TITLE: MISOPROSTOL ADMINISTRATION FOR THE MANAGEMENT OF RETAINED PLACENTA

PURPOSE: PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE IN OBSTETRICS AND GYNAECOLOGY, UNIVERSITY OF NAIROBI

RESEARCHER:

DR. BENSON N. WAWERU, MB.Ch.B
POSTGRADUATE STUDENT,
DEPT. OF OBSTETRICS AND GYNAECOLOGY
UNIVERSITY OF NAIROBI

SUPERVISORS:

1. PROF. JOSEPH G. KARANJA, MB Ch.B, MMED OBS/GYN (UON).
   ASSOCIATE PROFESSOR,
   DEPT. OF OBSTETRICS AND GYNAECOLOGY,
   UNIVERSITY OF NAIROBI.

2. DR. JOHN KINUTHIA, MBCh.B., MMED OBS/GYN (UON), MPH.
   HONORARY LECTURER,
   DEPT. OF OBSTETRICS AND GYNAECOLOGY
   UNIVERSITY OF NAIROBI.

DECLARATION

This is to declare that this research is my original work and that it was done with the guidance of my supervisors.

DR. BENSON N. WAWERU, MB.Ch.B
POSTGRADUATE STUDENT,
DEPT. OF OBSTETRICS AND GYNAECOLOGY
UNIVERSITY OF NAIROBI

Signature ……. Date ……..

CERTIFICATE OF SUPERVISION

This is to certify that this research was carried out by Dr. Benson N. Waweru under my guidance and it has been submitted with my approval.

1. PROF. JOSEPH G. KARANJA, MB Ch.B, MMED OBS/GYN (UON).
   ASSOCIATE PROFESSOR,
   DEPT. OF OBSTETRICS AND GYNAECOLOGY,
   UNIVERSITY OF NAIROBI.

   Signature …….. Date …….

2. DR. JOHN KINUTHIA, MBCh.B., MMED OBS/GYN (UON), MPH
   HONORARY LECTURER,
   DEPT. OF OBSTETRICS AND GYNAECOLOGY
   UNIVERSITY OF NAIROBI.

   Signature …….. Date …….

CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the original work of Dr. Benson Ndegwa Waweru, Reg. No. H58/71406/2007, a student of Master of Medicine in the Department of Obstetrics and Gynaecology, University of Nairobi (2007-2011). The research was carried out in the Department of Obstetrics and Gynaecology, School of Medicine, College of Health Sciences. It has not been presented in any other University for award of a degree.

Signature.....

Date.....

Prof. Koigi Kamau,
Associate Professor of Obstetrics and Gynaecology
Senior Consultant in Obstetrics and Gynaecology,
Chairman, Department of Obstetrics and Gynaecology
University of Nairobi

ACKNOWLEDGEMENT

I thank God for the provision of this invaluable chance to carry out this research in pursuit of better services to the sick. My sincere gratitude to my supervisors Prof. J. G. Karanja and Dr. J. Kinuthia for their relentless guidance and encouragement. Special thanks to Drs. Z. Qureshi and W. Khisa for their meticulous review and fine-tuning of my thesis.

Finally, I am humbled by all the patients who took part in this research for unconditionally offering themselves and trusting the research team for the sake of others. May God reward them abundantly!

DEDICATION

I dedicate this work to all the mothers who have lost the fight against postpartum hemorrhage particularly due to retained placenta.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AMTSL – Active Management of Third Stage of Labor

BP – Blood Pressure

CCT - Controlled Cord Traction

EmOC – Emergency Obstetric Care

GXM – Grouping and Cross Match

HB - Hemoglobin

FIGO - International Federation of Gynecology and Obstetrics

G/dl – Grams per deciliter

Hrs - Hours

IU – International Units.

IV – Intravenous

KSPA – Kenya Service Provision Assessment

LMP – Last Menstrual Period

MRP – Manual Removal of Placenta

Mcg – Micrograms

Mls - Milliliters

PPH - Postpartum Hemorrhage

PMH – Pumwani Maternity Hospital

PR – Pulse Rate

RCT – Randomized Clinical Trial

RP – Retained Placenta

SPSS – statistical Package for Social Sciences

USA – United states of America

UVI – Umbilical Vein Injection

WHO – World Health Organization

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Postpartum hemorrhage due to retained placenta remains a major cause of maternal morbidity and mortality in the developing countries. Manual removal of retained placenta is an element of basic EmOC but currently, only 46% of health facilities offering delivery services in Kenya provide this procedure. Therefore, an affordable medical solution which is applicable even in the basic health settings is seriously needed.

Objectives: To describe the effect of sublingual misoprostol in the management of retained placenta and associated adverse effects.

Methods: This was a cross sectional survey carried out in Pumwani Maternity Hospital involving 50 mothers with retained placenta, and no PPH, recruited through consecutive sampling, from Jan to April 2011. Misoprostol, 600mcg sublingual was administered at enrollment and manual removal was performed if the placenta was not delivered within 30 minutes. Data was collected using an interviewer administered structured questionnaire and was analyzed using SPSS computer package.

Results: 84% of the mothers delivered the placenta within 30 minutes. A further 6% delivered the placenta within the next 10 minutes as they awaited manual removal. A history of previous uterine surgery negatively impacted on the outcome. 14% of the mothers reported no side effects, while 60% reported transient chills. Other reported side effects included nausea (14%), abdominal cramps (10%) and vomiting (4%).

Conclusion: Sublingual misoprostol 600mcg was effective in reducing the need for manual removal of placenta and its transient side effects were well tolerated

Recommendations: Misoprostol should be registered and included in the clinical guidelines for the management of retained placenta. However, further research preferably a large RCT is recommended.

INTRODUCTION

Retained Placenta is diagnosed when part or whole of the placenta is retained, usually after 30 minutes, following delivery of the infant. It leads to maternal morbidity and mortality mainly through postpartum hemorrhage (PPH) and puerperal sepsis.

The current management of retained placenta is manual removal under sedation and aseptic environment. If this fails, a well equipped theatre and highly trained personnel will be required for adequate intervention. This is a difficult situation to replicate in remote areas where lack of facilities and expertise is common. In such situations, the retained placenta is usually evacuated in the ward. Besides increased risk of puerperal sepsis and PPH, evacuation in the ward exposes the patient to psychological and physical trauma, including the risk of uterine perforation. Introduction of active management of the third stage of labour has significantly reduced the incidence of retained placenta but an ideal substitute for manual removal has not been found.

Misoprostol, a drug initially introduced for the management of peptic ulcers, has gained great popularity as an abortificient and as a drug for the management of PPH due to its cervical priming and powerful uterotonic effects. The later effect is expected to cause separation and expulsion of a retained placenta. Misoprostol has a wide safety margin, its readily available, is affordable and easy to administer. It would therefore be an ideal drug in the medical management of retained placenta.

LITERATURE REVIEW

Delivery of the placenta is usually a very rapid event after vaginal delivery of the neonate. In an investigation by Dombrowski, [1] 50% of the placental deliveries occurred within 5 minutes, and 90% had been delivered by 15 minutes. Another large investigation confirmed the rapid delivery of the placenta, with a mean of 9 minutes.[2] A third stage of labor longer that 18 minutes is associated with a significant risk of postpartum hemorrhage. After 30 minutes the odds of having postpartum hemorrhage are 6 times higher than before 30 minutes.[3] Therefore, retained placenta is usually diagnosed after 30 minutes following delivery of the infant. Based on this cut-off point, the incidence of retained placenta has been reported as 3.3% in singleton pregnancies in a study conducted in California, USA, involving more than 12000 births.[4] However, the local incidence of retained placenta is not known.

Causes of retained placenta include unrecognized succenturiate placenta, morbidly adherent placenta (e.g. placenta accreta, increta and percreta) and mismanagement of third stage of labor.Atonic uterus, preterm labour, augmented labour, previous vigorous curettage, previous caesarean or other uterine surgery and underlying myomas all predispose to retained placenta.[5]
High parity and advanced maternal age especially above 35 yrs have been associated with increased incidence of retained placenta.[6] However, social economic status does not seem to influence the incidence of retained placenta.[7]

Complications of retained placenta have been found to steeply increase after the half-hour mark.[2,4] These are mainly PPH and puerperal sepsis both of which make the list of top five causes of maternal mortality in the developing countries. It contributes approximately 5- 10% of PPH. [5] It is estimated that 52% of all pregnant women in the developing countries are anemic and hence the need for aggressive prevention of PPH**.**[8] A WHO review of trials of active versus expectant management in third stage of labor showed that AMTSL significantly

reduced the risk of PPH (RR 0.38; 95% CI 0.32–0.46) and also reduced the duration of third stage of labor (WMD -9.77 minutes, 95% CI -10.00 to -9.53).[9]

The current management of retained placenta is manual removal of the placenta (MRP). Divergent views exist on the diagnosis and subsequently the timing of manual removal of the retained placenta. In the absence of bleeding, intrapartum guidelines produced for the National Institute for Health and Clinical Excellence (NICE) suggest intervention when the placenta has been retained for 30 minutes after birth despite AMTSL, but at 60 minutes when the third stage has been managed physiologically.[10] This is based on data from trials of active versus expectant management of third stage which have shown that it takes 30 minutes with AMTSL to retain the same number of placenta as in 60 minutes of expectant management**.**[11]

On the other hand, the WHO manual for childbirth[12] suggests waiting for 60 minutes before intervention in the absence of bleeding because of the finding that between 30 and 60 minutes, a further 40% of placentas will spontaneously deliver though with a loss of an average of 300mls f blood.[13] According to this manual, in the first 30 minutes, AMSTL is done and in the next 30 minutes, the bladder is emptied, CCT continued coupled with breast feeding after which MRP is performed. In a randomized trial of management of retained placenta that recruited women after 60 minutes of the third stage had elapsed, the spontaneous delivery rate over the subsequent 30 minutes in the nonintervention (control) group was 0 percent **[14]**

In Kenya, AMTSL is performed. This involves administration of IM oxytocin 10 IU within 1 minute of delivery of the infant followed by clamping and controlled cord traction timed to correspond with uterine contractions while applying counter-pressure on the uterus. Delivery of the placenta is followed by uterine massage to prevent atony. [15] MRP is subsequently prescribed at the expiry of 30 minutes or in event of hemorrhage. Unfortunately, according KSPA 2010**,** [16] only 46% of

the health facilities offering delivery services in Kenya are currently able to perform MRP. Some experts advice a trial of 20 to 40 IU of oxytocin in normal saline as an IV infusion but a WHO consultation found no empirical evidence in support of this practice in the absence of hemorrhage.[17]

Medical treatment is still elusive and contradicting results from the available research have not helped the situation. For instance, in a cochrane review of 15 trials (1704 women), umbilical vein injection (UVI) of oxytocin compared with saline showed a reduction in MRP but this was not statistically significant (RR 0.91; 95% CI 0.82 to 1.00). On the other hand, prostaglandin solution compared with saline solution alone was associated with a statistically significant lower incidence in manual removal of placenta (RR 0.42; 95% CI 0.22 to 0.82) though this was from two small trials. The authors concluded that UVI of oxytocin may be performed while placental delivery is awaited. [18]

In a related study, 577 women were randomly assigned to 30 mL saline containing either 50 IU oxytocin (n=292) or 5 mL water (n=285) which was injected into the placenta through an umbilical vein catheter. There was no difference between the groups in the need for manual removal of placenta (oxytocin 179/292 [61·3%] versus placebo 177/285 [62·1%]; relative risk 0·98, 95% CI 0·87—1·12; p=0·84). Therefore, oxytocin delivered to the retained placenta via the umbilical vein had no significant contribution in negating the need of MRP. [19] However, siting lack of adequate evidence, WHO weakly recommends the use of intraumbilical vein oxytocin and saline in retained placenta but with a warning against the likelihood of delaying the administration of other effective interventions such as MRP

A double-blinded sequential randomized controlled trial of sulprostone versus placebo was conducted among 103 patients with retained placenta by van Beekhuizen HJ, et al.(2005).[20] In the first phase of this sequential study, Intravenous sulprostone was compared with placebo. The null hypothesis of

equal effectiveness of both treatments was rejected after 50 patients. In patients with retained placenta, the placenta was expelled after sulprostone in 13 of 24 cases (51.8%, bias adjusted), whereas expulsion after placebo was achieved in only 4 of 26 cases (17.6%, bias adjusted). The difference was significant (P = 034). In the second phase of the study, in which the placebo arm was stopped, results were confirmed; in 25 of 53 patients (47%), the placenta was expelled. It was concluded that sulprostone reduces the need for the manual removal of the placenta by 49%. However, sulprostone is an expensive drug hence unsuitable in resource poor set up.

Bider D. et. Al, [14] compared the effect of intraumbilical prostaglandin F2 alpha and oxytocin injection in retained placenta in a randomized protocol. Prostaglandin F2 alpha, 20 mg diluted to 20 ml in normal saline solution (10 women, group 1), 30 IU of oxytocin, diluted to 20 ml in normal saline solution (11 women, group 2), or 20 ml of normal saline solution alone (7 women, group 3), were injected into the umbilical vein 1 h after delivery. Nine women (group 4, controls) underwent manual removal of the retained placenta.

In group 1, placental expulsion occurred in all patients and the duration of the placental expulsion after prostaglandin F2 alpha injection was 6.8 +/- 1.36 (mean +/- SE) min: in group 2, six placental expulsions occurred after 13.3 +/- 1.97 min (mean +/- SE); and in group 3, no effect was recorded after intraumbilical saline injection. This showed that UVI of prostaglandin F2 alpha might be beneficial in treating retained placenta while oxytocin might achieve partial success. However, a larger study is needed to corroborate these findings besides the fact that prostaglandin F2 alpha is also expensive and UVI requires considerable expertise.

The role of tocolysis has also been studied in the pursuit of a suitable treatment for retained placenta. In a study involving 24 women, sublingual nitroglycerin was compared against a placebo after treatment with oxytocin failed. [21] There was a

statistically significant reduction in the need for manual removal of placenta (risk ratio (RR) 0.04, 95% confidence interval (CI) 0.00 to 0.66). There was also a statistically significant reduction in mean blood loss during the third stage of labour (mean difference (MD) -262.50 ml, 95% CI -364.95 to -160.05). It was cocluded that sublingual nitroglycerin, given when oxytocin fails, seems to reduce both the need for manual removal of placenta and blood loss during the third stage of labour. However its routine use cannot be recommended based on a single small study.

Chedraui and Insuasti [22] studied the use of IV nitroglycerin as an aid for delivering retained placenta in 30 patients using a dose of 50 – 200 mcg. All the retained placentas were extracted within 5.3 +/- 1.1 minutes of drug administration. However, there was a significant fall in systolic and diastolic blood pressure from 111 +/- 7.5 to 103 +/- 6 mm Hg and from 74 +/- 6.7 to 67 +/- 6.6 mm Hg, respectively ($p<0.05$). Although statistically significant, this was not evident clinically and there were no complications. They concluded that IV nitroglycerin at a dose of 200mcg or less is safe, effective and predictable and could negate the need for general anesthesia. Again, this was a small study and the risk of hypotension amongst patients already at risk of PPH works against IV nitroglycerin

Misoprostol, a synthetic prostaglandin E1 analogue which was initially developed for the treatment of peptic ulcers, has been extensively used in obstetric and gynecology practice due to its potent uterotonic and cervical priming effects. It can be given orally, sublingually, buccally, rectally and vaginally. [23] Its clinical application include medical abortion, cervical priming before surgical procedures, induction of labor and management of PPH.

In Kenya, misoprostol is licensed for use in incomplete abortion, termination of pregnancy, induction of labor, prevention and treatment of PPH and also for the management of peptic ulcer disease. However, its not licensed for the treatment

of retained placenta.[24,25] Its ability to cause strong and sustained uterine contractions is the mode of action in PPH management and the same is expected to cause separation and expulsion of a retained placenta. In comparison to other prostaglandin analogues, it has the advantage of being cheap, widely available, stable at room temperature and has fewer side effects. [23] These make it an ideal drug for use in the developing world.

When misoprostol is used to treat PPH, hyperpyrexia (fever >40°C) has been reported in several cases following 1000mcg delivered orally, sublingually or rectally.[26] Hyperpyrexia has also been reported following 800mcg orally or sublingually.[27] When used at a dose of 600mcg orally, 0.1% women experienced hyperpyrexia.[28] Those experiencing hyperpyrexia can be offered paracetamol and physical cooling. Chills, a common but a transient side effect, were reported in 32% - 57% of women receiving misoprostol. [28-31]Nausea and vomiting may occur and will resolve within 2 to 6 hours of taking misoprostol and no action is needed except reassurance. Diarrhea may also occur and usually resolves within a day with no treatment required. Abdominal cramps are also a transient side effect and can be treated with paracetamol. [26]

According to WHO and FIGO, in the absence of AMTSL, the recommended dose of misoprostol for the prevention and treatment of PPH is 600mcg orally or sublingually at once.[17, 32] Both routes have the fastest onset of action but sublingually, a higher peak of concentration is achieved because first-pass metabolism is side stepped.[23]The same dose, administered sub-lingual, is expected to be adequate and safe in the management of retained placenta given that the targeted mode of action is similar in both conditions.

In the only published study, Li YT et al.[33] administered 800mcg of misoprostol rectally to 18 parturients with retained placenta diagnosed 40 minutes after child birth; all the placentas were spontaneously expelled within 35 minutes. However, absorption of misoprostol per rectal is inconsistent and unpredictable despite

having a slower onset of action as compared to the sublingual route. These explains why the smaller dose will be used in this study with comparable results expected plus less side effects and lower cost of treatment.

In conclusion, retained placenta is an important factor as far as maternal morbidity and mortality is concerned. Its management through MRP is notably challenging especially in resource poor set-ups. Despite various studies, effective, affordable and feasible medical treatment is not yet defined. To that end, sublingual misoprostol in a dose of 600mcg was evaluated with positive results.

RESEARCH QUESTION

Can misoprostol be used for management of retained placenta as a safe and affordable alternative to manual removal of placenta?

JUSTIFICATION

Retained placenta is a significant cause of maternal morbidity and mortality through PPH and sepsis. This situation is aggravated by lack of personnel and adequate health facilities especially in rural areas to perform the age old procedure of MRP. Besides facing the risk of suboptimal management in event of retained placenta leading to severe PPH, 52% of all pregnant women in the developing countries are usually anaemic.[8] A combination of these factors greatly increases maternal morbidity and mortality.

A search for a medical alternative to MRP is still on and has resulted in multiple trials involving various drugs and different modes of administration with minimal gains. This includes UVI of oxytocin, oxytocin plus saline solution and prostaglandin F2 alpha.[14, 18, 19] IV sulprostone, [20] and sublingual nitroglyceride, [21] have also been tried but none of these have given a lasting solution. The highest success was noted with the use of misoprostol 800mcg administered per-rectal but this has also not been adopted as further evidence is required.[33]

This study tested the effectiveness of sublingual misoprostol, 600mcg, in averting the need for MRP with the aim of providing the elusive medical treatment for retained placenta. Sublingual misoprostol, which has not been tested before, has more consistent and faster absorption rate and attains a higher pick of concentration as compared to the rectal route hence the lower dose of 600mcg was used in this study. It is also easy to administer and compared to MRP, it is economical, safer and accessible. Besides, its associated side effects - nausea, vomiting, fever, chills, diarrhea and abdominal cramps - are usually transient and well tolerated.

STUDY OBJECTIVES

Broad Objective

Describe the effect of sublingual misoprostol in the management of retained placenta.

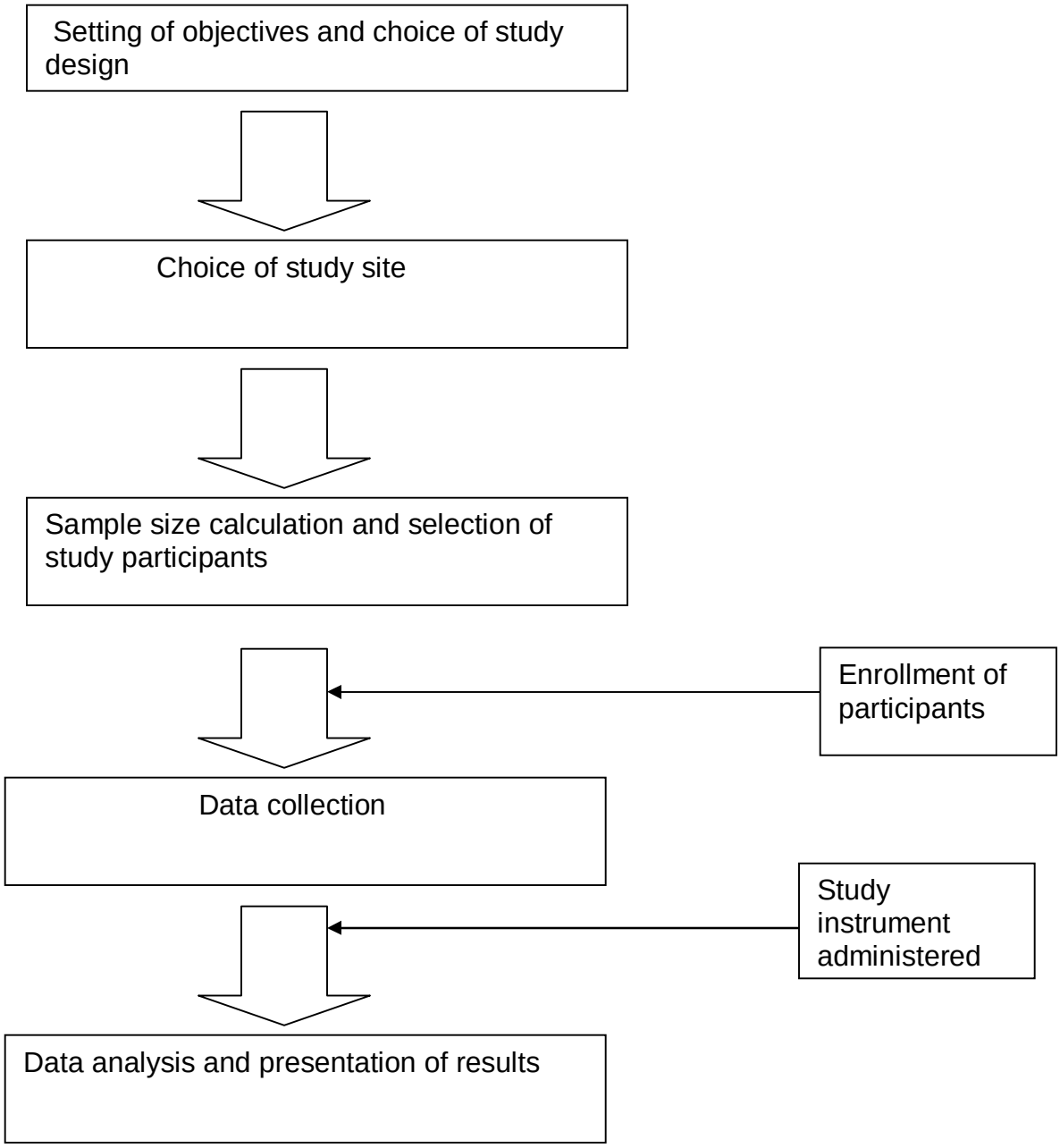
Specific objectives:

- Describe the success rate of misoprostol in the expulsion of retained placenta.

- Describe the time between administration of sublingual misoprostol and expulsion of retained placenta.

- Describe notable adverse effects to misoprostol

CONCEPTUAL FRAMEWORK



The study began with the recognition that retained placenta is a common obstetric emergency contributing significantly to maternal morbidity and mortality and a medical treatment is yet to be found. A research question was formulated to capture the effect of misoprostol on retained placenta. Objectives for the study were set and a crossectional study design chosen. Pumwani Maternity Hospital

was chosen as the study site due to the large volume of mothers that it handles. A suitable sample size was calculated and study participants enrolled.

METHODOLOGY

Study design

This was a hospital based cross-sectional survey, targeting mothers with retained placenta at Pumwani Maternity Hospital.

Study area

Pumwani Maternity Hospital is the largest maternity hospital in East and Central Africa. It is situated in Nairobi, Kenya about 3 kilometers to the east of the central business district. This hospital caters for maternity patients from Nairobi and its environs majority of them being of low social economic status.

The study site was chosen because it exclusively handles maternity cases. Approximately 27000 deliveries are conducted in the hospital annually, of which 90% are normal deliveries and hence a good chance of attaining the sample size within reasonable time. Its proximity to the Nairobi central business district makes it easily accessible to the research team. The hospital has a well equipped laboratory and blood bank and the labor ward is run by qualified doctors and midwives, therefore any complications arising from the study would be competently handled.

Study population.

This consisted of women with retained placenta, for at least 30 minutes after delivery of the infant despite active management of third stage of labor. The mothers must have attained a gestation of at least 28 weeks at the time of delivery, the age at which a pregnancy is considered viable in the country.

Inclusion criteria.

1) Consenting mothers with retained placenta 30 minutes after delivery of the infant.
2) Heamodynamically stable mothers: BP ≥ 90/60 and PR < 100/minute

3) No active vaginal bleeding
4) Antepartum hemoglobin of at least 11g/dl and above.
5) Gestational age of 28 weeks and above at delivery.
6) 18 yrs of age and above.

Exclusion criteria.

1) Clinically pale mothers
2) Mothers referred from other hospitals with retained placenta
3) Mothers with known allergy to misoprostol
4) Mothers who decline or are unable to give consent.

Pre-testing of the questionnaire

The questionnaire was administered, randomly, to ten per cent of the study population (10% of 50 = 5) by the researcher and trained research assistants after full explanation of the purpose of the study. Any issues regarding clarity, ambiguity and relevance of the questions were noted by the research team mainly through observation and the feedback from the test population. Subsequently, the researcher made relevant corrections and fine tuning of the questionnaire. However, the test population was not included in the main study

Data collection procedure

Study participants were recruited at PMH by the researcher or trained research assistants. A diagnosis of retained placenta was made 30 minutes after delivery and AMTSL. Screening of eligible mothers (those who met other criteria besides retained placenta) began 10 minutes before the diagnosis of retained placenta and the study aims and procedures clearly explained to them. This avoided time wastage between diagnosis and misoprostol administration. Upon diagnosis of retained placenta, those agreeing to participate were asked to promptly sign the consent form (appendix A). Sublingual misoprostol, 600mcg, was then administered. This was done by placing the tablets under the patients tongue and

any remnant after 30 minutes was swallowed.

All mothers with retained placenta had an I.V. cannula (gauge 18 or bigger) sited and blood sample taken for grouping and cross-match. A theatre list and consent for MRP were filled. For those who were participating in the study, the questionnaire (Appendix B) was then administered. They were then continually monitored for hemorrhage and signs of placenta separation for the next 30 minutes. CCT was not performed during this period. Those patients who expelled the placenta within this period were taken to recovery ward for the usual management of 4^{th} stage of labor. Those who failed to expel had a final CCT to confirm failure and MRP was performed immediately. The research team monitored for and managed any side effects to misoprostol for the next 24 hours. The following flow chart depicts the data collection procedure.

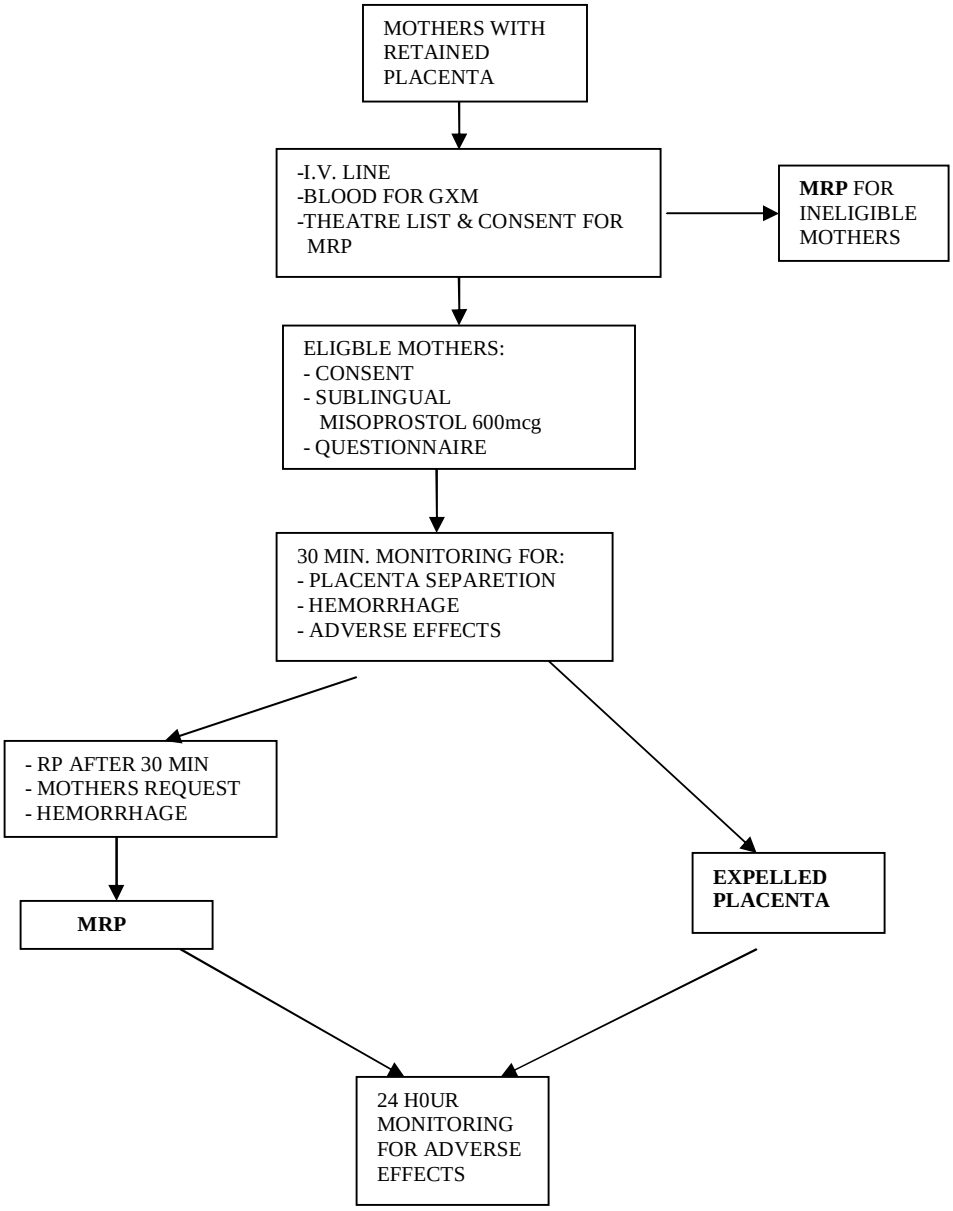


Figure 1: A flow chart of data collection procedure

Sampling

Consecutive sampling was used until the required sample size was attained. This was suitable for this study as it avoided bias and at the same time allowed the sample size to be attained within the time frame of the study.

Sample size

A sample size of 50 cases was obtained using the Cochran formula[34] as shown below

$$n = \frac{Z^2\, p(1-p)}{e^2}$$

where,

n, is the desired sample size

Z = 1.96, the corresponding confidence level for 95%

p = 0.033, the estimated value for the proportion of a sample that have the condition of interest.[4]

e = 0.05, the error margin of ± 5%

$$n = \frac{1.96 \times 1.96 \times 0.033 \times (1-0.033)}{0.05 \times 0.05} = 49.036$$

n = 50

Outcome measures

The following are the variables that were measured.

1. Time between administration of misoprostol and placenta delivery.
2. Number of mothers who deliver the retained placenta after receiving Misoprostol.
3. Adverse effects to misoprostol within the next 24 hours (immediate puerperium) .

Data collection instrument

A structured questionnaire was used covering the following areas:

1. Social demographic data.
2. Antenatal parameters
    - Previous uterine surgeries.
    - Parity.
    - Hb level.
    - Gestation at delivery
3. Pregnancy outcome:
    - Duration of labour
    - Number of infants born (single/multiple)
    - Estimated blood loss during delivery
4. Response to misoprostol
    - Time of misoprostol administration
    - Time of placenta delivery
    - Time when MRP was prescribed
    - Reason for prescribing MRP
    - Adverse effects to misoprostol if any

Quality control

The research assistants were trained in history taking, physical examination and phlebotomy. They were also trained in filling the questionnaire accurately during its pretest phase. Misoprostol tablets used were from the same manufacturer. They were stored in room temperature, below 30ºC, in a secure cupboard, under lock and key. The tablets were only accessible to the researcher and the research assistants.

Data Management and Analysis

Data forms were allocated unique serial numbers without any participant identifier information and safely stored by the investigator. Data was then entered into a password protected Microsoft Access Database and reviewed by the investigator for completeness. Data analysis was done using the Statistical Package for Social Sciences and presented in figures and tables.

Ethical Considerations

This was approved by the Ethics and Research Committee of Kenyatta National Hospital and that of Pumwani Maternity Hospital where the study was conducted. The purpose of the study was clearly explained to the eligible patients and informed consent sought before enrolment. Confidentiality of information was maintained at all levels with no identification of individual mothers during data collection analysis and presentation. Patients who declined to participate received standard care without discrimination

Misoprostol has been used in higher doses during the post partum period with no life threatening adverse effects and therefore the safety of the participants in this study plus that of their babies was assured.

Time frame

The study was carried out between Jan 2011 and April 2011.

Study limitations

About 40% of retained placentas might spontaneously deliver between 30 and 60 minutes albeit with some blood loss while in this study, all the placental deliveries between 30 and 60 minutes were attributed to misoprostol. Also, chills occurring naturally during third stage of labor could not be differentiated from those caused by misoprostol administration

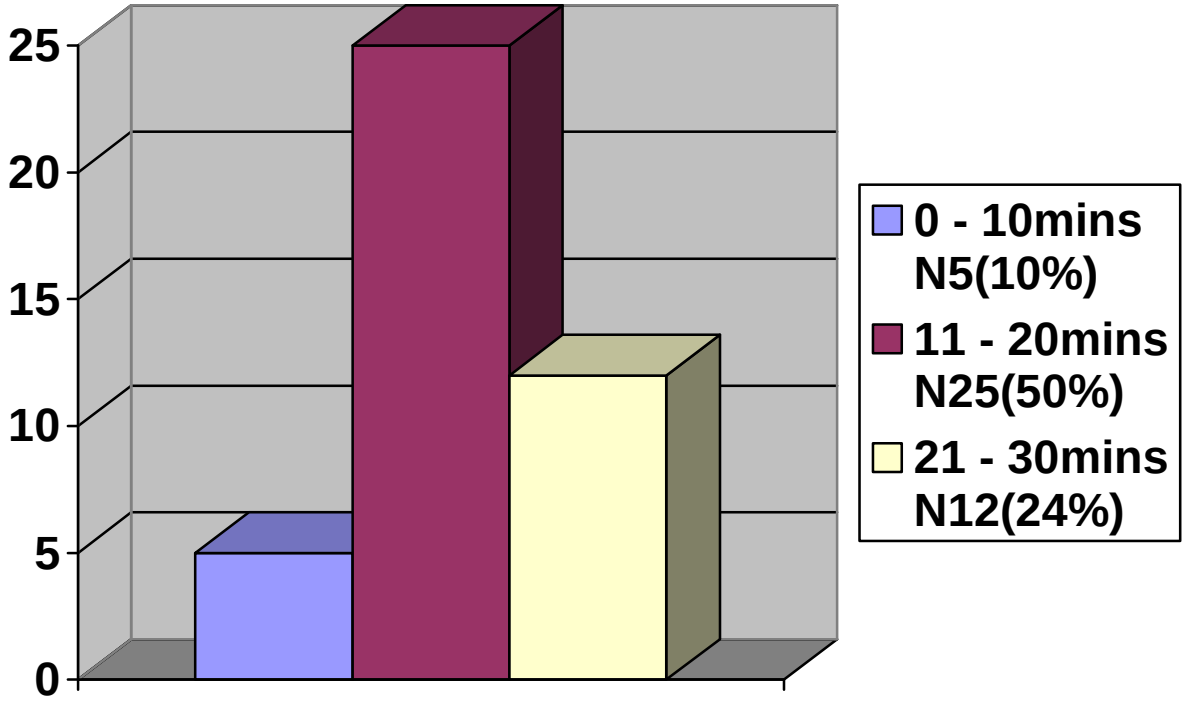
RESULTS

Table 1: Demographic and obstetric characteristics of the participants

Characteristic	Number	%
Age in years		
< 20	6	12.0%
20 - 29	28	56.0%
30 - 39	13	26.0%
≥ 40	3	6.0%
Marital Status		
Married	44	88.0%
Single	3	6.0%
Divorce	3	6.0%
Education Level		
Uneducated	5	10.0%
Primary	22	44.0%
Secondary	23	46.0%
Tertiary	0	0.0%
Occupation		
Employed	5	10.0%
Self employed	8	16.0%
Unemployed	37	74.0%
Number of previous pregnancies		
0	17	34.0%
1	9	18.0%
2	18	36.0%
3	4	8.0%
4	2	4.0%
Gestation in weeks		
Not sure	10	20.0%
28 – 32	16	32.0%
33 – 36	7	14.0%
37 – 40	12	24.0%
> 40	5	10.0%
History of previous uterine surgery		
None	32	64%
Caeserian section	11	22%
Uterine curettage	5	10%
Myomectomy	2	4%

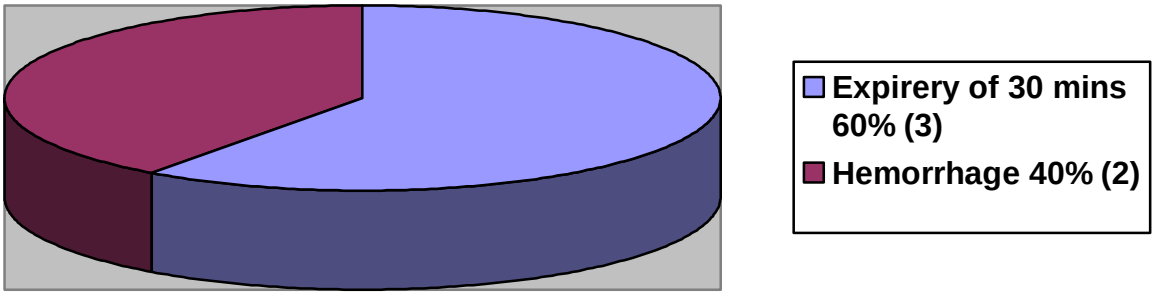
The above table shows that most respondents were aged 20 – 29 yrs and none had tertiary education. The most prevalent gestation was 28 – 32 weeks and 64% of the respondents had no prior uterine surgery.

Figure 2: Timing of placenta expulsion within 30 minutes of sublingual misoprostol



A total of 42 (84%) retained placentas were delivered within 30 minutes of misoprostol administration out of a possible 50. The bulk of them were delivered between 11th and 20th minute.

Figure 3: Reasons for manual removal of placenta



A total of 8(16%) of the 50 patients with retained placentas had MRP prescribed. The main reason was due to expiry of the allowed 30 minutes following sublingual misoprostol. However, three (3) of these patients expelled the placenta in the next 10 minutes as they awaited manual removal and therefore only 5(10%) of respondents eventually had MRP. Two respondents had PPH estimated at 750mls and 900ml prompting MRP before the expiry of 30 minutes.

Table 2: Characteristics of patients who had MRP prescribed (A) in comparison With those who expelled the placenta within 30 minutes (B)

Attribute	A (N=8)	B (N=42)
Prior pregnancies		
0	37.5% (3)	33.3%(14)
1	0.0% (0)	21.4%(9)
2	37.5% (3)	35.7% (15)
3	25.0% (2)	4.7%(2)
4	0.0% (0)	4.7%(2)
Prior uterine surgery		
None	37.5% (3)	69.0%(29)
Caesarean section	25.0% (2)	21.4%(9)
Uterine Curettage	25.0% (2)	7.1%(3)
Myomectomy	12.5% (1)	2.4%(1)
Gestation in weeks		
Not sure	50% (4)	14.2%(6)
28 – 32	25% (2)	33.3%(14)
33 – 36	12.5% (1)	14.2% (6)
37 – 40	0.0% (0)	28.6%(12)
> 40	12.5% (1)	2.4%(1)

In group A, 5/8 (62.5%) had a history of prior uterine surgery while 4/8 (50%) were not sure of their gestation. No parity was predominant in these cases. In contrast, most of those in group B had no prior uterine surgery, but similarly, no parity was predominant.

Table 3: Reported side effects to misoprostol

Side effects	**percentage (N=50**)
None	14% (7)
Chills	60% (30)
Nausea	14% (7)
Abdominal cramps	10% (5)
Vomiting	6% (3)

Chills were the commonest side effects and required only a warm cover. Nausea, abdominal cramps and vomiting required no treatment and they resolved within a few hours of onset. 4% of the patients had more than one side-effect.

DISCUSSION

This study shows that sublingual misoprostol 600mcg is an effective alternative to manual removal of retained placenta with 84% of women having responded positively. This indicates that sublingual misoprostol can be offered as a first line of therapy to stable patients with retained placenta. A similar study using rectal misoprostol 800mcg, (LI YT et al, 2001), showed a 100% success rate amongst 35 parturients within 35 minutes of drug administration. The difference could be explained by the fact that in the earlier study, retained placenta was diagnosed at 40 minutes as compared to 30 minutes, and it allowed more time after misoprostol administration i.e. 35 minutes as compared to 30 minutes.

In this study, most placentas were expelled within 20 minutes of misoprostol administration. This correlates with the rapid absorption and action of sublingual misoprostol attaining pick serum concentration within 30 minutes. It is noteworthy that three more mothers expelled the placenta within 40 minutes of misoprostol administration as they awaited manual removal. This indicates that if stable patients are allowed a longer time (more than 30 minutes) after misoprostol administration, the success rate could be significantly higher and research in this area is needed.

The safety profile of misoprostol is reaffirmed in this study as no serious side effect was reported. While 14% of the participants had no side effects, a sizeable number (60%) complained of chills. This resolved within a short while after reassurance and covering the client in warm beddings. Nausea, vomiting and abdominal cramps were reported in smaller proportions and they were transient and required no treatment. Hyperpyrexia, which is a serious side effect with higher doses of misoprostol, and diarrhea were not reported. This compares well with various studies where chills have been reported in up to 57% of patients and hyperpyrexia in only 0.1% when 600mcg of misoprostol was used.[26-29] Women should be counseled about the expected side effects which are generally well tolerated.

Parity seamed not to have a bearing on the incidence nor influence the outcome of retained placenta. Conversely, prior uterine surgery had a clear negative effect on the outcome of retained placenta with more than half (62.5%) of those who required manual removal of placenta having had prior uterine surgery. This calls for further exploration to see if any particular uterine surgery has a significant negative impact on the outcome of misoprostol use in retained placenta hence making such patients ineligible for the same. Endometrial scarring following uterine surgery compromises formation of deciduas basalis hence abnormal placentation with subsequent delayed third stage of labor.

Retained placenta is known to be more prevalent in mothers above the age of 35 years [5] but in this study, most mothers were 20 – 29 (56%) years of age. This could be due to the inclusion criteria that mainly required stable patients and those with retained placenta but were excluded were not accounted for in this study. While studies have shown no association between social-economic status and retained placenta, [7] most of the mothers in this study were of low social economic status. 74% had no form of employment and none of them had tertiary education. This could be explained by the fact that PMH caters for mothers mainly from a poor background.

While a sizeable number of mothers (20%) could not date their gestation neither by dates nor an early ultrasound scan, retained placenta appeared more prevalent amongst mothers who delivered at 28 – 32 weeks (32%). This confirms preterm delivery as a known risk factor. The same group had the highest success rate with misoprostol which was unexpected because misoprostol mainly acts through its profound uterotonic effect and uteri in older gestations are expected to be more responsive.

CONCLUSION

1. Sublingual misoprostol can be an effective treatment for retained placenta and reduces the need for manual removal
2. Sublingual misoprostol is well tolerated when used at a dose of 600mcg for the management of retained placenta

RECOMMENDATIONS

1. Misoprostol should be registered and licensed for use in the management of retained placenta
2. Misoprostol should be included in the clinical guidelines for the management of retained placenta.
3. A large RCT study is recommended to strengthen the evidence found in this Study.

REFFERENCES

1. Dombrowski MP, Bottoms SF, Saleh AA, et al. Third stage of labor: analysis of duration and clinical practice. *Am J Obstet Gynecol* 1995;172:1279-84.

2. Bugalho A, Daniel A, Faundes A, et al. Misoprostol for prevention of postpartum hemorrhage. *Int J Gynaecol Obstet* 2001;73:1-6.

3. Magann EF, Evans S, Chauhan SP, et al. The length of the third stage of labor and the risk of postpartum hemorrhage. *Obstet Gynecol*. 2005 Feb; 105(2) 290 – 3.

4. Combs CA., Laros, RK. Prolonged Third stage of Labour: Morbidity and Risk Factors. *Obstetrics and Gynecology* 1991; **77:** 6

5. Decherney AH, Nathan L, Goodwin TM, et al. Ed. Current Diagnosis and Treatment, Obstetrics and Gynecology. 10th Ed. McGraw Hill, 2007.

6 Soltani MH, Khashoggi T. Retained placenta and associated risk factors. J J Obstet Gynaecol 1997; 17: 245-7.

7. Owolabi AT, Dare FO, Fasubaa OB, et al. Risk factors for retained placenta in southwestern Nigeria. Singapore Med J 2008; 49(7) : 532

8. UNICEF/UNU/WHO. Iron deficiency anemia: assessment, prevention, and control. Geneva, World Health Organization, 2001. WHO/NHD/01.3

9. Abalos E. Active versus expectant management of the third stage of labour: RHL commentary (last revised: 2 March 2009). *The WHO Reproductive Health Library*; Geneva: World Health Organization.

10. National Collaborating Centre for Women's and Children's Health childbirth. (NCCWCH). Intrapartum Care. Care of healthy women and their babies during childbirth. RCOG Press, London 2007.

11. Weeks AD. The retained placenta. Best Pract Res Clin Obstet Gynaecol. 2008; 22:1103

12. World Health Organization (WHO). Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice, 2nd ed, WHO, Geneva 2006. p.B11. ISBN 92 4 159084 X

13. Carroll G, Belizan JM, Grant A, et al. Grupo Argentino de Estudio de Placenta Retenida, author. Intra-umbilical vein injection and retained placenta: evidence from a collaborative large randomised controlled trial. Br J Obstet Gynaecol. 1998;105:179–185

.

14. Bider D, Dulitzky M, Goldenberg M, et al. Intraumbilical vein injection of
. prostaglandin F2 alpha in retained placenta. Eur J Obstec Gynecol Reprod Biol 1996:64:59

15.WHO Recommendation for the Prevention of Postpartum Hemorrhage (report). WHO, 2007. WHO/MPS/07.06

16. National coordinating Agency for Population and Development, Ministry of Medical Services, Ministry of Public Health and Sanitation, Kenya National Bereau of Statistics, ICF micro 2010. The Kenya Service Provision Assessment Survey. National Coordinating Agency for Population and Development [Kenya] 2010.

17. WHO guidelines for the management of postpartum hemorrhage and retained placenta. WHO, 2009. ISBN: 978 92 4 159851 4

18.Carroli G. Berger E. Umbilical vein injection for management of retained placenta. *Cochrane Database of Systematic Reviews.* **http://www.cochrane.org/reviews/en/ab001337.html.** Accessed; 23rd oct. 2010

19. Weeks AD, Alia G, Vernon G, et al. Umbilical vein oxytocin for the treatment of retained placenta (Release Study): a double – blind , randomized controlled trial. *The Lancet* 2010; **375:**9709:416 -7

.

20. van Beekhuizen HJ, De Groot AN, De Boo T, et al. Sulprostone reduces the need for manual removal of the Placenta in patients with retained placenta; a randomized controlled trial *American Journal of Obstettrics and Gynecology* 2006; **194:** 446-50

21. Abdel-Aleem H, Abdel-Aleem MA, Shaaban OM. Tocolysis for management of retained placenta. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007708. DOI: 10.1002/14651858.CD007708.pub2.

22. Chedraui PA, Insuasti DF. Intravenous nitroglycerin in the management of retained placenta. *Gynecol Obstet Invest.* 2003; 56(2):61-4.

23. Tang OS, Genzell-Danielsson K, Ho PC. Misoprostol: Pharmacokinetic profiles, effects on the uterus and side-effects. *International Journal of Obstetrics and Gynecology* 2007; **99**:160 - 7

24. Kenya Essential Medicines List 2010. Ministry of Medical Services & Ministry of Public Health, 2010

25. Margaret C. Ed. Clinical Management and Referral Guidelines – Vol.III. Ministry of Medical Services and Ministry of Public Health, 2009.

26. Hofmeyr GJ, Ferreira S, Cheryl VK, et al. Misoprostol for treating postpartum hemorrhage: a randomized controlled trial. *BJOG* 2004; **111(9):** 1014-9.

27. Chong YS, Chua S, Arulkumaran S. Severe hyperthermia following oral Misoprostol in the Immedidate postpartum period. *Obstet Gynecol* 1997 Oct;90(4):703-4

28. Gulmezoglu AM, Villar J, Ngoc NN, et al, for the WHO Collaborative Group to Evaluate misoprostol in the Management of the Third Stage of Labour. The WHO multicentre double-blind randomized controlled trial to evaluate the use of misoprostol in the management of third stage of labour. *Lancet* 2001; **358:** 689-95

29. Derman RJ, Kodkany BS, Goudar SS, et al Oral misoprostol in preventing postpartum hemorrhage in resource poor communities: A randomized controlled trial. *Lancet* 2006; **368:**1248-53

30. Hoj L, Cardosa P, Nielsen BB, Hvidman L, et al. Effects of Sublingual misoprostol on severe postpartumHemorrhage in a primary health Centre in Guinea-Bissau: a randomized Double blind clinical trial. *BMJ* 2005;**331:** 723

31. Walraven G, Blum J, Dampha Y, et al. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia; a randomized controlled trial. *BJOG* 2005; 112: 1277-83

32. misoprostol in obstetrics and Gynecology: clinical guidelines. **www.misoprostol.org/File/guidelines.php**

33. Li YT, Yin CS, Chen FM. Rectal administration of misoprostol for the Management of retained placenta-a preliminary report. *Pubmed* 2001; **64**: 721 – 4.

34. Cochran, W.G. Sampling Techniques, 2nd Ed. John Wiley & Sons, 1963

APPENDICES

APPENDIX A: CONSENT FORM

Dr. Benson N. Waweru is a post-graduate student in the Department of Obstetric and Gynecology, University of Nairobi. He is carrying out a study on the use of misoprostol in the management of retained placenta. This entails administration of sublingual misoprostol to mothers who have delayed third stage of labour, instead of manual removal of the retained placenta, as the first option, in an attempt to avoid manual removal all together. This will be done at no extra cost. Please be informed that participation is voluntary and the information obtained will be confidential. Declining to participate will not deny you any conventional management of your condition. The treatment given will not harm you or your newborn baby.

Procedure

Upon consenting, three misoprostol tablets will be placed beneath your tongue. You will then be observed for a period of 30 minutes to see if the placenta will be delivered. Should this not happen within 30 minutes, or should you develop active vaginal bleeding or upon your request, the placenta will be manually removed promptly. As usual, you will stay in the hospital for the next 24 hours and you will be keenly monitored for adverse reaction to misoprostol, if any, and appropriate measures instituted.

Benefits

You may avoid the need for manual removal of placenta at no extra cost. Results obtained from this study may be used to inform the treatment of patients with retained placenta and save lives in future. Participating in this research will give you more time with the medical personnel hence a good chance to learn more about your condition.

Risks

There are no serious risks associated with this study. However, you may experience mild side effects of misoprostol which include fever, chills, vomiting, diarrhea and abdominal cramps all of which are self limiting. However, paracetamol tablets may be administered for fever

Declaration

I have been explained to about the study and I accept to participate. I have not been coerced or enticed in any way.

Participant's signature……. Date…….

Contacts

In case of any eventuality or for further information, please contact the following:

1. Researcher

   Dr. Benson N. Waweru Tel. 0722 255 542

2. Supervisors

   Prof. Joseph G. Karanja, Dept. of Obstetrics and Gynaecology, UoN
   Tel. 020-272 6360

   Dr. John Kinuthia, Dept. of Obstetrics and Gynaecology, UoN
   Tel. 020-272 6360

APPENDIX B: QUESTIONNAIRE

Serial number…….

Date …….

SECTION A: SOCIAL DEMOGRAPHIC DATA

1. Age in years ……..

2. Marital status
   (a) Married ☐
   (b) Single ☐
   (c) Divorced ☐
   (d) Widowed ☐

3. Education level
   (a) Uneducated ☐
   (b) Primary ☐
   (c) Secondary ☐
   (d) Tertially ☐

4. Occupation
   (a)Employed ☐
   (b)Self employed ☐
   (c)Unemployed ☐

SECTION B: ANTENATAL PARAMETERS

1. Parity; Para……. + ……

2. Last menstrual period (LMP)
   (a) Date……..
   (b) Not sure ☐

3. Gestation at admission in weeks …….

4. Latest ante partum hemoglobin: ……. g/dl

5. A. Previous uterine surgeries: Yes ☐ No ☐

   B. If yes, tick the appropriate field below:
   (a) Caesarean section(s): yes ☐ no ☐ Date(s) ……, ……, ……
   (b) Uterine curettage/ manual vacuum aspiration: yes ☐ no ☐ number..
   (c) Manual removal of placenta: yes ☐ no ☐ number…
   (d) Myomectomy: yes ☐ no ☐ number….

SECTION C: PREGNANCY OUTCOMES

1. Duration of labour ……..hrs.

2. Number of infants
   (a) Single infant ☐
   (b) Multiple infants ☐
   (c) Still birth ☐

3. Infant(s) birth weight
   (a) 1000 – 1499 grams ☐
   (b) 1500 – 2499 grams ☐
   (c) 2500 – 4000 grams ☐
   (d) Above 4000 grams ☐

3. Estimated blood loss during second stage of labour? …….. mls

SECTION D: RESPONSE TO MISOPROSTOL

1. Time when misoprostol was administered. ……Hrs

2. Time when the placenta was delivery ……. Hrs

3. Time when manual removal of placenta was prescribed …….. Hrs

4. Reason(s) for manual removal of placenta
   (a) Hemorrhage ☐
   (b) Expiry of 30 minutes after misoprostol administration ☐
   (c) Patient's request ☐
   (d) Any other reason(s) …….

5. Adverse effects
   (a) Chills/shivering ☐
   (b) Fever ☐
   (c) Abdominal cramps ☐
   (d) Diarrhea ☐
   (e) Vomiting ☐
   (f) Others……..

APPENDIX C: KNH ERC APPROVAL