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THE USE OF HISTOGRAMS TO ASSESS THE EFFICACY OF UTEROTONIC TREATMENT FOR POSTPARTUM HAEMORRHAGE: A FEASIBILITY STUDY.

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Abstract

Postpartum haemorrhage (PPH) is a major killer of women worldwide. Its initial treatment has largely been reliant on uterotonics. This paper examines the use of histograms to assess the efficacy of uterotonic treatment for PPH. The main aim was to explore whether post treatment peaks are routinely seen in postpartum blood loss histograms and whether the peaks are only seen in treated women. This is secondary data analysis using histogram. It has been noted that the presence of secondary peak was not only seen in treated cases. A secondary peak was noted in many of the histograms and includes many women who did not receive uterotonic treatment. Many women received treatment despite having blood loss of under 500 mls, and many women who stopped bleeding with final blood losses of over 500 mls did not receive any uterotonics. So the routine use of histogram analysis to assess the efficiency of uterotonic therapy is not recommended. The paper provides further insights into clinical practice, with clinicians frequently using uterotonic therapies even when the volume of the blood loss is low. This demonstrates how uterotonic use in practice is often not linked with the standard 500 mls definition of postpartum haemorrhage.

Keywords: Postpartum haemorrhage, Treatment, additional uterotonic, histogram

Introduction

Postpartum haemorrhage (PPH) is a major killer of women worldwide, but its treatment has largely been developed empirically. Given that an atonic uterus is thought to be the most common cause of PPH, the standard management of PPH starts with the administration of a dose of uterotonic, even if the mother has received prophylaxis. There is little evidence behind this treatment strategy, but the finding that prophylactic uterotonics markedly reduce both the mean blood loss and rates of PPH (1-3) justifies the use of uterotonics as a first line treatment option. ~~Recent~~ research has shown that a single dose of misoprostol 800 mcg ~~administered sublingually can be used for atonic PPH in women who have received oxytocin prophylaxis, as well as those who have received no oxytocin prophylaxis~~ (4, 5). It is not known, however, whether oxytocin treatment has benefits over placebo alone due to the ethical imperative to provide treatment for all women. Furthermore, recent evidence from double-blind randomized controlled trials (RCTs) suggests that concurrent treatment with two drugs (i.e. misoprostol in addition to oxytocin, or an oxytocin infusion in addition to an oxytocin bolus) has little or no benefit.(6, 7) A question remains therefore over the absolute efficacy of uterotonic therapies.

The technique of evaluating the effect of an intervention by measuring the size of a post-intervention response in continuously collected data is widely used in laboratory experiments, but rarely in epidemiology. With accurate measurement of blood loss the same principles can be applied to large blood loss datasets where the response to uterotonic treatment is seen on blood loss histograms as a post treatment peak. This represents the number of mothers who responded immediately to treatment. This method was used in a recent secondary analysis of 2 large randomized trials, (4, 5) where Weeks and others measured the size of the post-treatment peaks to

compare the effect of misoprostol and placebo on women who had received oxytocin prophylaxis or none (8). It is not known whether this data can be replicated in other data sets, or whether the same attenuation of efficacy is seen with other uterotonics.

We therefore explored the data sets from large randomized studies with measured postpartum blood loss in which participants have been managed according to an explicit protocol for the prophylaxis and treatment of PPH.

Materials and methods

This study sought to examine the databases of all clinical trials of postpartum haemorrhage prophylaxis of over 1000 women which included individual patient data on measured blood loss, type of prophylaxis used and type of treatment used.

In order to identify suitable studies, we searched the Cochrane library database including Cochrane Central of Controlled Trials (CENTRAL), Embase, Ovid version of Medline, Web of knowledge and Scopus for relevant RCTs, using different keywords and medical subject headings (MeSH) without language restrictions. Examples of used MeSH and keywords are postpartum haemorrhage, any intervention used for PPH prevention such a oxytocin, ergometrine, misoprostol, carbetocin, oxytocin analogues, prostaglandin. Wildcards were used to improve the search sensitivity.

Titles and abstracts of 4170 papers were identified initially; removal of duplicates resulted in 1975 articles. Several types of studies were assessed as ineligible for inclusion, such as research on cost effectiveness or hemodynamic effect of drugs or the assessment of drug side effects within population. Conference abstracts, non-randomized, observational and retrospective studies were also not included. Further

exclusion left 125 papers for review. Nineteen fulfilled the study inclusion criteria described above. These studies' principal investigators were contacted by email to request their original data for secondary reanalysis. The protocol of the study was emailed to those who initially agreed to participate, and the datasets from 4 studies were obtained for analysis. The data set for each randomized trial was divided into groups according to the type of prophylaxis used. The reported final blood loss for each woman was categorized into 100 mls increments from 0-2000 mls, according to the definition of PPH in the included studies, and then graphically displayed in a histogram. The percentage of women in every increment was obtained by divided the number of women in each increment by the total number of women within the study arm from which women where extracted. This process was repeated for each group.

In order to assess whether the peaks seen in the histogram had occurred as a result of the treatment administered, a second graph was ~~also produced~~ containing only the data for those women who received treatment with a uterotonic. This allowed an assessment of whether any fluctuation in the histogram was due to uterotonic treatment. Women with missing data on total blood volume were excluded.

All studies received ethical approval prior to recruitment to the individual randomised trials and the data upon which this analysis was based had already been published. No further ethical approval was therefore sought for this additional analysis of data.

Results

All of the included studies compared prophylactic misoprostol (either alone or in addition to other uterotonic) with another uterotonic or placebo in women having a vaginal birth. Two of the included studies were conducted in primary health care centers in India and compared 600mcg of oral misoprostol either with ergometrine (9) or with placebo (10), in low risk women. The two other trials were placebo-controlled, double-blind trials which examined the effect of the additional administration of 400 mcg of sublingual misoprostol to a routine prophylactic uterotonic. One was conducted in Nigeria (11) and the other was multi-country (12).

1. Chandhiok , 2006 (9)

Chandhiok and colleagues (9) investigated whether oral misoprostol administered by paramedical workers from rural primary health centers in India, was effective at preventing PPH. The researchers used prophylaxis with 600 mcg misoprostol or ergometrine in low risk women undergoing vaginal delivery. The blood loss was collected and measured for 1 hour after delivery (or 2 hours for those bleeding was persisting). In this study, there was a low incidence of PPH (<1%) in both groups, but a significant reduction was noticed in median blood loss after delivery (100 mls vs. 200 mls; $p < 0.001$) in the misoprostol arm (Figure 1). In the misoprostol 2 small peaks were seen consisting of 4 women who treated with uterotonic. The first peak was at a total blood loss 600-900 mls and the other was at 1200-1300 mls (Figure 2).

In the methergine group, 4 women were diagnosed with PPH and of these, only 2 women received treatment. Two others, with a total blood loss between 600 and

800mls, did not receive a uterotonic but stopped bleeding spontaneously (Figure 3). The treatment peaks of similar size were noted in misoprostol and methergine groups.

In this study, very few women had a PPH, and all settled quickly with maximum blood loss of 1200-1300 ml. No women with a blood loss of < 500 mls received treatment and almost all those diagnosed with PPH had treatment.

2. Derman, 2006 (10)

The second study was a RCT conducted by Derman and co-workers (10). This was a placebo-controlled trial of 600 mcg oral misoprostol for the prevention of PPH conducted in rural India. Oral misoprostol was associated with a significant reduction in the rate of PPH ≥ 500 mls (12.0% to 6.4%, $p < 0.0001$) and severe PPH ≥ 1000 mls (1.2% to 0.2%, $p < 0.0001$). Misoprostol was also associated with a decrease in mean postpartum blood loss (262.3 mL to 214.3 mL, $p < 0.0001$). This is shown graphically in the histogram figure 4.

Despite the frequency of PPH in both study groups (6.4% in the misoprostol group and 12.0% in placebo group), very few women with PPH received treatment (2 in misoprostol group and 6 in the placebo arm). In addition, some women with blood loss < 500 mls received treatment (Figures 5 & 6). In the misoprostol arm, both treated women had final blood losses of under 500 mls, whilst all of those with a PPH of over 500 mls stopped bleeding spontaneously without receiving further uterotonic therapy. In the placebo arm, one woman received treatment despite a final blood loss of only 200mls (200<300). The remaining 5 treated women all had blood losses of over 500mls. However, of 97 women with PPH in the placebo arm, only 5

women (5%) ~~required~~ treatment – the remainder stopped spontaneously without the need for oxytocic therapy.

3. Hofmeyr and Fawole (11,12)

The two final studies compared the use of misoprostol and placebo in addition to routine uterotonic prophylaxis (11, 12). These two studies were double-blind, placebo-controlled multicenter randomized trials undertaken in hospitals to investigate the administration of 400 mcg sublingual to augment routine active management of the third stage of labour to prevent PPH. In both studies the measurement of blood loss was for one hour after delivery. Neither trial found any significant difference in the primary outcome of blood loss of 500 mls or more within 1 hour of randomization: misoprostol 40 [6.1%] versus placebo 42 [6.4%] (11) and misoprostol 22 [4.0%] versus placebo 35 [6.3%] (12). This can be also seen graphically in the histograms in figures 7 and 10.

In both studies, the majority of women who received treatment had blood losses of under 500ml (Figures 8, 9, 11 and 12). As with the previous studies, small secondary peaks were seen in all study arms, despite many women within the secondary peaks not having received uterotonic therapy.

Comment

This exploratory study examined the distribution of blood loss for women during the third stage of labour using histograms. All of the included studies compared the prophylactic effect of oral or sublingual misoprostol (either alone or in addition to routine uterotonic) with placebo or another uterotonic in preventing PPH during vaginal birth.

The only previous description of this methodology is a study examining the data from 2 large randomized trials conducted by Gynuity Health Projects in which 40,403 women were recruited and had intrapartum blood loss measured. Those with blood loss over 700 mls were randomized to receive 800 mcg sublingual misoprostol or 40 IU intravenous oxytocin. In a secondary analysis similar to this one, no peak was seen for non-treated cases, but clear peaks were measurable for those who received either oxytocin or misoprostol (8). The size of the treatment peak was attenuated by the use of oxytocin prophylaxis. The data analyzed here is from smaller studies which were examining the effect of prophylaxis on blood loss. The time of initiating treatment was left to the clinical team and the histograms thus represent “real life” care. Whilst it cannot be stated that the uterotonic treatment was given immediately before bleeding stopped, the final blood loss represents the latest point at which it could have been given. The treatment graphs are therefore conservative examples, representing the highest blood loss at which uterotonic treatment could have been used. This is in contrast to the Gynuity PPH management studies~~,~~. In those, there were rigorous diagnostic and treatment protocols which were necessary because they were specifically examining PPH treatment, and so the accuracy of the diagnosis, randomization and initiation of treatment were critical.

An important finding from this study is that presence of a peak was not specific for treated cases. A secondary peak was noted in many of the histograms and contains many women who did not receive uterotonic treatment. In the Chandhiok study for example the group who received ergometrine for prophylaxis but did not receive any treatment still had a secondary peak at a blood loss of around 600-800 mls (Figure 3). This could reflect the effect of other therapies rather than uterotonics in treating PPH such as bimanual uterine compression or/and uterine massage. The presence

of this peak should caution against the over-interpretation of histogram data and ascribing the presence of treatment peaks to uterotonics alone.

Although postpartum blood loss was objectively measured in all of the included studies, the use of oxytocic therapy was not consistent with the use of therapy only at the traditional blood loss cut off of 500 mls. In the studies of Fawole (11) and Hofmeyr (12) the vast majority of uterotonic therapy was given to women with a final blood loss of under 500 mls. This reflects reality, where the decision to initiate therapy is based not only on the volume of blood lost, but also on the speed of the blood flow, the underlining cause of the bleeding and the woman's clinical condition. This was also highlighted in a review on postpartum blood loss estimation (13). Thus a severely anemic woman with a prolonged labour who has a gush of blood postnatally would rightly be given treatment immediately, even though the final blood loss might amount to only 100 mls in total. Although this reflects usual practice, it limits the use of the histogram analysis to studies with a very clear and rigorously enforced protocol for the uterotonics use.

Of more concern is the number of women who bled over 500 mls but did not receive uterotonic therapy. This again reflects clinical practice where underestimation of blood loss is common, especially if the woman is otherwise healthy, and there is a slow trickle of blood thought to be coming from vaginal lacerations. This surprise finding provides a fascinating insight into clinical practice in PPH treatment.

The implications of these findings are that: a) in prophylaxis trials, the rate of uterotonic use appears to be a poor surrogate for PPH; b) the recommendations to treat PPH at 500 mls may not be commonly used in clinical practice and need to be reviewed; and c) the size of the histogram "treatment peaks" are not a good indicator

of the efficiency of uterotonics, unless the clinicians follow a very strict treatment protocol (which may not reflect clinical practice).

Furthermore, it appears that vaginal blood loss in women having a PPH usually stops and frequently does so even without uterotonic therapy. ~~A change in direction of future research is required to explore these in more detail~~This presents a dilemma for clinicians. Whilst reassuring, it is impossible to predict who will spontaneously stop bleeding and who will continue bleeding to life-threatening levels. In addition, PPH causes significant problems through postpartum anaemia and the use of uterotonics is likely to hasten the cessation of bleeding. Understandably therefore, clinicians tend to use uterotonics frequently and at very early stages to prevent progression.

Summary

The findings from this study do not support the routine use of histogram analysis to assess the efficiency of uterotonic therapy. The analysis of histograms should be limited to PPH treatment studies in which strict protocols are used for the timing and nature of PPH treatment. Even then, the finding of a secondary peak in untreated women in these studies should warn against ascribing all the effect to uterotonic therapy; other physical therapies may also be used concurrently and may have an effect.

In addition, the analysis of these histograms provide further insights into clinical practice, with clinicians frequently using uterotonic therapies even when the volume of the blood loss is low. This demonstrates how uterotonic use in practice is often not linked with the standard 500 mls definition of PPH- this is important both for researchers and for those producing clinical guidelines.

Practice points

This study suggests that PPH treatment is not usually given when 500mls volume is reached, but often much earlier. Whilst the PPH definition of 500mls blood loss is widely used, it should not be assumed that treatment is usually given at this point – the decision to treat seems to be based on other factors.

Research Agenda

1. Histograms of final blood loss, both for all woman and just those treated, ~~should~~ be used in the analysis of clinical trials to explore clinicians' habits

2. Studies ~~should~~ explore what factors (other than blood loss volume) influence clinicians to commence treatment

3. In future research studies into PPH treatment, treatment should be administered when clinicians would normally give it, not at a pre-specified volume.

Acknowledgement

We dedicate this paper to Doctor Bukola Fawole who died recently, but will be always in our hearts.

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Declaration of conflicting interests: AW has on-going relationships with multiple interested parties on misoprostol use including FIGO, WHO and Gynuity Health Projects. He also runs an independent, non-profit making website called www.misoprostol.org which seeks to disseminate guidelines on the optimal doses for misoprostol use. It does not receive any funding or sponsorship. Other authors declare that there is no conflict of interest.

Contributorship: AW had the original idea for the paper; NA search for illegible studies contacted the authors and wrote the first draft of the paper. All authors participated in editing the paper and approved the manuscript before submission.

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References

(1) Liabsuetrakul T., Choobun T., Peeyananjarassri K., Islam, Q., M. Prophylactic use of ergot alkaloids in the third stage of labour. Cochrane Database of Syst Rev, 2007,(2), CD005456.

(2) Westhoff G., Cotter A. M., and Tolosa J.E.,Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev, 2013, CD001808.

(3) Tuncalp O., Hofmeyr G. J., and Gulmezoglu A. M. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev, 2012, CD000494.

(4) Winikoff B., Dabash R., Durocher J., Darwish, E., Nguyen, T. N., Leon, W., et al.Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. Lancet 2010; (9710), 210-6.

(5) Blum J., Winikoff B., Raghavan S., Dabash R., Ramadan, M. C., Dilbaz, B., et al.Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. The Lancet 2010, (9710), 217-223.

(6) Sheehan S. R., Montgomery A. A., Carey M., Mcauliffe, F. M., Eogan, M., Gleeson, R., et al.Oxytocin bolus versus oxytocin bolus and infusion for control of blood loss at elective caesarean section: double blind, placebo controlled, randomised trial. BMJ 2011;343, d4661.

(7) Widmer M., Blum J., Hofmeyr G. J., Carroli, G., Abdel-aleem, H., Lumbiganon, P.,et al.Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. The Lancet 2010; (9728):375, 1808-13.

(8) Weeks A. D., Lane S., Durocher J., Alfirevic, Z., Winikoff, B.Uterotonic approaches for management of atonic haemorrhage in hospital settings: a histogram analysis of postpartum bleeding (unpublished data) 2012.

(9) Chandhiok N., Dhillon B. S, Datey S., Mathur, A., Saxena, N. C.Oral misoprostol for prevention of postpartum hemorrhage by paramedical workers in India. Int J Gynaecol Obstet 2006; 92: 170-5.

(10) Derman R. J., Kodkany B. S., Goudar, S. S., Geller, S. E., Naik, V. A., Bellad, M. B., et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. The Lancet 2006; (9543): 1248-53.

(11) Fawole A. O., Sotiloye O., S., Hunyinbo KI, Hunyinbo, K. I., Umezulike, A. C., Okunlola, M. A., Adekanle, D. A., et al.A double-blind, randomized, placebo-controlled trial of misoprostol and routine uterotonics for the prevention of postpartum hemorrhage. Int J Gynaecol Obstet, 2011;(2): 107-11.

(12) Hofmeyr, G. J., Fawole, B., Mugerwa, K., Godi, N. P., Blignaut, Q., Mangesi, L., et al. Administration of 400 mug of misoprostol to augment routine active management of the third stage of labor. International Journal of Gynaecology & Obstetrics, 2011; 112 (2), 98-102.

(13) Hancock, A., Weeks A.D., Lavender,T., Is accurate and reliable blood loss estimation the 'crucial step' in early detection of postpartum haemorrhage: an integrative review of the literature. BMC Pregnancy Childbirth.,2015 Sep 28;15:230. doi: 10.1186/s12884-015-0653-6.

Figure Legend

Figure 1. Histogram showing the main study results in the Chandhiok trial (9). The red line represents the blood loss in all participants in the methergine group. Whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm,

Figure 2. Histogram showing blood loss distributions of women in the Chandhiok trial (9) who were randomised to receive misoprostol. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

Figure 3. Histogram showing blood loss distributions of women in the Chandhiok trial (9) who were randomised to receive methergine. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

Figure 4. Histogram showing the main study results in the Derman trial (10). The red line represents the blood loss in all participants in the placebo group, whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm

Figure 5. Histogram showing blood loss distributions of women in the Derman trial (10) who were randomised to receive misoprostol. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

Figure 6. Histogram showing blood loss distributions of women in the Derman trial (10) who were randomised to receive placebo. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

Figure 7. Histogram showing the main study results in the Fawole trial (11). The red line represents the blood loss in all participants in the placebo group, whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm

Figure 8. Histogram showing blood loss distributions in women in the Fawole trial (11) who were randomised to receive Misoprostol. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

Figure 9. Histogram showing blood loss distributions of women in the Fawole trial (11) who were randomised to receive placebo. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

Figure10. Histogram showing the main study results of the Hofmeyr trial (12). The red line represents the blood loss in all participants in the placebo group, whilst the

blue line shows the blood loss distribution for all women included in the misoprostol arm

Figure 11. Histogram showing blood loss distributions in women in the Hofmeyr trial (12) who were randomised to receive placebo. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment

Figure 12. Histogram showing blood loss distributions in women in the Hofmeyr trial (12) who were randomised to receive misoprostol. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment

Table (1) included study details

Study	Participants- risk to PPH	Study type	Setting	Prophylaxis received	PPH definition and measurement
Chandhiock, 2006 (9)	1200 – low risk	RCT	At 30 peripheral health centres from 5 states in India	**Intervention:** 600 mcg of oral misoprostol (600) **Control:** (600) an intramuscular injection of 0.2 mg of methergine (88.5%) + oral tablet of 0.125 mg methergine (9.7%)	PPH was defined as > 500ml bleeding and a calibrated blood collection drape (BRASS-Drape) was used to measure blood loss for 1hour after delivery (and for 2 hours if bleeding persist)
Derman, 2006 (10)	1620- low risk	RCT	At four primary-health centres areas in rural India	**Intervention:** A single oral dose of 600 mcg of misoprostol (812) **Control:** Placebo (808)	PPH was defined as ≥ 500 ml bleeding and was assessed using a polyurethane blood collection drape for 1hour after delivery (and for 2 hours if bleeding persist)
Fawole, 2011 (11)	1345- not specified	RCT	At 6 hospitals in Nigeria	**Intervention:** A sublingual dose of 400 mcg of misoprostol(672) **Control:** A placebo (673), in addition to standard active management of the third stage of labour (oxtocine or ergometrine)	PPH was defined as ≥ 500 ml bleeding and was assessed using a low-profile plastic bedpan for a period of 1 hour
Hofmeyr, 2011(12)	1103- not specified	RCT	Gynuity health project and 4 hospitals in South Africa, Uganda, and Nigeria	**Intervention**: A sublingual dose of 400 mcg of misoprostol (547) **Control:** A placebo (556), in addition to standard active management of the third stage of labour (oxtocine or ergometrine)	PPH was defined as ≥ 500 ml bleeding and was assessed using a low-profile plastic bedpan for a period of 1 hour or until bleeding stop

Table (2) study outcomes

Study	Number of women with PPH	uterotonic given	Additional intervention used	Maternal mortality
Chandhiock, 2006 (9)	**Total:** 9 **Intervention:** 4 (0.7%) **Control:** 5 (0.8%)	**Total:** 6 **Intervention:** 4 **Control:** 2 **Type:** Methergine and oxytocin injection	• Manual removal of placenta (30 women in the methergine group) • One woman in the intervention group lost > 1000 mL of blood. Uterine exploration was carried out and a blood transfusion administered	No maternal mortality was reported
Derman, 2006 (10)	**Total:** 149 **Intervention:** 52 (6.4%) **Control:** 97 (12.0%)	**Total:** 10 **Intervention:** 3* **Control:** 6 **Type:** Methergine, oxytocin and carboprost injection	• One in the intervention group and 8 in the placebo arm had surgical intervention (repair of perineal, cervical, and high vaginal lacerations, manual removal of placenta) • One women in the placebo group received bimanual uterine compression alongside medical treatment	There was one non-haemorrhage related maternal death in the placebo group.
Fawole, 2011(11)	**Total:** 82 **Intervention:** 40 (6.08%) **Control:** 42 (6.36%)	**Total:** **Intervention:** 162 **Control:** 97 **Type:** Methergine and oxytocin injection	• Manual placenta removal (23 in misoprostol group, 27 in placebo group)	There was no death in either group
Hofmeyr, 2011 (12)	**Total:** 57 **Intervention:** 22 **Control:** 35	**Total:** 58 **Intervention:** 31 **Control:** 27 **Type:** : Methergine oxytocin and syntometrine injection	• Manual placenta removal (32 in misoprostol group, 33 in placebo group)	There was no death in either group

***Data of blood loss was available for 2 women only

Practice points

This study suggests that PPH treatment is not usually given when 500mls volume is reached,but often much earlier. Whilst the PPH definition of 500mls blood loss is widely used, it should not be assumed that treatment is usually given at this point – the decision to treat seems to be based on other factors.

Research Agenda

1. Histograms of final blood loss, both for all woman and just those treated, should be used in the analysis of clinical trials to explore clinicians' habits

2. Studies should explore what factors (other than blood loss volume) influence clinicians to commence treatment

3. In future research studies into PPH treatment, treatment should be administered when clinicians would normally give it, not at a pre-specified volume.

Highlight of the review

The findings from the analysis of histograms from 4 studies with measured blood loss do not support its routine use to assess the efficiency of uterotonic therapy. However, histograms show how clinicians frequently use uterotonic therapies prior to the usual definition of PPH (500mls blood loss). Clinicians' clinical concerns appear to be only partially based on volume of loss, and uterotonic use not linked with the standard 500 mls definition of PPH.

Figure

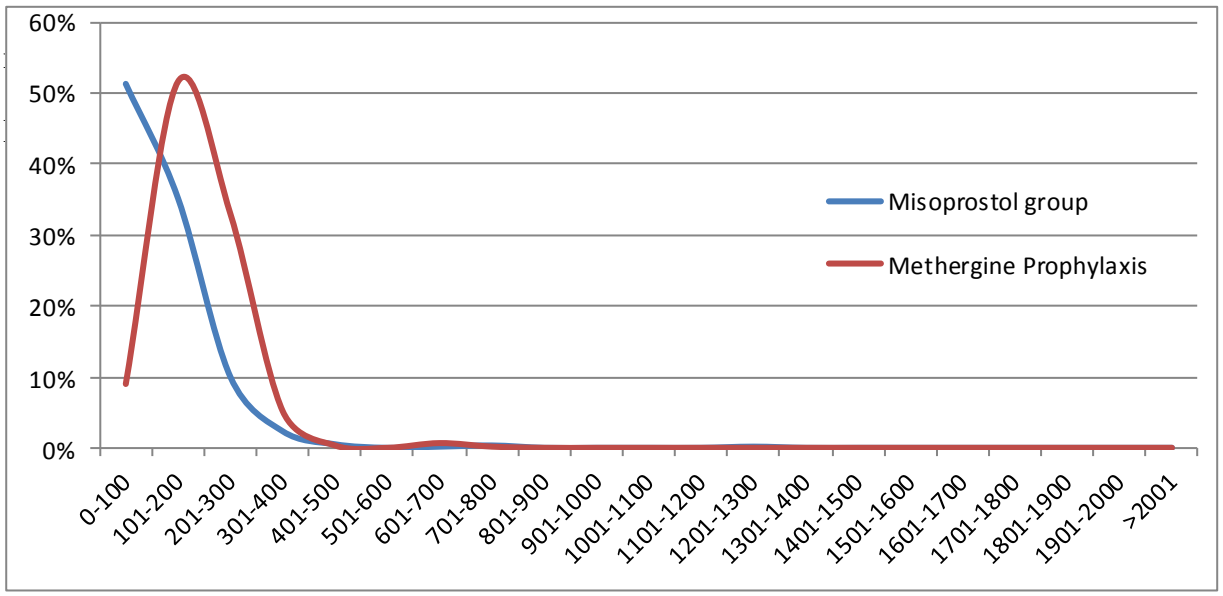

Figure 1. Histogram showing the main study results in the Chandhiok trial (9). The red line represents the blood loss in all participants in the methergine group. Whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm,

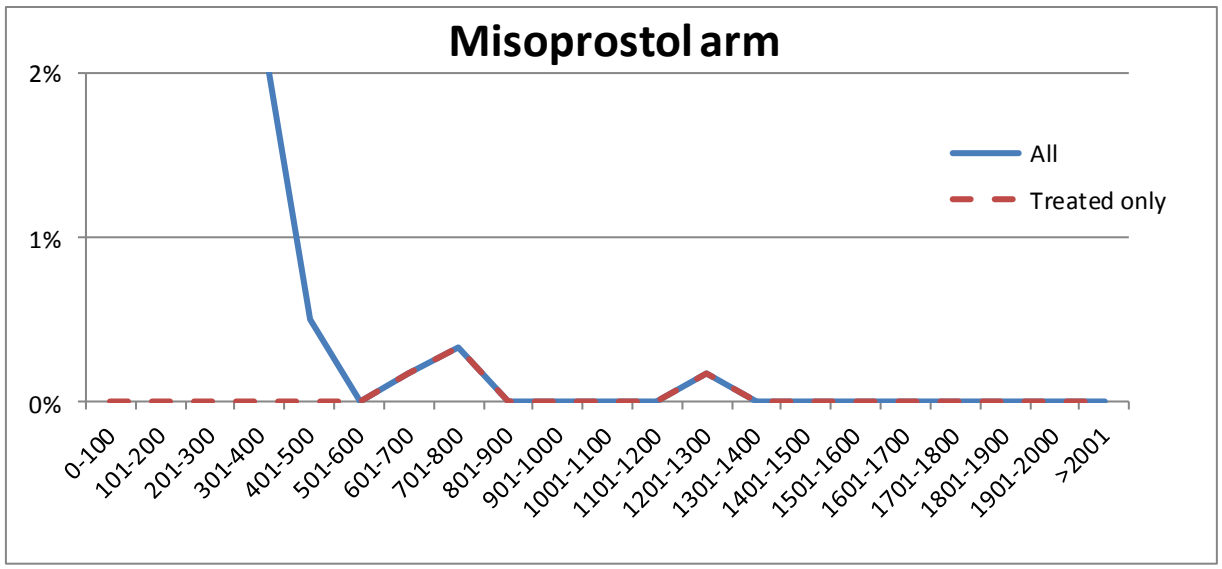

Figure 2. Histogram showing blood loss distributions of women in the Chandhiok trial (9) who were randomised to receive misoprostol. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

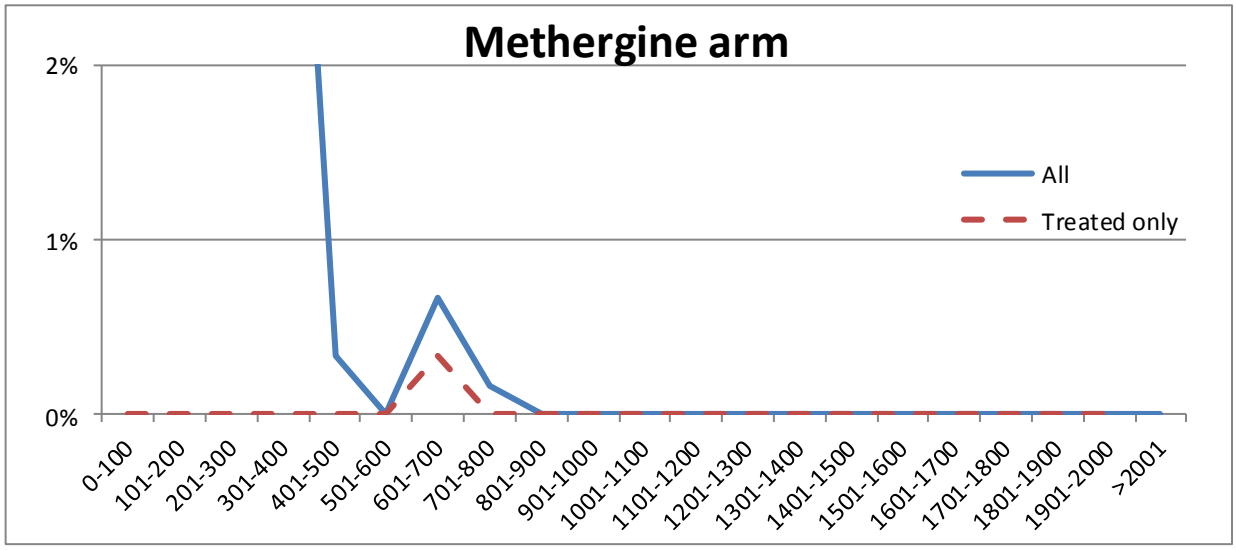

Figure 3. Histogram showing blood loss distributions of women in the Chandhiok trial (9) who were randomised to receive methergine. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment

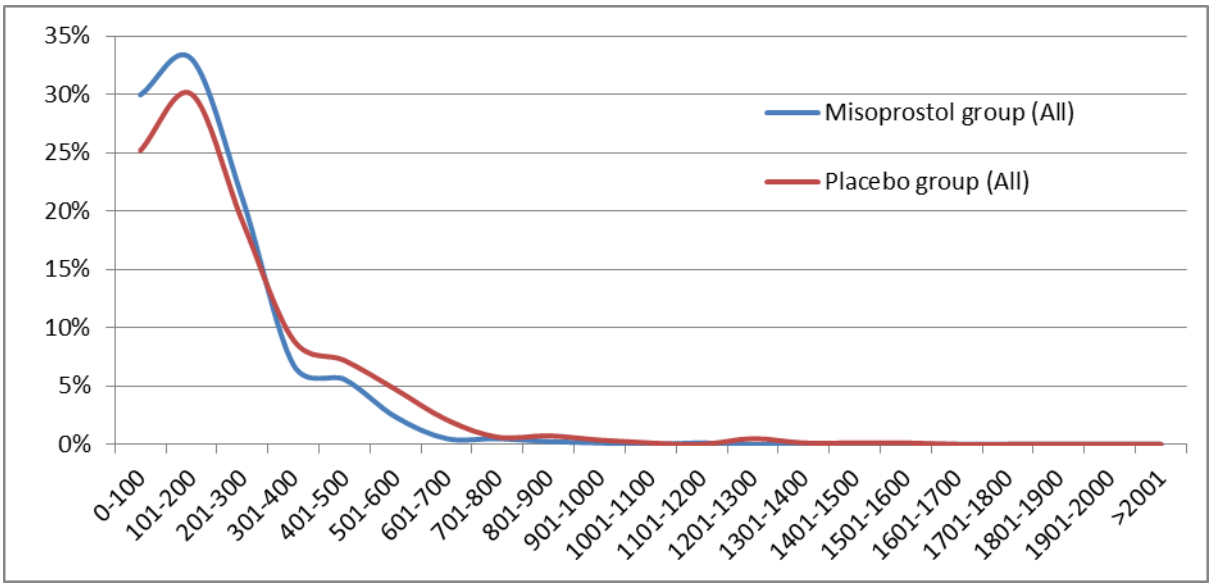

Figure 4. Histogram showing the main study results in the Derman trial (10). The red line represents the blood loss in all participants in the placebo group, whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm

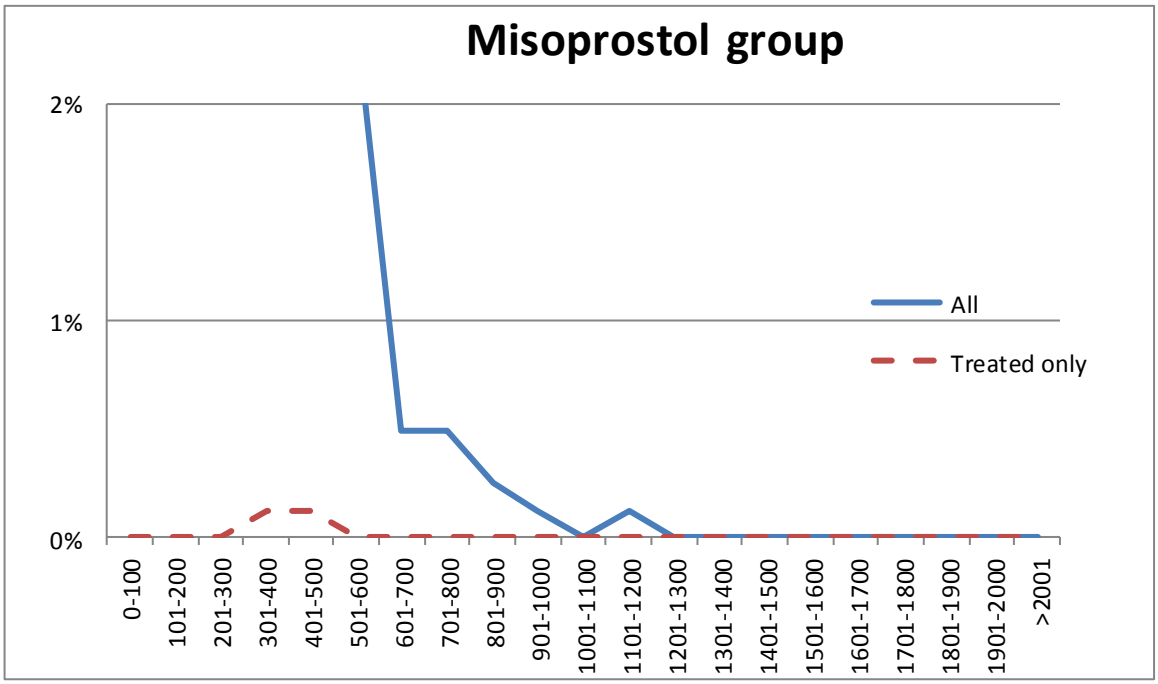

Figure 5. Histogram showing blood loss distributions of women in the Derman trial (10) who were randomised to receive misoprostol. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

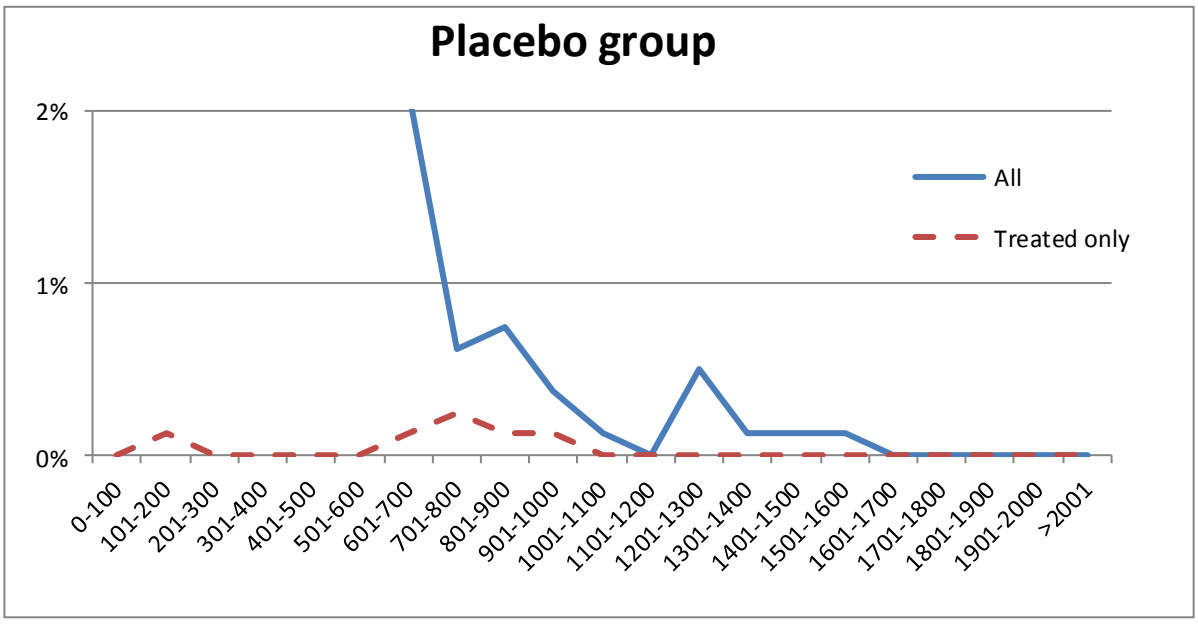

Figure 6. Histogram showing blood loss distributions of women in the Derman trial (10) who were randomised to receive placebo. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

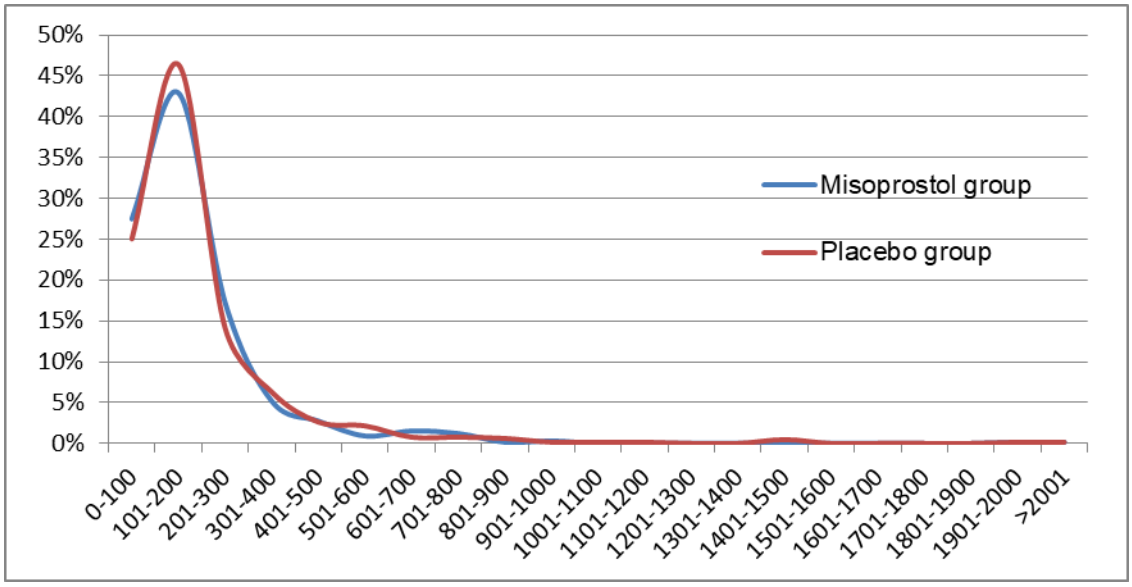

Figure 7. Histogram showing the main study results in the Fawole trial (11). The red line represents the blood loss in all participants in the placebo group, whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm

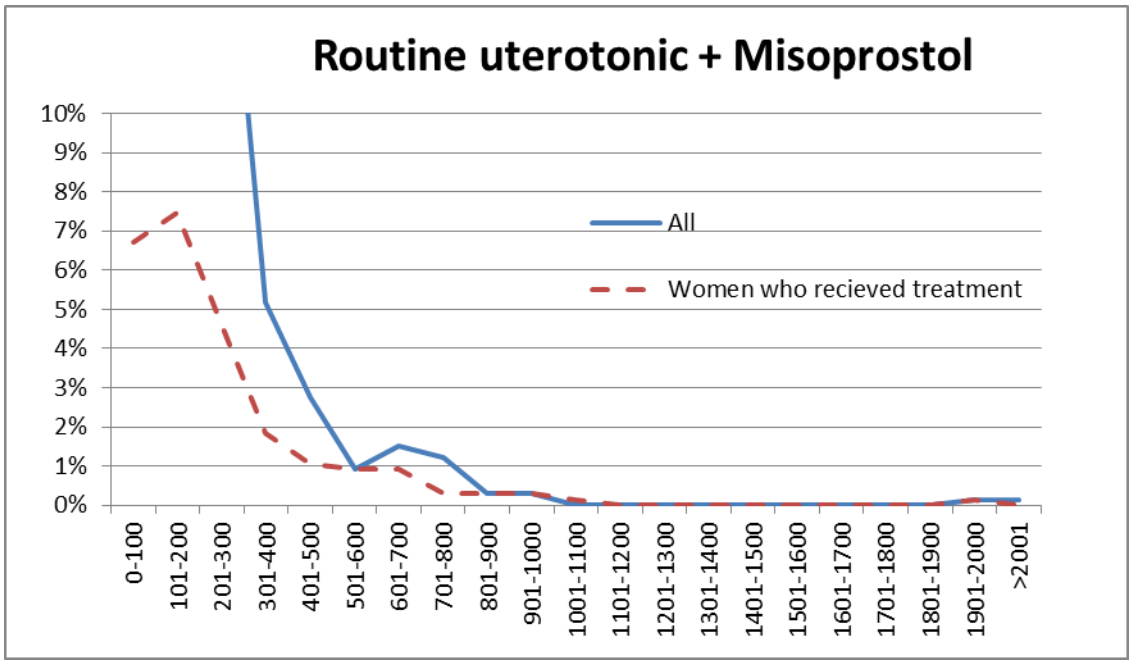

Figure 8. Histogram showing blood loss distributions in women in the Fawole trial (11) who were randomised to receive Misoprostol. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

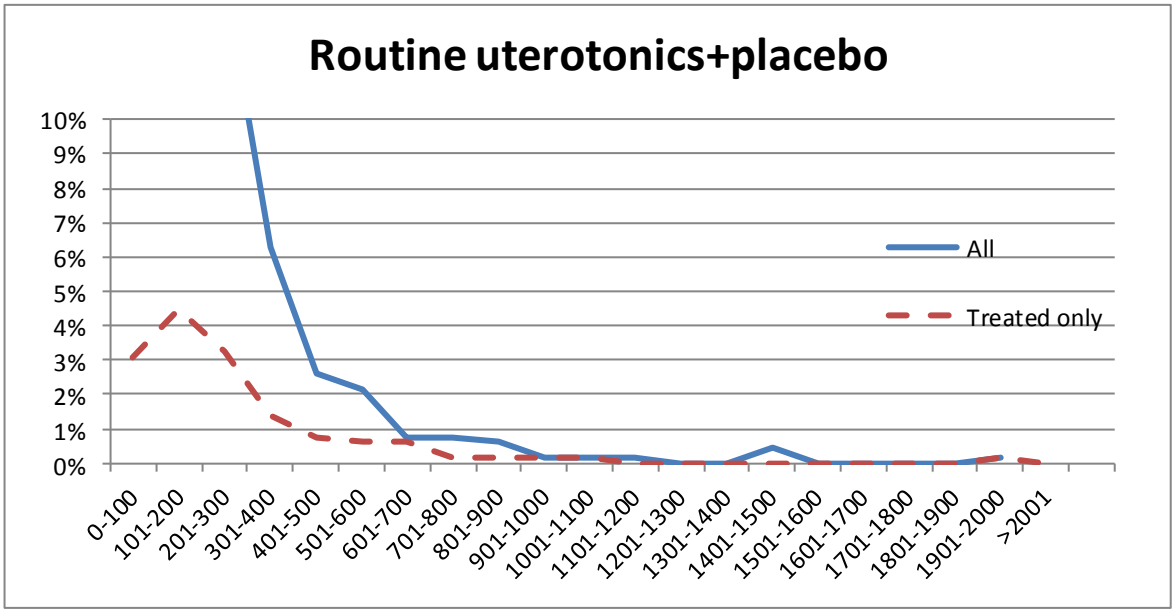

Figure 9. Histogram showing blood loss distributions of women in the Fawole trial (11) who were randomised to receive placebo. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment.

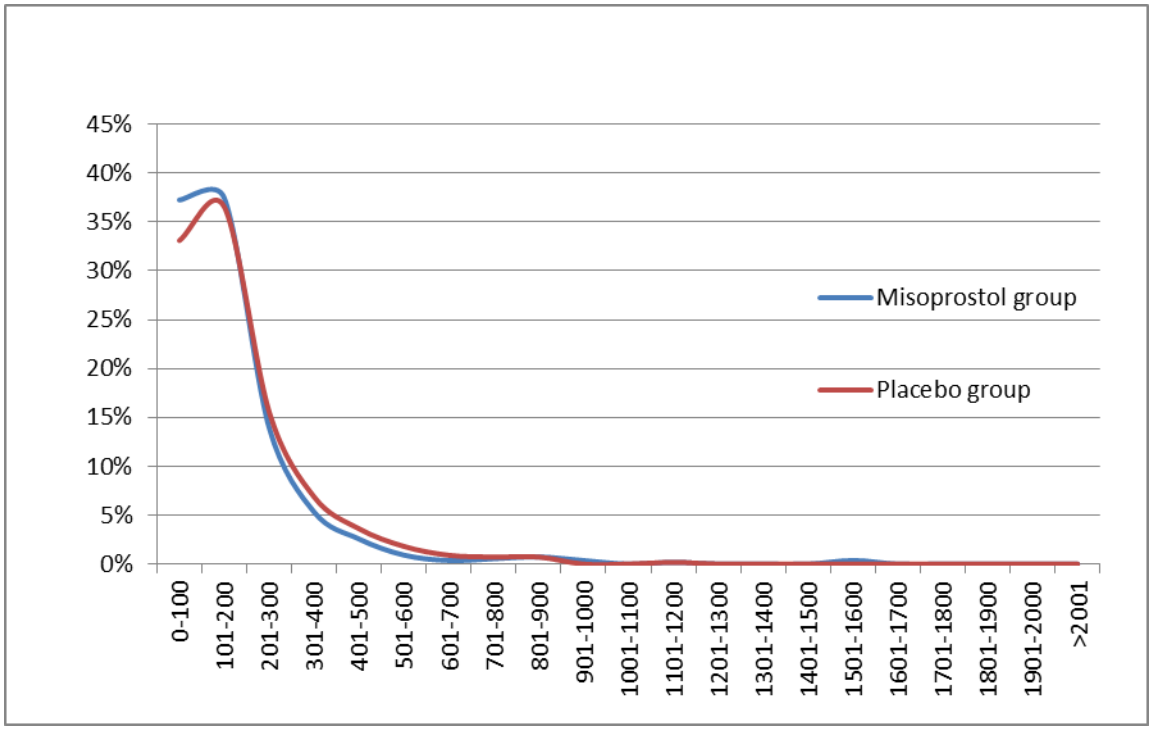

Figure 10. Histogram showing the main study results of the Hofmeyr trial (12). The red line represents the blood loss in all participants in the placebo group, whilst the blue line shows the blood loss distribution for all women included in the misoprostol arm

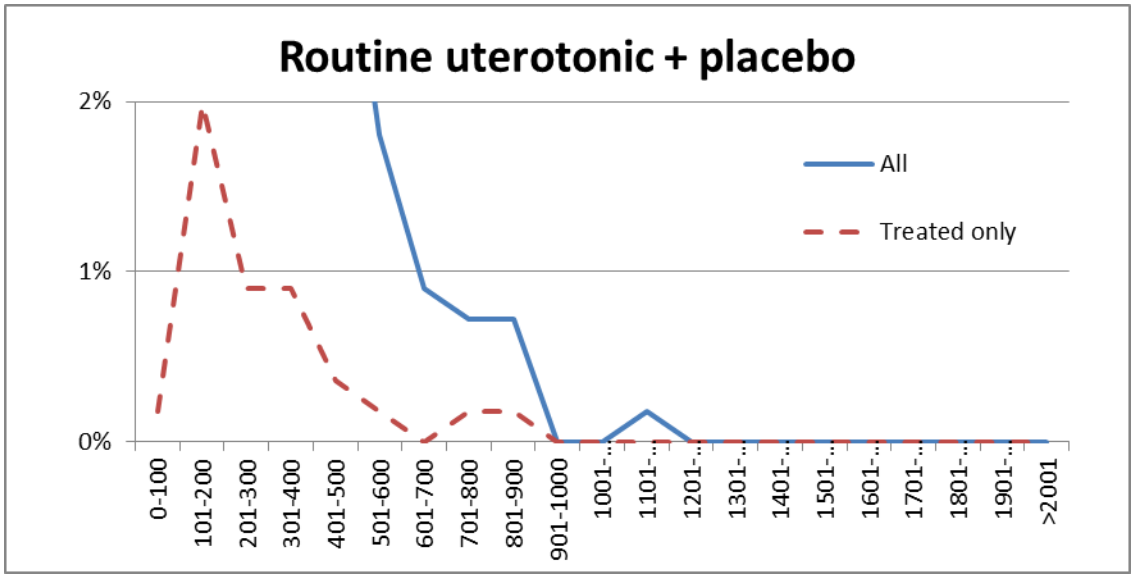

Figure 11. Histogram showing blood loss distributions in women in the Hofmeyr trial (12) who were randomised to receive placebo. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received
treatment

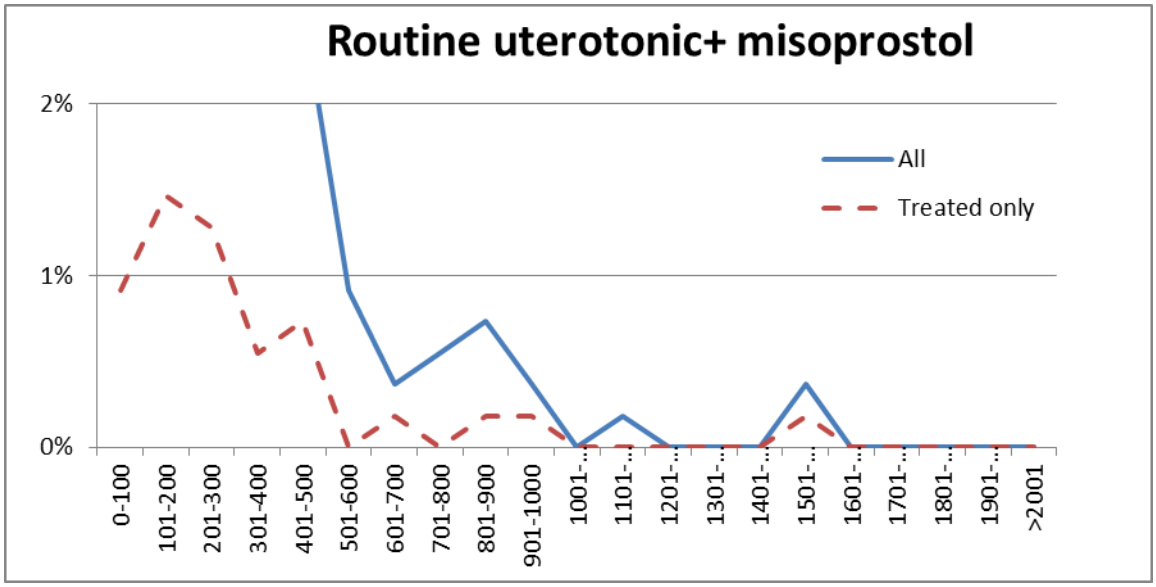

Figure 12. Histogram showing blood loss distributions in women in the Hofmeyr trial (12) who were randomised to receive misoprostol. The blue line shows the distribution for all included women, whilst the dotted line represents the blood loss in only those who received treatment

MCQ relating to postpartum haemorrhage

Question 1

A blood loss histogram:

A. shows the proportion of women with a postpartum haemorrhage in a study

B. shows the speed women's blood loss

C. shows the number (or proportion) of women with various levels of blood loss

D. ~~can~~ show the volume of blood loss at the time when study participants received treatment

Answer to question 1

(A) F (B) F (c) T (d) F

Explanation:

A blood loss histogram is created to show the number (or proportion) of women at each ~~level~~ of final blood loss. It cannot show how rapidly women reached that final rate. Whilst you can analyse those who received treatmentseparately (as in this study), you cannot assume that they stopped bleeding immediately after treatment. The histogram therefore shows the final blood loss, not the loss when the treatment was given.

To calculate the rate of blood loss over a certain volume (eg 500mls or 1000mls), you would need to measure the area under the curve ~~after~~ that blood loss increment. You cannot read the proportion off the graph directly.

Question 2

According to the histograms analysed in this study: in most women, the first dose of uterotonic treatment for PPH is given

A. when the blood loss is ~~over~~ 500mls

B. ~~Virtually all women with blood loss over 500mls receive uterotonic treatment~~

C. ~~Uterotonic treatment is commonly given~~ before the blood loss volume reaches ~~300~~mls

Answer to question 2

(A) F (B) F (c) T

Explanation

Although postpartum blood loss was objectively measured in all of included studies, ~~many~~ women receiving uterotonic treatment had blood loss under 500mls whilst those with large blood loss volumes received no treatment.

Cover Letter

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E nasreen.aflaifel@gmail.com

31st Jan 2019

Dear Beverly Burns,

Re: The Use Of Histograms To Assess The Efficacy Of Uterotonic Treatment For Postpartum Haemorrhage: A Feasibility Study.

Please find attached a study to be considered for publication in the Elsevier

The initial treatment of PPH has largely been dependant on uterotonics. This paper examined the use of histograms to assess the efficacy of uterotonic treatment for PPH. The findings from this study do not support the routine use of histogram analysis to assess the efficiency of uterotonic therapy. The paper provides further insights into clinical practice, with clinicians frequently using uterotonic therapies even when the volume of the blood loss is low. This demonstrates how uterotonic use in practice is often not linked with the standard 500 mls definition of PPH.

Declaration of conflicting interests: Anderw Weeks has on-going relationships with multiple interested parties on misoprostol use including FIGO, WHO and Gynuity Health Projects. He also runs an independent, non-profit making website called www.misoprostol.org which seeks to disseminate guidelines on the optimal doses for misoprostol use. It does not receive any funding or sponsorship. Nasreen Aflaifel declare that there is no conflict of interest.

We declare that this work has not been submitted to other journals for publication.

Best wishes,

Yours faithfully,

Dr. Aflaifel

***Detailed Response to Reviewers**

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16.04.2019

Re: The Use Of Histograms To Assess The Efficacy Of Uterotonic Treatment For Postpartum Haemorrhage: A Feasibility Study

Dear Elsevier Editor

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Thank you for revising our paper on" Third stage blood loss histogram". Most of the revisions prompted by the reviewers' comments are minor and require no further explanation than what appears in my responses below.

I made the requested changes to the manuscript and added the reference to the tables as well. I also checked the revised manuscript to that it is within the word limit and correctly formatted.

We hope the revised manuscript will better suit the Best Practice & Research Clinical Obstetrics & Gynecology but are happy to consider further revisions, and we thank you for your continued interest in our research.

Yours sincerely

Dr Aflaifel