REPEAT INDUCTION VERSUS EXPECTANT MANAGEMENT AFTER FAILED PRIMARY LABOR INDUCTION AT TERM AT KENYATTA NATIONAL HOSPITAL: A RANDOMISED CLINICAL TRIAL.

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H58/75511/2014

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2019

DECLARATION

I declare that **'Repeat induction versus expectant management after failed primary labor induction at term at Kenyatta National Hospital: a randomised clinical trial'** is my original work. All resources and materials i have used or quoted have been indicated and acknowledged by means of reference. I further declare that this research proposal has not been published elsewhere or submitted for the award of any other degree to any university or institution.

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DEDICATION

This book is dedicated to my dear mother, Rukia Salim Sued and brother Mustapha for their unwavering support.

I am because of you.

ACKNOWLEDGEMENTS

I wish to express my gratitude to the Most High God for the gift of life, passion and dedication to my career and future. It is my wish to sincerely acknowledge the immense support and input of my supervisors, Professor Koigi Kamau, Dr. Alfred Osoti and Dr. Lydia Okutoyi into my research work and realizing it to its completion. I also thank my research assistants who helped with data collection, Dr. Kola Mark for his contribution in analysis with the entire DSMB members who offered to monitor the trial.

May the Almighty bless you all.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynaecologists
B hCG	B human Chorionic Gonadotrophins
CS	Caesarean Section
CTG	Cardiotocography
ERC	Ethics and Research Committee
FHR	Fetal Heart Rate
IOL	Induction of Labor
IRB	Independent Review Board
KNH	Kenyatta National Hospital
NICU	Neonatal Intensive Care Unit
OVD	Operative Vaginal Delivery
PGE1	Prostaglandin E1 (Misoprostol)
PPH	Postpartum Haemorrhage
PV	Per Vagina
RCOG	Royal College of Obstetricians and Gynaecologists
SVD	Spontaneous Vertex Delivery
UON	University of Nairobi
USG	Ultrasonography
WHO	World Health Organisation

OPERATIONAL DEFINITIONS

Bishop score- It was developed as a predictor of success for an elective induction. Determinant includes dilatation, effacement, station, position and consistency with regard to the cervix. Each variable is assigned a maximum value of 2 points (for a maximum score of 10). An unfavorable cervix generally has been defined as a Bishop score of <6. Women with a score of >8 are equally likely to deliver vaginally whether induced or allowed to labor spontaneously.

Cervical ripening- The use of pharmacological or other means to soften, efface, or dilate the cervix to increase the likelihood of a vaginal delivery

Chorioamnionitis- Intrapartum temperature of at least 38° C, with at least one of the following present: uterine tenderness, foul smelling vaginal discharge or amniotic fluid, maternal or fetal tachycardia (greater than 160 beats per minute).

Elective induction- Induction of labor in the absence of acceptable fetal or maternal indications.

Endometritis- Defined on a clinical diagnosis and a post-partum temperature of at least 38° C.

Expectant management- Defined as observation from the time the diagnosis of failed primary labor induction is perceived to 48 hours resting period followed by caesarean delivery if spontaneous labor does not result within the 48 hours time frame.

Failed labor induction- Inability to enter into active phase within 12 hours after IOL is instituted with misoprostol administered as 25ug pv 4 hourly to a maximum of three doses

Failed primary labor induction- Failure to enter into active phase of labor within 12 hours during primary labor induction

Failed repeat labor induction- Failure to enter into active phase of labor within 12 hours during repeat labor induction

Hyperstimulation- Excessive uterine contractions (tachysystole or hypertonus) with abnormal FHR changes such as persistent decelerations, tachycardia or decreased short-term variability.

Hypertonus- Excessive uterine contractions lasting > 120 seconds without FHR changes.

Perinatal and maternal morbidity and mortality: are composite outcomes. There is lack of universally accepted definitions of serious infant or maternal morbidity hence they are defined on the basis of clinical diagnoses as identified previously by trialists in similar studies as important measures of associated morbidity.

Primary labor induction- Initial or first cycle of labor induction instituted with misoprostol administered as 25ug pv 4 hourly to a maximum of three doses

Postpartum hemorrhage- Diagnosed by a clinical estimation of blood loss more than 500 mL for a vaginal delivery or more than 1,000 mL for a caesarean delivery.

Repeat labor induction- Second cycle of labor induction instituted with misoprostol administered as 25ug pv 4 hourly to a maximum of three doses after 24 hours resting period when the diagnosis of failed primary labor induction is perceived

Tachysystole -> 5 contractions per 10-minute period averaged over 30 minutes. This is further subdivided into two categories, one with and one without fetal heart rate changes.

Term- Gestation at or beyond 37 weeks 0 days (37 0/7) as defined by ACOG. This is further subdivided into *early term* (37 0/7 weeks of gestation through 38 6/7 weeks of gestation), *full term* (39 0/7 weeks of gestation through 40 6/7 weeks of gestation), *late term* (41 0/7 weeks of gestation through 41 6/7 weeks of gestation), and *post term* (42 0/7 weeks of gestation and beyond)

Time from randomization to active labor- Time taken in hours between randomization and entry into active phase of labor

Time from randomization to second stage- Time taken in hours between randomization and entry into second stage of labor

LIST OF FIGURES AND TABLES

TABLE OF CONTENTS

1.0 ABSTRACT

BACKGROUND: While the rates of labor induction have increased globally, occurring in about 20% of facilities, Africa reports of an average rate of 4.4% (Kenya 3.9%) with a high rate of unmet need (66.0 –80.2%). Despite it being a common obstetric procedure, criteria for successful and failed induction of labor (IOL) have not been standardized and no universal consensus has been reached. Caesarean delivery is thus often erroneously perceived to be the solution to failed labor induction. A failure rate of 26% is reported in Kenyatta National Hospital (KNH) with 24.1% in West Africa and 17.3% in Ethiopia. Primary caesarean delivery (CS) rate due to failed IOL in KNH in patients undergoing primary IOL is 51.5%, in contrast to 10% in the United States (U.S) and 3% in Australia. The need for uniformity in its definition and management in creating standards on both the duration and number of times the induction can be attempted creates the necessity to study the value of repeat induction after failed primary labor induction.

OBJECTIVE: To determine the effect of repeat induction versus expectant management on rates of failed induction among women who have primary failure of induction.

SETTING: Labor ward, antenatal wards and neonatal unit in Kenyatta National Hospital.

STUDY DESIGN: A single center double arm block Randomized Clinical Trial non-blinded to both participants and researchers, blinded to the analyst.

STUDY POPULATION: Eligible women with medical and elective indications for labor induction who have failed primary labor induction at KNH.

SAMPLE SIZE: Based on the formulae for comparison of means between two groups. A total of 86 gravid women with failed primary induction were randomized to either expectant management (n = 43) or repeat induction (n = 43).

OUTCOME MEASURES: Primary outcome was onset of active labor. Secondary outcomes included randomization-delivery interval, mode of delivery, adverse maternal and early neonatal outcomes.

DATA COLLECTION: Structured questionnaire in line with the study objectives was used.

DATA ANALYSIS: Statistical analysis was performed using R Studio Version 3.5.1. Simple linear regression model was used to analyze variables measured on a continuous scale. Simple logistic regression model was used to assess association between outcomes measured on a binary scale and the treatment groups. Probability values <.05 were considered statistically significant. Intention to treat principle was utilized in data analysis.

RESULTS: Demographics and clinical characteristics were similar between groups. There were significant differences in the primary outcome between the two treatment groups. The time from randomization to active phase was 8 hours shorter in the repeat induction group (18.20 vs 26.01 hours; mean difference, 7.81 h; 95% confidence interval 12.27 to 3.35, p=0.001). Time from randomization to vaginal delivery was >8 hours less in the repeat induction group (24.78 vs 33.37 hours, mean difference 8.59 h, 95 % CI 13.63 to 3.56, p=0.002). Failure rates was higher in the expectant management group (44.2 % vs 20.9%,
OR = 2.99, 95% CI 1.18 to 8.02, p = 0.023). No significant differences in maternal outcomes, early neonatal outcomes and mode of delivery between the 2 groups was observed
(p value>0.05).

CONCLUSION: Repeat labor induction using vaginal Misoprostol was superior to expectant management in achieving active phase of labor in patients with a low Bishop score not responsive to primary labor induction using vaginal PGE1.

RECOMMENDATION: Consider change of policy with regard to definition and management of failed primary labor induction at the hospital.

2.0 INTRODUCTION

Labor induction is the artificial initiation of labor after the period of viability with the intention of accomplishing delivery (1–3). It should be instituted when the benefits of expeditious delivery to either mother or fetus outweigh the risk of continuing the pregnancy (4,5). Based on this

realization, the rates of labor induction have increased globally, with overall rates in many countries now exceeding 20% of all births (3)(6–8). However, in Africa, the average rate of labor induction is 4.4% (Kenya 3.9%) with a high rate of unmet need (66.0 –80.2%) being reported (9).

Indications for labor induction include maternal, fetal, social or a combination of these factors (10,11). Higher rates of labor induction is associated with low perinatal mortality rate (6)(12,13) and has potentials for preventing maternal complications and improving pregnancy outcome (11)(13) in addition to lowering CS rates without increasing other adverse pregnancy outcomes (4,5)(14–16). Despite IOL being a common procedure, criteria for successful and failed IOL have not been standardized and no universal consensus has been reached to date (8)(17,18) hence caesarean delivery is often erroneously perceived to be the solution to failed labor induction (3)(7)(19–23).

Minimizing caesarean section rates without increasing other adverse pregnancy outcomes is a priority consideration especially in low income countries where available resources need to be judiciously utilized. The need to create standards on both the duration and number of times the induction can be attempted emerges within this contextual framework and this creates necessity to study the value of repeat labor induction after failed primary induction.

3.0 LITERATURE REVIEW

3.0.1 Incidence, Pattern and Indications of labor induction

Labor induction history dates back to Hippocrates' descriptions of mammary stimulation and mechanical dilation of the cervical canal (10)(24,25) giving way recently to sophisticated methods including pharmacological manipulation using prostaglandins (10)(26). While the incidence of labor induction continues to rise over the past several decades in developed countries (7)(27), African countries report of lower rates of induction of labor (4.4%) compared

with Asian and Latin American counterparts (6). This high unmet need in Africa (75.3% in Kenya) is an indicator for poor quality obstetric care as well as inadequate access to reproductive health care (9). Rate of labor induction in KNH has risen from 5.6% in 1984 to 12.7% in 2002 (20).

Medical indications for IOL refers to conditions for which the benefits of expediting birth supersedes the risks of continuing the pregnancy (6)(11)(13), while elective induction refers to those that are performed in the absence of medical indications for social or convinience purposes such as logistics, patient or provider preference (2)(4)(5)(28).

Indications for labor induction include maternal, fetal, social or a combination of these factors (2)(11)(16)(29) with IOL for post term gestation and preterm rupture of membranes at term being supported by the evidence (11). Post term pregnancy is by far the most frequent IOL indication in the west (2)(8) while PROM accounted for the majority of inductions in Africa and Latin American countries (6). In KNH, the commonest indication for induction was postdates (50.8%) followed by hypertensive disease (16%) (20).

3.0.2 Effects of labor induction

Higher rates of labor induction is associated with low perinatal mortality rate (4)(6)(13) and has potentials for preventing maternal complications and improving pregnancy outcome (28)(30,31). Contrary to popular belief (32,33), it may also contribute to lowering CS rates without increasing other adverse pregnancy outcomes (5)(13,14)(16)(34). However, some findings of elective induction suggest higher rates in the number of preterm infants and obstetric costs (35), increased risk for emergency caesarean section (32)(35), higher risk of hysterectomy, prolonged first stage, chorioamnionitis and a higher admission to NICU (4)(6). In addition, uterine over

activity, failed induction, greater need for pain relief and uterine rupture have been implicated as side effects (1)(7).

3.0.3 Pre-induction assessment

Thorough examination of the maternal and fetal condition must be performed to assess the likelihood of successful induction and the risks together with the benefits and other alternatives should be discussed with the patient (1).When the cervix is favorable the usual method of induction is amniotomy and oxytocin, whereas with an unfavorable cervix vaginal prostaglandins are commonly used (2)(36). Labor induction should be performed at a center where qualified staff and operating theatre facilities are available (11)(21) due to the risks associated with the procedure (36).

Regarding timing of labor induction, it is generally advised that it should be carried out in the morning because of higher maternal satisfaction (37)(38) with finding that maternal and fetal safety outcomes do not seem to differ whether prostaglandins are administered in the morning or evening (38).

3.0.4 Induction of labor using Misoprostol

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a prostaglandin E1 analog that was first marketed in the 1980s for the prevention and treatment of peptic ulcers due to its gastric acid anti-secretory properties (36). It was first used for the induction of labor with a dead fetus in 1987 (39) and evidence has shown that misoprostol may be the best prostaglandin for labor induction (26)(40,41). Its advantages over other synthetic prostaglandin analogues are its low cost, long shelf life, lack of need for refrigeration and worldwide availability makes it particularly useful in resource-poor settings (36)(42,43) in addition to achieving a higher rate of vaginal delivery in 24 hours (40,41).

Although vaginal or oral misoprostol is recommended by WHO as first-line induction agents (4)(21), it is available as a licensed low dose product for labor induction in very few countries due to logistical problems emanating from difficulty in cutting the tablets accurately, legal liability and potential dosage mistakes resulting from the lack of dosage instructions on the packet (29)(39). In addition, the ease with which misoprostol can be used to induce abortions and its wide availability has led to a very cautious approach to its introduction from both the manufacturer and national governments (43).

When using misoprostol for labor induction, the general principle is that it should be used at a low dose given the increasing sensitivity of uterine receptors to misoprostol with increasing gestational age (21)(39)(41). The recommended doses for labor induction using misoprostol are 25 mcg per vaginal 6 hourly or 25 mcg orally every 2 hours (21). In case low dose misoprostol is unavailable, an oral misoprostol solution is equally effective as vaginal misoprostol in achieving vaginal delivery but with a much lower rate of uterine hyperstimulation (26)(40)(43).

The risk of uterine rupture with the use of misoprostol after caesarean section is increased up to 12% thus its use is therefore contraindicated (39)(41)(43).

Once induction is commenced, uterine activity and electronic fetal monitoring (EFM) should be undertaken and for each planned misoprostol dose, the patient should be clinically reassessed beforehand. If the cervix remains unfavorable after a complete course of misoprostol dose, alternatives include switching to an alternative method, a repeat course of misoprostol or a caesarean section depending on the clinical situation (21)(39)(44).

Misoprostol's effects are dose dependent (40) and include cervical softening and dilation, chills and/or fever, abdominal cramps, gastrointestinal side effects (42)(43)(45,46), fetal abnormalities (43) and uterine rupture (2)(41). Uterine hyperstimulation and rupture is associated with usage of

excessive or repeated doses but with the low dosage recommendation (21)(41–43), the incidence of hyperstimulation is similar to that of dinoprostone at 4–12% (43).

3.0.5 Normal progress of induced labor

Historically, the course of labor has been managed by using labor curves first generated by Friedman in the 1950s even though subsequent studies have suggested that this curve is obsolete and may not apply to current obstetrical care (47,48).The most common definition of or diagnostic criteria for prolonged labor is protraction disorders or arrest disorders(49). Obstetricians should know that women being induced may remain in latent labor for many hours (18)(48)(50) and caesarean delivery for dystocia should not be performed in women who remain in latent labor (27)(49)(18). Difficulty in defining the onset and progress of the latent phase of labor may contribute to the high proportion of women diagnosed with dystocia in this phase (19)(47) as defining normal and abnormal labor progression has been a long-standing challenge. This, in essence, may contribute to many unnecessary caesarean delivery without giving ample time to possibility of progress of the labor process.

The most commonly employed definition for latent phase is a period of time, not necessarily continuous, when there are painful contractions and some cervical change including cervical effacement of at least 90% and dilatation up to 4 cm or at a cervical dilation of 5 cm regardless of effacement and the onset of active labor as when there are regular painful contractions with progressive cervical dilatation from 4 cm (8)(18).

3.0.6 Management of term premature rupture of the membranes (PROM)

Term premature rupture of membranes (PROM) at term is defined as rupture prior to the onset of labor at or beyond 37 weeks gestation and occurs in about 8% of term pregnancies (51). PROM can be a physiological variation rather than a pathological event (52)(51) and spontaneous labor follows term PROM at 24, 48 and 96 hours in 70%, 85% and 95% of women (53) with a Cochrane review reporting that 79%–95% of women will labor spontaneously within 12–24 h

(54). The most significant maternal risk of term PROM is intrauterine infection, a risk that increases with the duration of membrane rupture (55).

Fetal risks associated with term PROM include umbilical cord compression and ascending infection. The risk of neonatal sepsis increases with duration of membrane rupture in a linear fashion during the first 36 hours, independently of labor duration (56). Initial assessment of women presenting with term PROM should include confirmation of the diagnosis, confirmation of gestation and presentation and assessment of maternal and fetal wellbeing.
Digital vaginal examination should be avoided unless immediate induction is planned as this has been shown to increase the rate of neonatal infection (53)(51).

However, there is lack of consensus and clear evidence on optimal management of PROM at term. Management of these women includes either expectant management for/ beyond 24 hours or early induction of labor (immediately or up to 12 hours after presentation with term PROM) depending on cervical status. The NICE guidelines recommends that this group of women should be offered immediate IOL or induction approximately 24hours after rupture of the membranes (57)(44) while WHO recommends induction of labor within 24 hours for women with PROM at term (21). A meta-analysis suggests that little is to be gained by delay and accordingly, labor should be induced within 24 hours of rupture of membranes (54) as opposed to expectant management to reduce the risk of chorioamnionitis. Duration of active labor was found to be the strongest independent predictor of clinical chorioamnionitis (58). As per ACOG, labor should be induced at the time of presentation, generally with oxytocin infusion, to reduce the risk of chorioamnionitis. However, an adequate time for the latent phase of labor to progress should be allowed (29).

RCOG recommends that oxytocin should be regarded as the first option for labor induction (53) as with WHO (21) but in the sub set of women with an unfavorable cervix, prostaglandins may have an important role (53). ACOG (29) with Society of Obstetricians and Gynaecologists of Canada (59) do advocate for use of intravaginal PGE2 for induction of labor as it appears to be safe and effective. According to NICE guidelines, Vaginal PGE2 is less invasive than oxytocin, which requires intravenous access and continuous EFM, thus reducing women's mobility during induction (44)(57).

The largest randomized study to date found that oxytocin induction reduced the time interval to delivery as well as the frequencies of chorioamnionitis amongst others (60). A recent Cochrane review compared oral misoprostol with intravenous oxytocin found the percentage of women with meconium-stained liquor was similar to that in the overall results (61).
A study in KNH by Mbaluka et al concluded that oral misoprostol is as safe and effective as the standard intravenous oxytocin (62). Intravaginal misoprostol has been reported to be effective, safe and economical to use in cases with low Bishop scores (52)(63)(64) and both PGE1and PGE2 are similar in efficacy for labor induction (65)(66). Some trials report of oxytocin being superior to PGs in these group of patients with unfavorable cervix (67)(68) while others reported that PGs and oxytocin individually were both comparable, effective and safe for induction (69)(70). Cervical priming with prostaglandin prior to oxytocin infusion results in higher rate of vaginal delivery and shorter induction to vaginal delivery interval (71). One trial reported that concurrent administration of intravaginal misoprostol and oxytocin resulted in a significant shorter induction to delivery interval without adverse maternal and neonatal outcomes (72), another trial reported that this model did not expedite delivery (73).

Regarding use of antibiotics prophylaxis for term or near-term PROM , a systematic review and meta-analysis concluded that it is not associated with any benefits either in maternal or in neonatal outcomes (74)(75). According to NICE guidelines, in the absence of clinical signs of

infection, there is no evidence to support the routine use of prophylactic antibiotics, irrespective of the duration of PROM (57). However, with RCOG, antibiotic use in term PROM appears to be associated with a reduced risk of maternal infectious morbidity (53).

3.0.7 Failed induction of labor

Despite IOL being a common procedure in the obstetrical settings, criteria for successful and failed IOL have not been standardized and no consensus has been reached to date due to heterogeneity between IOL protocols and definitions (7)(8)(19) making it very difficult to draw conclusions based on published studies as majority of guidelines do not specify a time limitation from the initiation of IOL to delivery (29) and neither has consensus about the duration of the latent and active phase been reached thus adding to the confusion (17,18).

Regarding IOL outcome, a variety of end points such as mode of delivery (vaginal delivery or caesarean section), vaginal delivery within a certain time interval or achievement of the active phase of labor have been suggested (18,76)**.** This difficulty adds more variability to clinical judgement regarding the decision to proceed with surgical delivery after induction as the numbers of caesarean sections caused by failed labor will differ according to the definitions that are adopted in practice.

Most literature reviews define failed IOL as the inability to achieve a vaginal delivery which is a very general outcome thus adding confounding factors that may appear during labor that may hinder vaginal delivery and this may explain why a robust predictor is yet to be found (8). Baños proposed that failed IOL should be defined as the inability to achieve the active phase of labor, considering that the definition of IOL is to enter the active phase of labor, in line with Caughey et al recommendation that since the purpose of IOL is to cause a non- laboring woman to go into labor, a reasonable definition would be to achieve active labor as a measure of success (8).

Rouse indicated that a definition for IOL failure should maximize the number of women progressing to the active phase of labor (and ultimately delivering vaginally) while maintaining a low incidence of adverse maternal and neonatal outcomes (17)(18). Rouse et al reported a minimum requirement of 12 hours of oxytocin administration after membrane rupture before diagnosing failed labor induction, with 75% success rate in nulliparas and 91% success rate in parous women using this criteria, and eliminated failed labor induction as an indication for caesarean birth in parous women (17).

Spong et al proposed that failed induction be defined as the inability to achieve cervical dilatation of 4 cm and at least 90 percent effacement or 5 cm (regardless of effacement) after a minimum of 12 hours of both oxytocin administration and membrane rupture (18).
ACOG acknowledges that "allowing at least 12-18 hours of latent labor before diagnosing a failed induction may reduce the risk of caesarean delivery" (29). Simon et al observed that a latent phase of as long as 18 hours during induction of labor in nulliparous women allows the majority of these women to achieve a vaginal delivery without being subject to an increased risk of significant maternal or neonatal morbidity (50).

Grobman et al reported that a huge number of women undergoing labor induction will have entered the active phase by 15 hours after oxytocin has started and rupture of membrane has occurred, culminating into vaginal delivery with few adverse outcomes (77). In essence, the diagnosis of "failed induction" should only be made after an adequate attempt as long as the maternal and fetal conditions permit.

When the diagnosis of failed primary labor induction is perceived, options include expectant management up to 72 hours, repeat induction with same / alternative PG regime or mechanical method after a gap of 48 hours or Caesarean delivery after 48-72 hours if induction or

conservative management is not acceptable (7). A failure rate of 26% (20) is reported in KNH with 24.1% in West Africa (78) and 17.3% in Ethiopia (79).

In KNH, the commonest indication for primary caesarean delivery amongst women undergoing primary labor induction was a diagnosis of failed induction of labor (51.5%), which was defined as failure to achieve vaginal delivery within 24 hours of initiating induction in term pregnancies with average duration from induction to delivery being 19.1 hours (20).

In contrast, 10% of caesarean deliveries in the USA are being performed for failed induction, with data from Norway citing an induction failure rate of 4% and about 3% in Australia (3). In KNH, there is no protocol offering other options on management of these group of women thus CS is favored as an intervention. Recent guidelines on IOL recommend that failure of induction does not necessarily necessitate caesarean delivery (19)(21)(44) as continuing the induction process beyond a failed IOL diagnoses at a given time point will lead to vaginal delivery (8)(18)(51). The rising trend in operative delivery has been attributed to patient and physician factors such as the medical- legal pressures, changing patient demographics, or low threshold to opt for operative delivery (12)(19). Not only is caesarean delivery associated with increased maternal and neonatal adverse effects in the index pregnancy, it has serious implications for future gestations (15)(19)(34).

However, it is imperative to diagnose failed IOL at an appropriate time in order to counsel the patients and to decide whether to continue with the IOL based on the low probability of entering the active phase of labor as prolonged latent phase is associated with shoulder dystocia (80), endometritis and uterine atony. In addition, a prolonged latent phase of over 12 hours was also linked with a significantly longer duration of active labor (18). Higher rates of chorioamnionitis (from 20–22 to 25–27%) and PPH (from 11 to 16%) have been reported after 6 and 12 h of latent phase, respectively, not forgetting increased economic costs and the need for caesarean section (8). Simon et al reported that prolonged latent phases of labor greater than 18 hours was

associated with chorioamnionitis and postpartum hemorrhage rate of 16% and 26%, respectively, although these diagnoses did not translate into greater risk of transfusion, hysterectomy, or prolonged hospitalization. Neonatal outcomes, including meconium passage, fetal acidemia, neonatal intensive care unit admission, or other morbidity did not increase in conjunction with longer latent phases (50).

3.0.8 Factors determining induction of labor outcome

No good predictive factors are known to successfully predict those who will not respond to induction in achieving the active phase of labor due to the heterogeneity between the outcomes in published studies (8). Pre labor cervical status has been recognized as the most important predictor of induction success and can be evaluated using Bishop score and TV US (8) with a recent Cochrane review not demonstrating superiority of one method over the other in terms of the main outcomes assessed (81).

Overall, there appears to be a hiatus of information regarding diagnosis of failed induction of labor and cut offs have been arbitrary, depending on the institution in question. For this reason, this creates a necessity for exploitation of this opportunity to determine whether a second chance may significantly increase success rates of vaginal delivery in induced labor.

3.1 JUSTIFICATION OF THE STUDY

Labor induction has become a common obstetric procedure worldwide based on risk-benefit ratio of discontinuation or continuation of pregnancy in relation to the fetus and the mother. However, there has been no solid universal criteria of determining for how long induction of labor should take place and the clinical uncertainty in diagnosis of failed induction compounded by the fact that there are limited studies that exploits the benefits of repeat labor induction has favored caesarean delivery as the universal intervention when the diagnosis of failed labor induction is perceived. There is need to define this entity and offer alternatives to caesarean delivery in the

management of this group of women. At KNH, the principal training medical school in Kenya, prostaglandin E1, prostaglandin E2 and oxytocin are used for pharmacological labor induction of viable pregnancies at or near term. According to the hospital protocol, when misoprostol is used it is administered as 25mcg inserted to the posterior fornix every 4-6 hours to a maximum of 6 doses.

A diagnosis of failed induction of labor is made when there is failure to achieve vaginal delivery within 24 hours of initiating induction upon which caesarean delivery is undertaken as the preferred intervention in this group of women. However, proposing vaginal delivery as the main IOL outcome is a very general outcome which does depend on many other factors interacting during labor which are not necessarily related to the induction process thus adding confounding factors that may appear during labor that may hinder vaginal delivery.

We proposed to define 'failed induction of labor' as the inability to enter into active phase within 12 hours after IOL is instituted with misoprostol administered as 25ug pv 4 hourly to a maximum of three doses. This requirement before declaring an induction to have failed in the latent phase reasonably balances maternal benefits, i.e, the opportunity for entry into active phase of labor culminating in vaginal delivery, with maternal risks, specifically chorioamnionitis and uterine atony thus will allow parturients who remain in the latent phase for up to 12 hours to achieve vaginal deliveries that they otherwise would not have as shown by literature evidence. In addition, reassuringly, with contemporary management, any fetal/neonatal risks associated with labor induction do not seem to be affected by latent phase duration.

This study sought to exploit this opportunity of diagnosing failed labor induction through instituting a repeat labor induction process with the intention of reducing what would have been high caesarean delivery in addition to identifying the rate of success, maternal and neonatal outcomes of pregnancies with viable fetuses after pharmacological repeat induction of labor.

There have been no studies done locally or globally to evaluate whether repeat induction of labor using vaginal misoprostol carries increased risk for operative delivery, increased risk for maternal complications or poor fetal outcomes. The study will thus contribute towards review of induction protocols at the hospital and nationally as well.

3.2 RESEARCH QUESTION

What is the effect of repeat induction versus expectant management on rates of failed induction among women who have primary failure of induction at KNH?

3.3 NULL HYPOTHESIS

There is no effect of repeat induction versus expectant management on rates of failed induction among women who have primary failure of induction at KNH.

CONCEPTUAL FRAMEWORK

Narrative

Recent evidence shows that policy of labor induction does reduce both maternal and perinatal mortality and morbidity in addition to lowering CS rates. Since there is no universal consensus regarding management of failed induction of labor, caesarean delivery is often perceived to be the solution. Not only is caesarean delivery associated with increased maternal and neonatal adverse effects in the index pregnancy, it has serious implications for future gestations. Given that failed IOL diagnosis does not always necessitate operative delivery, the high unmet need for induction of labor in Kenya coupled with the high rate of caesarean deliveries due to failed primary labor induction calls for a review into induction policies in the hospital.

The challenge is whether repeat labor induction will improve the success rate in achieving active phase of labor culminating in vaginal delivery without compromising maternal and early neonatal outcomes. Hence, the study outcomes will influence on policy related to labor induction and duration together with the frequency of use of misoprostol.

This was a double arm open label prospective randomized clinical trial that sought to determine the rate of success, maternal and neonatal outcomes of pregnancies with singleton viable fetus in vertex presentation at term in eligible women undergoing other labor interventions after failed primary induction of labor at KNH.

Women having failed primary labor induction were randomized to undergo either expectant management or repeat IOL using vaginal misoprostol. Study participants were recruited from labor ward and antenatal wards immediately after admission. Once voluntary informed consent was obtained, the participants were interviewed for socio-demographic and obstetric history and information obtained was entered into a structured questionnaire. Labor and delivery records, neonatal records in addition to the operating theatre notes were reviewed and any missing information was obtained from the primary care giver.

Outcome variables measured:

Maternal

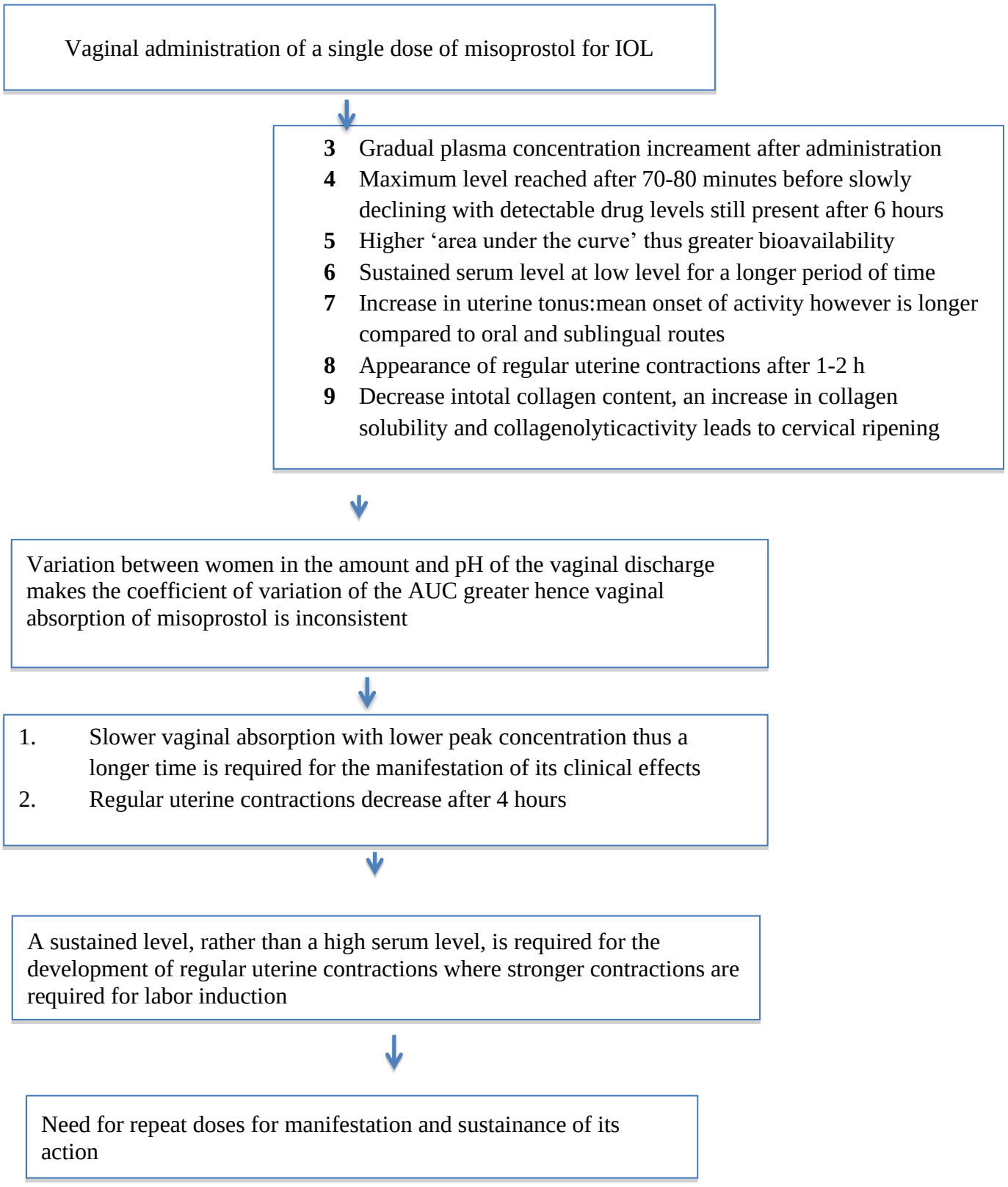
- Time from randomization to active phase of labor
- Time from randomization – vaginal delivery interval
- Mode of delivery- vaginal or caesarean delivery
- Maternal morbidity – maternal nausea, vomiting, diarrhea, postpartum haemorrhage, uterine hyperstimulation with FHR changes, uterine rupture, instrumental/operative vaginal delivery, intensive care unit admission, chorioamnionitis, duration of hospital stay, maternal death

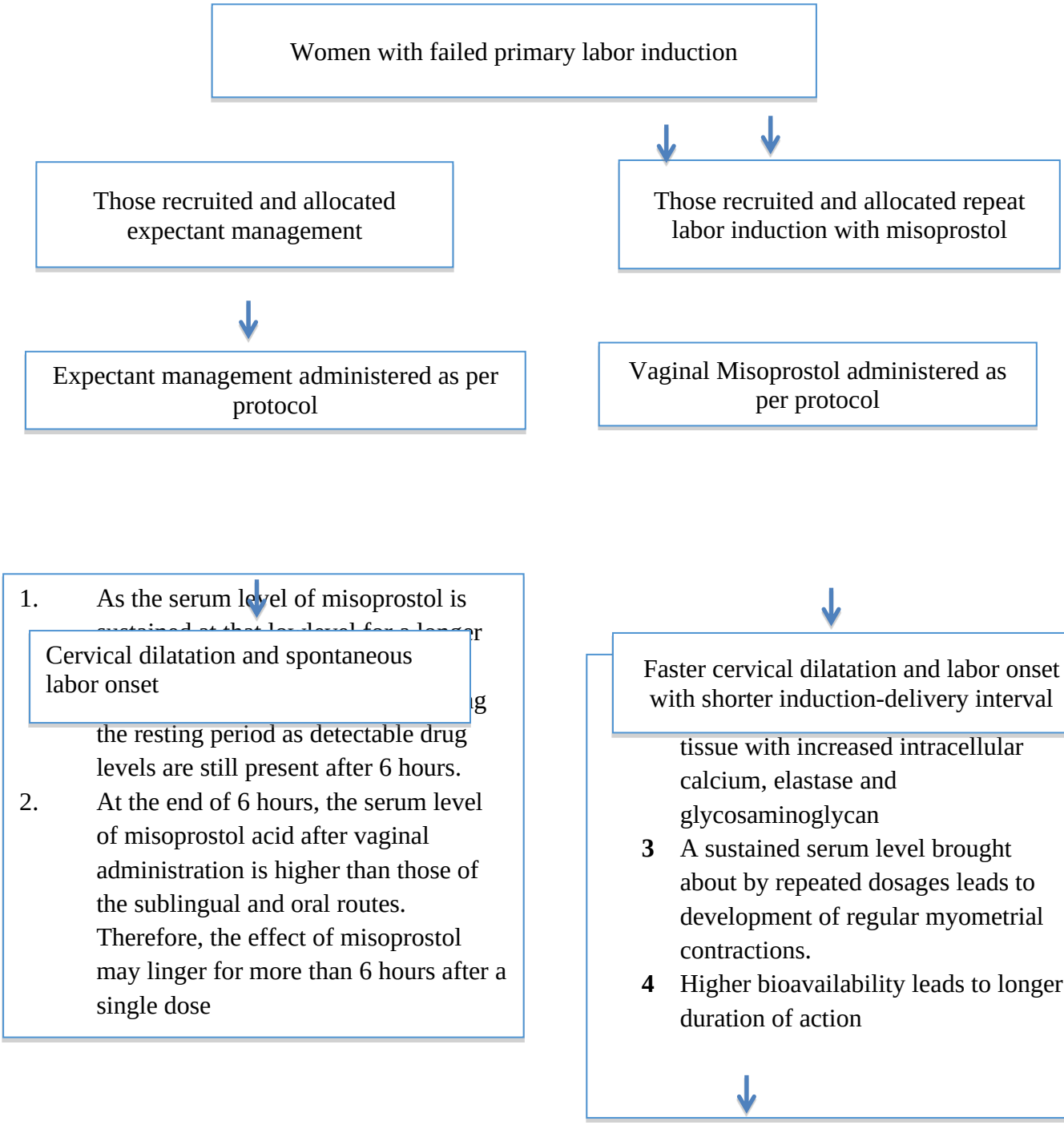
Fetal

- Apgar score 5 minutes
- Intrapartum complications- FHR changes (bradycardia, tachycardia), meconium-stained liquor
- Birth weight
- Neonatal morbidity -meconium-stained liquor, a 5-minute Apgar score below 7, admission to neonatal intensive care unit (NICU) for more than 48 hours, perinatal death

SCHEMATIC CONCEPTUAL FRAMEWORK

Pharmacokinetic properties of vaginal misoprostol and its effects on the uterus and the cervix




Women with failed primary labor induction
Those recruited and allocated expectant management
Those recruited and allocated repeat labor induction with misoprostol
Expectant management administered as per protocol
Vaginal Misoprostol administered as per protocol
1. As the serum level of misoprostol is
the resting period as detectable drug levels are still present after 6 hours.
2. At the end of 6 hours, the serum level of misoprostol acid after vaginal administration is higher than those of the sublingual and oral routes. Therefore, the effect of misoprostol may linger for more than 6 hours after a single dose
Cervical dilatation and spontaneous labor onset
Faster cervical dilatation and labor onset with shorter induction-delivery interval
tissue with increased intracellular calcium, elastase and glycosaminoglycan
3 A sustained serum level brought about by repeated dosages leads to development of regular myometrial contractions.
4 Higher bioavailability leads to longer duration of action

Acute phase of labor achieved or Failed repeat labor intervention

4.0 OBJECTIVES

4.1 Broad objective

To determine the effect of repeat induction versus expectant management on rates of failed induction among women who have primary failure of induction at KNH.

4.2 Specific objectives

Among women who have primary failed induction randomized to either repeat induction or expectant management, to compare:

1. Interval times;
   a) Time from randomization to active labor (failed induction rates)
   b) Time from randomization to vaginal delivery
2. Rates of adverse maternal and early neonatal outcomes
3. Mode of delivery

5.0 METHODOLOGY

5.1 STUDY DESIGN

This trial was designed as a single center, double arm Randomized Controlled Clinical Trial, non-blinded to both participants and researchers, blinded to the statistician, of eligible women with medical and elective indications for labor induction. Randomization was performed as block randomization with a 1:1 allocation. Participants having failed primary labor induction underwent randomization to either expectant management for 48 hours or repeat induction of labor using vaginal misoprostol after 24 hours.

5.2 STUDY SITE AND SETTING

The setting was in labor ward, antenatal wards and the neonatal unit in KNH. It is the largest hospital in Kenya and is situated in Nairobi, approximately 4km from the city center along Ngong Road. It serves as a national referral hospital that receives high risk patients, self-referrals and many un-booked patients from Nairobi and its environs. In addition, it also serves as a teaching hospital for the under-graduate and post-graduate students from the UoN Faculty of Medicine and for the students from the Kenya Medical Training College, Nairobi. The Obstetric unit is managed as a collaboration of Department of Obstetrics and Gynaecology (OBGYN) of UoN and KNH.

It consists of an antenatal clinic, three antenatal/postnatal wards with a labor ward having two operating theatres and the staff who are led by consultants. The maternity unit caters for about 13735-16074 deliveries annually (2014-2015 statistics data) thus offers comprehensive obstetric care. The two operating theatres are run on 24 hours, seven (7) days a week schedule. There is also a neonatal unit manned by pediatric department. This therefore made it a suitable site particularly because the numbers are adequate and the maternity unit is well staffed.

At KNH, prostaglandin E1, prostaglandin E2 and oxytocin are used for pharmacological labor induction of viable pregnancies at or near term. According to the hospital protocol, when misoprostol is used it is administered as 25mcg inserted to the posterior fornix every 4-6 hours to a maximum of 6 doses. A diagnosis of failed induction of labor is made when there is failure to achieve vaginal delivery within 24 hours of initiating induction upon which caesarean delivery is undertaken as the preferred intervention in this group of women.

5.3 STUDY POPULATION

This comprised of women with a singleton viable fetus in vertex presentation at term, defined as gestation at or beyond 37 weeks 0 days (82), who failed primary labor induction, defined as inability to enter into active phase of labor within 12 hours during primary IOL and fit the inclusion criteria.

ELIGIBILITY CRITERIA

The inclusion and exclusion criterias (1)(2)(29) were chosen in line with systematic reviews and meta-analysis by Mozurkewich (11) and Wood et al (14) regarding indications for labor induction where trials reported latency to delivery of about 1 week in the expectant management group.

5.3.1 Inclusion criteria

The participants included were mothers with:

1. Singleton, live gestation in cephalic presentation
2. Gestation at or beyond 37 weeks 0 days (37 0/7)
3. Post-term pregnancy
4. Bishop score <-6 at failed primary labor induction diagnosis
5. Reactive fetal heart rate pattern
6. Intact membranes
7. Oligohydramnios
8. Hypertensive disorders (preeclampsia without severe features and pregnancy induced hypertension)
9. Diabetes mellitus requiring insulin
10. Maternal cardiac disease: mild cardiac disorders

11. Fetal growth restriction without evidence of fetal compromise on Doppler U/S
12. Elective induction
13. Willing to participate and give a signed informed consent

5.3.2 Exclusion criteria

The participants excluded for primary labor induction were those who had:

1) Contraindications to induction

   Absolute: more than 2 previous uterine scar, previous myomectomy, malposition

   Relative: malpresentation, non-reactive non stress test, severe maternal heart disease, severe maternal hypertension, polyhydramnios

2) Contraindications to vaginal delivery e.g. contracted pelvis, type 4 placenta praevia, umbilical cord prolapse, active genital herpes infection, invasive cervical cancer

3) Estimated fetal weight >4000 or <2000 grams

4) Hypersensitivity to prostaglandins

5) Severe asthma

The participants excluded at failed primary labor induction diagnosis were those who had:

1) Uterine hyperstimulation with FHR changes

5.4 SAMPLE SIZE AND SAMPLING PROCEDURE

All eligible pregnant women meeting the inclusion criteria were randomized to undergo either expectant management or repeat induction using vaginal misoprostol after failed primary labor induction through block randomization to assign the participants to either method.

A recent retrospective cohort study conducted in 2013 of 34 women who had repeat IOL with dinoprostone (PGE2), Umoren et al reported success rate of active labor as 63% (83).
We postulated that Misoprostol being more efficacious would increase this rate to 80% compared to expectant management of 50%.

This 30% difference is clinically significant as it may reduce length of hospitalization, caesarean section rates and eventually the cost of care. Therefore for us to detect a 30% difference, we estimated using the sample size formula as used by Allan Donner (84).

Sample size formula:

$$n = \frac{2\left(z_{1-a_{/2}}\sqrt{2\bar{p}(1-\bar{p})} + z_{1-b}\sqrt{p_c(1-p_c)+p_a(1-p_a)}\right)^2}{(p_c - p_a)^2}$$

Where:

Z_β=1.28 representing 80% power

Z_α=1.96 representing 95 % level of confidence

p_c = Proportions of women in the repeat induction arm, .80

p_a = Proportions of women in the expectant management arm, .50

$\bar{p} = (p_C + p_a)/2$ ($Z_{0.25}$ =1.960, and $Z_{0.8}$ =0.842

That we needed to study a total of 78 women (39 per group) at 80% power to detect the stated difference of 30% at a two-sided alpha=0.05 level of significance. Assuming a 10% loss to follow-up or missing data, we enrolled and followed up 86 women (43 in each arm) with failed primary induction. With an overall failure rate of 26%, we expected to obtain this 86 from 344 women undergoing primary induction of labor.

Total (2n) = 86 patients

5.5 STUDY PROCEDURE

Recruitment: Primary labor induction description

Gravid women with a singleton viable fetus in vertex presentation at term who had been admitted for primary labor induction and did fit in the inclusion criteria were recruited.
An informed written consent was obtained from the participants upon admission in the labor ward and the antenatal wards.

The labor ward was the point of reference where all inductions were instituted, whether primary or repeat labor induction. Socio-demographic data and obstetric history was obtained through verbal interview. Thorough examination of the maternal and fetal condition was performed to assess the likelihood of successful induction and the risks together with the benefits and other alternatives was discussed with the patient.

Maternal assessment included confirming indication, ruling out contraindications, performing clinical pelvimetry to rule out cephalopelvic disproportion and assessment of cervical condition (Bishop score). The fetal assessment included confirmation of gestational age, fetal well-being, fetal weight (clinically or USG), confirming fetal presentation and lie. As per ACOG's recommendation, confirmation of term gestation was done using ultrasound measurement at less than 20 weeks of gestation supporting gestational age of 39 weeks or greater or fetal tones have been documented as present for 30 weeks by Doppler ultrasonography or it had been 36 weeks since a positive serum or urine B hcg pregnancy test result. Bishop Score was determined by a digital exam before IOL was commenced.

CTG trace was carried out for 20 minutes prior to induction thereafter primary labor induction was instituted with misoprostol administered as 25mcg inserted to the posterior fornix every 4 hourly to a maximum of three doses. Once in labor, the standard of care for labor monitoring and delivery was followed.

The starting time for counting primary labor induction was from the time the first dose of misoprostol was administered as 25ug pv in the initial cycle of induction to when the third final dose was administered as 25ug pv. A diagnosis of 'failed primary labor induction' was made when there was inability to enter into active phase within 12 hours after induction of labor was instituted with misoprostol administered as 25ug pv 4 hourly to a maximum of three doses during this initial/first cycle.

The starting time for counting failed primary labor induction was from the time the diagnosis of failed primary IOL was made when after the 3rd dose of misoprostol had been administered as 25ug pv, the participant had not achieved active phase. Women having failed primary labor induction were randomized to undergo either expectant management or repeat induction of labor using vaginal misoprostol.

Randomization/allocation concealment

Randomization was stratified by parity, gestational age, cervical status, indication for induction/intervention, duration of intervention, and mode of delivery due to the potentially strong association between maternal and early neonatal outcomes and each of these factors. Since the treatment assignment was open and the sample size was small, a block randomization procedure with randomly chosen block sizes was used to help maintain balance of treatment assignment and reduce the potential for selection bias.

Randomization was performed as block randomization with a 1:1 allocation with randomly selected block sizes of 4, 8 and 12 using SAS computerized sequence generation. In order to reduce the risk of randomizing an ineligible participant, randomization occurred immediately before the intervention or comparator procedure was to be performed after failed primary labor induction. Upon enrollment, an opaque envelope containing the participant's enrollment number and assignment to either expectant management or repeat induction of labor using vaginal misoprostol was opened. Each participant was assigned a unique subject number for identity and confidentiality. Participants and health providers were aware of the treatment allocation at the time of treatment assignment.

Research assistants completed a data collection form at the end of the procedures (for the intervention and control arms) outlining indication, the treatment allocation, clinical findings, and whether or not the procedure was successful. Adherence with treatment allocation was monitored by comparing these datasheets with the computer randomization records.

Intervention arm: This constituted participants for repeat induction of labor using vaginal misoprostol after failed primary labor induction.

Explanation for choice of intervention

As per the literature review, vaginal misoprostol has been shown to have the highest probability of achieving a vaginal delivery within 24 hours compared to other methods of labor induction.

The intervention in current practice

Recent various guidelines on IOL recommend that failure of induction does not necessarily necessitate caesarean delivery as continuing the induction process beyond a failed IOL diagnoses at a given time point will lead to vaginal delivery. However, there has been no solid universal criteria of determining for how long induction of labor should take place and the clinical uncertainty in diagnosis of failed induction compounded by the fact that there are limited studies that exploits the benefits of repeat labor induction has favored caesarean delivery as the universal intervention when the diagnosis of failed labor induction is perceived.

This trial addressed an important clinical question concerning a commonly used procedure that has the potential to reduce operative delivery and its associated complications.
Thus demonstration of efficacy will provide substantial scope for the intervention to be introduced into widespread practice with this trial being the pioneer in this field with the use of vaginal misoprostol.

The efficacy of the intervention

After extensive literature review, we did not find any preliminary studies done both locally and globally that exploits the benefits of repeat labor induction using vaginal misoprostol despite it being highly recommended as one of the mechanisms to curb the skyrocketing caesarean delivery rates.

Intervention description

Following the diagnosis of failed primary labor induction, participants for repeat induction of labor had a CTG and USG scan for biophysical profile performed. If both were reassuring, repeat induction using misoprostol was reinstituted after a gap of 24 hours provided that there was no fetal, placental or maternal compromise. The 24 hour resting period was necessary so as to avoid uterine hyperstimulation that is associated with multiple doses of misoprostol.

During this resting period, the mothers were accommodated in the labor ward for ease of monitoring and were reviewed on a daily basis. In the setting of labor induction, non-intervention in the latent phase when the fetal heart tracing is reassuring and maternal and fetal statuses are stable seems to reduce the risk of caesarean delivery (85). Hence, Intermittent auscultation (IA) of FHR for fetal well-being was done using Pinards fetoscope as there are no professional guidelines that recommend EFM for women who are in latent labor with available evidence not indicating superiority of EFM over intermittent auscultation (86)(87). Evidence is lacking on the optimal interval for IA but for the purpose of this study, it was carried out for at least 60 seconds duration every 4 hourly for those participants who were in the latent phase. Mothers were encouraged to ambulate in addition to being taught the danger signs to watch out for like reduced fetal movements (<6 distinct movements within 2 hours) or spontaneous rupture of membranes as an additional precaution during this latent phase.

Upon lapse of 24 hours resting period following failed primary labor induction diagnosis, the participants had repeat induction of labor reinstituted if they still were in latent phase with a

Bishop score of <6. Thorough examination of the maternal and fetal condition was performed prior to re-induction of labor. Maternal assessment included confirming indication, ruling out contraindications, performing clinical pelvimetry to rule out cephalopelvic disproportion and assessment of cervical condition (Bishop score). The fetal assessment included confirmation of gestational age, fetal well-being, fetal weight (clinically or USG), confirming fetal presentation and lie. The Bishop Score was determined by a digital exam and cervical dilation documented in centimeters ranging from 0 to 10 cm. CTG trace was carried out for 20 minutes before induction thereafter repeat labor induction was commenced with misoprostol administered as 25mcg inserted to the posterior fornix every 4 hourly to a maximum of three doses during this second cycle of labor induction.

For each planned misoprostol dose, the patient was clinically reassessed beforehand for the best way to achieve optimal contractions (3-5 strong contractions in 10 minutes). A vaginal exam was done at 4 hours unless there was an indication to do it earlier such as severe lower abdominal pain or drainage of liquor. After the first 4 hours, it was done as necessary. The bishop's score was repeated for each participant prior to administration of subsequent doses.

As per 2014 NICE guideline on intrapartum care, a woman was considered to be in the latent phase of labor when there were painful contractions with some cervical change, including effacement and dilatation up to 4cm. Established active phase was denoted by regular painful contractions and progressive cervical dilatation from 4cm. Once the mother experienced contractions or vaginal exam confirmed favorable Bishop score, amniotomy and augmentation of labor was done using oxytocin from 4cm cervical dilatation if no adequate contractions were perceived after 4hours from the last misoprostol dose administration.

Oxytocin infusion rates was administered as per WHO protocol starting with 5IU in 500mls of normal saline at 10 drops/minute, increased at 10 drops ½ hourly to a maximum of 60 drops/min or 3 strong contractions in 10 minutes. Misoprostol administration was stopped if active phase of

labor was achieved, at which point ongoing assessment of the participant in active labor was instituted with the aid of the WHO partograph. Uterine activity and electronic fetal monitoring (EFM) was undertaken from the time at which regular contractions of every 3 minutes or more commenced. Once in active labor, the standard of care for labor monitoring and delivery was followed. Fetal heart rate, maternal pulse rate and the number of contractions was recorded half hourly while maternal blood pressure and temperature was assessed 4 hourly.

The starting time for counting repeat induction of labor was from the time the first dose of misoprostol was administered as 25ug pv in the second round of labor induction after a resting period of 24 hours. A diagnosis of failed repeat labor induction was made when there was inability to enter into active phase within 12 hours after repeat induction of labor was instituted with misoprostol administered as 25ug pv 4 hourly to a maximum of three doses during this second cycle of labor induction. Women who did not go into active phase after the 3rd dose of misoprostol administered as 25ug pv were considered to have failed repeat induction of labor. All participants having failed repeat labor induction in this arm subsequently underwent caesarean delivery.

Criteria for discontinuing or modifying the intervention

The intervention was discontinued if there was a clinical necessity or at the request of the participant. This applied where there was evidence of maternal and/ or fetal compromise necessitating emergent delivery or if the participant was in significant discomfort. Participant could also opt out at any time in absence of maternal and/ or fetal compromise.

The control arm: This were participants for expectant management after failed primary labor induction**.**

Explanation for choice of comparator

While Caesarean delivery is a favored universal intervention when the diagnosis of failed primary labor induction is perceived as per the literature review, for women not willing to undergo CS or repeat IOL due to the associated risks with either of the process, demonstration of efficacy of this intervention will offer solution to this particular group and improve its adoption into current practice in addition to help minimize the high rate of caesarean delivery. As the serum level of misoprostol is sustained at that low level for a longer period of time, late effects of PGE1 may cause uterine contractions thereby initiating labor as detectable drug levels are still present after 6 hours.

Comparator description

When the diagnosis of failed primary labor induction was perceived, those for expectant management had a CTG and USG scan for biophysical profile performed. If both were reassuring, expectant management was commenced from the time the failed primary labor induction diagnosis was made for up to 48 hours. The 48 hours was chosen as it is the minimal threshold duration for this intervention not forgetting the maternal anxiety that may arise with longer waiting period.

During the resting period, the mothers were accommodated in the labor ward for ease of monitoring and were reviewed on a daily basis. Intermittent auscultation (IA) of FHR for fetal well-being was done using fetoscope for at least 60 seconds duration every 4 hourly. Mothers were encouraged to ambulate in addition to being taught the danger signs to watch out for like reduced fetal movements (<6 distinct movements within 2 hours) or spontaneous rupture of membranes as an additional precaution during the latent phase.

Upon lapse of 48 hours from when the diagnosis of failed primary labor induction was perceived, if spontaneous labor had not set in by this time, CTG and liquor volume assessment followed. All women in this arm with unfavorable cervical score at this time confirmed by digital examination were considered to have failed expectant management and subsequently underwent

caesarean delivery. The starting time for counting expectant management was from the time the diagnosis of failed primary labor induction was made to the lapse of 48 hours resting period thereafter.

Management of PROM

During the resting period following failed primary labor induction diagnosis, one anticipated issue was PROM at term as some participants in both arms were expected to go into spontaneous labor. The diagnosis was made based on the patient noting a "gush of fluid" and direct observation of amniotic fluid in the posterior vaginal vault (pooling) on physical examination. Speculum examination for confirmation of PROM, assessment of cervical status, and exclusion of cord prolapse was done. Oxytocin infusion rates was administered immediately as per WHO protocol starting with 5IU in 500mls of normal saline at 10 drops/minute, increased at 10 drops ½ hourly to a maximum of 60 drops/min or 3 strong contractions in 10 minutes. No antibiotics prophylaxis was given as explained in the literature review. The degree of caesarean delivery urgency in both arms was based on the presence or absence of maternal and fetal compromise as recommended by RCOG (88). This proposed classification avoids time-based definitions thus allowing individualized approach to assessment of urgency of delivery in all cases. The classification is shown in the Appendix 3.

Management of fetal heart rate tracings

Category III fetal heart rate tracings that did not respond to intrauterine resuscitative efforts including maternal repositioning and oxygen supplementation, assessment for and correction of hypotension with tachysystole were prepared for imminent delivery.

Since Category II tracings are indeterminate, continued surveillance, initiation of appropriate corrective measures when indicated and re-evaluation was done on individual basis (85). For the purpose of this study, in case of uterine tachysystole or hypertonia, electronic fetal monitoring

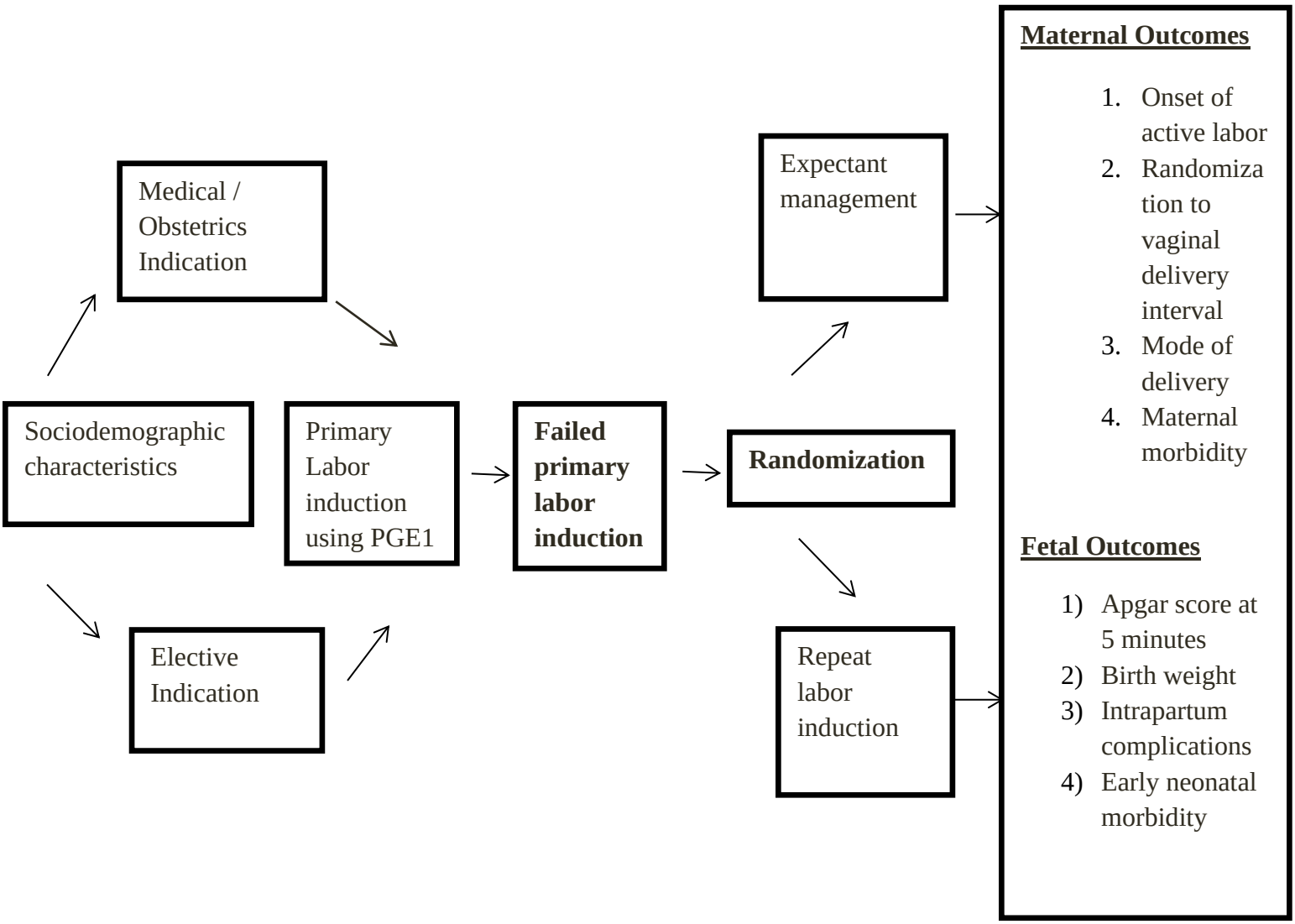
was commenced with administration of tocolytics if abnormal fetal heart rate was persistent while with uterine hyperstimulation, labor induction was stopped and $MgSO_4$ 1g / hour given in normal saline and the CTG done as the patient was being prepared for an emergency caesarean delivery.

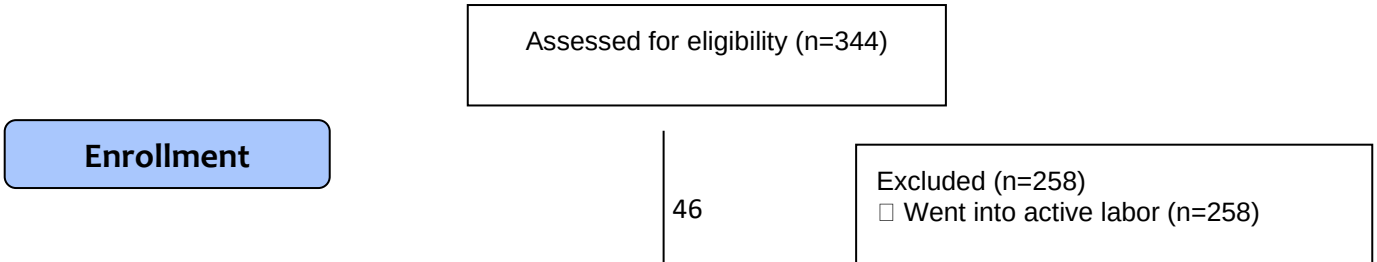
Clinical decisions were made daily during the major ward rounds which were done in the morning and in the evening headed by the consultants and involved the entire team covering the labor ward. During the day, the resident along with the research assistants did carry out frequent reviews and made decisions as necessary. If in doubt, the consultant was contacted on the way forward concerning contentious issue at hand.

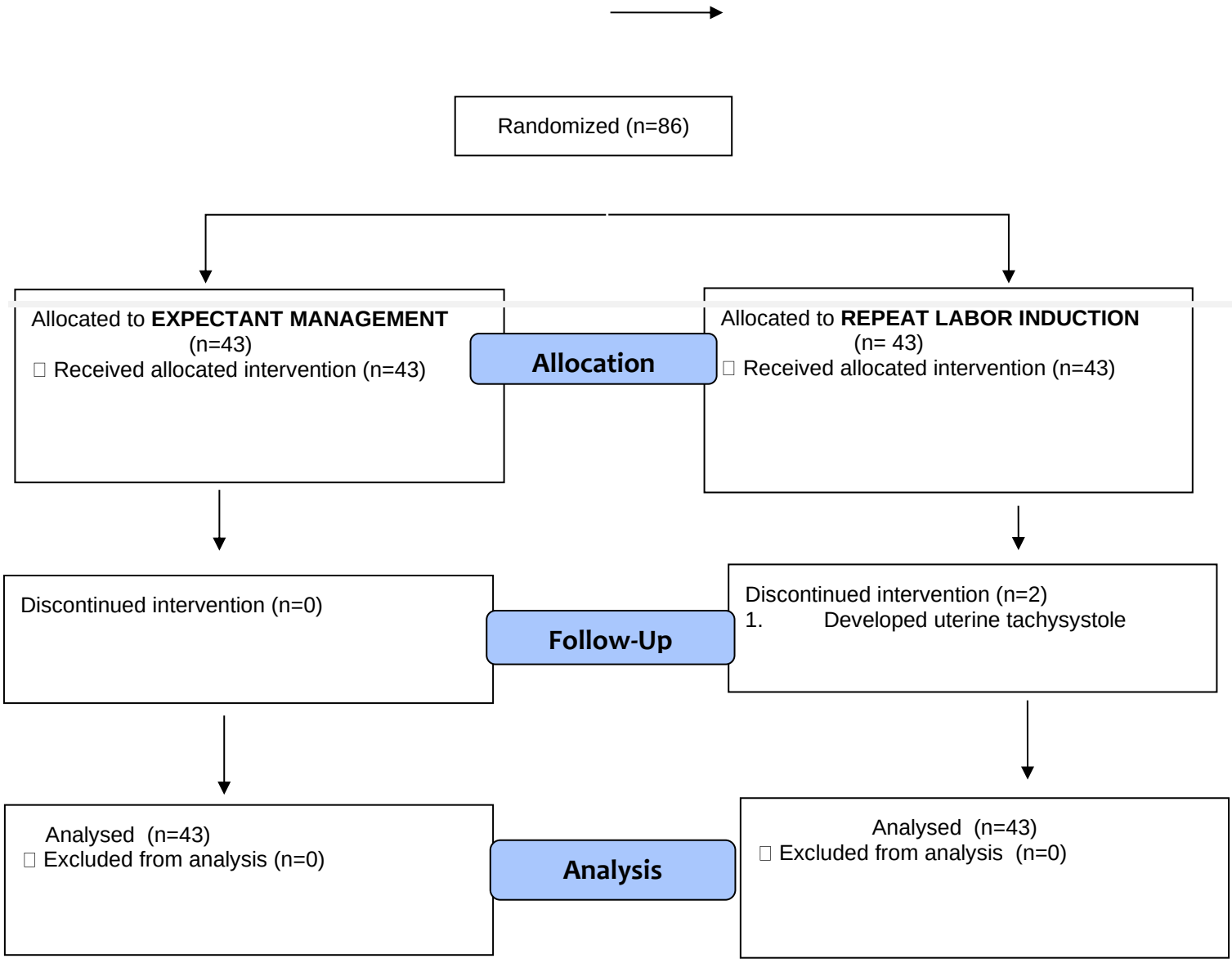
The research assistants monitored administration of the drugs to ensure compliance to the medication during induction of labor. Misoprostol was outsourced from a reputable supplier and the batch number noted. It was stored in a locked cupboard at the labor ward away from direct exposure to light, moisture and heat for easy accessibility by the research assistants.

The occurrence and outcomes of labor induction was entered in the patient's records and in a questionnaire attached to the patient's file on admission. All participants were followed up until discharge from the hospital. The study primary endpoint was onset of active labor with maternal and early neonatal mortality and morbidity as one of the secondary outcomes.

5.6 RECRUITMENT FLOW CHART OF STUDY PARTICIPANTS


Medical / Obstetrics Indication
Sociodemographic characteristics
Primary Labor induction using PGE1
Failed primary labor induction
Randomization
Expectant management
Elective Indication
Repeat labor induction
Maternal Outcomes
1. Onset of active labor
2. Randomization to vaginal delivery interval
3. Mode of delivery
4. Maternal morbidity
Fetal Outcomes
1) Apgar score at 5 minutes
2) Birth weight
3) Intrapartum complications
4) Early neonatal morbidity


Assessed for eligibility (n=344)
Enrollment
Excluded (n=258)
Went into active labor (n=258)



This flowchart shows that 344 women were approached for enrollment, 258 did not meet the inclusion criteria and were excluded, leading to a final sample size of 86 participants. All 86 participants were analyzed.

5.7 STUDY VARIABLES

Independent variables

From the literature review, several factors have been shown to influence outcomes of labor induction which includes parity, gestational age and indication of IOL. This formed our exposure variables.

 Socio-demographic characteristics e.g. age, marital status, occupation

 Obstetric characteristics e.g. parity, gestational age

 Indication for induction of labor/ intervention

Outcome variables

a) Maternal

 Randomization to active labor (onset of active labor)

 Randomization – vaginal delivery interval

 Mode of delivery- vaginal or caesarean delivery

 Maternal morbidity – maternal nausea, vomiting, diarrhea, postpartum haemorrhage, uterine hyperstimulation with FHR changes, uterine rupture, instrumental/ operative vaginal delivery, intensive care unit admission, chorioamnionitis, duration of hospital stay, maternal death

b) Fetal

 Apgar score at 5 minutes

 Intrapartum complications- FHR changes (bradycardia, tachycardia), meconium-stained liquor

 Birth weight

- Neonatal morbidity -meconium-stained liquor, a 5-minute Apgar score below 7, admission to neonatal intensive care unit (NICU) for more than 48 hours, perinatal death

Infants who experienced more than one component of the composite were represented only once in the composite outcome.

Primary and secondary outcome variables

Primary outcome

1) Onset of active labor: This was chosen as a primary outcome in line with literature review that failed IOL should be defined as the inability to achieve active phase of labor. In this instance, final outcome of pregnancy (mode of delivery) which is associated with confounders is not considered.

Secondary outcomes

1) Randomization – vaginal delivery interval
2) Mode of delivery: vaginal vs caesarean delivery
3) Adverse maternal outcome defined as or including maternal nausea, vomiting, diarrhea, postpartum haemorrhage, uterine hyperstimulation with FHR changes, uterine rupture, instrumental/ operative vaginal delivery, intensive care unit admission, chorioamnionitis, duration of hospital stay, maternal death
4) Early neonatal morbidity defined as or including meconium-stained liquor, Apgar score less than seven at five minutes, NICU admission for more than 48 hours, perinatal death

Perinatal and maternal morbidity and mortality are composite outcomes and there is lack of universally accepted definitions of serious infant or maternal morbidity, thus, they are defined on the basis of clinical diagnoses as identified previously by trialists in similar studies as important measures of associated morbidity.

The outcomes for this study were the clinically important benefits and harms of labor induction as specified by Cochrane review of vaginal misoprostol for cervical ripening and induction of labor (41) with other systematic reviews (26) and network meta-analysis (40).

5.8 RESEARCH INSTRUMENT

This consisted of structured questionnaire with pre-coded and coded answers. It had the following sections in line with the study objectives:

A) Maternal socio-demographic characteristics and obstetric history
B) Primary labor induction: procedure and determinants of outcomes of labor- obstetric course, primary and secondary outcomes
C) Failed labor induction: procedure and determinants of outcomes of labor- obstetric course, primary and secondary outcomes

Questionnaires were filled through verbal interviews on admission prior to primary induction of labor. The questionnaire was pretested in the labor ward by the principal investigator a few weeks before the study to establish the reliability of the study questions and to ensure that any errors or ambiguities were corrected beforehand. Additional information was obtained from the participant's records and partograph.

6.0 DATA COLLECTION, MANAGEMENT AND ANALYSIS

6.1 Data Collection Instruments

Primary data collection was done by the principal investigator with the help of two research assistants. Registered nurse-midwives were recruited as research assistants and the principal investigator trained them on recruitment, induction of labor and data collection. The research assistants' duties and responsibilities included recruitment of participants, monitoring of the participants during induction and in labor, data entry and overall coordination of the study in the absence of the principal investigator. The other members of the department were also given an overview of the study.

All women in labor and antenatal wards who met the eligibility criteria were recruited to participate on admission after being informed in depth about the purpose and procedure of the study including the associated risks and other available alternatives. They were given ample opportunity to ask questions and were informed that they had the right to change their mind at any time without penalty. Allocation of treatment was done by block randomization and the trial was not masked to the participants, care givers and investigators. Those who gave voluntary informed consent were consecutively enrolled to reach the targeted sample size. The study

participants and primary care givers were interviewed verbally for sociodemographic and obstetric data. Additional information such as labor and delivery course including medications, induction data, length of labor stages, mode of delivery, maternal and neonatal outcomes with the postpartum record were obtained from the labor and delivery records and filled into the questionnaires. The filled questionnaires were kept in a safe and confidential place only accessible to the principal investigator and supervisors. As randomization was done immediately after the diagnosis of failed primary labor induction, we had 100% ascertainment for the primary outcome while mode of delivery, maternal and early neonatal outcomes were easily obtained from the participants records that were kept in the hospital for safe guarding purposes.

6.2 Data Entry And Management

The data collected during this study included quantitative and qualitative data that was generated from clinical measurements and questionnaire. All the collected data was de-identified and anonymized. Both the hard copy records and the electronic database included the study identification number but no directly identifying data such as name, medical record number or date of birth. The collected and processed data was stored in hard and soft copy by the principal investigator. Any hard copy records carried for analysis was stored under lock and key. Data was entered into a Microsoft excel database with inbuilt consistency and validation checks.

It was cleaned and stored in a password protected computer and backed up on external storage device [USB/disc] with data being accessible only to the principle investigator, supervisors, statistician, IRB and ERC. All electronic data was checked for accuracy by a second member of the research team and any apparent data entry errors was discussed by the primary investigators and investigated/corrected as required. Data sharing was done with utmost confidentiality according to good clinical practice. Once processed, the primary investigator plans to publish the trial findings in reputable journals. The data will be stored and accessed for a period of 3 years from the time of collection where it will be discarded responsibly thereafter.

6.3 Data Analysis

Data analysis was conducted with the assistance of the trial statistician and involved intention to treat analysis. Simple linear regression model under the generalized linear model (glm) package (with the Gaussian family specification) of R Studio was used to analyze variables measured on a continuous scale. These included onset of active labor, duration of second stage, and randomization to vaginal delivery time in the assessment of interval times. Simple linear regression was also used to assess estimated blood loss and duration of hospital stay among maternal outcomes and birth weight among neonatal outcomes. The model was fitted by regressing the continuous outcomes against the treatment groups. Residual assessment was done to confirm the assumptions of linearity, normality and constancy of variance.

Logistic regression model under the glm package (with the Binomial logit family specification) of R Studio was used to assess outcomes measured on a binary scale. These included active phase at 36 and 48 hours, oxytocin augmentation and mode of delivery. The same model was used to assess GIS symptoms and postpartum hemorrhage among maternal outcomes; and NICU admission, APGAR score at 5 minute, meconium passage and abnormal CTG among neonatal outcomes.

The results were then exponentiated to yield the OR. Cross tabulation of the outcome variables against the treatment groups (Expectant Management and Repeat Induction) was done using CrossTable function in R Studio. This yielded group frequencies and their respective percentages. Data cleaning and all the subsequent analysis were done using R Studio Version 3.5.1. The P value <0.05 was considered as statistically significant. Losses to follow-up for the primary outcome did not occur. The analyst was blinded by naming participants in standard care as Group A and those in intervention arm as group B. Formal interim analyses for efficacy and/or effectiveness was conducted when 60% participants completed follow-up. The final results was reported in tables according to CONSORT guidelines.

6.4 Data Safety And Monitoring Board (DSMB)

A Data Safety and Monitoring Board was constituted to include members from other institutions serving in individual capacities who provided the requisite expertise and recommendations for conducting a drug clinical trial in the department. It was an independent group of four experts that advised the KNH-UoN Ethics and Research Committee, Department of OBGYN - Kenyatta National Hospital and the study investigators. The committee consisted of Dr. Samuel Wachira Ndungu who was the chair person with Dr. Caroline Asin, Dr. David Gathara and Dr. Frankline Onchiri as members.

Dr. Samuel Wachira is a Reproductive Health Specialist with over six years experience and department head at Mbagathi Hospital who participates in Obstetric and Gynecological research. Dr. David Gathara is a Clinical Epidemiologist at KEMRI with over seven years experience in quality of care assessment, epidemiology, research methodology, biostatistics, health informatics, data management and clinical trials. Dr. Caroline Asin is a Program Officer/ Clinical Pharmacist at NASCOP who is well versed in Pharmacy oriented issues. Dr. Frankline Onchiri is a Clinical Epidemiologist/ Biostatistician with advanced medical statistics training and experience in health services research. All the members had undergone training in Good Clinical Practices (GCP).

Roles and responsibilities of the committee headed by Dr. Samuel Wachira included the following:

a) Reviewing study conduct of the trial with regard to good clinical practice for participant safety.
b) Reviewing progress of study and accumulated data with regard to trial efficacy.
c) Making recommendations to all those involved concerning the continuation, modification, or termination of the trial.
d) Facilitating the smooth running of the trial.

Since severe adverse outcomes requiring reporting were not observed, the trial proceeded as planned with no stoppage at any point.

7.0 ETHICAL CONSIDERATIONS

The principal investigator instituted all measures to ensure that the ethical rights of the study participants were safeguarded through the following measures:

1. **Approval**: The trial was designed to comply with international ethical guidelines that govern human research and was carried out after approval was obtained from Ethics and Research Committee of Kenyatta National Hospital and from the University of Nairobi Department of Obstetrics and Gynaecology before commencement of the study. The approval number is P66/09/2016.

2. **Participation**: Participation was entirely voluntary and the participants were adequately informed about the study in a language that they understood. The session included explanations of the purpose of the study, the study procedures, the risks associated with either of the interventions and the participant's right to discontinue participation at any time without penalty. No form of inducement or coercion was offered to participants and women who were not willing to participate in the study were neither victimized nor denied care.

3. **Informed Consent**: A written informed consent was obtained from each person who wanted to participate in the study prior to undertaking primary labor induction. This was to ensure that the participant was under no duress in making the decision to participate in the trial as they were not in labor. Both the participants and the investigator signed and dated the consent form. The volunteer's signature confirmed that the study information had been explained to her and all her concerns had been adequately addressed. For illiterate individuals, the informed consent process was conducted in the presence of an impartial witness. The participant thumb print acted as consent and the witness was required to sign and date the form. In case of any amendments to the protocol resulting in changes in study procedures, the volunteers were to be informed and additional informed consent obtained if necessary. The informed consent form is found in Appendix 5 and available in English.

This form described the purpose of the study, the procedures to be followed, the risks and benefits of participation in adherence to the regulations put forth.

4. **Confidentiality**: For confidentiality purposes, the questionnaires were numbered serially and did not bear any other identifying information. Hard copies of data collection forms were stored in a locked office. The electronic database was on Microsoft excel, password-protected, and only accessible by research staff for the purpose of this study.

5. **Risks and benefits:** Induction of labor helps to avert adverse effects associated with prolonged pregnancy such as fetal demise. Repeat labor induction is anticipated to reduce the high rate of caesarean delivery and caesarean related mortality and morbidities. However, the process is not without risks. All efforts took into consideration the associated risks of the study and the investigators actively looked out for the following risks: uterine contractile abnormalities, uterine rupture, chorioamnionitis among others. Information obtained from this study may lead to the implementation of protocol involving management of failed labor induction.

6. **Serious adverse effects**: Any serious adverse effect that might occur to the participants during this study was to be reported by the primary investigator to the supervisors, IRB, consultant obstetrician/ gynaecologist on call and KNH Ethics Research Committee within 24 hours. A written report and a completed form with details of the event and the outcome was to be submitted to the same within 48 hours. The possible serious adverse effects in this study included persistent uterine contractile abnormalities, chorioamionitis, uterine rupture, poor perinatal outcomes and death. To mitigate this, participants were thoroughly counseled at enrollment, vigilant monitoring during induction/ intervention till delivery to ensure early intervention was instituted. Misoprostol is routinely used in our setting and our experienced nurses could easily pick such abnormalities and institute appropriate management with the residents and consultants on duty. In case of serious adverse effects, the standard protocol of management for the individual complication was to be instituted immediately.

Where there was suspected uterine hyperstimulation, induction of labor was to be stopped, $MgSO_4$ at 1g/hour in normal saline started as the participant was prepared for an emergency CS.

7. **Blinding**: Only the statistician who performed the analysis was blinded. The investigators together with the participants and the care givers were not blinded. While empirical evidence suggests that blinding reduces bias in randomized controlled trials, however, blinding may be difficult in the case of procedural interventions.

8. **Protocol amendments**: If modification to the study protocol was considered necessary, then permission was to be sought from the KNH/ UoN Ethics Research Committee and the changes described in the final report. The sample size was revised from 220 to 344 and the change was approved by the KNH/ UoN ERC.

9. **Information sharing**: The relevance of the study was shared with all the maternity staff in KNH to enhance co-operation. The clinically significant results will be shared with the relevant teams including KNH/ UoN (Department of Obstetrics and Gynaecology) and the Ministry of Health.

10. **Registration of Clinical Trial**: The study is registered under Pan African Clinical Trial Registry and the unique identification number for the registry is PACTR201805002872322.

8.0 STUDY RESULTS

Between the months of February 2018 and August 2018, pregnant women at a gestational age of 37 weeks and above undergoing pharmacological induction of labor using vaginal Misoprostol at KNH were recruited. Three hundred forty-four (344) women were approached for enrollment. During primary IOL, 258 participants achieved active phase of labor and were excluded from recruitment. Remaining 86 patients were randomized into two different regimens: 43 patients to the repeat vaginal misoprostol group and 43 patients to the expectant management group following the diagnosis of failed primary labor induction. Outcome data were available for all 86 participants and analysis was done using the intention to treat principle.

TABLE 1: Socio-demographic characteristics of participants by treatment group

Characteristic	GROUP Expectant Management (N = 43) No (%)	Repeat Induction (N = 43) No (%)	P-Value
Maternal Age (Years)	26.3 (5.3)	25.3 (4.6)	0.353
≥35	40 (93.0)	41 (95.3)	
< 35	3 (7.0)	2 (4.7)	
Marital Status			
Married	37 (86.0)	35 (81.4)	0.770
Single	6 (14.0)	8 (18.6)	
Education			
Primary Sch. and Below	6 (14.0)	8 (20.9)	0.302
≥Secondary	37 (86.0)	35 (79.1)	
Employment			
Yes	30 (69.8)	24 (55.8)	0.264
No	13 (30.2)	19 (44.2)	

Table 1 shows there were no significant differences in the baseline (socio-demographic) characteristics of both treatment groups including maternal age, marital status, education, and

occupation (p value>0.05). Therefore, randomization process was effective for socio-demographic characteristics.

The mean age of women in the expectant management group was 26.3 ± 5.3 years compared to 25.3 ± 4.6 years in the repeat induction group. Most pregnant women were 35 years and above (expectant management 93.0% vs 95.3% repeat induction group). Majority of women were married; 37 (86%) in the expectant management versus 35 (81.4%) in the repeat induction arm.

More than three-quarters of mothers had either secondary or higher education level (expectant management 86% vs 79.1 % repeat induction). More than half of the mothers reported that they were currently engaged in employment; with 30 (69.8%) in expectant management compared to 24 (55.8%) in repeat IOL group.

Table 2: Obstetric characteristics of participants by treatment group

	GROUP		
Obstetric Characteristic	Expectant Management (N = 43)	Repeat Induction (N = 43)	P-Value

	No (%)	No (%)	
Parity			
Multiparous	18 (41.9)	15 (34.9)	0.657
Nulliparous	25 (58.1)	28 (65.1)	
Gestational Age (weeks)			
Early Term (37 0/7 - 38 6/7)	2 (4.7)	3 (7.0)	0.331
Full Term (39 0/7 - 40 6/7)	7(16.2)	8 (18.6)	
Late Term (41 0/7 - 41 6/7)	11 (25.6)	9 (20.9)	
Post Term (42)	23 (53.5)	23 (53.5)	
Bishop Score at randomization			
< 6	38 (88.4)	37 (86.0)	1.000
6	5 (11.6)	6 (14.0)	
Indication for Intervention			
False Labor	20 (46.5)	19 (44.2)	1.000
Oligohydramnios	0 (0.00)	1 (2.3)	
Post Term	23 (53.5)	23 (53.5)	

Regarding obstetric characteristics (Table 2), there was no statistically significant difference in parity, gestational age, Bishop score at randomization, and indication for intervention (p value>0.05). Both groups had unfavorable cervix (modified Bishop's score _<6) at point of randomization following failed primary labor induction. Majority of participants were primigavidas (expectant management 58.1 % vs 65.1 % repeat IOL group) suggesting that induction of labor is more necessary in the first pregnancies. Gestational age at delivery was similar in the two groups (p= 0.331) with the commonest indication for intervention being post term pregnancy (53.5 %).

Table 3: Interval Times by treatment group

	GROUP				
Interval Times	Expectant Management	Repeat Induction	Mean/ OR	(95% CI)	P-Value

	(N=43)	(N=43)			
	No (%)	No(%)			
Randomization to active labor (h)	26.01 (8.96)	18.20 (7.91)	-7.81	(-12.27, -3.35)	0.001
Duration of Second Stage (min)	21.22 (9.27)	22.82 (11.56)	1.59	(-4.54, 7.74)	0.612
Randomization to Vaginal Delivery Time (h)	33.37 (8.77)	24.78 (8.27)	-8.59	(-13.63, -3.56)	0.002
Active Phase Achieved (36 h)	24 (55.8)	34 (79.1)	2.99	(1.18, 8.02)	0.023
Active Phase Achieved (48 h)	31 (72.1)	34 (79.1)	1.46	(0.54, 4.03)	0.453

The primary outcome is presented in Table 3 above. Number of hours for onset of active labor (randomization to active labor) and randomization to vaginal delivery interval were significantly different among the two groups (p value 0.001, 0.002 respectively).

The time from randomization to active phase was 8 hours shorter in the repeat induction group (18.20 vs 26.01 hours; mean difference, 7.81 h; 95% confidence interval -12.27 to -3.35, p=0.001). Fewer women in the repeat induction group remained in latent phase after 36h (20.9 % vs 44.2 %, p= 0.023).

Time from randomization to vaginal delivery was >8 hours less in the repeat induction group (24.78 vs 33.37 hours, mean difference -8.59 h, 95 % CI -13.63 to -3.56, p= 0.002). There was however no significant difference in the mean duration of second stage labor among mothers randomized to the two treatment groups (p = 0.612).

Mothers subjected to repeat induction were more likely to transition into active phase of labor within 36 hours of induction compared to their counterparts in the expectant management arm (79.1 % vs 55.8 %, OR = 2.99, 95 % CI 1.18-8.02, p = 0.023). There was no significant

difference in the odds of achieving active labor when results obtained from mothers in the expectant management group at the 48th hour were compared to those of their counterparts in the repeat induction group observed at the 36th hour (72.1 % vs 79.1 %, OR 1.46, 95 % CI 0.54-4.03, p= 0.453). Seven mothers in the expectant management group transitioned into active labor between the 36 and 48 hours.

Table 4: Mode of Delivery by treatment group

Mode of Delivery	GROUP: Expectant Management (N=43) No (%)	Repeat Induction (N=43) No (%)	Mean / OR	(95% CI)	P Value
CS	22 (51.2)	20 (46.5)	0.83	(0.35, 1.93)	0.666
Vaginal	21 (48.8)	23 (53.5)			

There was no significant difference in the mode of delivery between the two groups (table 4). 21 (48.8 %) women in the expectant management group had vaginal delivery compared to 23 (53.5%) in the repeat induction group (OR 0.83, 95 % CI 0.35-1.93, p=0.666).

Table 5: Maternal Outcomes by treatment group

Maternal Outcomes	GROUP Expectant Management (N = 43) No (%)	Repeat Induction (N = 43) No (%)	Mean/OR	(95% CI)	P-Value
Estimated Blood Loss (ml)	487 (203)	508 (247)	0	(0, 0)	0.671
Duration of Hospital Stay (days)	5 (1)	5 (1)	0	(0, 0)	0.472
Oxytocin Augmentation	13 (30.2)	23 (53.5)	2.65	(1.11,6.56)	0.030
Uterine Tachysystole					
Yes	0 (0.00)	2 (4.7)			
No	43 (100.0)	41 (95.3)			
GIS Symptom					
Yes	11 (25.6)	15 (34.9)	1.55	(0.61, 4.01)	0.349
No	32 (74.4)	28 (65.1)			
Postpartum Hemorrhage					
Yes	11 (25.6)	11 (25.6)	1.00	(0.37, 2.65)	1.000
No	32 (74.4)	32 (74.4)			

***Negative Findings**: Hypertonus, Chorioamnionitis, Uterine Hyperstimuli, Uterine Rupture, ICU Admission, Maternal Death*

Table 5 shows there were no significant differences in maternal outcomes between the 2 groups (p value>0.05). The commonest adverse effects reported were GIS symptoms and postpartum haemorrhage. Mean blood loss was comparable between the groups (487 ± 203 ml vs 508 ± 247 ml). Mothers for repeat induction were at higher probability to need Oxytocin augmentation compared to their counter parts (53.5 % vs 30.2 %, p value=0.030, OR 2.65, 95% CI 1.11 to 6.56). There were 2 cases of uterine tachysytole in the repeat induction group which resolved with conservative management. Mean duration of hospital stay was similar between the groups, reported as 5 days (p= 0.472). There were no cases of hypertonus, uterine hyperstimulation, uterine rupture, choriamnionitis, ICU admission or maternal death reported in either of the groups.

Table 6: Early neonatal outcomes by treatment group

Neonatal Outcomes	GROUP Expectant Management (N = 43) No (%)	Repeat Induction (N = 43) No (%)	Mean/ OR	(95% CI)	P-Value
Birth Weight (kg)	3.24 (0.52)	3.32 (0.52)	0.08	(-0.13,0.3)	0.464
NICU Admission	7 (16.3)	1 (2.3)	0.12	(0.01,0.73)	0.054
Reason for NICU Admission					
Birth Asphyxia	2 (28.6)	0 (0.0)			
Meconium Aspiration Synd.	1 (14.3)	0 (0.0)			
RDS	4 (57.1)	1 (100.0)			
APGAR Score at Minute 5					
7	41 (95.3)	43 (100.0)	1.22	(0.78,2.01)	0.379
<7	2 (4.7)	0 (0.0)			
Meconium Passage	10 (23.3)	11 (25.6)	1.13	(0.42,3.07)	0.801
Abnormal CTG	7 (16.3)	5 (11.6)	0.67	(0.18,2.31)	0.535

***Negative Findings**: Neonatal Death*

Neonatal outcomes presented in Table 5 above shows there were no significant differences in early neonatal outcomes between the 2 groups (p value>0.05).

A large proportion of babies born of mothers in the expectant management arm were not admitted to the ICU (83.7 %). Birth asphyxia, Meconium Aspiration Syndrome and RDS accounted for 28.6 %, 14.3 % and 57.1 % of the reasons for neonatal ICU admission among babies of mothers in this group. Only one baby born of a mother in the repeat induction group was admitted to the neonatal ICU. Other early neonatal outcomes including Apgar score in 5 minutes, meconium passage, abnormal CTG, and birth weight were not significantly different (p value>0.05). There was no case of neonatal death reported in either of the groups.

9.0 DISCUSSION

The study evaluated 86 women (with singleton live fetus at 37 weeks and above gestation) who had failed primary induction of labor using vaginal Misoprostol at the Kenyatta National Hospital Labor ward unit over a period of seven months (February 2018 to August 2018).

We found that time from randomization to active labor and randomization to vaginal delivery interval were significantly different between the two groups. There are however no comparable studies done locally or globally. The onset of active labor was 7.81 hours shorter in the repeat induction group. Similarly, the randomization to vaginal delivery interval was 8.59 hours shorter compared to the expectant arm. Pretreatment with prostaglandins has been shown to increase the myometrial response to oxytocin significantly and decrease the latency period (89). Antonazzo et al reported that on vaginal dinoprostone (PGE2) versus intravenous oxytocin for repeat labor induction, the induction to onset of labor interval and labor induction to delivery interval were lower in the group treated with oxytocin (90). However, the primary outcome of interest in their study was the rate of vaginal delivery in 24 hours.

Beckmann et al compared women after primary treatment with PGE2 gel that were assigned into either amniotomy or repeat-PGE2 gel group. The time for IOL-to-delivery was >5h shorter in the amniotomy group (91). The primary outcome measure was time from start of induction until delivery. The results of this study apply to patients in which amniotomy is feasible but not to those who still have unfavorable cervix despite exposure to PGE2. In an observational study by Mohr Sasson et al, time to delivery from second PGE2 or Foley transcervical balloon did not differ significantly between the two groups (92). The primary outcome was mode of delivery in 24 hours.

Participants for repeat induction were at higher probability to need Oxytocin augmentation (53.5 % vs 30.2 %). Since prostaglandins have a close functional interaction with oxytocin, pretreatment with prostaglandins has been shown to increase the myometrial response to oxytocin significantly (89).

We observed that the failure rate was higher in the expectant management group. A retrospective study by Umoren et al reported that 12 women (63%) achieved active labor following insertion of the second PGE2 pessary in repeat induction, and 10 of these (83%) delivered vaginally (83). Of the methods of labor induction, evidence has shown that PGE2 and vaginal misoprostol are more effective in bringing about vaginal delivery within 24 hours (26)(40,41)(93). In contrast, Mohr-Sasson et al reported a relatively high failure rate using second dose of PGE2 vaginal insert compared to Foley transcervical balloon for IOL following primary failure of cervical ripening with PGE2 (74% vs 60%) (92). Beckmann et al (91) reported of fewer failure rate in the amniotomy group compared to the PGE2 (47.1% vs 67.7%). Antonazzo et al reported that the rate of vaginal deliveries was significantly higher in the second line treatment with PGE2 vaginal insert compared to oxytocin (55% vs 34.0%) (90).

There was no significant difference in the mode of delivery between the two groups in our study. Beckmann et al reported similar findings in their study comparing amniotomy with repeat prostaglandin gel (91). Petrovic Barbitch et al. (94) evaluated efficacy of cervical ripening with repeated administration of dinoprostone slow release vaginal pessary and reported that in more than half of the cases (53.1%), the cervical ripening by two slow release PGE2 was efficient and allowed a vaginal delivery. Antonazzo et al. (90) reported that the rate of vaginal deliveries was significantly higher in the second line treatment with PGE2 vaginal insert compared to oxytocin (55% versus 34.0%).

ACOG acknowledges that “allowing at least 12-18 hours of latent labor before diagnosing a failed induction may reduce the risk of caesarean delivery” (29). In women with spontaneous labor with a first stage more than 30 hours, 75% still proceeded to have vaginal deliveries (95). Therefore, surgical intervention simply based on the elapse of time during labor should not be advocated for.

We did not find significant differences in maternal outcomes between the 2 groups. This is in keeping with Beckmann et al findings that reported no difference in maternal outcomes when comparing amniotomy with repeat prostaglandin gel (91). A major concern with use of prostaglandins in combination with oxytocin is the risk of uterine hyperstimulation as both drugs carry a risk of this complication (26). In our study, there were 2 cases of uterine tachysystole in the repeat induction group which resolved with conservative management. Umoren et al reported of two cases of uterine hyperstimulation that resolved on removal of the PGE2 pessary (83). Antonazzo et al reported uterine tachysystole was observed in 4 (8.5%) patients treated with a double dose of dinoprostone and in 6 (12.8%) women treated with dinoprostone and oxytocin (90).

Mean blood loss was comparable between the two groups in our study. Beckmann et al reported of similar findings in their trial (91). In a study by Antonazzo et al, the mean blood loss was significantly higher in patients treated with oxytocin compared to women who received a second dose of PGE2 (90). Our mean duration of hospital stay was similar between the two groups (5 days) in keeping with similar findings by Beckmann et al (91). One study reported that a policy of administering more PGE2 when the Bishop score is poor was associated with increased health care costs compared with a policy of performing an amniotomy in repeat labor induction (96).

Of early neonatal outcomes, there were no significant differences observed between the 2 groups. Beckmann et al reported no significant differences regarding admission to neonatal

nursery between amniotomy versus repeat prostaglandin gel groups (91). Antonazzo et al observed no significant differences between PGE2 and oxytocin groups for neonatal weight, umbilical artery pH, umbilical artery base excess, meconium passage and 5-minute Apgar scores <7 (90). Cheng et al reported that longer labor than 30 hours in women with spontaneous labor was not associated with any adverse neonatal outcomes (95).

9.1 CONCLUSION

Repeat induction using vaginal misoprostol was superior to expectant management in achieving active phase of labor and could represent a safe therapeutic option in patients at >_37 weeks gestation with a low Bishop score not responsive to primary labor induction using vaginal PGE1. However, women who do not wish to undergo repeat labor induction, expectant management is a viable option provided that diligent fetal monitorisation is undertaken.

9.2 STUDY LIMITATIONS

1. This was an unblinded trial to the researchers and participants but the primary outcome measure was unambiguous, thereby minimizing the risk of ascertainment bias.

2. Assessment of cervical ripeness using Bishop score is subjective. However, it was performed by the same investigators across the study subjects to limit discrepancies.

3. The intention-to-treat analysis potentially weakens any observed treatment effect size because it does not measure the effect of treatment received.

9.3 STRENGTHS OF THIS STUDY

Our study has several strengths. The management of patients after primary failure is important, topical and poses a significant challenge to the caring physician as currently there is no consensus as to preferred methods of IOL after primary failure. The data concerning further management in this population are lacking. To the best of our knowledge, this is the first randomized controlled trial in the literature to determine the efficacy of repeat induction using vaginal Misoprostol versus expectant management to compare second line treatment after failure of primary labor induction using vaginal PGE1. Personalization of treatment, i.e. consideration of clinical specifics of the patient, the pros and cons of each intervention, as well as clinical and other considerations and the incorporation of patient preferences into the decision-making process are required to ensure an expedited delivery with a favorable outcome.

9.4 RECOMMENDATIONS

1. Consider change of policy with regard to definition and management of failed primary labor induction at the hospital. This should factor in the following:

a) Creation of institution specific protocol and adherence to the same so as to streamline management of this group of women as this has been arbitrarily done across board by the different specialists.

b) Review criteria of failed labor induction. Since the purpose of IOL is to cause a non- laboring woman to go into labor, a reasonable definition would be to achieve active labor as a measure of success.

2. Repeat induction of labor shortens onset of active labor and induction- delivery interval.

3. Diligent monitorisation is required in case expectant management is opted for.

4. Future studies should explore health care costs that are associated with IOL protocols and women's experiences and preferences in cases of failed primary labor induction.

5. A larger multi-center study will follow, in order to add power to this data.

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11.0 APPENDICES

APPENDIX 1: QUESTIONNAIRE

Number……

Date of admission…….time (am/pm)…….

A. SOCIO-DEMOGRAPHIC AND OBSTETRIC DATA:

Socio-demographic characteristics

1. Age……

2. Marital status (a) single [ ] (c) divorced/separated [ ]

(b) married [ ] (d) widowed [ ]

3. Education level attained (a) no formal education [ ] (b) primary [ ]

(c) secondary [ ] (d) college / university[ ]

4. Occupation (a) student [ ] (b) unemployed [ ]

(c) formal employment [ ] (d) self-employed [ ]

(e) casual worker [ ]

Obstetric History

1. Gravidity..... Parity.....

2. LMP……..EDD……Gestational age in completed

weeks……Gestation by u/s……..

3. Diagnosis (Indication for induction)……

B. PRIMARY INDUCTION

I) Induction Data

1. Pre-induction Bishop score…....

2. Prostaglandin used.....

Time of 1st dose (am/pm).....2nd dose……..3rd dose……

 Total number of doses administered……. …….

3. Was oxytocin used for augmentation.....a) yes b) no

If yes..... a) Dosage used.....b) Rate of infusion……c) Total volume of fluid

infused……..

4. Time in latent phase of labor.....

5. Active phase of labor achieved……..a) yes b) no

6. Time in active labor……. Induction to active labor (hours)…….

7. Time in second stage of labor…….... Induction to second stage (hrs)……..

8. Time of delivery……. Induction to delivery time…….

II). Induction success

1. Induction to active phase of labor.....

2. Induction to delivery interval.....

3. Mode of delivery (a) spontaneous vaginal [ ]

(b) operative vaginal [ ]

(c) caesarean section [ ]

4. Indication for Caesarean section

(a) failed induction [ ] (b) non-reassuring fetal status [ ]

(c) CPD [ ] (d) other (specify)……..……

5. Degree of urgency of caesarean delivery a) category 1[ ] b) category 2 [ ]

c) category 3 [ ] d) category 4[ ]

III). Maternal outcomes

1. Tachysystole (5 or more contractions in 10 minutes) experienced (a) yes [ ] (b) no [ ]

2. Hypertonus (a contraction lasting at least 2 minutes) experienced (a) yes [ ] (b) no [ ]

3. Hyperstimulation (tachysystole or hypertonus resulting in fetal heart changes necessitating intervention) experienced (a) yes [ ] (b) (no) [ ]

4. Other side effects experienced (a) vomiting [ ] (b) diarrhea [ ]

(c) shivering [ ] (d) fever [ ]

(e) other (specify) (f) none [ ]

5. Postpartum haemorrhage (a) uterine rupture (b) uterine atony [ ]

(c) tears (cervical/vaginal/perineal) (d) retained placenta [ ]

(e) other (specify) (f) none [ ]

6. Estimated blood loss ……..

7. Duration of hospital stay ……..

8. Final maternal outcome (a) delivery without complications [ ]

(b) delivery with complications [ ]

(c) maternal death [ ] Cause of maternal death……..

IV) Early Neonatal Outcomes

1. Fetal heart-rate abnormality requiring treatment (a) yes [ ] (b) no [ ]

2. Meconium passed (a) yes [ ] What grade (I, II, or III)…….....

(b) no [ ]

3. Birth weight (grams)……

4. Apgar score in 1 minute……..5minutes……..... 10 minutes……

5. Admitted to NBU (a) yes [ ] (b) no [ ]

6. Reason for NBU admission (a) birth asphyxia [ ]

(b) meconium aspiration syndrome [ ]

(c) other……

7. Final Fetal outcome (a) live birth [ ]

(b) fresh stillbirth [ ]

 Cause of stillbirth (i) non reassuring fetal status [ ]

(ii) uterine rupture[ ]

(iii) other…….

V) Final Results

Was induction successful.....1) Yes 2) No

If unsuccessful, give reasons and the intervention taken.....

C. FAILED INDUCTION

I) Intervention Data

1. Study arm a) Repeat induction b) Expectant management

2. Bishop score at randomization…....

3. Prostaglandin used.....

Time of 1st dose (am/pm).....2nd dose……..3rd dose……

 Total number of doses administered……. …….

4. Was oxytocin used for augmentation.....a) yes b) no

If yes..... a) Dosage used.....b) Rate of infusion……c) Total volume of fluid infused……..

5. Time in latent phase of labor.....

6. Active phase of labor achieved……..a) yes b) no

7. Time in active labor……. Randomization to active labor (hours)…….

8. Time in second stage of labor…….... Randomization to second stage (hrs)……

9. Time of delivery……. Randomization to delivery time…….

II). Induction success (for repeat arm only)

1. Induction to active phase of labor.....

2. Induction to delivery interval.....

3. Mode of delivery (a) spontaneous vaginal [ ]

(b) operative vaginal [ ]

(c) caesarean section [ ]

4. Indication for Caesarean section

(a) failed induction [ ] (b) non-reassuring fetal status [ ]

(c) CPD [ ] (d) other (specify)……..……

5. Degree of urgency of caesarean delivery a) category 1 [ ] b) category 2 [ ]

c) category 3 [ ] d) category 4 [ ]

III). Maternal outcomes

1. Tachysystole (5 or more contractions in 10 minutes) experienced (a) yes [ ] (b) no [ ]

2. Hypertonus (a contraction lasting at least 2 minutes) experienced (a) yes [ ] (b) no [ ]

3. Hyperstimulation (tachysystole or hypertonus resulting in fetal heart changes necessitating intervention) experienced (a) yes [ ] (b) (no) [ ]

4. Other side effects experienced (a) vomiting [ ] (b) diarrhea [ ]

(c) shivering [ ] (d) fever [ ]

(e) other (specify) (f) none [ ]

5. Postpartum haemorrhage (a) uterine rupture (b) uterine atony [ ]

(c) tears (cervical/vaginal/perineal) (d) retained placenta [ ]

(e) other (specify) (f) none [ ]

6. Estimated blood loss ……..

7. Duration of hospital stay …….

8. Final maternal outcome (a) delivery without complications [ ]

(b) delivery with complications [ ]

(c) maternal death [ ] Cause of maternal death……..

IV) Early Neonatal Outcomes

1. Fetal heart-rate abnormality requiring treatment (a) yes [ ] (b) no [ ]

2. Meconium passed (a) yes [ ] What grade (I, II, or III)…….....

(b) no [ ]

3. Birth weight (grams)……

4. Apgar score in 1 minute……..5minutes……..... 10 minutes……

5. Admitted to NBU (a) yes [ ] (b) no [ ]

6. Reason for NBU admission (a) birth asphyxia [ ]

(b) meconium aspiration syndrome [ ]

(c) other……

7. Final Fetal outcome (a) live birth [ ]

(b) fresh stillbirth [ ]

 Cause of stillbirth (i) non reassuring fetal status [ ]

(ii) uterine rupture[ ]

(iii) other…….

V) Final Results

Was intervention successful.....1) Yes 2) No

If unsuccessful, give reasons and the action taken.....

APPENDIX 2: BISHOP SCORING

	Score			
Factor	0	1	2	3
Dilatation (cms)	0	1-2	3-4	5-6
Length (cms)	3	2	1	0
Station (-3 to 3)	-3	-2	-1 or 0	+1 or +2
Consistency	Firm	medium	Soft	
Position	Posterior	middle	anterior	

APPENDIX 3: CLASSIFICATION OF URGENCY OF CAESAREAN SECTION

Figure 1. A classification relating the degree of urgency to the presence or absence of maternal or fetal compromise

Urgency	Definition	Category
Maternal or fetal compromise	Immediate threat to life of woman or fetus	1
	No immediate threat to life of woman or fetus	2
	Requires early delivery	3
No maternal or fetal compromise	At a time to suit the woman and maternity services	4

APPENDIX 4: STUDY PARTICIPATION CONSENT FORM

This is an informed consent form for pregnant women in labor and antenatal wards in KNH who we are inviting to participate in the research.

Title of Study: Repeat induction versus expectant management after failed primary labor induction at term at Kenyatta National Hospital : a randomized clinical trial.

Name of the Principal Investigator: Dr. Subaha Mohamed, University of Nairobi, Dept of Obstetrics and Gynaecology, Registration no. H58/75511/2014, Contacts: mobile number 0720255153, email address: sabahhania@gmail.com

Introduction:

I am Dr. Subaha Mohamed, a Masters in Medicine student at the University of Nairobi doing a research on labor induction in part fulfillment of my Masters degree. I am going to give you information and invite you to be part of the research after which you'll ask any question and seek clarifications. The information is to help you know about the study so that you can make an informed decision to participate or not. The research will involve a total of 344 participants chosen randomly. You will be given ample time to make a decision on whether to participate or not and any questions you may have later on, during the research, can be directed to me or the research assistant in the ward.

Purpose of the study

Induction of labor is a method used in the hospital to assist pregnant women initiate labor before the natural labor starts so as to avert fetal demise and a drug called Misoprostol has been used for

this purpose for several decades. However, labor induction may sometimes fail and the mother is required to have a repeat induction which has its associated complications.

The research I am undertaking is to compare repeat labor induction versus expectant management to find out which method is better in terms of delivery outcomes to both the mother and the baby in case the initial induction process fails. The information obtained from this study will help us improve the management of women undergoing induction of labor at our facilities.

Participant right in this study

Your participation in the research is entirely voluntary and you will not be victimized in case you opt out prior to and in between the study duration. You do not have to offer reasons for withdrawing from the study to the researchers. You will be offered full services availed to others as well.

Procedure

If you agree to participate, you will be in a pool of participants who will be divided into two groups. The groups are selected by chance as one would by flipping a coin. Initially, labor induction will be instituted with vaginal misoprostol every 4 hours up to a maximum of 3 doses. You will be monitored for established labor during this period by the symptoms you will relay to us and by physical examination- abdominal and vaginal. Once in labor, monitoring will be done as per standard protocol until delivery. In case of any adverse reaction, the standard protocol will be followed. If you have not gone into active labor by the 3rd dose of misoprostol, you will then be assigned to either expectant management or repeat labor induction. Participants to undergo expectant management will be taken to operating theatre after 48 hours resting period if they have not gone into labor by then. Those for repeat induction will be allowed to rest for 24hrs before the induction process is reinstituted with the same drug. During this period, you will be accommodated in the labor ward where you will be monitored on a daily basis.

After lapse of 24hrs, induction will be repeated again. If you will not have gone into active labor by the 3rd dose of misoprostol during this second round, you will then be taken for caesarean delivery. The research will take approximately 6 months but for each participant we will monitor you from the time of initiating labor induction up to when you will be discharged from the hospital.

Risks and Side effects associated with this study

The drug used may have the rare side effects of a gastrointestinal nature-nausea and or diarrhoea. In case of this, nausea will be treated by using nosic while the diarrhoea will be treated using loperamide. Induction of labor helps to avert adverse effects associated with prolonged pregnancy such as fetal demise. However, the process is not without risks. This study will take into consideration and look out for the following risks: uterine contractile abnormalities, chorioamnionitis, uterine rupture among others. In case any of the above occurs, the standard protocol of management for the individual complication will be instituted immediately.

Benefits and compensations in this study

There will be no reimbursement for participating in this study. Similarly, being in this trial will cost you nothing as delivery is free. The research may enable us to change labor induction policies at KNH and contribute to policy formulation in reproductive health that may be beneficial to pregnant women in future.

Confidentiality

The information that will be collected will be kept confidential. No personal identifying details of yours will be revealed. However, the researchers, the Independent Review Board and the Ethics Review Committee may have access to the information.

We intend to publish the results in order to add knowledge to healthcare professionals, however, confidential information will not be shared.

Who to contact regarding this study

If you have more questions later about the study, you can ask the investigator on 0720255153 at any time. In the unlikely event that I am unreachable, you can contact the midwife or the doctor attending to you. If you have any questions on your rights as a research participant, you may contact the Secretary Prof. M.L.Chindia, KNH-UoN Ethics& Research Committee on Telephone No 02 726 300 Ext. 44102 email uonknh_erc@uonbi/ac.ke. You will be reimbursed for the call charges by the study staff if it is related to the study.

Consent to participate in the study:

I, the undersigned, have read the foregoing information and voluntarily consent to this study. I am aware of the process of labor induction and the procedures involved as explained to me. I am also aware of the available options, the benefits and risks associated with this process. I have asked questions which have been answered to my satisfaction and have been assured of confidentiality and freedom to withdraw at will and at any stage of the study without any victimization. I will receive a copy of this consent form.

Participant signature (or thumb print)..... Date.....

Participant name ….....

Witness name (if witness is necessary)…….. Date.....

Witness signature (or thumb print).....

Researcher's statement

I, the undersigned, have fully explained the relevant details of this trial to the above signed participant and believe that she has fully understood and knowingly given her informed consent without any form of coercion.

Researcher name…… Date……..

Researcher signature……..

Role in the study……

APPENDIX 5: SERIOUS ADVERSE EFFECT (S.A.E.) REPORT FORM

TIME FRAME FOR ADVERSE EVENT REPORTING: **48 HOURS**

1) DATE EVENT OCCURRED:__ __/__ __/__ __

2) STOP DATE OF SAE (Duration of SAE):__ __/__ __/__ __

3) Was this an unexpected adverse event?

A) Yes B) No

4) On which arm of the study did it occur?

A) Repeat induction B) Expectant management

5) Brief description of the participant:

Serial number:

Age:

Parity:

Vitals:

6) Brief description of the nature of the SAE:……

7) Category of the SAE:

A) Death

B) Life threatening/ Near miss

C) Required intervention

D) Other

8) Type of intervention

A) Medical

B) Surgical

9) Relationship of event to study

A) Unrelated

B) Possible

C) Definite

10) Was study discontinued due to event?

A) Yes B) No

11) How was this SAE managed? Explain in detail.

_____

_____

_____

_____

_____

12) Relevant medical/ obstetric/ surgical history of participant:

_____

_____

_____

_____

SIGNATURE OF PRINCIPAL INVESTIGATOR ……

DATE:__ __/__ __/__ _

APPENDIX 6: DATA SAFETY AND MONITORING BOARD MEMBERS (DSMB) DETAILS

1.	Dr. Samuel Wachira: Consultant Obstetrician Gynaecologist, Mbagathi Hospital	Chairperson
2.	Dr. Caroline Asin: Program Officer/ Clinical Pharmacist, NASCOP	Member
3.	Dr. David Gathara: Clinical Epidemiologist, KEMRI	Member
4.	Dr. Frankline Onchiri : Supervisor Biostatistician, Seattle Children's Research Institute	Member