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UNIVERSITY OF MALAYA MEDICAL CENTRE

RESEARCH PROTOCOL

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TITLE OF RESEARCH PROPOSAL

HIGH VS. STANDARD OXYTOCIN CONCENTRATION FOR LABOUR DYSTOCIA IN OBESE NULLIPARAS:A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL

KEY WORDS

BACKGROUND/ JUSTIFICATION

Worldwide, the proportion of overweight adult women increased between 1980 and 2013 from 29·8% to 38·0%.[1] By 2014, in many countries, more than half of pregnant women were overweight, and nearly a third of women were obese.[2] Malaysian data from 2014 indicate that at booking the maternal obesity rate was 28.1%.[3]

Obese women were more likely to have cesarean deliveries and labor inductions, greater length of stay after cesarean deliveries and vaginal deliveries. They were also more likely to have pregnancy-related hypertension, preeclampsia, gestational diabetes, premature rupture of membranes, chorioamnionitis, venous thromboembolism, excessive fetal growth, and fetal distress.[4]

Among obese women, the labor curves indicate longer overall duration (from 4 cm to 10 cm dilatation) and slower progression of the early first stage of labor (from 4-6 cm) after adjusting for confounders.[5] Obese women have longer labors but are equally able to achieve adequate uterine contractions[6] but obese nulliparas need more powerful contractions to reach the active stage of labour (> 6 cm cervical dilation) though this phenomenon does not exist in obese multiparas[7]. Not only is reaching the active stage of labour more difficult among the obese, failed induction of labour is also more common.[7] BMI was higher in women with labour dystocia (inadequate labour progress) and pre-pregnancy BMI also had a strong association with dystocia risk such that for BMI increment of 1 kg/m^2, the caesarean section risk increased by a relative 10%.[8]

Oxytocin is a peptide hormone (a self-produced natural agent) that plays a key role in regulating the female reproductive system, including during labor and lactation. Oxytocin can also be administered as a medication to initiate (induce labour) or augment uterine contractions (to overcome inadequate labour progress). Oxytocin has a plasma half-life of 6 minutes 53 seconds in female serum.[9, 10]

A 2024 meta-analysis of high and low oxytocin dose regimen analysed 21 studies (a total of 14.834 patients including from 18 RCTs) reports that “no statistical differences were found in cesarean delivery, neonatal mortality, postpartum hemorrhage and vaginal instrumentation rate. However, uterine tachysystole (frequent contractions) incidence was significantly higher with high-dose oxytocin”.[11] A 2024 expert review comments “randomized trials demonstrated that active management of labor and high-dose oxytocin regimens can shorten the length of labor and reduce the incidence of clinical chorioamnionitis. The safety of high-dose oxytocin regimens is also supported by no associated differences in fetal heart rate abnormalities,

postpartum hemorrhage, low Apgar scores, neonatal intensive care unit admissions, and umbilical artery acidemia. Most studies reported no differences in the cesarean delivery rates with active management of labor or high-dose oxytocin regimens, thereby further validating its safety."[12] A 2013 expert review states "high-dose infusions of oxytocin may shorten the duration of labor by up to 2 hours".[13] A 2020 review by the Agency for Healthcare Research and Quality (US) on comparative effectiveness of interventions for labor dystocia reports that high-dose oxytocin is associated with a lower cesarean delivery rate (moderate strength of evidence) with no difference in maternal hemorrhage (low strength of evidence) in nulliparous women.[14] A 2013 Cochrane systematic review and meta-analysis reports a higher dose of oxytocin was associated with a significant reduction in length of labour (mean reduction of 3.5 hours, reported from one trial[15]) and no significant differences for instrumental vaginal birth, epidural analgesia, hyperstimulation, postpartum haemorrhage, chorioamnionitis or women's perceptions of experiences.[16]

The above findings indicate that the undesirable increase in tachysystole[11] with high dose oxytocin does not translate to adverse maternal outcome (e.g., postpartum haemorrhage[11-14, 16] epidural analgesia[16] or women's perceptions of experiences[16]) or adverse neonatal outcome (e.g., fetal heart rate abnormalities, low Apgar scores, neonatal intensive care unit admissions, umbilical artery acidemia, neonatal mortality)[11, 12]. On the other hand, chorioamnionitis[12], caesarean birth[14] and the length of labour[12, 13, 15, 16] could be decreased with high dose oxytocin.

A 2023 secondary analysis of data from a multicentre USA trial of 1003 participants focused on the impact of high oxytocin dosing where the maximum oxytocin rates used ranged from 2 to 90 mIU/min finds no significant differences in maternal or perinatal adverse outcomes with higher oxytocin dose concluding that oxytocin dosing should be individualized to each patient and not be based on arbitrary limits.[17]

"Oxytocin infusion protocols for labor induction and augmentation differ widely, in part, because a predictable dose response for uterine contractions or labor does not exist."[13] A 2020 survey performed in 12 European countries shows starting rates of 1 to 15 mIU/min, maximal infusion rates of 15 to 60 mIU/min, different intervals for infusion rate variation and the predicted total oxytocin infused during 8 hours ranging from 2.38 to 27.00 IU demonstrating the substantial diversity in European national practice.[18]

Physiological changes caused by obesity can impact all the four principal pharmacokinetic phases of absorption, distribution, metabolism and elimination[19] warranting the consideration of obesity in drug dosing regimens. A 2024 trial of misoprostol induction of labour in obese patients reports a reduction in labor time when comparing high and standard doses without maternal or neonatal detriment[20] supporting the proposition of benefit with higher doses in obese parturients in the management of labour.

The overall impression from these data suggest safety and potential benefit from higher dose oxytocin for labour dystocia. Plausibly in obese nulliparas there is an even stronger case for overall benefit, warranting responsible further investigation.

We propose a trial on two oxytocin dosing regimens for labour dystocia in obese parturients. Infusion solutions will be made with 15 IU (experimental) or 10 IU (control, standard dose) in a

container of 500 ml Hartmann's. The experimental regimen will start at a higher dose (3 vs 2 mIU/min – European national starting rates of 1 to 15 mIU/min[18]) and be bounded to a higher maximum dose limit (48 vs 32 mIU/min - European national maximal rates of 15 to 60 mIU/min[18] and up to 90 mIU/min used in a 2024 large multicentre USA-based trial[17]) compared to our standard regimen. In both arms, consideration for rate increment will be at every 30 minutes in the escalation phase to be titrated to uterine contraction frequency and strength as longstanding UMMC practice protocol of doubling the infusion rate as needed (from 6 ml hr to 12 ml/hr to 24 ml/hr hour to 48 ml/hr to 96 ml/hr). The infusion rate will be increased stepwise until the 'ideal' 3-to-4 every 10 minutes of moderate-to-strong contractions is achieved. Thereafter the infusion rate will be maintained to birth provided that the 'ideal' contraction response is sustained. Subsequently, any deviation from this ideal response may require infusion rate adjustments which will be at the full discretion of care providers guided by the principle of their usual practice in the best interest of the patient.

OBJECTIVES & EXPECTED OUTCOMES

PRIMARY OBJECTIVE:

A shortened interval from initiation of titrated oxytocin to birth (faster labour)

PRIMARY OUTCOME

We hypothesise that obese patients (BMI ≥ 27.5- Asian criteria) administered with a higher concentration solution regimen, hence higher initial and maximum allowable dose of oxytocin in augmentation of labour will have their birth hastened in comparison with our current standard regimen

SECONDARY OBJECTIVE:

Secondary use, performance and safety outcomes partly derived from the core outcome set for reporting trials on induction of labour: CROWN21

- Maternal secondary outcomes

1) Maximum oxytocin infusion rate used
2) Duration of oxytocin infusion
3) Total volume infused (to derive total oxytocin dose infused)
4) Cardiotocographic abnormality (through first stage of labour)-assessed by a blinded assessor
a) Tachysystole (contractions ≥6 in 10 minutes)
b) Hypertonus (sustained contraction ≥2 minutes)
c) Hyperstimulation syndrome (tachysystole and/or hypertonus with concurrent fetal deceleration [defined as decrease in fetal heart rate of ≥15 bpm from baseline for ≥15 second])
5) Number of doses of tocolytic given if any
6) Mode of delivery
a) spontaneous
b) vacuum
c) forceps
d) caesarean section
7) Indication for caesarean section
8) Indication for instrumental vaginal delivery

9) Maternal satisfaction with the birth process (11-point 0-10 NRS – numerical rating scale)
10) Blood loss during delivery
11) Third- or fourth-degree tear
12) Maternal infection
13) Intrapartum therapeutic antibiotics (excluding prophylactic antibiotics)
14) Epidural in labour
15) Length of hospital stay
16) ICU admission
17) Cardiorespiratory arrest
18) Needing hysterectomy

- Neonatal outcomes

1) Apgar score at 1 and 5 minutes
2) NICU admission
3) Cord pH
4) Neonatal sepsis
5) Birth weight
6) Birth trauma
7) Hypoxic ischaemic encephalopathy/need for therapeutic hypothermia

METHODOLOGY

Study design

Single centre, parallel group, conveniently sampled, double blinded, randomized controlled trial.

Population of Study:

Term obese (BMI ≥ 27.5 kg/m2) parturient with singleton pregnancies requiring oxytocin augmentation for labour dystocia

Inclusion criteria

1. BMI ≥27.5 kg/m^2
2. Spontaneous labour (contraction >2:10 minutes and cervical dilatation ≥3cm)
3. Inadequate progress as clinically determined
4. Nulliparous (no previous pregnancy ≥22 weeks)
5. Term ≥37 weeks
6. Age 18-45 years old
7. Membranes ruptured (including prelabour rupture of membranes)
8. Singleton pregnancy
9. Cephalic presentation
10. Reassuring fetal heart rate tracing at initiation of oxytocin infusion

Exclusion criteria

1. Induced labour (prior Foley, prostaglandin or oxytocin)
2. Previous uterine scar (caesarean/myomectomy/perforation)
3. Known major fetal anomaly
4. Fetal weight clinically estimated to be ≤2 kg & ≥4 kg and confirmed by ultrasound

Recruitment

Potentially eligible nulliparas in the antenatal or labour ward in spontaneous labour with the decision made to augment labour with oxytocin will be screened with the Eligibility Assessment Form [EAF]. Screened patients will be verbally engaged regarding study participation and the Participant Information Sheet [PIS} with be given. Queries about the study will be invited and answered by the recruiting care provider. Informed written consent will be required of all participants.

Randomisation

The randomisation sequence will be generated an investigator not involved in the recruiting or care process in random blocks of 4 or 8 using an online randomiser (https://www.sealedenvelope.com/simple-randomiser/v1/lists).
Allocated intervention oxytocin-Hartmann solution will be enclosed in numbered boxes. The lowest numbered box still available will be allocated for the latest recruit. A co-numbered sealed opaque envelope with external writing of "UNBLINDING INFORMATION: Open Only If Necessary" and containing a card with "Study Number xxx, OXYTOCIN STUDY DRUG 10 IU (Standard dose) in 500 ml Hartmann" or "Study Number xxx, OXYTOCIN STUDY DRUG 15 IU (High dose) in 500 ml Hartmann" will be pasted to the box.
The reason for the necessary opening of this envelope for clinically necessary unblinding will be recorded. Contents of the numbered boxes unused will be discarded and replaced every 24 hours.
The numbered trial boxes containing the trial oxytocin solutions will be stored in our air-conditioned delivery suite with ambient temperature set at 22-24 0C25.

Interventions

The interventions are titrated oxytocin infusions using

a) Higher starting dose and higher maximum dose
Starting dose (3 mIU/min) increasing as needed to a maximum of 48 mIU/min)
(infusion rate of 6 ml/hr to a maximum rate of 96 ml/hr of 15 IU oxytocin in 500 ml Hartmann's solution)

OR

b) Standard starting dose and standard maximum dose
a standard starting dose (2 mIU/min) increasing as needed to a maximum of 32mIU/min)
(infusion rate of 6 ml/hr to a maximum rate of 96 ml/hr of 10 IU oxytocin in 500 ml Hartmann's solution)

An electric pump will be used for oxytocin infusion. Total volume infused, duration of infusion and maximum rate of infusion will be recorded.

In both arms, the regimen for titrating the oxytocin infusion rate will be the usual care regimen of doubling the infusion rate (from 6 ml hr to 12 ml/hr to 24 ml/hr hour to 48 ml/hr to 96 ml/hr as needed) every 30 minutes until 3-4 moderate-to-strong contractions is achieved following which the infusion rate will be maintained until delivery if there are no interim events. Tocolysis use will be recorded.

In the event of cardiotocograph abnormalities or other clinical concern, the care provider has full discretion to pause, restart and discontinue the oxytocin infusion.

Blinding

Oxytocin-Hartmann infusion packs (10 or 15 IU oxytocin in 500 ml Hartmann's solution) will be made daily and discarded if unused after 24 hours by an investigator not involved in recruitment. Three packs of allocated strength oxytocin solution will be labelled with a number matched to the number on the linked randomisation envelope, OXYTOCIN STUDY DRUG (Pack 1, Pack 2 or Pack 3). The participant's hospital label will also be stuck to these three number and Pack list-ordered OXYTOCIN STUDY DRUG packs once the envelope assigned. The three OXYTOCIN STUDY DRUG packs (total volume 1500 ml) is sufficient for more than 16 hours of oxytocin infusion even after reaching and sustaining the maximum rate of 96 ml/hr.

Suggested rescue measure for uterine overstimulation

Uterine overstimulation	Suggested Remedy
1) Tachysystole (contractions ≥6 in 10 minutes without fetal heart rate abnormality)	a) Halve the oxytocin infusion rate b) If inadequate response after 10 minutes, pause infusion c) If inadequate response after 10 minutes, administer 500 mcg terbutaline subcutaneously
2) Hypertonus (sustained contraction ≥2 minutes without heart rate abnormality)	a) Pause the oxytocin infusion if persistent b) If inadequate response after 2 minutes, administer 500 mcg terbutaline subcutaneously c) If inadequate response after another 2 minutes, administer another 500 mcg terbutaline subcutaneously
3) Hyperstimulation syndrome (tachysystole and/or hypertonus with concurrent fetal deceleration decrease in fetal heart rate of ≥15 bpm from baseline for ≥15 second)	a) Pause infusion, consider concomitantly, administer 500 mcg terbutaline subcutaneously b) If inadequate response after 2 minutes, administer another 500 mcg terbutaline subcutaneously c) Consider caesarean delivery if cardiotocograph deteriorates from suspicious to pathological

Care providers shall pause, restart (at appropriate dose) and discontinue the oxytocin infusion according to best judgment.

Intrapartum care, delivery and postnatal care.

Continuous electronic fetal monitoring with the cardiotocogram will be instituted until birth. Monitoring of maternal pulse, blood pressure, temperature, urinalysis, vaginal assessment for progress, etc. will be carried out at the usual intensity, Interim events detected will be responded to according to standard practice at the complete discretion of care providers. Decisions on timing and mode of delivery will be made as normal. Similarly, delivery and postnatal care will be managed along the same principles.

Stopping rules

- Study stopping rule

1) The study will be paused in the event of occurrence of any major harms of

a) Neonatal hypoxic ischaemic-encephalopathy requiring cooling therapy due to uterine hyperstimulation syndrome
b) Maternal convulsions due to water-intoxication

and reported to competent oversight by the department safety monitoring committee in first instance. The study shall not resume until subsequently authorise to do so.

- Participant stopping rule

1) If there is a clinical need, the concentration of oxytocin in the infusion solution can be immediately revealed by opening the unblinding sealed opaque envelope that contained the required information
2) If there is further clinical need, the allocated study infusion pack can be stopped and replaced by oxytocin infusion solution of a different strength at the discretion of the care provider

Interim analysis

The primary outcome is the interval from start of oxytocin augmentation to birth and the study is powered to this clinically relevant but not critical outcome. The target sample size is not large at 126. In view of the aforementioned considerations, an interim analysis is not planned.

Sample size

A 2023 nulliparous labour induction trial from UMMC reports that the interval from start of oxytocin infusion start to birth was 7.6±3.7 vs 8.2±3.3 across arms.26

A 2013 expert review states “high-dose infusions of oxytocin may shorten the duration of labor by up to 2 hours”.13 A 2013 Cochrane systematic review and meta-analysis reports that a higher dose of oxytocin was associated with a significant reduction in length of labour reported from one trial15 (mean difference (MD) -3.50 hours; 95% confidence interval (CI) -6.38 to -0.62; one trial, 40 women).16

Applying a conservative standard deviation of 4 hours (vs. 3,3-3,7 hours)26 and a mean difference of 2 hours (213-3.516 hours), utilising online calculator OpenEpi (https://www.openepi.com/SampleSize/SSMean.htm) and additionally inputting alpha 0.05, power 80% and 1 to 1 ratio, and by t-test analysis, a total of 126 participants are needed for a powered study. We plan to recruit 126 patients (63 in each arm).

Data Analysis

Statistical software package SPSS (Version 27, IBM, SPSS Statistics) will be used. The Student t-test will be used for analysis of continuous data with normal distribution, the Mann-Whitney U test for non-normally distributed or ordinal data and Chi-square test for nominal data (Fisher exact test was used if the expected cell number <5 in ≥20% of cells evaluated). 2-sided p values will reported and the level of significance is set at $p<0.05$. Analysis will be on intention-to-treat basis.

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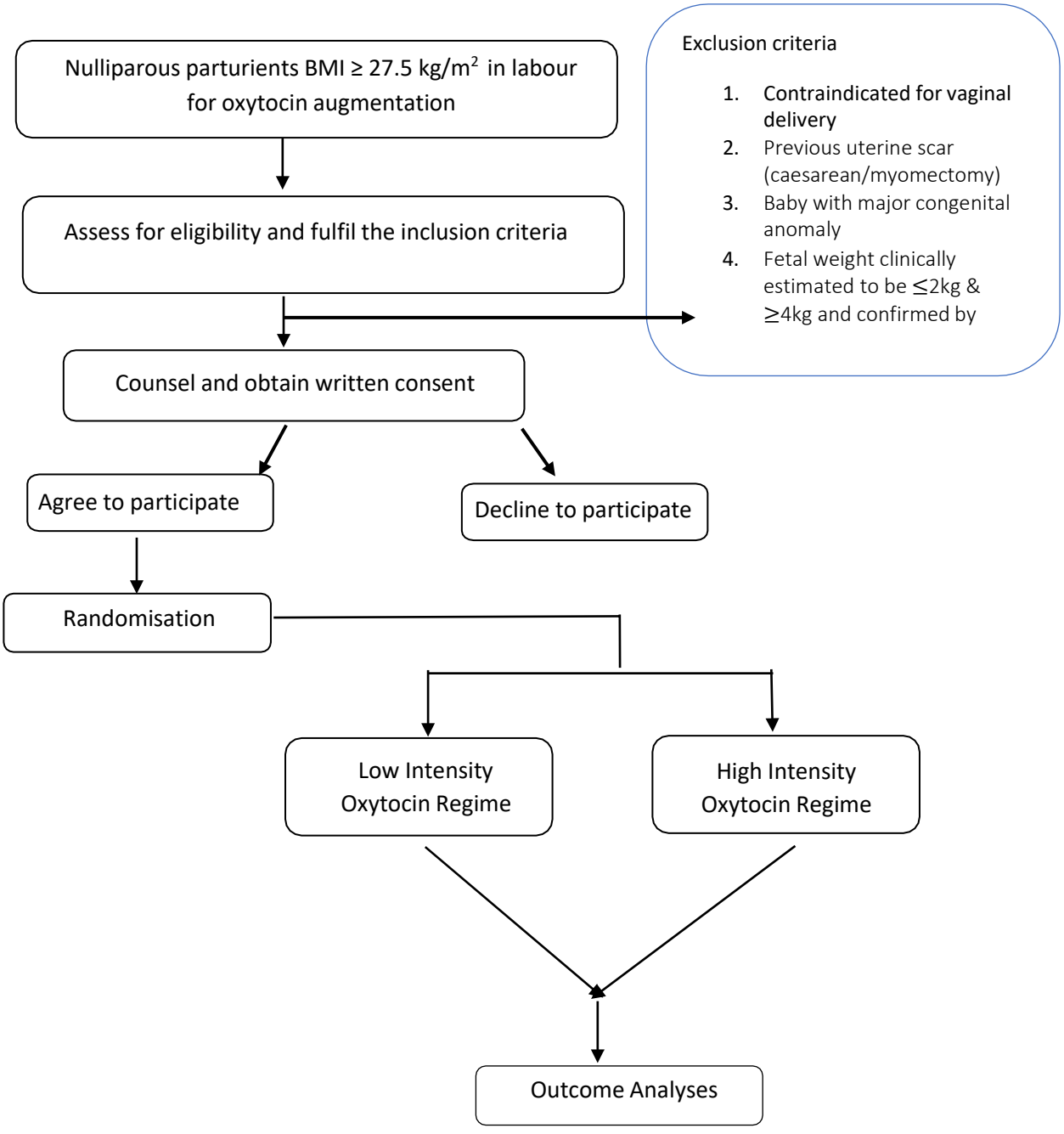
PROTOCOL FLOW CHART



RESEARCH DATA

Where will the data be kept?

The data will be kept in a secured locker with a lock in the Obstetric & Gynaecology Department of UMMC. The keys to the lock will be kept only by the primary investigator.

Who will have access to the research data?

Only the investigators. Anonymized (where individuals cannot be identified) trial data may be released to other researchers in the future as permitted by the Ethics committee.

How long will the data be kept? The data will be kept for a minimum of 10 years.

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POTENTIAL IMPACT

3. Please state whether you have submitted this research proposal for funding, now or before
- ϒ Yes: If Yes, which grant? _____
- ✓ No

This proposal will be kept strictly private and confidential. It will not be shared with anyone without your prior approval.

Name of Researcher (CAPITAL):

Signature of Researcher: ……

Date: …25 AUGUST 2024.