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Induction of labour at 39 weeks versus expectant management in low-risk obese women: study protocol for a randomised controlled study

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ABSTRACT

Introduction Obesity is associated with many pregnancy complications, including both fetal macrosomia and prolonged labour. As a result, there is often also an increased risk of caesarean section. In other settings, labour induction near to term reduces adverse outcomes such as stillbirth and birth injury, without causing more caesarean deliveries. It has been suggested that induction will reduce adverse events in this setting too, but there have been no trials and the effect on caesarean section is unknown. The objective of this study is to compare induction of labour in gestational week 39 with expectant management on the risk of caesarean section in women with body mass index ≥30 kg/m^2.

Methods and analysis An open label randomised controlled multicentre trial are conducted at Danish delivery departments with an in-house neonatal intensive care unit. Recruitment started October 2020. A total of 1900 women with a prepregnancy body mass index ≥30 kg/m^2 are randomised in a 1:1 ratio to either labour induction at 39 weeks and 0 to 3 days of gestation or to expectant management; that is, waiting for spontaneous labour onset or induction if medically indicated. The primary outcome is caesarean section. Data will be analysed according to intention-to-treat.

Ethics and dissemination The Central Denmark Region Committee on Biomedical Research Ethics approved the study. The study is 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 trial findings will be disseminated to participants, clinicians, commissioning groups and via peer-reviewed publications.

Trial registration number NCT04603859.

Strengths and limitations of this study

- ► This is the first randomised study to examine the effect of induction of labour at gestational week 39 in obese women.
- ► The study is a pragmatic, multicentre study conducted in Danish delivery departments with an in-house neonatal intensive care unit.
- ► The study is not designed to assess the effects of labour induction on stillbirth.
- ► Blinding of participants or staff is not possible.

INTRODUCTION

The WHO defines obesity as a body mass index (BMI) of ≥30 kg/m^2.[1] According to this definition, more than 650 million adults were obese in 2016, which corresponds to 13% of the adult population worldwide.[1] The prevalence is one-third of fertile women in the USA, 20% in the UK and 12%–13% in Denmark.[2 3] The latest European Perinatal Health Report from 2015 showed rates of obesity in women giving birth at 8%–26% in 15 European countries, and only two countries had obesity rates below 10%.[4]

The risk of gestational complications increases with increasing BMI.[2] Obesity in pregnancy is associated with gestational diabetes, preeclampsia, macrosomia, shoulder dystocia, stillbirth, postpartum haemorrhage, neonatal death and caesarean section.[5–9] Compared with normal weight women, the risk of caesarean section is doubled in obese women.[2] Furthermore, delivery by caesarean section is associated with an increased risk of wound infection or other infectious morbidity in obese women as compared with non-obese women.[9–11] Additionally, caesarean section also adds significant risk to future deliveries.[12] Knowledge is sparse on strategies to lower the rate of caesarean section in the obese pregnant population and research in this area is needed.

Three observational studies found some 10%–50% reduced odds of caesarean section in obese women with induced labour at 39 gestational weeks compared with awaiting labour onset.[13–15] Two randomised trials[16 17] of which the largest, the ARRIVE trial, with more than 6000 low-risk pregnant women from all BMI categories found that induction of labour at 39 gestational weeks was

associated with lower caesarean section rates.[17] In 'Care of women with obesity in pregnancy' from the Royal College of Obstetricians in the UK, it is advocated that the option of induction of labour should be discussed with the pregnant women.[18] In August 2018, the American College of Obstetricians and Gynaecologists advised that it is reasonable to offer induction of labour to low-risk women at 39 gestational weeks in consideration of the women's preferences.[19] Nonetheless, to our knowledge, no randomised studies compared induction of labour at 39 gestational weeks with expectant management in obese women.

Current practice in Denmark is to offer induction of labour at 41 gestational weeks and 0 days to women with a BMI of 35 or more, whereas women with BMI of 30 kg/m^2 to 35 kg/m^2 are offered induction of labour at 41 gestational weeks and 3–5 days. Danish obstetrical practice differs from other parts of the world (eg, the USA), in particular, with regards to a universal prenatal care free of charge, outpatient induction regimes in low-risk pregnancies, fewer obese and multiparous women and caesarean delivery rates of 20% compared with 30%–35% in the USA.

The objective of this study is to investigate how the caesarean section rate is affected when inducing labour at 39 gestational weeks compared with expectant management among women with prepregnancy BMI ≥30 kg/m^2.

METHODS AND ANALYSIS

Trial acronym

When to INDuce for OverWeight? The WINDOW study.

Study design

The study is a multicentre randomised controlled trial and complies with the Consolidated Standards of Reporting Trials guideline (figure 1).

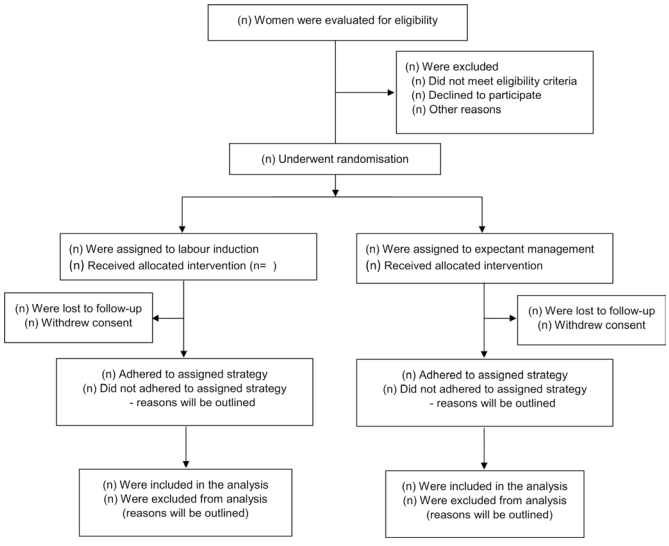

Figure 1 Eligibility, enrolment, randomisation and assessment.

Sites

Recruitment will take place at 11 Danish delivery departments with an in-house neonatal intensive care unit. Recruiting sites are listed at ClinicalTrials.gov.

Recruitment

Pregnant women with a prepregnancy BMI ≥30 kg/m^2 referred to one of the recruiting sites are screened for eligibility. A screening based on the medical record is performed two times; at about gestational week 32 and again at about gestational week 38 and no later than 39 weeks and 0 days, identifying eligible women who receive written information on the study via an Identity-personal digital postbox as well as verbal information. Written informed consent is obtained electronically prior to randomisation (online supplemental appendix 1, written in Danish). The procedures concerning the screening, patient information, randomisation and data collection are performed by formally trained midwives or doctors of the local clinical team.

Participants

The trial includes pregnant women with a prepregnancy BMI ≥30 kg/m^2 obtained by the general practitioner in early pregnancy. The prepregnancy BMI is either based on self-reported weight and height or an actual measurement of weight and height by the general practitioner.

Exclusion criteria are as follows:

- Multiple pregnancy.
- Previous caesarean section.
- Gestational age estimated by other methods than Crown–Rump–Length in early pregnancy.
- Scheduled for elective caesarean section at the time of randomisation.
- Known fetal contraindications to induction at the time of randomisation.
- Known fetal contraindications to expectant management at the time of randomisation: for example, history of continuously abnormal or pathologic cardio toco graphy, fetal growth restriction or macrosomia or major malformations diagnosed by ultrasound.
- Known maternal contraindications to induction at the time of randomisation: for example, placenta previa/accreta, vasa previa.
- Known maternal contraindication to expectant management at the time of randomisation: for example, maternal medical conditions*, signs of labour, including prelabour rupture of membranes.
- Legal or ethical considerations: maternal age <18 years, inability to read or understand Danish.

*Maternal medical conditions: for example, insulin-treated diabetes mellitus, any hypertensive disorder with blood pressure >140/90 mm Hg, cardiac disease, renal insufficiency, other medical or psychological conditions suggesting delivery <41 gestational week and 0 days.

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Randomisation

Before 39 weeks of gestation, and before the onset of labour, women who give informed consent are randomised to one of the two interventions using an internet-based randomisation programme in a 1:1 ratio and with permuted and random block sizes of 2, 4 and 6. Site stratification is used to take into account that sites could differ in participant characteristics and in the clinical management. The randomisation programme automatically transfers the entry data to an electronic case record forms in the database Research Electronic Data Capture (REDCap).[20] REDCap is a secure, web-based database compliant with all regulatory guidelines and enables a complete audit-trail for data entry validation.

Interventions

Induction of labour in pregnancy at 39 gestational weeks and 0–3 days

Induction performed according to local clinical practice for induction of labour (prostaglandin E1, E2, foley catheter, cervical ripening, balloon catheter, artificial rupture of membranes or oxytocin infusion when applicable).

Expectant management

Awaiting spontaneous labour onset or intervene as usual, for example, induction at a later gestation if an indication for delivery arises. All women with prolonged pregnancy can be offered induction from 41 gestational weeks and 0 days in accordance to local clinical practice.

Blinding

The study is open label. No attempt to blind are made given that it would be infeasible to fully accomplish with the large difference between the two interventions.

Outcome measures

The primary outcome is maternal, caesarean section. A primary neonatal composite outcome is also defined. However, since it is plausible that the effect of induction on fetal trauma might differ from the effect on fetal hypoxia, two secondary fetal composite outcomes are labelled as 'of special interest'.

Primary outcome

- Caesarean section

Secondary outcomes

Maternal follow-up is set 30 days' postpartum unless specified otherwise.

- Mode of delivery if not by caesarean section.
- If operative vaginal delivery; vacuum or forceps.
- Indication for caesarean section or operative vaginal delivery.
- Epidural analgesia.
- Minor shoulder dystocia defined as the need for McRoberts manoeuvre.
- Major shoulder dystocia defined as the need for procedures other than McRoberts manoeuvre.
- Clinical suspicion of abruption of the placenta leading to an intervention in labour.
- Cord prolapse.
- Intrapartum fever (defined as >38.2°C with epidural, without epidural: >38.0°C).
- Perineal third or fourth degree laceration.
- Episiotomy.
- Damage to internal organs (bladder, bowel or ureters).
- Uterine scar dehiscence or rupture.
- Estimated postpartum haemorrhage.
- Blood loss >500 mL within the first 48 hours from delivery.
- Blood loss >1000 mL within the first 48 hours from delivery.
- Blood transfusion within the first 48 hours from delivery.
- Hysterectomy.
- Puerperal infection treated in hospital.
- Other severe postpartum conditions treated in hospital, including any thromboembolic event.
- Maternal admission to intensive care unit.
- Maternal cardiopulmonary arrest.
- Maternal death.

Neonatal follow-up is set 28 days after birth unless specified otherwise.

The following is the primary neonatal composite outcome, including any of the following:

- Stillbirth or neonatal death, 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 intensive care unit, Apgar score <4 at 5 min, moderate to severe hypoxic ischaemic encephalopathy (defined as the need for therapeutic hypothermia), seizures, infection (defined as antibiotic treatment continuously for 7 days minimum), meconium aspiration syndrome, birth trauma (any fracture, Duchenne-Erbs palsy or retinal haemorrhage), intracranial or subgaleal haemorrhage or hypotension requiring vasopressor support. All components of the above neonatal composite will additionally be reported separately

The following are the neonatal secondary outcomes. The first two neonatal secondary outcomes, namely, the trauma composite and the asphyxia composite, are considered of special interest.

- Neonatal trauma composite including any of the following; birth trauma (bone fracture, Duchenne-Erbs palsy or retinal haemorrhage), intracranial or subgaleal haemorrhage
- Neonatal asphyxia composite including any of the following; seizures, Apgar score <4 at 5 min, umbilical arterial cord pH <7.0, umbilical arterial cord standard Base Excess (sBE) <−15.0 mmol/L or hypoxic–ischaemic encephalopathy (defined as the need for therapeutic hypothermia)
- Apgar score at 5 min (<4, 4 to 7)

- Umbilical cord arterial pH <7.0 and standard base excess value <−15.0 mmol/L
- Neonatal intensive care admission within 72 hours after delivery
- Treatment during admission (CPAP, HNFC, oxygen supplement treatment, mechanical ventilation, therapeutic hypothermia, vasopressor support, antibiotic treatment continuously for 7 days minimum)

Neonatal characteristics:

- Birth weight.
- >4500 g.
- Female sex.

Maternal experience on birth:

- Childbirth Experience Questionnaire[21] assessed 4–6 weeks postpartum.

Maternal postnatal depression:

- Major Depression Inventory[22] and Edinburgh Postnatal Depression Score[23] assessed 4–6 weeks postpartum.

All data are registered in an electronic Case Record Form (eCFR).[20] A detailed data dictionary clearly defines all included variables.

Sample size

The power calculation was based on the assumption of a caesarean section rate in the expectant management group of 25% and in the induction of labour group of 19%. These data were based on the caesarean section rate among women with a prepregnancy BMI ≥30 kg/m^2 who delivered at Aarhus University Hospital in 2018. On the basis of these numbers and with an alpha of 0.05, a total sample size of 854 per group would provide a power of at least 85% to detect a difference of 6% in the caesarean section rate between the two groups. Anticipating dropout and allowing crossover the sample size was increased to 950 participants in each group (1900 in total).

Statistical analysis plan

Basic demographic data and labour characteristics are presented with number (no.) and percentages (%) for categorical variables, mean and SD for continuous Gaussian distributed variables, median and IQR for continuous non-Gaussian variables.

The primary analysis follows the intention-to-treat principle.

The primary outcome variable will be assessed by comparing the event rates in the two groups using a χ^2 test with a two-tailed p value of 0.05. Results will be presented as absolute and relative risks along with 95% Cls and number needed to treat (if applicable). Categorical secondary outcomes will be assessed in the same way as the primary outcome. For continuous secondary outcome differences will be assessed between groups using the student's t test or a non-parametric Mann-Whitney U test as appropriate. For composite outcomes, the individual outcomes will be also examined.

Subgroup analyses will be undertaken for the subgroups; BMI ≤ or ≥ 35 kg/m^2, parity 0 versus ≥1 and gestational diabetes mellitus (GDM) versus no GDM. A per protocol analysis of the primary outcome is also made.

STATA 17.0 will be used for data management and analyses.

Adherence to assigned care

Adherence to assigned care strategy in the induction group will be defined as delivery from randomisation until 39 weeks and 3 days, as are initiation of induced labour or spontaneous onset of labour before 39 weeks and 4 days. Adherence to assigned care strategy in the expectant management group will be defined as delivery from randomisation and onwards. The adherence to the allocated group is presented in terms of number (no.) and percentage (%).

Data collection and management

Data collection process and method

A few dedicated and trained research staff members from the local clinical team are responsible for data collection and entry. Except from some of the baseline data and data from the postpartum questionnaires, all data will be obtained from the in-hospital electronical medical record. Data will be collected on eCFRs on which almost every response is precoded. The forms are generated using REDCap[20] hosted at Aarhus University. If participants discontinue or deviate from the intervention protocol data collection continues, unless the participant specifically state otherwise.

Data management

Data quality and validity are optimised by having dedicated research staff members entering all data according to a detailed data dictionary clearly defining all included variables. All outcome data are managed in REDCap. REDCap is designed with data forms containing field-specific validation checks to ensure that mandatory fields are filled out and that continuous variables are within predefined ranges. Furthermore, REDCap allows for data quality rules warning of potential incorrect data. These data are assessed continuously and corrected if relevant.

Patient and public involvement

Project material

A number of pregnant women at Aarhus University Hospital within the target group reviewed the written information material and gave verbal feedback to the coordinating investigator in a non-structural manner.

Patient perspectives

An explorative qualitative study is performed aiming to investigate the experience of induced labour, and the information needs among women in the intervention arm. A purposive sample of participants is recruited from a minimum of two hospitals in Central Denmark Region and interviewed 4–12 weeks postpartum by a social scientist researcher. Interviews are conducted at a time and place of the participants' choice using a semistructured

interview guide. All interviews are recorded, transcribed verbatim and analysed using thematic analysis.

Trial oversight

The trial is yearly monitored by an independent monitor familiar with the principles of Good Clinical Practice who performs audit on selective predefined outcome measures. Serious adverse events are defined as an untoward and unexpected medical occurrence that results in maternal or perinatal death, that is life threatening to the participant or the fetus/neonate at the time of the event, or that requires hospitalisation or prolongation of existing inpatient hospitalisation. All serious adverse events are monitored and handled by the principal investigator and sponsor.

Three independent members are appointed to a Data Monitoring and Ethics Committee (DMEC) and a Trial Steering Committee (TSC), respectively. The DMEC members are to safeguard the interests of trial participants by assessing the safety of the intervention and monitor the overall conduct of the trial. The DMEC reviews data at two predetermined milestones (600 and 1300 enrolled participants) but as a minimum once annually. Any serious adverse event is presented to the DMEC. The TSC members are to provide advice to the trialists based on recommendations from the DMEC on two predetermined occasions. No formal stopping criteria are predefined.

ETHICS AND DISSEMINATION

The Central Denmark Region Committee on Biomedical Research Ethics approved the study. The study is 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. All the eligible women both get written and verbal information about the study methods, the aims of the research and the possible adverse events related to the interventions and give written informed consent prior to randomisation. The results of this trial have the potential to generate important knowledge for the improvement of delivery in obese women and add key information to an ongoing discussion of the effects of labour induction before term. The inclusion of quantitative and qualitative approaches in the study design enables balanced discussions of benefits and drawbacks of induction of labour. The trial findings are disseminated to participants, clinicians, commissioning groups and through peer-reviewed publication. After publication of the last trial results, deidentified data will be publicly available.

Protocol amendments

In case of significant protocol amendments are 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.

Ancillary and post-trial care

There are no provisions for trial participants. The participants are insured during and after the trial according to the Act on Patient Safety in the Danish Health Care System.

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Contributors JG and SB conceived the idea for the trial and wrote the first protocol draft. JG, SB and LQK secured funding. LQK further developed the trial design with substantial contributions from JG, SB, JF, TBH and JT. LQK drafted the protocol for publication. JG, SB, JF, TBH and JT revised the manuscript critically and approved the final version to be published.

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Disclaimer The trial sponsor and funders have no ultimate authority over any aspects of the trial design, conduct, or reporting.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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