PROTOCOL

Public title:

Use of preoperative sodium bicarbonate among women with obstructed labor (SoBicOL- II).

Scientific title:

Effectiveness and Safety Dosing of Sodium Bicarbonate in Women with Obstructed Labor in Eastern Uganda: A Phase III Randomized placebo-controlled Trial (SoBicOL- II Study)

Sponsor: Busitema University

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ReGRoW Repurposing Research for Low and Lower-Middle Income

Countries (LMICs)

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Abstract

Introduction

Oral bicarbonate is a safe, cheap and effective acid buffer, widely used in sports to improve performance because of its ability to prevent and reverse the effects of metabolic acidosis. Clinically, it is used in intensive care units to treat patients with overwhelming infections or poisoning. In low resource settings, obstructed labor (OL) is a major problem that accounts for 22% of maternal deaths. The fetal harm of OL comes from intrapartum asphyxia, characterized by accumulation of hydrogen ions that cross the placental barrier to cause fetal acidosis. Acidosis causes failure of basic cellular functions resulting into cell death. In a recent RCT, we found that 61% of 477 women with OL were acidotic (lactate >4.8 mmol/L), with a median capillary blood lactate level of 6.9 (3.4–13) mmol/L.

A potential way of improving maternal and perinatal outcomes among women with OL would be to buffer the excess lactic acid with sodium bicarbonate, achieving intrauterine resuscitation whilst awaiting an emergency cesarean section. However, in this situation, there is inadequate time (or staff) to correct the acidaemia through careful titration of the bicarbonate infusion. A universal safe and effective dose would therefore facilitate its use. In our previous RCT, a single dose of 4.2g was insufficient to achieve changes in maternal or neonatal lactate levels. It is not known if a higher dose of bicarbonate would reverse the acidosis (pH and lactate) and achieve clinical benefits for the mother and baby.

Methods

An early phase III, placebo-controlled dose-ranging trial is proposed to determine the efficacy and safety of a pre-operative infusion of sodium bicarbonate in women with obstructed labour (OL). In a ratio of 1:1:1: 1 100 mls (8.4g), 150 mls (12.6g) and 200 mls (16.8g) of 8.4% sodium bicarbonate solution, or placebo (50 mls of NS 0.9%). The primary outcome will be mean change in acidosis (pH and lactate levels) from baseline. The secondary outcomes will be neonatal death, safety of sodium bicarbonate, pharmacokinetics of sodium bicarbonate in pregnant women, primary PPH, sepsis, and maternal death.

Conclusion

Our results will inform the design of an effectiveness phase III trial to determine the effect of this preoperative infusion on maternal and perinatal outcomes.

Introduction

Unlike normal labour, obstructed labour is characterized by higher levels of lactic acid in maternal blood and amniotic fluid [1, 2]. Repetitive, prolonged, strong uterine contractions in obstructed labour impair oxygen supply to the placental bed which promotes anaerobic respiration and accumulation of lactic acid as a byproduct [3]. The accumulated lactic acid depletes the maternal and fetal buffer systems, with resultant metabolic acidosis [1, 3]. Without timely intervention to relieve the obstruction, coupled with diminishing maternal and fetal compensatory mechanisms, the accumulated hydrogen ions easily cross the placental barrier to cause fetal acidosis. The acidosis causes failure of basic cellular functions resulting into cell death.

Obstructed labor is a major problem that accounts for 22% of maternal deaths and 70% of perinatal deaths due intrapartum asphyxia in low resource settings [4]. In Uganda, half of the 26,000 perinatal deaths audited and reported in 2021/2022 were due to intrapartum birth asphyxia [5]. The maternal and fetal harm of OL comes from intrapartum asphyxia, characterized by accumulation of hydrogen ions that cross the placental barrier to cause fetal acidosis. Acidosis causes failure of basic cellular functions resulting into cell death, especially if it remains uncorrected for an extended period. In a recent RCT, we found that 61% of 477 women with OL were acidotic (lactate >4.8 mmol/L), with a median capillary blood lactate level of 6.9 (3.4–13) mmol/L. In Mbale hospital, perinatal mortality rate is twice the national average of 48 per 1,000 total births [6]. In the Sodium Bicarbonate in Obstructed Labour (SoBicOL) trial, 34% of the newborns had an Apgar score of less than seven, and 12% resulted in early neonatal deaths despite being resuscitated [7]. At two years of age, two thirds of the children born in this cohort had a neurodevelopmental delay [8]. These adverse outcomes may be averted by correcting the metabolic acidosis in obstructed.

Currently, preoperative intravenous fluid infusion (1.5L of normal saline) is a component of the standard preoperative care for all women with OL [9]. Although this practice is adequate to correct electrolyte imbalances and dehydration in most women, it may not be sufficient to reverse the metabolic acidosis. In the SoBicOL trial [7], a single dose of 4.2g was insufficient to achieve significant changes in maternal or neonatal lactate levels in comparison to a placebo. We postulate that our choice of a single dose regimen was too conservative, and only one measurement for the primary outcome at one hour was not ideal. The effect of sodium bicarbonate on maternal blood lactate was only noticeable more than one hour after the intervention. Currently, it is not known if a higher dose of bicarbonate would reverse the acidosis and achieve clinical benefits for the mother and baby.

Therefore, we propose to undertake a placebo-controlled, dose-ranging pilot trial to determine the efficacy and safety of a preoperative infusion of sodium bicarbonate on acidosis, compared with placebo among women with obstructed labour (OL). We believe this is important because very often, in this situation, there is inadequate time (or staff) to correct the acidaemia through careful titration of the bicarbonate infusion. A universal safe and effective dose would therefore facilitate its use in a low resource setting. Our results will inform the design of a full-scale effectiveness phase III trial to determine the effect of this preoperative infusion on maternal and perinatal outcomes.

We hypothesize that a higher dose of bicarbonate, can safely lower the pH and lactate levels (metabolic acidosis) by at least 20%. Therefore, we aim to determine the effect and safety of a preoperative infusion of sodium bicarbonate on pH and lactate levels (metabolic acidosis) among women with obstructed labour.

Problem statement

In Uganda, obstructed labour (OL) directly accounts for 8% of all maternal deaths and up to 14.2% of the perinatal mortality rate [7]. In a recent RCT at Mbale hospital, we found that 61% of 477 women with OL were acidotic (lactate >4.8 mmol/L), with a median capillary blood lactate level of 6.9 (3.4–13) mmol/L [7]. In the same RCT, 34% of the newborns had an Apgar score of less than seven (7), and 12% resulted in early

neonatal deaths despite being resuscitated. A potential way of improving maternal and perinatal outcomes among women with OL would be to buffer the excess lactic acid with sodium bicarbonate, achieving intrauterine resuscitation whilst awaiting an emergency cesarean section. However, in this situation, there is inadequate time (or staff) to correct the acidosis through careful titration of the bicarbonate infusion. A universal safe and effective dose would therefore facilitate its use. In our previous RCT, a single dose of 4.2g was insufficient to achieve changes in maternal or neonatal lactate levels. It is not known if a higher dose of bicarbonate would reverse the acidosis and achieve clinical benefits for the mother and baby. Therefore, we propose to undertake a placebo-controlled, dose-ranging pilot trial to determine the efficacy and safety of a preoperative infusion of sodium bicarbonate on acidosis, compared with placebo among women with obstructed labour (OL).

Justification

Undertaking a placebo-controlled, dose-ranging pilot trial shall establish a universal safe and effective dose of sodium bicarbonate for use to correct the acidosis among women with obstructed labour. Our results will inform the design of a full-scale effectiveness phase III trial to determine the effect of this preoperative infusion on maternal and perinatal outcomes. Furthermore, this information will facilitate the inclusion of sodium bicarbonate infusion in the standard preoperative preparation for women with obstructed labour in a low resource setting.

Objectives

General objective

To determine the efficacy and safety of a preoperative infusion of sodium bicarbonate on pH and lactate levels (metabolic acidosis) among women with obstructed labour.

Specific objectives

1. To determine the efficacy of a preoperative infusion of sodium bicarbonate on acidosis, compared with placebo among women with obstructed labour (OL).
2. To determine the safety of a preoperative infusion of sodium bicarbonate compared with placebo among women with obstructed labour (OL).

Hypothesis

We hypothesize that a higher dose of bicarbonate can safely lower the lactate levels (metabolic acidosis) by at least 20%.

Methods and materials

Study design

We will conduct a dose-finding phase III, randomized, double-blind, placebo-controlled, parallel-group trial.

Study setting

Mbale regional referral and teaching hospital is a busy center in Eastern Uganda with a catchment population of over 4-5 million people. Based on the annual hospital medical records, over 10,000 births occur annually with a caesarean section rate of 35%; about 12% of these operations are due to obstructed labour.

Study population

Eligibility criteria:

Inclusion Criteria:	Exclusion Criteria:
We will include patients with OL carrying singleton, term pregnancies (≥37 weeks of gestation) in cephalic presentation.	We will exclude patients with other obstetric emergencies such as antepartum haemorrhage, preeclampsia and eclampsia (defined as elevated blood pressure of at least 140/90 mm Hg, urine protein of at least 2+, any of the danger signs and fits), premature rupture of membranes and intrauterine fetal death. Patients with comorbidities such as diabetes mellitus, sickle cell disease, renal disease, liver disease and heart disease. We will also exclude those patients with hypokalaemia (148 mmol/L) and alkalosis (bicarbonate >22 mmol/L) because they are more likely to develop adverse drug reactions.

Study procedures

A research team member will inform all patients and their attendants while in the waiting/admission area about the ongoing study as part of the routine health education talks in the unit. Mothers that express no further interest in participating in the study will be noted and not approached again about the same.

On the other hand, those that express interest in knowing more about the study will be approached by a study team member once a diagnosis of obstructed labour is confirmed by the attending physician. The mother will be given more information about the study and a verbal consent will be obtained using a pre-written script in their local language following the short verbal consent in **Appendix 2**. She will also be informed that the research midwife will approach her after the birth to seek formal consent to the use of the data and specimens collected during labour.

After getting consent from the mother, the research midwife will take the next sequentially labelled study drug package and administer its contents to the consented eligible participant. At baseline, five milliliters of maternal venous blood will be collected: 2 mls in an Ethylenediaminetetraacetic acid (EDTA) vacutainer for a full blood count, and 3 mls in a general vacutainer (red top) for electrolytes, renal function tests, liver function tests and for grouping and cross matching. Ten milliliters of fresh urine will also be collected in a sterile container for analysis. All the specimens will be analysed using the RAPID Point® 500e Blood Gas System which is stationed in the surgical HDU, a short distance away from the labour ward. Lactate in amniotic fluid will be measured at the bedside using a hand-held Lactate Pro2 device (Arkray Factory,

Japan). After administration of the study drug, all the participants will be actively monitored by a research midwife up to 24 hours in order to identify any adverse effects. The research midwife will also use an electronic interviewer administered questionnaire to collect sociodemographic and clinical information from the participant at recruitment and during their stay in the hospital up to 14 days postpartum. Details of the study procedures are in the study flow diagram, figure 1.

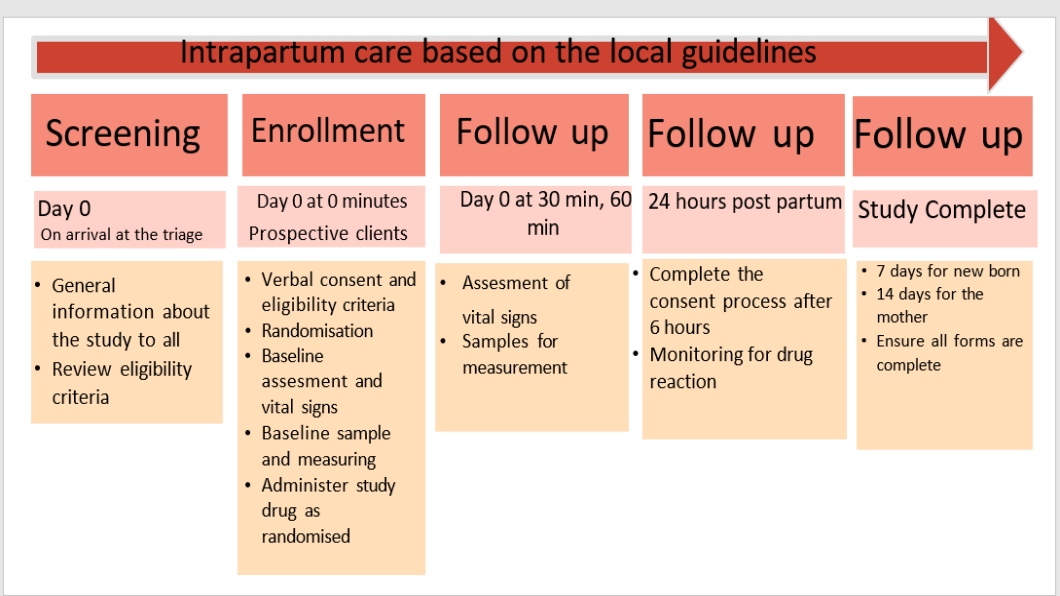

Figure 1: Study flow diagram for the proposed procedures

Sample size estimation and sampling

We will recruit 280 participants; 70 in each of the four arms. Wiberg-Itzel et al [2] observed mean umbilical artery pH 7.23 (SD 0.07) in the non-intervention group. With our sample size, we will have 80% power (significance level 0.05) to detect mean pH changes of 0.04 and above in each arm. We are interested in detecting an effect size of 0.2 and above, which we deem to be a moderate effect size. The total sample size needed to detect a between-factor mean effect size of 0.2, by repeated measures analysis of variance (ANOVA) with a type 1 error margin of 5%, across 4 groups with 5 repeated measurements; was 224 at a power of 91%. Assuming a 20% loss to follow up in our study; we will need 280 participants (70 in each of the 4 groups). The sample size was calculated using G* Power software version 3.1 using the test family for the F test, and the statistical test for ANOVA repeated measures, between factor analysis & within-between interaction [10]. Therefore, our sample size will also be sufficient to detect a within and between-subject interaction (intervention and time interaction) with a power of 99%. To obtain these estimates, we will construct an interaction term between the intervention and the time variable. We are confident that we shall be able to accrue this number of participants in a period of six calendar months, on the basis of our experience working in the same hospital [7]. In order to detect a change in maternal pH, a minimum of two measurements are needed from a participant. However, with improvement of obstetric care, many women deliver within 30 minutes of taking the baseline measurements and hence no second measurement is obtained. To account for this form of right censoring, we have inflated our sample size by 192 participants to ensure that we have at least 280 women with at least two pH measurements. We will recruit 472 participants; 118 in each of the four arms.

Outcome variables

The primary outcome measure will be the mean change in maternal pH from baseline in each group. The secondary outcomes will include, mean pH and lactate in maternal and umbilical blood, early neonatal death, safety (side effects) of sodium bicarbonate, primary PPH, sepsis and death. Furthermore, the plasma concentrations of HCO3 levels will be measured as well to accurately estimate the required dose.

Secondary outcomes will include neonatal death, postpartum haemorrhage and sepsis, in addition to the pharmacokinetics of sodium bicarbonate infusion in pregnant women. Details of measurements are in table 1.

The independent variables will include the sociodemographic, clinical, and obstetric characteristics of the study participants at different time points as indicated in table 1.

Table 1: Measurements to be taken from the participant samples

Activity/ procedure	**Time in minutes**							**Comment**
	Baseline (0)	**30**	**60**	**90**	**120**	**150**	**At birth**	
Metabolites (lactate & glucose)	X	X	X	X	X	X		Bedside using the RAPID Point 500e or YSTE-BG100 Blood gas analyzer
Blood gases (pH, pCO_2, pO_2)	X	X	X	X	X	X	X	
Serum Electrolytes (Na^+, K^+, Ca^{2+}, Cl^-)	X	X	X	X	X	X	X	
Umbilical cord blood for lactate							X	Bedside using the RAPID Point 500e or YSTE-BG100 Blood gas analyzer
Myometrial Lactate only collected at Caesarean section							X	Bedside using the RAPID Point 500e or YSTE-BG100 Blood gas analyzer
Creatinine	X							Total of 5 mL of venous blood will be taken to a central laboratory; these are part of the standard care for each patient.
Liver function tests (ALT&AST)	X							
Full blood count	X							
Amniotic fluid lactate*	X							Lactate Pro device
Bicarbonate concentrations in plasma	X	X	X	X	X	X	X	Bedside using the RAPID Point 500e or YSTE-BG100 Blood gas analyzer

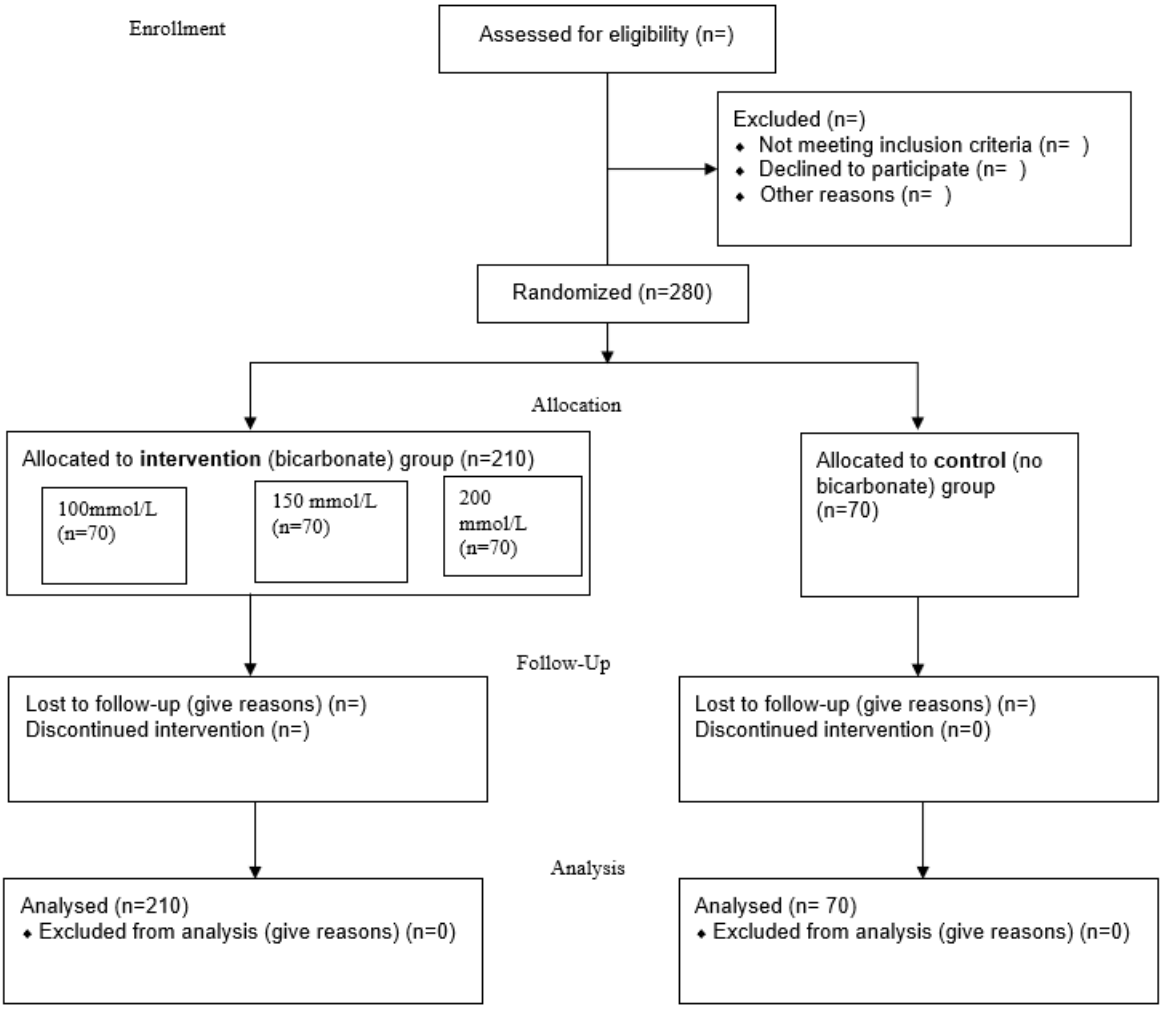

Figure 2: Flow of participants in the trial from screening to analysis

Recruitment and data collection from participants

Participants: Obstructed labour will be diagnosed by either an obstetrician or medical officer using a definition of the American Association of Obstetricians and Gynaecologists (ACOG). In the first stage of labour, the participant should have cervical dilatation >6 cm with ruptured membranes, adequate contractions lasting >4 hours with no change in cervical dilatation or delay in the second active stage of labour (nullipara >2 hours, multipara >1 hour) with adequate uterine contractions. In addition, any two of: the obvious signs of severe obstruction such as caput formation, severe moulding, Bandl's ring, subconjunctival haemorrhages or an oedematous vulva.

Randomisation: A sequence of random numbers will be generated by an independent biostatician using an online randomization service at www.sealedenvelope.com in permuted block sizes of four, six and eight. An independent, off-site pharmacist will prepare and consecutively number identical study packages using

the generated random numbers. This will ensure that the allocation is concealed. At the study site, after gaining consent, the research midwife will take the next sequentially labeled study drug package and administer its contents to the eligible participant. Therefore, both the participants and data collectors will remain blinded throughout the study.

Intervention/ Comparator: Eligible participants will be randomly assigned to receive 100 mls (8.4g), 150 mls (12.6g) and 200 mls (16.8g) of 8.4% sodium bicarbonate solution, or placebo (50 mls of NS 0.9%) in a ratio of1:1:1:1. The study drug (Sodium Bicarbonate 8.4% and Normal Saline 0.9%) will be contained in identical 25 mL glass vials (Neon Laboratories Ltd, Mumbai, India), administered intravenously as a single bolus dose. Since the average waiting time for CS in our labour ward is approximately 110 minutes [11], there will be no need for a repeat dose.

In addition, all patients will receive the available Ministry of Health recommended standard preoperative care for all patients with OL which includes antibiotic prophylaxis, intravenous fluid replacement (1.5 L of normal saline), bladder drainage and lying in left-lateral position as they are being prepared for caesarean section [23]. Details in flow diagram 1.

Data collection

Our research assistants will be qualified midwives with training in data collection, using dedicated password protected android devices. We will also review relevant health facility records such as antenatal care cards, case notes/file, the maternity and theatre registers. Laboratory parameters including lactate will be measured at baseline, and every thirty minutes after study drug administration until delivery to obtain samples for lactate measurement in umbilical cord blood and the myometrium. The participants will be followed for 7 days postnatal to ascertain the secondary perinatal outcomes and for 14 days postpartum to determine the secondary maternal outcomes. In the first 24 hours after study drug administration, the participants will be closely monitored to identify any drug reactions/adverse events. After administration of the study drug, all the participants will be actively monitored by a research midwife up to 24 hours. The women will be examined and asked directly about the presence of side effects.

Sample collection quality control

Qualified and well-trained research midwives will draw five millilitres (ml) of blood by venipuncture at the antecubital fossa of the non- dominant arm from each participant using a five millilitres syringe. After removing the epidermal needle and the tops of the vacutainers, two millilitres will be emptied into a purple top vacutainer for a full blood count, blood grouping and cross-matching as part of the standard preoperative preparation for all patients with obstructed labour in the hospital. The remaining three millilitres will be emptied into a red top vacutainer for blood chemistries including electrolytes, these are not part of the routine preoperative preparation for patients before caesarean section. Each blood sample will be transported to the laboratory in an ice-cooled container within 30 minutes of collection. Urine samples: Mid-stream urine, ten millimeters will be collected in sterile urine container from the mothers. We will monitor strict adherence to the standard operating procedures for collecting and handling participant samples through ongoing training and spot checks.

Cord blood collection

After the baby is born, the midwife will double clamp and cut the umbilical cord. Cleanse a 4”- 6” area of the umbilical cord with alcohol to remove maternal blood and contaminants (before the delivery of the placenta, if possible). Then blood will be drawn from the cord with a needle.

Data analysis plan

Data will be analyzed using Stata version 17.0 (StataCorp; College Station, TX, USA). We will describe categorical variables as proportions and compare them with chi-squared tests or Fischer's exact tests as appropriate. We will describe continuous variables as means (SD) OR medians (IQR) and compare them with t tests or Mann-Whitney U tests as appropriate. Our analysis will be by intention to treat. To determine the safety of sodium bicarbonate infusion, we will compare the incidence of side effects in each arm and report risk differences.

For the primary outcome of acidosis (pH and lactate) between-subjects repeated measures ANOVA will be conducted. We will also conduct within-subject interaction repeated measures ANOVA to assess for differences in the rate of change of pH between the groups.

We will use histograms, P-P plots, k-density, and Q-Q to assess the distribution of normality of continuous outcomes. In case the distribution of normality is not met; we shall transform our data and this decision will be guided by Stata's *gladder* command that shows various transformation options.

All analyses will be followed by a Bonferroni posthoc test for multiple comparisons, a Friedman test to compare rates of change between the various groups, and a Mauchly's test of Sphericity to check for equal variance among the combinations of the various groups. We will use Margins and Margins plots to obtain marginal means and graphical descriptions of the interaction between various groups and time.

Data Monitoring

Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) will be appointed consisting of 3 members: a statistician, an obstetrician/gynaecologist, and a paediatrician. They will operate according to the IDMC charter, which will be developed with the members. IDMC will be encouraged to follow the recommendations of the international DAMOCLES group for IDMC activities.[12] The IDMC will monitor the trial once with a focus on issues relating to the quality of trial conduct, such as overall and site-specific rates of recruitment, adherence to trial interventions, visit schedules, losses to follow-up, and administrative and safety data. It will review administrative and safety data approximately every three months. The treatment groups will be masked in the IDMC reports.

Interim analyses and stopping guidelines

Interim analyses: The interim analysis of efficacy data will be performed by the IDMC statistician. One analysis will be conducted according to the group sequential design when 50% of the inclusions are recorded. According to the O'Brien-Fleming alpha spending function, using a group sequential design and assuming a power of 80% and a significance level of 5%, the first interim analysis includes 140 subjects and has an information rate of 50%, efficacy bounds of -2.96 and 2.96, and p-value 0.003 (figure 3). These calculations were made using the RPACT RShiny app (https://rpact.shinyapps.io/public/). Interim trial data will be kept confidential and restricted to the IDMC, except if early stopping of the trial is recommended.

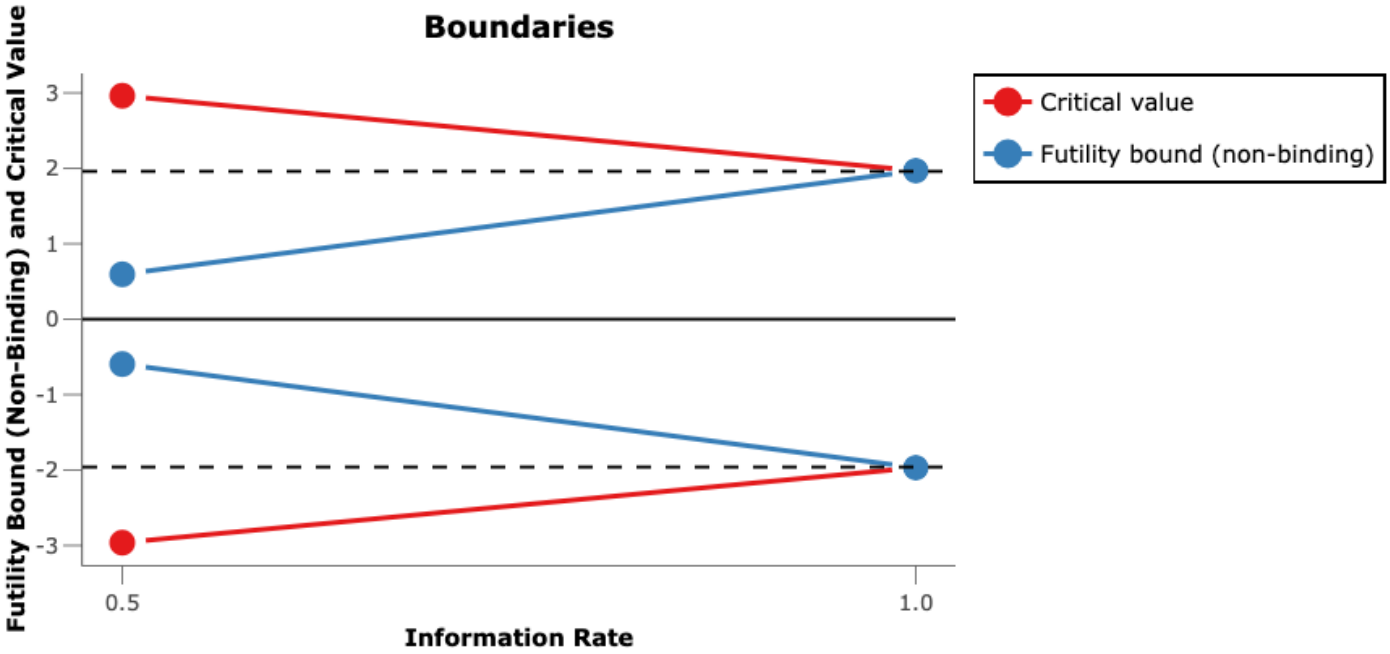

Figure 3: Figure showing efficacy bounds (critical value) at the interim analyses (50% accrual rate) and how these will change as the study progresses

Stopping guidelines

1. We propose the following stopping rule: "a statistically significant difference (p<=0.003) at the interim analysis according to the O'Brien-Fleming spending function for group sequential design) in the primary outcome between the treatment arms.

2. SAEs will be continuously monitored during data entry and reported to the IDMC. Any imbalance between expected occurrence and actual occurrence will be assessed by the IDMC statistician when 50% inclusions are recorded, and discussed with the IDMC.

3. The IDMC will provide a recommendation to stop or alter the design or conduct of the trial in case of high efficacy and/or poor adherence or unacceptable side effects that can be ascribed to the intervention according to pre-determined stopping rules and criteria. While the reviews of safety will consider both expected or unexpected adverse events, and the relative rates of death.

4. If the IDMC recommends stopping the trial early, a meeting of the principal investigator, the trial sponsor, the trial steering committee and the IDMC will be held to decide on the trial discontinuation. In case of disagreement, the advice of independent external experts will be sought. A report will be submitted to the Local IRB (BUIRB) as soon as possible and not later than 14 days after the decision.

Ethics and consent process

Ethical approval will be sought from the Busitema University Research and Ethics Committee (REC), and the Uganda National Council for Science and Technology (UNCST). We shall also seek ethical clearance from the University of Bergen in Norway, since it is a requirement for our collaborators. Administrative clearance to conduct the study will be obtained from the Mbale Hospital Research and Ethics Committee. The Ministry of Health and hospital protocols will be followed in management of emergencies such as neonatal resuscitation during the study [13].

Informed consent will be obtained in two steps as suggested in the differed consent pathway for intrapartum research [14]. In step one, a research team member will inform all patients and their attendants while in the waiting/admission area about the ongoing study. This will be done by the staff on

duty as part of the routine general health education talks before a diagnosis of active labour or even obstruction is made by the attending physician. Those who will express interest in knowing more about the study will be taken through the process of obtaining a short verbal consent if they become eligible (Appendix 3). We will keep an inventory of those that decline to participate at this stage, they will not be approached again and no data will be obtained regarding their births or outcomes. Once eligible, women will be informed about the study and verbal consent obtained using a pre-written script in their local language. Those who accept to be in the study will be administered the medication, whilst those who decline or are in any way unsure will not be included. In step two, after delivery in the postpartum period, the participant will be visited by a member of the research staff for the formal informed consent process. From past experience in this same labour ward this might be the scenario for most of the participants. In the case of illiterate participants, an independent witness will also be asked to witness the consent process and sign the consent form besides the participant's thumb print. Pregnant women between 16 - 18 years of age will be included as emancipated minors, who can give a valid informed consent as per the national guidelines [15].

Budget

Budget in USD	**Unit price**	**No of units**	**Frequency**	**Total**	**Justification**
Personnel					
Research Assistants	500	4	12	24,000	To offer 24-hour coverage, in the recruitment phase
Project Initiation costs					
REC approval	800	1	1	800	Both local and national, including a onetime annual renewal
NDA clearance	4000	1	1	4,000	Mandatory Fee, for all drug trials.
Clinical trial insurance	5000	1	1	5,000	One-time mandatory cost required by the National drug authority
IDMC	920	1	1	920	To facilitate one physical meeting, at the half way mark of data collection
Site Initiation trainings	500	1	1	500	One physical training every six months, one at initiation and one refresher
Patients' costs					
Participants compensation	8	290	1	2,320	This is mandatory by REC to compensate for participants time in study
Sundries and supplies- CS kit	14	100	1	1,400	To try and reduce delays to access emergency CS due to lack of sundries. Assuming CS rate will remain 35%
Treatment/Placebo costs					
Sodium bicarbonate infusion	4	2000	1	8,000	Purchase of the active drug
0.9% Normal Saline	3	100	1	300	Purchase of the placebo
Non-treatment consumables					
Lactate Pro 2 Device	340	1	1	340	One additional device to supplement the two we have from the previous project

Lactate Pro 2 test strips	2	290	4	2,320	Every patient will need a minimum of four tests through labour
Cartridges	16	290	1	4,640	To be purchased from the local supplier for the RAPID Point® 500e Blood Gas System (Bedside Testing)
Laboratory test	12	290	1	3,480	Full blood count blood grouping and cross matching at baseline. Plasma concentrations of bicarbonate(pK)
Antiseptic	1	290	2	580	For collection of samples, at phlebotomy.
Community engagement					
Community engagement involvement	700	1	2	1,400	To facilitate the conduct of community engagement meetings
Total	`			**60,000**	**This excludes 15% institutional overheads.**

Management

The Principal Investigator (Dr. Milton Musaba) is an Obstetrician and Gynaecologist, who has just completed a trial on the use of sodium bicarbonate in obstructed labour in the same maternity unit, as part of his PhD training[7]. Dr. David Mukunya, is trial manager for BabyGel. He has managed several large trials and recently completed his PhD in Newborn morbidity and mortality under the Survival Pluss project in Northern Uganda. Prof Julius Wandabwa is an Obstetrician and Gynaecologist/Dean of the Busitema University Faculty of Health Sciences that will administer this grant as a lead institution. Dr. John Mulangwa will be providing support as a study pharmacist, he will import and blind the study drugs in liaison with the statistician.

Independent Data Monitoring Committee

We plan to conduct one interim analysis, when half (25%) of the participants have been recruited. This will be undertaken by the independent data monitoring committee (IDMC) composed of an obstetrician, a paediatrician and a statistician with research experience. These will be appointed by the sponsor of the study, Busitema University. The stopping rules agreed upon in the terms of reference for the IDMC will be based on: safety concerns, outstanding benefit, and futility. The IMDC will have the mandate to halt the study if the occurrence of adverse events (Safety) in any of the intervention arms is greater or equal to 10% in comparison to the placebo arm. All the serious adverse events (SAE's) will be reported and closely followed, until resolution following the existing statutory guidelines. However, this is unlikely to happen because the active drug (sodium bicarbonate) has a very good safety profile in both clinical use and research even among pregnant women in children. Furthermore, we will ensure that our study protocol is approved by both the Busitema University Faculty of Health Sciences Research and Ethics committee (BUFHS), and the Uganda National Council for Science and Technology (UNCST).

Quality control: All our research assistants will be qualified midwives/nurses, with training in good clinical practice (GCP). They will also receive training in the study protocol procedures during the trial dry run phase and at regular intervals throughout the implementation of the trial. The electronic questionnaire will be coded with checks and skips to ensure internal consistency. All the required blood tests will be done at the bedside using the RAPIDPoint® 500e Blood Gas System (Siemens Healthcare GmbH)[16]. Our choice of this system was informed by its ability to measure a range of parameters, using only 100 microliters of blood. Additionally, women with obstructed labour requiring urgent intervention, hence the need for a

short turnaround time on blood results to inform clinical decision making. In the event of system downtime, we will use a YSTE-BG100 Blood Gas Analyzer (Yuesen Med, China) as a backup. The YSTE-BG100 is a compact and user-friendly device that can rapidly assess key parameters including pH, lactate, glucose, electrolytes, and blood gases [17], thereby ensuring continuity of care even when the RAPIDPoint® 500e Blood Gas System is down. In our previous trial the study drug was sourced from the local supplier accredited by the National Drug Authority (NDA). We intend to use 8.4% sodium bicarbonate (intervention), and sodium chloride 0.9% (placebo) from NEON laboratories Ltd, Mumbai, India.

Adverse events/side effects: Based on the package insert labelling for sodium bicarbonate and a review of the literature [18], we will actively monitor for the following; increased thirst, continuing loss of appetite, swelling of the lower limbs, venous irritation, muscle pain or twitching, continuing headache, nausea or vomiting, stomach crumps, unusual tiredness or weakness, nervousness or restlessness, mood or mental changes, frequent urge to urinate, slow breathing and cellulitis at the injection site. This will be done hourly for the first six hours, six hourly for the next 18 hours and then daily throughout the period of hospitalization.

Follow-on plan

We plan to publish our results in a peer reviewed journal irrespective of the findings, as we have demonstrated in the past. Furthermore, we have established contact with Dr. Trond Michelsen in Oslo to advise on the setup of our current study. His group is undertaking similar work (https://ichgcp.net/clinical-trials-registry/NCT05719467), and they could be potential collaborators on a larger grant application if the results are positive (see attached support letter). We have a community advisory group that is crucial in disseminating our findings to the lay public. Dr Musaba is also a member of National Safe Motherhood Executive Committee (NASMEC), a ministry of health technical advisory group on maternal health. He will disseminate the findings in this group.

Table 2: Proposed study timelines

Activity	**2024**												**2025**					
	Jan	**Feb**	**Mar**	**April**	**May**	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**June**
REC & UNCST approvals	*	*	*	*	*													
Recruitment of staff					*	*	*											
Procurements		*	*	*	*	*	*	*	*	*	*							
Data collection							*	*	*	*	*	*	*	*	*	*	*	*
Data analysis											*	*	*	*	*	*	*	*
Dissemination and Publications															*	*	*	*

Pharmacokinetics of sodium bicarbonate

Study design: This will be a population-based pharmacokinetics study of sodium bicarbonate using plasma levels in pregnant women with obstructed labour. We propose to investigate the association between the exposure of various doses of sodium bicarbonate (i.e. 8.4g, 12.6g and 16.8g) in pregnant women with obstructed labour, and identify determinants to inform dosing policy guidelines.

Study population: We will establish a cohort of pregnant women with obstructed labour in Mbale regional referral hospital. Only mothers that consent to participate in the study will be included.

Data collection: Following the administration of sodium bicarbonate, a blood sample will be collected from the mother at time 30, 60, 90, 120 and 150 minutes and at the time of childbirth; and then umbilical cord blood will be collected at birth for testing. Consequently, the concentrations of sodium bicarbonate will be determined using liquid chromatography (HPLC) method with electrochemical detection as described by Rodriguez [19]. The HPLC analysis will be conducted at Busitema University Ministry of Science, Technology and Innovation supported laboratory. Data from the respective participants will include PK, socio-demographics, adverse events and other clinical parameters including weight and age.

Data analysis: Non-compartmental analysis will be used to analyse the intensive PK data for sodium bicarbonate and a population pharmacokinetic model will be developed to analyse the sparse PK data. Any disparate treatment approached, additional medications or relevant clinical information, will be captured and adjusted for in the model. We will use nonlinear mixed-effects modelling (also known as population PK) to interpret the sodium bicarbonate pharmacokinetic data and assess the effect of variation. PopPK modelling offers a semi-mechanistic platform to interpret PK data, in that it evaluates the effect of patient covariates on physiological PK parameters (such as clearance and bioavailability), as opposed to hydroxyurea concentrations summary values (such as AUC and Cmax). The concentration-time data for the drugs of interest will be analysed using popPK (nonlinear mixed-effects) modelling in NONMEM.

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Appendix 1: Data collection tool

A. Sociodemographic details
    1. Study ID…….
    2. Today date …/…./……
    3. Date of admission …/…./……
    4. Time of admission …/…./……
    5. Contact details of participant …….
    6. Participants next of kin
        i. Partner
        ii. Sibling
        iii. In-law
        iv. Others
    7. What is the contact of the next of kin?.....
    8. Age of the participant ……..
    9. What best describes your religion?
        i. Catholic
        ii. Anglican
        iii. Muslim
        iv. SDA
        v. Pentecostal
        vi. Others
    10. What best describes the participants marital status?
        i. Single
        ii. Married
    11. What best describes the participants completed level of education?
        i. No education
        ii. Primary
        iii. Secondary
        iv. Tertiary
    12. What best describes the participants occupation?
        i. Salaried employee
        ii. Self employed
        iii. Housewife
    13. How would the participant best describe her place of residence?
        i. Urban
        ii. Rural
    14. How far is the participants home from the nearest health facility
        i. < 5Km
        ii. > 5Km
B. Obstetric history
    1. What is participants parity?
        i. 0
        ii. 1 to 2
        iii. 2 to 4
        iv. 5+
    2. What is the estimated gestation age of the current pregnancy?
    3. Did the participant attend ANC for the current pregnancy?
        i. Yes
        ii. No
    4. If yes, how many times did you attend?

5. Date of labour onset
6. Time of labour onset
7. Have your waters broken?
    i. Yes
    ii. No
    iii. Not sure
8. If yes, when did the waters break?
    i. Date
    ii. Time
9. Did the participant come in as a referral?
    i. Yes
    ii. No
10. If yes, from which facility
    i. Hospital
    ii. HC II
    iii. HC III
    iv. HC IV
    v. Private
    vi. TBA
11. Has the participant use any traditional medicines in the current pregnancy?
    i. Yes
    ii. No

C. Clinical examination findings
1. Weight
2. Height
3. BMI
4. Cardiovascular system
    i. BP
    ii. Pulse
    iii. SPO2
5. Respiratory system
    i. Respiratory rate
6. Abdominal examination
    i. Does the participant have a visible Bandl's ring?
    ii. Doe the participant have palpable uterine contractions?
    iii. What is fetal heart rate?
7. Vaginal examination
    i. Is the vulva and vagina oedematous?
    ii. Is the caput present?
    iii. Is the pelvis adequate?
    iv. Have the membranes ruptured?
    v. What is the colour of the liquor?

D. Baseline laboratory test results - Maternal

Parameter	Blood	Amniotic fluid	Urine
pH		Not Applicable	Not applicable
Blood gasses		Not Applicable	Not applicable
Lactate			

E. Study drug administration

Time	
Package number	

F. Maternal outcomes after study drug administration

Time (minutes)	Lactate in maternal blood sample	Lactate in amniotic fluid sample	Maternal arterial blood gasses	Maternal pH
0				
30				
60				
90				
120				
150				

G. Maternal outcomes at birth
   1. Mode of delivery
      i. SVD
      ii. CS
   2. For all those that delivered by CS, record the myometrial lactate here
   3. What was the duration of labour?
   4. Measured blood loss at birth
   5. How well did the uterus contract after birth? (scale 1-10)
   6. Assistant at delivery?
      i. Midwife
      ii. Specialist
      iii. Medical Officer
      iv. Intern
      v. Student
      vi. Others
   7. Did the participant sustain any injuries in the birth canal?
      i. Yes
      ii. No

H. Newborn outcomes at birth
   1. Record the Agar score here
      i. At one minute
      ii. At five minutes
   2. Record the birth weight here
   3. Lactate in arterial cord blood
   4. Lactate in venous cord blood

Within one minute of child birth	Lactate in maternal blood sample	Lactate in amniotic fluid sample	Maternal arterial blood gasses	Maternal pH
Arterial cord blood				
Venous cord blood				

I. Monitoring of side effects and adverse events for 24 hours period after administration of study drug

(Tick all that apply)

1. Frequent urge to urinate		10. Swelling of feet or lower legs	
2. Headache (continuing)		11. Unpleasant taste	
3. Loss of appetite (continuing)		12. Increased thirst	
4. Mood or mental changes		13. Unusual tiredness or weakness	
5. Muscle pain or twitching		14. Venous irritation	
6. Nausea or vomiting		15. Cellulitis	
7. Stomach crumps		16. IV site pain	
8. Nervousness or restlessness			
9. Slow breathing			

J. Follow up outcomes
   1. Perinatal outcomes on the 7th day postnatal
      i. Alive and well
      ii. Alive and not well
      iii. Dead
   2. If baby is alive and not well or Dead, please specify why;
   3. Maternal outcomes on 4th day postpartum
      i. Alive and well
      ii. Alive and not well
      iii. Dead
   4. If mother is alive and not well or Dead, please specify why;

K. Pharmacokinetic of hydroxy urea in pregnant women

Time (minutes)	Maternal blood	Urine	Amniotic fluid	Umbilical blood
0				
30				
60				
90				
120				
150				

Appendix 2: Short Verbal Consent form [20]

i. When the process of your labour does not happen as expected, it is called obstructed labour. This may need you to have a caesarean section for a safe delivery.
ii. Most women in your situation have built up a lot of acid in their blood and this can be harmful for both you and your baby. An infusion called sodium bicarbonate can reduce this acidity, improving outcomes for you and your baby. However, we do not know how much of the drug, women need, nor whether mothers and babies do better if they receive it.
iii. If you want to take part in this research, we will use a computer to decide what dose of the drug we will give you – or whether we just give you plain water. Neither you nor the doctor will know what dose you have received but we will monitor you carefully and take off some samples at different time points. We will use that information to improve the care for women in the future who have the same condition as you.
iv. We have independent committees reviewing the study to make sure that the study is safe for you and your baby. However, if you do not want to take part in research you can simply refuse and we will give you the usual treatment instead.
Would you like to take part in this research?

Name of Participant	Signature/Thumbprint	Date
…….	……	……..
Name of person obtaining consent	Signature	Date
…….	……	……..

Appendix 3: English Consent form

Title of the study: Effectiveness and Safety Dosing of Sodium Bicarbonate in Women with Obstructed Labor in Eastern Uganda: A Phase III Randomized placebo-controlled Trial (SoBicOL- II Study)

Principal investigator: Dr. Milton Musaba, Associate Professor of Obstetrics and Gynecology, Busitema University.

Background of the study

When a woman is in labor, sometimes the baby can get stuck possibly due to the baby being big or the birth canal being small, making it difficult for the baby to come out. This is called obstructed labor. When this happens, the muscles that make up the womb work really hard and for a long time, this extra effort reduces the oxygen that eventually reaches the unborn baby through the muscles of the womb. As a result, a substance called lactic acid can build up in the mother's blood and around the unborn baby. If the arrested labour process is not relieved quickly, the acid accumulates in the mother's womb and blood stream, the excess acid can also easily reach the unborn baby through the umbilical cord leading to unwanted consequences for the mother and baby pair including death.

We believe that giving a solution called sodium bicarbonate (**SODA ASH**) to women with arrested labour as they wait to get a caesarean section, can help to reduce this excess acid and improve outcomes for both the mother and unborn baby. Based on results from our previous work and that of other colleagues in the world, this drug is very safe for pregnant women and their unborn babies. However, what remains unknown to date is what the most effective and safe dose should be?

Study purpose

The purpose of this study is to identify the safest effective dose that can be used to reduce acidosis in women with arrested labour in Mbale hospital. Knowing what the right dose should be, will inform the design of a larger study to determine the usefulness of this treatment to improve maternal and fetal outcomes among women with obstructed labour in our region and beyond.

Who is requested to participate?

Mothers with obstructed labour admitted at the labour ward of Mbale regional referral hospital

Study procedures

If you choose to participate in this study, we will collect five milliliters (5mls) of blood from you; 2 mls in a purple top container for a full blood count, and 2 mls in a red top container for electrolytes, renal function tests, liver function tests and grouping and cross matching and one ml will be taken in six equally divided portions for measuring lactate in your blood, glucose, and blood gases (pH, pCO_2, pO_2) at different time points. We will also collect ten milliliters (10 mls) of fresh urine in a sterile container for analysis. Further, lactate in the fluid around the baby will be measured at the bedside using a hand-held Lactate Pro2 device. You will also be assigned by chance to one of four treatment groups to receive different doses of the sodium bicarbonate (SODA ASH) drug. Additionally, one treatment group will receive only water for injection. Since, this allocation is purely based on chance, neither you nor any of the study team members can influence the choice of which group to belong to. After administration of the study drug, you will be

actively monitored by a research midwife up to 24 hours. You and your baby will be followed up till 14 days postpartum.

Risks/discomforts:

There may be minimal medical risks due to the drawing of blood samples such as mild, temporary discomfort at the venipuncture site, minor pain, bruising or bleeding. On rare occasions, there could be a risk for infection, fainting. However, these are not expected to happen since blood samples will be collected by qualified medical personnel. The volume of the blood sample to be collected is not likely to cause faintness and will not interfere with the normal process of pregnancy/labour.

Benefits

You will not receive and direct benefit from this study. However, information obtained from this study will improve maternal and fetal outcomes among women with obstructed labour in our region and beyond. In addition, a copy of all the results from the laboratory tests will be availed in your file for use by the attending clinicians to help in decision making regarding your care.

Voluntary participation and right to withdraw consent:

You are free to join the study or not to join. Your participation in this study is completely voluntary. If you would like to participate, please sign the consent form at the end of this document. If you join the study, you will be free to withdraw from it any time, and if you decline to participate in the study, you will still receive the same care and attention from the medical personnel(s). There will be no negative consequences for you or your baby if you do not want to participate or if you choose to withdraw at a later stage. If you withdraw your consent, your health data and biological material will not be used in any further research. You can request access to the data held on you, and this will be provided within 30 days. You can also apply for your data in the project to be deleted.

The right to have your data and material destroyed, deleted or returned does not apply if the material or data are anonymized or have already been published. Access may also be restricted if the data have been included in analyses already performed.

Confidentiality:

Your names will not appear anywhere on the study forms. A study identification number will instead be used. Only researchers involved in the study will be allowed to work with your blood and see your information. The information will only be used for the purpose of this study and no publication of this study will use your name or identify you personally.

Reimbursement:

Twenty thousand Ugandan shillings (UGX 20,000) will be given to you for your refreshment or time compensation. This is in accordance with guidelines of the Uganda National Council for Science and Technology (UNCST).

Follow up project:

In future, if funding is available, we may contact you for a follow up study.

Contact details:

If you have any questions about your rights as a participant in this study, you can call the Busitema University Research and Ethics Chair chairperson, Dr. Richard Katuramu on 0752900344. If you have any other questions about the study, you can ask them now or later. If you wish to ask questions later, you may contact the Principal investigator: Prof. Milton Musaba, Associate Professor of Obstetrics and Gynecology, Busitema University. P.O. Box 1460 Mbale, Uganda. Mobile: 0704913791. miltonmusaba@gmail.com

STATEMENT OF CONSENT:

I …… confirm that the researcher has explained to me all the above information. I have understood what will be done, the risks, the benefits involved and my rights regarding this study. I understand that my decision to participate in this study will not alter my usual medical care. In the use of this information, my identity will be kept confidential. I am aware that I may withdraw at any time. I understand that by signing this form, I do not waive any of my legal rights but merely indicate that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

Name of Participant	Signature/thumb print	Date
…….	……	……..

Name of Witness	Date
……	……

Name of person obtaining consent	Signature	Date
…….	……	……..