doi:10.1111/j.1447-0756.2007.00661.x J. Obstet. Gynaecol. Res. Vol. 33, No. 6: 810–817, December 2007

Oral misoprostol for the prevention of primary post-partum hemorrhage during third stage of labor

Christopher A. Enakpene[1], Imran O. Morhason-Bello[1], Evbu O. Enakpene[2], Ayodele O. Arowojolu[1] and Akinyinka O. Omigbodun[1]

Departments of [1]Obstetrics and Gynecology and [2]Medicine, University College Hospital, Ibadan, Nigeria

Abstract

Aim: To assess the effectiveness of oral misoprostol compared with methylergometrine in the prevention of primary post-partum hemorrhage during the third stage of labor.

Methods: This was a randomized controlled trial of 864 singleton low-risk pregnant women. The outcomes were total blood loss, duration of the third stage of labor and peripartal change in hematocrit. Comparisons were by the χ^2-test and Student *t*-test. Relative risks were calculated for side-effects profile. A *P*-value of less than 0.05 was statistically significant.

Results: The biodata of all the participants were similar. The mean blood loss for the misoprostol and methylergometrine groups was 191.6 ± 134.5 mL and 246.0 ± 175.5 mL, respectively (95% CI: –79.3 to –39.5 mL). The mean duration of the third stage of labor was 19.6 ± 2.4 min and 9.4 ± 3.3 min in the misoprostol and methylergometrine groups, respectively (95% CI: 9.82–10.58 min). More subjects had blood loss >500 mL, 42 (9.7%) versus 6 (1.4%), and peripartal hematocrit change greater than 10%, 38 (8.8%) versus 5 (1.2%), in the methylergometrine group than in the misoprostol group, respectively. Also, more subjects received additional oxytocic in the methylergometrine group, compared to the misoprostol group (80 [18.5%] versus 33 [7.6%] patients, respectively).

Conclusions: Orally administered misoprostol was more effective in reducing blood loss during the third stage of labor than intramuscular methylergometrine. However, there were more subjects in the misoprostol group in whom duration of the third stage of labor was greater than 15 min and who also had manual placental removal than in the methylergometrine group.

Key words: methylergometrine, misoprostol, prevention, primary post-partum hemorrhage, third stage of labor.

Introduction

Maternal mortality is a catastrophe which affects not only the woman but also her family and the community at large. An estimated 515 000 women die yearly as a result of pregnancy-related complications, and about 98% of these deaths occur in developing countries.[1]

Post-partum hemorrhage still remains a major cause of maternal morbidity and mortality in developing countries, and accounts for 25% of maternal deaths.[2] There are an estimated 14 million cases of pregnancy-related hemorrhage every year worldwide, and at least 128 000 of these women bleed to death, especially within 4 h of birth, from uterine atony due to poor management of the third stage of labor.[3,4] While the

Received: September 7 2006.
Accepted: April 24 2007.
Reprint request to: Dr Christopher A. Enakpene, P. O. BOX 21379, University of Ibadan Post Office, Ibadan, Oyo State, Nigeria.
Email: christdew2002@yahoo.com

riskof dying from post-partum hemorrhage is about 1 in 100 000 deliveries in the USA and in the UK, it is 100-fold higher in developing countries.[5,6] The prophylactic use of oxytocics in the third stage of labor has been shown to significantly reduce the risk of post-partum hemorrhage, and it is generally advocated as the most important component of the active management of the third stage of labor.[7] The common oxytocics in use are oxytocin, methylergometrine and syntometrine (Sandoz, Basel, Switzerland) and these have been shown to significantly reduce the risk of severe post-partum hemorrhage (greater than 1000 mL) and the need for blood transfusions after delivery.[8] However, their widespread use in resource-poor settings is limited because they need to be administered by skilled attendants via a parenteral route with sterile needles and syringes as well as cool storage conditions (between 2°C and 8°C) and away from light.

Misoprostol is a prostaglandin E_1 analog. It is an effective uterotonic agent, stable in high tropical temperature, cheap, relatively free of overt adverse effects and it does not require skilled attendants in its administration. Its effectiveness at high doses of 600–800 μg has been demonstrated in diverse obstetric and gynecologic conditions. However, frequently occurring adverse effects such as fever, shivering, abdominal cramps, nausea, vomiting and diarrhea necessitated the consideration of a lower effective dose such as 400 μg to produce fewer side-effects for this study. This is also in line with current international feeling within the misoprostol research community that further research should be conducted using 400 μg.

Most of the deliveries in the developing countries take place either at home without supervision or are supervised by traditional birth attendants who have little or no skills to conduct them. While about half of all pregnant women deliver with the help of a skilled attendant, only 40% deliver in hospitals or health centers.[9] Unfortunately, even in the health centers where there are skilled attendants, storage facilities are either not available or are out of use due to frequent outage of the power supply. The results of several studies have questioned the potency of these routine oxytocics in tropical climates.[10]

This study was therefore born out of the need to identify an alternative uterotonic agent that is effective, cheap, stable at high tropical temperatures, relatively free from adverse effects, and that can easily be administered without the need for skilled attendants especially in the remote rural areas where most of the maternal mortality due to post-partum hemorrhage occurs.

Materials and Methods

This is a prospective single-blinded, randomized controlled trial that was conducted from 4 January 2004 to 30 January 2005 at the Adeoyo Maternity Hospital, Yemetu, Ibadan, Nigeria. This is a secondary health center located in the semiurban area of Ibadan, the capital city of Oyo state. However, the standard of patient care in this hospital is quite poor and can be compared with what is obtained in most rural health centers in Nigeria. It was therefore used as a model health center for possible implementation of the outcome of this study to the society at large. This hospital serves over 1 million people who are mainly from low socioeconomic classes with a high maternal mortality ratio. There are more than 6000 deliveries per annum in this hospital and the maternal mortality ratio is 1200 per 100 000 live births. Post-partum hemorrhage contributes more than 32% of the maternal death in this hospital. The ethical committee of the Oyo state ministry of health and the hospital management board approved the research protocol. The only uterotonic agent in use in this center is intramuscular methylergometrine (Swiss Pharma Nigeria, Agege, Lagos, Nigeria) because it is cheap and readily available. Although this hospital has cold storage facilities, the frequent power outage may distort the maintenance of cool storage conditions. Hence, drugs such as methylergometrine used in this study might have lost their potency due to poor storage conditions.

The study group consisted of women with singleton, low-risk pregnancy who had spontaneous vertex delivery. A written informed consent was obtained from every participant who met the inclusion criteria at admission into the labor ward with a diagnosis of active phase of labor, singleton pregnancy with anticipated spontaneous vertex delivery. Exclusion criteria were the presence of contraindications to the use of either misoprostol and methylergometrine, such as pre-eclampsia and other hypertensive diseases in pregnancy, pre-existing cardiac disease, severe anemia, history of asthma, renal or hepatic disorders, allergy to prostaglandin, and the presence of conditions requiring prophylactic oxytocin infusion after delivery such as grand multiparity, multiple pregnancy, polyhydramnios, previous history of post-partum hemorrhage, and uterine fibroid. Randomization was by simple random selection in the second stage of labor. In order to

eliminate selection bias, an independent statistician generated sets of four random letters, which were in boxes, and each box contained four separate random allocations which was equivalent to an opaque sealed envelope stratified in a block of four. Randomization was carried out when vaginal delivery was imminent and a piece of paper was picked from the next treatment envelope. At the delivery of the anterior shoulder, each subject randomly received either 400 μg of oral misoprostol or 500 μg of intramuscular methylergometrine.

Performance bias was significantly minimized by ensuring that the accoucheurs adhered strictly to the standardized care protocol, which was boldly written on cardboard and pasted on the walls of the labor rooms. All the intrapartum parameters were assessed by the usual accoucheurs who normally supervise deliveries in this center, and this significantly reduced detection and measurement bias.

The third stage of labor was managed by waiting for signs of placental separation before delivery of the placenta by controlled cord traction. Blood loss was estimated by a combination of careful measurement of blood collected in a receptacle after the delivery of the baby, visual estimation of blood loss and extrapolation of blood loss using weight difference of the total perineal pad used up to 24 h in the post-partum period. Irrespective of the assigned medication that was given during the third stage of labor, an additional dose of 500 μg of methylergometrine and/or i.v. infusion of 20 IU of syntocinon in 500 mL of normal saline was given when the accoucheur diagnosed post-partum hemorrhage due to excessive blood loss. Blood was transfused to women with hematocrit less than 21% in the post-partum period or whenever there was symptomatic anemia.

The primary variables that were assessed in this study were the estimated blood loss during delivery and within the first 24 h post-partum, the duration of the third stage of labor and additional oxytocic given to treat post-partum hemorrhage. The occurrence of primary post-partum hemorrhage was defined as blood loss more than or equal to 500 mL or the need to transfuse blood due to hemodynamic instability within 24 h of delivery.[11] In addition, an objective estimation of blood loss was done using a peripartal fall in hematocrit of at least 10% as a definition of post-partum hemorrhage. Hence, all participants had hematocrit done on admission into the labor ward, and this was repeated 24 h after delivery. Other variables that were assessed were maternal vital signs, which were recorded immediately after delivery and repeated 15, 30 and 60 min later. The duration of the third stage of labor was adjudged prolonged when longer than 30 min. Adverse effects such as nausea, vomiting, headache, chest pain, abdominal cramps, fever and shivering were documented up to 24 h post-partum.

The sample size in this study was calculated to detect at least 5% difference in the effectiveness between methylergometrine, which was found to be 96% effective in preventing primary post-partum hemorrhage from previous studies and misoprostol, which is anticipated to achieve 91% effectiveness. With 80% power and *P*-value of 0.05, 378 participants were required for each study arm making a total of 756 subjects. A deliberate over-sampling of 25% allowed for participants that dropped out from the study and also to increase the power of the observations. The total number of participants who gave their consent at admission into the labor ward was 945. However, only 864 participants who met the inclusion criteria and had imminent spontaneous vertex delivery were randomized during the second stage of labor. Hence, each study arm had a sample size of 432. Eighty-one participants who initially gave their consent were not randomized due to 33 participants who voluntary withdrew from participating for personal reasons, 17 patients had an emergency caesarean section, 24 patients had augmentation of labor, and 7 patients had intrapartum complications such as pre-eclampsia (5 patients) and antepartum hemorrhage (2 patients).

Data obtained were coded and entered into a computer running Statistical Package for Social Science version 12 for windows (SPSS, Chicago, IL, USA). The module of the same program was used to validate all entries. Initial analysis was done by generation of frequency tables while further analyses were by cross-tabulation to explore the statistical relationship between variables in the two groups. The differences between the misoprostol and methylergometrine group were assessed using the non-parametric test and the χ^2-test for categorical variables. The mean and standard deviation of normally distributed continuous variables were compared using Student's *t*-test. Variables not conforming to normal distribution were compared using the Mann–Whitney *U*-test. Proportions were compared by calculation of χ^2 with Yates' correction for continuity, and relative risks. Numerical values were reported as means ± standard deviation and 95% confidence interval were calculated. The difference between two parameters was taken as statistically significant when *P*-values were less than 0.05.

Results

Table 1 shows that the baseline characteristics of patients in either group were similar, $P > 0.05$.

Table 2 shows that the mean blood loss in the misoprostol group, 191.6 ± 134.5 mL, is lower than the mean blood loss in methylergometrine group, 246.0 ± 175.5 mL. The mean difference of –54.4 mL was statistically significant at $P < 0.0001$ (95% CI: –79.3 to –39.5 mL). The mean duration of the third stage of labor was 19.6 ± 2.4 min and 9.4 ± 3.3 min in the misoprostol and methylergometrine groups, respectively, with a mean difference of 10.2 min (95% CI = 9.82–10.58 min). However, the methylergometrine group had a higher mean post-delivery hematocrit of 32.7 ± 3.7%, mean change in hematocrit of 1.2 ± 1.5 and mean percentage change in hematocrit between admission and post-delivery hematocrit of 3.5 ± 4.5% as compared with the misoprostol group where these values were 32.1 ± 3.4%, 0.4 ± 0.6 and 1.2 ± 1.8%, respectively. These differences were statistically significant (95% CI:–1.07 to –0.13, –0.95 to –0.65 and –2.76 to –1.84).

Table 3 shows that there were fewer subjects with blood loss greater than 500 mL in the misoprostol group (six patients; 1.4%) than in the methylergometrine group (42 patients; 9.7%), with a relative risk of 0.14. There were fewer subjects with a percentage change of hematocrit greater than 10% in the misoprostol group (five patients; 1.2%) than in methylergometrine group (38 patients; 8.8%), with relative risk of 0.13. Moreover, there were more subjects whose duration of third stage of labor was greater than 15 min, in the misoprostol group than in the methylergometrine group: 264 (61.1%) versus 14 (3.2%). The relative risk was 18.86. These differences were statistically significant when analyzed with Pearson χ^2-test with Yates' correction for continuity. The proportion of patients who had an additional dose of oxytocics was significant in the methylergometrine group, 80 (18.5%) as against 33 (7.6%) patients in the misoprostol group.

Table 1 Baseline characteristics of continuous variables of patients

Parameters	Misoprostol $n = 432$	Ergometrine $n = 432$	*P*-value	95% CI
Age (years)	26.8 ± 5.4	28.2 ± 5.4	0.928	–2.14–0.71
Parity	1.3 ± 1.2	1.6 ± 1.2	0.053	–0.43–0.13
Gestation (weeks)	38.7 ± 1.5	39.5 ± 1.3	0.051	–0.35–1.27
Admission PCV (%)	32.5 ± 3.4	33.8 ± 3.6	0.268	–1.80–0.86
Admission systolic BP (mmHg)	119.5 ± 9.7	115.7 ± 8.9	0.174	–2.56–5.04
Admission diastolic BP (mmHg)	75.6 ± 6.2	74.2 ± 6.2	0.626	–2.26–0.60
Admission mean arterial BP (mmHg)	90.5 ± 6.8	88.0 ± 6.3	0.241	–3.33–1.58
Maternal height (cm)	167.3 ± 5.4	166.5 ± 5.2	0.763	0.45–1.22
Maternal weight (kg)	71.0 ± 4.0	71.9 ± 4.0	0.106	–0.0.56–1.24
Body mass index (kg/m^2)	30.5 ± 2.3	30.8 ± 2.1	0.116	–0.65–1.46
Birthweight of baby (kg)	3.2 ± 0.4	3.3 ± 0.4	0.763	–0.17–1.59
Admission pulse rate (b.p.m.)	84.1 ± 7.2	83.3 ± 4.5	0.059	–1.20–0.32
Admission temp. (°C)	36.7 ± 0.4	36.7 ± 0.3	0.626	–5.85–1.54

Values are mean ± standard deviation. Student's *t*-test at $P > 0.05$ not statistically significant. BP, blood pressure; b.p.m, beats per minute; PCV, packed cell volume.

Table 2 Post-partum features of patients: misoprostol group versus ergometrine group

Parameters	Misoprostol $n = 432$	Ergometrine $n = 432$	*P*-value	Mean differences	95% CI of the difference
Total estimated blood loss (mL)	191.6 ± 134.5	246.0 ± 175.5	<0.0001	–54.4	–79.3 to –39.5
Duration of third stage of labor (min)	19.6 (4) ± 2.4	9.4 ± 3.3	<0.0001	3.01	9.82 to 10.58
Post-delivery PCV (%)	32.1 ± 3.4	32.7 ± 3.7	0.032	–0.6	–1.07 to –0.13
Differences in PCV (%)	0.4 ± 0.6	1.2 ± 1.5	<0.0001	–0.8	–0.95 to –0.65
Percentage changes in PCV (%)	1.2 ± 1.8	3.5 ± 4.5	<0.0001	–2.3	–2.76 to –1.84

Comparison of means of post-partum parameters between the two groups. Values are in mean ± standard deviation. Independent samples Students' *t*-test was used for normally distributed variables, and variables not conforming to normal distribution such as blood loss, duration of third stage of labor and post-delivery PCV were compared by Mann–Whitney U-test. $P < 0.05$ is statistically significant. PCV, packed cell volume.

Table 3 Comparison of proportion of post-partum parameters between the misoprostol group and the ergometrine group

Parameters	Misoprostol $n = 432$	Ergometrine $n = 432$	*P*-value Exact sig. (two-sided)	Relative risk
Manual placental removal	23 (5.3%)	17 (3.9%)	0.419	1.35
Additional oxytocic	33 (7.6%)	80 (18.5%)	<0.0001	0.41
PPH (blood loss >500 mL)	6 (1.4%)	42 (9.7%)	<0.0001	0.14
Percentage PCV change >10%	5 (1.2%)	38 (8.8%)	<0.0001	0.13
Duration of third stage of labor >15 min	264 (61.1%)	14 (3.2%)	<0.0001	18.86

Values are in number and proportion (percentage). χ^2-test with Yates' correction for continuity. $P < 0.05$ is statistically significant. PPH, post-partum hemorrhage; PCV, packed cell volume.

Table 4 Profile of side-effects in the study groups

Side-effects	Misoprostol $n = 432$	Ergometrine $n = 432$	*P*-value	Relative risk
Fever (temp. >38°C)	31 (7.2)	7 (1.6)	<0.05	4.71
Shivering	23 (5.3)	21 (4.9)	>0.05	1.09
Nausea	10 (2.3%)	16 (3.7%)	<0.05	0.63
Vomiting	1 (0.23%)	12 (2.8%)	<0.05	0.08
Headache	1 (0.23)	54 (12.5)	<0.05	0.02

Values are in numbers (percentage). Pearson χ^2. Mann–Whitney *U*-test, 81 822.500. Wilcoxon W, 174 918.5. Z = –4.665. Two-tailed. $P < 0.05$ is statistically significant.

There was no significant difference in the number of participants who had manual removal of retained placenta in the two groups.

Table 4 shows the side-effects profile of the two groups. The relative risk of developing pyrexia was more than fourfold with misoprostol use than methylergometrine. More subjects developed fever with temperature greater than 38°C within 24 h of delivery in the misoprostol group than in the methylergometrine group, 31 (7.2%) as compared to 7 (1.6%). However, there were more subjects who had headache, nausea and vomiting, 54 (12.5%), 16 (3.7%) and 12 (2.8%), respectively, in the methylergometrine group than in the misoprostol group in which these side-effects occurred in 1 (0.23%), 10 (2.3%) and 1 (0.23%) subjects, respectively. These were statistically significant when analyzed by Pearson's χ^2 ($P < 0.05$). Other symptoms such as shivering occurred in not statistically significantly higher proportion in subjects in the misoprostol group than in subjects in the methylergometrine group. No subjects in either group developed diarrhea during the study period.

Discussion

Most studies in contemporary obstetric practice have shown that active management of the third stage of labor by early cord clamping, controlled cord traction and prophylactic use of oxytocics are a useful means of preventing post-partum hemorrhage. Reports have also shown that by these means, the incidence of post-partum hemorrhage was reduced from 18% to 5%, the need for therapeutic oxytocics dropped from 30% to 6% and the duration of the third stage of labor fell from 15 min to 5 min[12,13] These remarkable outcomes are achieved when accompanied by adequate supervision in labor, prompt intervention and improved facilities in delivery rooms. The role of methylergometrine in the prevention of primary post-partum hemorrhage has been long established. However, in the tropics, storage of methylergometrine may be problematic due to the high environmental temperature, which reduces the potency of the drug. Moreover, the drug has some side-effects that may be devastating in untrained hands. One of the alternatives to methylergometrine in modern day obstetric practice are the prostaglandins. Unfortunately most prostaglandins; $F_{2\alpha}$ and E_2 are heat labile and too expensive for a resource-constrained environment. On the other hand, misoprostol is an inexpensive drug, easy to store, and systemically absorbed orally and across mucous membranes. Hence, it stands to be a promising substitute for other well-established injectable agents if found to be effective in reducing the incidence of primary post-partum hemorrhage.[13–15] Absorption of misoprostol is very

rapid, being detected within 2 min after oral ingestion and peaking between 12 and 30 min.[16]

This study shows that misoprostol is effective in the prevention of primary post-partum hemorrhage in women with low-risk pregnancy. Although misoprostol was more effective than methylergometrine as demonstrated from the results of this study, the incidence of post-partum hemorrhage in both study groups falls relatively within the universally acceptable range of 5% to 8% in places where some form of prophylaxis is practiced, as against 18% where a physiological approach is the norm.[13] The low incidence of post-partum hemorrhage observed in this study could be due to the fact that women with notable risk factors for post-partum hemorrhage were excluded from participation in the study. In addition, all women were delivered under controlled circumstances in hospital settings that were not exclusively high risk for post-partum hemorrhage.

The outcome of this study, which demonstrated that oral misoprostol is effective for the prevention of primary post-partum hemorrhage when compared with intramuscular methylergometrine, further buttresses the clinical usefulness of this drug in obstetrics care especially in a resource-poor setting. A similar study done in South Africa to determine the therapeutic efficacy of misoprostol in primary post-partum hemorrhage showed that 800 μg of misoprostol per rectum was more effective than the combination of parenteral syntometrine and syntocinon in stopping primary post-partum hemorrhage due to uterine atony.[17] The results of other trials comparing misoprostol and placebo or no treatment were somewhat equivocal. In three trials in South Africa, misoprostol seemed to reduce blood loss, which is similar to the findings of this study. However, in two other trials in South Africa and France; misoprostol was less effective than placebo or no treatment.[18] The results of the large 2001 World Health Organization trial conducted in nine countries with 18 530 participating women, which compared 600 μg of oral misoprostol with i.v. or i.m. 10 IU oxytocin, demonstrated that there was associated higher risk of blood loss and the use of additional uterotonics (up to 16% of women) with the use of misoprostol compared to other uterotonics.[18] A systematic review of 16 randomized controlled trials of misoprostol to prevent post-partum hemorrhage in 28 138 women concluded that misoprostol is less effective than injectable oxytocin or oxytocin-methylergometrine preparations as part of active management of the third stage of labor.[19] On the other hand, a more recent study by Wright and Newton showed that misoprostol is as effective as oxytocin but less effective than a combination of oxytocin and methylergometrine in the prevention of primary post-partum hemorrhage.[20] The usefulness of oral misoprostol is further corroborated by the findings of Derman *et al*. where they found in a randomized controlled trial that oral misoprostol was associated with significant decreases in the rate of acute post-partum hemorrhage and mean blood loss in rural India when compared with placebo.[21] Moreover, this study also showed that 33 (7.6%) patients in the misoprostol group required additional oxytocic as against 80 (18.5%) patients in the methylergometrine group.

However, the conclusion drawn from most previous studies which showed that misoprostol was less effective than other uterotonic agents at statistically significant levels cannot be translated verbatim into clinical practice. Gertrude Stein once said: "A difference, to be a difference, must make a difference".[22] A clinically important difference by definition is not whether it is statistically significant. Further, a statistically significant difference may have no clinical importance.[23]

Misoprostol normally does not cause any adverse cardiovascular effect such as hypertension[24] as compared with methylergometrine, which is known to stimulate alpha-adrenergic and dopaminergic receptors causing hypertension, abdominal pain because of smooth muscle contraction, and nausea, vomiting, diarrhea, headache and tachycardia.[22,25] Pyrexia greater than 38°C was observed in 31 (7.2%) patients within 1 h of delivery and they responded well to oral acetaminophen tablets within 2 h of medication. Conversely, shivering was reported by two studies to be the main side-effects, which occurred in 19% of women while pyrexia occurred in 2% of women in one study using 400 μg of misoprostol, as against this study in which 23 (5.3%) patients had shivering as a complication. In other recent studies[26,27] using a higher dose of oral misoprostol (600 μg), both shivering (28% to 42%) and pyrexia (7.5% to 34%) were more common.

This study shows that misoprostol has a place in the prevention of primary post-partum hemorrhage during the third stage of labor especially in resource-poor settings where cool storage facilities for other oxytocics are not feasible. Misoprostol was more effective than methylergometrine at statistically significant levels in this study with a power in excess of 80%. The provision of oral misoprostol in addition to existing oxytocics to maternity centers in the remote resource-poor settings of developing countries may be the

solution to curbing the high maternal mortalities that result from primary post-partum hemorrhage because it is highly effective, cheap, heat stable (requires no refrigeration), has a long shelf life and has fewer deleterious adverse effects. The outcome of this study may explain the reasons for the high maternal mortality ratio in the study center despite their routine usage of intramuscular methylergometrine in active management of the third stage of labor. The cold storage facilities in this hospital can be adjudged to be below standard and this situation is similar to what is obtained in many other health institutions in Nigeria due to either nonexistence or inadequate power supply.

Conclusion

Orally administered misoprostol was more effective than intramuscular methylergometrine in reducing blood loss during the third stage of labor in a resource-poor setting. However, more subjects in the misoprostol group had a duration of the third stage of labor greater than 15 min and also had manual removal of the placenta than the methylergometrine group. In view of the established efficacy of oral misoprostol in the prevention of primary post-partum hemorrhage during third stage of labor, coupled with the recent recommendation of the misoprostol research committee of the International Federation of Obstetricians and Gynecologists, the National Agency of Food and Drugs Administration and Control (NAFDAC) of the Federal Republic of Nigeria have recently licensed the use of oral misoprostol for the prevention of primary post-partum hemorrhage especially in rural settings where most post-partum hemorrhages occur due to home deliveries and/or lack of health facilities.

Acknowledgments

We wish to acknowledge the tremendous input of some students of the Dokita editorial board who worked tirelessly and consistently in the data collection for this study. We must commend the efforts and the cooperation of the midwives and doctors in Adeoyo Maternity Hospital where this study was carried out. They were wonderful, steadfast and made studious efforts in ensuring strict adherence to the study protocol. Our appreciation also goes to Professor Rosano Happy Arenata of the Department of Public Health, University of California, San Diego, USA and Dr Ayede of the Department of Paediatrics, University College Hospital, Ibadan, Nigeria who offered useful advice in the study design and statistical analysis.

This study was carried out in part fulfillment for the award of the fellowship of the National Postgraduate Medical College, Faculty of Obstetrics and Gynecology.

References

1. World Health Organization. *WHO Global Estimates of Maternal Mortality for 1995: Results of an In-Depth Review, Analysis and Estimation Strategy (Statement)*. Geneva: The Organization, 2001.
2. Walder J. Misoprostol: preventing postpartum haemorrhage. *Mod Midwife* 1997; **7**: 23–27.
3. Thornburg KH, Jacobson SL, Giraud GD, Morton MJ. Hemodynamic changes in pregnancy. *Semin Perinatol* 2000; **24**: 11–14.
4. World Health Organization. *WHO Mother-Baby Package*. WHO/RHT/MSM/94. II. Rev. I. 9 Revision. Geneva: The Organization, 1998.
5. Centers for Disease Control and Prevention (USA). *NCHS. Vital Statistics of the United States. Mortality 1985–1995*, Vol. II, Part A. Atlanta: The Centers, 1997.
6. Her Majesty's Stationery Office. *Report of Confidential Enquiries Into Maternal Deaths, United Kingdom 1991–1993*. London: The Stationery Office, 1996.
7. Bjørnerem A, Acharya G, Øian P, Maltau JM. [Postpartum haemorrhage prophylaxis and treatment in Norway.] *Tidsskr Nor Laegeforen* 2002; **122**: 2536–2537. (In Norwegian.)
8. Association of the British Pharmaceutical Industry. *ABPI Data Sheet Compendium*. London: Datapharm Publications Ltd, 1993.
9. World Health Organization. *Care of the Umbilical Cord*. WHO/RHT/MSM/984. Geneva: The Organization, 1998.
10. Walker JA, Hogerzeit HY. Potency of ergometrine in tropical countries. *Lancet* 1988; **II**: 393.
11. Jouppila P. Postpartum haemorrhage. *Curr Opin Obstet Gynecol* 1995; **7**: 446–450.
12. Coombs CA, Murphy EL, Laros RK Jr. Factors associated with postpartum hemorrhage with vaginal birth. *Obstet Gynecol* 1991; **77**: 69–76.
13. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. *Br J Obstet Gynecol* 1998; **105**: 971–975.
14. Hogerzeil HV, Walker GJ. Instability of (methyl)ergometrine in tropical climates: an overview. *Eur J Obstet Gynecol Reprod Biol* 1996; **69**: 25–29.
15. Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo controlled trial. *Am J Obstet Gynecol* 1998; **179**: 1043–1046.
16. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; **90**: 88–92.
17. Lokugamage AU, Sullivan KR, Niculescu I *et al.* A randomized study comparing rectally administered misoprostol versus syntometrine combined with an oxytocin infusion for the cessation of primary postpartum hemorrhage. *Acta Obstet Gynecol Scand* 2001; **80**: 835–839.

18. Hofmeyr GJ, Walraven G, Gülmezoglu AM, Mahowana B, Alfirevic Z, Villar J. Misoprostol to treat postpartum hemorrhage: A systematic review. *BJOG* 2005; **112**: 547–553.
19. Villar J, Gülmezoglu AM, Hofmeyr GJ, Forma F. Systematic review of randomized controlled trials of misoprostol to prevent postpartum hemorrhage. *Obstet Gynecol* 2002; **100**: 1301–1312.
20. Wright JM, Newton W. Is rectal misoprostol as effective as oxytocin in preventing postpartum hemorrhage? *J Fam Pract* 2003; **52**: 281–282.
21. Derman RJ, Kodkany BS, Goudar SS *et al.* Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomized controlled trial. *Lancet* 2006; **368**: 1248–1253.
22. DerSimonian R, Charette LJ, Mcpeek B, Mosteller F. Reporting on methods in clinical trials. *N Engl J Med* 1982; **306**: 1332–1337.
23. Lang TA, Secic M. *How to Report Statistics in Medicine: Annotated Guidelines for Authors, Editors, and Reviewers*. Philadelphia: American College of Physicians, 1997; 77.
24. Zuest S, Hösli I, Surbek D, Holzgreve W. [Adverse effects of misoprostol in pregnancy.] *Z Geburtshilfe Neonatol* 2001; **205**: 43–48. (in German).
25. Mantyla R, Kanto J. Clinical pharmacokinetics of methylergometrine. *Int J Clin Pharmacol Ther Toxicol* 1981; **19**: 386–391.
26. Lumbiganon P, Hofmeyr J, Gülmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the management of the third stage of labour. *Br J Obstet Gynecol* 1999; **106**: 304–308.
27. Surbek DV, Fehr PM, Hösli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. *Obstet Gynecol* 1999; **94**: 255–258.