OBSTETRIC OUTCOMES OF IMMEDIATE VERSUS DELAYED OXYTOCIN ADMINSTRATION FOLLOWING AMNIOTOMY IN HYPOTONIC UTERINE CONTRACTIONS AT TERM AT KNH: A RANDOMIZED CONTROLLED TRIAL

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DEDICATION

To our Almighty Lord be all the glory. I dedicate this book to my wonderful husband Victor Wambua, ourlovely daughter Alyona Kioko and my parents ZadorhozhnayaMariya Ivanovna, Ekaterina Mwok-Handa, Dr. Odhiambo Sule and Col.Dr. George Adari. Victor, I thank you for your immense support, understanding and love. Alyona, there is no limit to what you can and will achieve, I love you. To my parents; all that I am is because of who you raised me to be and I thank you. To my extended family and everyone who made sure I was comfortable while studying, God bless you all.

DECLARATION

This is to certify that the work presented herein is my original work, and has not been presented for a degree course in any other university and was supervised by senior members of the of Department of Obstetrics and Gynecology, School of Medicine, College of Health Sciences, University of Nairobi, Kenya.

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LIST OF ABBREVIATIONS

ACOGAmerican College of Obstetricians and Gynecologists

AFEAmniotic Fluid Embolism

AMLActive Management of Labour

APGARAppearance, Pulse, Grimace, Activity, Respiration

ARMArtificial Rupture of Membranes

CPDCephalo-pelvic disproportion

CTGCardiotocograph

DICDisseminated Intravascular Coagulation

DSMBData Safety Monitoring Board

EOGBSEarly Onset Group B Streptococcal disease

ERCEthics Review Committee

FGRFetal Growth Restriction

FHR Fetal Heart Rate

GBSGroup B Streptococcus

GCPGood Clinical Practice

IVIntravenous

KNHKenyatta National Hospital

NBUNew Born Unit

NRFSNon Reassuring Fetal Status

OAOxytocin Administration

PGE2Prostaglandin E2

RCTRandomized Controlled Trial

SOPStandard Operating Procedure

SVDSpontaneous Vertex Delivery

UoNUniversity of Nairobi

WHOWorld Health Organization

LIST OF FIGURES,TABLES AND GRAPHS

DEFINITION OF TERMS

Artificial Rupture of Membranes- an intervention in the labour process whereby the amniotic sac is deliberately broken or punctured so as to release and assess the amniotic fluid.

Active Management of Labour-Medical and obstetric interventions in labour with the aim of advancing the smooth progress of labour , as opposed to allowing it to progress with minimal medical intervention.

Cardiotocograph-A machine used to technically monitor the fetal heart rate against maternal uterine contractions in order to make intrapartum decisions.

Cephalo-pelvic disproportion- A condition, commonly diagnosed towards term pregnancy, whereby the fetal head does not fit into the maternal pelvis because it is too large or the maternal pelvis is too small- commonly resulting in prolonged labour.

Amniotic Fluid Embolism- A rare condition in pregnancy where the fetal cells cross into maternal circulation and end up in the maternal pulmonary system causing cardio-respiratory and hematological symptoms.

Disseminated Intravascular Coagulation- A pathological process characterized by the widespread activation of the clotting cascade that results in the formation of blood clots in the small blood vessels throughout the body.

Immediate oxytocin-Administration of oxytocin within15-30min of ARM.

Delayed oxytocin-Administration of oxytocin 2hours after ARM.

Augmentation of labor-The iatrogenic process of increasing strength and frequency of uterine contractions to hasten labour with the aim of achieving vaginal delivery by the use of uterotonics

Contents

1. ABSTRACT

Background

Amniotomy or Artificial Rupture of Membranes (ARM)/ and Oxytocin administration (OA) are integral parts of active management of labour. Literature is scanty regarding the optimal timing of OA after ARM. Obstetric and neonatal outcomes in expedited versus delayed oxytocin administration succeeding ARM has not been undertaken in our setting despite routine administration of OA after ARM in selected mothers. Evaluating the effect of immediate versus delayed oxytocin administration after ARM for hypotonic uterine contractions on obstetric and perinatal outcomes is critical to maximize the benefits to both the mother and newborns.

Study Objectives

Tocompare the obstetric outcomes among parturients randomized to immediate versus delayed oxytocin administration after amniotomy for hypotonic uterine contractions at Kenyatta National Hospital between February and July 2018.

Study Site

Kenyatta National Hospital Labour Ward.

Study Design

A pragmatic, single blind Randomized Controlled Trial conducted among women in labour with no contraindications to ARM, vaginal delivery or OA. The intervention and the control arms entailed ARM and OA within 15- 30 minutes and 2 hours respectively. The investigators evaluated the maternal and neonatal outcomes after the two

approaches. Continuous variables were summarized using means and standard deviations. Categorical variables were summarized using counts and proportions and compared between the study groups. Proportions were compared using Chi2 test, 95% CI, two tailed hypothesis with p-value significant at $p<0.05$.

Results

There were no statistically significant differences in the social- demographic and obstetric characteristics of the participants between the two arms. There were no statistically significant differences in the primary and secondary outcomes between the two arms.In the delayed arm 27.7% of women avoided oxytocin. The mean amniotomy to vaginal delivery interval in the immediate oxytocin administration arm was 277min while that in the delayed oxytocin administration arm was 298 min(P=0.418). The mean amniotomy to decision for cesarean section interval in the immediate oxytocin arm was 345 min and that in the delayed oxytocin arm was 338min(P=0.458).. APGAR score at 5' was 8.53 and 8.56 in the immediate and delayed arms respectively (P=0.793). Maternal satisfaction was 4.25 and 4.26 (on a Likert scale of 1 to 5) in the immediate and delayed arms respectively ,P=0.941.

Conclusions

Among women with hypotonic uterine contractions at ≥ 4 cm cervical dilation administering oxytocin immediately (within 15-30 minutes) following ARM does not reduce duration of labour, lower cesarean section rate, improve neonatal outcomes or enhance maternal satisfaction. Delaying oxytocin administration by 2 hours decreases the need for oxytocin by 28%.

Recommendations

In women at term with a favourable Bishop's score, administration of oxytocin following ARM should be delayed by at least 2 hours.This can avoid oxytocin use by 27.7% It is also encouraged that labour augmentation protocols be developed in KNH. Adherence to partograms in high patient burden settings should be strengthened for early detection of hypotonic uterine contractions and subsequent appropriate interventions.

2. INTRODUCTION AND LITERATURE REVIEW

2.1. Maternal and neonatal morbidity and mortality due to slow progress of labour

Slowly progressing (or prolonged) labour due to inefficient uterine contractionsis an important cause of maternal and perinatal morbidity and mortality as a result of infections, uterine rupture and operative deliveries(3). In 2015 the WHO estimated that 303,000 women died as a result of pregnancy and childbirth-related complications(2). Most of these deaths occurred in low- and middle-income countries (LMIC). In Nigeria, in 2014, prolonged labour was found to account for nearly 18% of the maternal deaths (4).

"Failure to progress" or "slow progress in labor" is also one of the leading indications for primary caesarean section. Between 2002 and 2008 nearly half (41.3%) of the Cesarean sections in first-time parturients in the United States were due to failure to progress(5). High primary caesarean section rates not only lead to high repeat caesarean section rates but also increased maternal and neonatal morbidity and mortality.

2.2. Augmentation of labour

Augmentation of labour is the process by which the uterus is iatrogenically primed to contract more intensely, more frequently and at an appropriate contraction duration in order to hasten delivery after the onset of labour(6).Labour augmentation is routinely done in clinical care as part of Active Management of Labour (AML)(7).

The practice of augmentation of labour revolves around Artificial Rupture of Membranes (ARM) and intravenous oxytocin administration (OA). ARM is a medical intervention involving deliberate exogenous puncture of the amniotic sac in order to release the amniotic fluid. ARM is done using an amniotic sac perforator of any kind, such as an Amniocot and is best done in a controlled manner so as to avoid complications such as umbilical cord prolapse and abruptio placentae among others. ARM enhances labour by effecting release of circulating prostaglandins-notably Prostaglandin E2 (PGE2) which in turn increases the frequency and intensity of uterine contractions(8). In addition to augmentation of labour, ARM is done forobservation of colour of amniotic fluid which in the event of meconium staining, further interventions may be necessary depending on the stage of labour and grading of the meconium stained liquor(9). It is also indicated where; a fetal scalp electrode needs to be applied for fetal monitoring, for fetal scalp blood sampling in situations where non-reassuring fetal status (NRFS) is suspected via Cardiotocogram (CTG)(10).

When amniotic fluid is released via rupture of membranes, the fetal presenting part becomes well applied to the dilating cervix. The physical pressure on the cervix causes release of Oxytocin. The major effect of Oxytocin is on uterine smooth muscle contraction, effected via oxytocin receptors in the uterine myometrium. The physical pressure on the cervix causes further contraction of the uterus and further pressure on the cervix leading to cervical dilatation and eventual delivery of the fetus. This neuroendocrine reflex causing sustained uterine contractions is called the Ferguson reflex(11). It demonstrates that ARM and Oxytocin (exogenous or other)

work in synergy to advance the progress of labour in the attempt of a vaginal delivery

Augmentation of labour is performed in active phase to arrest disorders of uterine hypo stimulation which may lead to prolonged labour(12). According to the World Health Organization (WHO), labour is considered as prolonged when the rate of cervical dilation and the descent of the presenting part is less than 1cm per hour respectively observed for at least 4 hours, hence providing health workers with a clear clinical way of evaluating and identifying slowly progressing labour. Although the identification of the exact cause of a delayed labour can pose a challenge to health workers(6), the most common cause is inefficient uterine contractions. No major advances have been made in the development of affordable methodology for monitoring uterine contractions in high patient number low resource settings(12) making the need for high clinical acumen and evidence based resource utilization very important. Although the global need for augmentation of labour is not defined, a 5 year Norwegian study estimated that 51% of nulliparas and 20% of multiparous women were augmented with intravenous Oxytocin (13). Local studies on the incidence of labour dystocia, the most favourable approach of augmentation regarding the timing of OA after ARM and their effects on obstetric and neonatal outcomes are scanty.

Augmentation of labour is contraindicated inprior classical uterine incision, placenta previa, pelvic bone deformities, umbilical cord presentation and fetal presentations other than cephalic(6)(14) and where vaginal delivery is contraindicated.

One of the risks of ARM is umbilical cord prolapse. Uygur D et al reported on 32,457 births subsequent to ARM and noted an incidence of only 23 umbilical cord prolapses, hence concluding that ARM was not a major contributor to umbilical cord prolapse (15).

Oxytocin administration poses a risk of uterine hyperstimulation with subsequent FHR irregularities. In a randomized trial, Hinshaw et al found that only 14% of patients required a Caesarean section after immediate OA following ARM and of these only 7.7% were due to uterine hyperstimulation(16). In the same study, a similar proportion, 14 % of patients required a Caesarean section following delayed OA but only 2.9% of these were due to uterine hyperstimulation.

2.3. Guidelines for labour augmentation

O'Driscoll et al published some of the earliest findings on Active Management of Labour (AML) in the National Maternity Hospital in Dublin (2). What they referred to as active management was a package that included special classes preparing women for labour, strict criteria for determining the onset of labour, psychological support, regular supervision by senior staff, routine amniotomy and the use of intravenous oxytocin under supervision of a midwife.

According to WHO augmentation of labour should be done with amniotomy and oxytocin administration(6), hence solitary amniotomy is not recommended.Fetal Heart Rate (FHR) should be observed prior to and after performing ARM in augmentation of labour(10) in order to detect adverse changes in fetal status and consequently institute corrective measures. Whether to perform routine or selective

amniotomy has been a subject under debate causing differing practices in different facilities and even countries(17) (1). In Randomized Control Trials and Metanalysis of early routine amniotomy it was noted that early amniotomy only offers a modest benefit in terms of decreasing the duration of first stage of labour (approximately 1 hour) compared to selective amniotomy (11)(18) without significantly affecting maternal or neonatal outcomes.

American College of Obstetricians and Gynecologists (ACOG) guidelines recommends that augmentation of labour should be considered in labour when uterine contractions are less than 3 contractions in 10 minutes or where the intensity of the contractions is less than 25 mmHg above the baseline or both(14). Thus, augmentation should be limited to patients with uterine hypotonia to avert subsequent prolonged labour.

WHO recommends that the guiding principles of augmentation should include presence of a medical indication, initially excluding Cephalo-Pelvic Disproportion (CPD), performing and documentation of Bishop's Score, closely monitoring fetal wellbeing, conducting augmentation in a facility that can manage delivery other than vaginal and bearing in mind the adverse effects of augmentation(6).

Augmentation of Labour should be performed with caution. This is because of various adverse effects associated with both ARM and Oxytocin . Adverse effects of ARM include but are not limited to Umbilical Cord Prolapse(15),increased incidence of chorioamnionitis(19), minor fetal scalp trauma, umbilical cord compression(19) and Early Onset Group B Streptococcal (EOGBS) disease of the newborn (as fetal

membranes have an inhibitory effect on GBS)(20), however all of these are rare. Adverse effectsassociated with oxytocin mainly include uterine hyper stimulation which in turn may result in uterine rupture and fetal distress(21).

2.4. Effect of amniotomy and augmentation with intravenous oxytocin on obstetric outcomes

Amniotomy and/or OA are interventions commonly used to increase the frequency, duration and intensity of uterine contractions for slowly progressing labour with uterine hypotonia. In contrast, in labour onset following chemical induction, intravenous oxytocin is used in a more reserved fashion due to the already existing effects of the inducing agent such as ability to initiate uterine contractions in addition to cervical ripening.

The effects of augmentation with amniotomy and oxytocin on duration of labour, caesarean birth rate and maternal and neonatal morbidity have not been widely studied in low resource settings(6). Besides, wide disparity in the current practice of augmentation between countries and even between hospitals in the same country(6). As a common intervention to treat delayed labor, improving the practice of labour augmentation through provision of evidence-based guidelines would have significant implications for labour outcomes.

A Cochrane systematic review (2008) of seven RCTs seeking to determine whether a package of care for active management of labour involving ARM and oxytocin administration reduced caesarean section rate and improved maternal satisfaction found that oxytocin did not significantly affect the maternal and neonatal outcomes

although it significantly reduced the duration of labor and rates of caesarean section(23). Bugg et al in an incidence study of 2745 women conducted over a 5 year period to assess the differences in mode of delivery between nulliparous women augmented with Oxytocin and those not augmented noted that only half (51%) of women who were augmented achieved vaginal delivery as opposed to three quarters (76.5%) of those not augmented with intravenous oxytocin(24).

A Randomized Control Trial conducted on 213 women experiencing prolonged latent phase of labour in a university teaching hospital in Afula, Israel, noted that amniotomy is best combined with Oxytocin as opposed to either used on their own in order to produce a shorter ARM to delivery interval(25).This study further demonstrated greater maternal satisfaction with the process of labour in the amniotomy plus Oxytocin group and comparable neonatal outcomes and mode of delivery outcomes in the mothers who had received Oxytocin alone, amniotomy alone, a combination of the two and even in the control group.

2.5. Effect of oxytocin timing on obstetric outcomes

It is recommended that ARM precede Oxytocin administration during labour augmentation. This is because administration of oxytocin with intact membranes may cause of Amniotic Fluid Embolism (AFE); a very rare obstetric condition where fetal cells are deposited into the maternal pulmonary system(26), causing maternal cardiorespiratory collapse, altered mental status and Disseminated Intravascular Coagulation (DIC).

Administration of Oxytocin for augmentation of labour should be initiated only in active phase arrest and in diagnosis of uterine hypo function(12). Even in these situations the exact timing of oxytocin is highly variable and what is considered early administration versus that which is delayed differs from study to study and settings.An RCT conducted in Sweden defined delayed oxytocin administration as 2-3 hours after ARM(27), while a larger RCT in North East England defined delayed oxytocin administration as 8 hours after ARM(16) and an RCT conducted in Kuala Lampur, Malaysia defined delayed administration as 4 hours after ARM (28).

Studies of the effects of early versus delayed oxytocin administration (regardless of the definition of the delay) have produced varying results. A randomized control trial conducted at two delivery units in Sweden to evaluate the effects of early oxytocin augmentation on maternal and neonatal outcomes in nulliparous women with spontaneous but prolonged labour found that time to delivery was significantly shortened- by approximately 85 minutes (~1.5 hours). There were no significant differences in the rates of Caesarean section (9% in early administration group and 11 % in the delayed-OR 0.8, 95% CI 0.5–1.4) and instrumental vaginal delivery rates(17% in the early administration group and 12% in the delayed-OR 1.5, 95% CI 0.97–2.4) and no significant differences in maternal and neonatal outcomes (APGAR, birth weight , admission to and stay in NICU) between study groups(27), however, maternal satisfaction with the process was not assessed.

A larger RCT of nulliparous patients with dysfunctional labour in 12 maternity units in North East England found that early Oxytocin administration did not reduce the rates of Caesarean Sections but shortened time to delivery by approximately 3

hours(P < 0.001)(16). In Kuala Lampur, Malaysia, an RCT found that women who were randomized to receive oxytocin immediately had a delivery time shortened by approximately 1.5 hours but a higher rate of fetal heart rate abnormalities were noted on CTG (by 11.8%)(28). There were no significant differences in rates of vaginal delivery([CI] 0.92–1.04, P5.72), Caesarean section and adverse neonatal outcome between study groups(28). In this study both immediate and delayed oxytocin groups rated the birthing process at 3 in a numerical scale of 1 to 10 where 1 signified most satisfied with the process and 10 signified most dissatisfied with the process(P=.36)(30). The rating was done at/within 24 hours after birth.

A 2014 Longitudinal Cohort study of the association of different timings of intrapartum interventions with duration of labour and mode of delivery found that on average OA was initiated 6 hours after the onset of spontaneous labour in nulliparous patients and after 4 hours in multiparous patients(29). In this study, early initiation of oxytocin augmentation in nulliparous women was associated with decreased duration to full dilatation and increased risk of Caesarean section during first stage and increased risk of operative vaginal delivery during second stage and decrease in spontaneous birth rate in multiparous women who received delayed oxytocin.

Furthermore, another Cochrane systematic review published in 2013 found that in women making slow progress in spontaneous labour, early treatment with oxytocin as compared with delayed oxytocin treatment did not result in any significant differences in the number of caesarean sections performed or in a range of maternal and neonatal outcomes(30)

A Meta-analysis of RCTs evaluating the effect of early versus delayed oxytocin augmentation on the mode of delivery and maternal and neonatal outcomes, delayed oxytocin being administered at approximately 4-8 hours after active phase of labour began, revealed that early OA was associated with increased rates of spontaneous vaginal delivery(RR 1.09, 95% CI 1.03–1.17). There were no significant effects on the rate of Caesarean section (RR 0.87, 95% CI 0.71–1.06) , operative vaginal delivery(RR 0.84, 95% CI 0.70–1.00) , maternal or neonatal morbidity(31). Of note this meta-analysis recommended that further studies on oxytocin with and without amniotomy should be conducted(31) in order to provide definitive evidence.

In Kenya, grey data from a UoN dissertation by Kihara et al on a descriptive study of neonatal outcomes of neonates born to women in labour who received and those who did not receive oxytocin infusion found no statistically significant differences in the APGAR scores (numerical scoring system from zero to ten which evaluates Appearance, Pulse, Grimace, Activity and Respiration of neonates) between these two groups of women. This study, however did not take into account the timing of amniotomy nor that of oxytocin administration. The locally available protocols, such as those of Moi Teaching and Referral Hospital (MTRH)(32) state that OA with ARM should be done when uterine contractions and cervical dilatation progress have proven to be inadequate on 2 hourly vaginal examinations of slowly progressing labour.

2.6. Management of adverse effects associated with labour augmentation

The adverse effects of labour augmentation such as uterine hyperstimulation emphasize the need to conduct augmentation in a facility capable of managing these adverse effects and performing a Caesarean section (1). KNH is well capable of managing the same, as it is the National Teaching and Referral Hospital.

Umbilical cord prolapse is a feared adverse effect of amniotomy. It is prevented by performing controlled ARM. Umbilical cord presentation is diagnosed on performing a vaginal examination. Umbilical cord prolapsecan be noted only after ARM or spontaneous rupture of membranes. It is ultimately managed by facilitating immediate vaginal delivery (if it is imminent) or performing an emergency Caesarean section.

Regardless of the status of the foetus, uterine hyperstimulation is defined and diagnosed as occurrence of uterine contractions lasting more than 60 seconds, or occurrence of more than four contractions within 10 minutes. WHO recommends that uterine hyperstimulation(being the major effect of OA) be prevented by initiation of low doses of oxytocin and proceeding with incremental dose adjustment depending on the strength and frequency of uterine contractions (1). Howevera Cochrane systematic review on high dose versus low dose Oxytocin for augmentation of delayed labour involving 644 patients(1) noted that high dose Oxytocin resulted in decreased duration of labour, decreased rate of Caesarean section and increased rate of vaginal delivery. In this review high dose was

considered as starting dose and increment of more than or equal to 4Mu per minute and Low dose being starting dose and increment of less than 4Mu per minute.

According to a Metanalysis, uterine hyperstimulation during augmentation of labour is managed by discontinuation of oxytocin(33). In addition, a role of administering tocolytics is described in this metanalysis, however, this is during hyperstimulation caused by misoprostol during induction of labour (20).Tocolytics used are like Terbutaline.However in KNH Nifedipine is commonly used. Magnesium sulphate, Atosiban and Nitroglycerine have little effect (34)

3. CONCEPTUAL FRAMEWORK

Narrative

Slow progress in labour causes significant maternal and neonatal morbidity and mortality. Amniotomy and intravenous oxytocin administration are the pillars of Active Management of Labour (AML). The mode of action of amniotomy is by release of Prostaglandin E2 which causes increased uterine contractions, increased cervical ripening and dilatation. This in turn activates the Ferguson's reflex; a neuroendocrine reflex initiated by prostaglandin release and application of physical pressure on the cervix by the presenting fetal part. It causes the release of endogenous oxytocin, contraction of the uterus and further dilatation and ripening of the cervix in a continuous repetitive cycle of events.

Exogenous administration of intravenous oxytocin causes uterinesmooth muscle contraction via oxytocin receptors in the myometrium. It is proposed that exogenous intravenous oxytocin administration acts synergistically to amniotomy and the

Ferguson's reflex. We sought to determine whether an early or delayed synergistic effect contributed towards a difference in ARM to delivery interval, mode of delivery, maternal satisfaction and neonatal outcome.

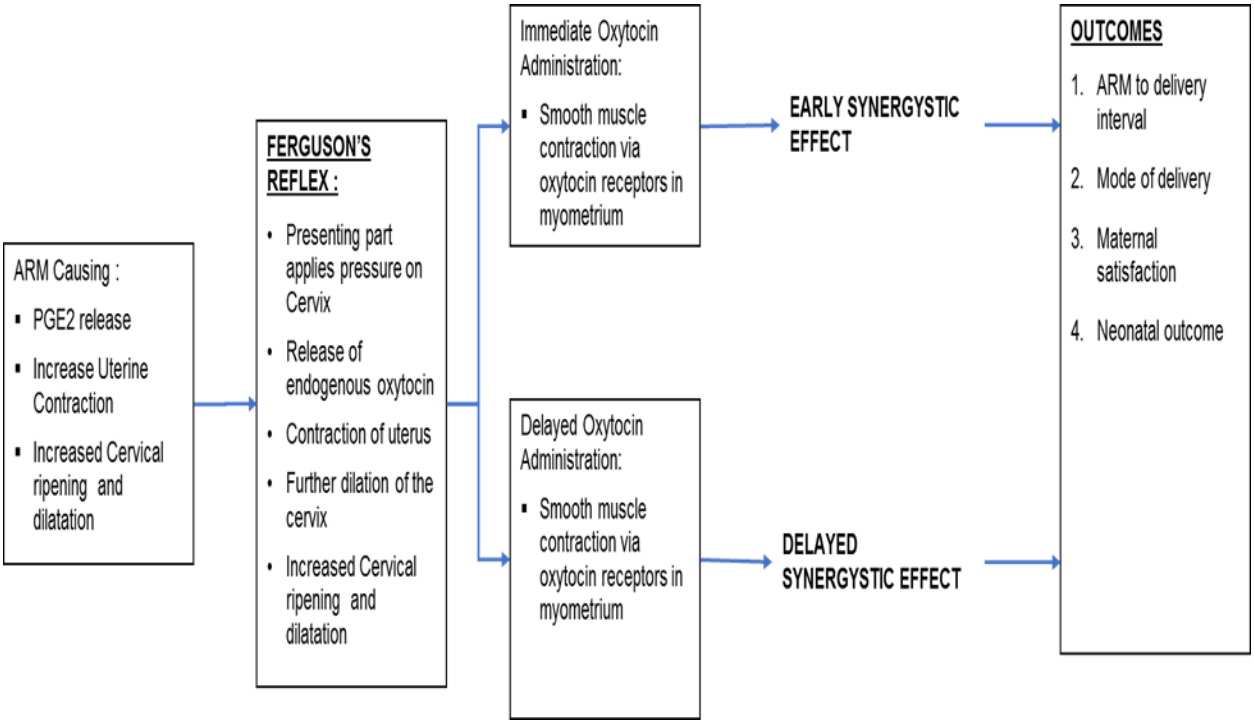


Figure 1: Schematic framework

4. STUDY JUSTIFICATION

Active Management of Labour (AML) has been taken up by KNH without specific protocols on how to conduct augmentation of labour. Currently, there is limited published literature about the timing of oxytocin in women with slowly progressing labor who require augmentation in order to positively impact on both maternal and fetal outcomes. This information is critically needed to inform development of evidence-based guidelines on augmentation of labour in KNH where such guidelines do not currently exist. WHO suggests utilization of AML interventions in a standardized and most effective manner in order to have successful outcomes especially in a resource

limited setting(6). This will be made possible with the information that will ensue from this study.

Definitions of immediate versus delayed Oxytocin vary from study to study which makes it difficult to compare and generalize their effects on maternal and neonatal outcomes. Furthermore, a Cochrane Systematic Review of amniotomy and oxytocin on delivery outcomes recommended inclusion of evaluation of the appropriate time interval between amniotomy and a secondary intervention and evaluation of maternal satisfaction of labour augmentation and induction (28). This study seeks to address the above issues pertaining to augmentation of labour.

Results from this study will be important at informing evidence-based development of locally relevant protocols or revision of existing SOPs on ARM and oxytocin augmentation of labour so as to meet the specific needs of national and local health services.

5. RESEARCH QUESTION

Are there obstetric outcome differences among women in labour at term who receive immediate versus delayed oxytocin administration following ARM?

6. HYPOTHESIS

6.1. Null hypothesis

There are no obstetric outcome differences between women in labour at term who receive immediate versus delayed intravenous oxytocin administration following ARM.

6.2. Alternate hypothesis

There are differences in obstetric outcomes between women in labour at term who receive immediate versus delayed intravenous oxytocin following ARM.

7. OBJECTIVES

7.1. Broad objective

To compare obstetric outcomes in women under augmentation of labour at term receiving immediate versus delayed intravenous oxytocin following ARM

7.2. Specific objectives

Among women in labour at term randomized to either immediate or delayed intravenous oxytocin following ARM for augmentation of labour, compare:

1. ARM to delivery interval
2. Mode of delivery.
3. Neonatal outcomes.
4. Maternal satisfaction.

8. METHODS

8.1. Study design

The study was a pragmatic, two arm, single blind Randomized Clinical Trial. The intervention arm was immediate OA (within 30 min of ARM) and the control arm was delayed OA (2 hours after ARM). The study assessed whether differences exist in

ARM to delivery interval, mode of delivery, maternal satisfaction and immediate neonatal outcomes.

8.2. Study site and setting

The study was conducted at Kenyatta National Hospital (KNH) Labour Ward. KNH is the largest national referral hospital in Kenya and isa teaching hospital for the University of Nairobi (UON), College of Health sciences and the Kenya Medical Training Center for paramedical personnel. The hospital also participates in national health policy planning and has 50 wards, 22 out-patient clinics, 24 theaters (16 specialized) and an Accident & Emergency Department.

The KNH Labour ward has a bed capacity of 28, however, with the introduction of free maternity services by the Kenya government, the ward is conducting 1200 to 1500 deliveries a month- approximately 50 % of these being Cesarean sections. Hence, KNH has become one of the busiest public hospitals offering maternity services thus is an ideal setting for conducting this study.

Currently in KNH labour ward, ARM is performed on women in active phase of labour at varying degrees of cervical dilations for augmentation and assessment of fetal wellbeing after ruling out contraindications to vaginal delivery. Oxytocin does not require specialized storage and is constituted in Normal saline by the primary midwife attending to the patient and administered when necessary according to the SOP. Oxytocin is only administered after membranes are ruptured either artificially or spontaneously and only if no amniotic fluid or FHR abnormalities are noted, however, it may be administered at any point where the clinician notes inadequate

uterine contractions. Women with contraindications to oxytocin administration are excluded from augmentation. Administration of intravenous oxytocin is as described in detail in the study procedure.

8.3. Study population

Eligible study participants were women at term who provided informed, written consent and required augmentation of active labour due to slowarising from uterine hypo stimulation. The parturients had no contraindications to vaginal delivery or oxytocin administration.

8.4. Inclusion and Exclusion criteria

8.4.1. Inclusion Criteria

Women in labour who:

1. Provided informed consent
2. Had intact membranes at 37 completed weeks or greater.
3. Had singleton vertex pregnancies.
4. Had inadequate uterine contractions upon ARM at cervical dilatation of 4-5 cm.

8.4.2. Exclusion Criteria

Women in labour with**:**

1. Multiple gestation.

2. Malpresentation (non-vertex)
3. Previousuterine surgery.
4. Virally unsuppressed HIV infection.
5. Non-reassuring fetal status prior to amniotomy.
6. Post amniotomy meconium stained liquor, fetal tachycardia, fetal bradycardia, umbilical cord or limb prolapse.
7. Antepartum hemorrhage due to any cause.
8. Hypertensive disorders, Diabetes and Cardiac disease in pregnancy.
9. Known/ suspected fetal growth restriction.
10. Parity > 5 (grand multipara)

8.5. Sample size and sampling procedure

8.5.1. Sample size calculation

The sample size was based on the outcomes of time from randomization and the proportion of women undelivered after 12 hours from randomization. A Cochrane review(35)of RCTs of the effects of early use of intravenous oxytocin versus delayed use on time from randomization to delivery found that early oxytocin administration was associated with a significant reduction in the time to delivery interval of approximately 2 hours (5.6 ± 2.9 vs. 7.6 ± 3.6). Using this study by Simpkin et al and these estimates in the sample size calculation formula below

for comparing the independent two-sample means by Donner et al, we estimated that at least 30 women per group; 60 women total wererequired to have an 80% power at 5% level of significance to detect difference between study arms.

$$\frac{2\left(Z_{\beta}-Z_{\frac{\alpha}{2}}\right)^{2}(\sigma_{I}^{2}+\sigma_{D}^{2})}{(\mu_{I}-\mu_{D})^{2}}$$

Where case Z_{β} and $Z_{\frac{\alpha}{2}}$ are normal deviates corresponding to the chosen power and significance level respectively. For 80% power $\beta = 0.2, Z_{\beta} = 0.84$ and for significance level of $\alpha = 0.05$, $Z_{\frac{\alpha}{2}} = 1.96$. In the context of our study, $\mu_I = 5.6$ the average time from randomization to delivery in the immediate oxytocin group while $\mu_D = 7.6$ was the average time from randomization to delivery in the delayed oxytocin group. $\sigma_I^2 = 2.9^2$ and $\sigma_D^2 = 3.6^2$were the variances of time from randomization to delivery in the immediate and delayed oxytocin groups respectively.

The same review also found that the proportion of women undelivered after 12 hours from randomization were 19.2% in the early oxytocin administration and 39.8% in the delayed oxytocin arm. Using these estimates in the sample size calculation formula by Donner et al for comparing independent two-sample proportions test, we estimated that at least 101 women per group; 202 total, will be required to have an 80% power at two-sided 5% level of significance to detect 20.6% difference between study arms in proportion of women undelivered after 12 hours from randomization.

$$N = \frac{2\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2 \bar{p}(1-\bar{p})}{(p_I - p_D)^2}$$

where

$$\bar{p} = \frac{p_0 + p_1}{2}$$

For this study $p_I = 0.192\ and\ p_D = 0.398$ are the proportions of women undelivered after 12 hours from randomization in the early and delayed oxytocin administration groups respectively. $\bar{p} = \frac{0.192+0.398}{2} = 0.295$.

From these two calculations, a sample size of 202 was selected as this covered sample size requirements for other aims. An additional 5% was added for attrition as a high loss to follow up was not expected. The final sample size was 212. Due to block randomization in blocks of 20 with the sample size being 212 and after attrition, the immediate arm had 108 participants while the delayed arm had 101.

8.5.2. Study procedure

Patients being admitted to Labour ward came from home or from the Antenatal clinics. A resident and midwife were stationed in the Labour Ward triage unit. Patients presenting were clinically reviewed and if determined to be in labour were admitted to the Labour ward. The diagnosis of inadequate uterine contractions was made by the resident covering Labour ward and midwife attending to the patient when less than three uterine contractions lasting less

than 40 seconds were noted in 10 minutes by manual palpation of the abdomen. The decision to perform augmentation of labour was team decision involving the consultant. After the diagnosis was made the principal investigator or research assistants engaged the patient. Patients found to be eligible and who had given written informed consent were enrolled.

Block randomization (in blocks of 20) was done by computer generated random sequences and a randomization ratio of 1:1. Upon enrollment, an opaque envelope (containing the participant's enrollment number and assignment to either Immediate or Delayed Oxytocin administration) was opened. Each participant was assigned a unique 4-digit-long subject number for subject identity and confidentiality. Participants were unaware of the treatment allocation at the time of assignment of treatment. Researchers were unaware at the time of allocation of treatment but may have become aware after 2hours when a review and new intervention was instituted or prior intervention was maintained.

8.6. Research Assistants

Three Good Clinical Practice (GCP)-trained research assistants who are experienced midwives were trained by the principal investigator on study procedures for two weeks. They were also trained on randomly assigning the intervention and filling of the data collection questionnaire. They were evaluated on performing a vaginal examination and determination of Bishops Score prior to ARM to ensure uniformity in the examination results among the research assistants and principal investigator. . There were daily checks by the principal investigator to ensure

collection of data was complete by retrieval of the patient file and corroboration of the file findings with the data entered in the questionnaire.

8.7. Intervention Arm

Patients receiving intravenous oxytocin immediately (within 15-30 min) following ARM.

8.8. Control Arm

Patients receiving delayed intravenous oxytocin (at 2 hours following ARM).

8.9. Outcomes

8.9.1. Primary outcome

The primary outcome was ARM to delivery duration in minutes.

8.9.2. Secondary outcomes

The secondary outcomes included ARM to decision for cesarean section, mode of delivery (cesarean vs vaginal), maternal satisfaction with the labour and augmentation process, neonatal 5 minute APGAR score, incidence of umbilical cord prolapse, incidence of uterine hyperstimulation and incidence of admission to NBU.

8.10. Description of interventions

Patients randomized to the immediate Oxytocin arm underwent a vaginal examination, Bishop's score and FHR measurement prior to ARM which was then

performed using an Amniocot. FHR was then measured after ARM and if found to be satisfactory was followed by intravenous Oxytocin administration within 15- 30 minutes of ARM if the liquor was noted to be clear. The Oxytocin was administered by the principal investigator or research assistants as per the standard in KNH Labour ward and as per KNH standard operating procedure. Although Oxytocin is administered in KNH by counting drops manually, the study utilized IV Flow regulators to ensure accuracy of administration. Oxytocin was initiated at 5IU in 500ml of Normal Saline starting at a rate of 10 drops per minute and escalated by 10 drops per min every 30 minutes. The dose was escalated until 3 uterine contractions in 10 minutes, each lasting 40 seconds or more, were achieved and maintained at that rate. If there were not 3 contractions in 10minutes at 60 drops per minute, then the solution was completed at that rate. A new bottle with 15 units of oxytocin in 500mls was started, infusing at 30 drops per min and escalate by 10 drops every 30 minutes to a maximum dose of 40 drops per minute. If adequate uterine contractions were achieved and could be maintained at the appropriate rate, Oxytocin was continued at the preceding rate to avoid uterine hyperstimulation. Labour and fetal wellbeing was monitored using manual palpation of uterine contractions, partogram and intermittent fetal auscultation as per the KNH SOPs. If uterine hyperstimulation (>6 contractions per 10 minutes lasting 40 seconds or more) was to occur the infusion would be stopped, Nifedipine administered, and further clinical review conducted to rule out placental abruptio, non-reassuring fetal status, uterine rupture or other adverse effects that may have necessitated performing a Caesarean section.

Patients randomized to the delayed Oxytocin administration arm also underwent ARM following examination in an identical fashion and if liquor and FHR were noted to be normal they then received Oxytocin 2hours following ARM only if they were noted to require it. It was administered as per the protocol described above. If the patient was noted to have established adequate contractions following ARM alone, this was noted and the results analyzed with an intention to treat basis. FHR was monitored and recorded with other labour parameters in the partograph. FHR was monitored via intermittent auscultation. This was noted to be acceptable for augmentation monitoring in an RCT in a Cochrane systematic review on active management of labour (13). All precautions to avoid adverse effects in the Intervention arm were followed in the Control arm as well. The Amniocots and IV Flow regulators were purchased by the principal investigator and stored together with the data collection questionnaires in a locked cupboard in Labour ward with the keys accessible only to the research assistants and principal investigator.

9. DATA COLLECTION, MANAGEMENT AND ANALYSIS

A questionnaire was used to collect the primary data for the study. The questionnaire was filled by the principal investigator or research assistants. The research assistants were trained in the clinical and clerical work as described above. The respondents were patients who were considered eligible for the study and participated in either arm of the study following provision of informed consent. The questionnaire was filled at enrolment, during labour and within 12 hours of delivery.

The questionnaire is divided into 8 sections labeled section 1 through section 8 which included information on the social- demographic characteristics and obstetric characteristics, initial vaginal examination, ARM and oxytocin timing, ARM to delivery interval, intrapartum fetal status, mode of delivery, immediate neonatal outcome and maternal satisfaction with the augmentation process. Information was obtained from history, review of medical records and clinical examination. The information was stored safely in a password-protected computer and backed up on a dedicated USB drive. Collected questionnaires were kept confidential and under lock by the principal investigator and data entered into a computer within 2 days of receipt of the questionnaire. Any other hard copy records carried for analysis were stored under lock and key as well. Patients' confidentiality was observed throughout the process. A qualified statistician analyzed the data with intent to treat analysis using SPSS version 21.

9.1. Statistical Analyses

Socio-demographic, clinical and laboratory characteristics of the study participants collected at randomization, were summarized presented by study arm. Continuous variables were summarized using means (and standard deviations) and compared between study arms using the two-sample t-test if normality assumptions are met; otherwise they were summarized using medians and interquartile ranges and compared using nonparametric Wilcoxon-Rank (Mann-Whitney test) (a nonparametric alternative to the independent two-sample t-test). Categorical variables were summarized using counts and proportions and compared between study groups using Pearson's chi-square tests or Fisher's exact tests as appropriate.

The primary outcome was duration from ARM to delivery and secondary outcomes were mode of delivery and maternal and perinatal outcomes. Proportions were compared using Chi2 test, 95% CI, two tailed hypothesis with p-value significant at $p<0.05$.

9.2. Analyses of study outcomes

The final statistical analysis was conducted at the time when the last pregnant woman delivered.

The differences in obstetric and neonatal outcomes between women receiving intravenous oxytocin immediately following ARM versus those in whom oxytocin was delayed was evaluated using t-test for continuous outcomes and chi-square test of independence for categorical outcome variables.

9.3. Secondary Analyses

Secondary outcomes included mode of delivery, maternal satisfaction with the Labour process incidence of umbilical cord prolapse, incidence of uterine hyperstimulation and neonatal APGAR score.

These outcomes were compared between the two arms using t-test for continuous outcomes and chi-square test of independence for categorical outcome variables.

10. ETHICAL CONSIDERATIONS.

10.1 Ethical Review

The study proposal was presented to and approved by the Department of Obstetrics and Gynecology of the school of medicine, University of Nairobi that comprises the faculty and fellow colleagues before submission to the Kenyatta National Hospital/University Of Nairobi Ethics Research Committee (ERC). All study protocols and the template informed consent form found in the Appendices were reviewed and approved by the ERC prior to use. The study protocols and informed consent form were also reviewed and approved by the ERC.

I submitted regular safety and progress reports to the Data Safety Monitoring Board (DSMB) and within a month of study completion. These reports included the total number of participants enrolled in the study, the number of participants who completed the study and any challenges faced.

10.2 Informed Consent

Written informed consent was obtained from adult female pregnant participants. The participants in the study were in labor, however, adequate counseling was offered before consenting and the wishes of the single participant who declined were respected. Where the partner was available, they were equally informed of the study and if the participant preferred a discussion with the pregnancy partner who was within the facility then they were given the opportunity to do so. The partner after then appended a signature or thumb print as a witness as provided for in the informed consent. The participant's consent was deemed tacit from her partner.The

informed consent form found in the appendices section was translated into Swahili as well as independently back translated to evaluate the veracity. The form described the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations.

Literate participants documented their provision of informed consent by signing their informed consent forms. Non-literate participants were asked to document their informed consent by marking their informed consent forms with a thumbprint in the presence of a literate third party witness. Any other local ERC requirements for obtaining informed consent from non-literate persons was followed. Participants who were interested were provided a copy of their informed consent forms and this fact was documented in the participant's record.

10.3 Risks

The potential risks were anticipated and addressed. Amniotomy is a frequently performed procedure in KNH. The principal investigator ensured that all research assistants were proficient in performing controlled ARM. If , however, cord prolapse was noted the patient was to be taken for Caesarian Section within minutes of diagnosis as is the norm in KNH.

Oxytocin is routinely used in KNH. In the event that uterine hyper stimulation was to be diagnosed, appropriate management would be instituted by the residents, midwives and consultants on duty. The consultant covering labor ward would be informed of this or any other adverse effect within 15 minutes and the Augmentation infusion stopped and tocolysis with Nifedipine instituted. In the event that tocolysis

was not achieved, the patient would be taken to the operating theatre for an emergency caesarean section. If tocolysis was achieved but the CTG demonstrated features of NRFS the patient would have to proceed for a Caesarean section.

We made every effort to protect participant privacy and confidentiality. We did not think there was any stigma related to the study and very effort to prevent that and alleviate any potential harm caused was made.

10.4 Insurance

Oxytocin is on the list of essential drugs, according to WHO. In addition it is very commonly used in KNH labour ward, locally, regionally and globally with ARM for augmentation of labour and for prophylaxis and treatment of post-partum hemorrhage. The clinical and non-clinical effects of Oxytocin are well documented in literature. For this reason, it was agreed upon presentation of the study proposal to the department of Obstetrics and Gynecology and the Data Safety and Monitoring Board (DSMB), that participants would not require additional special insurance cover.

10.5 Benefits

The benefits offered by this study to the participant included having a resident doctor or primary midwife on a personal basis who offered attention to the participant and closely monitored her labour progress. This translated to prompt identification and management of adverse effects of labour and the augmentation process. There was, however, no monetary benefit to the participants.

10.6 Confidentiality

All study-related information was stored securely at the study site. All participant information was stored in locked file cabinets in areas with access limited to study staff. A coded number identified all reports, collected data, and administrative forms in order to maintain participant confidentiality. All local databases were secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that linked participant ID numbers to other identifying information was stored in a separate, locked file in an area with limited access.

Participants' study information was not released without the written permission of the participant, except as necessary for monitoring by the DMSB or ERC.

10.7 Data Safety And Monitoring Board (DSMB)

This study was subject to monitoring by an independent Data Safety and Monitoring Board (DSMB), which met twice, checking initially for balance in randomization and later monitoring patient safety and signals of efficacy, futility or harm at each interim analysis. The chairperson of the committee was Dr. Frank Kagema (Honorary lecturer, UON, Consultant Obstetrician/Gynecologist). The members were Dr. Weston Khisa (Consultant Obstetrician/Gynecologist, Fistula specialist), Dr. I.S.O. Maranga(Consultant Obstetrician/Gynecologist, Oncologist, Head of Reproductive services, KNH) and Dr. Frankline Onchiri (MS ,PHD, Biostatistician University of Washington). All members of the DSMB were GCP trained.

The DSMB was to provide a recommendation to terminate or alter the design or conduct of the trial if unacceptable safety results emerged. While the reviews of

safety considered both expected and unexpected adverse events, particular focus was given to monitoring occurrence of uterine rupture and fetal demise whether or not it was related to the intervention. The DSMB also gave careful consideration to emerging evidence about safety from any upcoming trials. If significant safety concerns were to emerge, the DSMB would have full access to relevant efficacy and safety data to assess the relative benefit-to-risk profiles of the study regimens when developing their recommendations**.**

11. STUDY REGISTRATION AND CONSORT GUIDELINES

The study was registered with the Pan African Clinical Trial registry at commencement (PACTR201803003123163) and the study conduct and analysis adhered to the consort guidelines.(37)

12. RESULTS

The trial enrollment period was from February 13, 2018, to July 24, 2018. Trial recruitment was stopped after targeted sample size was achieved. The trial recruitment flow is as shown in Figure 1. Study drug infusion was started for all participants allocated to the immediate arm. Initiation of delayed oxytocin was done only for participants who had persistent hypotonic uterine contractions 2hours following ARM. There were no withdrawals or dropouts**.**

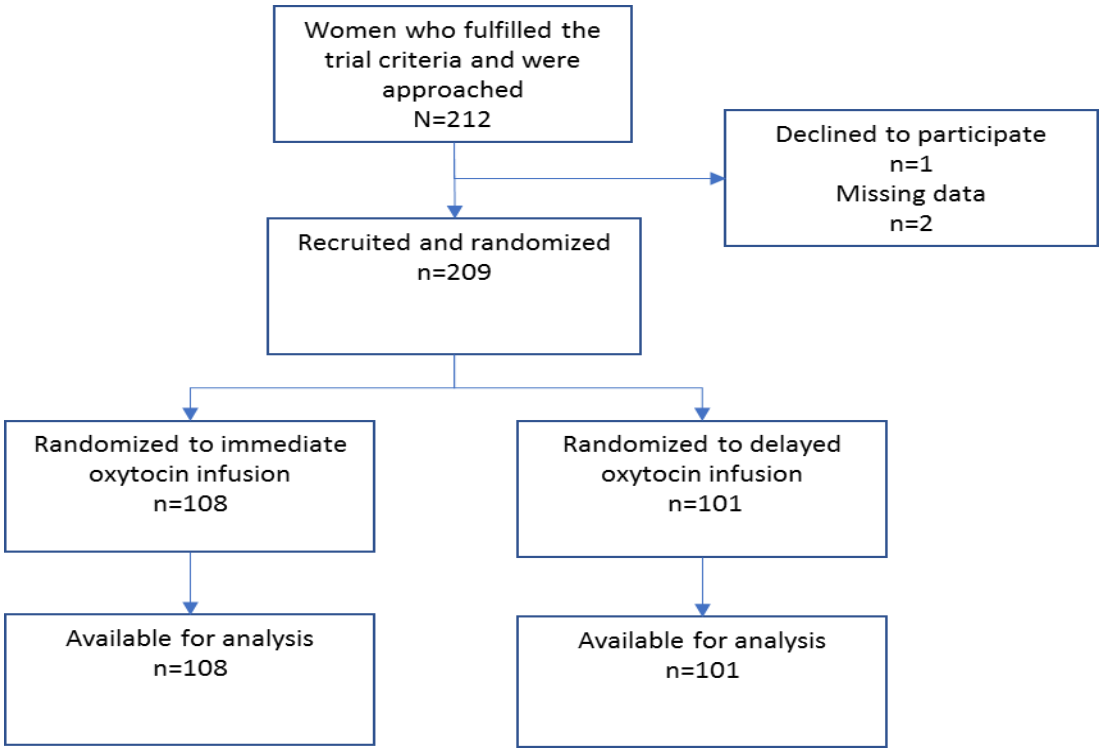


Figure 1: Trial Recruitment

Table 1 shows the characteristics of the participants stratified according to their randomization to either immediate or delayed oxytocin arms. There was no statistically significant difference in the participants' sociodemographic and obstetric characteristics. Majority of the participants (47.2% and 45.5% in the immediate and delayed arms respectively, P=0.857) were aged 20-24 years. A large percentage of the participants were married (83.3% vs 90.1% in the immediate and delayed arms respectively),with a secondary level of education, however, unemployed. Majority of participants were primiparous and at 40 weeks gestation. Bishop's score prior to amniotomy was favorable in both groups at 8.4 and 8.8 in the immediate and delayed arms respectively, P=0.166. Presence of meconium at amniotomy was low and comparable between the two arms at 13.9% and 10.9% in the immediate and delayed arms respectively, P=0.513. Birth weight of neonates was identical between the two arms at 3200g,P=0.445.

Table 1 Characteristics of Trial Participants According to Randomization to Immediate or Delayed (after 2 Hours) Oxytocin Infusion After Amniotomy for Labor Augmentation in Women of Mixed Parity With Favorable Cervixes

Characteristic		Time to oxytocin administration		
		Immediate (N = 108)	Delayed (N = 101)	
		n (%)	n (%)	P value
Age	<20 years	7(6.5)	7(6.9)	
	20-24 years	51(47.2)	46(45.5)	0.857
	25-29 years	24(22.2)	26(25.7)	0.895
	30-34 years	21(19.4)	14(13.9)	0.524
	35 years +	5(4.6)	8(7.9)	0.548
Marital status	Married	90(83.3)	91(90.1)	
	Single	17(15.7)	8(7.9)	0.092
	Other	1(0.9)	2(2.0)	0.58
Education	Primary	29(26.9)	33(32.7)	
	Secondary	55(50.9)	36(35.6)	0.097
	Tertiary	24(22.2)	32(31.7)	0.669
Employment status	Unemployed	65(60.2)	57(56.4)	
	Employed	43(39.8)	44(43.6)	0.583
Parity	Para 0	44(40.7)	41(40.6)	
	Para 1	35(32.4)	32(31.7)	0.954
	Para 2	23(21.3)	21(20.8)	0.956
	Para 3 / 4	6(5.6)	7(6.9)	0.707
MSL at time of ARM	Clear liquor	93(86.1)	90(89.1)	
	Meconium stained liquor	15(13.9)	11(10.9)	0.513
Mean Bishop's score (SD)		8.8(±1.7)	8.4(±1.5)	0.166
Gestation at birth	Median gestation at birth (IQR)	40(38.0-42.0)	40(38.0-42.0)	0.683
Birth weight	Median weight at birth (IQR)	3200(2400-4200)	3200(2240-4150)	0.445

Table 2 shows the results of the primary outcome-ARM to delivery interval compared between the two arms. The median duration in minutes from ARM to second stage in the immediate arm was 260 minutes while that in the delayed arm was 278 minutes [CI] 0.999-1.0, P=0.327. The median duration in minutes from ARM to decision for cesarean section in the immediate arm was 345 minutes while that in the delayed arm was 338 minutes [CI] 0.998-1.01, P=0.458. The ARM to SVD interval in the immediate arm was 277 minutes while that in the delayed arm was 298 minutes [CI]0.999-1.0, P=0.418. Delayed oxytocin was found to be non-inferior to immediate oxytocin in the primary outcome.

Table 2: ARM to Delivery Interval Following Immediate or Delayed (after 2 hours) Oxytocin Infusion After Amniotomy for Labor Augmentation in Women of Mixed Parity With Favorable Cervixes

	Time to oxytocin administration		
	Immediate (N = 108)	**Delayed (N = 101)**	**P value**
Median duration in minutes (IQR)			
ARM to second stage	260(70-840)	278(80-840)	0.327
ARM to decision for C/S	345(150-666)	338(2-915)	0.458
ARM to SVD	277(75-890)	298(85-890)	0.418

Figure 2 depicts the curves for ARM to delivery interval (P=0.239) with comparable amniotomy to delivery intervals between immediate and delayed arms.

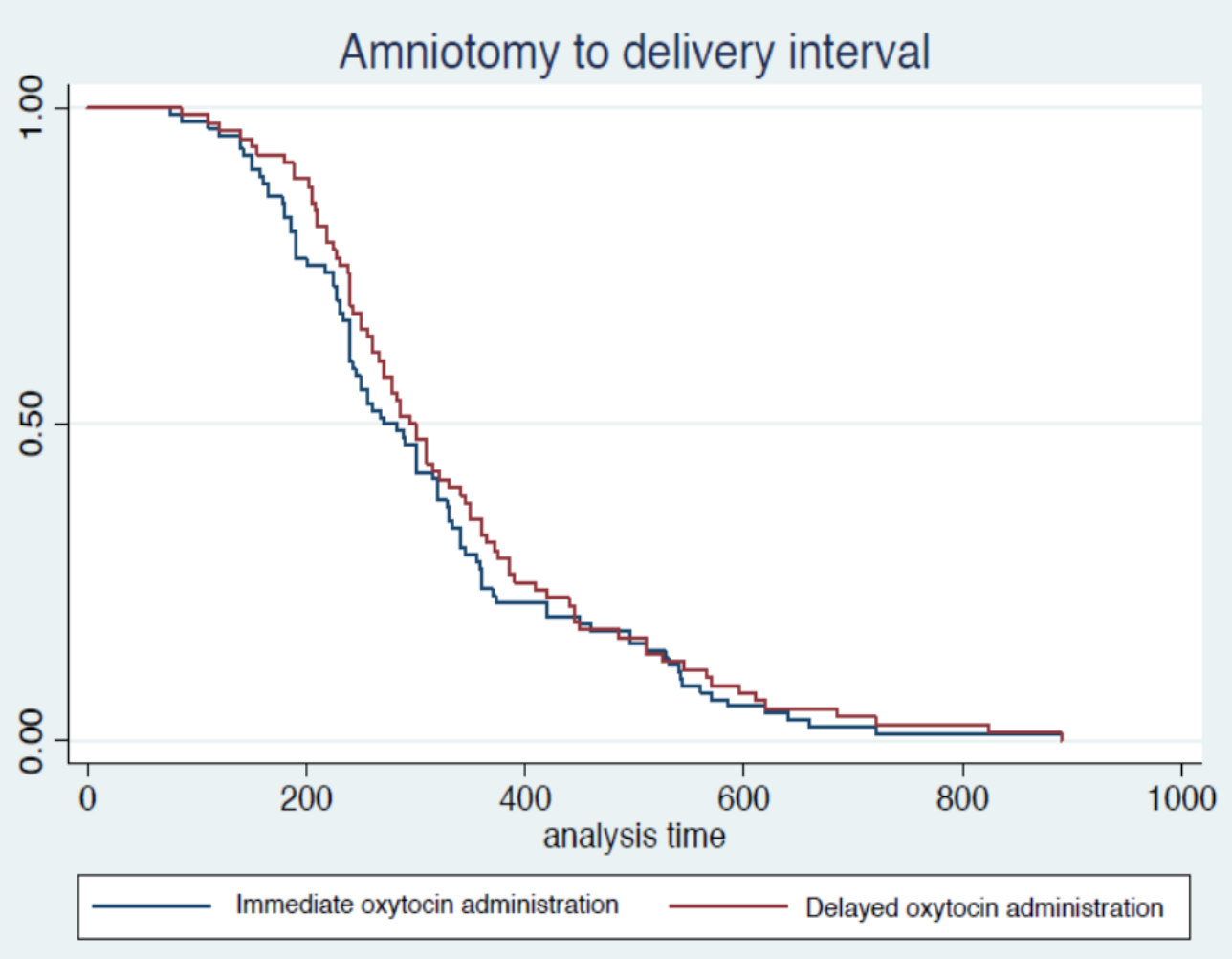


Figure 2: Time to delivery analysis

Majority of the trial participants had a vaginal delivery; 84.3% in the immediate arm versus 78.2% in the delayed arm. Cesarean section rates were at 15.7% in the immediate arm versus 21.8% in the delayed (P=0.264). with no statistically significant differences. Table 3 shows results of the mode of delivery compare between the two arms.

Table 3: Mode of Delivery Interval Following Immediate or Delayed (after 2 hours) Oxytocin Infusion After Amniotomy for Labor Augmentation in Women of Mixed Parity With Favorable Cervixes

	Time to oxytocin administration		
	Immediate	**Delayed**	
	(N = 108)	**(N = 101)**	**P value**
Median duration in minutes (IQR)			
Mode of delivery			
SVD	91(84.3)	79(78.2)	
Caesarean section	17(15.7)	22(21.8)	0.264

Fetal bradycardia in labour was detected via intermittent fetal auscultation in 5.6% of participants in the Immediate arm while that in the Delayed arm was 1% [CI]0.02-1.44,P=0.104. APGAR score at 5 minutes was 8.53 and 8.56 in the immediate and delayed arms respectively and was comparable between the two arms(P=0.793). There was no statistically significant difference in APGAR between the arms. Admissions of neonates to the new born unit were 3.7% and 2.0% from the immediate and delayed arms respectively,[CI]0.09-2.93,P=0.463 ,showing no statistically significant differences. Table 4 shows a comparison of the neonatal outcomes between the immediate and delayed oxytocin arms.

Table 4: Neonatal Outcomes Following Immediate or Delayed (after 2 hours) Oxytocin Infusion After Amniotomy for Labor Augmentation in Women of Mixed Parity With Favorable Cervixes

	Time to oxytocin administration		
	Immediate (N = 108)	**Delayed (N = 101)**	**P value**
Median duration in minutes (IQR)			
NBU admission			
Stable baby	104(96.3)	99(98.0)	
NBU admission/ unstable baby	4(3.7)	2(2.0)	0.463
APGAR at 5'	8.53	8.56	0.793
Bradycardia			
No bradycardia	102(94.4)	100(99.0)	
Bradycardia present	6(5.6)	1(1.0)	0.104

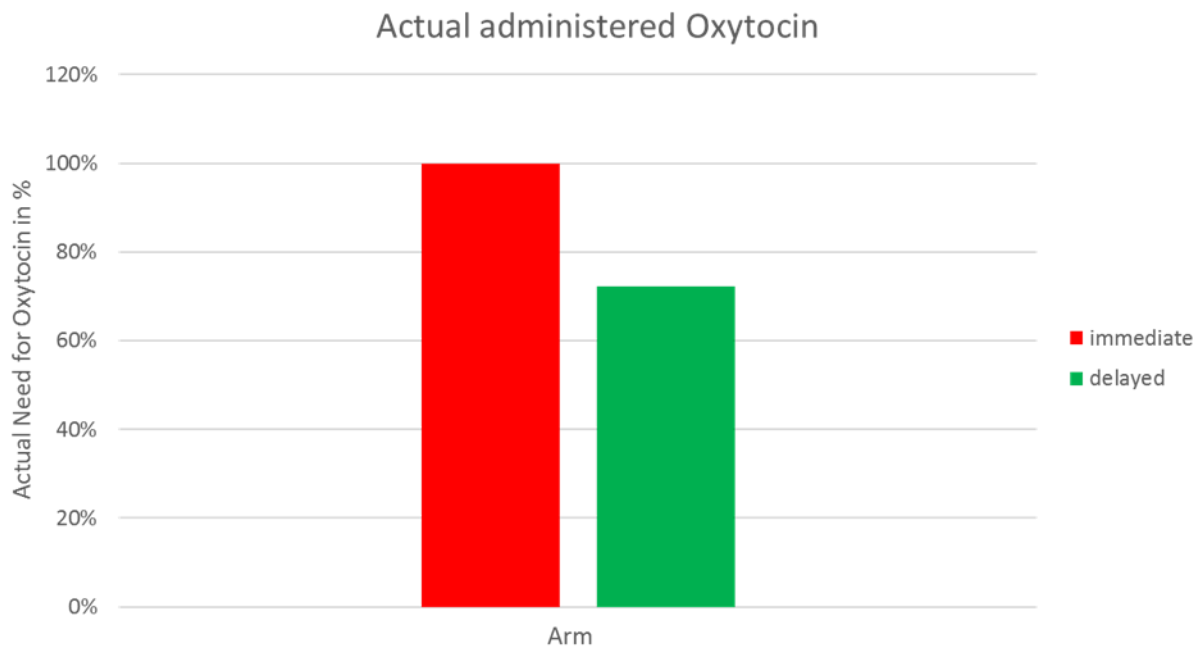
Maternal satisfaction was comparable between the two arms with the Immediate arm rating being 4.25 and the Delayed arm rating being 4.26 ,[CI]0.72-1.43, P=0.941. Table 5 depicts a comparison of maternal satisfaction between the two arms.

Table 5: Maternal Satisfaction Outcomes Following Immediate or Delayed (after 2 hours) Oxytocin Infusion After Amniotomy for Labor Augmentation in Women of Mixed Parity With

	Time to oxytocin administration			
	Immediate N=108	Delayed N=101	OR (95% CI)	P Value
Mean score (SD)				
Mean maternal satisfaction score	4.25	4.26	1.01	0.941

Upon the 2 hour review in the Delayed arm, it was noted that 27.7% of patients did not require Oxytocin augmentation. Graph 1 shows the actual administered Oxytocin in the two arms.

Graph 1: Percentage of Participants Actually Receiving Intravenous Oxytocin Following Immediate Versus Delayed Oxytocin After ARM



There were no incidences of uterine hyperstimulation detected. One case of umbilical cord prolapse was noted. No cases of operative vaginal delivery were reported**.**

13. DISCUSSION

Clinical trials on oxytocin administration in labour have had varied indications, varied definitions of delay in administration and hence have produced varied and conflicting results. Our main findings were that there were no statistically significant differences between the two groups as regards ARM to delivery interval, mode of delivery, neonatal outcomes or maternal satisfaction. More importantly, 27.7% of participants in the delayed arm did not require oxytocin at the 2hour review, due to established, adequate uterine contractions. Analysis, however was carried out on an intention to treat basis.

Our study showed an ARM to SVD interval of 277 and 298 minutes in the immediate and delayed oxytocin administration arms respectively, ([CI]0.999-1.0, P=0.418), which was comparable between the two arms. A similar study conducted by Shafik et al in Cairo, Egypt found an amniotomy to delivery interval of 360 and 465 minutes in the immediate and delayed arms respectively, P=0.001(37). This demonstrated a statistically significant decrease in the amniotomy to delivery interval in the immediate arm. These differences could be explained by a small sample size of 120 women in the latter study. In addition, the study by Shafik et al included primiparous women only and excluded of women over 35 years of age. Our study included women of mixed parity and even advanced maternal age. Delay in oxytocin administration was defined as 4 hours and use of misoprostol for poor Bishops score prior to amniotomy was employed by Shafik et al, which may further explain our differing results.

P. Tan et al in an RCT conducted in Kuala Lampur, Malaysia also found a shortened ARM to vaginal delivery interval of 5.36 +/-3.1 compared with 6.9+/- 2.9 hours, P.001, in

the immediate and delayed oxytocin arms respectively(28). They conducted ARM at a cervical dilatation of 2 cm, included only parous women and delay in oxytocin administration was defined as 4hours. These are plausible explanations for the differences noted in our results.

In a randomized controlled trial involving twelve obstetric units within the Northern and Yorkshire regions in the North East of England, Hinshaw et al found a median randomization to delivery interval in of 5 hours 52 minutes (3:57–8:28) and 9 hours 8 minutes (5:06–13:16) ($P < 0.001$) in the immediate and delayed arms respectively(16). The disparity with our results findings, may be due to assessment from time of randomization (not time of ARM) , inclusion of only nulliparous women and definition of delayed oxytocin administration being 8 hours. Dencker et al in an RCT conducted in two delivery units in Sweden demonstrated that the randomization to delivery interval was shortened by 85 minutes in the immediate oxytocin administration arm(27). These findings may be explained by exclusively nulliparous participants and delay in oxytocin administration defined as 3 hours. Furthermore they included participants with spontaneous rupture of membranes and cervical dilatation ranging from 4 to 9cm, while our study excluded those with previously ruptured membranes and participants with cervical dilatation beyond 5 cm.

No study in literature sought to describe an ARM to decision for Cesarean section interval. We demonstrated this interval to be 345 minutes and 338 minutes([CI] 0.998-1.01, P=0.458) in the immediate and delayed arms respectively and this was comparable between the two arms. Our cesarean section rates were15.7% and 21.8% in the immediate and delayed oxytocin arms respectively (P=0.264). P. Tan et al and

Hinshaw et al also demonstrated comparable cesarean section rates between immediate and delayed arms (P=0.80)(28)(16). A metanalysis conducted by Wei et al showed a modest decrease in the Cesarean section rates in early oxytocin administration however this metanalysis excluded RCTs in which amniotomy was performed in both intervention and control arms(30). This could explain the discrepancy in our findings. The rates of vaginal delivery in our study were also comparable between the two arms and formed a majority of the deliveries (84.3% and 78.2% in the immediate and delayed arms respectively).

Neonatal outcomes in our study were comparable between the immediate and delayed arms. We noted no statistical difference between the two arms in detection of fetal bradycardia, APGAR score at 5' and NBU admissions. APGAR at 5' was identical in both arms in the study carried out by P. Tan et al who noted a 1% NICU admission in the immediate arm and no admissions in the delayed arm(28). Hinshaw et al demonstrated a neonatal unit admission rate of 2.9% and 2.5% in the active and conservative management groups respectively and an APGAR <7 at 5' of 2.5% and 1.5% in the active and conservative groups respectively(16). Shafik et al found an identical APGAR at 5' of 8 between both groups and similar rates of APGAR at 1' and Transient Tachypnea of the Newborn(37). Dencker et al noted an APGAR <7 at 5' of 1.6% and 1.9% in the immediate and expectant arms and a comparable NICU admission rate of 8.3% and 8.2% respectively(27). The higher rates of NICU admission compared to those in our study could be explained by inclusion of patients with spontaneous rupture of membranes where prolonged rupture of membranes may

influence neonatal outcomes. Another plausible explanation is a lower threshold for admission with a higher NICU capacity in this middle and high income setting.

Maternal satisfaction with the labour and augmentation process on a Likert point scale of 1-5 was almost identical between the two arms of our study. A score of 4.25 and 4.26 was noted in the immediate and delayed arms respectively (P=0.941). P. Tan et al noted an identical maternal satisfaction of 3 between the immediate and delayed arms (P=0.36)(28). Hinshaw et al studied the incidence of post-natal depression according to the Edinburgh Post Natal Depression scale and Attitudes Towards the Pregnancy and the Baby Scale and found no statistically significant differences between the two arms(16). A greater maternal satisfaction was noted in the immediate oxytocin arm compared to the delayed oxytocin arm (38.3% versus 15% ,P=0.004) in the study carried out by Shafik et al(37). This, however, may be attributable to the factors mentioned above.

Our study found that 27.7% of participants in the delayed arm did not require oxytocin following amniotomy. P. Tan et al reported that 35.6% of their participants avoided oxytocin administration(28). The higher value reported in the latter study could be attributable to the fact that participants were exclusively parous while our study included participants of mixed parity. This implies that oxytocin administration may be avoided to a large extent if administration is delayed following ARM.

We reported no incidences of uterine hyperstimulation. Uterine hyperactivity was reported at 2.9% and 1.0% in the immediate and delayed oxytocin arms respectively (P=0.62) by P. Tan et al(28). It is probable that our inability to detect uterine

hyperstimulation may be attributable to the fact that monitoring of labour and uterine contractions was done via partogram, palpation of uterine contractions and intermittent fetal auscultation, as per the KNH SOPs. Monitoring of labour and fetal well-being was by continuous CTG in the former study. These findings, however, did not result in adverse outcomes.

Our study had strengths and limitations. This was the first study of its kind in our region, producing high level evidence on an equipoise in practices and opinions. The study population comprised mixed parity participants, making it generalizable to all women, regardless of parity. Our study setting also makes our findings generalizable to high patient burden settings. The pragmatic nature of our study means that our findings are applicable to everyday practice that is similar to ours. This is with the exception of use of IV flow regulators that we employed to administer oxytocin for accuracy, which does not form part of the SOPs at KNH. Performance of the IV flow regulators was not assessed. Uterine hyperstimulation and other fetal heart rate patterns may have been missed in our studydue to lack of equipment and our adherence to KNH labour and fetal monitoring SOPs, however, they were clinically noted without consequences and thus did not adversely affect outcomes. The study did not include patients in advanced labour as they are less likely to require oxytocin augmentation hence inferences could not be made to the effect of ARM and timing of oxytocin augmentation. These patients, however, are likely to deliver with minimal intervention unless they develop other obstetric complications. We excluded women with medical diseases in pregnancy due to the low threshold for cesarean section in these cases, making our findings non

generalizable to this population. This area, however, may be explored in future research.

14. CONCLUSION

Among women with hypotonic uterine contractions at ≥ 4 cm cervical dilation at KNH who undergo ARM, administration of oxytocin immediately (within 15-30 minutes) :

1. Does not reduce duration of labour.

2. Does not lower cesarean section rate.

3. Does not improve neonatal outcomes.

4. Does not enhance maternal satisfaction.

Delaying oxytocin administration by 2 hours decreases the need for oxytocin by 28%.

15. RECOMMENDATIONS

1. It is encouraged that labour augmentation protocols be developed in KNH using now available evidence for optimum obstetric and neonatal outcomes.
2. Partograph use should be strengthened in high patient burden settings to closely monitor labour for timely and accurate identification of slow progress in

labour,assessment of need for oxytocin administration and institution of appropriate interventions.

3. We recommend allowing at least a 2hour interval following ARM to assess whether spontaneous contractions improve and the need, if any, for oxytocin.

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17. APPENDICES

APPENDIX 1: INFORMED CONSENT FORM

TITLE

Obstetric outcomes following immediate versus delayed intravenous oxytocin after amniotomy among parturients.

INTRODUCTION

The consent form is to provide information about my study which is about whether there are any differences in the labour , type of delivery , outcome of babies and the mother's satisfaction in patients who are given Oxytocin immediately after waters are broken versus those in whom Oxytocin is delayed. You are free to accept or decline to be in the study, to ask any question about the study and any benefits or risks that

may arise by one being in the study. If the language in the form is not clear or one cannot read then the principal investigator or research assistant will clarify or read it out loud. If there is a language barrier then translation will be done. You are also free to have a copy if need be.

OBJECTIVES OF THE STUDY

The objective of the study is to compare women who receive Oxytocin immediately to those who have it delayed after breaking the waters in order to observe whether there are any benefits in either group in terms of how soon and in which way they deliver, how their babies fair and whether they are satisfied with the labour process. My purpose is to provide information in order to deliver the patient in the most optimum time with the best outcomes for mother and baby.

BENEFITS

There will be no monetary gain but this may give us more information on how to manage labour for the best results.

RISKS

The procedures involved in this study will be similar to those performed in patients in labour who are not participating in the study. The adverse effects will be similar to patients not in the study but undergoing the same procedures and will be managed in an identical manner

The membranes or baby's sac will be ruptured using a small rubber appliance with a

plastic tip. This will cause some discomfort to the patient. This procedure is called Artificial Rupture of Membranes (ARM). The procedure is used to observe the amniotic fluid for abnormalities and start oxytocin amongst other uses. Both ARM and oxytocin cause the uterus to contract more efficiently. The principal investigator and research assistants will monitor for adverse effects of ARM and institute appropriate management. The risks of ARM are rare (mainly cord prolapse and infection).

Oxytocin will be administered according to a specific protocol and the principal investigator and research assistants will monitor for adverse effects, identify them in time and institute appropriate management for them. The risk of receiving oxytocin is mainly uterine hyperstimulation.

VOLUNTARISM

Patient is to be approached by the investigator or assistants and given information on the study and is free to accept or decline without any reprimand or change in care afforded to them by the clinician.

RESEARCHERS INFORMATION

Principal Investigator : Kristina A. Sule MBChB, MMed student in the Department of Obstetrics and Gynaecology, University of Nairobi.

Telephone number: 0770311224

KNH/UON/ERC INFORMATION

Ethics review committee KNH.

CONSENT

I agree to participate in the study that compares outcomes of women (and newborns) in labour after Rupture of Membranes who receive Intravenous Oxytocin immediately versus those who receive it delayed. I understand that there is no financial benefit to be acquired by being in the study. I understand that all the information I provide will be confidential and my treatment will not be compromised by participating in this study. I have the right to leave the study at whatever point of my choosing. If I have any query I am free to contact the Principal Investigator on the contacts provided or the Ethics Review Committee.

Signature of the subject Date

Witness Date

I certify that I have provided information to the subject about the purpose and the nature of the study, the potential benefits, risks .

Signature of principal investigator Date

APPENDIX 2:ELLIGIBILITY CHECKLIST

Prior to Amniotomy

( ) 37 completed weeks

( ) Intact membranes

( ) Singleton pregnancy

( ) Inadequate uterine contractions-(less than 3 contractions in 10 minutes lasting less than 20 sec)

( ) Favourable cervix at 4cm dilatation

( ) Normal fetal heart rate :110-160 bpm

( ) No APH

( ) No previous uterine scar

( ) No history of Cardiac or Hypertensive disease or Diabetes

( ) HIV positive with undetectable viral load

( ) No congenital anomalies or evidence of IUGR

Post Amniotomy

( ) No or Thin MSL

( ) Normal fetal heart rate : 110-160 bpm

( ) No cord or limb prolapse

ELLIGIBLE…….

EXCULDED……

Reason for exclusion……

APPENDIX 3:DATA COLLECTION QUESTIONNAIRE

SECTION 1: (Social-Demographic and Obstetric Characteristics) Write response or tick where appropriate

1.Age……

2. Marital status

( ) Single

( ) Married

( ) Divorced

3.Employment

( ) Employed

( ) Unemployed

4.Education level

( )Primary

( )Secondary

( )Tertiary

5.Parity……..

6.Gestation……

…

SECTION 2 (Initial Vaginal Examination) Tick where appropriate

1. Appearance of External Genitalia…….

……

2. Assessment of Pelvic Adequacy

( ) CPD Noted

( )No CPD

3. Bishop's Score

PARAMETER	SCORE			
	0	1	2	3

POSITION	Posterior	Middle	Anterior	-
CONSISTENCY	Firm	Medium	Soft	-
EFFACEMENT	0-30%	40-50%	60-70%	80 +%
DILATATION	Closed	1-2cm	3-4cm	5+cm
FETAL STATION	-3	-2	-1,0	+1,+2

Total Score…….....

SECTION 3 (ARM and Oxytocin Timing)

1. Time of ARM……

2. Findings following ARM

i) Meconium Stained Liquor

( )Yes

Thin……Thick……..

( )No

ii) Bleeding following ARM

( ) Yes

( ) No

iii) Other Liquor Abnormalities……...

3.Fetal Heart Rate following ARM……..

4.Incidence of Cord Prolapse following ARM

( ) Yes

Management……..

( ) No

5.Incidence of any other adverse effects of ARM

( ) Yes

Which……..

Management……..

( ) No

6. Time of Oxytocin administration……..

( ) Delayed

Administered:

( ) Yes

( ) No. Reason……..

( ) Immediate

7. Occurrence of uterine hyperstimulation

( ) Yes

Management……..

( )No

8. Any other adverse reactions noted to Oxytocin

( ) Yes

Which……..

Management…….

( ) No

SECTION 4 (ARM to delivery interval)

1.ARM to second stage interval in hours and minutes……..

2.ARM to SVD interval in hours and minutes……..

3. ARM to decision for Cesarean Section in hours and minutes……..

4. Time between ARM and Cesarean Section in hours and minutes……..

5. Duration of 2nd stage……..

6. Time of delivery……..

SECTION 5 (Intrapartum Fetal Status)

1.Fetal Bradycardia detected on intermittent auscultation

( ) Yes

FHR……..

Management……

( )No

2.Fetal Tachycardia detected on intermittent auscultation

( ) Yes

FHR…….

Management……..

( ) No

SECTION 6(Mode of Delivery) Tick where appropriate

1. ( ) SVD

2. ( ) Caesarean Section

3. ( ) Operative Vaginal Delivery

4. ( ) Vacuum Delivery

SECTION 7 (Immediate Neonatal Outcome)

1.APGAR Score…….

2. Management……..

SECTION 8(Maternal Satisfaction)

Rate Maternal Satisfaction on a scale of 1-5. Tick where appropriate.

( ) 1 Very Bad

( ) 2 Bad

( ) 3 Average

( ) 4 Good

( ) 5 Very good

APPENDIX 4: PARTICIPANT IDENTIFICATION, SCREENING AND MONITORING STANDARD OPERATING PROCEDURE

1.Introduce yourself to client.

2.Screen client using screening tool.

3. Identify potential participant using eligibility checklist.

4. Introduce study to potential participant.

5. Perform VE and rupture membranes using amniocot. If eligible obtain informed written consent

6. Inform randomizing nurse of readiness to randomize

7. Receive randomization fluid as assigned by the randomizing nurse

8. Administer the fluid for the next 2 hours as per administration protocol

9. After two hours confirm whether to continue or discontinue the fluid from the randomizing nurse

10. For those continuing, continue fluids at the current rate

11. For those starting, start the fluids at the rate of 4 drops per minute and escalate by 4 drops per min every 30 minutes

12. Assess for any complications associated with the fluids

13. Monitor the rest of the labor as per monitoring protocol

14. Assess for labour outcomes:

Assess and record interval in hours and minutes that participant takes from ARM to 2nd stage or to decision to Cesarean Section, duration of 2nd stage ,delivery time and mode of delivery. For SVD delivery perform Active Management of Third stage of labour and 3rd stage monitoring as per KNH SOP.

15.Perform 4th stage monitoring a per KNH SOP.

Administration Protocol:

Initiate fluid (5IU of Oxytocin in 500ml of Normal Saline or placebo of 500ml Normal Saline) at a rate of 4 drops per minute and escalate by 4 drops per min every 30 minutes until 3 uterine contractions in 10 minutes, each lasting 40 seconds or more, are achieved and maintained at that rate. If there are not 3 contractions in 10minutes at 60 drops per minute, then the fluid will be completed at that rate. Start a new bottle (10

units of oxytocin in 500mls or placebo of 500ml Normal Saline) at 30 drops per min and escalate by 4 drops every 30 minutes as before, to a maximum dose of 40 drops per minute. If adequate uterine contractions are achieved and can be maintained at the appropriate rate, continue solution at the preceding rate and continue monitoring patient as per partogram.

After 2hours review patient with vaginal examination to determine Bishop's score and assess strength of uterine contractions. Revert to randomizing nurse to start new infusion or continue with current infusion (delayed oxytocin or immediate respectively) If less than 3 contractions are noted in 10 minutes (hypotonia) initiate new solution provided by randomizing nurse (delayed oxytocin). If more than 3 in 10 contractions are noted, however, do not initiate new infusion but indicate on the data collection questionnaire that patient was in delayed group, however had established adequate contractions and hence drug was not administered (intention to treat analysis).

Monitoring Protocol:

Use partogram to monitor mother and foetus during labour and act accordingly if any abnormalities are noted in the labour process. The goal for uterine contractions is at least 3 contractions in 10 minutes lasting at least 40 seconds. Assess fetal heart rate as per partogram. After 2 hours If more than 6 contractions are noted in 10 minutes-diagnose uterine hyperstimulation, stop augmentation, call for help and manage as per Hyperstimulation protocol. If fetal bradycardia (FHR <110BPM)or tachycardia(FHR>160 BPM) are noted at any point-stop augmentation, call for help, place patient in left lateral

position and manage as per Non Reassuring Fetal Status KNH Standard Operating Procedure (SOP).

Hyperstimulation Protocol:

If more than 6 contractions in 10 min are noted

-Stop oxytocin infusion

-Call for help

-Perform vaginal examination to assess progress of labour

-Exclude placental abruptio

-Place patient in left lateral position

Attach CTG and assess FHR. If normal- consider half the previous oxytocin dose and reassess. If abnormal-administer tocolytic (Nifedipine 20 mg) and institute emergency management for immediate delivery.