission time on delivery ward
9. Cervix length at admission time on delivery ward
10. If caesarean; urgency of caesarean
11. If caesarean; Cervical dilation prior to caesarean section
12. If caesarean; Caput station prior to caesarean section
13. If caesarean; Cervix length prior to caesarean section
14. Use of oxytocin augmentation during labour (y/n)

11.4 Postpartum characteristics

1. Surgical removal of placenta due to retention. Time frame 0-2 hours postpartum
2. Puerperal complications other than infections treated in hospital (free text). Time frame 0-30 days postpartum
3. Thromboembolic event (deep venous thrombosis or venous pulmonary embolism). Time frame 0-30 days postpartum
4. Acute colon pseudo obstruction. Time frame 0-30 days postpartum
5. Surgical procedures in the puerperal period and indication. Time frame 0-30 days postpartum

11.5 Maternal experience on birth, breastfeeding and mental health

1. Birth experience (Childbirth Experience Questionnaire, CEQ1)[19]. Time frame 4-6 weeks postpartum
2. Breastfeeding indicators. Time frame 4-6 weeks postpartum
3. Mental health as assessed by Major Depression Inventory (MDI)[20] and Edinburgh Postnatal Depression Score [21]. Time frame 4-6 weeks postpartum

11.6 Characteristics on health resource utilization

1. Telephone consultations from randomisation to admission for delivery (n)
2. Outpatient visits from randomisation to admission for delivery (n)
3. Hospital admissions from randomisation to admission for delivery (n)
4. Time on the delivery unit (hours)
5. Maternal postpartum length of hospital stay (days)
6. Neonatal length of hospital stay (days)
7. Telephone consultations from delivery till 30 days postpartum (n)
8. Outpatient visits from delivery till 30 days postpartum (n)
9. Hospital admissions from delivery till 30 days postpartum (n)

11.7 Outcomes

The primary outcome is caesarean section (y/n). Time frame at any time from inclusion.

Secondary outcomes will include:

11.7.1 Maternal outcomes

1. Mode of delivery if not by caesarean
   - vaginal delivery
   - vaginal assisted delivery
2. Vaginal assisted delivery
   - Forceps
   - Ventouse
3. 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 (free text)
   - Other (free text)
4. Indication for vaginal assisted delivery (more than one is possible):
   - Labour dystocia
   - Fetal distress
   - Maternal request
   - Other indication for assisted vaginal delivery (free text)
5. Use of epidural (y/n)

   <u>Complications:</u>
6. Minor shoulder dystocia defined as the need McRoberts maneuver (y/n)
7. Major shoulder dystocia defined as the need for procedures other than McRoberts maneuver (y/n)
8. Clinical suspicion of abruption of the placenta leading to an intervention in labour (y/n)
9. Cord prolapse (y/n)
10. Maternal fever defined as temperature >38,2 / >38,0 ^{o}C with / without epidural (y/n)
11. Perineal 3rd degree laceration (y/n)
12. Perineal 4th degree laceration (y/n)
13. Episiotomy (y/n)
14. Damage to internal organs (bladder, bowel or ureters)

    <u>Postpartum morbidity:</u>
15. Postpartum haemorrhage in milliliters (continuous variable). Time frame 0-2 hours postpartum
16. Blood loss >500ml. Time frame 0-2 hours postpartum
17. Blood loss >1000ml. Time frame 0-2 hours postpartum
18. Blood transfusion. Time frame 0-2 days postpartum
19. Hysterectomy
20. Puerperal infection treated in hospital. Time frame 0-30 days postpartum
21. Admission to Intensive Care Unit. Time frame 0-30 days postpartum

22. Maternal cardiopulmonary arrest (y/n). Time frame from randomisation to 30 days postpartum
23. Maternal death (y/n). Time frame from randomisation to 30 days postpartum

11.7.2 Neonatal outcomes

1. 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
   All components of the above neonatal composite will additionally be reported separately.
2. Neonatal trauma composite including any of the following; birth trauma (bone fracture, Duchenne-Erbs palsy, or retinal hemorrhage), intracranial or subgaleal hemorrhage. Time frame birth during delivery hospitalisation
3. 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 birth during delivery hospitalisation
4. Apgar score at 5 minutes (absolute number)
   - <4
   - 4-7
5. Umbilical cord arterial pH and standard base excess value (continuous variable) - allow data missing
   - pH < 7.0
   - sBE < -15.0 mmol/l
6. Umbilical cord venous pH and standard base excess value (continuous variable) - allow data missing
   - pH < 7.0
   - sBE < -15.0 mmol/l
7. Neonatal admission (y/n). Time frame 0-72 hours
8. Treatment during admission. Time frame 0-28 days
   - CPAP (y/n)
   - HNFC (y/n)
   - Oxygen supplement treatment (y/n)
   - Ventilator treatment (y/n)
   - Therapeutic hypothermia (y/n)
   - Vasopressor support
   - Antibiotic treatment continuously for 7 days' minimum

11.8 Long-term follow-up

A follow-up on long-term maternal and pediatric outcomes will be reported. An additional study specific protocol on the long-term outcomes will be sent to evaluation at the Central Denmark Region Committee on Biomedical Research Ethics when time for follow up is approaching. The initial consent form will include permission to contact the participant after the primary trial for the purpose of follow-up. The follow-up data will be reported separately.

11.9 Patients perspectives

Understanding the patient perspective is essential to support patient-centered care both in the present study and in potential, future implementation. Thus, an explorative qualitative study will be performed with the aim to investigate experiences, information needs and birthing experiences among women in the intervention arm. A purposive sample of app. 20 participants will be recruited from Aarhus University Hospital and interviewed 4 to 8 weeks' post-partum by a social scientist researcher. Interviews are conducted at a time and place of the participant's choice and a semi-structured interview guide will be used. All interviews will be digitally recorded, transcribed verbatim and analyzed using thematic analysis. Participation is dependent on informed consent and consent can be withdrawn at any time.
An amendment covering written participant information, consent form, and wording of the questions encompassed in the interview for this subgroup of participants will be submitted later to evaluation at the Central Denmark Region Committee on Biomedical Research Ethics. Recruitment for this sub study will not take place before approval from the Central Denmark Region Committee on Biomedical Research Ethics is obtained.

12. Harms

12.1 General considerations

All antenatal management and all types of medicinal products used in the trial are used according to standard procedures and caretaking for pregnant women.
The inherent risk of complications from carrying a child and giving birth exists regardless of the conduct of this trial. Any possible risks associated with the conduct of the study are not, neither on their own nor compared to the expected gain from the study, expected to reach an indefensible extent. The therapeutic and public health gain of the study is expected to justify the study. The sake of the study participants will at any time override the sake of the conduct of the study.

12.2 Potential benefits

Among other potential benefits for participants in the intervention group, termination of the pregnancy at 39 gestational weeks might reduce the risk of known gestational complications e.g. pre-eclampsia, fetal macrosomia, stillbirth etc. Studies have indicated that women undergoing eIOL have fever antepartum visits, and shorter maternal and neonatal hospital duration after delivery.

12.3 Potential disadvantage

Among potential disadvantages for participants in the intervention group is that women undergoing eIOL might experience a longer duration of the stay at the delivery ward, may get side effects to medicinal products used for induction, and that the risk of failure to induce is present. Whether the birth experience will be influenced negatively is not known. To our knowledge this matter has not been fully explored among women undergoing eIOL at 39 weeks of gestational weeks, however IOL due to medical indication including postterm pregnancy has been reported to impact the birth experience negatively.

12.4 Adverse event definitions

Definitions cover both maternal and fetal/neonatal events.

Adverse event (AE): Any toward medical occurrence in a study participant.
Serious adverse event (SAE): Any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalization, or prolongation of existing inpatients' hospitalization
- Results in persistent, or significant disability or incapacity

The following is not considered as adverse events:

- Admissions or outpatient attendance for;
  - fetal monitoring
  - maternal hypertension
  - antepartum haemorrhage
  - preterm labour
  - abdominal pain
  - non-cephalic presentation
  - placenta praevia
- Hospitalisation for;
  - labour
  - induction of labour
  - normal delivery
  - caesarean
  - elective treatment for pre-existing condition
- Admission for common postpartum problems e.g.;
  - maternal hypertension
  - perineal problems
  - urinary problems
  - breastfeeding challenges
  - mental health problems
  - infections

12.5 Adverse event reporting

All AE should be recorded. Regarding SAE, a SAE form should be completed by the responsible physician investigator and send to the Principal Investigator and Sponsor within 24 hours from the knowledge of the event. The SAE will be assessed by the WINDOW study group. Assessment of the adverse and serious adverse events will be based on available laboratory values and clinical data. If related to any drug administrated as part of the intervention, the summary of product characteristics will be included in the assessment of causality and expectedness of the event. Any SAE will be presented to the Data monitoring and ethics committee.

13. Sample size

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

Assuming a caesarean rate in the non-intervention group (based on the caesarean section rate among women with a pre- or early pregnancy BMI ≥ 30 who delivered at Aarhus University Hospital in 2018) is 25%. This sample size will demonstrate a reduction to 19% (alpha 0.05 and power of 85%), 854 participants are needed in each group.

14. Statistical analysis plan

Data will be analysed according to intention-to-treat but also per protocol.
Basic demographic data will be presented 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.
The primary outcome variable will be assessed by comparing the event rates in the two groups using a chi-square test with a p-value of 0.05. Results will be presented as absolute and relative risks along with 95% confidence intervals (CI) and numbers needed to treat (if applicable). 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's t-test or a non-parametric Mann-Whitney U test as appropriate.

Subgroup analyses will be undertaken for the following subgroups

- BMI ≤ or ≥ 35
- Parity 0 versus 1+
- No GDM versus GDM

We will use STATA for data management and analyses.

15. Data collection

15.1 Data access prior to consent

Pursuant to Danish Health Care Act (Sundhedsloven), section 1, paragraph 46, data* from all pregnant women meeting the inclusion criteria when referred from the general practitioner will be passed on to the project to clarify if the potential participant meets the inclusion and exclusion criteria. The data will be entered into the screening log in REDCap. For those not randomised, a specific reason for non-inclusion/exclusion will be documented. All randomised participants will be entered into the main database when informed consent is obtained.

*The following data will be accessed from the in-hospital electronical medical record aiming to clarify if the potential participant meets the inclusion and exclusion criteria:

- Unique patient identifier (Danish Central Personal Register number)
- Patient name
- Telephone number
- Pre- or early pregnancy BMI
- Age
- Estimated and ultrasound determined date of delivery
- Information on:

- Previous caesarean section
- Singleton or multiple pregnancy
- Certainty of gestational age
- Planned elective caesarean section
- Presentation of the foetus
- Maternal pre-existing or gestational conditions
- Fetal conditions

And for the purpose of validating the internal strength and secure the generalisability of the study, the following characteristics will be collected on all the screened women not randomised.

- Unique patient identifier (Danish Central Personal Register number)
- Pre- or early pregnancy BMI
- Age
- Parity
- Gestational diabetes mellitus treated by diet alone (GDM)
- Planed site of delivery
- Reason for exclusion/non randomisation

15.2 Data collection following consent

15.2.1 Data collection process

The responsible physician investigator or an assigned and educated research staff member from the local clinical team will be responsible for data collection and entry. 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.

1. Data collection methods; Data will be collected on eCRFs on which almost every response is pre-coded. The forms are generated using REDCap.
2. 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.

15.2.2 Characteristics and variables

A detailed data dictionary that clearly defines all included variables will be created prior to patient enrolment. The data dictionary will provide the name of the variable (including the code used in the database), a detailed definition of the variable, categories for categorical variables, and units and ranges for continuous variables. Below is provided a brief overview of the included variables collected from the in-hospital electronical medical record, but details are reserved for the data dictionary.

Maternal demographics and pregnancy characteristics

- Unique patient identifier (Danish Central Personal Register number)
- Name
- Labour date
- Name of delivery site
- Age
- Parity

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

Neonatal characteristics
- Unique patient identifier (Danish Central Personal Register number)
- Sex
- Birthweight

Labour characteristics
- Gestational age at delivery
- Onset of labour
- If induction; Indications for induction
- If induction; Methods of induction
- If induction; Time from induction of labour until delivery
- At admission time on delivery ward; Cervical dilation, caput station and cervical length
- If caesarean; Urgency of caesarean
- If caesarean; Cervical dilation, caput station and cervical length prior to caesarean section
-
- Use of oxytocin augmentation

Postpartum characteristics:
- Surgical removal of placenta due to retention
- Puerperal complications other than puerperal infections treated in hospital
- Thromboembolic event
- Acute colon pseudoobstruction
- Surgical procedures in the puerperal period and indication

Characteristics on health resource utilization:
- Telephone consultations from randomisation to admission for delivery
- Outpatient visits from randomisation to admission for delivery
- Hospital admissions from randomisation to admission for delivery
- Time on the delivery unit
- Maternal postpartum length of hospital stay
- Neonatal length of hospital stay
- Telephone consultations from delivery till 30 days postpartum
- Outpatient visits from delivery till 30 days postpartum
- Hospital admissions from delivery till 30 days postpartum

Outcomes:
Maternal outcomes:

- Mode of delivery
- Indication for caesarean section
- Indication for vaginal assisted delivery
- Use of epidural
- Minor or major shoulder dystocia
- Clinical suspicion of abruption of the placenta
- Cord prolapse
- Maternal fever
- Perineal laceration
- Episiotomy
- Damage to internal organs (bladder, bowel or ureters)
- Postpartum haemorrhage
- Blood transfusion
- Hysterectomy
- Puerperal infection treated inhospital
- Admission to Intensive Care Unit
- Maternal cardiopulmonary arrest
- Maternal death

Neonatal outcomes:

- Perinatal death
- Apgar score at 5 minutes
- Umbilical cord arterial and venous pH and standard base excess values
- Need for respiratory support
- Hypoxic–ischemic encephalopathy
- Seizures
- Infection
- Birth trauma
- Meconium aspiration syndrome
- Hemorrhage
- Hypotension requiring vasopressor support
- Neonatal admission
- Treatment during admission

16. Data management

All outcome data will be registered in an eCRF designed for the trial using the REDCap database Study. Data will be collected and managed using REDCap electronic data capture tools hosted at Aarhus University [22]. 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.
Data will be handled according to all relevant Danish laws including the General Data Protection Regulation (“Databeskyttelsesforordningen”) and the Data Protection Act (“Databeskyttelsesloven”). The project is registered with the Central Denmark Region’s internal list of research projects.

17. Access to data

Beginning three months and ending three years after the publication of the last trial results, the final dataset will be publicly available in an anonymised form using i.e. Zenodo open data repository (CERN) or another equivalent database[23].

All relevant trial-related documents will be shared along with the data. Data will be available for any research purpose to all interested parties who have approval from an independent review committee. Interested parties will be able to request the data by contacting the trial sponsor. Authorship of publications emerging from the shared data will follow standard authorship guidelines and will include authors from the WINDOW study group depending on the nature of their involvement.

18. Monitoring

18.1 Data monitoring and ethics committee (DMEC) and trial steering committee (TSC)

Three independent members will be appointed to the DMEC prior to initiation. The DMEC members are to safeguard the interests of trial participants by assessing the safety of the intervention during the trial.

Three independent members will be appointed to the TSC prior to initiation. The aim of the TSC is to provide oversight for the trial on behalf of the Sponsor and Funder. And to provide advice throughout its independent Chair to the Principal Investigator on all aspects 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 review data. After the reviews, the DMEC will create a short report to the TSC with recommendations for continuation, modifications, or terminations of the trial. There will be no formal stopping criteria. Recommending termination will be at the discretion of the DMEC, and there will be no formal statistical criteria for termination due to safety.

Documents describing the roles and responsibilities of the DMEC and the TSC, including the timings of meetings, methods of providing information to and from the DMEC and the TSC, frequency and format of meetings, statistical issues and relationships with other committees will be described in the relevant charters.

18.2 Trial monitoring

The trial is continuously monitored by a Good Clinical Practice (GCP) certified monitor. A detailed monitoring plan will be developed prior to trial commencement.

19. Enrolment

19.1 Feasibility

At Aarhus University Hospital, 9% of all pregnant women have a pre- or early pregnancy BMI ≥ 30 (data first quarter of 2019). From these, approximately one third had a pre- or early pregnancy BMI ≥ 35. With the assumption that women from Aarhus Municipality are less overweight than the Danish average, and according to the national obstetrical guideline on obesity in pregnancy, we estimate the proportion of women with BMI ≥ 30 on a Danish national level to be 12%. From 60.000 proposed deliveries in 2019, 7200 would be eligible based on their BMI; with further exclusion of decliners (~70 %) and ineligible women (~15%), we assume that 1080 women can be included per year. With respect to delays in project

implementation as well as other challenges in project management, we expect the inclusion period to last 6 years or until 1900 pregnant women have approved participation.

19.2 Enrolment

Enrolment at each trial site will be continuously monitored by the local site collaborator and the principal investigator. Adequate participant enrolment will be achieved by an engaged and visible WINDOW study group, local trial site initiatives and various web-based initiatives.

20. Ethics and dissemination

20.1 Ethics

The study will be conducted in accordance with the ethical principles outlined in the latest version of the 'Declaration of Helsinki' and the 'Guideline for Good Clinical Practice' related to experiments on humans. The Central Denmark Region Committee on Biomedical Research Ethics are to approve the study.

20.2 Perspectives

More than 39% of the world's population is overweight and 13% are obese by the WHO classification. Pregnant overweight women are at increased risk of pregnancy and delivery complications, and we are obliged to seek knowledge to improve maternity care for this subgroup of women. The results of this trial have the potential to generate important knowledge for the improvement of delivery in obese women and they will add key information to an on-going discussion of the effects of labour induction before term. The inclusion of quantitative and qualitative approaches in the study design opens for balanced discussions of benefits and drawbacks of induction of labour.

21. Publication plan

Positive, inconclusive as well as negative results from the study will be published. We aim at publishing at least three manuscripts in peer reviewed international scientific journals. Anticipated publications:

1) Maternal and neonatal outcomes with induction of labour versus expectant management in obese women: A systematic review
2) When to induce for overweight? (WINDOW RCT)
3) Childbirth experience and mental health with term induction in obese women: Analysis from the WINDOW trail

The principal investigator will draft these papers as first author, and the trial sponsor will be last corresponding author. Additional authorship will follow standard authorship guidelines and will include all members of the WINDOW study group and the representatives from the trial sites. Authorships of additional publications will depend on the nature of involvement.

22. Confidentiality

The investigators will preserve the confidentiality of the participants taking part in the study according to the Danish national legislation (The General Data Protection Regulation (GDPR) and the Data Protection Act).

23. Ancillary and post-trial care

Participants taking part in clinical studies in Denmark are insured during and after the trial according to the Act on Patient Safety in the Danish Health Care System.

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