THE USE OF MISOPROSTOL IN THE ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOUR

CHONG YAP SENG

MBBS, MMed (O&G), MRACOG, FAMS

A THESIS SUBMITTED

FOR THE DEGREE OF DOCTOR OF MEDICINE

NATIONAL UNIVERSITY OF SINGAPORE

2005

I dedicate this thesis to my wife, Ping, and my children, Timothy, Sarah, and Katharine, who continuously surprise and inspire me with their love and support.

ACKNOWLEDGEMENTS

Acknowledgements are due to many people who have been instrumental in helping me begin, continue and complete this thesis. First and foremost, I would like to acknowledge the mothers who participated in these studies, as well as the staff of the delivery suite. This thesis could not have been started if not for their generous participation, patience, and forbearance.

In particular, I must express my deepest appreciation to Professor Sabaratnam Arulkumaran, my supervisor, whose insistence that I start this thesis sparked my interest in research, and whose gentle persistence ensured that I completed it.

I wish to specially thank Dr Selina Chua, my mentor, who set the example and taught me everything about clinical research. Much of my initial work was conducted with Selina's kind assistance and inspirational guidance.

I thank Associate Professor PC Wong for his staunch support and for generously granting me the protected time to complete my thesis.

I would like to acknowledge the contributions of Dr Su Lin Lin, and the staff at CTERU, especially Dr Miny Samuel and Shen Liang.

I would also like to acknowledge Dr Chan Yiong Huak of the NUS Yong Loo Lin School of Medicine Biostatistics Unit, and the NUH-NUS Medical Publications Support Unit for their invaluable assistance in the preparation of this thesis.

COPYRIGHT CLEARANCE

Permission is granted by **Lippincott Williams & Wilkins (LWW)** for use of the following journal articles in the respective chapters 1, 2 and 6 of this thesis:

- Chong YS, Su LL, Arulkumaran S. Current strategies for the prevention of postpartum haemorrhage in the third stage of labour. Curr Opin Obstet Gynecol 2004; 16(2):143-150.

- Chong YS, Su LL, Arulkumaran S. Misoprostol: a quarter century of use, abuse, and creative misuse. Obstet Gynecol Surv 2004; 59(2):128-140.

- Chong YS, Chua S, Arulkumaran S. Severe hyperthermia following oral misoprostol in the immediate postpartum period. Obstet Gynecol 1997; 90(4 Pt 2):703-704.

I acknowledge **Blackwell Publishing** for the use of "Chong YS, Chua S, El-Refaey H, Choo WL, Chanrachakul B, Tai BC, Rodeck C, Arulkumaran S. Postpartum intrauterine pressure studies of the uterotonic effect of oral misoprostol and intramuscular syntometrine. BJOG 2001;108(1):41-47" in Chapter 4 of this thesis.

I acknowledge **Elsevier Scientific Publishers** for the use of "Chong YS, Chua S, Shen L, Arulkumaran S. Does the route of administration of misoprostol make a difference? The uterotonic effect and side effects of misoprostol given by different routes after vaginal delivery. Eur J Obstet Gynecol Reprod Biol 2004; 113(2):191-198" in Chapter 5 of this thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY

SUMMARY

The use of oral misoprostol for the prevention of postpartum haemorrhage was first suggested in 1996 in a small uncontrolled observational study. This formed the basis for my hypothesis that misoprostol, given in the correct dose and route, should produce a uterotonic effect similar to conventional oxytocics used for preventing postpartum haemorrhage.

I reviewed the literature to examine the current strategies for the management of the third stage of labour as well as the history and development of misoprostol. Rather than the cumbersome and imprecise blood loss measurements used in large clinical studies, I followed the lead of Dr Selina Chua and Professor Sabaratnam Arulkumaran in using intrauterine pressure measurements of postpartum uterotonic activity to directly measure the uterotonic effect of misoprostol. The reliability of Gaeltec® catheter-tip transducers for measuring postpartum uterine activity was confirmed using double catheters studies.

The first objective was to determine the dose of misoprostol that was most effective. I identified that the dose of misoprostol that provided the most uterotonic activity with the least side effects was 400 μg. Subsequently, I found that the route of administration that produced the fastest and greatest uterotonic effect was an oral aqueous solution of misoprostol. Unfortunately, this route also produced the most side effects, even with a dose of 400 μg. During the course of these studies, I discovered that even normal doses of misoprostol produced distinct side effects i.e. shivering and pyrexia in women after delivery. In all the literature prior to my report, severe side effects of misoprostol had only been reported with massive

overdoses. I found that shivering and pyrexia was, on the contrary, a very common side effect of misoprostol that was significantly associated with the dose of misoprostol given as well as its route of administration.

I then tested a dose of 200 μg oral solution misoprostol and found that this produced significantly less side effects than oral solution misoprostol 400 μg while not affecting its onset of action. The uterine activity produced with 200 μg oral solution misoprostol was less than that with 400 μg oral solution misoprostol and intramuscular Syntometrine 1 mL but the difference was not statistically significant.

Finally, I performed a systematic review of the randomised clinical trials using misoprostol administered by different routes for the prevention of postpartum haemorrhage and concluded that misoprostol, given as oral tablets or rectally, was less effective than conventional oxytocics with significantly more side effects. This may be because misoprostol administered as oral tablets or rectally has a significantly slower onset of action than conventional injectable oxytocics. Unfortunately, the randomised trials using oral solution misoprostol were underpowered statistically and were inconclusive.

My recommendation is that low doses of oral solution misoprostol might be the best and safest way to use misoprostol in future studies as it produces a fast onset of action, good uterotonic effect, and little side effects. Whether oral solution misoprostol 200 μg will be really effective or safe in clinical practice needs to be tested in large-scale randomised controlled studies.

THE HYPOTHESIS

Misoprostol, given in the correct dose and by the correct route, should produce a similar uterotonic effect to other oxytocics commonly used in the prophylaxis of postpartum haemorrhage.

CHAPTER 1

INTRODUCTION

Current strategies for the prevention of postpartum haemorrhage in the third stage of labour

Introduction

Excessive bleeding at or after childbirth accounts for almost half of all the postpartum maternal mortalities in developing countries [Li et al 1996], and is the single most important cause of maternal death worldwide. Effects on maternal morbidity are less well documented, but are likely to include such inter-related outcomes as anaemia, fatigue and depression. Many factors influence the severity of the consequences of postpartum haemorrhage [Tsu 1993]. The high incidence of severe anaemia in developing countries contributes to its high mortality there. Other factors include the large number of deliveries conducted at home by traditional birth attendants or family members, and the relative inaccessibility of medical expertise when complications occur.

Postpartum haemorrhage can occasionally lead to irreversible shock and death within a short time. A study in Egypt found that 88% of deaths from postpartum haemorrhage occur within four hours of delivery [Kane et al 1992]. Postpartum haemorrhage is a true obstetric emergency that demands fast vigorous treatment and proactive preventive management strategies. The introduction of the concept of active management of the third stage of labour and, in particular, the prophylactic use of oxytocics [Moir 1932; 1955] led to a significant decrease in the incidence of postpartum haemorrhage [Prendiville et al 1988] in many countries. However, not all maternity units practice active management of the third stage of labour. In this review, we will examine the evidence for the various strategies currently practised for the prevention of primary postpartum haemorrhage.

Strategies for the prevention of postpartum haemorrhage

Active management of the third stage of labour

The principle of the active management of the third stage is to hasten and augment uterine contraction and retraction at and after delivery of the baby and placenta to prevent postpartum haemorrhage due to uterine atony, thus reducing the blood loss. The main components include:

1. administration of a prophylactic uterotonic agent at or soon after delivery of the baby,
2. early clamping and cutting of the umbilical cord, and
3. early delivery of the placenta by controlled cord traction after the uterus has contracted.

Expectant management of the third stage of labour

Expectant or physiologic management involves waiting for signs of placental separation and allowing the placenta to deliver spontaneously or aided by gravity or nipple stimulation. Expectant management is also known as conservative or physiological management and is popular in some northern European countries, and in some units in the USA and Canada. It is also the usual practice in domiciliary practice in the developing world.

Practice preferences in different countries

The Global Network for Perinatal and Reproductive Health (GNPRH) conducted an observational, cross-sectional survey of 15 university-based obstetric centres in ten developing and developed countries to assess the use of active management of the third stage of labour and to determine whether evidence-based

practices were being used [Festin et al 2003]. Centres surveyed included those in cities as varied as Dublin (100% prophylactic oxytocic usage) to Trivandrum (0% prophylactic oxytocic usage). Data on approximately 30 consecutive vaginal deliveries in each centre (452 in total) were included. Significant intra-country and inter-country variation in the practice of the active management of the third stage of labour was found. Only 24.6% deliveries were conducted with active management of the third stage. This confirmed the existence of a large gap between knowledge and practice. The number of women who received prophylactic oxytocic agents (0–100%), additional dosages of oxytocin during the third stage of labour (4.6–100%), and controlled cord traction (13.3–100%) varied greatly. Most centres administered some form of oxytocic during the third stage of labour, but overall prophylactic oxytocic usage was only 44% (0–100%). As a result, the authors recommended the urgent implementation of evidence-based practice defined as the active management of the third stage of labour.

In Europe, a questionnaire survey of Dutch midwives and obstetricians about the standard practice during the third stage of labour revealed that prophylactic oxytocics in the third stage were used as a routine by 55% of the obstetricians and only 10% of the midwives. Where given, oxytocin was the drug of first choice [de Groot et al 1996]. Another questionnaire survey of 55 out of 57 institutions with delivery units in Norway showed that routine third stage prophylaxis with 5-10 IU oxytocin was practiced in less than half (47%) of the delivery units [Bjornerem et al 2002].

A recent review from a midwifery unit in Dallas concluded that, on the basis of current evidence, an active approach to the third stage should be adopted if a decrease in postpartum bleeding or avoidance of manual removal is desired [Brucker 2001]. However, an earlier questionnaire survey of 1500 obstetricians in Texas (two-thirds in urban, and one-third in rural practices) showed that 94% of them used oxytocics routinely in managing the third stage of labour. However, only 14.9% administered the oxytocics before delivery of the placenta, in contrast to 92.1% who gave oxytocics after the delivery of the placenta. Oxytocin was the chosen oxytocic drug (95%) for routine third-stage management. Thus, Texan obstetricians use oxytocin routinely in the management of the third stage of labour, but few are converted to conventional active management [Phillips & Kinch 1994]. In the United States, administration of oxytocics after delivery of the placenta appears to be the standard practice. The rationale for this is the worry that giving oxytocics immediately following delivery may hamper management of undiagnosed second twins or placenta accreta [O'Brien et al 1996]. To support this view, a recent large randomized controlled trial showed that the administration of prophylactic oxytocin before placental delivery did not reduce the incidence of postpartum hemorrhage or third-stage duration when compared with oxytocin administered after placental delivery [Jackson et al 2001].

In the United Kingdom, mothers and midwives who had participated in the Bristol randomised controlled trial of active versus physiologic management of the Third Stage of Labour were asked for their views on their management [Prendiville 1988a]. Both mothers and midwives commented adversely about the length of the third stage under physiologic management [Harding et al 1989]. The management of

the third stage in the United Kingdom and Australia is generally active [Garcia & Garforth 1989] but expectant management is more prevalent in Europe and the developing countries [McCormick et al 2002].

The findings of systematic reviews comparing various strategies for the prevention of postpartum haemorrhage

Active versus expectant management in the third stage of labour

A Cochrane systematic review analyzed the results of five randomised controlled trials comparing active versus expectant management in the third stage of labour [Prendiville et al 1988; Begley 1990; Thilaganathan et al 1993; Khan et al 1997; Rogers et al 1998]. The interventions assessed included early clamping and cutting of the umbilical cord, controlled cord traction, and the prophylactic administration of one of the following uterotonics agents- intramuscular oxytocin, intramuscular syntometrine, or intravenous ergometrine. No comparisons were made among the three types of uterotonics agents used. The reviewers found that active management was associated with reduced risks of maternal blood loss, postpartum haemorrhage of more than 500 mL, and prolonged third stage of labour [Prendiville et al 2003]. The reviewers also found that active management was associated with an increased risk of maternal nausea, vomiting and raised blood pressure, probably due to the use of ergometrine. There were no apparent advantages or disadvantages for the baby. They recommended that active management should be the routine management of choice for women delivering a baby by the vaginal route in a maternity hospital but stated that the implications are less clear for other settings, including domiciliary practice in developing and industrialised countries.

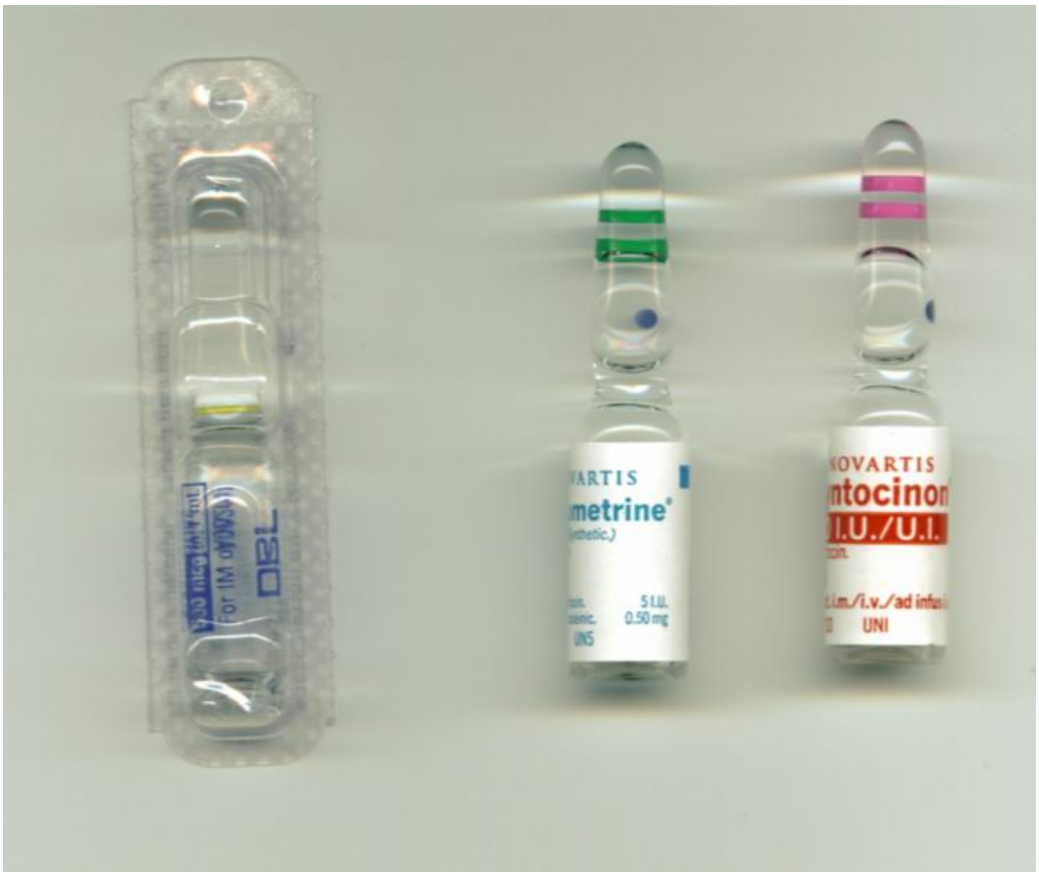


Figure 1.1: Commonly used oxytocics- Ergometrine, Syntometrine® and Syntocinon®

Prophylactic syntometrine versus oxytocin in the third stage of labour

Another Cochrane review compared the prophylactic use of the two most widely used uterotonics agents - intramuscular syntometrine and intramuscular oxytocin - in the third stage of labour [McDonald et al 2003]. The review included six randomised controlled trials [Nieminen & Jarvinen 1963; Dumoulin 1981; McDonald et al 1993; Mitchell & Elbourne 1993; Khan et al 1995; Yuen et al 1995], and concluded that the use of intramuscular syntometrine as part of the routine active management of the third stage of labour appears to be associated with a statistically significant reduction in the risk of postpartum haemorrhage when

compared to intramuscular oxytocin where blood loss is less than 1000mL. No difference was seen between the groups for severe postpartum haemorrhage. However, the use of syntometrine is associated with more adverse effects. A recent large randomised controlled trial not included in the review showed that there were no important clinical differences in the effectiveness of intramuscular syntometrine and intravenous oxytocin for the prevention of postpartum blood loss although intravenous oxytocin is less likely to cause hypertension [Choy et al 2002].

Prophylactic use of oxytocin in the third stage of labour

A third Cochrane review [Elbourne et al 2003] examined the use of various uterotonics agents in the third stage. In seven trials [Newton et al 1961; Howard et al 1964; Ilancheran & Ratnam 1990; Poeschmann et al 1991; Pierre et al 1992; De Groot et al 1996a; Nordstrom et al 1997], prophylactic intramuscular oxytocin showed benefits in terms of reduced blood loss and need for additional therapeutic uterotonics agents compared to no uterotonics. There was a non-significant trend towards more manual removal of the placenta, and more blood transfusions in the expectant management subgroup. In six trials [McGinty 1956; Fugo & Dieckmann 1958; Howard et al 1964; Sorbe 1978; Ilancheran & Ratnam 1990; De Groot et al 1996], there was little evidence of any difference between oxytocin and ergot alkaloids, although ergot alkaloids are associated with more manual removals of the placenta, and more raised blood pressure than with oxytocin. In five trials [Barbaro & Smith 1961; Bonham 1963; Soiva & Koistinen 1964; Francis et al 1965; Ilancheran & Ratnam 1990], there was little evidence of a synergistic effect of adding oxytocin to ergometrine versus ergometrine alone. The reviewers concluded that oxytocin alone was beneficial in terms of preventing postpartum haemorrhage,

and the need for additional therapeutic oxytocics. There was insufficient information about other outcomes and side-effects. There was little evidence in favour of ergot alkaloids alone compared to either oxytocin alone, or to syntometrine. They suggested that more trials were needed in domiciliary deliveries in developing countries where third stage complications are most common.

The evidence from systematic reviews

From these comprehensive systematic reviews, the following conclusions may be drawn:

1. Routine active management of the third stage of labour is superior to expectant management in terms of blood loss, postpartum haemorrhage and other serious complications, but is associated with an increased risk of unpleasant side effects, and hypertension, where ergometrine is used.
2. The use of intramuscular syntometrine as part of the routine active management of the third stage of labour reduces the risk of postpartum haemorrhage when compared to intramuscular oxytocin. However, the risk of severe postpartum haemorrhage is not increased with oxytocin, and the use of syntometrine is associated with more adverse effects.
3. There was little evidence in favour of ergot alkaloids alone compared to either oxytocin alone, or to syntometrine alone.

Other uterotonics agents used for prevention of primary postpartum haemorrhage

Intraumbilical uterotonic agents

In 1987, the first report of a randomized, double-blind, placebo-controlled trial was made on the influence of umbilical vein administration of oxytocin on the third stage of labour. Intraumbilical oxytocin produced no significant difference in the duration of the third stage compared to intraumbilical saline [Chestnut & Wilcox 1987]. The subsequent randomized trials yielded conflicting results. Three other studies concluded that intraumbilical oxytocin was no more effective than intraumbilical saline in influencing the duration of and blood loss in the third stage [Young et al 1988; Bider et al 1991; Ozcan et al 1996]. Two placebo-controlled trials showed that intraumbilical oxytocin was effective in decreasing the length of the third stage but not the blood loss [Athavale et al 1991; Kovavisarach & Rojsangruang 1998]. Two studies reported that intraumbilical oxytocin was more effective than intravenous oxytocin in reducing the duration of and blood loss in the third stage [Reddy & Carey 1989; Dahiya et al 1995], while one study concluded the converse with increased blood loss and fetomaternal transfusion in the intraumbilical oxytocin group [Porter et al 1991].

Several other studies and systematic reviews have been published with regard to the use of intraumbilical oxytocics but these studies assessed the utility of intraumbilical oxytocin for the treatment of retained placenta instead of postpartum haemorrhage prophylaxis. From the existing evidence, it would appear that the routine use of intraumbilical oxytocin for the prevention of postpartum haemorrhage

is questionable, although its use for the management of retained placenta may be promising [Carroli & Bergel 2003].

In 1992, Bider et al [Bider et al 1992] investigated the effect of umbilical vein injection of prostaglandin F2 alpha on the third stage of labour in a small double-blind randomised controlled trial. The authors concluded that the intervention did not influence the duration of the third stage of labour.

Oral ergometrine and methylergometrine

The uterotonic activity of oral methylergometrine was first reported in 1972 [Reichev et al 1972]. Oral ergometrine and methylergometrine were considered as possible alternatives to conventional oxytocics as they were easy to administer. Both these oral drugs are known for their strong uterotonic effect, and for their relatively slight vasoconstrictive properties. They act differently from oxytocin and prostaglandins, and have different adverse effects. Unfortunately, both are unstable even when stored under refrigerated conditions. Their pharmacokinetic and dynamic properties are unpredictable and no clinical effect on reduction of blood loss after childbirth has yet been shown [Andersen et al 1998; de Groot et al1996]. In a comprehensive review by de Groot et al, it was suggested that because of their unreliability, they had no place as routine prophylactic uterotonic agents but could be considered when conventional oxytocics failed to prevent postpartum haemorrhage [de Groot et al 1998].

Sublingual oxytocin

De Groot AN et al [1995] assessed the bioavailability and pharmacokinetics of sublingual oxytocin in a small number of subjects. The study showed great inter-individual variability in bioavailability. It was concluded that the sublingual route of administration of oxytocin, with its long lag-time and absorption half-life, did not seem a reliable route for the routine prevention of postpartum haemorrhage.

Injectable prostaglandins

The uterotonic activity of prostaglandins is well known. In a randomised controlled study, the prophylactic use of intramuscular prostaglandin 15-methyl F2 alpha (Carboprost, Astra, India) in the active management of the third stage of labour gave similar results to prophylactic intramuscular syntometrine in terms of length of the third stage of labour, incidence of postpartum haemorrhage and total blood loss after delivery. However it had the disadvantage of higher cost, as well as statistically significant increase in the incidence of profuse and frequent diarrhoea [Chua et al 1995].

In another randomized trial comparing Hemabate (Pharmacia-Upjohn Pharmaceuticals, Milton Keynes, Buckinghamshire) an analogue of 15-methyl-prostaglandin (PGF2alpha) with syntometrine, the study was discontinued early because of unacceptable gastrointestinal side effects [Lamont et al 2001]. The most common side effect was diarrhoea which occurred in 21% of women who received Hemabate compared to only 0.8% of syntometrine users. PGF2alpha is as effective as syntometrine in the prophylaxis of primary postpartum haemorrhage in women delivered by caesarean section or vaginally in both high and low risk groups but

there was a statistically significant increased risk of diarrhoea among users of PGF2alpha.

Cochrane reviews have found that injectable prostaglandins were associated with decreased blood loss and shortened duration of third stage when compared to other uterotonics. Adverse effects (vomiting, diarrhoea and abdominal pain) were more common with prostaglandins when compared to other uterotonic agents. Although injectable prostaglandins appear to be effective in preventing postpartum haemorrhage, concerns about safety and costs limit their suitability for routine prophylactic management of third stage of labour. However, injectable prostaglandins should continue to be used for the treatment of postpartum haemorrhage when other measures fail [Gulmezoglu 2000].

Carbetocin

The uterotonic activity of carbetocin, a long-acting oxytocin analogue, was first described in 1987 [Atke & Vilhardt 1987]. In pharmacokinetic studies, intravenous injections of carbetocin produced tetanic uterine contractions within 2 minutes, lasting about 6 minutes, followed by rhythmic contractions for a further hour. Intramuscular injection also produced tetanic contraction in less than 2 minutes, lasting about 11 minutes, and followed by rhythmic contractions for an additional two hours. The prolonged duration of activity after intramuscular compared with the intravenous carbetocin was significant [Hunter et al 1992]. Carbetocin produces side effects of mild lower abdominal cramping, flushing and warmth. Its prolonged uterine activity may offer advantages over oxytocin in the management of the third stage of labour.

In a dose tolerance study, carbetocin was given as an intramuscular injection immediately after the birth of the infant in 45 healthy women with normal singleton pregnancies who delivered vaginally at term [van Dongen et al 1998]. The dose-limiting adverse events recorded were hyper- or hypotension in three women, and retained placenta in four women. Serious adverse events occurred in seven women. Six had blood loss greater or equal to 1000 ml, four required manual removal of placenta, five required additional oxytocics, and five patients were given blood transfusion. Maximum blood loss was greatest at the upper and lower dose levels, and lowest in the 70-125 mcg dose range. The maximum tolerated dose was found to be 200 mcg carbetocin. Women receiving this dose experienced the most adverse events, including excessive blood loss.

In a Canadian multicentre, double-blind, randomised clinical trial of patients undergoing elective cesarean section, a single 100 micrograms intravenous injection of carbetocin appeared to be more effective than a continuous infusion of oxytocin in maintaining adequate uterine tone and preventing excessive intraoperative blood loss during cesarean section. Carbetocin was well tolerated with a similar safety profile to oxytocin [Boucher et al 1998; Dansereau et al 1999].

No clinical trials have yet reported the efficacy of intramuscular carbetocin for preventing postpartum haemorrhage in the third stage of labour for vaginal deliveries. The potential advantage of intramuscular carbetocin over intramuscular oxytocin is its longer duration of action. Its relative lack of gastrointestinal and cardiovascular side effects may also prove advantageous compared to syntometrine and other ergot alkaloids. The only limiting factor would appear to be its cost.

Misoprostol

Misoprostol is a synthetic analogue of prostaglandin E1 approved by the United States Food and Drug Administration in 1988 to be taken orally for the prevention and treatment of gastric ulcers associated with the use of nonsteroidal anti-inflammatory drugs. Because of its uterotonic and cervical-ripening activity, wide-ranging off-label uses have been found for misoprostol, and it has been described as "one of the most important medications in obstetrical practice" [Goldberg et al 2001]. The first use of misoprostol for the prevention of postpartum haemorrhage in the third stage of labour was reported in 1996 in a prospective uncontrolled study [El-Refaey et al 1996]. A further review of the history, development and use of misoprostol will be given in the next chapter.

Conclusion

Despite sound evidence that active management of the third stage of labour reduces the incidence of postpartum haemorrhage and other serious third stage complications, recent surveys, show that there are wide variations in practice around the world with expectant management still widely practised. Factors accounting for this situation include the desire for a more natural experience of childbirth, the philosophy that active management is unnecessary in low risk women, and avoidance of the adverse effects of conventional uterotonic agents. Intramuscular and intravenous oxytocin have proved to be as clinically effective as oxytocic preparations containing ergot alkaloids without the unfavourable side effects. Much recent interest has been focused on the use of misoprostol for the prevention of postpartum haemorrhage.

CHAPTER 2

Misoprostol: the accidental uterotonic agent

Introduction

Misoprostol is a synthetic analogue of prostaglandin E1 approved by the United States Food and Drug Administration (FDA) in 1988 to be taken orally for the prevention and treatment of gastric ulcers associated with the use of nonsteroidal anti-inflammatory drugs (NSAID). In 2001, annual sales for Cytotec® (misoprostol) reached approximately US$95 million. However, annual sales for this product have been declining in recent years, which may be partially due to the introduction of COX-2 inhibitors that largely eliminate the need for the mucosal protective effect of misoprostol [Express scripts 2002]. Ironically, since the early 1990s, misoprostol has been viewed with increasing interest by an unintended audience- obstetricians and gynaecologists. Because of its uterotonic and cervical-ripening activity, wide-ranging off-label uses have been found for misoprostol, and it has been described as "one of the most important medications in obstetrical practice" [Goldberg et al 2001]. Yet until very recently, misoprostol was not approved by the FDA for use in pregnant women, a stand strangely and strongly supported by its manufacturer (Searle, Chicago, USA) [Friedman 2001].

Natural and synthetic prostaglandins are known to affect the female reproductive system and misoprostol is not different in this respect. However, misoprostol has several advantages over other forms of prostaglandins that have made it a central focus of research in the specialty of obstetrics and gynaecology over the past two and a half decades. Misoprostol is rapidly absorbed orally [Zieman et al 1997] and, though not formulated for parenteral use, can also be administered sublingually [Tang et al 2002a], rectally [Khan & El-Refaey 2003], and vaginally [Zieman et al 1997]. It is substantially less expensive than other preparations of

prostaglandins and does not require refrigerated transport or storage [Searle 1995]. These characteristics make it particularly suitable for use in the setting of developing countries. The history of misoprostol and the development of this medication for the various indications are described in this review.

The pharmacological properties of misoprostol

Prostaglandins are naturally occurring 20-carbon cyclopentane carboxylic acids present in nearly all tissues, and are metabolized like fatty acids. Unlike hormones, they exert their effect locally, and are metabolized where they are produced.

Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methyl analogue of the naturally occurring prostaglandin E1. Misoprostol contains approximately equal amounts of the two diastereomers presented below (Figure 2.1).

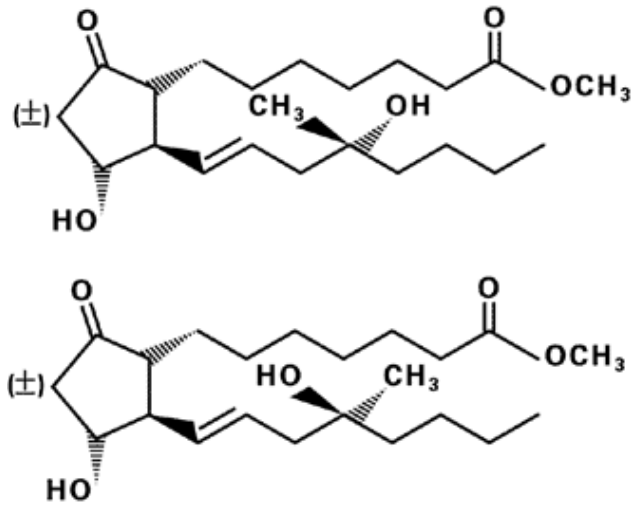


Figure 2.1: Misoprostol Chemical Structure

Formula: C22H38O5 Molecular wt.: 382.5

(±) methyl 11{α}//{alpha}, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate

Source: G.D. Searle & Company

Misoprostol is a water-soluble, viscous liquid. The commercial preparation commonly available are Cytotec® (Searle, Chicago, USA) tablets that contain the inactive ingredients hydrogenated castor oil, hydroxypropyl methylcellulose, microcrystalline cellulose, and sodium starch glycolate. The tablets are either 200 μg scored tablets or 100 μg unscored tablets.

Pharmacokinetics

The pharmacokinetic profile of misoprostol is characterized by rapid absorption, extensive metabolism and rapid excretion. Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogues.

Misoprostol is rapidly absorbed after oral administration with a Tmax of misoprostol acid of 12 ± 3 minutes and a terminal half-life of 20-40 minutes. There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200 to 400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days. Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid [Searle 1995].

Misoprostol is primarily metabolised in the liver, and less than 1% of its active metabolite is excreted in the urine [Foote et al 1995]. Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme systems in animals. The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range. Misoprostol has no known drug interactions.

Pharmacokinetic studies in pregnant women show that the peak plasma levels of misoprostol are sustained for up to 4 hours after vaginal administration [Zieman et al 1997]. Studies have also shown that sublingual and oral tablet misoprostol used for first-trimester abortions produce earlier and higher peak plasma concentrations [Danielsson et al 1999; Tang et al 2002a; Khan & El-Refaey 2003] than vaginal or rectal misoprostol, resulting in earlier, more pronounced uterine tonus. Gemzell Danielsson and colleagues' study also reported the times of onset of action for oral tablet (7.8 min, SD 3.0 min) and vaginal misoprostol (20.9 min, SD 5.3 min). These findings have very recently been validated in women after delivery [Abdel-Aleem et al 2003].

Misoprostol tablets are not designed for parenteral administration and may lead to slow or erratic absorption if given rectally or vaginally. This may be overcome by its proper formulation into vaginal pessaries and rectal suppositories. In the pharmacokinetic study by Tang et al, the peak plasma level of misoprostol acid was highest and earliest with sublingual misoprostol. This information has important significance in the clinical setting as it helps clinicians decide the most effective regime for their individual purpose.

Pharmacodynamics

Nonsteroidal anti-inflammatory drugs block the COX-1 enzyme from forming beneficial prostaglandins, such as PGE1. PGE1 plays a role in protecting the stomach and duodenum. Administering naturally occurring PGE1 orally is ineffective because it is unstable in an acidic environment. Misoprostol differs structurally from naturally occurring PGE1, allowing it to become metabolized. When metabolized it acts systemically to stimulate mucous production. To a lesser extent, misoprostol acts locally on the stomach wall. At doses 200 micrograms and above misoprostol also reduces gastric acid secretion. It is not possible to determine if misoprostol's ability to prevent gastric ulcers is the result of its anti-secretory effect, its mucosal protective effect, or both [Searle 1995]. Misoprostol has not been shown to aid in the healing of existing NSAID-induced ulcers, but it does prevent them.

Since misoprostol is a synthetic prostaglandin of type E1, it can be expected to have an effect in other areas of the body where regulatory prostaglandins are created. In addition to the stomach, two areas where misoprostol has an effect are the kidneys and uterus.

Normal prostaglandins in the kidneys are released to compensate for renal vasoconstriction. The prostaglandins PGE2 and PGI2 stimulate vasodilatation [Delmas 1995]. Use of NSAIDs reduces these prostaglandins by blocking constitutive cyclooxygenase. It follows that the addition of a synthetic prostaglandin such as misoprostol may help protect against renal impairment in chronic NSAID users. Misoprostol has been studied as a renal-protective agent [Shield 1995;

Weinblatt et al 1994; Wong et al 1995] but no statistically significant results have been reported.

Natural prostaglandins also ripen the cervix and induce uterine contractions during pregnancy. It is for this reason that misoprostol has found a novel application in the area of obstetrics and gynaecology.

Misoprostol does not produce clinically significant effects on serum levels of hormones, creatinine, or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function, and the cardiovascular system are not modified by recommended doses of misoprostol.

The development of misoprostol

Early interest in the pharmacologic activity of misoprostol centered on its effects on the gastrointestinal tract [Dajani et al 1976; Colton et al 1978]. The activity of misoprostol on other organ systems, including the uterus, had been investigated in preclinical studies [Bauer 1985] and clinical studies [Rabe et al 1987] but were largely ignored initially.

The antisecretory activity of misoprostol was confirmed in human subjects as early as 1982 [Akdamar et al 1982]. Misoprostol was first used in a multicenter randomized double-blind trial for patients with peptic ulcer disease in 1985 [Agrawal et al 1985]. It inhibits the secretion of acid and pepsin in the stomach and has been shown to have a mucosal protective effect on the gastrointestinal mucosa [Hunt et al 1983]. It is therefore widely marketed for use in the prevention and

treatment of peptic ulcer disease. It was noted that there was no significant adverse effects on blood pressure, pulse, platelets, the immune system, pulmonary function, or the endocrine system [Steiner 1985].

Misoprostol, taken as an oral tablet, was approved by the FDA in 1988 for the prevention and treatment of gastric ulcers associated with the use of nonsteroidal anti-inflammatory drugs.

Figure 2.2: Commercial misoprostol tablets

Approved use and known adverse effects

Misoprostol is the only approved agent for prophylaxis of NSAID-induced ulcers and is recommended in high risk patients if NSAIDS cannot be avoided. Misoprostol has not been shown to reduce the risk of duodenal ulcers in patients

taking NSAIDs. Misoprostol should be taken for the duration of NSAID therapy. It has no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

Side effects

Common side effects include diarrhoea and abdominal pain. Diarrhoea is more common with higher doses of the medication used, and usually goes away with continued administration. Rarely, profound and persistent diarrhoea necessitates stopping the medication. Less common side effects include headache, menstrual cramps, nausea, and flatulence, chills, shivering and fever, all of which are dose-dependent. It is interesting to note that prior to its use in pregnant women, chills, shivering and fever were not commonly reported side effects.

Pregnancy warning

Women of childbearing potential using misoprostol to decrease the risk of NSAID induced ulcers should be told that they must not be pregnant when misoprostol therapy is initiated, and they must use an effective contraception method while taking misoprostol. Package warnings are very clear that misoprostol is not to be taken by pregnant women [Searle 1995]. Physicians are advised to have the female patient start misoprostol for ulcer protection only on the second or third day of her next menstrual period. It is also necessary for her to have a negative serum pregnancy test result within two weeks prior to misoprostol therapy, and use birth control while taking misoprostol They should be warned that misoprostol may cause abortion (often incomplete), premature labour, or birth defects if given to pregnant

women. Misoprostol should also be avoided in nursing mothers because of concern over causing diarrhoea in the baby [Abdel-Aleem et al 2003].

Teratogenic effects

Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient [Pastuszak et al 1998; Gonzalez et al 1998] but the drug's teratogenic mechanism has not been elicited. Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects [Orioli & Castilla 2000]. Misoprostol is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively [Searle 1995]. Misoprostol is listed as a pregnancy category X drug.

Nonteratogenic effects

Misoprostol may endanger pregnancy and thereby cause harm to the fetus when administered to a pregnant woman. Misoprostol may produce uterine contractions, uterine bleeding, and expulsion of the products of conception. Abortions caused by misoprostol may be incomplete. If a woman is or becomes pregnant while taking this drug to reduce the risk of NSAID induced ulcers, the drug should be discontinued and the patient apprised of the potential hazard to the fetus [Searle 1995].

Early off-label use of misoprostol

The first report suggesting a potential off-label use of misoprostol for the termination of first trimester pregnancy was published in 1987 [Rabe et al 1987]. Two separate studies were conducted in patients in the first trimester of pregnancy who were about to undergo legal termination of pregnancies. In the first study, intrauterine pressure was monitored in eight patients by a transducer. In comparison with placebo, misoprostol was shown to cause a consistent increase in the frequency and intensity of uterine contractions and in the frequency of bleeding. In the second study, the effects of misoprostol 400 μg and 800 μg were compared with placebo in 300 patients at 9 to 12 weeks of gestation the evening before a legally permitted termination of first-trimester pregnancy. The incidence of spontaneous partial or complete abortion, vaginal bleeding and softening of the cervix were all significantly increased by misoprostol treatment. Although the investigators consequently recommended that misoprostol should not be used in pregnant women, their results must have formed the nidus for the subsequent interest in the use of misoprostol for termination of pregnancy. The first formal clinical trials on the use of misoprostol for obstetric [Fletcher et al 1993], and gynaecological purposes [Norman et al 1991] followed just over three years later.

Misoprostol and illegal abortion

Of the 46 million abortions occurring worldwide each year, 20 million take place in countries where abortion is prohibited by law, and every year, approximately 78,000 women die from complications due to illegal or unsafe abortions [“Facts in Brief: 2003”]. Unfortunately, in this matter, misoprostol has been a major factor over the last 15 years. The abuse of misoprostol for illegal

abortion was reported as early as 1991 by Klitsch [1991]. Misoprostol was widely used as an abortifacient following its introduction in 1986, especially by women in countries where abortion was illegal or where it was legal only in limited circumstances such as rape or to save a woman's life. Most of the publications and reports were therefore from Brazil and other countries in South and Central America. The widespread popular misuse of this drug is partly due to the low cost and the convenience of use, and partly because it is less traumatic than the other abortion methods and can be taken in privacy. In the late 1980s and early 1990s, the media, pharmacies, physicians and manufacturers also spread the news that misoprostol could be used to induce abortion and the medication could be purchased over-the-counter in pharmacies in some countries. Many epidemiological surveys were performed to investigate the percentage of women using misoprostol for self-induced abortion and the demographic characteristics of these women [Barbosa & Arilha 1993; Costa & Vessey 1993]. By 1990, about 70% of women hospitalised with abortion-related diagnoses reported use of the drug.

Several studies in the early 1990s suggested that misoprostol was an inefficient abortifacient [Coelho et al 1993; Fonseca et al 1996; Gonzalez et al 1998]. In retrospect, it was probably because the appropriate dosage and interval of administration had not been subject to detailed research at that time and the use of misoprostol in the setting of illegal abortion was likely to be amateurish at best. Coelho and colleagues reported in 1993 [Coelho et al 1993] that many women who used misoprostol for self-induced abortion had incomplete abortions and required subsequent uterine evacuation. The number of uterine evacuations in the obstetric

hospital in their study was noted to fall substantially when sales of misoprostol in the state was suspended in 1991.

In addition to incomplete abortion, misoprostol was also associated with failed abortion attempts and continued pregnancy. This raised concerns about the effects of *in utero* exposure of the fetus to misoprostol. The initial evidence came from case reports of congenital anomalies after maternal use of misoprostol. Gonzalez et al [1993] reported in 1993 on seven infants whose mothers attempted to abort using misoprostol in the first trimester of pregnancy without success. The seven infants were born with limb defects and, in four of them, a diagnosis of Mobius syndrome was made. Bond and Van Zee [1994] reported in the subsequent year a case of overdosage of misoprostol in pregnancy, and showed that toxicity could be manifested as hypertonic uterine contractions with fetal demise, hyperthermia, rhabdomyolysis, hypoxaemia, respiratory alkalosis and metabolic acidosis. Concerns were expressed with respect to the use of misoprostol as an illegal abortifacient. Following these case series, more studies were performed to define the effects of *in utero* exposure of the fetus to the drug. In the report by Gonzalez et al [1998] in 1998, the distinctive phenotypes included equinovarus with cranial nerve defects, arthrogryposis confined to the legs and terminal transverse limb defects. The authors suggested that these deformities were attributed to vascular disruption, which could be due to the uterine contractions induced by misoprostol. It was concluded that greater awareness of the widespread use of misoprostol to induce abortion should lead to public health interventions to prevent teratogenic effects. Schuler et al [1999] conducted the first prospective controlled study on fetal safety after misoprostol use. Even though they suggested that a potent

teratogenic effect of misoprostol exposure during pregnancy was unlikely, the study had limited statistical power.

Although sales of this abortifacient were suspended by health authorities in certain countries due to concerns about congenital malformations following unsuccessful abortion attempts in 1991, the drug remains widely available on the black market at an inflated price. Continued surveillance has since indicated that women have acquired more experience with the drug over time, resulting in lower and safer dosages used, and more effective use [Costa 1998]. However, the risks of self-induced abortion cannot be over-emphasized. Recent studies such as that by Pongsatha and colleagues [2002] indicate that the use of misoprostol for self-induced abortion is an ongoing problem. There is no quick and easy solution. Public health education plays an essential role in encouraging the use of contraception and reducing the morbidity and mortality related to illegal abortion.

First trimester termination of pregnancy

First trimester termination of pregnancy is traditionally performed by surgical evacuation of the uterus. This procedure is not always safe, especially in the setting of developing countries, and complications range from infection and uterine perforation to cervical stenosis and incompetence. Prostaglandins have been shown to be effective at inducing early abortion since the 1970s [Karim 1971]. By the 1980s, more stable prostaglandin analogues were found to be effective for abortion. These include parenteral sulprostone and intravaginal gemeprost. However, the adverse side-effects of these medications made them unsuitable as sole agents for abortion.

Studies investigating the use of misoprostol on pregnancy were first published in 1987 [Rabe et al 1987] as mentioned earlier. The incidence of spontaneous partial or complete abortion, vaginal bleeding and softening of the cervix were all significantly increased by misoprostol treatment. In 1991, the landmark study by Norman and colleagues [1991] was published in the Lancet. The authors investigated the effect of misoprostol on uterine contractility and showed that misoprostol, with or without mifepristone, resulted in a significant increase in the amplitude and frequency of uterine contractions. These results showed misoprostol to be a promising uterotonic agent and sparked off tremendous research interest in this area. Misoprostol was investigated both as a cervical priming agent prior to surgical abortion and as an agent for medical abortion.

With regard to the use of misoprostol as a cervical priming agent prior to vacuum aspiration of the uterus, numerous randomised controlled trials were published. Bugalho et al [1994] compared the use of vaginal misoprostol versus placebo in 1994, and Ngai et al [1995] first compared the use of oral misoprostol, placebo and vaginal gemeprost in 1995. The studies generally showed that misoprostol is as effective as or more effective than placebo and vaginal gemeprost in terms of the degree of cervical dilatation achieved which helped to facilitate surgical vacuum aspiration. The risks of the surgical procedure of cervical dilatation and evacuation of the uterus could therefore be minimized. These results were replicated by numerous other randomised controlled trials involving a large number of subjects.

For medical abortion, the clinical testing of mifepristone, a progesterone antagonist, started in 1982. The initial results were that at best, only 80% of women treated with mifepristone alone during early pregnancy had complete abortion, a rate not clinically acceptable. In 1985, investigators reported that adding small doses of a prostaglandin analogue increased the efficacy of mifepristone as an abortifacient to nearly 100% [Swahn et al 1985; Bygdeman & Swahn 1985]. In 1992, Thong and Baird [1992] investigated the use of mifepristone followed 48 hours later by oral misoprostol, and reported the combination to be highly effective. Research looking at the use of methotrexate followed by misoprostol for early abortion also started in 1993 [Creinin & Darney 1993]. However, the methotrexate-misoprostol regime was found to have lower efficacy compared to the mifepristone-misoprostol regime [Peyron et al 1993; Creinin et al 1995; Creinin et al 1996; Creinin et al 1997; Creinin et al 1997a]. In the study published by Schaff et al in 1999 [Schaff et al 1999], the complete abortion rate of 97% did not differ between women at 49 days' gestation or less and those at 50-56 days' gestation. Generally, it is felt that when mifepristone is administered in conjunction with a prostaglandin analogue such as misoprostol, the abortion rate is comparable to that for vacuum aspiration.

In 1995, El-Refaey H et al [El-Refaey et al 1995] conducted a prospective, randomized trial to compare oral with vaginal administration of misoprostol for first trimester abortion in women treated initially with mifepristone. The results were published in the New England Journal of Medicine and they concluded that vaginal administration of misoprostol was more effective and better tolerated than oral administration for the induction of first trimester abortion. A similar study by Carbonell et al [2001] also concluded that vaginal misoprostol was the best route of

administration, as it obtained the same or greater priming effectiveness of the cervix in half the time and with a much lower frequency of side effects. However, some studies concluded that both oral and vaginal misoprostol were of similar efficacy.

As mifepristone is expensive and only available in a small number of countries, investigators started to evaluate the use of misoprostol without mifepristone or methotrexate pre-treatment. In 1996, Koopersmith and Mishell [1996] and Bugalho et al [1996] published the first papers about the use of misoprostol alone for termination of early pregnancy. The results were very promising and were supported by several other studies in the following years. However, over the years, complete abortion rates from the use of misoprostol alone varied from 20% to 93.9%. The studies employ different dosages and regimens of misoprostol administration, and the results are therefore difficult to compare. The success rate of abortion was also defined differently with respect to the time period at which it was measured, further clouding the assessment of the efficacy of misoprostol.

In most of the studies, the misoprostol regime described takes a few days to complete. The dosages studied varied from 600 to 1000 micrograms every 24 hours for a maximum of three doses [Carbonell et al 1997; Carbonell et al 2000; Carbonell et al 2001a]. Only two studies used regimens that could be completed within a day [Koopersmith & Mishell 1996; Tang et al 1999]. Singh et al [2003] showed in their recent report that repeated doses of vaginal misoprostol over nine hours in a day care setting is an effective method of medical abortion for pregnancy up to eight weeks of gestation.

In 2001, one pilot study [Tang & Ho 2001] was performed to assess the use of sublingual misoprostol for medical abortion. Even though it was a small study involving a total of 43 women, 92% of the women with first trimester gestation had complete abortion, and all women requesting second trimester abortion had complete abortion. The preliminary results showed that this was a promising method for medical abortion and it was suggested that prospective randomised studies should be conducted to compare its efficacy and side effects with vaginal misoprostol, and to work out the dosage and dosing interval. Two prospective randomised placebo-controlled study comparing sublingual misoprostol and placebo were published in 2003 [Saxena et al 2003; Vimala et al 2003]. They concluded that sublingual misoprostol was effective in facilitating cervical dilatation prior to surgical abortion, and its usage significantly decreased the time of surgical evacuation, and minimized blood loss during the procedure.

Early pregnancy failure

Several studies investigated the use of oral misoprostol for incomplete abortion and missed abortion. Henshaw et al [1993] published one of the first studies looking at the use of oral misoprostol for incomplete abortion in 1993. Since then, several other studies were conducted, the results of which were all very encouraging. Chung et al [1999] compared the complication rates between groups of women randomised to receive either misoprostol or surgical evacuation. The immediate, short-term and medium-term medical complications were significantly lower in the misoprostol group than in the surgical group. However, some practitioners may feel that incomplete abortion is associated with risks of bleeding and infection which may make immediate surgical evacuation of the uterus a better option.

Herabutya et al and Wakabayashi et al [Herabutya & O-Prasertsawat 1997; Wakabayashi et al 1998] evaluated the safety and efficacy of vaginal misoprostol for medical evacuation of first trimester missed abortions and the reports were published in 1997 and 1998 respectively. The authors suggested that this appeared to be a good alternative to dilatation and curettage. This was followed by a number of other studies which suggested that repeated doses of misoprostol result in high rates of complete expulsions with minimal side effects and complications. A small randomised study comparing the efficacy of oral and vaginal misoprostol for missed abortion found vaginal administration to be more effective (88% versus 25% respectively) [Creinin et al 1997b)

In 2001, Xu et al [2001] studied the safety of misoprostol in the presence of a scarred uterus and concluded that, for termination of early pregnancy in scarred uteri, administration of mifepristone and misoprostol was safe and effective, but they suggested that further large studies were needed to confirm its acceptability as a routine medication in such situations.

Mid-trimester termination of pregnancy / Intrauterine fetal death

Besides social reasons, indications for mid – trimester termination of pregnancy include chromosomal and structural fetal abnormalities detected in the second trimester of pregnancy. Surgical dilatation and evacuation of the uterus had been done and is still being practised in a limited number of centres. However, surgical evacuation of the uterus in the mid trimester is associated with greater maternal morbidity and mortality and complications include infection, uterine perforation and hysterectomy. Before the introduction of misoprostol, medical

methods which were used include intra-amniotic hypertonic saline instillation, intra-amniotic prostaglandin F2α infusion, oxytocin infusion and vaginal gemeprost administration.

In 1993, Bugalho et al studied the effectiveness of intravaginal misoprostol administration [Bugalho et al 1993]. During the course of the study, the 800 micrograms dosage was successively reduced to 600, 400 and 200 micrograms. Many studies that were subsequently conducted aimed to achieve a balance between the efficacy of the dose regime and the possible adverse effects caused. A number of studies conducted showed that doses of 400 micrograms are effective and are associated with less side effects.

Elsheikh et al [2001] concluded from their study that the high efficacy and low incidence of side effects make misoprostol a useful alternative for mid-trimester termination of pregnancy. Several studies were also performed which made direct comparison between misoprostol and the other modalities for mid-trimester termination of pregnancy. Three randomised controlled trials compared vaginal misoprostol with gemeprost among women with live and dead fetuses in the second trimester [Nuutila et al 1997; Dickinson et al 1998; Wong et al 1998]. In all these studies, misoprostol was found to be as effective as, or more effective than, gemeprost. Ashok and Templeton [1999] reviewed 500 consecutive cases of non-surgical mid-trimester termination of pregnancy and concluded in 1999 that the combination of mifepristone followed by misoprostol provided a non-invasive and effective regimen for this indication. In 2001, [Munthali & Moodley [2001] compared the effectiveness between vaginal misoprostol and extra-amniotic

prostaglandins and concluded that the former was as effective as the latter. Another study by Ghorab and El Helw [1998] compared endocervical misoprostol and extra-amniotic prostaglandins F2 α and showed that misoprostol was more effective. The paper by Perry et al [1999] compared the efficacy of vaginal misoprostol to intra-amniotic prostaglandins F2 alpha. Although the study concluded that intra-amniotic prostaglandin F2 alpha was more effective than vaginal misoprostol, it was a small study and the dose of misoprostol used in the study was suboptimal judging by the doses used in other studies. Ramin et al [2002] concluded in their study in 2002 that high-dose oral misoprostol is more effective than concentrated oxytocin infusion for mid-trimester pregnancy interruption.

As the dosage of misoprostol, used for mid-trimester pregnancy interruption, tends to be high, the side-effects are the main limiting factors when one studies the dosage and the interval between administration. In the study by Zieman et al [1997], the plasma concentration of 400 micrograms of misoprostol acid after administration reached maximum values between 60 and 120 minutes and declined slowly to an average of 60% of the peak at 240 minutes after administration. Wong and colleagues [2000] suggested that if the pharmacological effect of misoprostol is related to its concentration in the plasma, misoprostol could be administered at longer than 3 hours intervals which may have fewer side-effects. They therefore made a comparison of the efficacy and side-effects of 400 micrograms misoprostol administered 3 hourly and 6 hourly. The results were published in 2000 and the study concluded that the 3-hourly regime was more effective in terms of a significantly shorter drug administration to abortion interval and higher percentage of successful abortion within 48 hours. The incidence of side-effects was similar in

the two groups except that of fever but the temperatures returned to normal within 24 hours after the last dose of misoprostol.

The route of administration of misoprostol was also investigated. In 2000, Ngai et al [2000] suggested that oral misoprostol is as effective as vaginal misoprostol if the dose was doubled. However, the increased dosage was associated with a higher incidence of side effects. In the following year, Gilbert and Reid [2001] conducted a randomised trial of oral versus vaginal misoprostol and the results showed that the vaginal route of administration was significantly more effective as judged by drug administration to abortion interval and the need or otherwise to augment the therapy with oxytocin infusion.

Induction of labour

Induction of labour is primarily performed with the aim of reducing maternal or perinatal morbidity and mortality, and is the commonest obstetric intervention practised. The success rate of achieving vaginal birth increases if the physiological mechanisms of labour can be replicated. A variety of methods have been employed for this intervention which include catheter balloon insertion, laminaria tent insertion, prostaglandin E2 analogues and oxytocin infusion. Induction of labour in the presence of an unfavourable cervix presents the greatest challenge and the focus of continuing research has been the development of an effective pharmacological agent which encourages cervical ripening effectively, to advance the success of this common intervention.

Sanchez-Ramos et al and Fletcher et al [Sanchez-Ramos et al 1993; Fletcher et al 1993] were the first to look at the use of vaginal misoprostol for induction of labour in viable fetuses at term, and the results were published in 1993. The results suggested that misoprostol is a cost effective and safe alternative for induction of labour at term. With these promising results, the use of misoprostol became an area of active research in the following decade.

Many studies, including two systematic reviews by Hofmeyr et al in 1999 [Hofmeyr 1999; Hofmeyr et al 1999a] and a meta-analysis of published randomized trials [Sanchez-Ramos et al 1997], have shown misoprostol to be more effective than placebo or other prostaglandins for the induction of labour. Misoprostol can achieve a higher rate of vaginal delivery within 24 hours, a shorter induction to delivery interval, and significantly lower overall caesarean section rates than pooled figures for the control groups [Sanchez-Ramos et al 1997a]. It minimizes the expenses associated with prostaglandin E2 analogues and intravenous oxytocin infusion. The safety profile has been demonstrated and is felt to be comparable to that of dinoprostone (PGE2). Some studies showed that there was a higher frequency of uterine tachysystole but this generally did not translate into an increased risk of adverse intrapartum or perinatal outcomes. Many factors affect the likelihood of successful induction with vaginal misoprostol and these include parity, initial cervical dilatation and gestational age at entry [Wing et al 2002].

As the efficacy of misoprostol became more certain, clinical trials were conducted to detail the optimal route of administration. From 1997 [Toppozada et al 1997], results of studies investigating the use of oral misoprostol for induction of

labour were published. The oral form of administration is appealing due to the convenience, lack of invasiveness and fewer digital examinations are required which could potentially reduce the risk of infection. From 1998, many studies were conducted which made direct comparison between oral and intravaginal misoprostol. Some studies suggested that the efficacy of oral and intravaginal misoprostol were similar [Adair et al 1998]. However, others reported that intravaginal administration of misoprostol is associated with a shorter induction to delivery interval, lower number of doses and lower oxytocin use [Toppozada et al 1997; Nopdonrattakoon 2003].

Studies were also performed to compare the efficacy of vaginal misoprostol gel and tablets and the study by Carlan et al [1997] suggested that misoprostol gel is associated with fewer uterine contraction abnormalities than the tablet form of the drug but results in a slower time to labour or delivery. In 1999, Liu et al [1999] reported the use of intracervical misoprostol and suggested that it is an effective alternative route of administration. Recent studies published in 2003 also indicated that sublingual misoprostol is a promising route of administration [Shetty et al 2002; Shetty et al 2002a] for the induction of labour in the presence of a live fetus.

With regard to the safety of misoprostol, the dosage and the interval of administration of the drug is as crucial as the route of administration. At the same time that studies comparing different routes of administration of misoprostol were being conducted, researchers also started comparing the differing dosing regimens of the misoprostol in order to ascertain the optimal and safest dose. Generally the 50 micrograms dosage results in a shorter induction to delivery interval and a higher

rate of vaginal delivery after one dose [Farah et al 1997; Srisomboon et al 1996]. However, a vaginal dose of 25micrograms is often recommended as the more prudent dose for labour induction because it is associated with a lower incidence of uterine hyperstimulation. It is also comparable to the 50 microgram dosage in achieving delivery within 24 hours [Hofmeyr 1999; Farah et al 1997; Srisomboon et al 1996; Wing & Paul 1996; Diro et al 1999; Meydanli et al 2003]. Doses higher than the 50 micrograms dosage have been associated with an increased risk of serious complications [Majoko et al 2002].

In the literature, the interval of administration of misoprostol ranged from every 3 to 6 hours. In 1997, [Wing & Paul [1997] studied the intervals between the doses of misoprostol and found that the average induction to delivery interval was shorter in the 3-hourly dosing group than in the 6-hourly dosing group. The former was associated with a slightly higher prevalence of tachysystole even though the difference was not statistically significant in their study. However, due to the possible risk of tachysystole, many centres use 6-hourly dosing intervals in their protocol.

In 1996, Ngai et al [1996] investigated the effectiveness of oral misoprostol as a cervical priming agent for patients presenting with pre-labour rupture of membranes at term and suggested that oral misoprostol is an effective agent for this group of patients. Similar results were published by Sanchez-Ramos et al in 1997 [Sanchez-Ramos et al 1997] and Shetty et al in 2002 [Shetty 2002b]. The latter concluded that active management with oral misoprostol resulted in more women

going into labour and delivering within 24 hours of prelabour rupture of membranes with no increase in maternal or neonatal complications.

Case reports were published with regard to the risk of uterine rupture during induction of labour with misoprostol [Bennett 1997; Wing et al 1998]. However, the safety profile of misoprostol use was demostrated in the study by Bique et al [Bique et al 1999] who used it on a group of grand-multiparous women with no significant adverse maternal or neonatal outcome. However, vigilance should be exercised in these cases, as emphasized by the American College of Obstetricians and Gynaecologists Bulletin [American College of Obstetricians and Gynecologists 1999a]. The use of misoprostol in cases of previous caesarean section is another area of concern. It has been shown that misoprostol is associated with a higher frequency of disruption of prior uterine incisions compared to the use of dinoprostone or oxytocin. Many authors recommend that misoprostol should be avoided for women with prior caesarean deliveries. In their meta-analysis, Plaut et al [1999] reported a 5.6% rate of rupture of uterine scars associated with the use of misoprostol compared with 0.2% in patients attempting vaginal birth after caesarean delivery with no stimulation.

In studying the safety profile of misoprostol, Urban et al [2003] performed Doppler velocimetry of umbilical, uterine and arcuate arteries immediately before and two to three hours after the administration of vaginal misoprostol or cervical dinoprostone. The results, published in 2003, indicated that both increase the uteroplacental resistance but do not affect the umbilical blood flow, therefore suggesting that misoprostol should be as safe as dinoprostone.

Third stage of labour

The first use of misoprostol for the prevention of postpartum haemorrhage in the third stage of labour was reported in 1996 in a small, prospective, uncontrolled study [El-Refaey 1996]. This formed the basis for my hypothesis that misoprostol, given in the correct dose and route, should produce a uterotonic effect similar to conventional oxytocics used for preventing postpartum haemorrhage. I have performed a systematic review of the randomised controlled clinical trials conducted since I began this thesis on the use of misoprostol for the prevention of postpartum haemorrhage in Chapter 10.

Legitimacy at last

Research interest in the off-label use of misoprostol for obstetric and gynaecological purposes over the last 15 years has matched, if not exceeded, the interest in misoprostol for its intended and approved use for the prevention of NSAID-induced gastric ulcers in the preceding ten years. The FDA guidelines on the use of marketed drugs [United States Food and Drug Administration 1998] states that "if physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects". The large body of medical evidence for the efficacy and relative safety of misoprostol used judiciously in obstetric and gynaecology practice clearly provides the scientific basis for its "creative misuse" in pregnant women. In November 1999, the American College of Obstetricians and Gynecologists (ACOG) published an Obstetric Practice Committee opinion [American College of Obstetricians and Gynecologists 1999], and a practice bulletin [American College of

Obstetricians and Gynecologists 1999a], to provide guidelines for its members on the appropriate use of misoprostol.

Matters came to a head when Searle, the manufacturer of misoprostol (Cytotec®), sent a letter to obstetricians and other physicians in the United States on August 23, 2000, warning that misoprostol "administration by any route is contraindicated in women who are pregnant because it can cause abortion", and that misoprostol "is not approved for the induction of labour or abortion". The letter further stated that "Searle has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or for induction of labour, nor does Searle intend to study or support these uses". This drug warning was unusual because many other medications have been and are used for off-label indications without precipitating similar responses from their manufacturers. This letter resulted in the wide-spread refusal by many hospitals and pharmacies to allow misoprostol to be dispensed for off-label use. The issue was further confused when the FDA announced the approval of mifepristone (RU 486) for the termination of pregnancies less than 49 days' gestation one month later on September 23, 2000. The FDA protocol for mifepristone termination of pregnancy includes the use of misoprostol 400 μg as part of the management. In December 2000, the ACOG published another committee opinion [American College of Obstetricians and Gynaecologists 2000] to specifically address the Searle drug warning, reaffirming that misoprostol is safe and effective for cervical ripening and labour induction when used appropriately.

An irate editorial by representatives of the ACOG [Hale & Zinberg 2001] accompanying a major review article on misoprostol and pregnancy [Goldberg et al 2001] in the first issue of 2001of the New England Journal of Medicine, lamented the fact that Searle had made no attempt "to contact the ACOG or any scientific group to review the evidence regarding the benefits and risks of misoprostol in pregnant women" before issuing their warning letter. A reply by a Searle representative in the same issue [Friedman 2001] stated that they "fully support the role of physicians, using their own professional judgment, to prescribe an approved pharmaceutical product for a use outside of its FDA-approved indication in the best interest of their patients, on the basis of published research, expert clinical opinion, or their own clinical experience", and that they "fully recognize the importance of a better dialogue with the American College of Obstetricians and Gynecologists, and with caregivers, on the issues and concerns reflected in the editorial".

The result of the ensuing dialogue was that just over a year later, on April 17, 2002, the FDA finally approved a new label for the use of misoprostol during pregnancy [American College of Obstetricians and Gynecologists 2003]. The new labelling revises the contraindication and the precaution that misoprostol should not be used in pregnant women by stating that the contraindication is only for pregnant women who are using the medication to reduce the risk of nonsteroidal anti-inflammatory drug-induced stomach ulcers. Misoprostol is now a legitimate part of the FDA-approved regime for use with mifepristone to induce abortion in early pregnancy, and is also recognized for its use for induction of labour.

Conclusion

For obstetrics and gynaecology, misoprostol has been a central focus of research for the past quarter century. It plays an important role in the field of termination of pregnancy at various gestations and induction of labour, and possibly for the management of postpartum haemorrhage. The increased access to and information on the use of misoprostol could help improve women's health and decrease the morbidity and mortality associated with various obstetric and gynaecological conditions.

Chapter 3

Assessing the uterotonic effect of drugs for preventing postpartum haemorrhage

Introduction

The gold standard for the assessment of any intervention in the third stage of labour for preventing postpartum haemorrhage is quantitative measurement of blood loss. Unfortunately, like most reference standards, the objective measurement of blood loss in the third stage is impractical and difficult to achieve with any precision. Various methods have been described including direct collection using specially-designed birthing beds and bedpans [Calkins 1929; Murdoch 1958] with subsequent measurement of the blood collected. This is often combined with the collection of pre-weighed linen and pads that have been soaked with blood at delivery, which are then re-weighed to calculate the amount of blood collected [Hofmeyr et al 1998]. One major criticism of this method, besides the obvious inconvenience and unpleasantness of the collection, is the contamination of the collected fluids by liquor, leading to overestimation of the actual blood loss.

Another method involves collection of all fluids, blood loss and clots in large pads laid out under the woman when delivery is imminent [Razvi et al 1996]. The pads are then processed and the blood loss determined using colorimetric methods [Newton et al 1977]. This method is more accurate but still inconvenient, time-consuming, and difficult to perform for large studies. As a result, many investigators have resorted to clinical estimation of blood loss. This could be a simple visual estimation [Ng et al 2001], or estimation with the aid of various blood collection strategies [Cook et al 1999]. Unfortunately, it has been well documented that clinical estimation of blood loss is inaccurate by a large enough margin [Brant 1967; Duthie et al 1991; Razvi et al 1996] to render it next to useless for objective assessment of interventions in the third stage of labour.

Other indirect measures of blood loss such as changes in pulse rate, fall in blood pressure, the need for additional uterotonic drugs to stop excessive bleeding, the need for blood transfusion, and a fall in haemoglobin levels are thus commonly used to assess blood loss in the third stage. Although they are easier and more convenient to document in a clinical trial setting than direct measurement of blood loss, they all lack sufficient precision and objectivity for accurately assessing methods of intervention in the third stage of labour [Lavery et al 1995].

Even if a convenient method is found for accurately measuring the blood loss in the third stage of labour, it should be borne in mind that if the intervention being assessed is a uterotonic agent, then the blood loss may not always reflect the efficacy of the therapy. Blood loss in the third stage does not only come from the placental bed. Blood is also lost from episiotomy wounds, lacerations, and other trauma to the birth canal. The type of vaginal delivery performed, the size of the baby, and the skill of the accoucheur, all influence the amount of blood lost from sites outside the uterus. However, any uterotonic agent being used can only influence the blood loss by inducing contraction and retraction of the uterine muscles and, hence, occluding the open vessels in the placental bed. Interventions that influence more than one aspect of the third stage, such as comparing active versus expectant management, or non-uterotonic drugs such as tranexamic acid are still best assessed by measuring blood loss. But for uterotonic drugs, the key factor that should be assessed is the uterotonic effect they induce, as they do not affect blood loss from other factors. In a previous study [Choo et al 1998], we found that uterotonic activity had no linear correlation with measured blood loss after vaginal delivery. Rather than placing

doubt on the utility of intrauterine pressure measurements, this proves that blood loss after vaginal delivery is dependent on factors other than uterine activity, factors that are not influenced by uterotonic agents.

Finally, it is generally accepted that uterine atony is the commonest cause of postpartum haemorrhage [Prendiville et al 1990], and most drugs used for the prophylaxis of postpartum haemorrhage act by increasing myometrial contractility. Hence, it has been proposed that uterotonic drugs are best assessed using methods to directly measure the uterine activity they induce [Chua 1998].

Direct measurement of uterine activity

Intrauterine pressure measurements are known to reflect the pressure within the myometrium [Hendricks et al 1962]. A variety of methods have been used to measure postpartum intrauterine pressure changes [Smith 1984]. These range from microballoons, to open-ended fluid-filled catheters [Hendricks et al 1962], and more recently, intrauterine pressure transducers [Ulmsten & Andersson 1979; Forman et al 1982; Forman et al 1982a; Ingemarsson et al 1989]. The earlier systems were cumbersome and more difficult to use, and common problems included hydrostatic instability and damping in fluid-filled catheters, as well as changing elasticity, wall contact, and induced uterine activity associated with balloons. The electronic microtransducer catheters are simple to insert and give more reliable and reproducible readings. Intrauterine pressure transducers have been used to measure intrapartum uterine activity by many researchers [Steer et al 1978; Chua et al 1992], and have been proven to be accurate and reliable. The use of intrauterine pressure transducers is employed by many maternity units to allow safe monitoring of uterine

workloads for augmentation of labour in high risk situations e.g. when high doses of oxytocin are being used, in multiparous women, or when a trial of scar is being conducted [Arulkumaran et al 1992].

Intrauterine pressure transducers

Prior to the introduction of intrauterine pressure transducers, intrauterine pressure measurements were taken using fluid column techniques that transmit pressure changes through a fluid column contained within a catheter to a connected transducer for conversion to a recordable form. These methods are extremely sensitive to motion and to the relative position of the tip of the catheter to the externally placed transducer. Compliance of tubing, fluid leaks, the problems of damping and resonance all combine to induce errors and artefacts.

The intrauterine pressure transducer obviates the problems of hydrostatic instability, resonance, and damping of fluid columns, along with those of elasticity, wall contact, and induced uterine activity associated with fluid-filled systems. By moving the pressure sensor into the uterus, the inaccuracies of pressure wave transmission to an external manaometer or strain gauge are avoided. The first pressure transducer was a small carbon granule, and the resistance of the carbon granules were altered by pressure from the uterine walls in a proportionate way [Karlsson 1944]. This initial design was improved when Kelly & Schleifer introduced a small fine wire strain gauge in 1962 that could be passed through the cervical os [Kelly & Schleifer 1962]. The concept of the strain gauge for measurement of uterine contractions is based on the property of a wire to change its electrical resistance when subjected to stresses. It is, in essence, a rheostat where

resistance changes in proportion to the mechanical force to which it is subjected. Calibration of this strain gauge tocometer was performed in a simple pressure chamber connected to a mercury manometer [Kelly & Schleifer 1962]. The initial strain gauge was well tolerated by the patient and did not require severe restrictions of movement or position.

In 1973, Millar introduced an ultraminature catheter-tip pressure transducer based on a silicon strain gauge [Millar & Baker 1973]. These were shown to be useful in evaluating uterine activity during labour [Steer et al 1978]. This transducer was stronger, durable, and more stable than earlier semiconductor types. These improvements made it possible to provide stable in vivo calibration. It has gained wide acceptance for use in women in labour. Forman et al [1982; 1982a] first described the use of the microtransducer technique for recording postpartum uterine activity.

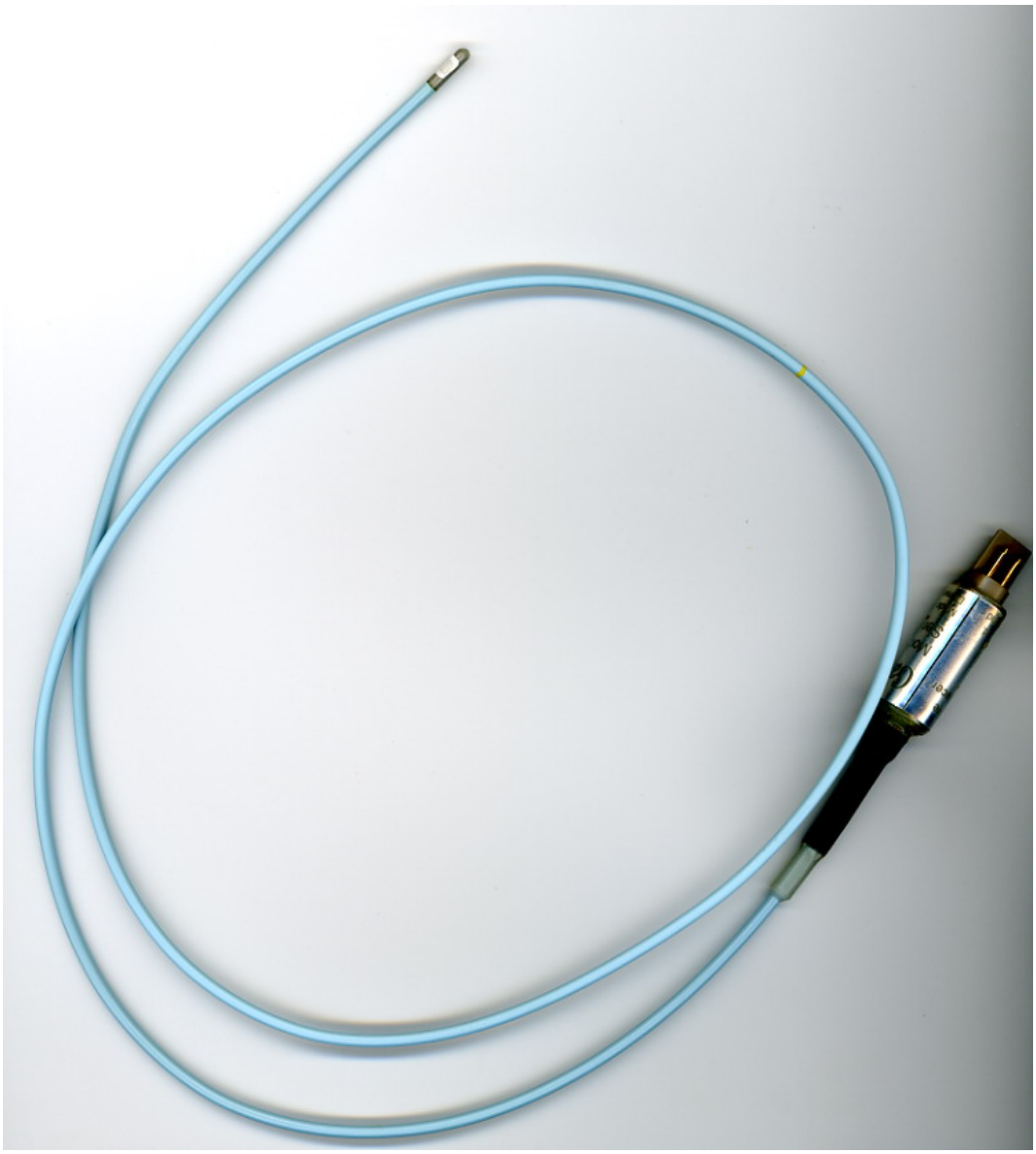


Figure 3.1: The Gaeltec® transducer-tipped pressure catheter

We used a commercially available transducer-tipped intrauterine catheter to measure uterine activity in the postpartum uterus. The pressure transducer (Gaeltec Ltd Dunvegan, Isle of Skye) is a bridge strain gauge deposited on the thin metal pressure-sensing surface (Fig. 3.1). The transducer is mounted on the end of a 900-mm woven Dacron catheter and is situated so that it measures lateral pressure and not head-on pressure. The sensing area is recessed to minimise the risk of damage

(Fig. 3.2). The catheter and transducer are sealed with a silicone rubber sleeve giving a diameter of 2.7 mm. The transducer is connected by a plug at the distal end of the catheter to a 2 m flexible extension cable, which is in turn connected to the contraction socket of the fetal monitor.

Figure 3.2: The recessed sensing area of the Gaeltec® transducer tip

The Gaeltec ® transducers have a specified full scale pressure range of 0-20 kPas (0-150 mmHg) within a temperature range of 0° to 4°C and a sensitivity of 37.5 μV/V/kPa (5 μV/VmmHg). They can be calibrated in a small sealed tube connected to a sphygmomanometer. The pressure reading drift is less than ±0.27 kPa (2 mmHg) in 24 hours. The catheters are connected to a Sonicaid Meridian fetal heart rate monitor (Oxford Sonicaid Ltd, Chichester, UK) and calibrated before use according to instructions set out in the Sonicaid handbook (Oxford Sonicaid Ltd,

Chichester, UK). The Sonicaid Meridian fetal monitor measures frequency, duration, and amplitude of uterine contractions automatically, and calculates the uterine activity or workload as area under the curve (active contraction area or uterine activity integral) every 15 minutes [Steer et al 1978].

The Gaeltec® transducer-tipped catheter is a reliable means of measuring intrauterine pressure in the first and second stage of labour [Chua et al 1992]. In the postpartum uterus, there is no amniotic sac. The microtransducer lies instead in a potential space, with the uterine walls separated by a film of blood and clots. The catheter, once placed in utero in this manner, is capable of giving an accurate reflection of the changes in the uterine contractility [Hendricks et al 1962], regardless of whether or not the amniotic cavity is present as is the situation after delivery. Theoretically, there are several problems associated with intrauterine pressure measurements after delivery:

1. the cervical os is open, allowing pressure generated by contractions to escape,
2. there is no amniotic fluid to transmit the intrauterine pressure accurately to the transducer,
3. placement of the intrauterine pressure transducer is difficult,
4. difficulty securing the intrauterine pressure transducer in a fixed place relative to the uterine fundus.

However, it has been shown that when a catheter is lying free within the upper portion of the puerperal uterus, it will record the same contractile pattern as does a catheter placed within the myometrium itself [Hendricks et al 1962].

To demonstrate the reliability of the Gaeltec catheter-tip pressure transducers for measuring postpartum uterine activity, we performed a study to check the correlation between the intrauterine pressure readings recorded by two catheter-tip pressure transducers inserted simultaneously into the postpartum uterus [Chua et al 1998].

Summary of study

Methods

We recruited 20 women who delivered vaginally without complications. Informed consent was obtained in the first stage of labour and the women were assigned randomly to two groups using a random number table. The study was approved by the department ethics committee.

The Gaeltec® (Gaeltec® Ltd., Dunvegan, Scotland) catheters were calibrated before use according to instructions in the Sonicaid handbook (Oxford Sonicaid Ltd, Chichester, UK). The delivery of the fetus was left entirely to the accoucheur, and routine administration of oxytocics in the third stage was carried out. Within 5 minutes of delivery of the placenta, a pair of calibrated Gaeltec® catheters was inserted transcervically into the uterine cavity. The women in Group 1 had two sterile Gaeltec® catheters inserted into the uterus with one inserted until the tip of the catheter could be felt to impinge on the fundus of the uterus, and the other catheter inserted similarly but then withdrawn 3-4 cm outwards and away from the tip of the first catheter. For Group 2, the two catheters were tied together with sterile catgut before insertion so that the tips of both catheters were next to each other at all times. The two catheters were inserted together into the uterine cavity until the tips

were felt to impinge on the uterine fundus. The catheters in both groups were then secured in place with adhesive tape to the maternal thigh and connected to a Sonicaid® FM6 fetal heart rate monitor individually (Sonicaid Ltd., Oxford Medical Instruments, Chichester, U.K.). The active pressures were recorded from the two catheters every 30 seconds in the 10 women in the two groups. The catheters that were tied together were checked on removal and showed no displacement from each other.

The agreement of the active pressure recorded by the two catheters for each woman was assessed in a 3-step procedure. Firstly, the Pearson's correlation was determined. Secondly, a Bland Altman plot was performed (± 2SD). Thirdly, the magnitude of the absolute difference in active pressures recorded by the two catheters was determined. All analyses were carried out using SPSS 13.0.

Results

Intrauterine catheters tied together

436 contractions were analysed with two catheters tied together. The Pearson's correlation between the readings was 0.993 ($p < 0.001$) (Figure 3.3), with 18/436 (4.1%) outside the mean difference ± 2SD range in the Bland Altman analysis (Figure 3.4). Table 3.1 shows that 2.5% of the absolute differences between the active pressures recorded by the two catheters were beyond 15 mmHg. If we set the acceptable clinical difference to be 10 mmHg, then only 8.2% (< 10%) were beyond. In 67.0% of these pairs, the active pressure values did not differ by more than 5 mmHg; and in 24.8% of the pairs, there was only a 6-10 mmHg difference in active pressure readings.

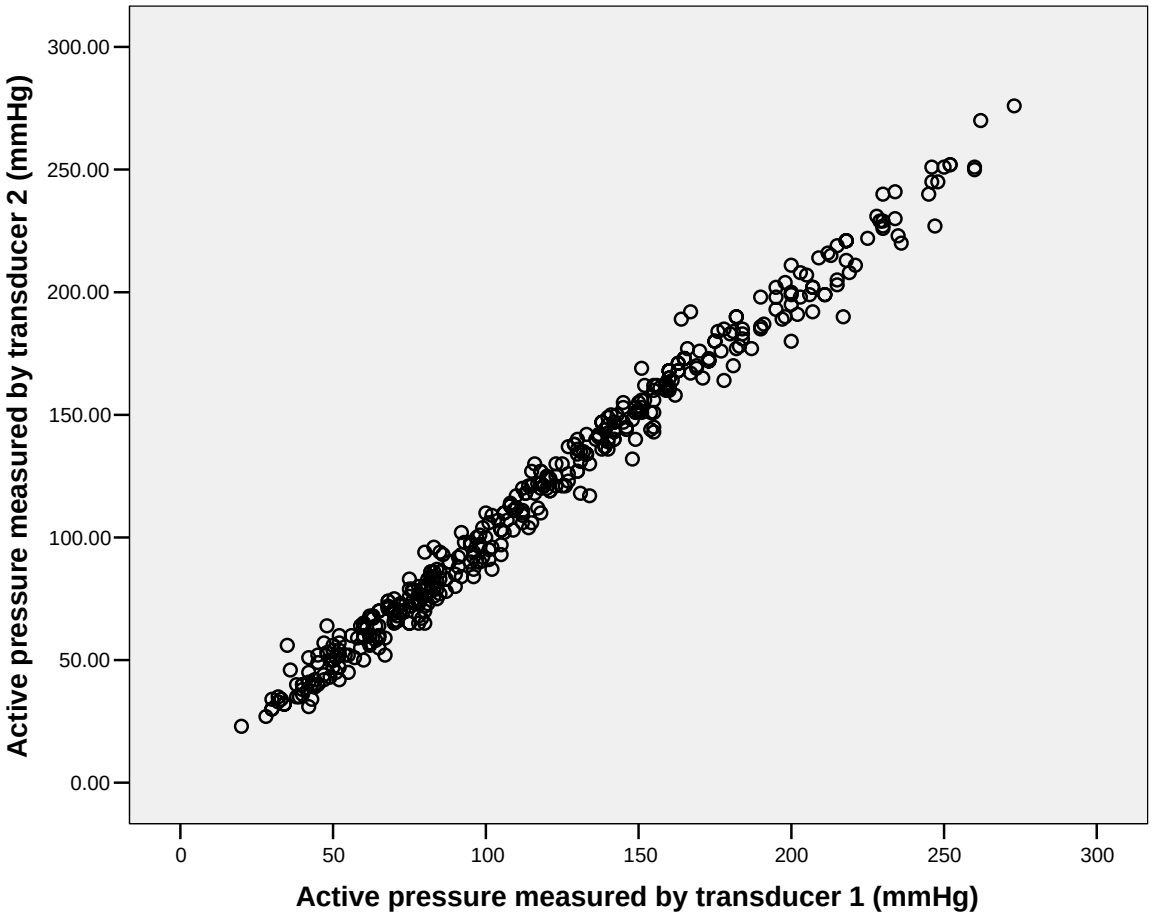
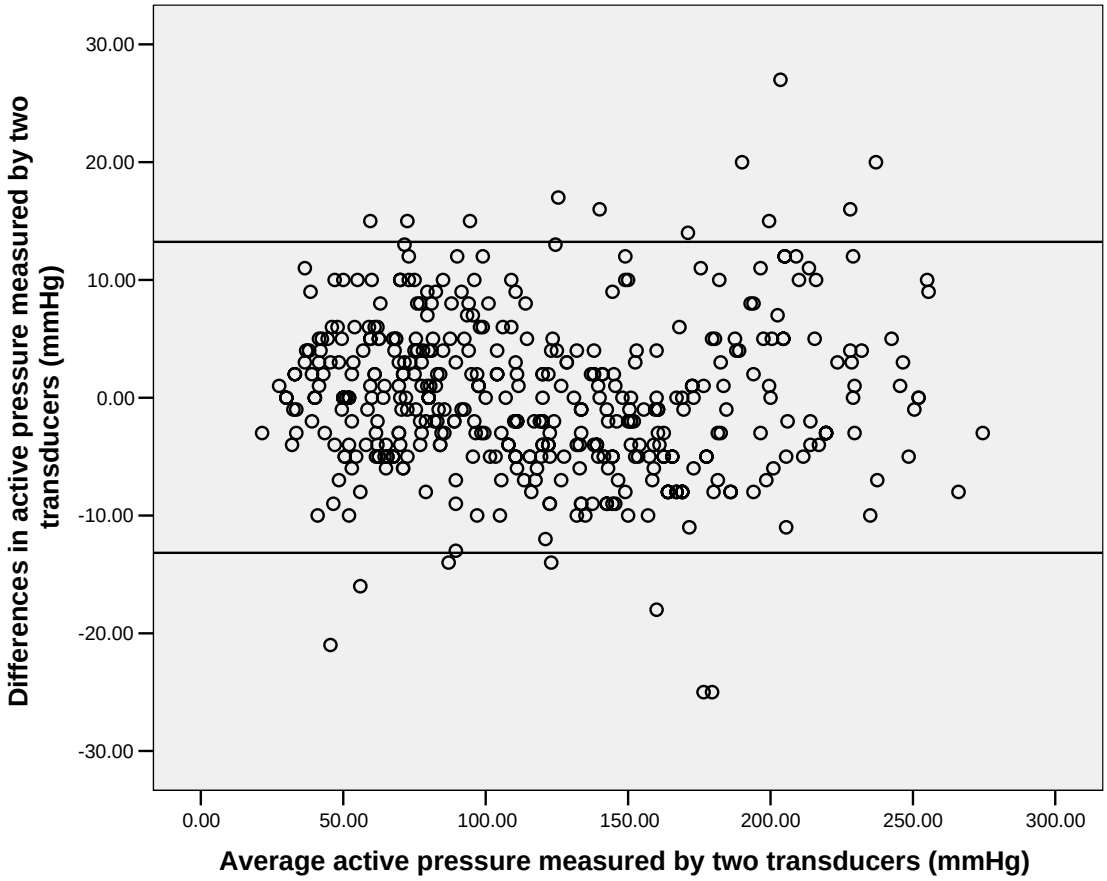


Figure 3.3: Scatter plot of active pressure readings between two transducers tied together and inserted into the uterine cavity



The upper and lower lines indicate mean difference ± 2SD (-13.17 to 13.23)

Figure 3.4: Bland Altman plot- Difference against mean active pressure from two transducers tied together and inserted into the uterine cavity

Table 3.1: Contraction to contraction difference in active pressure readings between two transducers tied together and inserted into the uterine cavity

Difference in active pressure readings between 2 catheters (mmHg)	Number	Percentage of total (%)
0 - 5	292	67.0
6 - 10	108	24.8
11 - 15	25	5.7
>15	11	2.5
Total	436	100

Intrauterine catheters inserted separately

975 contractions were analysed with transducers separately inserted. The Pearson's correlation between the readings was 0.970 ($p < 0.001$) (Figure 3.5), with 49/975 (5.0%) outside the mean difference ± 2SD range in the Bland Altman analysis (Figure 3.6). Table 3.2 shows that 7.2% and 14.0% of the absolute differences in active pressures recorded by the two catheters were beyond 15 and 10 mmHg respectively. In 56.7% of these pairs, the active pressure values did not differ by more than 5 mmHg and 29.3% of the pairs, there was only a 6-10 mmHg difference in active pressure readings.

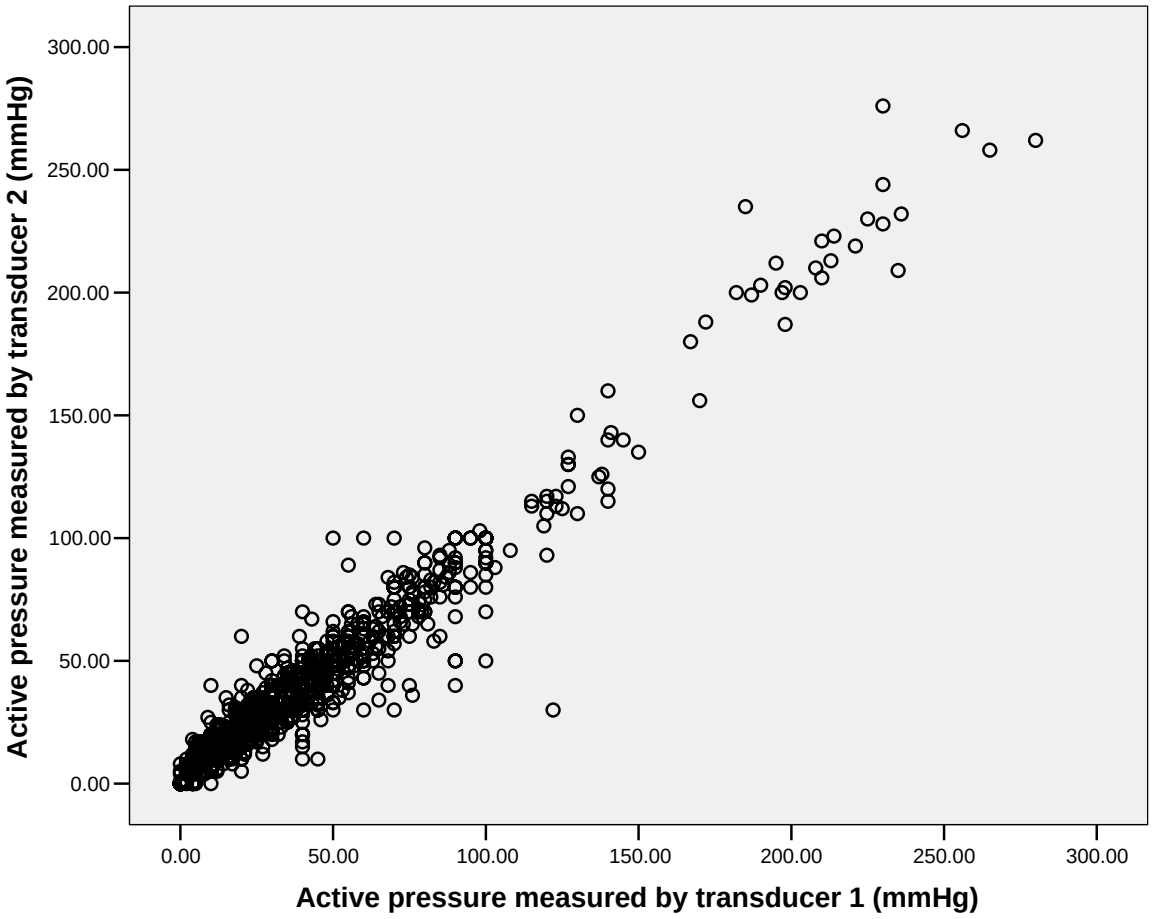
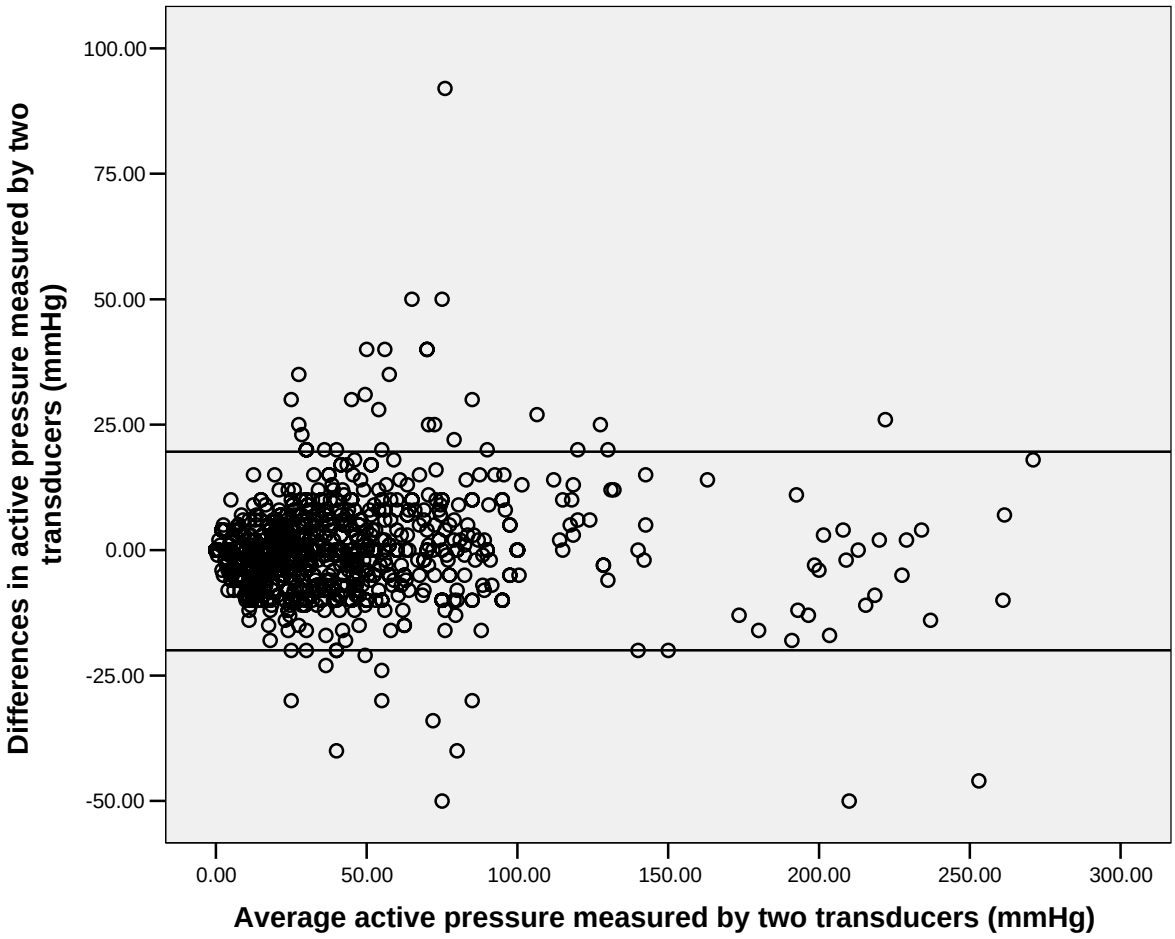


Figure 3.5: Scatter plot of active pressure readings between two transducers inserted separately into the uterine cavity



The upper and lower lines indicate mean difference ± 2SD (-19.96 to 19.64)

Figure 3.6: Bland Altman plot- Difference against mean active pressure from two transducers inserted separately into the uterine cavity

Table 3.2: Contraction to contraction difference in active pressure readings between two transducers inserted separately into the uterine cavity

Difference in active pressure readings between 2 catheters (mmHg)	Number	Percentage (%)
0 - 5	553	56.7
6 - 10	286	29.3
11 - 15	66	6.8
>15	70	7.2
Total	975	100

Discussion

The postpartum uterus provides a good model for in vivo evaluation of the uterine effect of drugs used in labour and the puerperium. We found that whether the transducers were inserted tied together in the uterine cavity near the fundus of the uterus, or separate within the uterine cavity, the correlation coefficient derived when the active pressures recorded by two transducers were compared showed good correlation ($r > 0.9$) with more than 85% of the absolute differences in the active pressures recorded being less than 15 mmHg.

The smaller variance in contraction to contraction differences when both catheters were tied together and inserted near the uterine fundus could be explained by the fact that when the catheters are inserted seperately, the second catheter was specifically pulled down towards the cervix away from the first catheter whose tip impinged on the uterine fundus. This could have resulted in some cases in the catheter tip being pulled near the cervix, and giving less accurate readings because of the pressure leak from an open cervix.

The results show that Gaeltec® transducer-tip catheters, which have been proven to be able to measure intrauterine pressure reliably during labour (Chua et al 1992), can also be used to measure uterine activity reliably in the immediate postpartum period. Although there is no liquor as in the intrapartum uterus, the blood between the apposed walls of the postpartum uterine cavity still provides a fluid medium to transmit pressure to the transducer. To reduce inaccuracies due to pressure leak from an open cervix, the transducer-tip catheters should be inserted as far into the uterine cavity as possible until the catheter is felt to impinge on the

uterine fundus. While there may be minor contraction by contraction differences in recordings of individual active pressure from two catheter-tip transducers, there was little difference when cumulative active pressures were compared, which matters in clinical practice.

Conclusion

The use of intrauterine pressure transducers to measure uterine activity after delivery has been validated by other researchers [Hendricks et al 1962; Forman et al 1982; Forman et al 1982a] and has been found to be reliable by us. In this setting, its use is purely for research as the measurement of uterine activity after delivery is not routinely practised. Recording uterine activity in the postpartum uterus will improve our ability to evaluate drugs of potential use in the puerperium. Based on this premise, we have chosen to assess the uterotonic effect of misoprostol using the Gaeltec® transducer-tipped catheter to measure intrauterine pressure in the postpartum uterus.

Chapter 4

Determining the optimum dose of oral tablet misoprostol using intramuscular syntometrine for comparison:

Postpartum intrauterine pressure studies of the uterotonic effect of oral misoprostol and intramuscular Syntometrine

Introduction

The practice of prophylactic administration of parenteral oxytocics in the active management of the third stage of labour has led to a 30% to 40% reduction in the incidence of postpartum haemorrhage [Prendiville et al 1988; Yuen et al 1995]. Despite this, postpartum haemorrhage remains a major cause of maternal deaths in the developing world [World Health Organisation 1991; Kwast 1991]. Maternal mortality and morbidity due to postpartum haemorrhage are 50 times commoner in developing countries than in the United Kingdom [Report of Technical Working Group 1990]. Several factors contribute to this including the paucity of supervised deliveries, blood transfusion resources and anaesthetic services. Another major factor could be the unavailability or ineffectiveness of routine oxytocic use in the third stage [Report of Technical Working Group 1990]. Oxytocin, ergometrine and Syntometrine® (Sandoz, Basel, Switzerland), the most commonly used oxytocic agents for this purpose, are parenteral drugs requiring sterile needles and syringes for administration as well as cool storage conditions (between 2°C to 8°C and away from light) [Data sheet compendium 1993]. Studies [Longland & Roebottom 1987; Walker et al 1988; Hogerzeil et al 1993; Chua et al 1993] have questioned the potency of injectable oxytocics in tropical climates. Financial constraints may also prevent both their routine use and proper storage. Early suckling has been suggested [Bullough et al 1989; Chua et al 1994; Irons et al 1994] as an alternative modality for reducing the incidence of postpartum haemorrhage in women in developing countries, but its efficacy is uncertain. There is thus a place for an effective but inexpensive uterotonic drug that can be administered orally and which does not require special storage conditions.

Misoprostol is an orally-administered prostaglandin E1 methyl analogue which has been used widely for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers and, more recently, for the induction of labour and abortion [Sanchez-Ramos et al 1993; Creinin & Vittinghoff 1994; El-Refaey et al 1995]. Misoprostol is very quickly absorbed orally [Karim 1987], has a shelf-life of three years [GD Searle & Co 1991] at room temperature (30°C) in the tropics, is relatively inexpensive and has recently been proposed for the active management of the third stage of labour [El-Refaey et al 1996; El-Refaey et al 1997]. We conducted a phase II study to determine the effect of oral misoprostol at various doses on uterine activity following normal vaginal delivery and compared these with the effect of intramuscular Syntometrine® 1 mL. We also documented the side effects associated with the use of these drugs.

Methods

We recruited 57 women who delivered vaginally after spontaneous labours not requiring induction or augmentation with oxytocin or prostaglandins. Informed consent was obtained in the first stage of labour and the women were assigned sequentially into six groups (Table 4.1) and prescribed either oral misoprostol (Cytotec®, Searle, Chicago) 200 μg, 400 μg, 500 μg, 600 μg, 800 μg or intramuscular Syntometrine 1 mL (oxytocin 5 units, ergometrine maleate 500 μg/mL). Exclusion criteria included anaemia (haemoglobin < 11.0 g/dL), multiple pregnancy, a history of postpartum haemorrhage in previous pregnancies or antepartum haemorrhage in the current pregnancy. The study was approved by the department ethical committee.

Table 4.1. Profile of women recruited for the study

Medication given	Intramuscular Syntometrine 1 mL	Oral misoprostol 200 μg	Oral misoprostol 400 μg	Oral misoprostol 500 μg	Oral misoprostol 600 μg	Oral misoprostol 800 μg
Number of women recruited	10	10	10	10	10	7*
Multiparous women	9	8	7	8	10	7
Mean age (years)	28	28	27	28	28	29
	[25-33]	[22-33]	[18-34]	[20-37]	[22-33]	[20-36]
Mean gestation (days)	271	276	272	272	272	268
	[260-286]	[261-287]	[245-284]	[253-287]	[259-281]	[209-289]
Mean length of labour (minutes)	190	234	198	234	230	145
	[56-482]	[24-560]	[17-665]	[60-435]	[110-487]	[16-351]
Mean birth weight (g)	3010	3385	3058	3306	3115	3396
	[2180-3470]	[2955-3470]	[2580-3890]	[2900-4100]	[2435-3600]	[2540-3830]

Figures in [ ] denote range.

*Recruitment of women into the 800 μg misoprostol group was stopped after one woman developed severe hyperthermia.

The delivery of the fetus was left entirely to the accoucheur. However, the routine administration of oxytocics in the third stage was omitted. Within 5 minutes of delivery of the placenta, a calibrated Gaeltec® (Gaeltec® Ltd., Dunvegan, Scotland) catheter with an intrauterine pressure transducer at its tip was inserted transcervically into the uterine cavity until the tip of the catheter could be felt to impinge on the fundus of the uterus. The catheter was then secured in place and connected to a Sonicaid® Meridian fetal monitor (Sonicaid Ltd., Oxford Medical Instruments, Chichester, U.K.), and uterine active contraction areas were recorded automatically. A researcher was with the woman throughout the two-hour period of the recording to document the temperature, pulse and blood pressure of the mother every 15 minutes, as well as any side effects experienced. The blood loss was closely monitored and if any women were thought to have excessive blood loss (> 500 mL), they would have been given conventional therapy for postpartum haemorrhage and taken out of the trial. No woman recruited for the study was excluded for excessive blood loss.

The baseline uterine activity of each woman was recorded for 30 minutes before the administration of the assigned medication. Uterine activity was then recorded for a further 90 minutes (Figure 4.1). Mean cumulative uterine activity in the 90-minute period after administration of the uterotonic drug was compared to the woman's baseline cumulative uterine activity in the 30 minutes before drug administration to determine the effect of the medication on the postpartum uterus as a percentage increase in uterine activity (i.e. each woman acted as her own control). The difference in uterine activity in the 90 minutes following the various doses of misoprostol relative to Syntometrine was compared using analysis of covariance,

with adjustment for the baseline uterine activity in the 30 minutes before treatment. The onset of action of the drug was calculated from each recording. The duration of action of the medication was defined as the period of time the mean uterine activity remained above the individual woman's baseline uterine activity. Statistical analysis was performed using the SPSS for Windows statistical package.

Results

Uterine activity

Ten women received intramuscular Syntometrine® 1 mL and 47 women were prescribed oral misoprostol (Table 4.1). Although the intention was to recruit 10 women in each group with different doses of misoprostol, the numbers were limited to seven in the group who were given 800 μg misoprostol. Because the seventh case developed severe hyperthermia [Chong et al 1997] that needed intense treatment, we felt it was unethical to continue with the 800 μg dosage.

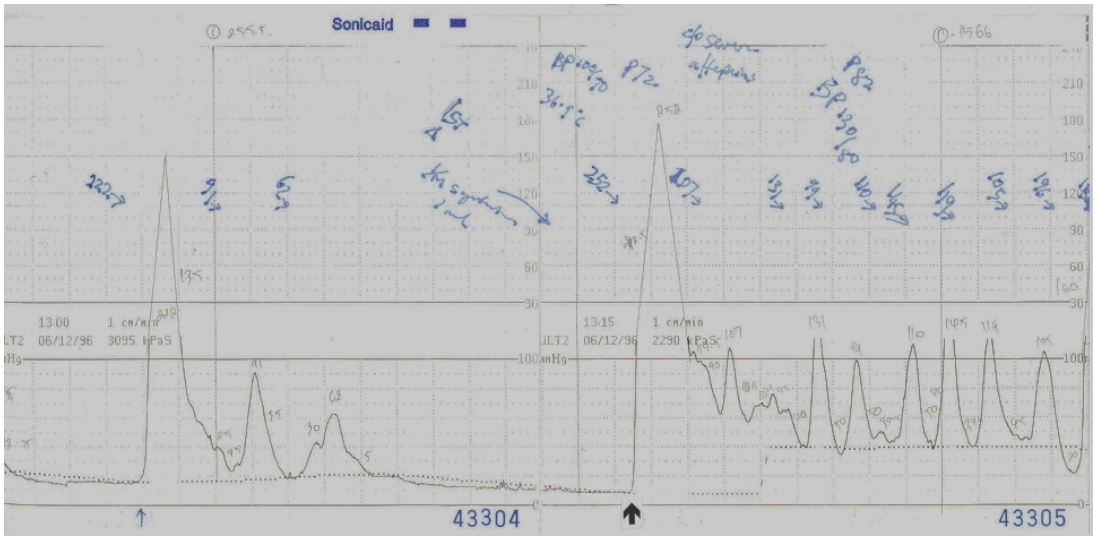


Figure 4.1: Intrauterine pressure recordings before and after intramuscular Syntometrine 1 mL

The largest increase in uterine activity (Table 4.2) was achieved with intramuscular Syntometrine 1 mL (152%, SD 67.0%), followed by oral misoprostol 600 μg (144%, SD 72.7%). However, there were no statistical differences in the mean increase in uterine activity following all the doses of oral misoprostol compared to intramuscular Syntometrine 1 mL (p=0.737). The mean onset of action (Table 4.2) of oral misoprostol (6.1, SD 2.1 min) was significantly (p=0.002) slower than that of intramuscular Syntometrine (3.2, SD 1.5 min) while the mean duration of action (Table 4.2) was similar in all the treatment groups (p=0.637).

There was substantial variation in the mean baseline cumulative uterine activity in the 30 minutes before medication across treatment groups, fluctuating from a low of 5358 to 7216 kPas sec. Thus the mean difference in cumulative uterine activity between the various doses of misoprostol and Syntometrine in the 90 minutes after treatment were compared after adjusting for the baseline cumulative uterine activity. There was no statistical difference (p=0.887) between the treatment groups, even with the largest difference of –2282 kPas sec (95% CI -7954 to 3390 kPas sec) comparing oral misoprostol 200 μg versus Syntometrine (Table 4.3, Figure 4.2).

Table 4.2. Details of the effect of intramuscular Syntometrine and oral misoprostol on the postpartum uterus

Medication given	Intramuscular Syntometrine 1 mL	Oral misoprostol 200 μg	Oral misoprostol 400 μg	Oral misoprostol 500 μg	Oral misoprostol 600 μg	Oral misoprostol 800 μg	*P*
Mean increase in uterine activity after medication (%)	152 [67.0]	123 [40.8]	122* [28.7]	142 [89.0]	144 [72.7]	117 [39.6]	0.737
Mean onset of action (minutes)	3.2 [1.5]	5 .3 [1.5]	6.4 [2.1]	5.9 [2.3]	5.4 [1.8]	7.4 [2.1]	0.002
Mean duration of action (minutes)	78 [18.8]	78 [15.5]	81 [14.0]	75 [18.6]	76 [13.2]	65 [16.6]	0.637

*The mean increase in uterine activity alone is not sufficient indication of the uterotonic effect of the drug as it is dependent on the baseline uterine activity before medication. The baseline uterine activity (see Table 4.3) allows each woman to act as her own control.

Figures in [ ] denote standard deviation.

Table 4.3. Mean cumulative uterine activity in the different treatment groups

Medication given	Baseline cumulative uterine activity over 30 min	Post treatment cumulative uterine activity over 90 min	Unadjusted mean difference in cumulative uterine activity (relative to Syntometrine)	Adjusted mean difference in cumulative uterine activity (relative to Syntometrine)
Intramuscular Syntometrine 1 mL	5806 (3610)	22530 (9521)	-	-
Oral misoprostol 200 μg	5838 (1559)	20309 (6168)	-2221 [-9758 to 5316]	-2282 [-7954 to 3390]
Oral misoprostol 400 μg	5358 (1877)	20000 (8860)	-2531 [-11171 to 6110]	-1683 [-7362 to 3996]
Oral misoprostol 500 μg	6212 (3650)	22203 (9937)	-328 [-9471 to 8815]	-1095 [-6773 to 4583]
Oral misoprostol 600 μg	6428 (2838)	24395 (7375)	1865 [-6136 to 9866]	689 [-4997 to 6375]
Oral misoprostol 800 μg	7216 (2776)	23049 (5383)	518 [-8656 to 9693]	-2147 [-8757 to 4463]

Figures in ( ) denote standard deviation, [ ] 95% confidence intervals.

All figures express cumulative uterine activity in kPas sec.

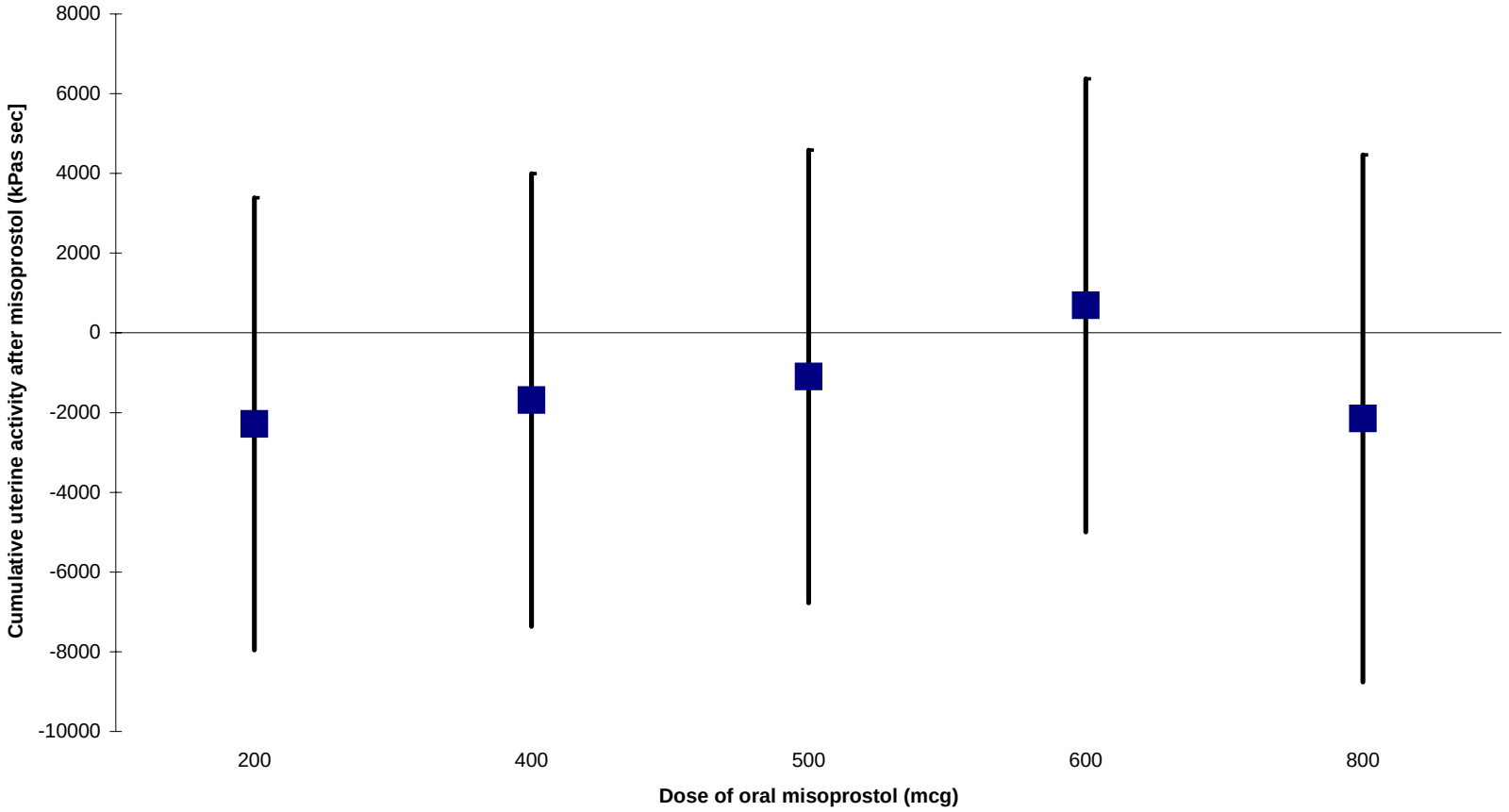


Figure 4.2. Adjusted mean difference in cumulative uterine activity after misoprostol relative to Syntometrine

Side effects

All the women in the study were observed closely for side effects in the two-hour period of uterine activity recording. These side effects are listed in Table 4.4. In the Syntometrine group, the most commonly observed side effect was moderate uterine pain of which nine women complained. A rise in diastolic blood pressure of 20 mmHg was noted in 2 women, as was nausea and retching.

In the misoprostol group, the commonest side effects were shivering (17, 36%) and a rise in body temperature above 38°C (19, 40%) (Figure 4.3). The shivering experienced by 16 of the 17 women was mild and transient starting between 12 minutes to 88 minutes (mean 26 mins) after misoprostol was taken, and lasting between 12 minutes to 55 minutes (mean 32 mins). The rise in body temperature in 18 of the 19 women varied between 38.2°C to 39.1°C (mean 38.7°C) and lasted from 10 minutes to 8 hours. The increase in body temperature was not accompanied by any ill effects except the shivering which usually preceded it. Most of the women were not aware of a sensation of fever. However, one woman receiving 800 μg of oral misoprostol experienced shivering for about an hour followed by severe hyperthermia requiring vigorous treatment [Chong et al 1997]. Shivering and mild pyrexia occurred in 60% of women given oral misoprostol 500 μg and 600 μg, and 43% of those given 800 μg. Shivering only occurred in 10%, and mild pyrexia in 20%, of the women given 200 μg and 400 μg of oral misoprostol. Only five women (11%) receiving oral misoprostol complained of uterine pain.

Table 4.4. Side effects of oral misoprostol and intramuscular Syntometrine

Medication given	Intramuscular Syntometrine 1 mL (n=10)	Oral misoprostol 200 μg (n=10)	Oral misoprostol 400 μg (n=10)	Oral misoprostol 500 μg (n=10)	Oral misoprostol 600 μg (n=10)	Oral misoprostol 800 μg (n=7)
Shivering	0	1	1	6	6	3
Temperature rise > 38 °C	0	2	2	6	6	3
Uterine pain	9	1	0	1	2	1
Rise in diastolic blood pressure > 20 mmHg	2	0	0	0	0	0
Nausea and retching	2	0	0	0	0	0

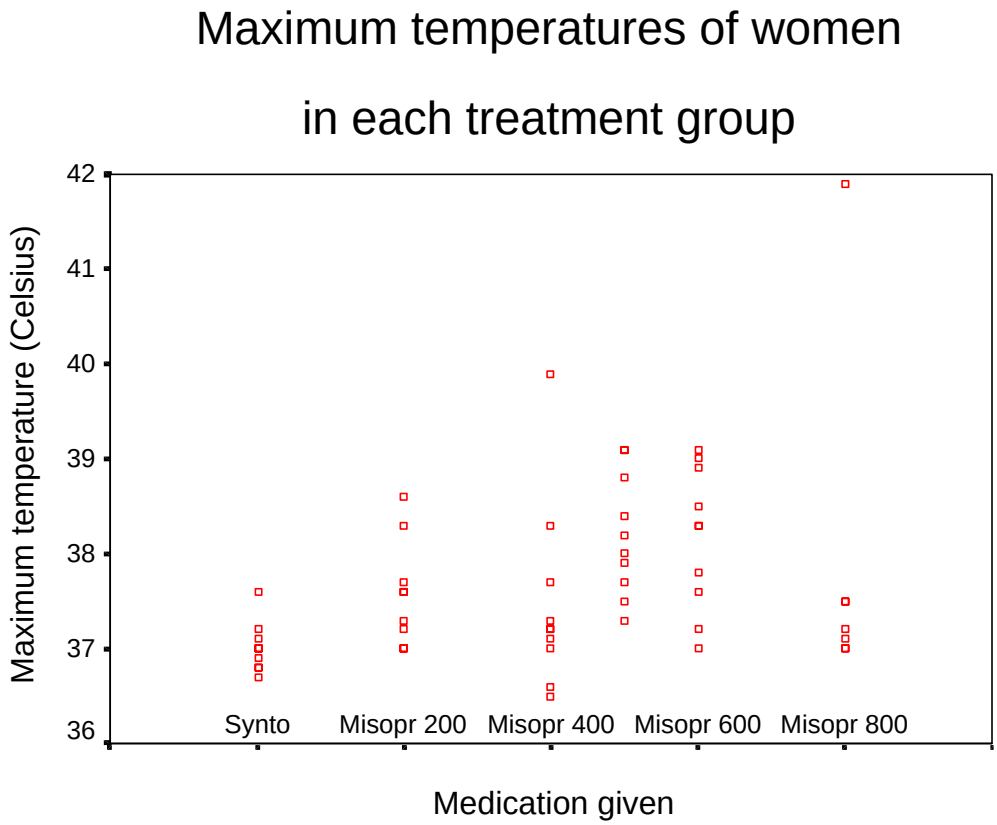


Figure 4.3. Maximum temperatures of women in each treatment group

Discussion

This pilot study was conducted to determine whether the effect of oral misoprostol on uterine activity after delivery would be similar to that of the commonly used oxytocic, intramuscular Syntometrine. The study was also designed to determine the optimum oral dose of misoprostol in terms of uterotonic effect and safety. Uterine activity was taken as a surrogate measure of the potential efficacy of oral misoprostol in the management of the third stage as all drugs given to prevent postpartum haemorrhage act by stimulating uterine contractions and retraction.

Catheter-tip pressure transducers have been used to measure uterine activity in the third stage of labour reliably and safely in various studies [Ingemarsson et al 1989; Chua et al 1993; Chua et al 1994; Chua et al 1998]. In our study, the women acted as their own controls to provide their own baseline uterine activity before administering an uterotonic drug. The change in uterine activity after drug administration should then be an accurate measure of the uterotonic effect of the drugs studied. Although the time of drug administration in this study was much later than in a normal situation, we felt that it was essential to account for biological variation in uterine activity by establishing each individual's baseline uterine activity before administering the drug. The delayed administration may not reflect the actual response if the drugs had been given immediately post delivery, but this was necessary to control for the biological variation in baseline uterine activity.

In our phase II study, we found that the uterotonic effect of oral misoprostol, at all the five doses tested, was not statistically different to that of intramuscular Syntometrine 1 mL (p=0.737) although intramuscular Syntometrine did produce the largest mean increase in uterine activity. While the uterotonic effect of oral misoprostol 500 μg and 600 μg were closest to that of intramuscular Syntometrine 1 mL (adjusted mean difference in cumulative uterine activity of –1095 kPas sec, 95% CI –6773 to 4583 kPas sec; and 689 kPas sec, 95% CI –4997 to 6375 kPas sec respectively), the incidence of shivering and pyrexia with these doses were high (60%).

Oral misoprostol 200 μg and 400 μg had definite but marginally lower uterotonic activity as compared with intramuscular Syntometrine 1 mL (adjusted

mean difference in cumulative uterine activity of –2282 kPas sec, 95% CI –7954 to 3390 kPas sec; and –1683 kPas sec, 95% CI –7362 to 3996 kPas sec respectively). The incidences of side effects with these doses (10% shivering and 20% mild pyrexia) were much lower than with doses above 400 μg. The safe oral dosage of misoprostol would thus seem to be 200 μg to 400 μg. These doses of misoprostol are already widely prescribed for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers and have been found to be safe for use in non-pregnant patients. Whether the uterotonic effect of oral misoprostol 200 μg to 400 μg will be sufficient to prevent postpartum haemorrhage is a question that will have to be answered by large randomised controlled clinical trials. The results so far are mixed. Two randomised controlled trials have compared rectal misoprostol 400 μg against Syntometrine 1mL [Bamigboye et al 1998a] as well as oral misoprostol 400 μg against placebo [Hofmeyr et al 1998]. These trials suggest that misoprostol at 400 μg may be as effective as Syntometrine and better than placebo. Conversely, two other trials found oral [Cook et al 1999] and rectal [Bamigboye et al 1998] misoprostol 400 μg to be significantly less effective than intramuscular oxytocin or Syntometrine, and no better than placebo. The data regarding side effects is clearer. Shivering was reported to be the main side effect in 19% of women in two of the studies [Hofmeyr et al 1998; Lumbiganon et al 1999] while pyrexia only occurred in 2% in one study [Lumbiganon et al 1999] using misoprostol 400 μg, and was not reported by the other authors. However, in three other recent studies [Amant et al 1999; Lumbiganon et al 1999; Surbek et al 1999] using a higher dose of oral misoprostol (600 μg), both shivering (28% to 42%) and pyrexia (7.5% to 34%) were more common.

The onset of action of oral misoprostol was significantly slower than that of intramuscular Syntometrine, but the durations of action of both drugs were similar. As the majority of postpartum haemorrhage occurs at separation of the placenta and in the moments immediately following due to uterine atony [Cunningham et al 1989; Still 1994] the critical period of action of uterotonic drugs used for the active management of the third stage of labour should be within the first 10 minutes of delivery of the neonate. However, regardless of when postpartum haemorrhage begins, it may not manifest as a sudden, massive bleed but rather as a steady, moderate ooze that persists unnoticed until serious hypovolaemia develops [Cunningham et al 1989]. The slower onset of action of oral misoprostol may require its earlier routine administration, perhaps at delivery of the fetal head rather than after the delivery of the neonate, but its long duration of action should prevent haemorrhage from delayed uterine hypotonia as effectively as Syntometrine.

The side effects observed with oral misoprostol were transient shivering and an asymptomatic rise in body temperature in all but one of the women affected. Shivering has been described as occurring in about 10% of women after routine vaginal deliveries while its incidence with epidural anaesthesia is as high as 33% to 60%, and it is regarded as being more of a nuisance rather than serious morbidity [El-Refaey et al 1997]. Mild pyrexia is a known but unexplained side effect of most prostaglandins used clinically. None of the other commonly reported side effects of prostaglandins such as nausea, vomiting, diarrhoea or significant changes in blood pressure was experienced by any of the women given oral misoprostol. Few women complained of uterine pain, probably because the increase in uterine contractility

following prostaglandin E1 tends to be a gradual one [Crowshaw 1983]. Women receiving intramuscular Syntometrine, however, uniformly complained of moderate uterine pain. Hypertension, nausea and retching also occurred in 20% of the women receiving Syntometrine.

In conclusion the results of this phase II study show that oral misoprostol has a definite uterotonic effect on the postpartum uterus. At doses of 200 μg to 400 μg, oral misoprostol has a uterotonic effect that is not statistically different to intramuscular Syntometrine® 1 mL, and side effects were less common than with the higher doses tested. It remains to be seen whether the slower onset of action of oral misoprostol will be an important factor in its use in the active management of the third stage of labour, perhaps necessitating its use in a more easily absorbable form or its earlier administration.

Chapter 5

Determining the optimum route of administration for misoprostol:

The uterotonic effect and side effects of misoprostol given by different routes after vaginal delivery

Introduction

Despite the findings of the World Health Organization multicentre randomized trial [Gulmezoglu et al 2001a] and the recent Cochrane systematic review [Gulmezoglu et al 2001] that injectable uterotonics are preferable to misoprostol for the routine active management of the third stage of labour in hospital settings, interest in misoprostol remains [Darney 2001; El-Refaey 2002; Khan & Sharma 2002; O'Brien et al 2002; Shannon & Winikoff 2002], especially in developing countries. The ease of use and storage of misoprostol relative to parenteral oxytocics, as well as its low cost are the main attractions of misoprostol. These properties make misoprostol practical for use in home deliveries, or by traditional birth attendants in less developed areas, and may help reduce the relatively high rate of maternal mortality from postpartum haemorrhage in these areas.

Since oral misoprostol was first suggested for use in the third stage of labour in 1996 [El-Refaey et al 1996], there have been at least 21 randomized controlled trials conducted on this subject, reflecting the importance placed on the use of misoprostol for preventing postpartum haemorrhage.

However, there has been little agreement on the optimum dose and route of administration of misoprostol for prophylactic use in the third stage of labour. The dose of misoprostol used in randomized controlled trials has varied between 400 μg in ten studies [Bamigboye et al 1998; Bamigboye et al 1998a; Hofmeyr et al 1998; Cook et al 1999; Walley et al 2000; Acharya et al 2001; Bugalho et al 2001; Gerstenfeld & Wing 2001; Kundodyiwa et al 2001; Karkanis et al 2002], 500 μg in

one study [El-Refaey 2000], 600 μg in nine studies [Zhao et al 1998; Amant et al 1999; Surbek et al 1999; Gulmezoglu et al 2001a; Hofmeyr et al 2001; Ng et al 2001; Caliskan et al 2002; Caliskan et al 2003; Oboro & Tabowei 2003], and 800 μg in one study [Lokugamage et al 2001]. The route of administration has been oral in 14 trials [Hofmeyr et al 1998; Zhao et al 1998; Amant et al 1999; Cook et al 1999; Surbek et al 1999; El-Refaey et al 2000; Walley et al 2000; Acharya et al 2001; Gulmezoglu et al 2001a; Hofmeyr et al 2001; Kundodyiwa et al 2001; Ng et al 2001; Caliskan et al 2003; Oboro & Tabowei 2003] and rectal in seven [Bamigboye et al 1998; Bamigboye et al 1998a; Bugalho et al 2001; Gerstenfeld & Wing 2001; Lokugamage et al 2001; Caliskan et al 2002; Karkanis et al 2002]. The common factor among all the trials using oral misoprostol was an increased incidence of shivering, going as high as 72% [El-Refaey et al 2000] and a rise in temperature as frequently as 34% [Amant et al 1999]. Interestingly, only three studies using rectal misoprostol [Bugalho et al 2001; Caliskan et al 2002; Karkanis et al 2002] reported a statistically significant increase in the incidence of shivering (38.1%, 23.6% and 11.8% respectively), and only one [Caliskan et al 2002] found a statistically significant increase in the incidence of pyrexia (4%).

In an earlier study using postpartum intrauterine pressure measurements as a surrogate endpoint for the uterotonic action of oral misoprostol [Chong et al 2001], we found that doses of oral misoprostol above 400 μg were associated with high incidences of shivering and pyrexia (60%). Oral misoprostol 400 μg produced a similar uterotonic effect to intramuscular syntometrine 1 ml while being associated with less shivering (10%) and pyrexia (20%). However, the onset of action of

misoprostol given as an oral tablet was significantly slower than that of intramuscular syntometrine. Earlier pharmacokinetic studies [Zieman et al 1997; Danielsson et al 1999] reported that oral misoprostol produced an earlier onset of action and greater initial increase in uterine tonus compared to vaginal misoprostol, mirroring the higher initial plasma levels of misoprostol acid achieved by the oral route, but did not compare oral misoprostol against parenteral oxytocics. With these findings in mind, we decided to study misoprostol 400 μg administered by different routes in order to identify the ideal route in terms of onset of action, uterotonic effect and side effects. Postpartum uterine activity was used as a surrogate measure [Danielsson et al 1999; Chong et al 2001] of the efficacy of misoprostol and syntometrine for the prevention of postpartum haemorrhage as all oxytocics work primarily by causing uterine contractions.

Materials and methods

Fifty women who delivered vaginally after spontaneous labours not requiring induction or augmentation with oxytocin or prostaglandins were recruited. None of the women used epidural analgesia. The women were all kept fasted except for sips of water in active labour to prevent oral intake from interfering with absorption of any oral medication. They were assigned sequentially into five groups (Table 5.1) and prescribed misoprostol (Cytotec®; Searle AG, Chicago, IL) 400 μg given as tablets orally, rectally, vaginally, or as an aqueous solution orally (two Cytotec® 200 μg tablets dissolved in 20 ml lukewarm water). The fifth group was given intramuscular syntometrine 1 ml (oxytocin 5 units, ergometrine maleate 500 μg/mL). Exclusion criteria included anemia (hemoglobin < 11.0 g/dl), maternal

infection, multiple pregnancy, a history of postpartum haemorrhage in previous pregnancies or antepartum haemorrhage in the current pregnancy. All women who met the criteria for inclusion and who consented to participate in the study were recruited if they did not require augmentation of labour, assisted or operative delivery and did not have retained placentas. The departmental ethics review committee approved the study, and informed consent was obtained from each participant. The study was conducted from August 1997 to November 1998.

Table 5.1. Characteristics of women recruited for the study

Medication given		Intramuscular syntometrine 1 ml	Misoprostol 400 µg Oral tablet	Misoprostol 400 µg Oral solution	Misoprostol 400 µg Rectal	Misoprostol 400 µg Vaginal
No. of women recruited		10	10	10	10	10
No. of multiparous women		10	10	9	4	8
Age (years)	mean	28.3	27.2	28.3	25.5	25.7
	SD	2.9	5.4	5.3	4.3	3.7
Gestation (days)	mean	271.3	271.8	272.8	270.2	270.1
	SD	8.4	12.2	7.2	12.3	17.1
Birth weight (g)	mean	3009.6	3058.0	3134.5	2900.7	2988.5
	SD	439.9	428.3	347.3	424.0	459.6
Pre-treatment uterine activity (kPa s)	mean	5806.0	5357.5	5825.1	4397.7	3772.5
	SD	3610.5	1876.7	2617.6	1639.6	3320.7

The delivery of the fetus was left entirely to the obstetrician. However, the routine administration of oxytocics in the third stage was omitted. Within 5 minutes of delivery of the placenta, a calibrated Gaeltec® (Gaeltec® Ltd., Dunvegan, Scotland, UK) catheter with an intrauterine pressure transducer at its tip was inserted transcervically into the uterine cavity until the tip of the catheter could be felt to impinge on the fundus of the uterus. The catheter was then secured in place and connected to a Sonicaid® Meridian fetal monitor (Sonicaid Ltd., Oxford Medical Instruments, Chichester, England, UK), and uterine activity contraction areas were recorded automatically every 15 minutes by the machine [Chong et al 2001]. Uterine activity is recorded as active pressures in real time continuously and the contraction areas for each 15-minute periods was automatically calculated every 15 minutes and printed on the recording paper. The summation of the 15-minute readings provides the cumulative uterine activity over specified periods of time e.g. 30, 60, and 90 minutes. A researcher was with the woman throughout the two-hour period of the recording to document the temperature, pulse and blood pressure of the mother every 15 minutes, as well as any side effects experienced. The blood loss was closely monitored and if any women were thought to have excessive blood loss (> 500 ml), they would have been given conventional therapy for postpartum haemorrhage and taken out of the trial. It was difficult logistically to blind the investigator monitoring the patient during the two hours of the study, and this was not attempted. The primary outcome was uterine activity recorded automatically and objectively by the Sonicaid® Meridian fetal monitor every 15 minutes. The onset of action was separately assessed later by investigators blinded to the type of treatment given. None of the mothers initiated breastfeeding until after the study period of two hours when they were transferred to the postnatal ward.

The postpartum uterine activity was measured for 30 minutes as a baseline before the assigned medication was administered, allowing each woman to be her own control The uterine activity was then monitored for a further 90 minutes. The uterine activity of each group after treatment was compared using the repeated measurement technique adjusted for the baseline pre-treatment uterine activity and parity. Repeated measurement technique or longitudinal data analysis was used to analyze the effect of time as well as other variables on the uterine activity outcome. The incidence of shivering and pyrexia (temperature >38°C) within the four misoprostol treatment groups were compared using Fisher's Exact test, and logistic regression was used to test the effect of the post-treatment cumulative uterine activity. The relationship between the maximum body temperature recorded and the cumulative uterine activity in the 90 minutes after misoprostol was administered, and the route of administration was assessed using linear regression. The onset of action of the treatment given was determined from the intrauterine pressure recordings as the time interval after treatment was administered till the commencement of an increase in uterine contractions. The investigator assessing the onset of action was blinded to the type of treatment given. The Kruskal-Wallis test was used to assess the difference among the times of onset of action of the five treatment groups. Multiple comparison was done using the Mann-Whitney U test. Statistical analysis was performed using the SAS 8.0 and SPSS 11.0 for Windows statistical package.

Results

Study population

The details of the women recruited are given in Table 5.1. There was a significant difference in parity between the treatment groups. There were more nulliparous women in the group given rectal misoprostol than in the other groups. The sequential recruitment of women for this study led to an uneven distribution of parity across the groups that was purely incidental. The pre-treatment cumulative uterine activity in both the rectal and vaginal misoprostol groups were less than that in the other three treatment groups. Both the effects of parity and pre-treatment cumulative uterine activity were taken into account in the analysis on uterine activity. The other parameters were similar in all the treatment groups. None of the women recruited were later excluded after the study treatment was given. No woman recruited for the study was excluded for excessive blood loss.

The uterotonic activity produced by misoprostol administered via different routes is shown in Table 5.2. Figure 5.1 is the error bar chart showing the mean uterine activity produced by each form of treatment in each 15-minute period after drug administration. Repeated measurement technique was used to evaluate the effects of route of administration, time elapsed, parity and pre-treatment baseline uterine activity, and the interaction between time and route. This statistical analysis method looks at differences between subjects (treatment groups) and within subjects (time trend), and whether there is any interaction between groups and time. We found that not only were the effects of the time elapsed and pre-treatment baseline uterine activity significant ($p<0.001$, $p<0.001$ respectively), but also the interaction between time and route ($p=0.009$). However, the effect of parity was not significant

(p=0.625). The mean uterine activity produced by each treatment in each 15-minute period is given in Table 5.2.

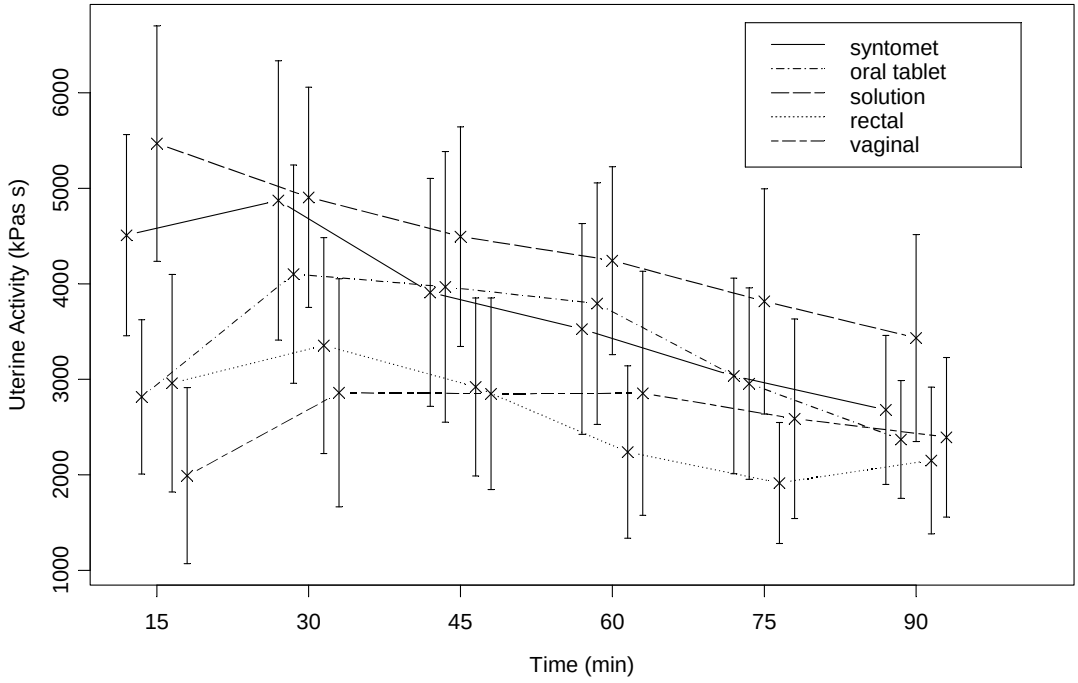


Figure 5.1. Error bar plot of uterine activity measured at 15-minute intervals after treatment

Table 5.2. Mean uterine activity in each 15-minute period after treatment

Time after treatment	Mean (95% CI) uterine activity [kPas s] in each 15-minute period				
	Intramuscular syntometrine 1 mL	Misoprostol 400 µg Oral tablet	Misoprostol 400 µg Oral solution	Misoprostol 400 µg Rectal	Misoprostol 400 µg Vaginal
15 min	4508 (3293 – 5723)	2815 (1885 – 3746)	5468 (4046 – 6890)	2958 (1644 – 4273)	1991 (928 – 3054)
30 min	4873 (3184 – 6561)	4101 (2782 – 5419)	4905 (3573 – 6236)	3353 (2048 – 4658)	2858 (1480 – 4235)
45 min	3910 (2532 – 5287)	3967 (2331 – 5604)	4494 (3167 – 5820)	2920 (1845 – 3996)	2848 (1690 – 4006)
60 min	3526 (2252 – 4799)	3792 (2333 – 5252)	4242 (3107 – 5377)	2237 (1195 – 3280)	2853 (1378 – 4327)
75 min	3035 (1853 – 4216)	2954 (1798 – 4111)	3816 (2454 – 5177)	1914 (1182 – 2646)	2586 (1380 – 3792)
90 min	2680 (1778 – 3581)	2370 (1658 – 3081)	3432 (2182 – 4681)	2150 (1263 – 3037)	2393 (1428 – 3357)

The mean uterine activity produced by the oral solution misoprostol group was highest within the first 15 minutes and gradually declined, while that of the other treatment groups reached their peak during the second 15-minute period before declining (Table 5.2). Looking into each treatment group (Figure 5.1), we found that the mean uterine activity produced by oral solution misoprostol was significantly higher than that produced by rectal misoprostol (p= 0.028), and vaginal misoprostol (p= 0.018). The mean uterine activity produced by oral solution misoprostol was higher than that produced by oral tablet misoprostol but the difference was not statistically significant (p=0.060). There was no significant difference between the mean uterine activity produced by oral solution and intramuscular syntometrine groups (p= 0.132).

Figure 5.2 is the error bar chart showing the mean cumulative uterine activity produced in the 30-, 60- and 90-minute periods after treatment. Again, the repeat measurement technique was used to evaluate the effects of route, time elapsed, parity and pre-treatment baseline uterine activity, and the interaction between time and route. We found that the effects of route, time elapsed and pre-treatment baseline uterine activity were significant (p=0.010, p< 0.001 and p<0.001 respectively). However, the interaction between time and route was not significant (p=0.131), and neither was the effect of parity (p=0.906). The mean cumulative uterine activity produced by oral solution misoprostol was significantly higher than that produced by oral tablet misoprostol (p=0.045, mean difference 4753.3 kPas s, 95% CI 110.0-9396.6), rectal misoprostol (p=0.004, mean difference 7152.7 kPas s, 95% CI 2397.1-11908.0) and vaginal misoprostol (p=0.002, mean difference 7731.0 kPas s, 95% CI 3079.5-12383.0).

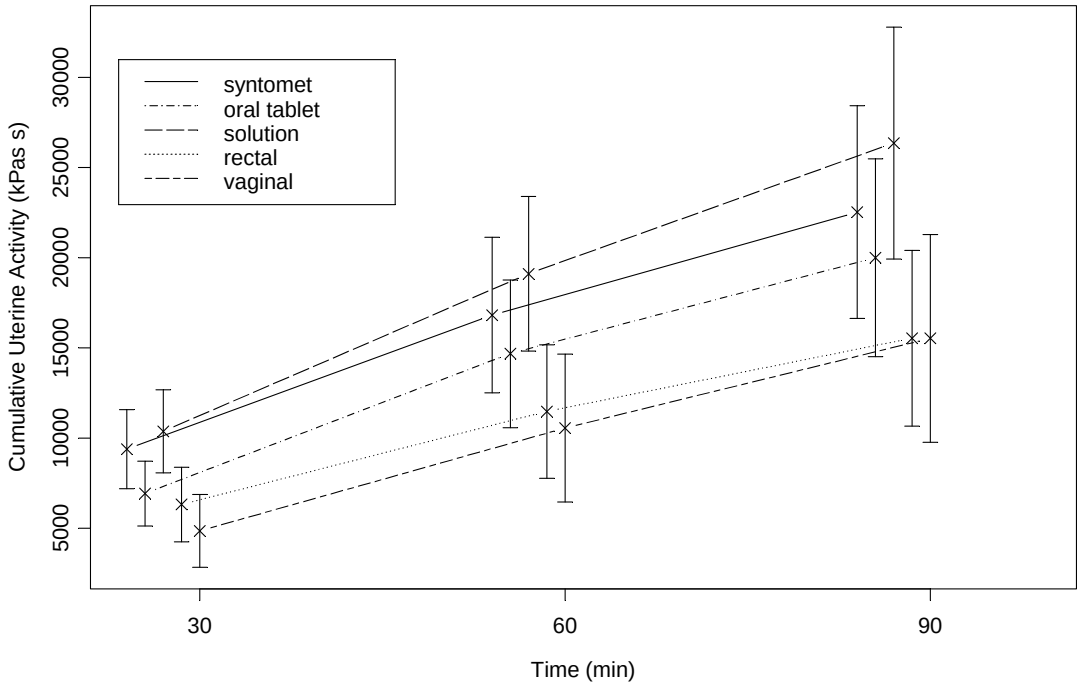


Figure 5.2. Error bar plot of cumulative uterine activity in the 90 minutes after treatment

Onset of action

The difference in time of onset of action among the different groups was highly statistically significant ($p<0.001$). Misoprostol given as an aqueous oral solution had a significantly shorter median onset of action (4.0 min, range 2.0 to 5.0 min) compared to misoprostol given as tablets orally (6.0 min, range 4.0 to 10.0 min, $p=0.01$), rectally (11.0 min, range 7.0 to 13.0 min, $p<0.001$) or vaginally (20.0 min, range 11.0 to 25.0 min, $p<0.001$) (Table 5.2). The time of onset of action for oral solution misoprostol 400 μg was not significantly different from that of intramuscularly administered syntometrine (2.5 min, range 2.0 to 6.0 min, $p=0.393$).

The side effects of misoprostol

The two main side effects noted in the women were shivering and pyrexia (body temperature >38°C). Women receiving intramuscular syntometrine and vaginal misoprostol experienced neither of these side effects. One of the women assigned to vaginal misoprostol had a temperature of 38°C before misoprostol was given to her but her temperature did not rise subsequently. In the group of 40 women receiving misoprostol via different routes, six women (15%), among whom five were from the oral solution group and one from the oral tablet group, experienced shivering lasting a median of 36.5 (range 11.0 to 50.0) minutes. The incidence of shivering was significantly different ($p=0.008$) among the women receiving misoprostol by different routes. Logistic regression was used to adjust for the 90-minute post-treatment cumulative uterine activity. We found that neither the route of administration of misoprostol nor the post-treatment cumulative uterine activity significantly affected the incidence of shivering ($p=0.54$ and $p=0.16$ respectively) after using logistic regression to adjust for the post-treatment cumulative uterine activity.

Twelve women (30%) (two from the oral tablet group, nine from the oral solution group and one from the rectal group), including the six with shivering, developed an increase in body temperature over 38°C (median maximum temperature 38.3°C, range 38.1°C to 39.9°C). The incidence of fever was significantly different ($p<0.001$) among women receiving misoprostol by different routes. Logistic regression was used to adjust for the 90-minute post-treatment

cumulative uterine activity. We found that the route of administration was significantly associated with pyrexia (p=0.04) but not the post-treatment cumulative uterine activity (p=0.27). Women who received oral solution misoprostol were significantly more likely to have fever than those who received oral tablet misoprostol (p=0.012, OR = 30.7, 95% CI 2.1 to 434.8) or rectal misoprostol (p=0.012, OR = 47.6, 95% CI 2.4 to 909.1).

The maximum body temperature experienced was also significantly different (p=0.001) among women receiving misoprostol via different routes (Figure 5.3). Linear regression was used to adjust for the 90-minute post-treatment cumulative uterine activity. We found that the route of administration was significantly associated with the maximum temperature (p=0.006) but not the post-treatment cumulative uterine activity (p=0.120). Women who received oral solution misoprostol had significantly higher maximum body temperatures than those who received oral tablet misoprostol (p=0.005, mean difference of maximum body temperature was 0.85°C [95% CI 0.28°C to 1.42°C]), rectal misoprostol (p=0.009, mean difference was 0.82°C [95% CI 0.21°C to 1.42°C]), or vaginal misoprostol (p=0.001, mean difference was 1.07°C [95% CI 0.47°C to 1.67°C]).

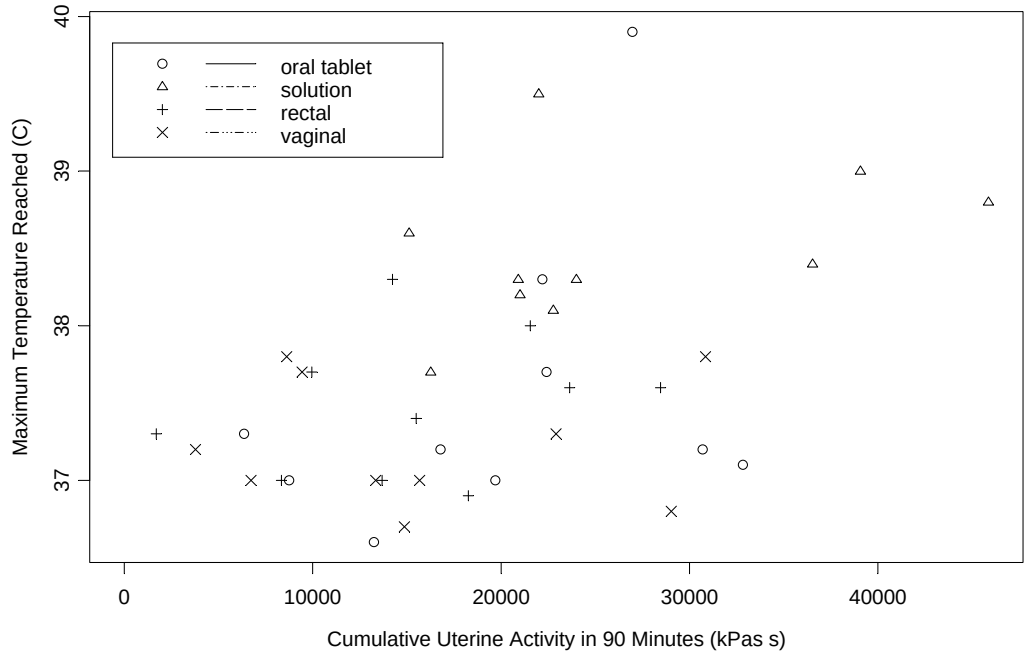


Figure 5.3. Maximum temperature reached plotted against cumulative uterine activity over 90 minutes

Comment

Despite the small size of this study, it is apparent that misoprostol, administered by different routes, results in significantly different uterotonic action, with an aqueous solution of misoprostol 400 μg taken orally producing uterotonic activity faster and greater than oral tablet, rectal or vaginal misoprostol. Oral solution misoprostol 400 μg also acted on the postpartum uterus as quickly and as strongly as intramuscular syntometrine 1 ml, which is the standard drug routinely given for the prevention of postpartum haemorrhage in many maternity units.

The work for this study was performed in 1997 to 1998 when the use of misoprostol for preventing postpartum haemorrhage was just beginning. As we were

uncertain of the efficacy of misoprostol at that time, we planned our pilot study one step at a time, beginning with oral tablets, oral solution, rectal, and finally the vaginal route. We acknowledge that random allocation of treatment would have been a superior method of allocation, possibly avoiding the problem of the imbalance in parity of subjects. However, our results have been adjusted for the difference in parity. The two main routes of administration being considered for misoprostol in the third stage in 1997 was oral tablet and rectal. However, prior to this, misoprostol had been administered successfully by the vaginal route for induction of labour and medical abortions and we decided to try this route of administration as well. Unfortunately, we did not think to include the buccal route. Sample size calculations were not performed *a priori* as the effect size was unknown and, as this was a pilot study using very labour-intensive methodology, we restricted the sample sizes.

The quick onset of action of misoprostol given as an aqueous solution orally is not surprising as time is not required for the dissolution of the tablets after swallowing, and, hence, absorption of the drug will be enhanced. The rapid absorption of misoprostol given as an oral solution may lead to higher peak plasma concentrations and stronger initial uterine contractions as opposed to gentler contractions with more gradual increases in plasma concentrations resulting from misoprostol administered rectally or vaginally. Pharmacokinetic studies have shown that sublingual and oral tablet misoprostol used for first-trimester abortions produce earlier and higher peak plasma concentrations [Zieman et al 1997; Danielsson et al 1999; Tang et al 2002a; Khan & El-Refaey 2003] than vaginal or rectal misoprostol, resulting in earlier, more pronounced uterine tonus [Danielsson et al 1999]. Gemzell

Danielsson and colleagues' study [Danielsson et al 1999] also reported times of onset of action for the oral tablet (7.8 min, SD 3.0 min) and vaginal misoprostol (20.9 min, SD 5.3 min) similar to those in our study. Misoprostol tablets are not designed for parenteral administration and may lead to slow or erratic absorption if given rectally or vaginally [Zieman et al 1997; Tang et al 2002a; Khan & El-Refaey 2003]. This may be overcome by its proper formulation into vaginal pessaries and rectal suppositories, or by the use of makeshift mini-enemas, as described by Bugalho and colleagues [Bugalho et al 2001]. Another reason for poor absorption via the vaginal route in the postpartum period is the presence of bleeding and passage of lochia that may dilute or wash out the misoprostol.

The finding of a 50% rate of shivering and 90% rate of pyrexia in the women given aqueous solutions of misoprostol was unexpected. The incidence of side effects in this group of women was significantly higher than in the other treatment groups. There was also a strong association between the route by which misoprostol was administered and the maximum body temperature reached. In our earlier study [Chong et al 2001], we found that doses of oral tablet misoprostol above 400 μg resulted in higher incidences of side effects. This study shows that, besides the dosage used, the route of administration of misoprostol also influences the rate of side effects.

We hypothesized that this was due to the higher peak plasma concentrations of misoprostol acid achieved by giving an oral solution of misoprostol. In the pharmacokinetic study by Tang et al [2002a], the peak plasma level of misoprostol acid was highest and earliest with sublingual misoprostol. They also reported the

highest rate of shivering and pyrexia with their pilot study using sublingual misoprostol for first trimester termination of pregnancy [Tang et al 2002]. It is probable that high plasma concentrations of misoprostol acid, besides acting on uterine receptors to produce contractions, also act on thermoreceptors, primed by the pregnancy state, resulting in disturbed thermoregulation. There is probably a threshold plasma concentration of misoprostol acid at which these side effects are triggered. This threshold level may be lowered in pregnancy, as shivering and pyrexia is uncommon when misoprostol is taken by women who are not pregnant. It is also possible that beyond a certain threshold plasma concentration, no further increase in uterine activity is produced as the uterine receptor sites may be saturated. We found that in women given misoprostol, the uterotonic activity produced was higher in those with side effects than in those without. But, when adjusted for the route of administration, this effect was not statistically significant. Another possible explanation could be that parenteral routes of administering misoprostol bypass certain metabolic pathways that increase the occurrence of these side effects. The rate of rise of the plasma levels of misoprostol acid may also be a factor in causing these side effects.

Shivering and pyrexia in women receiving misoprostol in the immediate postpartum period have both been widely documented. Although these side effects are usually mild and self-limiting, they can occasionally be severe [Chong et al 1997]. Authors have suggested the concomitant use of epidural anesthesia as a factor [Villar et al 2002], but none of the women in this study or our previous trial [Chong et al 2001] were on epidural anesthesia. Pregnant women given misoprostol, by any route, for induction of labor [le Roux et al 2002] do not experience significant

shivering or pyrexia as the dosages used in the presence of a live, term fetus are generally low. Initial reports about the use of misoprostol for abortion, when large doses were used, did not highlight these side effects. However, recent studies [Schaff et al 2001; Tang et al 2002] have documented high rates of fever (32% to 72%). The highest rates of fever (72%) and chills (82%) when misoprostol was used for first-trimester abortions were reported with sublingual misoprostol [Tang et al 2002]. The sublingual route has been shown to produce significantly higher serum peak concentrations of misoprostol acid than either oral tablet or vaginal misoprostol [Tang et al 2002]. These findings support our hypothesis [Chong et al 2002] that shivering and pyrexia are triggered off by high plasma concentrations of misoprostol acid.

The oral solution and sublingual routes promise to be the most effective ways of administering misoprostol, resulting in the fastest onset of action and strongest initial uterotonic effect. However, these routes also result in the highest rates of shivering and pyrexia. These side effects appear to be related to the peak plasma concentrations of misoprostol acid achieved. One strategy to consider for the safe routine use of misoprostol in the third stage would be to give lower doses of misoprostol by either the oral solution or sublingual route. Another strategy may be to aim for a more gradual and sustained increase in plasma levels of misoprostol using the rectal [Khan & El-Refaey 2003] or vaginal route, bearing in mind the slower onset of action and lower initial intensity of uterotonic effect. Perhaps, rectal misoprostol may be combined with injectable uterotonics to overcome its disadvantage of a slow onset of action. The authors of the World Health Organization multicentre randomized trial and the Cochrane systematic review on

the use of misoprostol for the prevention of postpartum haemorrhage have observed that the lesser efficacy of misoprostol compared to injectable uterotonics could be related to its later peak in plasma levels after oral or rectal administration [Abdel-Aleem et al 2003].

This study highlights the need to carefully reexamine the route and dose of misoprostol used for the purpose of preventing or treating postpartum haemorrhage. We suggest that misoprostol administered as an aqueous solution be further studied. A lower dose of misoprostol given as an oral solution may reduce the side effects observed in this study.

Chapter 6

The side effects of shivering and pyrexia when oral misoprostol is administered in the immediate postpartum period

Part 1: First case report

Introduction

Oral misoprostol has been prescribed in daily doses of 800 μg for preventing nonsteroidal anti-inflammatory drug-induced gastric ulcers since it was approved for this indication by the FDA in 1988. Its off-label use, both orally and vaginally, for inducing abortions and labour has been reported since the early 1990s [Sanchez-Ramos et al 1993; Creinin & Vittinghoff 1994]. Up to the time of this report, only two cases of misoprostol overdose had been reported in the literature [Graber & Meier 1991; Bond & Van Zee 1994]. Both involved doses (3 mg and 6 mg respectively) greatly exceeding the recommended daily dosage (400 μg to 800μg), and both patients exhibited hyperthermia as one of the toxic effects of misoprostol. Prior to this report, no cases of severe hyperthermia had ever been documented with normal doses. We observed a woman who developed severe hyperthermia after a single 800 μg oral dose of misoprostol given soon after a normal vaginal delivery.

Case report

A previously healthy 20-year-old woman, gravida 2, para 1 presented at 41 weeks' gestation in spontaneous labour after an uneventful antenatal period. She had not experienced any previous adverse drug reactions. After a short, uncomplicated labour, she had a normal vaginal delivery of a healthy female neonate weighing 3605 g. She was given 800 μg of misoprostol orally for prophylaxis against postpartum haemorrhage as part of a clinical trial. She received no other medication. Postpartum blood loss was 450 mls. Thirteen minutes after receiving misoprostol, the patient complained of chills and rigors. Her axilla temperature was 36.8°C and her pulse and blood pressure were 80 beats/min and 120/80 mmHg respectively. She

was given more blankets to keep herself warm but she continued to complain of chills. One hour later, she appeared to enter a trance-like state, refusing to open her eyes and not responding to questions despite being conscious. Her pulse was 80 beats/min, blood pressure 110/75 mmHg and axilla temperature was 37.0°C. Thirty minutes after that, she became restless and disoriented and she was then noted to have an axilla temperature of 41.4°C and pulse of 180 beats/min. Her blood pressure was normal, 130/70 mmHg. Her rectal temperature was measured at 41.9°C. Cooling was immediately started by splashing ice water on the patient and evaporating the water with fans. Ice packs and water-soaked sheets were also placed on the patient. Intravenous fluids (normal saline 0.9% and Hartman's solution) were started and she was catheterised to monitor her renal output and to watch for myoglobinuria. Core temperature was monitored continuously with a rectal probe. Oxygen was administered via a hudson mask at 15 L/min.

Initial investigations revealed essentially normal full blood counts and serum urea and electrolytes. Arterial blood-gas determination showed an oxygen partial pressure (PaO2) of 90.7 mmHg, carbon dioxide partial pressure (PaCO2) of 21.3 mmHg, pH of 7.43, bicarbonate level of 18.5 mmol/L and base deficit of -7.4 mmol/L indicating respiratory alkalosis with metabolic compensation. Serum ionised calcium was low, 1.05 mmol/L (1.15-1.35), while phosphate was normal, 1.18 mmol/L (0.85-1.45). Other abnormalities included serum alkaline phosphatase levels of 227 IU/L (38-126), lactic dehydrogenase (LDH) of 1416 IU/L (300-550), and creatinine phosphokinase of 504 IU/L (60-375). Coagulation studies were normal. Her electrocardiogram showed uncomplicated sinus tachycardia. Pulse oximeter readings showed oxygen saturation levels between 98%-100%.

Despite the measures taken to cool the patient, her core temperature remained above 40°C and she still had a tachycardia of 168 beats/min one hour after the start of treatment. A nasogastric tube was inserted and ice saline lavage was instituted. After 30 minutes of lavage, the core temperature was brought down to 38.9°C and the lavage was stopped to avoid inadvertent hypothermia. Cold sponging was continued until the core temperature reached 38°C forty-five minutes later. At this point, her pulse was 135 beats/min, blood pressure was 120/60 mmHg and she was no longer delirious. Her renal output after catheterisation was only 20 mls despite receiving 2.5 L of intravenous fluids. An intravenous bolus of furosemide 20 mg was given. After this, her urinary output remained constantly above 60 mls an hour and the urine was clear.

The patient's rectal temperature returned to 37.3°C three hours forty minutes after the commencement of treatment for her hyperthermia, and only then was she fully alert and coherent. She had no recall of the entire episode starting from the point she began experiencing chills and rigors.

Repeat investigations revealed that her serum ionised calcium and phosphate levels were normal 6 hours after the episode. Serum LDH reached a peak of 3075 IU/L (300-550) on the first postnatal day, while serum glutamic-oxaloacetic transaminase was 161 IU/L (5-40), and creatinine phosphokinase was 4715 IU/L (60-375). Subsequently, serum creatinine phosphokinase levels dropped to 1714 IU/L on the second postnatal day. Urine myoglobin index measured on the day of

delivery and the first postnatal day were both normal, 0.849 and 0.886 (myoglobinuria > 0,95) respectively. Other investigations were essentially normal.

The patient's subsequent postnatal course was uneventful. She remained afebrile and asymptomatic and unable to remember the events during the period of hyperthermia. She was discharged on the third postnatal day.

Discussion

This is the first published report [Chong et al 1997] in the medical literature of severe side effects with a non-excessive dose of oral misoprostol when used in the postpartum period. Single and repeated oral doses of 600-800 μg of misoprostol for inducing abortions have been used in various studies [El-Refaey & Templeton 1994; El-Refaey et al 1994a; El-Refaey et al 1995] with no adverse effects. The severity and rapid course of this patient's hyperthermia was thus unexpected.

In a previous case of misoprostol overdosage [Bond & Van Zee 1994] in pregnancy, a 19-year-old woman developed hyperthermia, tachycardia, dyspnoea, uterine tetany with resultant fetal death, metabolic acidosis, hypoxemia, and biochemical rhabdomyolysis after an intentional overdose of 30 tablets of 200 μg misoprostol and four tablets of 2 mg trifluoperazine. In the only other report of misoprostol overdose [Graber & Meier 1991], a 71-year-old woman experienced hyperthermia, tremor, tachycardia, hypertension, nausea and abdominal cramps after ingesting fifteen 200 μg tablets of misoprostol. Both patients recovered within 12 hours of misoprostol. Reports of fever following normal doses of misoprostol have

been rare, mild and of dubious causal relationship [Product Information, Cytotec®, G D Searle & Co., 1991].

Our patient developed chills and rigors 13 minutes after ingesting 800 μg of misoprostol. This coinciding with an increase in uterine activity measured by an intrauterine pressure transducer inserted after delivery of the placenta. Despite persistence of these symptoms and a change in sensorium later, her axilla temperature remained normal. However, within 30 minutes of the last measured axilla temperature of 37°C, she became restless and incoherent and her axilla temperature had risen to 41.4°C. Rectal temperature was 41.9°C and remained above 38°C for three hours despite intensive measures taken to lower her body temperature. She also developed hypocalcaemia and biochemical markers of rhabdomyolysis as well as transient hypoxaemia and respiratory alkalosis. All her symptoms resolved within eight hours of drug ingestion, and biochemical investigations were returning to normal levels by the second postnatal day. She had no persistent ill effects of the hyperthermia on discharge and subsequent follow-up.

The differential diagnosis of hyperthermia includes infection, hypothalamic injury, thyroid storm, phaeochromocytoma, heat stroke, malignant hyperthermia, the neuroleptic malignant syndrome and drug overdose. Our patient had no signs of infection before or following her delivery, and none of the medical problems listed above. She only received one drug, misoprostol, before the onset of the hyperthermia. Drugs may cause hyperthermia by several mechanisms including local inflammation, endotoxin release, tissue necrosis, haemolysis, hypersensitivity

immunologic reaction, idiosyncratic reaction or by altering thermo-regulation. Prostaglandin E1 and E2 are drugs known to be responsible for drug-induced fevers [Mackowiak & LeMaistre 1987]. Their fever-inducing property, as suggested by experiments on pigs [Parott et al 1995] and rats [Monda et al 1994], is thought to be mediated by its action on the anterior and posterior hypothalamus.

Figure 6.1: Even normal doses of misoprostol can cause severe side effects in the immediate postpartum period

Conclusion

Misoprostol overdose has been reported to cause serious toxic effects including hyperthermia [Graber & Meier 1991; Bond & Van Zee 1994]. This case shows that even routinely-prescribed maximal doses of misoprostol may cause an idiosyncratic hyperthermia that requires rapid and vigorous treatment. Clinicians are advised to watch for this rare but alarming complication in patients on misoprostol.

Chapter 7

The side effects of shivering and pyrexia when oral misoprostol is administered in the immediate postpartum period

Part 2: Relationship with dose of misoprostol, uterine workload produced, and route of administration

Introduction

Along with the case report of severe hyperpyrexia and shivering in a woman given 800 μg of oral misoprostol postpartum in 1997 [Chong et al 1997], I reported that doses of oral misoprostol above 400 μg were associated with high incidences of shivering and pyrexia [Chong et al 1997a; 2001]. My study suggested that the safe dose of misoprostol for use in the third stage would be 400 μg.

At that point in time (1997-1998), the Steering Committee of the World Health Organisation multicentre randomised controlled trial of oral misoprostol for the third stage were concerned about the side effects of shivering and pyrexia at the two doses they were considering (400 μg and 600 μg) for their study. They decided to evaluate the effects of these two doses in a randomised, double-blinded, placebo-controlled pilot trial [Lumbiganon et al 1999] conducted in South Africa and Thailand. They concluded that the side effects of oral misoprostol used in the third stage were dose-related with 600 μg having significantly more pyrexia (RR 3.7, 95% CI 1.3-10.9) and shivering (RR 1.5, 95% CI 1.0-2.1) than 400 μg. The reported rates of shivering and pyrexia were 19% and 2% for 400 μg, and 28% and 7.5% for 600 μg, respectively. The Steering Committee decided to use 600 μg misoprostol in the main trial "in order to achieve higher effectiveness" [Lumbiganon et al 1999]. Since then, other authors have reported incidences of pyrexia and shivering with misoprostol given in the third stage as high as 34% [Amant et al 1999] and 72% [El-Refaey et al 2000] respectively.

The relationship of the shivering and pyrexia produced by misoprostol with the dose administered, uterine activity produced, and the route of administration will now be examined.

Dose studies using oral tablet misoprostol

In the study to determine the optimum dose of oral misoprostol for use to prevent postpartum haemorrhage (Chapter 4), we documented the side effects of shivering and pyrexia (temperature above 38°C) in the 47 women given oral misoprostol after normal vaginal delivery. All the women in the study were observed closely for side effects in the two-hour period of uterine activity recording.

Methods

Informed consent was obtained in the first stage of labour from 47 women who delivered vaginally after spontaneous labours not requiring induction or augmentation. The women were assigned sequentially into five groups and received oral misoprostol 200 μg, 400 μg, 500 μg, 600 μg, or 800 μg. The study was approved by the department ethical committee.

The delivery of the fetus was left entirely to the accoucheur. However, the routine administration of oxytocics in the third stage was omitted. Within 5 minutes of delivery of the placenta, a calibrated Gaeltec® catheter with an intrauterine pressure transducer at its tip was inserted transcervically into the uterine cavity until the tip of the catheter could be felt to impinge on the fundus of the uterus. The catheter was then secured in place and connected to a Sonicaid® Meridian fetal monitor (Sonicaid Ltd., Oxford Medical Instruments, Chichester, U.K.), and uterine

active contraction areas were recorded automatically. A researcher was with the woman throughout the two-hour period of the recording to document any side effects experienced.

Statistical analysis was performed using the SPSS 11.0 for Windows statistical package with statistical significance set at $p < 0.05$. The association between misoprostol dosages with side effects (shivering & pyrexia) was assessed using Chi-square/Fisher's Exact test with odds ratios (OR) presented where applicable.

The relationship between cumulative uterine workload 90 min after misoprostol with the side effects of shivering and pyrexia was assessed using linear regression controlling for the cumulative uterine workload 30 min before misoprostol.

Results

Relationship of side effects with dose of oral tablet misoprostol given

These side effects are listed in Table 7.1. Shivering occurred in 17 women (36%), and pyrexia (defined as a rise in body temperature above 38°C) occurred in 19 women (40%). Shivering and pyrexia occurred in 60% of women given oral misoprostol 500 μg and 600 μg, and 43% of those given 800 μg. Shivering only occurred in 10%, and mild pyrexia in 20%, of the women given 200 μg and 400 μg of oral misoprostol.

Women given doses of oral tablet misoprostol more than 400 μg experienced significantly more shivering than women given doses 200 μg and 400 μg (OR 11.3, 95% CI 2.2-58.4, p=0.001).

Women given doses of oral tablet misoprostol more than 400 μg also experienced significantly more pyrexia than women given doses 200 μg and 400 μg (OR 5.0, 95% CI 1.3-19.0, p=0.014).

Table 7.1. Shivering and pyrexia in women given different doses of tablet misoprostol

Medication given	Oral misoprostol 200 μg (n=10)	Oral misoprostol 400 μg (n=10)	Oral misoprostol 500 μg (n=10)	Oral misoprostol 600 μg (n=10)	Oral misoprostol 800 μg (n=7)
No. of women with shivering	1	1	6	6	3
No. of women with temp >38°C	2	2	6	6	3

Relationship of side effects with uterine activity recorded

The cumulative uterine workload at 90 min produced by oral tablet misoprostol was not associated with the side effects of shivering (p=0.128) (Figure 7.1) and pyrexia (p=0.199) (Figure 7.2) controlling for the cumulative uterine workload 30 min before misoprostol.

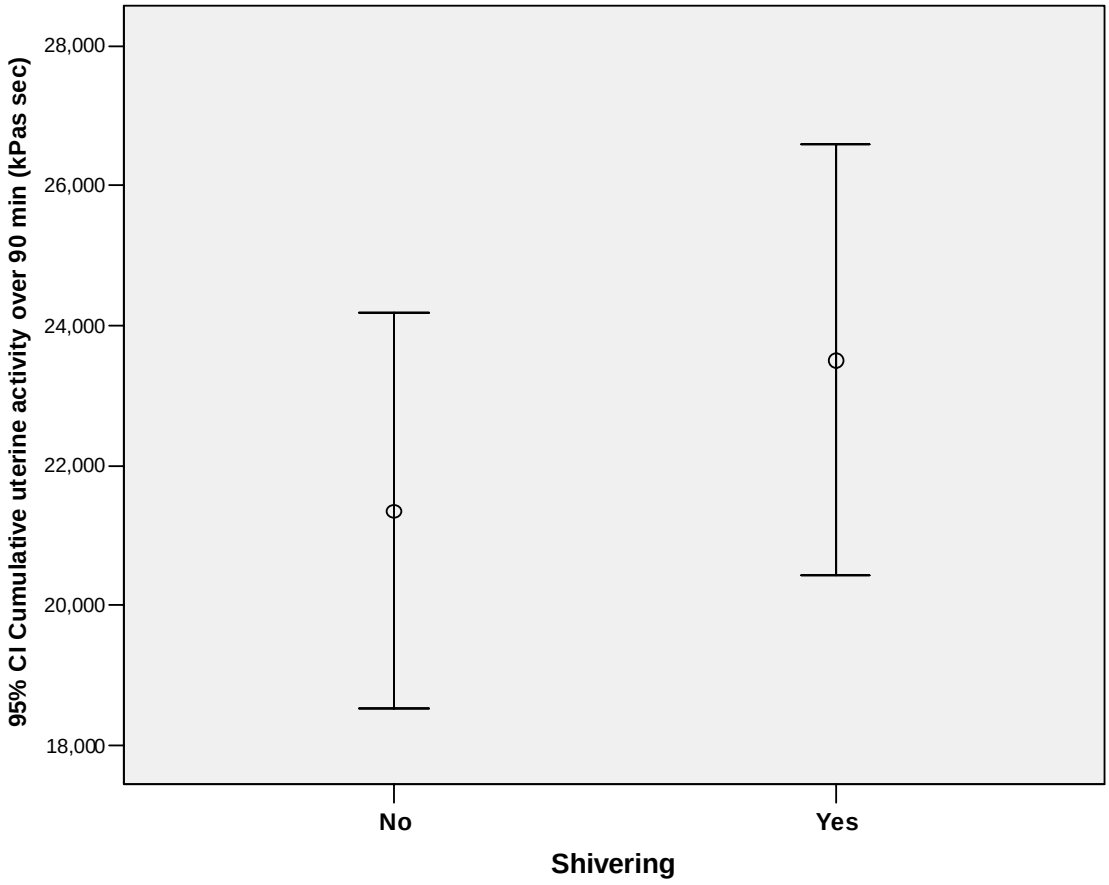


Figure 7.1. Relationship of shivering and uterine activity

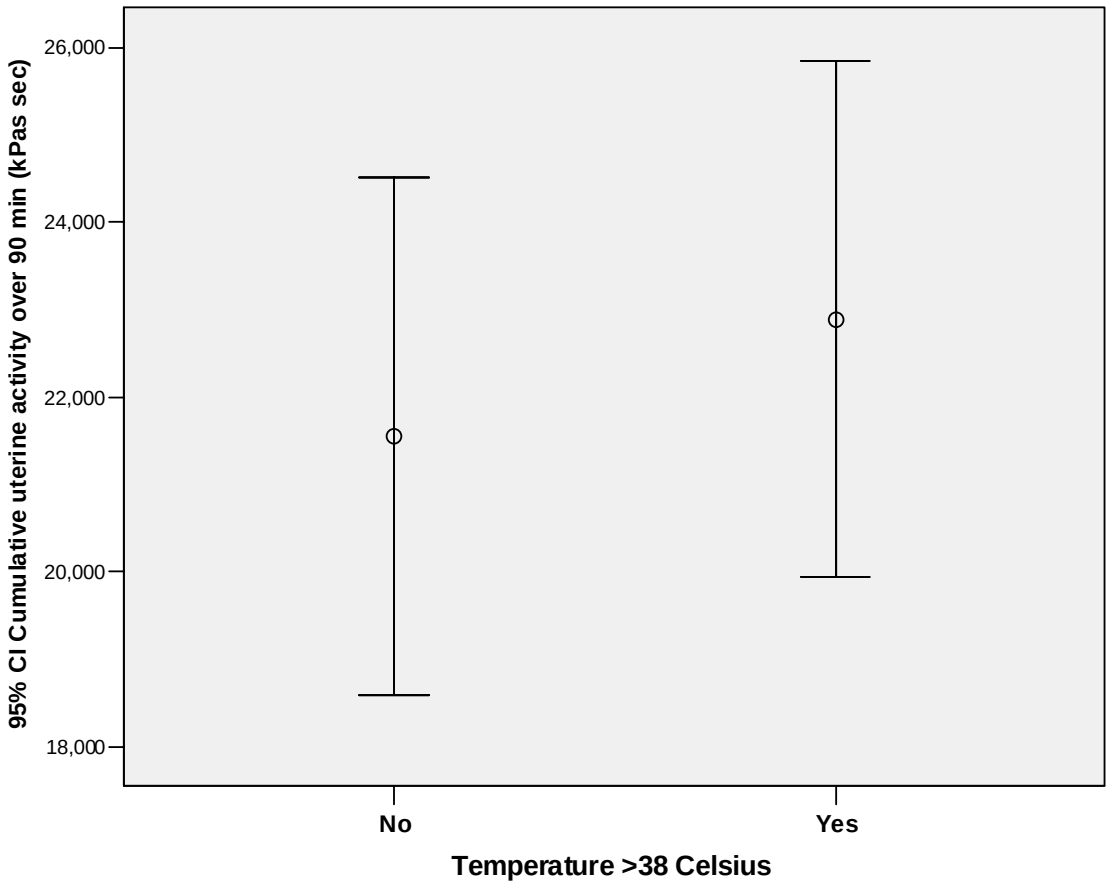


Figure 7.2. Relationship of pyrexia and uterine activity

Comment

The side effects of oral tablet misoprostol given after vaginal delivery are increased with doses above 400 μg, independent of the uterotonic activity produced.

Route of administration studies

Methods

In this study (Chapter 5), 40 women who delivered vaginally after spontaneous labours not requiring induction or augmentation with oxytocin or prostaglandins were assigned sequentially to receive misoprostol 400 μg given as

tablets orally, rectally, vaginally, or as an aqueous solution orally (two Cytotec® 200 μg tablets dissolved in 20 ml lukewarm water). The departmental ethics review committee approved the study, and informed consent was obtained from each participant.

The postpartum uterine activity was measured for 30 minutes as a baseline before the assigned medication was administered, allowing each woman to be her own control The uterine activity was then monitored for a further 90 minutes. The uterine activity of each group after treatment was compared using the repeated measurement technique adjusted for the baseline pre-treatment uterine activity and parity. The incidence of shivering and pyrexia (temperature >38°C) within the four misoprostol treatment groups were compared using Fisher's Exact test, and logistic regression was used to test the effect of the post-treatment cumulative uterine activity. The relationship between the maximum body temperature recorded and the cumulative uterine activity in the 90 minutes after misoprostol was administered, and the route of administration was assessed using linear regression. Statistical analysis was performed using the SPSS 11.0 for Windows statistical package.

Shivering

In the group of 40 women receiving misoprostol via different routes, the incidence of shivering was significantly different (p=0.008) among the women receiving misoprostol by different routes (Table 7.2). Logistic regression showed that neither the route of administration of misoprostol nor the post-treatment cumulative uterine activity significantly affected the incidence of shivering (p=0.54 and *P*=0.16 respectively).

Table 7.2. Shivering and pyrexia in women given misoprostol 400 μg by different routes

Medication given	Misoprostol 400μg Oral tablet (*n*=10)	Misoprostol 400μg Oral solution (*n*=10)	Misoprostol 400μg Rectal (*n*=10)	Misoprostol 400μg Vaginal (*n*=10)
No. of women with shivering	1	5	0	0
No. of women with temperature >38°C	2	9	1	0

Pyrexia

The incidence of fever was significantly different ($p<0.001$) among women receiving misoprostol by different routes. We found that the route of administration was significantly associated with pyrexia ($p=0.04$) but not the post-treatment cumulative uterine activity ($p=0.27$). Compared to the women who received oral solution misoprostol, those who received oral tablet misoprostol (OR = 30.7, 95% CI 2.1 to 434.8, $p=0.012$) or rectal misoprostol (OR = 47.6, 95% CI 2.4 to 909.1, $p=0.012$) were at risk of having pyrexia.

Maximum temperature

The maximum body temperature experienced was also significantly different (p=0.001) among women receiving misoprostol via different routes. Linear regression showed that the route of administration was significantly associated with the maximum temperature (p=0.006) but not the post-treatment cumulative uterine activity (p=0.120). Women who received oral solution misoprostol had significantly higher maximum body temperatures compared to those who received oral tablet misoprostol (*P*=0.005, mean difference of maximum body temperature was 0.85°C [95% CI 0.28°C to 1.42°C]), rectal misoprostol (*P*=0.009, mean difference was 0.82°C [95% CI 0.21°C to 1.42°C]), or vaginal misoprostol (p=0.001, mean difference was 1.07°C [95% CI 0.47°C to 1.67°C]).

Comment

Based on the findings of our dose and route studies, we conclude that the dose of misoprostol and the route by which it is administered after vaginal delivery are both significantly associated with its side effects of shivering and pyrexia.

Doses of 400 μg or less and both the rectal and vaginal routes give the least side effects. Oral solution misoprostol produces the most side effects. However, the side effects experienced are generally mild and self-limiting. Another option for avoiding the troublesome side effects of misoprostol, while retaining the better uterotonic effect of oral solution misoprostol, would be to give low doses (< 400 μg) of oral solution misoprostol.

Chapter 8

Comparing the uterotonic effect and side effects of oral solution misoprostol 200 μg and 400 μg:

Can low-dose oral solution misoprostol be used as a uterotonic agent after delivery?

Introduction

Two recent systematic reviews [Gulmezoglu et al 2001; Villar et al 2002a] on the use of misoprostol to prevent postpartum haemorrhage concluded that injectable oxytocin or oxytocin-ergot preparations were more effective than either oral or rectal misoprostol. The authors also concluded that the observed rate of side effects with misoprostol was already high and that it was unlikely that higher doses of misoprostol could be used to increase its efficacy for the routine prevention of postpartum haemorrhage [Villar et al 2002a] without unacceptable rates of side effects. However, an alternative approach to increasing the efficacy of misoprostol would be to administer it by either the sublingual [Tang et al 2002] or oral solution [Chong et al 2002] route, both of which have shown evidence of increasing the uterotonic effect of misoprostol. At the same time, lower doses of misoprostol administered by these routes could moderate the rates of side effects.

In an earlier study using postpartum intrauterine pressure measurements as a surrogate endpoint for the uterotonic action of oral misoprostol [Chong et al 2001], we found that doses of oral misoprostol above 400 μg were associated with high incidences of shivering and pyrexia (60%). Oral misoprostol 200 μg and 400 μg produced uterotonic effects similar to intramuscular syntometrine 1 ml while being associated with less shivering (10%) and pyrexia (20%). However, the onset of action of misoprostol given as an oral tablet was significantly slower than that of intramuscular syntometrine.

With these findings in mind, we studied misoprostol 400 μg administered by different routes [Chong et al 2004] and found that the uterotonic effect produced by

oral solution misoprostol 400μg was significantly higher than that of oral tablet, rectal and vaginal misoprostol. The onset of action after administering oral solution misoprostol was also significantly faster than by the oral tablet, rectal and vaginal routes. Unfortunately, shivering and pyrexia were also more common with oral solution misoprostol.

We thus hypothesized that a lower dose of oral solution misoprostol might produce a uterotonic effect similar to intramuscular syntometrine, with less side effects than solution misoprostol 400 μg. The aim of this study was to compare the uterotonic effect and side effects of a lower dose of misoprostol, 200 μg, administered by the oral solution route, to oral solution misoprostol 400 μg and intramuscular syntometrine 1 ml.

Materials and methods

Thirty women who delivered vaginally after spontaneous labors not requiring induction or augmentation with oxytocin or prostaglandins were recruited. None of the women used epidural analgesia, and they all had nil orally other than sips of water in active labor. The women were assigned sequentially into three groups (Table 8.1) and prescribed misoprostol (Cytotec®; Searle AG, Chicago, IL, USA) 200 μg or 400 μg given as an aqueous solution orally (Cytotec® tablets dissolved in 20 mls lukewarm water). The third group was given intramuscular syntometrine 1 mL (oxytocin 5 units, ergometrine maleate 500 μg/ml). Exclusion criteria included anemia (haemoglobin < 11.0 g/dl), maternal infection, multiple pregnancy, a history of postpartum hemorrhage in previous pregnancies or antepartum hemorrhage in the

current pregnancy. The departmental ethics review committee approved the study, and informed consent was obtained from each participant.

Table 8.1. Characteristics of women recruited for the study

Medication given		Intramuscular syntometrine 1 mL	Misoprostol 400 µg Oral solution	Misoprostol 200 µg Oral solution
No. of women recruited		10	10	10
No. of multiparous women		10	9	10
Age (years)	mean	28.3	28.3	29.2
	SD	2.9	5.3	5.0
Gestation (days)	mean	271.3	272.8	273.6
	SD	8.4	7.2	10.5
Birth weight (g)	mean	3009.6	3134.5	3168.9
	SD	439.9	347.3	250.6
Pre-treatment uterine activity (kPas s)	mean	5806.0	5825.1	4037.3
	SD	3610.5	2617.6	1810.9

The delivery of the fetus was left entirely to the obstetrician. However, the routine administration of oxytocics in the third stage was omitted. Within 5 minutes of delivery of the placenta, a calibrated Gaeltec® (Gaeltec® Ltd., Dunvegan, Scotland, UK) catheter with an intrauterine pressure transducer at its tip was inserted transcervically into the uterine cavity until the tip of the catheter could be felt to impinge on the fundus of the uterus. The catheter was then secured in place and connected to a Sonicaid® Meridian fetal monitor (Sonicaid Ltd., Oxford Medical Instruments, Chichester, UK), and uterine activity contraction areas were recorded automatically at 15-minute intervals by the machine [Chong et al 2001]. A researcher was with the woman throughout the two-hour period of the recording to document the temperature, pulse and blood pressure of the mother every 15 minutes, as well as any side effects experienced. The blood loss was closely monitored and if any women were thought to have excessive blood loss (> 500 ml), they would have been given conventional therapy for postpartum hemorrhage and taken out of the trial. No woman recruited for the study was excluded for excessive blood loss.

The postpartum uterine activity was measured for 30 minutes as a baseline before the assigned medication was administered. The uterine activity was then monitored for a further 90 minutes. The uterine activity of each group after treatment was compared using the repeated measurement technique adjusted for the baseline pre-treatment uterine activity. Repeated measurement technique or longitudinal data analysis was used to analyze the effect of time as well as other variables on the uterine activity outcome. The occurrence of shivering and pyrexia (temperature >38°C) within the two misoprostol treatment groups were compared using Fisher's Exact test, and logistic regression was used to test the effect of the

post-treatment cumulative uterine activity. The relationship between the maximum body temperature recorded and the cumulative uterine activity in the 90 minutes after misoprostol was administered and the treatment given was assessed using linear regression. The Kruskal-Wallis test was used to assess the difference among the times of onset of action of the three treatment groups. Multiple comparison was done using the Mann-Whitney U test. Statistical analysis was performed using the SAS 8.0 and SPSS 11.0 for Windows statistical package.

Results

Study population

The details of the women recruited are given in Table 8.1. Baseline characteristics of the women recruited were similar in all the treatment groups.

Figure 8.1 is the error bar chart showing the mean uterine activity produced by each form of treatment in each 15-minute period after drug administration. Repeat measurement technique was used to evaluate the effects of the treatment given, time elapsed and pre-treatment baseline uterine activity. We found that the time elapsed and pre-treatment baseline uterine activity significantly affected the mean uterine activity recorded ($p<0.0001$, $p<0.0001$ respectively), but the type of treatment given did not result in any significant difference in the mean uterine activity produced among the three groups ($p=0.702$). The mean uterine activity produced by oral solution misoprostol 200 μg and 400 μg was highest within the first 15 minutes and gradually declined, while that of the intramuscular syntometrine reached its peak during the second 15-minute period before declining. Looking into each treatment group (Figure 8.1), we found that the differences in mean uterine

activity between oral solution 200 µg and oral solution 400 µg (mean difference 145.0 kPas s, 95% CI -812.4 to 1102.4, p=0.758), and intramuscular syntometrine 1 mL (mean difference -231.7 kPas s, 95% CI -1188.4 to 724.9, p=0.623) were small and not statistically significant.

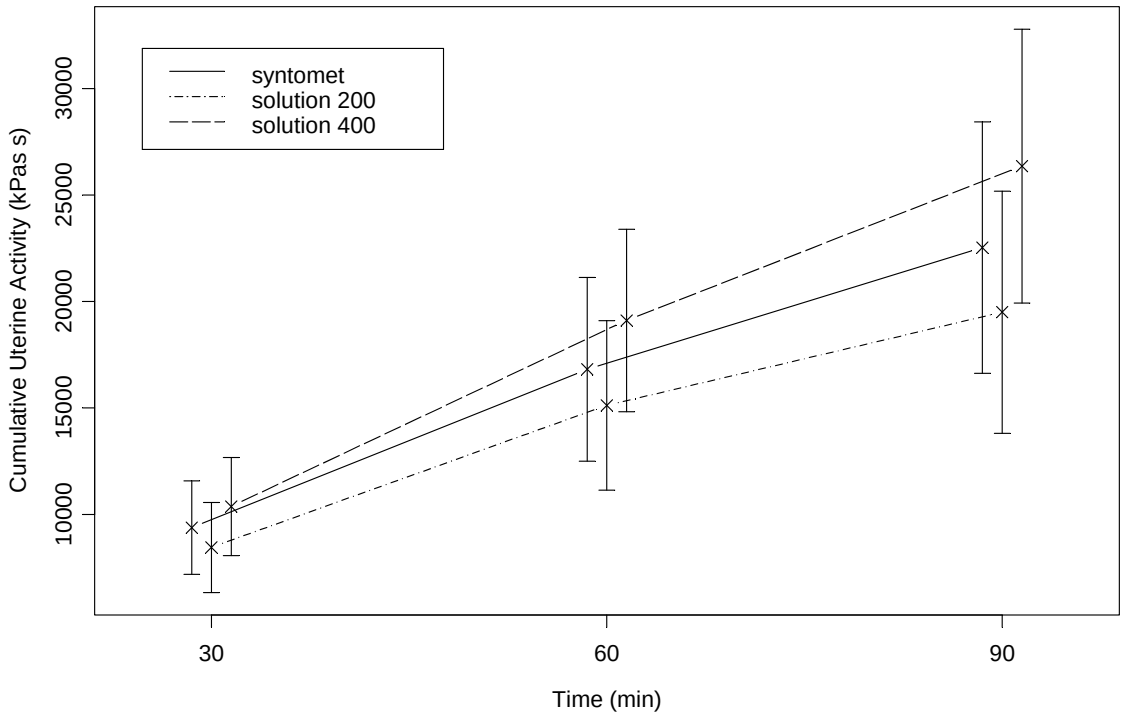


Figure 8.1. Error bar plot of uterine activity measured at 15-minute intervals after treatment

Figure 8.2 is the error bar chart showing the mean cumulative uterine activity produced in the 30-, 60- and 90-minute periods after treatment. Again, the repeat measurement technique was used to evaluate the effects of the treatment given, time elapsed and pre-treatment baseline uterine activity. We found that the time elapsed and pre-treatment baseline uterine activity significantly affected the mean cumulative uterine activity ($p<0.0001$ and $p=0.003$ respectively). However, the type

of treatment given did not result in any significant difference in the mean cumulative uterine activity produced among the three treatment groups (p=0.862). We also found that the mean cumulative uterine activity produced by oral solution misoprostol 200 µg was not significantly different from that of oral solution 400 µg (p=0.601, mean difference -360.9 kPas s, 95% CI -1761.0 to 1039.3), and intramuscular syntometrine 1 ml (p=0.693, mean difference -271.9 kPas s, 95% CI -1671.0 to 1127.2).

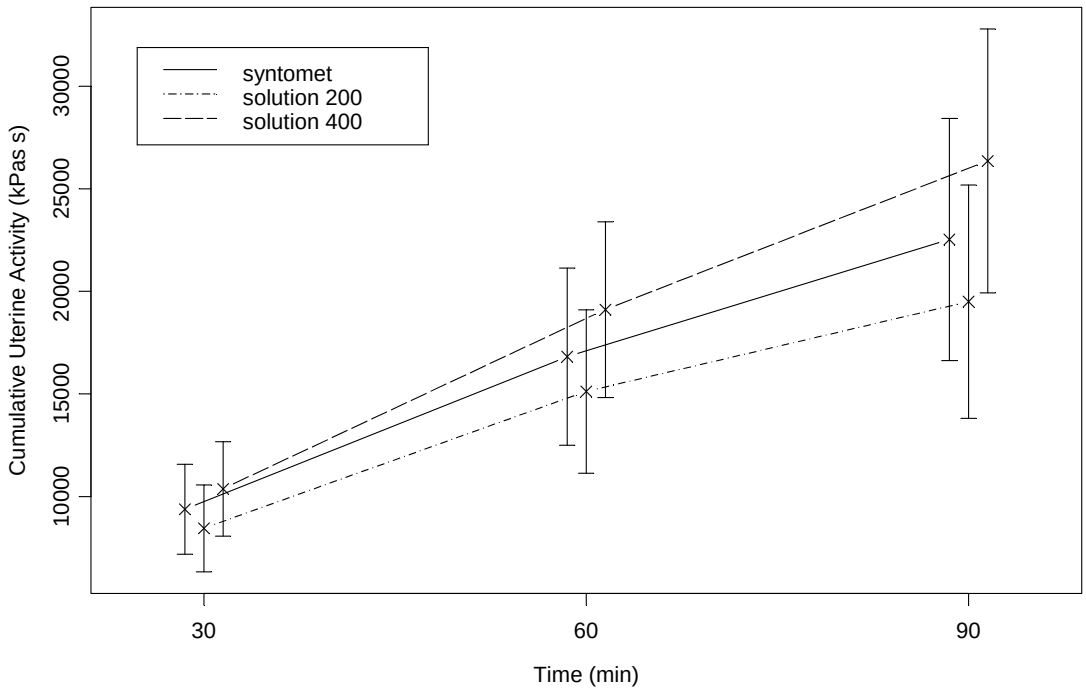


Figure 8.2. Error bar plot of cumulative uterine activity in the 90 minutes after treatment

Onset of action

The difference in time of onset of action among the different groups was not statistically significant (p=0.132). The median time of onset of action of oral solution misoprostol 200 µg (4.0, range 3.0 to 6.0 min) was not significantly

different from that of oral solution 400 μg (4.0, range 2.0 to 5.0 min, p=0.278) or intramuscularly administered syntometrine 1 ml (2.5, range 2.0 to 6.0 min, p=0.393).

The side effects of misoprostol

The two main side effects noted in the women were shivering and pyrexia (body temperature >38°C). Women receiving intramuscular syntometrine experienced neither of these side effects. In the group of 20 women receiving oral solution misoprostol, seven women experienced shivering lasting a median of 33.0 (range 11.0 to 50.0) minutes. The incidence of shivering was higher in the oral solution misoprostol 400 μg group (50%) than in women given oral solution misoprostol 200 μg (20%) but the difference was not statistically significant (p=0.350). Logistic regression was used to adjust for the 90-minute post-treatment cumulative uterine activity. We found that neither the effects of dose nor that of post-treatment cumulative uterine activity was significant (p=0.495 and p=0.112 respectively).

Ten women developed an increase in body temperature over 38°C (median maximum temperature 38.4°C, range 38.2°C to 39.5°C). The incidence of fever was significantly different (p=0.005) between women receiving oral solution misoprostol 200 μg (10%) and 400 μg (90%). Women taking oral solution misoprostol 200 μg had a significantly lower risk of developing pyrexia (OR=0.028, 95% CI 0.002 – 0.367). Logistic regression was used to adjust for the 90-minute post-treatment cumulative uterine activity. We found that the dose of misoprostol given was significantly associated with pyrexia (p=0.019) but not the post-treatment cumulative uterine activity (p=0.299).

The maximum body temperature experienced was also significantly different (p=0.001) between women given different doses of misoprostol (Figure 8.3). Linear regression was used to adjust for the 90-minute post-treatment cumulative uterine activity. We found that both the dose of misoprostol given (p= 0.001) as well as the post-treatment cumulative uterine activity (p=0.025) were significantly associated with the maximum temperature recorded. Women who received oral solution misoprostol 400 µg had significantly higher maximum body temperatures than those who received oral solution misoprostol 200 µg (p=0.001, mean difference of maximum body temperature was 0.95°C, 95% CI 0.48°C to 1.42°C).

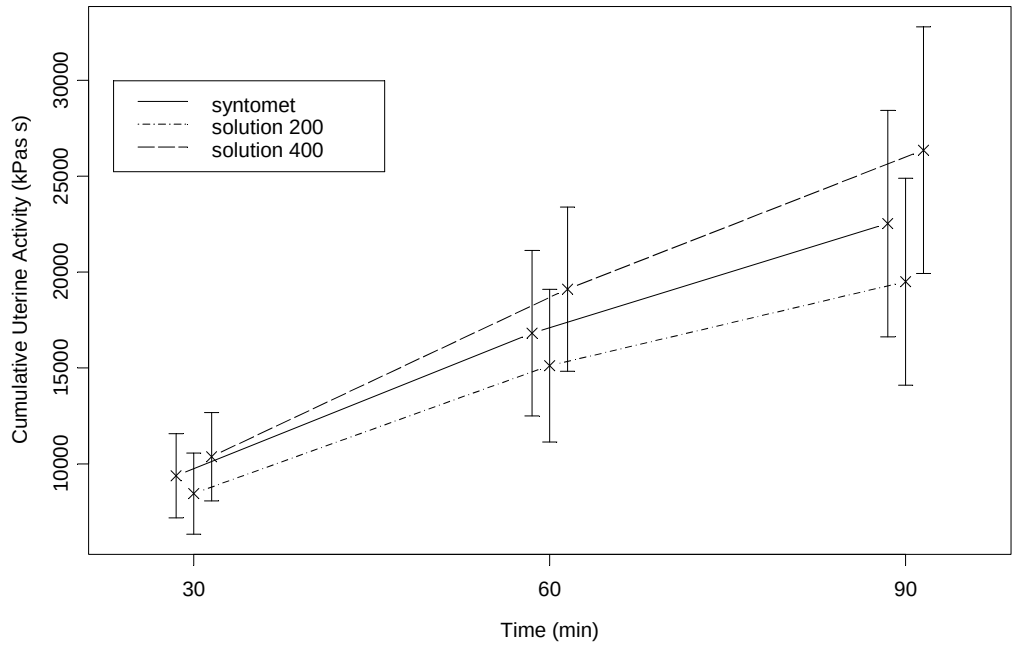


Figure 8.3. Maximum temperature reached plotted against cumulative uterine activity over 90 minutes

Comment

From the results of this study, it appears that low-dose (200 μg) misoprostol, administered by oral solution, results in similar times of onset of action and uterotonic activity as oral solution misoprostol 400 μg and intramuscular syntometrine 1 ml. Because of the small sample size in this study, there was insufficient power to prove equivalence or non-inferiority. However, the estimated differences in the uterotonic effect produced by oral solution misoprostol 200 μg compared to oral solution 400 μg and intramuscular syntometrine 1 ml were small and not likely to be of clinical significance. With regards to side effects, the lower dose of oral solution misoprostol (200 μg) produced less shivering (20% versus 50%, p=0.350) and pyrexia (10% versus 90%, p=0.005) than oral solution misoprostol 400 μg. The maximum temperature experienced was significantly associated with both the dose of misoprostol given and the cumulative uterotonic activity produced.

The quick onset of action of misoprostol given as an aqueous solution orally is not surprising as time is not required for the dissolution of the tablets after swallowing, and, hence, absorption of the drug will be enhanced. The rapid absorption of misoprostol given as an oral solution may lead to higher peak plasma concentrations and stronger initial uterine contractions as opposed to gentler contractions with more gradual increases in plasma concentrations resulting from misoprostol administered as oral tablets. Pharmacokinetic studies have shown that sublingual and oral tablet misoprostol used for first trimester abortion produce earlier and higher peak plasma concentrations [Zieman et al 1997; Danielsson et al 1999; Tang et al 2002a; Khan & El-Refaey 2003] than vaginal and rectal

misoprostol, resulting in earlier, more pronounced uterine tonus [Danielsson et al 1999]. Another recent study performed in women after delivery with oral tablet misoprostol confirmed that the pharmacokinetics did not differ in the postpartum period [Abdel-Aleem et al 2003]. Unfortunately, similar studies have not been conducted using oral solution misoprostol in pregnant women.

In our earlier study [Chong et al 2001], we found that doses of oral tablet misoprostol above 400 μg resulted in higher incidences of side effects. When we compared misoprostol 400 μg administered by different routes [Chong et al 2002], we found that, besides the dosage used, the route of administration of misoprostol also influenced the rate of side effects. We hypothesize that this was due to either the higher peak plasma concentrations of misoprostol acid achieved by giving an oral solution of misoprostol or the fact that parenteral routes of administering misoprostol bypass metabolic pathways that increase the occurrence of these side effects.

This study shows that the differences in uterotonic effect produced by misoprostol 200 μg and 400 μg administered as oral solutions and intramuscular syntometrine 1 ml were small, while the difference in side effects produced was significantly different. The limitations of the existing evidence against the routine use of oral misoprostol in the third stage of labor may lie in the fact that misoprostol administered as oral tablets have a slower onset of action [Chong et al 2001] than the parenteral oxytocics with which it was compared. This view is shared by the authors of the WHO misoprostol trial and the Cochrane systematic review on the use of misoprostol for the prevention of postpartum haemorrhage [Abdel-Aleem et al

2003]. We suggest that a strategy to consider for the safe routine use of misoprostol in the third stage would be to give low doses of misoprostol by either the oral solution or sublingual route. This study highlights the need to carefully re-examine the route and dose of misoprostol used for the purpose of preventing or treating postpartum haemorrhage.

Chapter 9

The use of misoprostol administered by different routes in the third stage of labour to prevent postpartum haemorrhage: A Systematic Review

Introduction

Although there has been marked improvement in the prevention of postpartum haemorrhage (PPH) in the third stage of labour in recent years, it is still a significant contributor to maternal morbidity and mortality in developing countries [Li et al 1996]. There is good evidence that clinicians should practice active management of the third stage of labour and administer appropriate prophylactic uterotonic agents to prevent PPH [Prendiville et al 2003]. Currently, the uterotonic agents used by most maternity units are injectable oxytocics and ergot alkaloids such as oxytocin, syntometrine, and ergometrine. The first use of oral misoprostol for the prevention of postpartum haemorrhage in the third stage of labour was reported in 1996 in a prospective uncontrolled study [El-Refaey et al 1996]. Within two years, the first randomised controlled trial (RCT) was published [Bamigboye et al 1998a], and over the next five years, another 26 RCTs were reported. Most were small to medium sized trials ranging from 40 to 2058 subjects. The largest single study was that by the WHO Collaborative Group, with 18530 subjects [Gulmezoglu et al 2001a].

The WHO Misoprostol multicentre trial concluded that oral tablet misoprostol 600 μg given in the third stage of labour was associated with a higher risk of severe postpartum haemorrhage, need for additional uterotonics, shivering, and pyrexia compared to intramuscular or intravenous oxytocin 10 IU. Until this study, none of the RCTs had proven conclusively that misoprostol was either more or less effective than injectable uterotonics in preventing postpartum haemorrhage or the need for additional uterotonics. Earlier studies [Cook et al 1999; Ng et al 2001] had shown that the blood loss was significantly greater with oral tablet misoprostol

than with injectable uterotonics, but the clinical significance of the increase in blood loss (less than 100 ml) was doubtful. As expected, the results of the large WHO study overwhelmed the existing evidence, and the resulting Cochrane review [Gulmezoglu et al 2003] that followed concluded that conventional injectable oxytocics were preferable to misoprostol for the routine prevention of postpartum haemorrhage. The Cochrane review combined the studies using oral tablet and oral solution misoprostol together and this could have influenced the overall treatment effect. Also, the injectable uterotonics used to compare with misoprostol were all analysed together in the review. When studies of misoprostol oral tablet were compared with injectable uterotonics, there was a significant increase in blood loss in the misoprostol oral tablet group. But when studies with oral solution misoprostol were combined the relative effect seemed to have decreased.

Based on our own observations [Chong et al 2002; Chong et al 2004], we feel that misoprostol given orally as a tablet may not be the optimal method of administering this drug for the purpose of preventing postpartum haemorrhage. Pharmacokinetic studies [Abdel-Aleem et al 2003; Khan & El-Refaey 2003] have shown that the peak plasma concentration of misoprostol acid with oral tablet administration after delivery is around 18 to 20 minutes. From our intrauterine pressure measurement studies, we have found that the onset of uterotonic action after swallowing misoprostol tablets is 6 minutes [Chong et al 2004]. This compares with a peak plasma concentrations of oxytocin within 3 minutes of intramuscular injection [Gibbens et al 1972], and onset of uterotonic action by 2.5 minutes [Chong et al 2004]. These few minutes difference in onset of action is of great clinical significance as delay in uterine contraction in the third stage can lead to a large

volume of blood loss within a very short period of time. The delay in onset of action for rectal misoprostol is even greater, with peak plasma levels at 40.5 minutes [Khan & El-Refaey 2003], and onset of uterotonic activity at 11 minutes [Chong et al 2004]. Hence, we feel that the current RCTs, which have either used misoprostol as oral tablets, or as rectal suppositories (for which most misoprostol tablets were not formulated), will not show misoprostol to be an effective uterotonic agent for the purpose of preventing postpartum haemorrhage in the third stage.

We separated out the two trials using oral solution misoprostol [Walley et al 2000; Oboro & Tabowei 2003] from those using oral tablet misoprostol as we feel that this method of administration may result in quicker absorption and greater uterotonic efficacy. In addition, we examined the use of misoprostol for the prevention of postpartum haemorrhage during caesarean sections. The hypotheses tested were:

1. oral tablet and rectal misoprostol are inferior to parenteral oxytocics in preventing postpartum blood loss,
2. oral solution misoprostol is equivalent to parenteral oxytocics in preventing postpartum blood loss,
3. misoprostol is more effective than placebo or no treatment, and
4. misoprostol produces dose-related side effects.

Methods

Search strategy for identification of studies

We used the same search strategy used by the earlier reviewers but did an extended search up to 2003. Randomised clinical trials of misoprostol used for the routine prevention of postpartum haemorrhage were identified from the Cochrane central register of controlled trials (CENTRAL) maintained by the Cochrane Library, and the MEDLINE and PubMed (National Library of Medicine, Bethesda,MD) computerised databases (1995 to 2003). We did not search for earlier studies as the first report of the use of misoprostol in the third stage was published in 1996 [El-Refaey et al 1996]. The date of the latest search was July 1, 2003. The medical search terms used included *misoprostol, third stage, prevention of postpartum haemorrhage, randomised controlled trial*.

Criteria for considering studies for this review

Eligibility criteria for inclusion included randomised clinical trials comparing misoprostol administered by any route for the active management of the third stage of labour with no treatment, placebo or other uterotonic drugs; random allocation to treatment and comparison groups; reasonable measures to ensure allocation concealment [Clarke & Oxman 1999]. Trials with inadequate allocation concealment or with primary outcomes other than clinical effectiveness were excluded.

Types of outcome measures:

1. Blood loss equal or more than 1000 mL
2. Blood loss equal or more than 500 mL
3. Need for additional oxytocic therapy

4. Side effect of shivering

5. Side effect of fever

These outcomes were selected as they were the ones most consistently documented in the RCTs as well as having the most clinical significance. Volume of blood loss, change in haemoglobin or haematocrit values, and other side effects were not consistently measured in the studies, and of doubtful clinical relevance.

Trials under consideration were evaluated for methodological quality and appropriateness for inclusion, without consideration of their results, independently by two reviewers. No language preferences were applied either during the search or selection of trials. Data were extracted independently by two reviewers.

In addition to the main outcomes, the following data were systematically extracted for each study:

1. trial entry criteria (high versus low risk, other specific exclusion criteria);
2. exclusions and missing data after randomization;
3. management of the third stage of labour;
4. the duration and technique of assessment of blood loss.

Comparisons:

Prespecified primary comparisons for oral tablet misoprostol 400 to 600 μg were as follows:

1. Misoprostol *vs* placebo

2. Misoprostol *vs* any injectable uterotonic

Prespecified primary comparisons for oral solution misoprostol 400 and 600 μg were as follows:

1. Misoprostol *vs* oxytocin

Prespecified primary comparisons for rectal misoprostol 400 μg were as follows:

1. Misoprostol *vs* placebo
2. Misoprostol *vs* any injectable uterotonic

Data Synthesis:

Data were extracted from the sources and entered into the RevMan computer software (Cochrane Collaboration, Copenhagen, Denmark) and double-checked for accuracy. For dichotomous data, relative risks (RR) and 95% confidence intervals were calculated; and for continuous outcomes weighted mean difference (WMD). If there was heterogeneity among the study results a random effects model was used and if there was not a fixed effects model was used.

Description of included studies

Twenty-seven randomized controlled clinical trials were identified and considered for inclusion in this review. These trials were conducted in both developing and developed countries, and their results were published from 1998 to 2003. Four studies were excluded (reasons given in Table 9.6). This review includes six trials [Daly et al 1999; Benchimol et al 2001; Caliskan et al 2002; Karkanis et al 2002; Caliskan et al 2003; Oboro & Tabowei 2003] not considered in the most recent Cochrane Review [Gulmezoglu et al 2003].

In 16 trials, the risk status of the women for postpartum haemorrhage was not mentioned. Low-risk women were studied in five trials, and one trial included women at both high and low risk of postpartum haemorrhage.

'Active' management of the third stage was described in 17 of the trials with cord traction being universally performed, but the actual practice varied in the different centres. In four studies, the management of the third stage was not described, while two studies involved caesarean deliveries.

Oral tablets were used in 13 trials [Hofmeyr et al 1998; Hofmeyr et al 1998a; Amant et al 1999; Cook et al 1999; Lumbiganon et al 1999; Surbek et al 1999; El-Refaey et al 2000; Benchimol et al 2001; Gulmezoglu et al 2001a; Hofmeyr et al 2001; Kundodyiwa et al 2001; Ng et al 2001; Caliskan et al 2003] for the prevention of postpartum haemorrhage after vaginal deliveries. Five of these studies compared oral tablet misoprostol against placebos [Hofmeyr et al 1998; Hofmeyr et al 1998a; Surbek et al 1999; Benchimol et al 2001; Hofmeyr et al 2001], while nine compared misoprostol to injectable uterotonics [Amant et al 1999; Cook et al 1999; Lumbiganon et al 1999; El-Refaey et al 2000; Benchimol et al 2001; Gulmezoglu et al 2001a; Kundodyiwa et al 2001; Ng et al 2001; Caliskan et al 2003]. Two other studies assessed the use of oral tablet misoprostol during caesarean deliveries [Acharya et al 2001; Lokugamage et al 2001a].

Oral solution misoprostol was given in two trials [Walley et al 2000; Oboro & Tabowei 2003]. In both these trials, powdered misoprostol was used to enable blinding of the drug identity, with powdered lactose as the identical placebo. The

powdered misoprostol and the lactose were dissolved in 50 mL of water before administration. Both these trials compared misoprostol with intramuscular oxytocin 10 IU. We did not find any studies that compared oral solution against placebo or no treatment.

The route of administration was rectal in six studies [Bamigboye et al 1998; Bamigboye et al 1998a; Bugalho et al 2001; Gerstenfeld & Wing 2001; Caliskan et al 2002; Karkanis et al 2002]. All except one used normal misoprostol tablets (meant for oral administration) inserted rectally. One group of investigators used microenemas composed of misoprostol 400 μg (2 tablets) made into a paste in 5 mL of saline [Bugalho et al 2001]. Only one study compared rectal misoprostol with placebo [Bamigboye et al 1998].

The injectable uterotonic used was intramuscular oxytocin in eight trials, intravenous oxytocin in nine trials, intramuscular syntometrine in four trials, intravenous ergometrine or methylergometrine in two trials, and intramuscular methyleronovine in two trials. Five studies used more than one type of injectable uterotonics.

The estimation of blood loss varied in precision. Eleven studies measured blood loss using various methods of collection and volume measurement, eight of these studies weighed linen and swabs as well. Nine studies used visual estimation only while three combined visual estimation with volume measurement and weighing of linen. Two studies used pre- and post-delivery haemaglobin measurements, one combined with linen weighing.

Most trials had postpartum blood loss, defined as severe postpartum haemorrhage ≥1000 ml or postpartum haemorrhage ≥500 ml, and the use of additional uterotonics as the primary outcome. The rate of side effects was the primary outcome in two trials [Hofmeyr et al 1998a; Lumbiganon et al 1999].

Overall, the methodological quality of the included trials was acceptable, with moderate risk of bias. All trials were properly randomised and allocation concealment efforts were made. Outcome assessment was not blinded in six trials [Cook et al 1999; Amant et al 1999; Bugalho et al 2001;Gerstenfeld & Wing 2001; Acharya et al 2001; Karkanis et al 2002]. No major protocol deviations were reported in most of the trials. Intention to treat analysis was not followed in six trials [Amant et al 1999; Cook et al 1999; Bugalho et al 2001; Gerstenfeld & Wing 2001; Karkanis et al 2002; Caliskan et al 2003]. Because of the diversity of the interventions, and our aim of categorizing misoprostol given by three routes separately, there were few studies in the meta-analysis for each comparison. Thus, it was not possible to conduct sensitivity analyses based on trial quality, risk status or method of blood loss ascertainment.

Results

Oral tablet misoprostol

Oral tablet misoprostol versus placebo/no treatment (five studies, 2367 women)

Five studies compared oral tablet misoprostol with placebo (Table 9.1). Four trials used oral tablet misoprostol 600 µg [Hofmeyr et al 1998a; Surbek et al 1999; Benchimol et al 2001; Hofmeyr et al 2001] and two used 400 µg [Hofmeyr et al 1998; Hofmeyr et al 1998a]. Two trials had three arms- 600 µg, 400 µg misoprostol,

and placebo [Hofmeyr et al 1998a]; 600 μg misoprostol, nothing, and intravenous oxytocin 2.5 mg bolus [Benchimol et al 2001].

One study [Hofmeyr et al 1998a] reported a significantly increased risk of severe haemorrhage (≥1000ml) when patients were treated with 600 μg of misoprostol but in two other studies [Hofmeyr et al 1998; Benchimol et al 2001] there were no significant differences between the two groups. The overall effect shows that there is an increased risk of severe postpartum haemorrhage when treated with 600 μg misoprostol oral tablet but the result was not statistically significant (RR 1.43, 95% CI 0.78 to 2.62) (Figure 9.1a). Two studies compared 400 μg misoprostol with placebo. One study showed that there was a significant increase in postpartum haemorrhage with misoprostol [Hofmeyr et al 1998a] but the other study [Hofmeyr et al 1998] reported a decrease in the number of severe postpartum haemorrhage (≥1000mls) cases compared to the control group. Overall treatment effect shows that the risk of having postpartum haemorrhage was high with 400 μg misoprostol but it was not statistically significant (RR 1.27, 95% CI 0.32 to 5.04). There was also significant result heterogeneity between these two studies (Chi^2=6.20, p=0.01). In one study [Surbek et al 1999], the risk of having postpartum haemorrhage (≥500 mls) was reported to be less in the misoprostol (600 μg) treated group compared to the placebo group, but the result was not statistically significant ((RR 0.44, 95% CI 0.09-2.10) (Figure 9.1b). There was less use of additional uterotonics in the oral tablet misoprostol groups (400 and 600 μg) compared to the placebo groups (RR 0.88, 95% CI 0.47 to 1.66; RR 0.84, 95% CI 0.48 to 1.47 respectively) (Figure 9.1d).

The risks of having shivering were significantly higher when patients were treated with 400 and 600 μg of oral misoprostol than if they were not treated or given placebo (overall treatment effect: RR 2.70, 95% CI 1.61 to 4.53; RR 3.40, 95% CI 2.39 to 4.85 respectively) (Figure 9.1e). Of the three studies that were considered for inclusion, only two of them had very precise estimates. The third study [Surbek et al 1999] had imprecise results, which were probably due to a small sample size. This study did not examine the side effect of pyrexia. The three other studies showed that oral tablet misoprostol at 400 μg and 600 μg significantly increased the risks of pyrexia compared to placebo (RR 5.60, 95% CI 2.21 to 14.21; RR 7.55, 95% CI 4.70 to 12.15 respectively) (Figure 9.1f). For the side effects of shivering and pyrexia, there was no significant result heterogeneity. All the studies showed that oral tablet misoprostol at both doses significantly increased the risk of these side effects, with a dose response relationship.

Table 9.1 Oral tablet misoprostol versus placebo/no treatment (5 studies)

Study	Methods	Participants	Interventions	Comments
Hofmeyr et al 1998	Random allocation. Tablets kept in numbered, sealed, opaque containers. Double-blinded, with non-identical placebo.	500 women after vaginal delivery. No mention of risk status. South Africa	Oral tablet misoprostol 400 µg versus placebo	Management of third stage: placenta delivered by cord traction once uterus contracted. No withdrawals after randomization. Measurement of blood loss: collected in bedpans and volume assessed; linen weighed.
Hofmeyr et al 1998a	Random allocation. Tablets kept in numbered, sealed, opaque containers. Outcome assessments blinded.	600 women after vaginal delivery. No mention of risk status or exclusion criteria. South Africa	Oral tablet misoprostol 600 µg versus oral tablet misoprostol 400 µg versus placebo	Management of third stage: placenta delivered by cord traction once uterus contracted. No withdrawals after randomization. Measurement of blood loss: collected in bedpans for 1 hour after delivery.
Surbek et al 1999	Random allocation by pharmacy. Double-blinded, with identical placebo.	65 low-risk women after vaginal delivery. Switzerland	Oral capsule misoprostol 600 µg versus placebo	Management of third stage: early cord clamping and cord traction. No withdrawals after randomization. Measurement of blood loss: estimated by delivering physician.
Hofmeyr et al 2001	Random allocation. Tablets kept in numbered, sealed, opaque containers. Outcome assessments blinded.	600 women after vaginal delivery. No mention of risk status or exclusion criteria. South Africa	Oral tablet misoprostol 600 µg versus placebo	Management of third stage: placenta delivered by cord traction once uterus contracted. No withdrawals after randomization. Measurement of blood loss: collected in bedpans and volume assessed; linen and sanitary towels weighed.
Benchimol et al 2001	Random allocation. Opaque envelopes for allocation. No blinding of outcome assessments.	602 women France	Oral tablet misoprostol 600 µg versus placebo versus i/voxytocin 2.5IU bolus	Management of third stage: early cord clamping. Withdrawals after randomization: no details. Measurement of blood loss: estimated by midwife; blood loss collected in special sheet placed under patient and weighed.

Review: The use of misoprostol administered by different routes to prevent postpartum haemorrhage: A Systematic Review (Version 03)
Comparison: 01 Oral misoprostol Vs Placebo/nothing
Outcome: 01 Severe postpartum haemorrhage (>1000 mls)

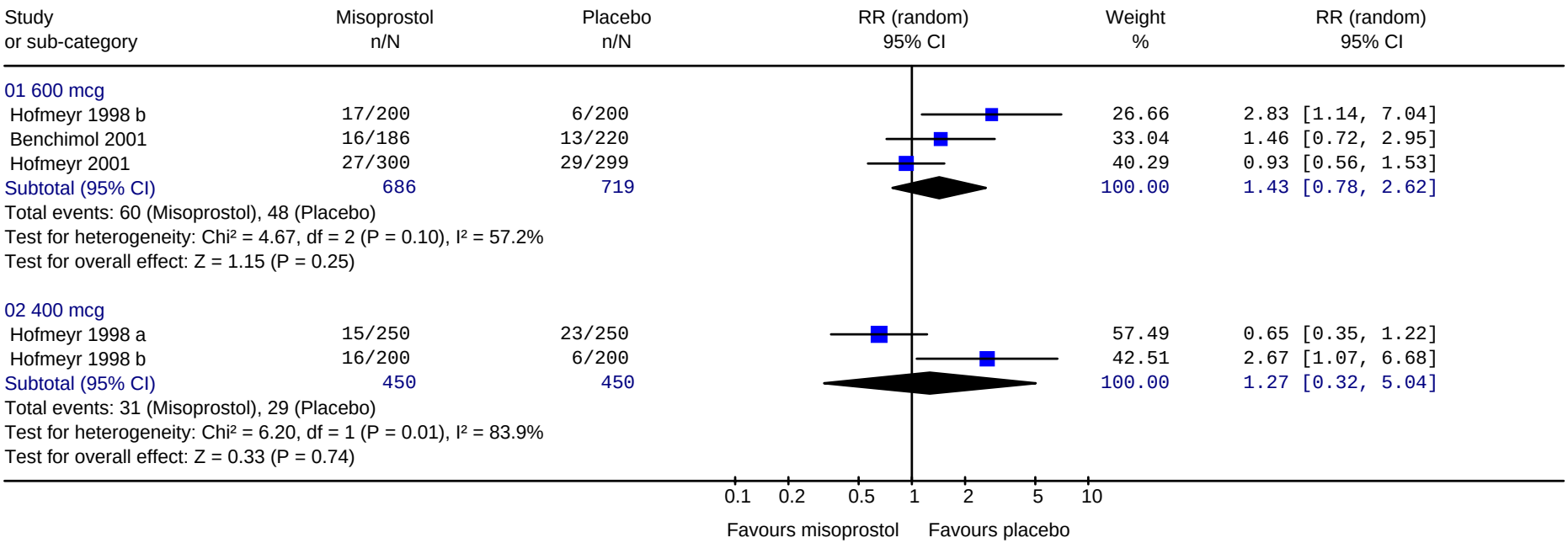


Figure 9.1a Oral misoprostol vs placebo, Outcome: Severe postpartum haemorrhage (>1000 mL)

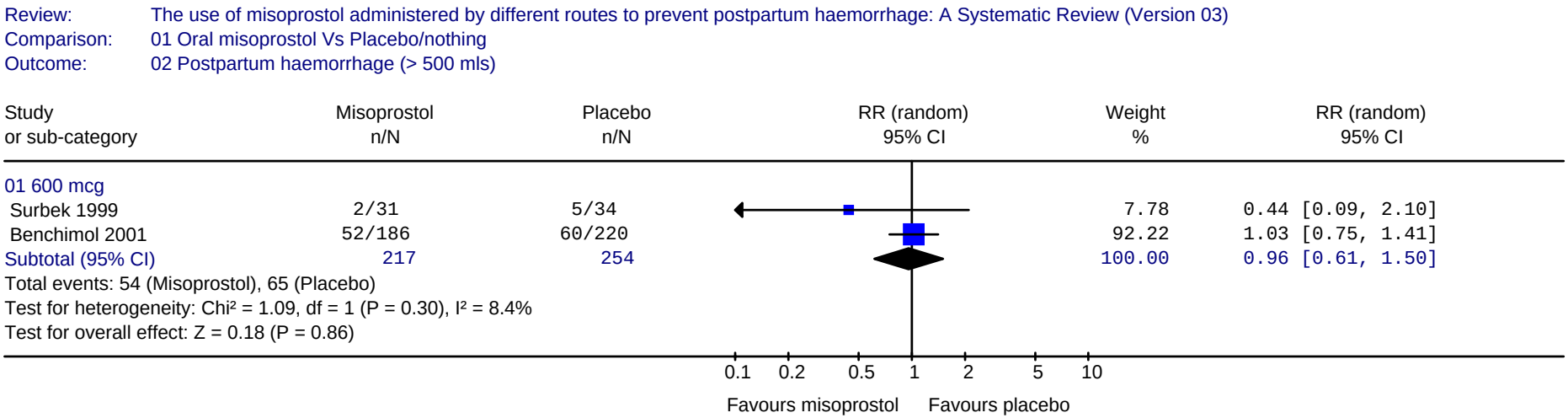


Figure 9.1b Oral misoprostol vs placebo, Outcome: Postpartum haemorrhage (>500 mL)

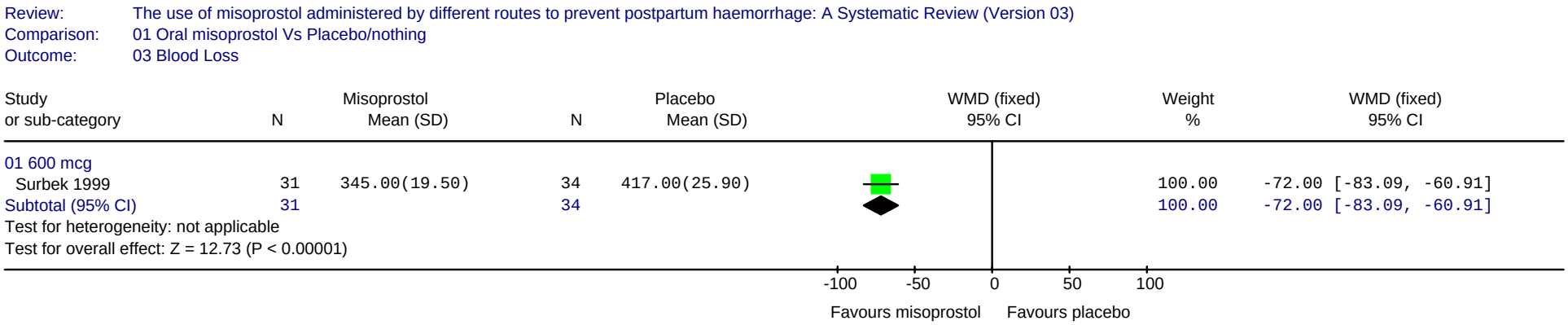


Figure 9.1c Oral misoprostol vs placebo, Outcome: Blood loss (mL)

Review: The use of misoprostol administered by different routes to prevent postpartum haemorrhage: A Systematic Review (Version 03)
Comparison: 01 Oral misoprostol Vs Placebo/nothing
Outcome: 04 Use of additional uterotonics

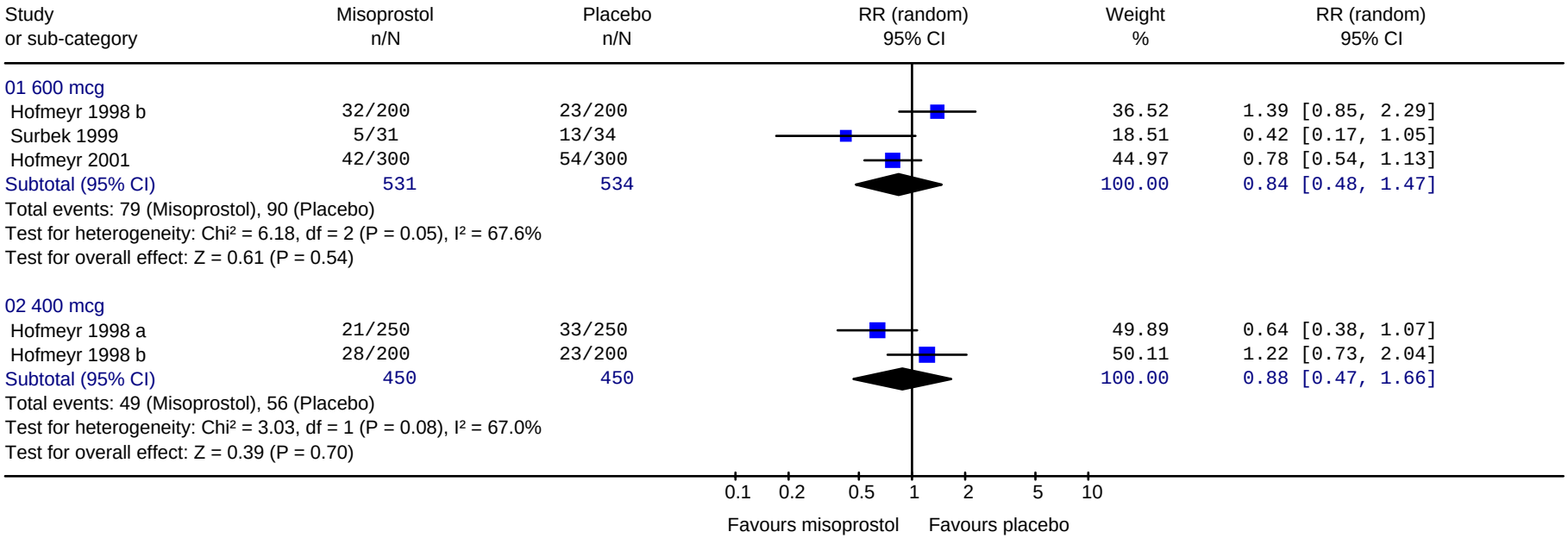


Figure 9.1d Oral misoprostol vs placebo, Outcome: Use of additional uterotonics

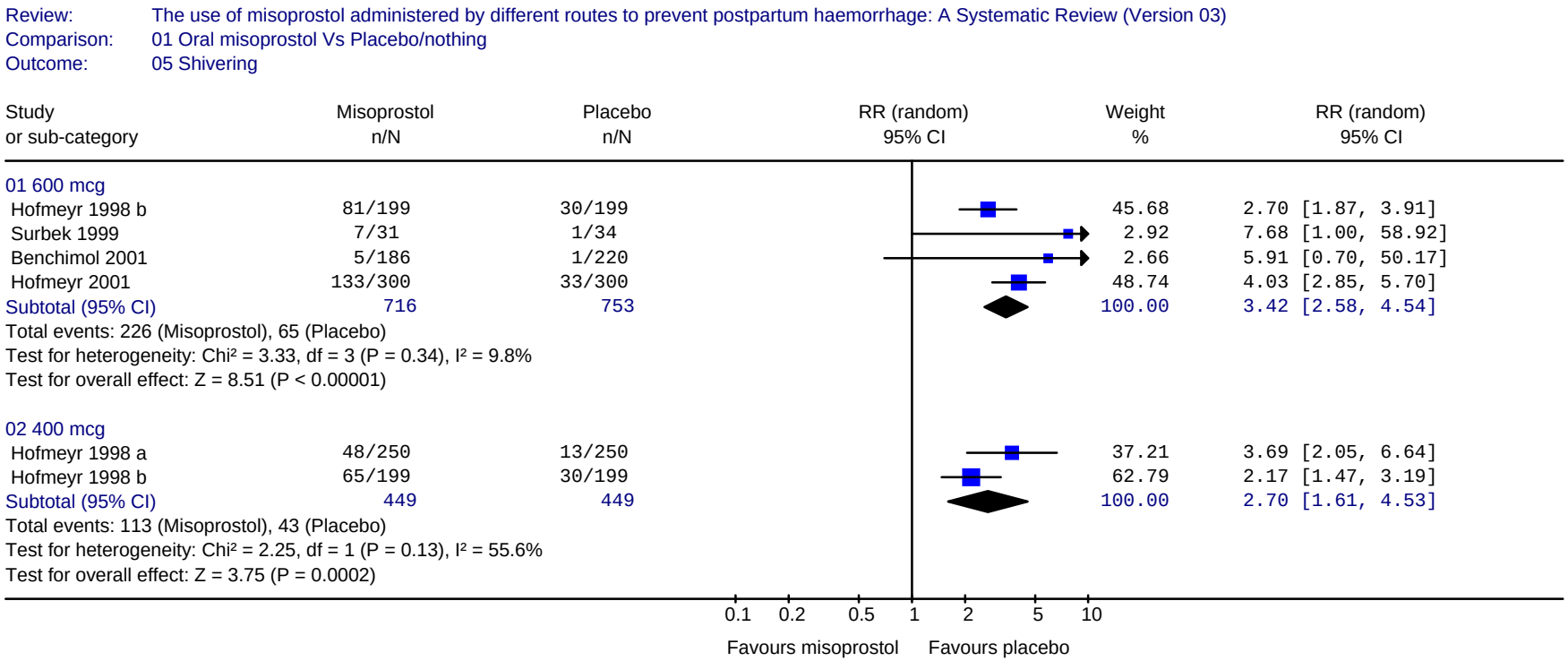


Figure 9.1e Oral misoprostol vs placebo, Outcome: Shivering

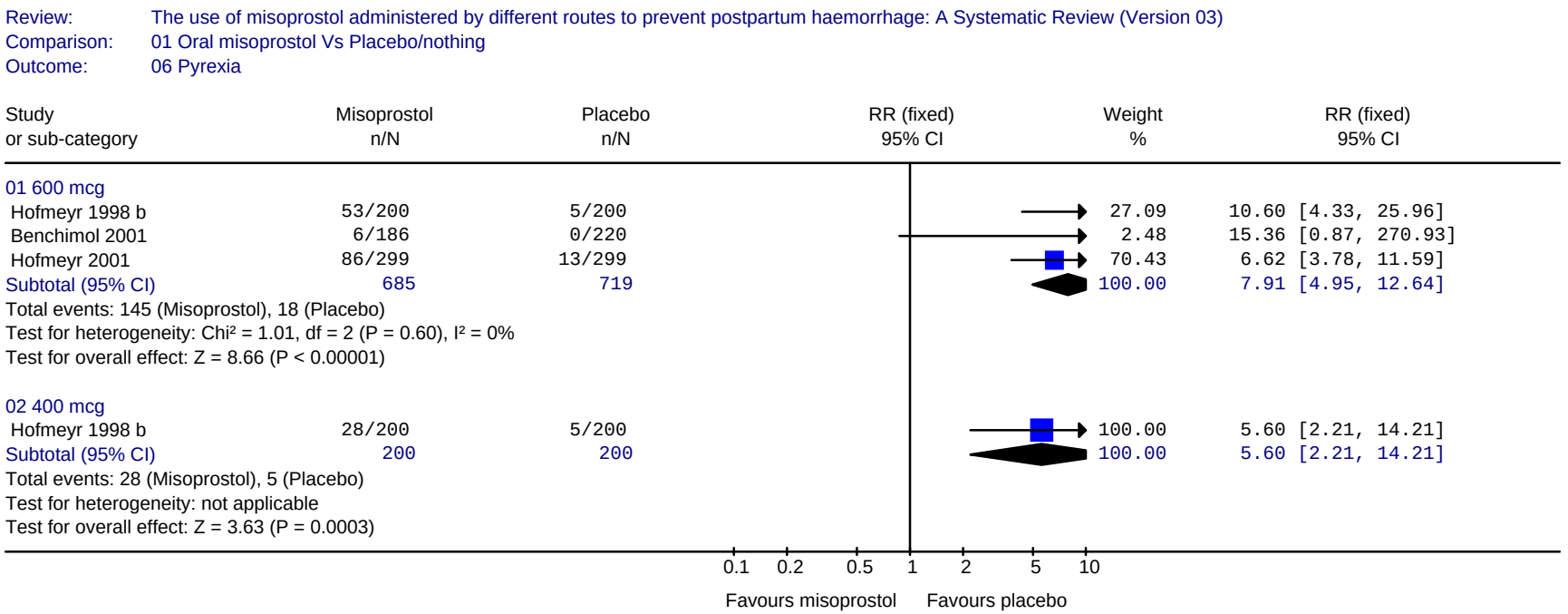


Figure 9.1f Oral misoprostol vs placebo, Outcome: Pyrexia

Oral tablet misoprostol versus injectable uterotonics (eight studies, 25402 women)

There were eight studies comparing oral tablet misoprostol with injectable uterotonics (Table 9.2). Their sample sizes ranged from 40 to 18403. Five studies used a dose of 600 μg [Amant et al 1999; Lumbiganon et al 1999; Gulmezoglu et al 2001a; Ng et al 2001; Caliskan et al 2003], one used 500 μg [El-Refaey et al 2000], and three used 400 μg [Cook et al 1999; Lumbiganon et al 1999; Kundodyiwa et al 2001]. One trial [Lumbiganon et al 1999] compared 600 μg and 400 μg oral tablet misoprostol with intramuscular oxytocin 10 IU. The injectable uterotonics used include intramuscular or intravenous oxytocin, syntometrine, ergometrine, and methylergometrine. The WHO study [Gulmezoglu et al 2001a], with 18530 subjects randomized to either oral tablet misoprostol 600 μg or injectable oxytocin 10 IU, dominated the results.

For the primary outcome of severe postpartum haemorrhage (≥1000 mL), there was no statistically significant result heterogeneity among the studies (Figure 9.2a). At all three doses, oral tablet misoprostol was either as effective, or less effective than injectable uterotonics. Only the WHO study showed a significantly increased risk of severe postpartum haemorrhage with oral tablet misoprostol 600 μg. However, the overall treatment effects were not statistically significant.

For postpartum haemorrhage (≥500 mL), and the use of additional uterotonics, there was statistically significant result heterogeneity among the studies at 600 μg and 400 μg. Oral tablet misoprostol 600 μg was significantly less effective than injectable uterotonics at preventing postpartum haemorrhage (RR 1.27, 95% CI 1.01 to 1.58) (Figure 9.2b). At 500 μg and 400 μg, the overall treatment effect

showed a slight increased risk of postpartum haemorrhage but the results were not statistically significant. With all three concentrations of oral misoprostol the risk of having to use additional uterotonics to prevent bleeding was higher when compared to the injectable uterotonics group but the overall effect was only statistically significant for oral tablet misoprostol 600 μg (RR 1.30, 95% CI 1.03-1.65) (Figure 9.2d).

The dose response effect was evident for both side effects. Oral tablet misoprostol at all three doses significantly increased the risk of shivering (overall treatment effect: RR 2.62, 95% CI 2.03 to 3.40 for 600 μg; RR 1.94, 95% CI 1.69 to 2.22 for 500 μg; and RR 1.77, 95% CI 1.20 to 2.62 for 400 μg) (Figure 9.2e). There was significant result heterogeneity at the doses of 600 μg and 400 μg. However, all except two studies showed that oral tablet misoprostol at all three doses significantly increased the risk of shivering. The remaining two studies showed a non-statistically significant increased risk of shivering. Oral tablet misoprostol 600 μg significantly increased the risk of pyrexia (RR 5.84, 95% CI 3.91 to 8.73) (Figure 9.2f). The overall treatment effects also showed an increased risk of pyrexia at lower doses of misoprostol compared to injectable oxytocics but these were not statistically significant. There was significant result heterogeneity at the dose of 400 μg.

Table 9.2 Oral tablet misoprostol versus injectable uterotonics (8 studies)

Study	Methods	Participants	Interventions	Comments
Lumbiganon et al 1999	Random allocation; pilot study for main WHO trial. Identical treatment packs drawn from a dispenser; identical double placebos. Double-blind.	597 women after vaginal delivery. No mention of risk status. South Africa and Thailand.	Oral tablet misoprostol 600 µg versus oral tablet misoprostol 400 µg versus i/m oxytocin 10 IU	Management of third stage: uterotonics, early clamping and cutting of cord, fundal or suprapubic pressure with cord traction after signs of placental separation. Exclusions after randomization: 1 (0.5%),1 (0.5%) and 8 (4%) women in the misoprostol 600 µg, 400 µg and oxytocin groups respectively. Measurement of blood loss: blood and small gauze swabs collected in standard measuring jar; linen not weighed.
Cook et al 1999	Random, block allocation. Tablets kept in sealed, opaque containers. Not blinded.	930 women after vaginal delivery. No mention of risk status. 4 centres in Australia (n=330), China (n=257), and Papua New Guinea (n=276).	Oral tablet misoprostol 400 µg versus i/m oxytocin 10 IU or i/m syntometrine 1 mL	Management of third stage: not mentioned. 31/455 women (7%) excluded after randomization in the misoprostol group; 36/475 (8%) excluded in the oxytocin/syntometrine group. Measurement of blood loss: estimated by clinician; measured with calibrated measuring jug; linen weighed; all combined.
Amant et al 1999	Random, block allocation. Identical, numbered study boxes; identical placebos. Blinded.	213 women after vaginal delivery. No mention of risk status. Belgium	Oral capsule misoprostol 600 µg versus i/v methylergometrine 200 µg	Management of third stage: uterine massage, cord traction, manual removal of placenta after 30-60 min. 5/100 women (5%) excluded after randomization in the misoprostol group; 8/108 (7.4%) excluded in the methylergometrine group. Measurement of blood loss: estimated by clinician.

El-Refaey et al 2000	Random, block allocation. Opaque envelopes. No blinding of outcome assessments.	1000 women after vaginal delivery. Both high and low risk status. United Kingdom	Oral tablet misoprostol 500 µg versus High risk women- i/v ergometrine (2%) or oxytocin (18%). Low risk- i/m syntometrine 1 mL (80%).	Management of third stage: cord traction, oxytocics at delivery of anterior shoulder. No withdrawals after randomization. Measurement of blood loss: estimated by midwives.
Ng et al 2001	Random, block allocation. Opaque envelopes. No blinding of outcome assessments.	2058 women after vaginal delivery. No mention of risk status. 3 hospitals in Hong Kong.	Oral tablet misoprostol 600 µg versus i/m syntometrine 1 mL	Management of third stage: cord traction after signs of placental separation. No withdrawals after randomization. Measurement of blood loss: estimated by clinician.
Gulmezoglu et al 2001a	Random, block allocation, stratified. Identical treatment packs drawn from a dispenser; identical double placebos. Double-blinded.	18530 women expecting vaginal delivery. No mention of risk status. Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam.	Oral tablet misoprostol 600 µg versus i/v or i/m oxytocin 10 IU	Management of third stage: uterotonics, early clamping and cutting of cord, fundal or suprapubic pressure with cord traction after signs of placental separation. Exclusions after randomization: 37 and 34 women with caesarean delivery, and 13 and 4 women lost to follow-up in misoprostol and oxytocin groups, respectively, for blood loss, and 2 and 4 women without information on the need for additional uterotonics. Measurement of blood loss: blood and small gauze swabs collected in standard measuring jar; linen weighed in some centres.

Kundodyiwa et al 2001	Random allocation. Opaque envelopes. Misoprostol similar in size and colur but not in shape to placebo; injectable medication and placebo identical.	500 women expecting vaginal delivery. Zimbabwe	Oral tablet misoprostol 400 µg versus i/m oxytocin 10 IU	Management of third stage: not mentioned. Exclusions after randomization: 1 woman because of undiagnosed twins (0.2%). Measurement of blood loss: linen soiled with amniotic fluid removed; fresh disposable incontinence pads with plastic backing placed under women; blood loss measured with calibrated jug; linen saver and sanitary pads weighed.
Caliskan et al 2003	Random allocation. Numbered, sealed, opaque envelopes. Misoprostol similar in size and colur but not in shape to placebo; injectable medication and placebo identical. Outcome assessment blinded.	1574 women expecting vaginal delivery. Turkey	Oral tablet misoprostol 600 µg in total plus i/v oxytocin 10 IU over 30 min versus Oral tablet misoprostol 600 µg in total or i/v oxytocin 10 IU over 30 min or i/m methylergonovine 0.2 mg plus i/v oxytocin 10 IU over 30 min	Management of third stage: early cord clamping, cord traction with uterine massage; manual removal of placenta if not delivered after 30 minutes. Exclusions after randomization: 226 women (12.6%) because of caesarean delivery or lack of haemoglobin testing; no details of distribution by group. Measurement of blood loss: estimated by physician in charge of labour; blood collected in bedpan for 1 hour after delivery; gauzes and pads weighed; haemoglobin on admission and 24 hours after delivery. .

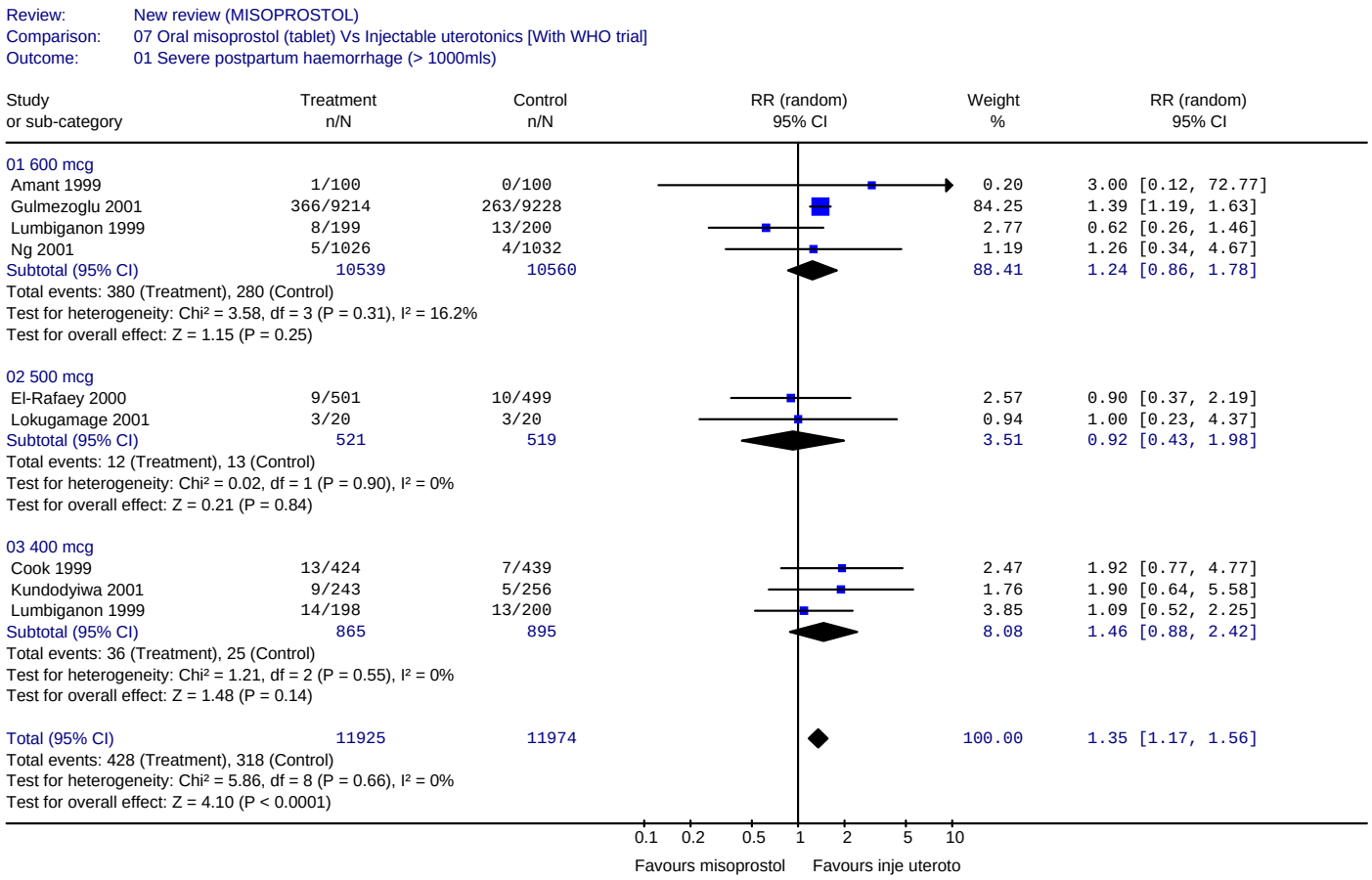


Figure 9.2a Oral misoprostol (tablet) vs injectable uterotonics; Outcome: Severe postpartum haemorrhage (>1000 mL)

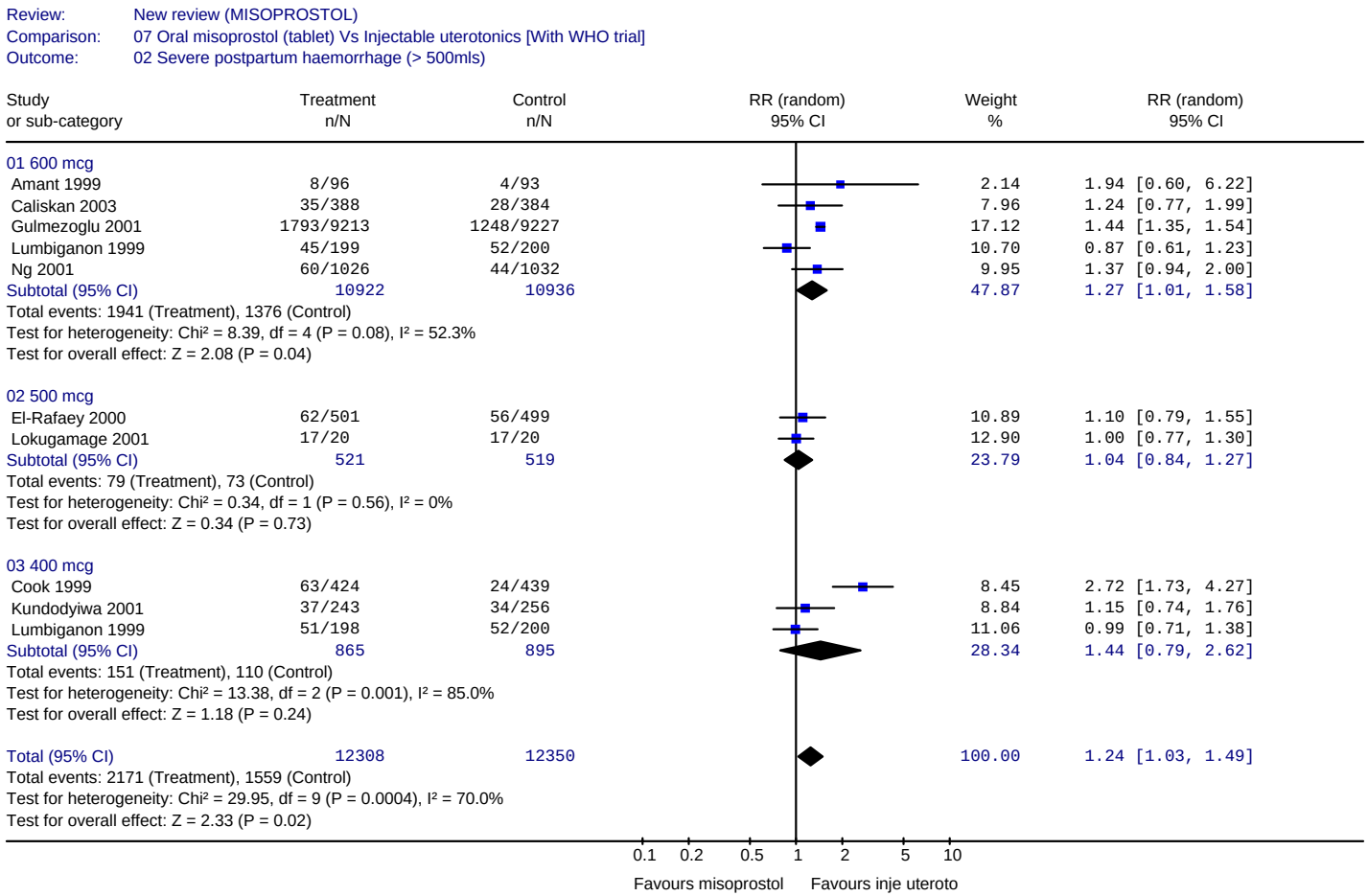


Figure 9.2b Oral misoprostol (tablet) vs injectable uterotonics; Outcome: Postpartum haemorrhage (>500 mL)

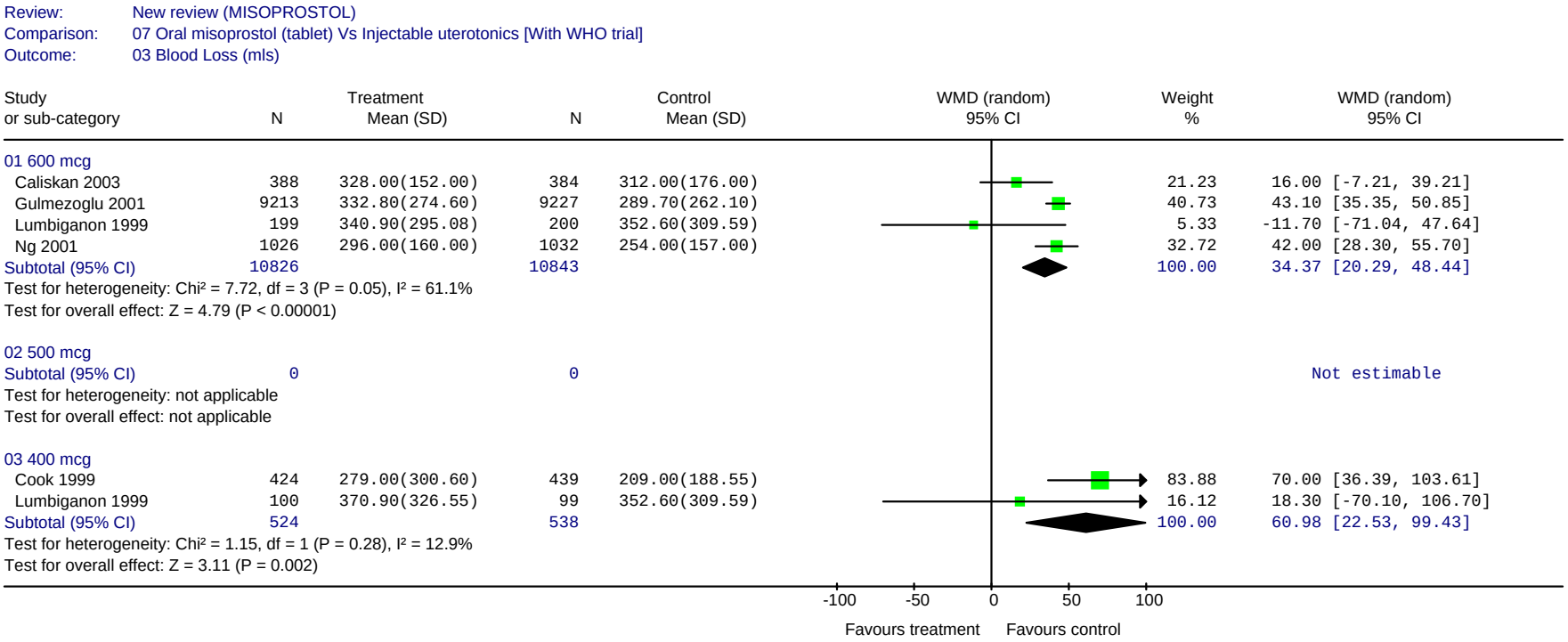


Figure 9.2c Oral misoprostol (tablet) vs injectable uterotonics; Outcome: Blood loss (mL)

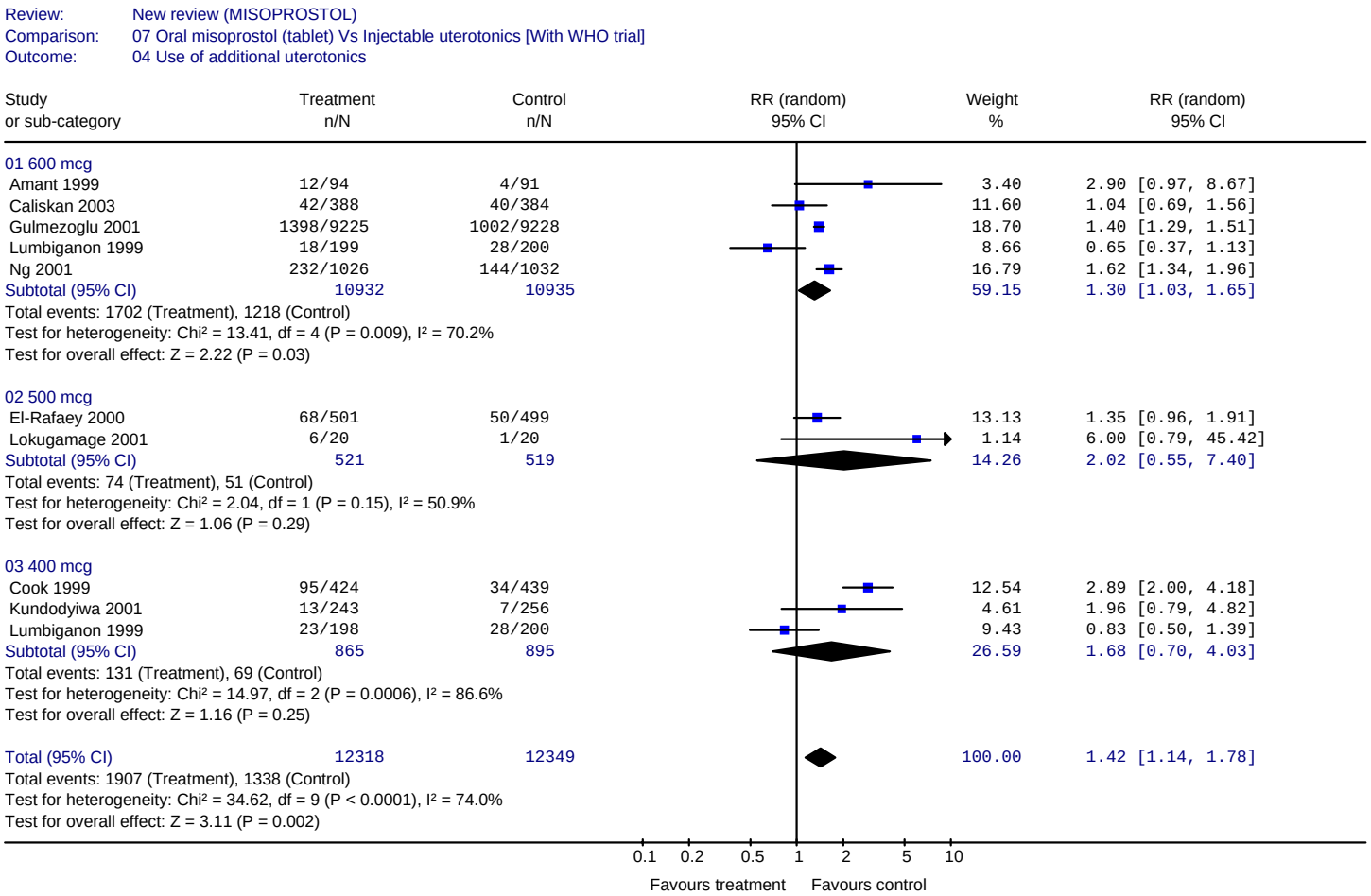


Figure 9.2d Oral misoprostol (tablet) vs injectable uterotonics; Outcome: Use of additional uterotonics

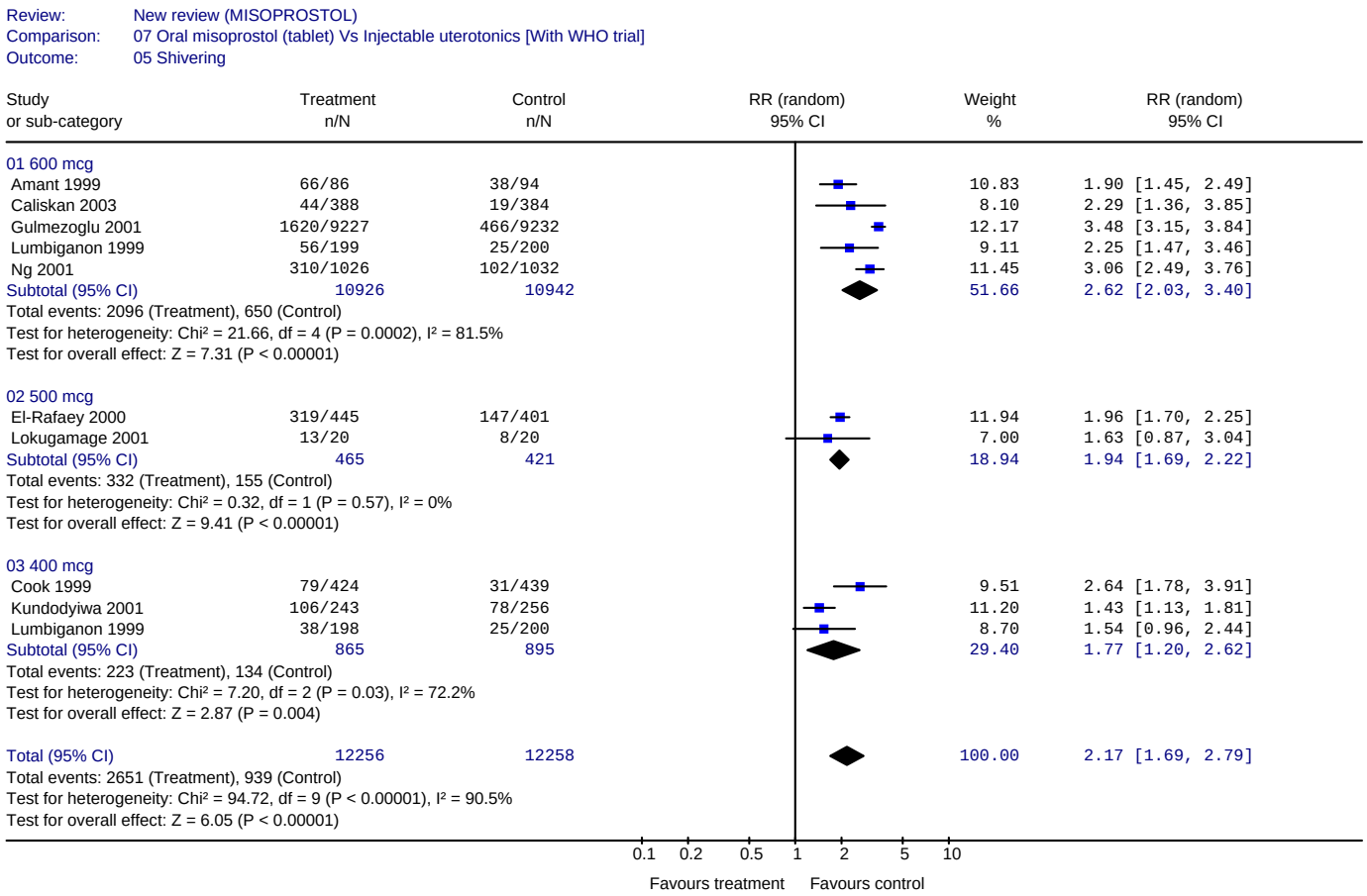


Figure 9.2e Oral misoprostol (tablet) vs injectable uterotonics; Outcome: Shivering

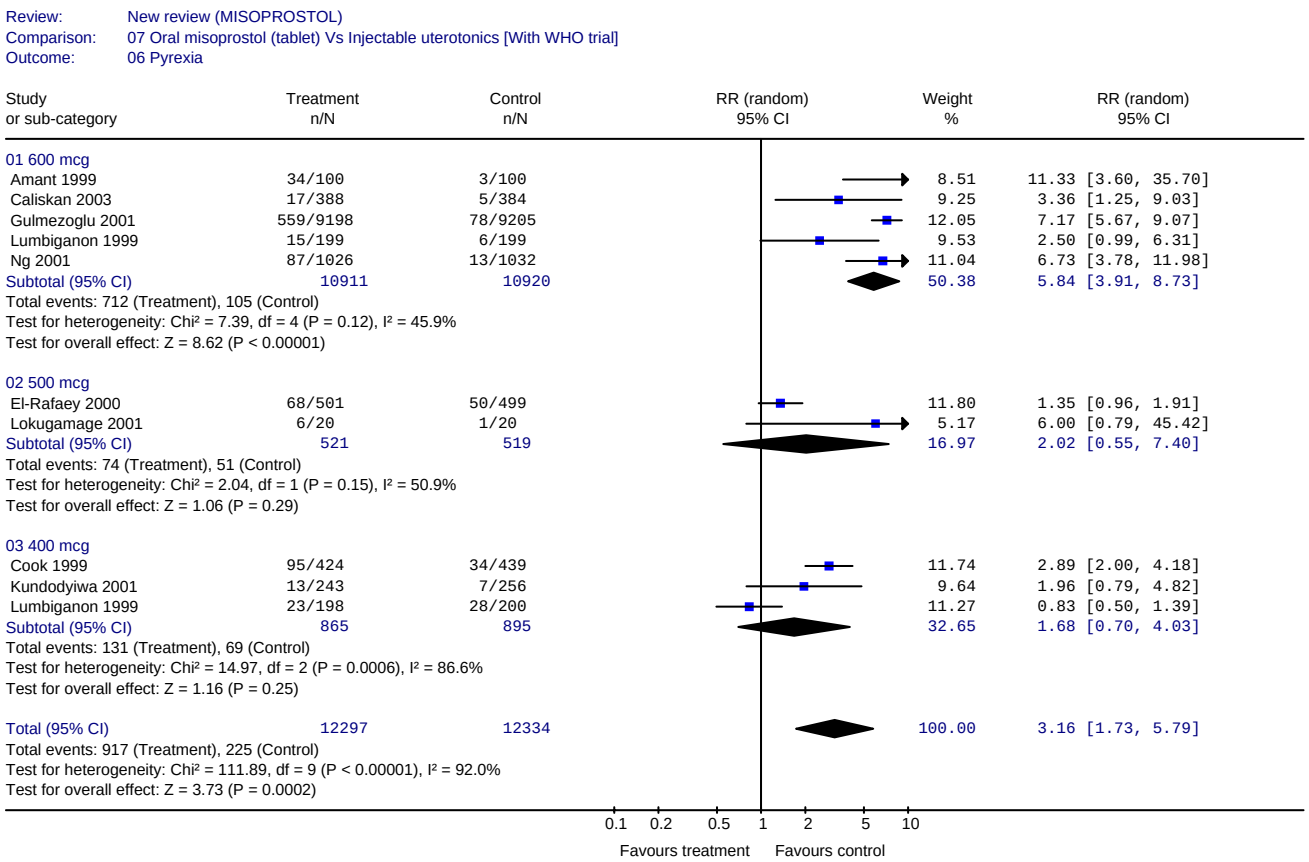


Figure 9.2f Oral misoprostol (tablet) vs injectable uterotonics; Outcome: Pyrexia

Oral solution misoprostol

Oral solution misoprostol versus intramuscular oxytocin (two studies, 897 women)

Misoprostol was given as an aqueous solution in two studies by dissolving the tablets in 50 mL of water before administration to the women (Table 9.3). One study used a dose of 400 µg [Walley et al 2000] while the other used 600 µg [Oboro & Tabowei 2003]. Both compared misoprostol to intramuscular oxytocin 10 IU.

The study using oral solution 400 µg showed that the risk of having postpartum haemorrhage (RR 0.19, 95% CI 0.01-4.02), and the use of additional uterotonics (RR 0.77, 95% CI 0.27-2.17) was reduced when compared with women given oxytocin. The study using oral solution 600 µg showed the converse results with an increased risk of postpartum haemorrhage (RR 3.02, 95% CI 0.32-28.88), and the use of additional uterotonics (RR 1.16, 95% CI 0.71-1.88). For both studies, the results were not statistically significant (Figure 9.3a).

Both studies confirmed that oral solution misoprostol resulted in a four-fold rise in the risk of shivering (RR 4.06, 95% CI 2.93-5.62; RR 3.90, 95% CI 2.01-7.57, respectively). However, there was a trend towards a dose-response effect with pyrexia, and 600 µg tended to increase the risk of fever (RR 3.02, 95% CI 0.32-28.88) while 400 µg tended to be protective (RR 0.77, 95% CI 0.27-2.17). Both these results were not statistically significant (Figure 9.3c).

Table 9.3 Oral solution misoprostol versus injectable uterotonics (2 studies)

Study	Methods	Participants	Interventions	Comments
Walley et al 2000	Random allocation. Medication and identical placebo kept in sealed, opaque packets. Double-blind.	401 women after vaginal delivery. No mention of risk status. Ghana	Oral solution misoprostol 400 µg (in 50 mL water) versus i/m oxytocin 10 IU	Management of third stage: cord traction. Outcome data missing for 9/401 (2.2%) women. Measurement of blood loss: estimated by clinician.
Oboro et al 2003	Random allocation. Medication and identical placebo kept in numbered, sealed, opaque packets. Double-blind.	496 women after vaginal delivery. No mention of risk status. Nigeria	Oral solution misoprostol 600 µg g (in 50 mL water) versus i/m oxytocin 10 IU	Management of third stage: cord traction, oxytocics at delivery of anterior shoulder. No withdrawals after randomization. Measurement of blood loss: estimated by delivering obstetrician.

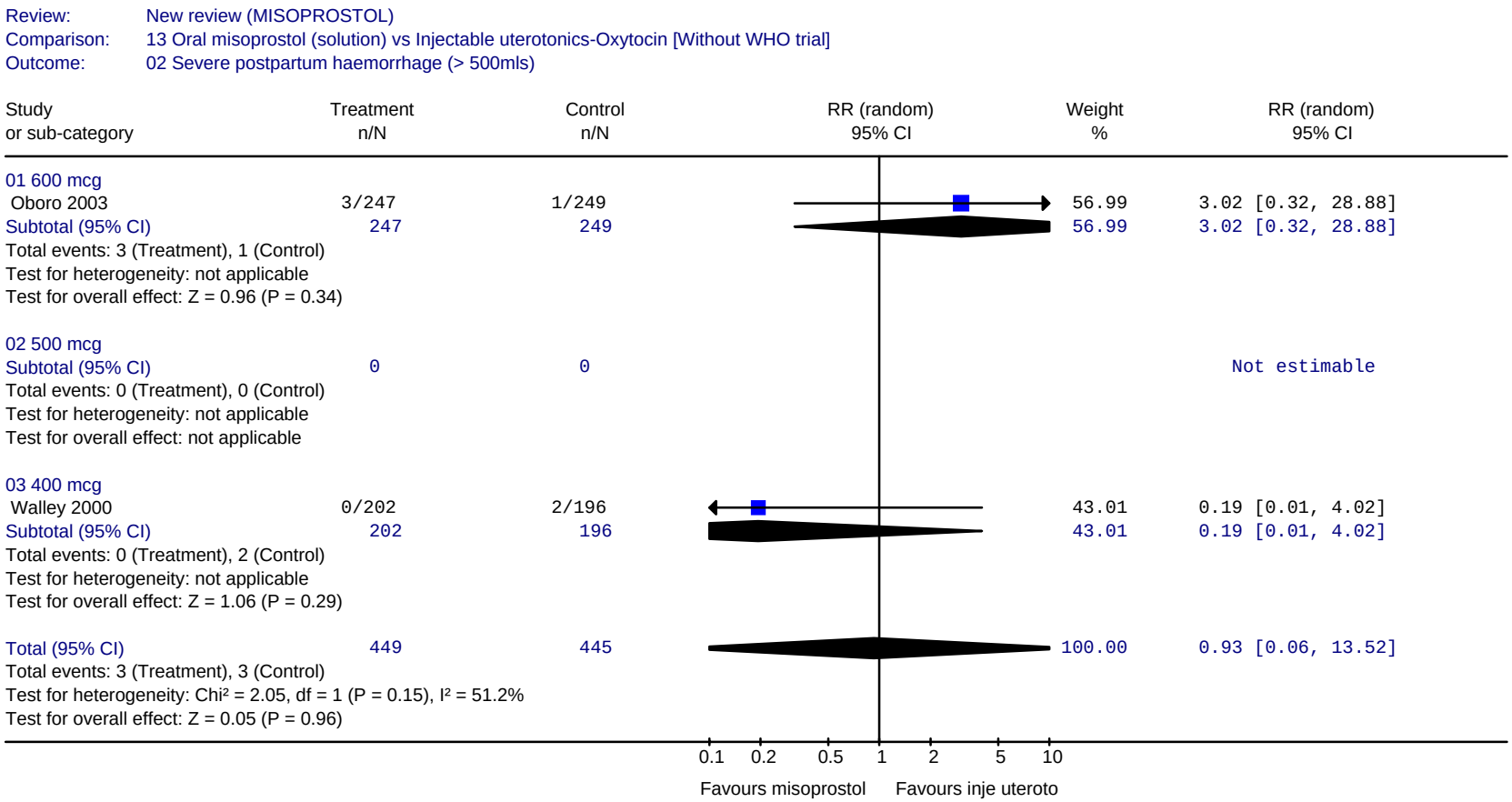


Figure 9.3a Oral misoprostol (solution) vs injectable uterotonics - oxytocin; Outcome: Postpartum haemorrhage (>500 mL)

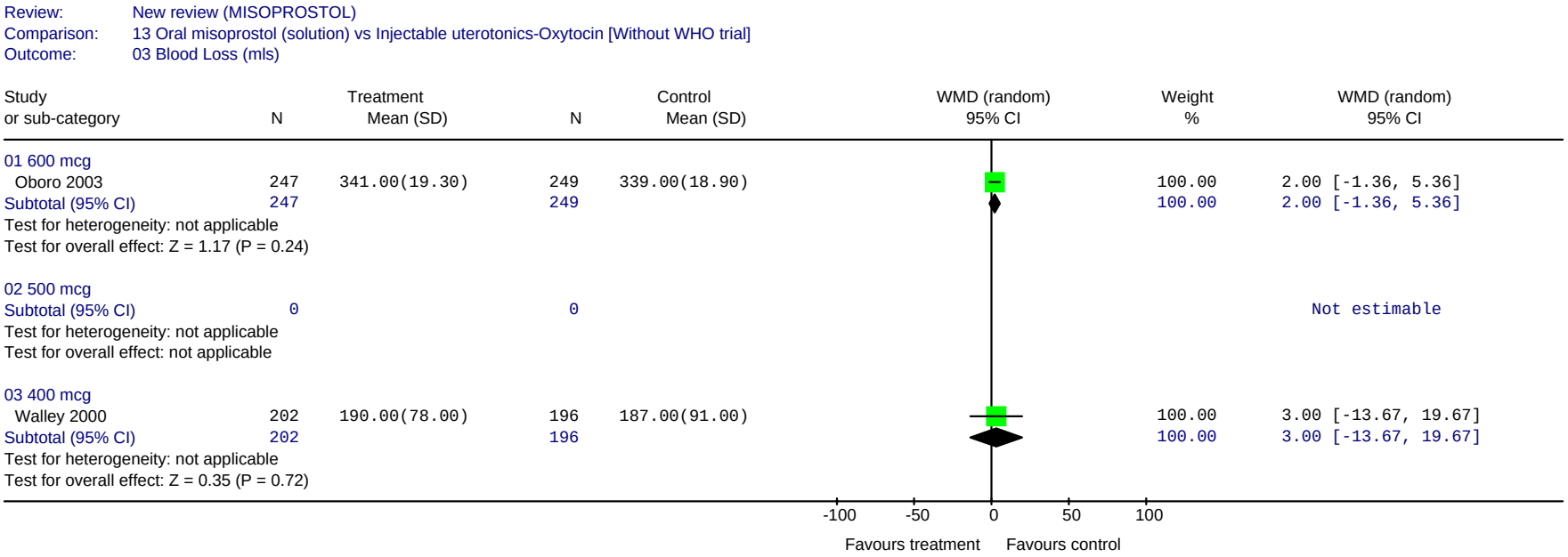


Figure 9.3b Oral misoprostol (solution) vs injectable uterotonics - oxytocin; Outcome: Blood loss (mL)

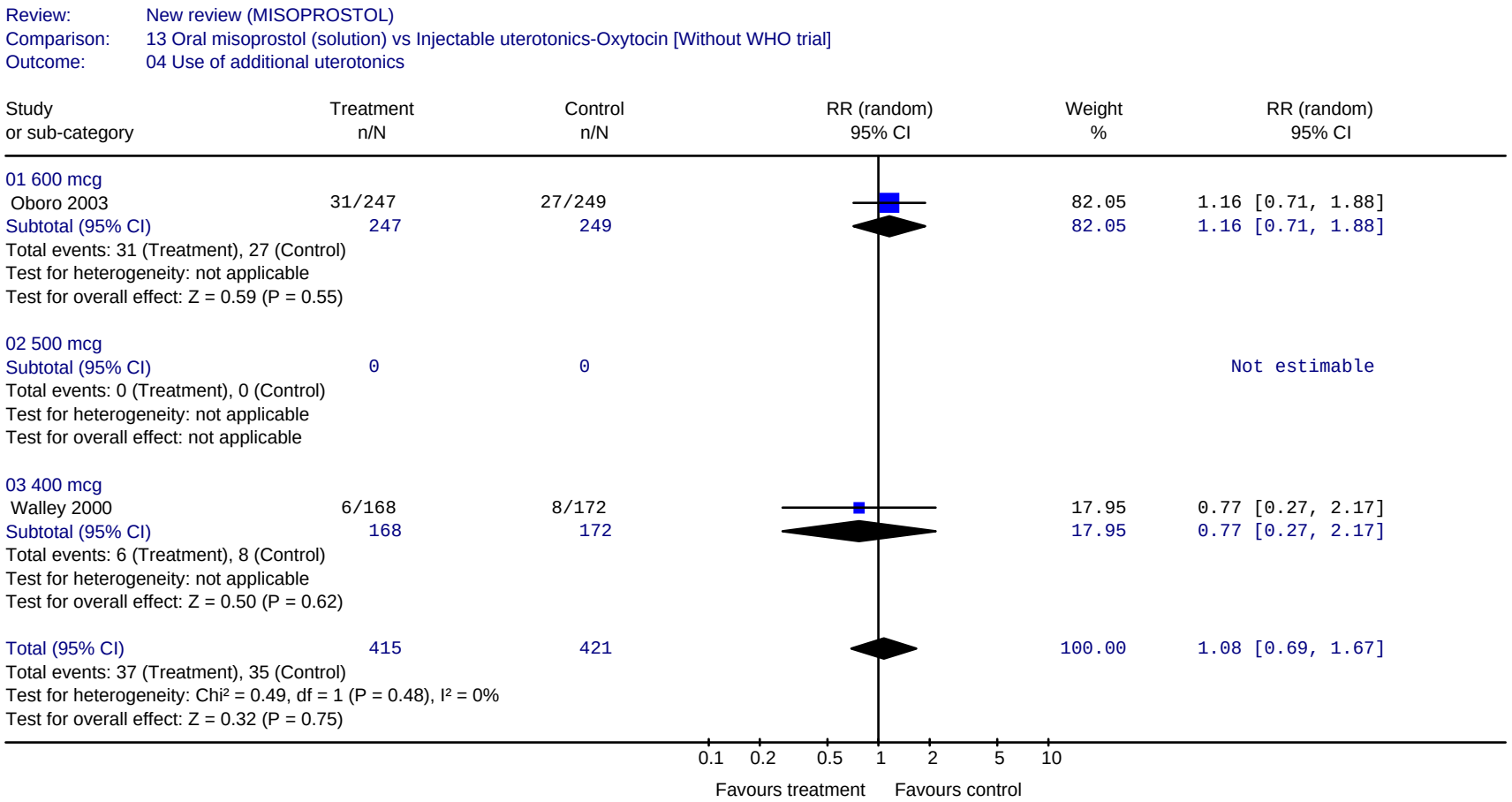


Figure 9.3c Oral misoprostol (solution) vs injectable uterotonics - oxytocin; Outcome: Use of additional uterotonics

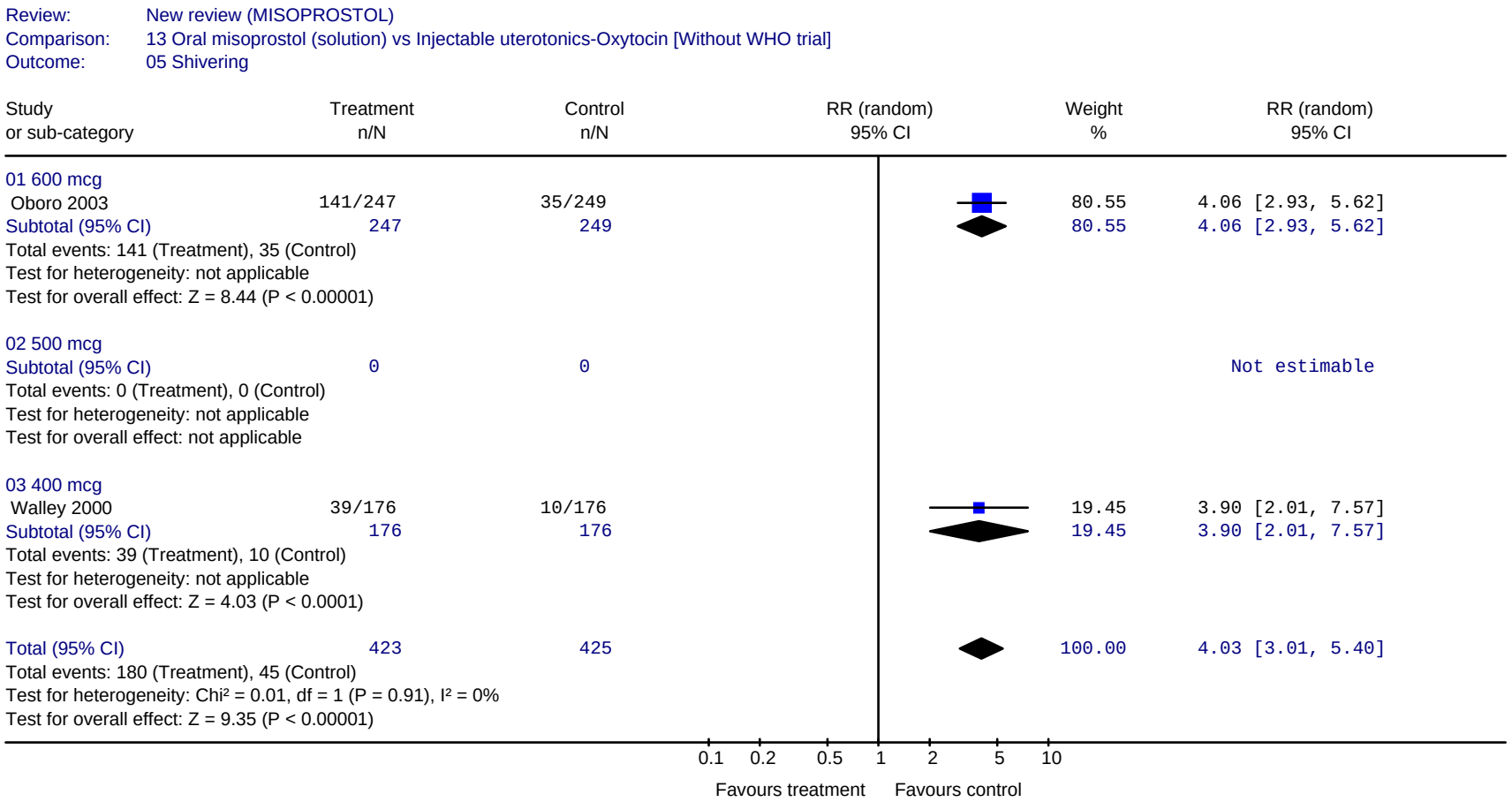


Figure 9.3d Oral misoprostol (solution) vs injectable uterotonics - oxytocin; Outcome: Shivering

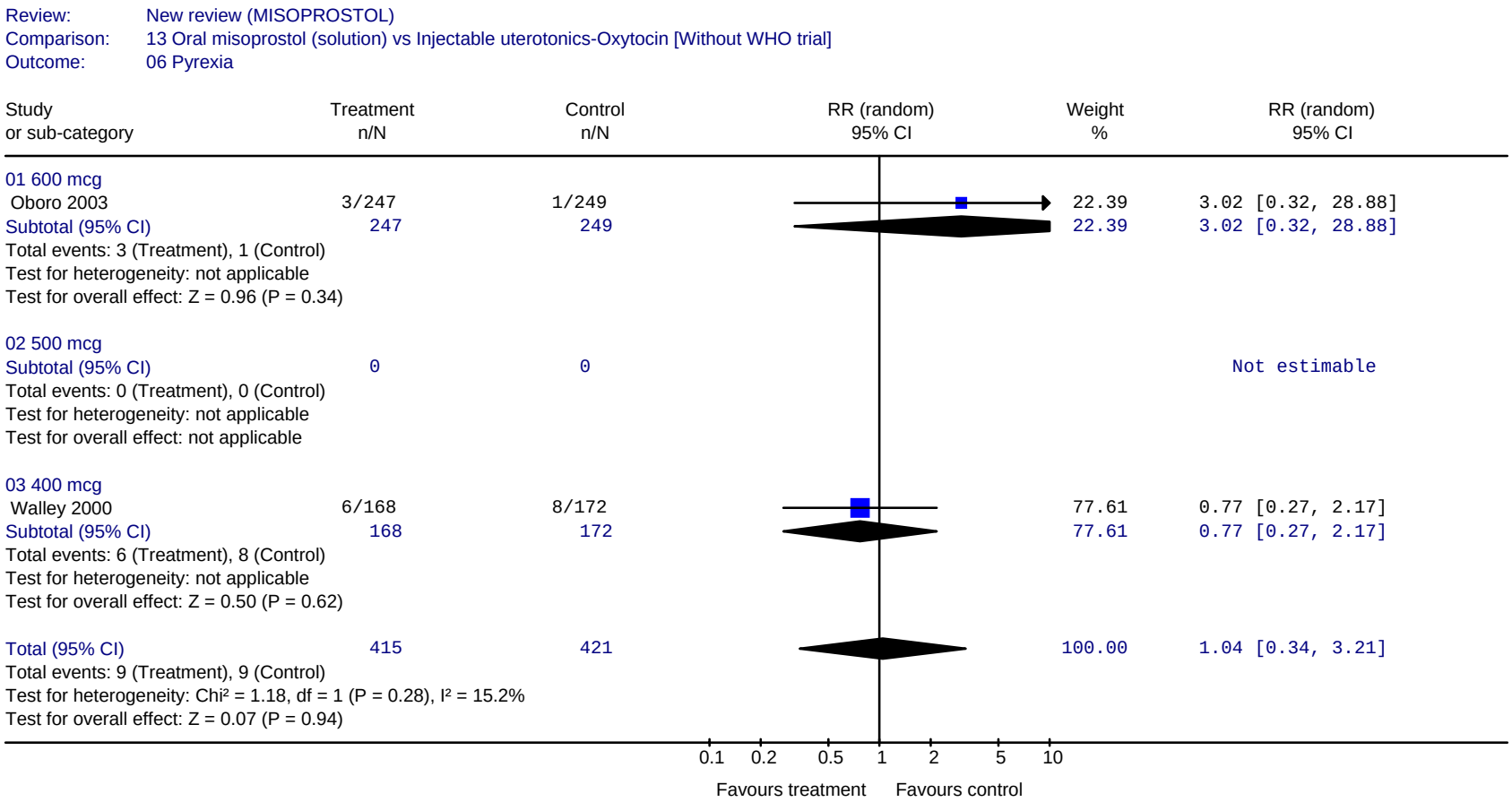


Figure 9.3e Oral misoprostol (solution) vs injectable uterotonics - oxytocin; Outcome: Pyrexia

Rectal misoprostol versus placebo or injectable uterotonics (six studies, 3975 women)

Only one study compared rectal misoprostol 400 μg with placebo [Bamigboye et al 1998] (Table 9.4). The results for severe postpartum haemorrhage (≥1000 mL) favoured rectal misoprostol but was not statistically significant (RR 0.69, 95% CI 0.35-1.37) (Figure 9.4a).

Four trials compared rectal misoprostol 400 μg with injectable uterotonic agents [Bamigboye et al 1998a; Bugalho et al 2001; Gerstenfeld & Wing 2001; Karkanis et al 2002]. One used 600 μg in separate doses- 400 μg, 100 μg, 100μg alone, and with intravenous infusion of oxytocin 10 IU over 30 minutes [Caliskan et al 2002].

The use of rectal misoprostol was associated with higher risks of severe postpartum haemorrhage (≥1000 mL) and postpartum haemorrhage (≥500 mL) compared to parenteral oxytocin, but the results were not statistically significant at 400 μg and 600 μg (Figure 9.4b, c). Use of additional uterotonics was significantly more common in patients treated with rectal misoprostol 400 μg compared with patients given parenteral oxytocin (RR 1.63, 95% CI 1.16-2.30) (Fig 9.4d).

For rectal misoprostol 600 μg, the risks of severe postpartum haemorrhage, postpartum haemorrhage, and use of additional haemorrhage were higher compared to intravenous oxytocin but the differences were not statistically significant. However, if intravenous oxytocin were given with intramuscular methylergonovine,

the combination was significantly more effective than rectal misoprostol 600 μg in preventing severe postpartum haemorrhage (RR 2.47, 95% CI 1.03-5.88) (Figure 9.4b), postpartum haemorrhage (RR 2.83, 95% CI 1.56-5.13) (Figure 9.4c), and the use of additional uterotonic agents (RR 3.72, 95% CI 1.80-7.68) (Figure 9.4d).

At both doses, rectal misoprostol caused significantly more shivering than parenteral oxytocin (400 μg: RR 2.01, 95% CI 1.34-3.04; 600 μg: RR 3.02, 95% CI 1.74-5.23). There was also significantly more pyrexia with rectal misoprostol 600 μg than with parenteral oxytocin (RR 2.74, 95% CI 1.08-6.93) (Figure 9.4f). However, this difference was not statistically significant with rectal misoprostol 400 μg (RR 1.71, 95% CI 0.88-3.33).

Table 9.4 Rectal misoprostol versus injectable uterotonics/placebo (6 studies)

Study	Methods	Participants	Interventions	Comments
Bamigboye et al 1998	Random allocation. Tablets kept in numbered, sealed, opaque containers; nonidentical placebos. Not blinded.	550 women after vaginal delivery. Low risk. South Africa	Rectal tablet misoprostol 400 µg versus placebo	Management of third stage: placenta delivered by cord traction or spontaneous expulsion. Exclusions after randomization: four women in placebo group (1.4%). Measurement of blood loss: blood collected in bedpan for 1 hour after delivery; linen weighed.
Bamigboye et al 1998a	Random allocation. Medication kept in sealed, opaque packets; no placebos. Not blinded.	491 women after vaginal delivery. Low risk. South Africa	Rectal tablet misoprostol 400 µg versus i/m syntometrine 1 mL	Management of third stage: not mentioned. Some women (number small but unspecified) allocated to syntometrine excluded after randomization because of high blood pressure. Primary outcome data missing for 2-3% of women; postpartum haemoglobin measured in only 65-67%. Measurement of blood loss: estimated by clinician.
Bugalho et al 2001	Random allocation. Identical double placebos. Double-blind.	663 women after uncomplicated vaginal delivery. Low risk. Mozambique	Rectal microenema misoprostol 400 µg (2 tablets in 5 mL saline). versus i/m oxytocin 10 IU	Management of third stage: not mentioned. Exclusions after randomization: 26/350 (7.4%) in the misoprostol group, and 11/350 (3.1%) in the oxytocin group, because of emergency caesarean delivery or incomplete data collection. Measurement of blood loss: metallic collector placed under buttocks after delivery until patient moved from delivery room.

Gerstenfeld et al 2001	Random allocation; number sequence concealed until after enrollment. Medication kept in sealed packets; identical placebos. Double-blind.	400 women in labour. No mention of risk status. United States	Rectal tablet misoprostol 400 µg versus i/v oxytocin 20 IU in 1 L of Ringer's lactate solution given as continuous infusion.	Management of third stage: not mentioned. Exclusions after randomization: 73 women (18.3%) because of caesarean delivery; no details of distribution by group. Measurement of blood loss: drape placed under buttocks; linen and sponges weighed; adjustments made "accordingly" for contamination with amniotic fluid; haemoglobin on admission and on postpartum day 1.
Karkanis et al 2002	Random, block allocation; number sequence concealed until after enrollment. Not blinded.	238 women in labour. Low risk. Canada	Rectal tablet misoprostol 400 µg versus i/v or i/m oxytocin 5 IU	Management of third stage: not standardized. Exclusions after randomization: 15 women (6.3%) because of caesarean delivery or loss to follow-up; no details of distribution by group. Measurement of blood loss: haemoglobin on postpartum day 1.
Caliskan et al 2002	Random, block allocation. Numbered, sealed, opaque envelopes. Misoprostol similar in size and colur but not in shape to placebo; injectable medication and placebo identical. Outcome assessment blinded	1633 women expecting vaginal delivery. Turkey	Rectal tablet misoprostol 600 µg in total plus i/v oxytocin 10 IU over 30 min versus Rectal tablet misoprostol 600 µg in total or i/v oxytocin 10 IU over 30 min or i/m methylergonovine 0.2 mg plus i/v oxytocin 10 IU over 30 min	Management of third stage: early cord clamping, cord traction with uterine massage; manual removal of placenta if not delivered after 30 minutes. Exclusions after randomization: 27 women (1.6%) because of lack of haemoglobin testing; no details of distribution by group. Measurement of blood loss: estimated by physician in charge of labour; blood collected in bedpan for 1 hour after delivery; gauzes and pads weighed; haemoglobin on admission and 24 hours after delivery.

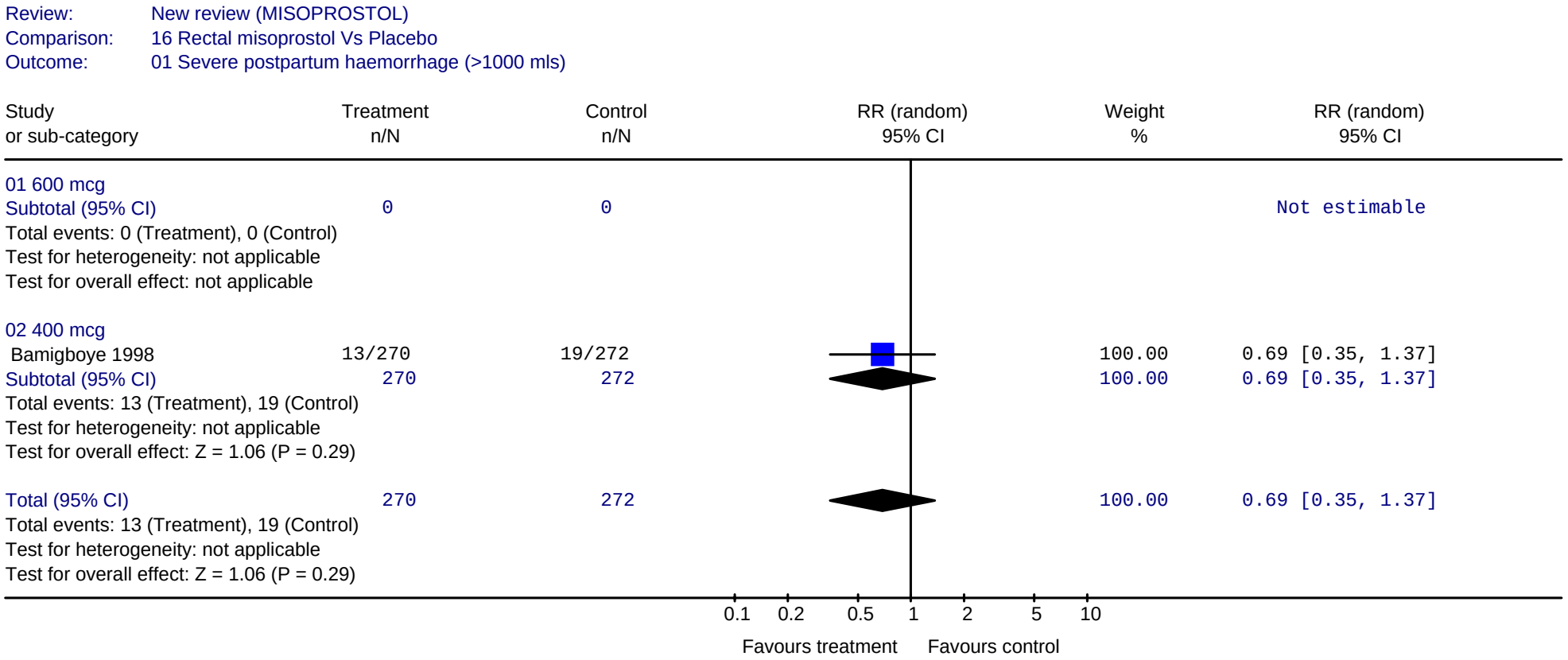


Figure 9.4a Rectal misoprostol vs placebo; Outcome: Severe postpartum haemorrhage (>1000 mL)

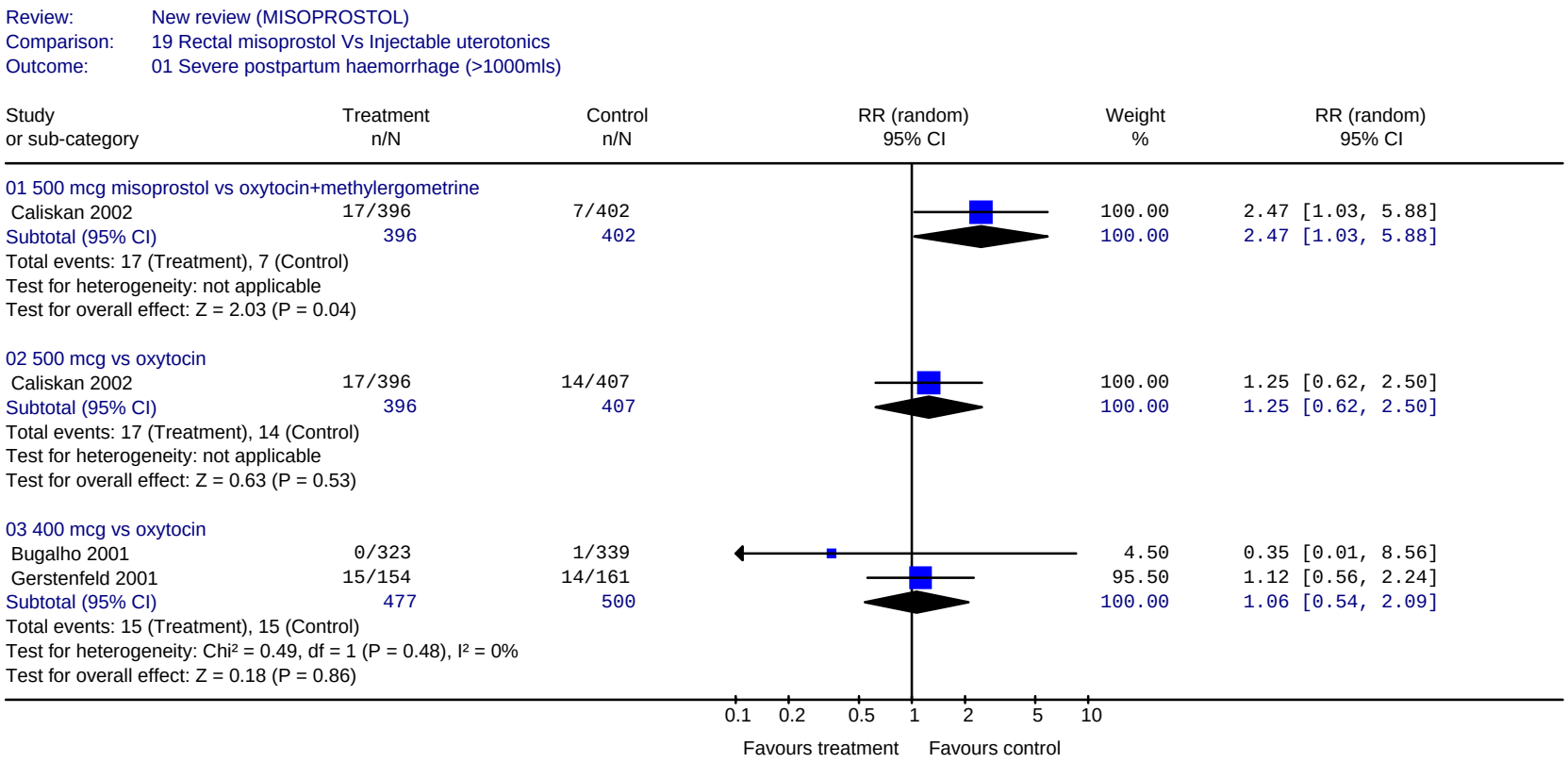


Figure 9.4b Rectal misoprostol vs injectable uterotonics; Outcome: Severe postpartum haemorrhage (>1000 mL)

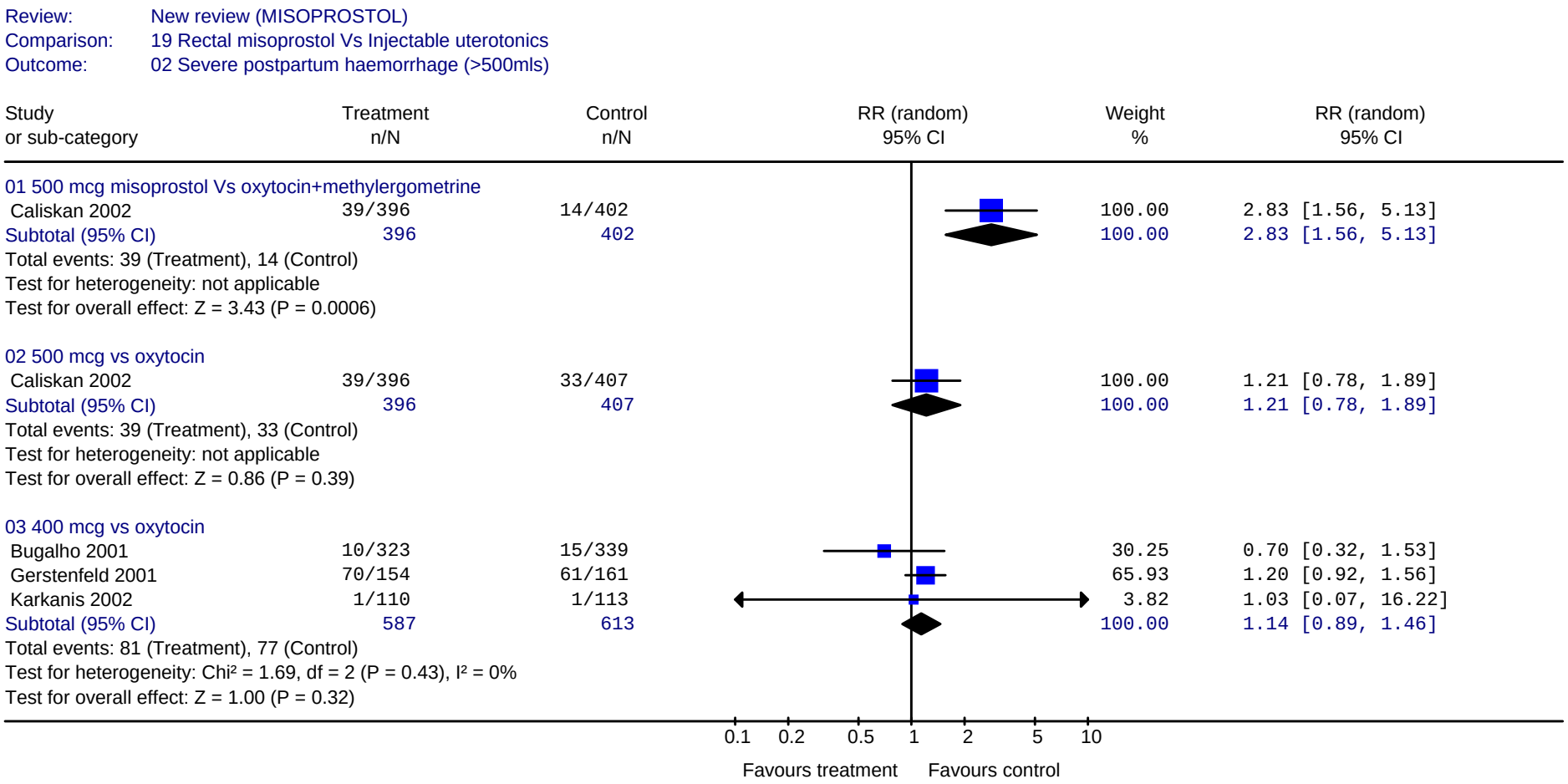


Figure 9.4c Rectal misoprostol vs injectable uterotonics; Outcome: Postpartum haemorrhage (>500 mL)

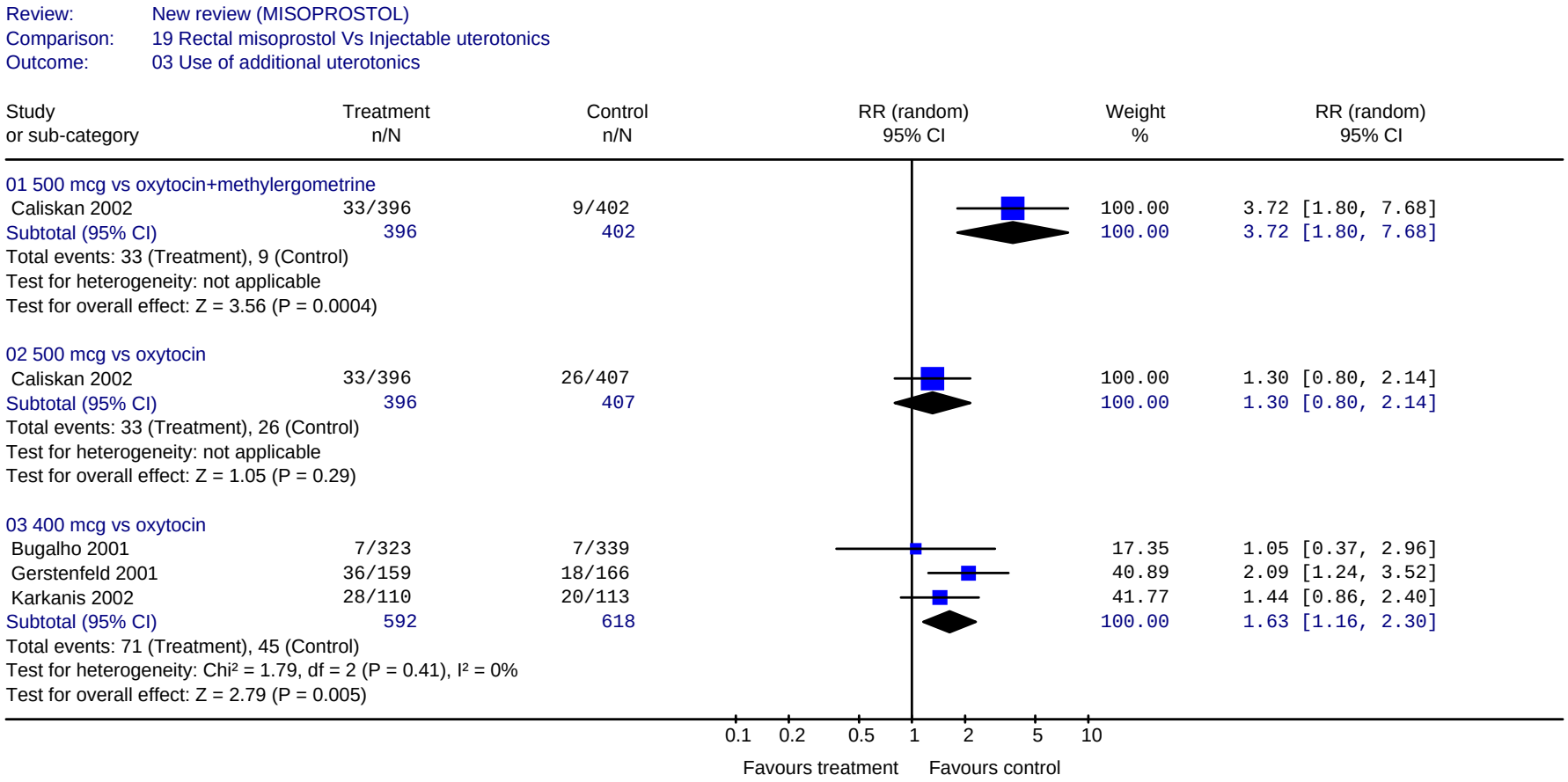


Figure 9.4d Rectal misoprostol vs injectable uterotonics; Outcome: Use of additional uterontonics

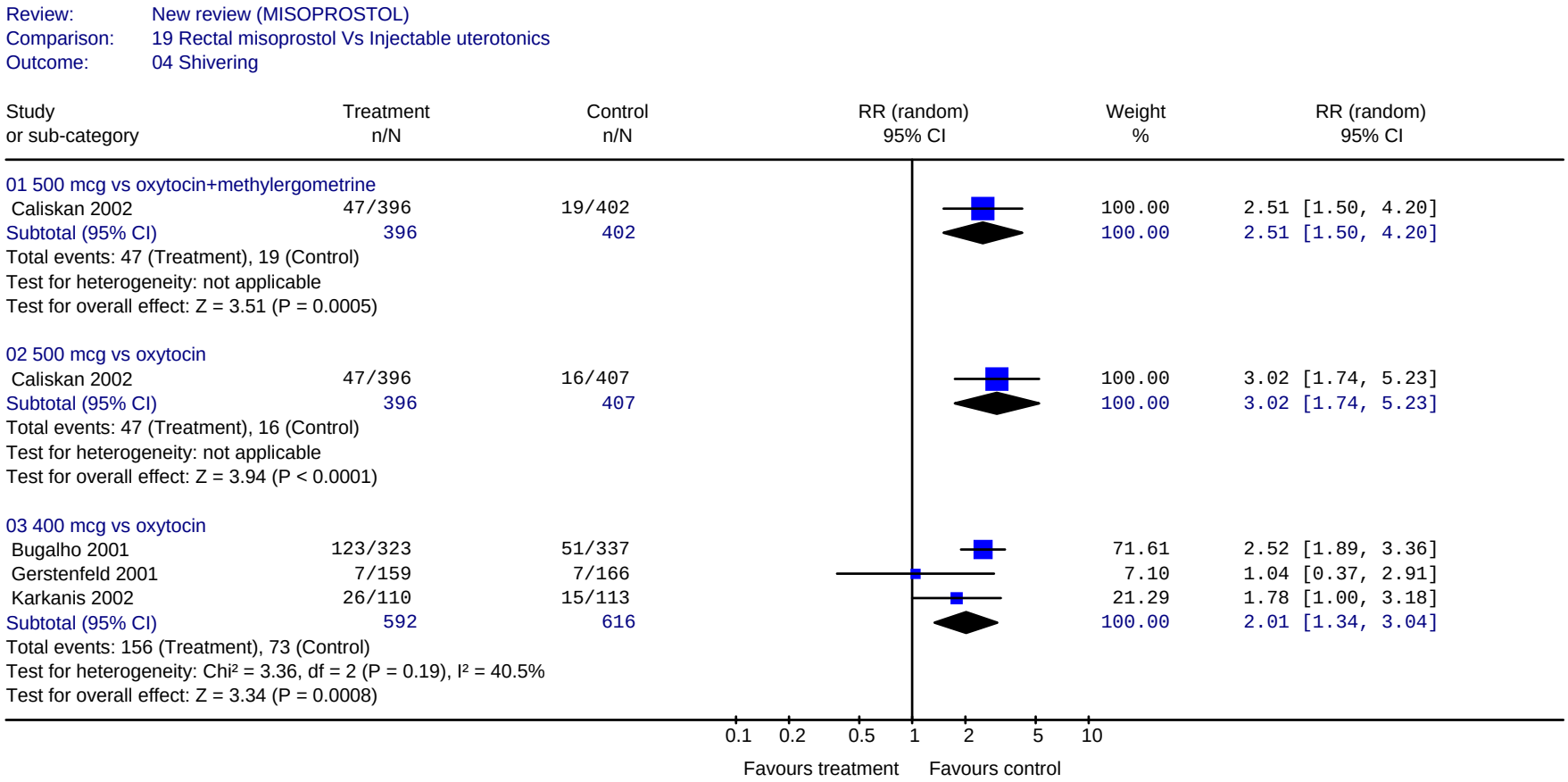


Figure 9.4e Rectal misoprostol vs injectable uterotonics; Outcome: Shivering

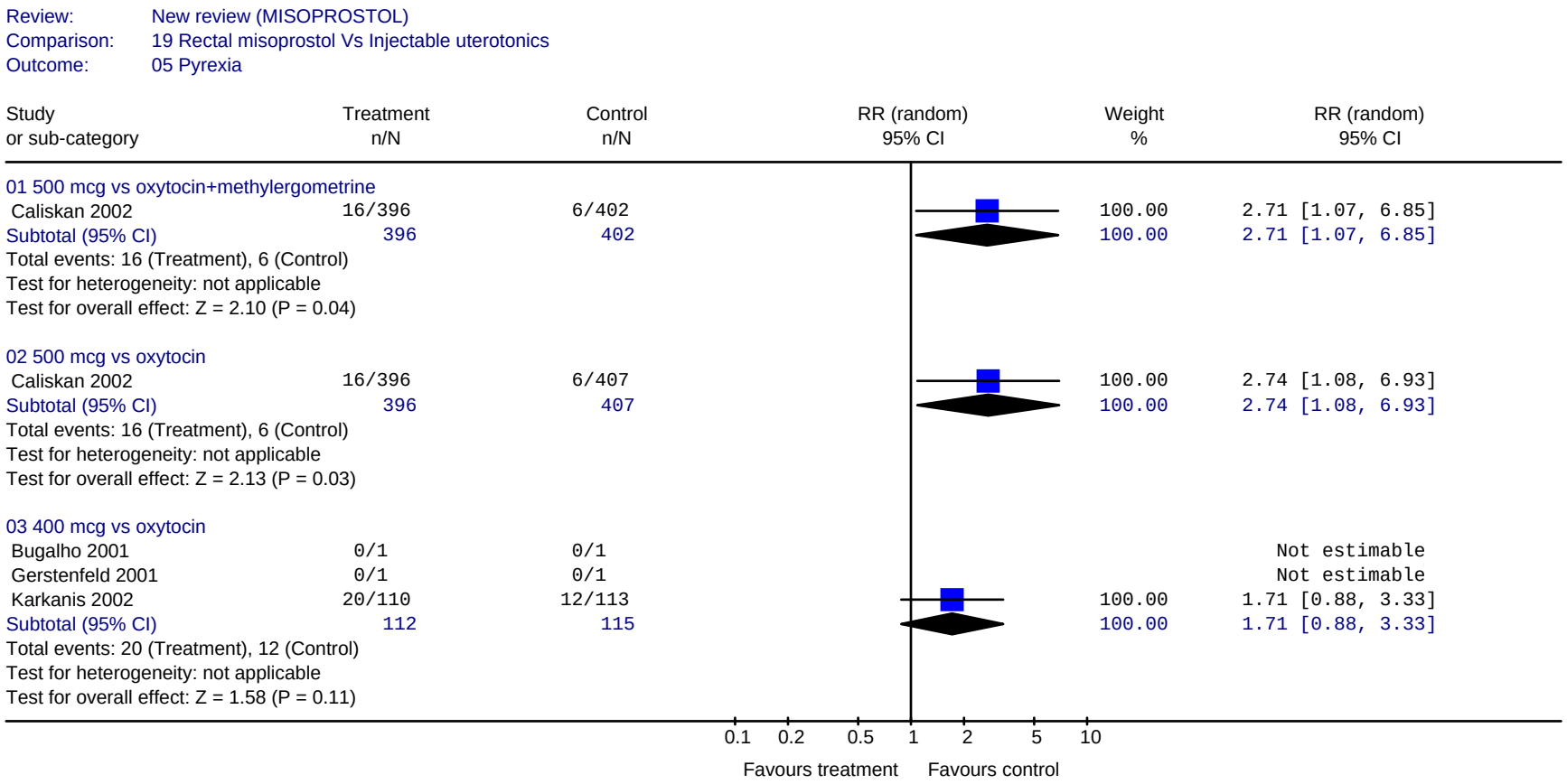


Figure 9.4f Rectal misoprostol vs injectable uterotonics; Outcome: Pyrexia

Oral misoprostol versus injectable uterotonics during caesarean delivery (two studies, 100 women)

Only two small studies [Acharya et al 2001; Lokugamage et al 2001a] compared oral tablet misoprostol against intravenous oxytocin during caesarean delivery (Table 9.5). The two studies used different doses of misoprostol so the treatment effects could not be combined. The risks of severe postpartum haemorrhage were equal with both doses of misoprostol compared to intravenous oxytocin (Figure 9.5a). For postpartum haemorrhage, the risk was equal with misoprostol 500 µg, but non-statistically decreased with misoprostol 400 µg (RR 0.20, 95% CI 0.01-4.00) (Figure 9.5b). Compared to intravenous oxytocin, misoprostol 500 µg increased the risk (RR 6.00, 95% CI 0.79-45.42) while misoprostol 400 µg decreased the risk (RR 0.67, 95% CI 0.12-3.71) of using additional uterotonics (Figure 9.5c). Both effects were not statistically significant. Oral tablet misoprostol 500 µg increased the risk of shivering (RR 1.63, 95% CI 0.87-3.04) (Figure 9.5d) and pyrexia (RR 6.00, 95% CI 0.79-45.42) (Figure 9.5e) but the effects were not statistically significant.

Table 9.5 Oral misoprostol versus injectable uterotonics during caesarean delivery (2 studies)

Study	Methods	Participants	Interventions	Comments
Acharya et al 2001	Random allocation. Sealed, opaque envelopes. No placebos. Not blinded.	60 women at elective caesarean section. No mention of risk status. United Kingdom	Oral tablet misoprostol 400 µg versus i/v oxytocin 10 IU	Management of third stage: individual caesarean section technique not specified. No withdrawals after randomization. Measurement of blood loss: estimated by surgeon and anaesthetist after inspecting swabs, drapes, suction apparatus and sanitary pads at end of operation.
Lokugamage et al 2001a	Random allocation. Sealed, opaque envelopes. Surgical team blinded to treatment group but not anaesthetist; nonidentical placebo tablets.	40 women at elective and emergency caesarean section. No mention of risk status. United Kingdom	Oral tablet misoprostol 500 µg (crushed) versus i/v oxytocin 10 IU	Management of third stage: "active" during caesarean section. No withdrawals after randomization. Measurement of blood loss: estimated visually from volume of blood in suction bottle plus soiling of swabs and bed sheets.

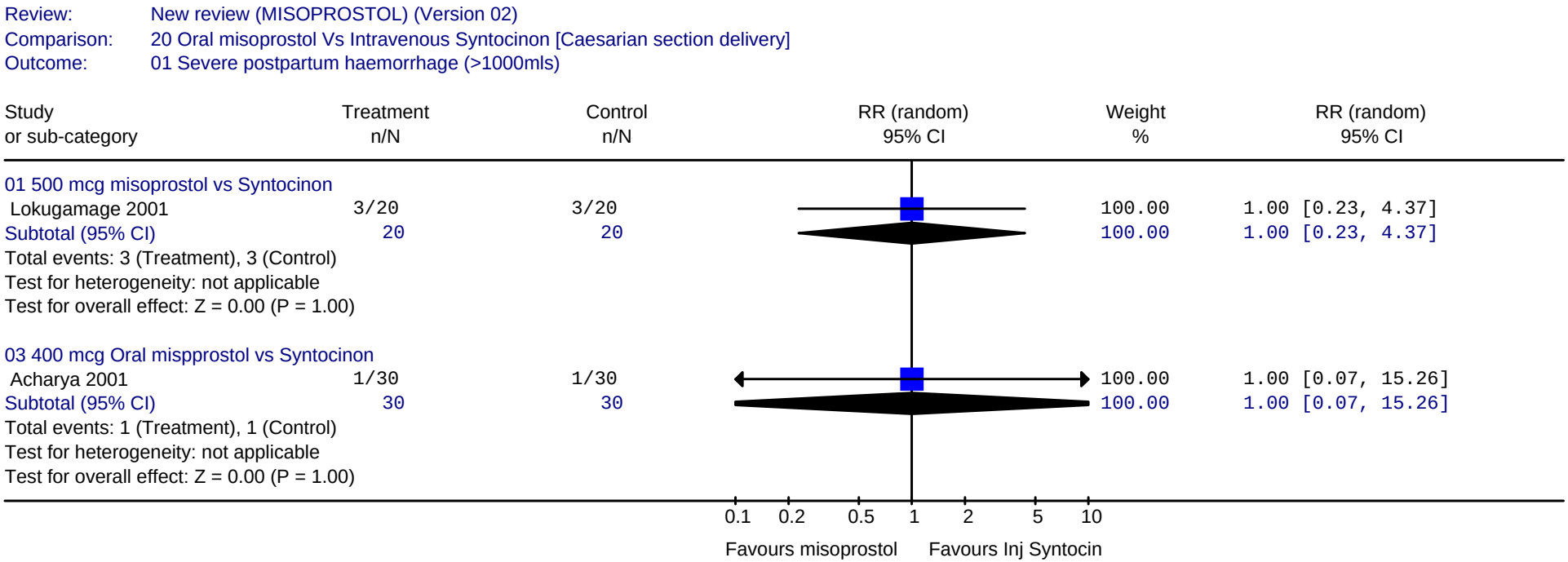


Figure 9.5a Oral misoprostol vs intravenous syntocinon (caesarian section delivery); Outcome: Severe postpartum haemorrhage (>1000 mL)

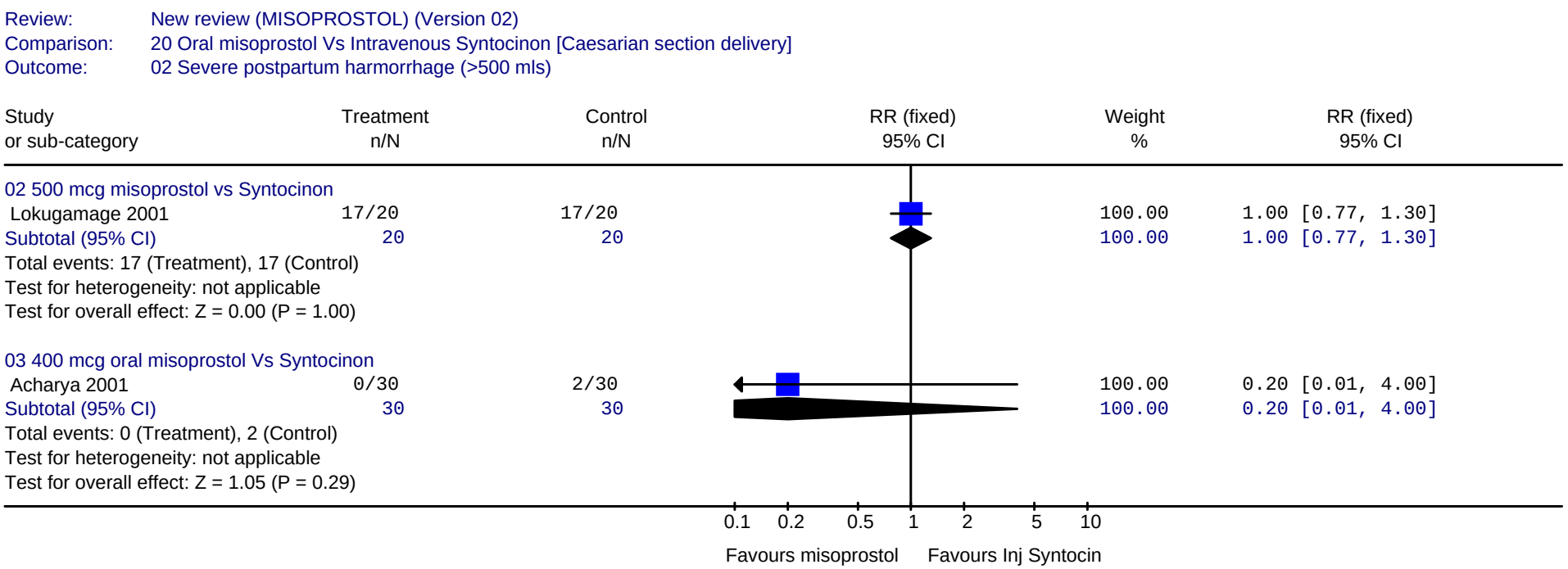


Figure 9.5b Oral misoprostol vs intravenous syntocinon (caesarian section delivery); Outcome: Postpartum haemorrhage (>500 mL)

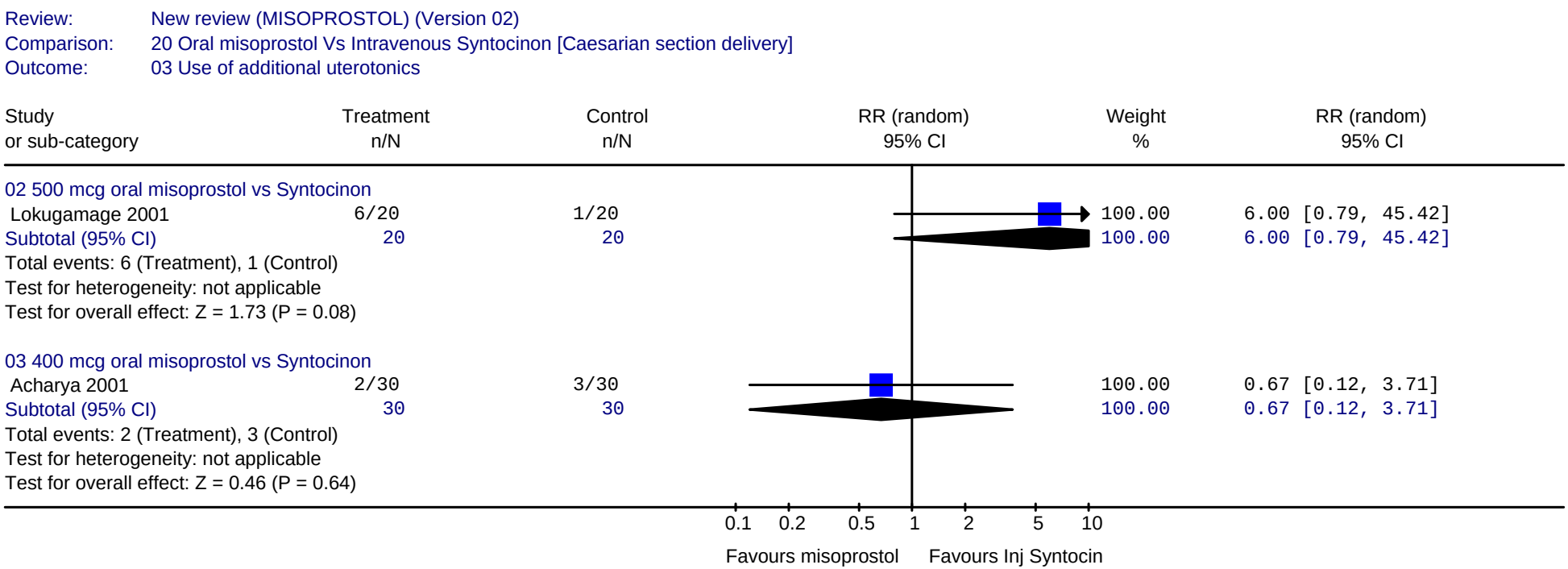


Figure 9.5c Oral misoprostol vs intravenous syntocinon (caesarian section delivery); Outcome: Use of additional uterotonics

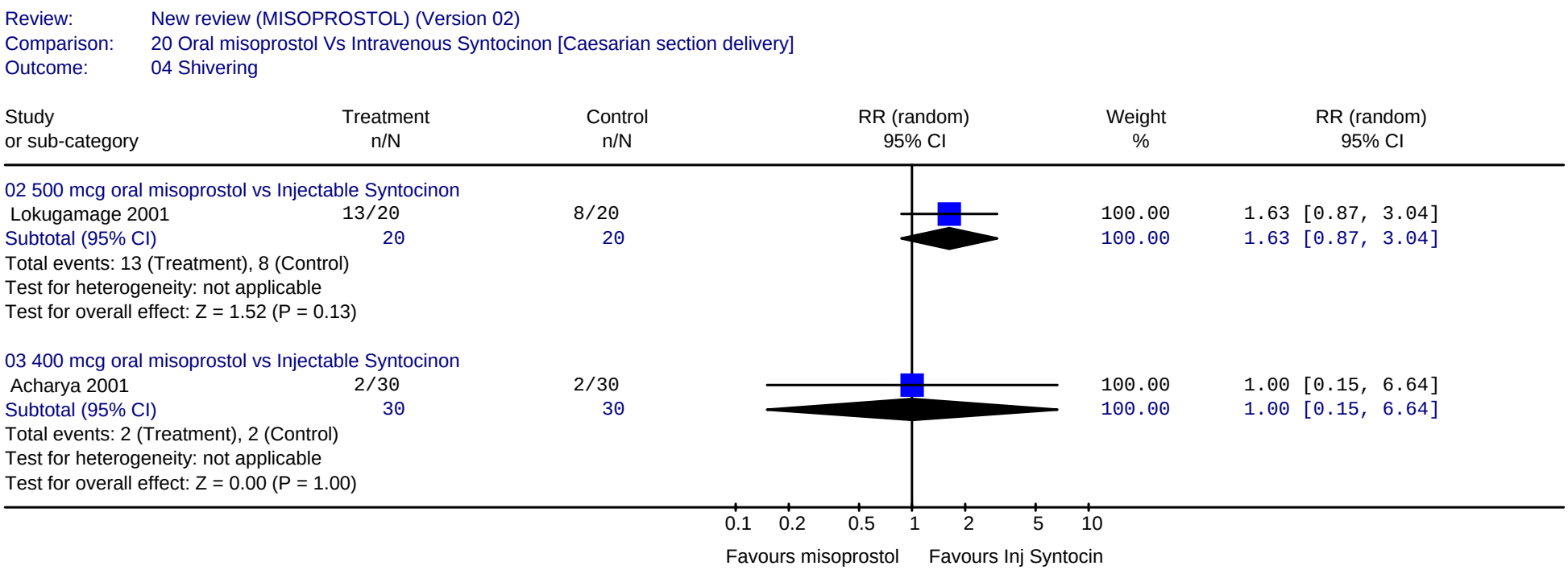


Figure 9.5d Oral misoprostol vs intravenous syntocinon (caesarian section delivery); Outcome: Shivering

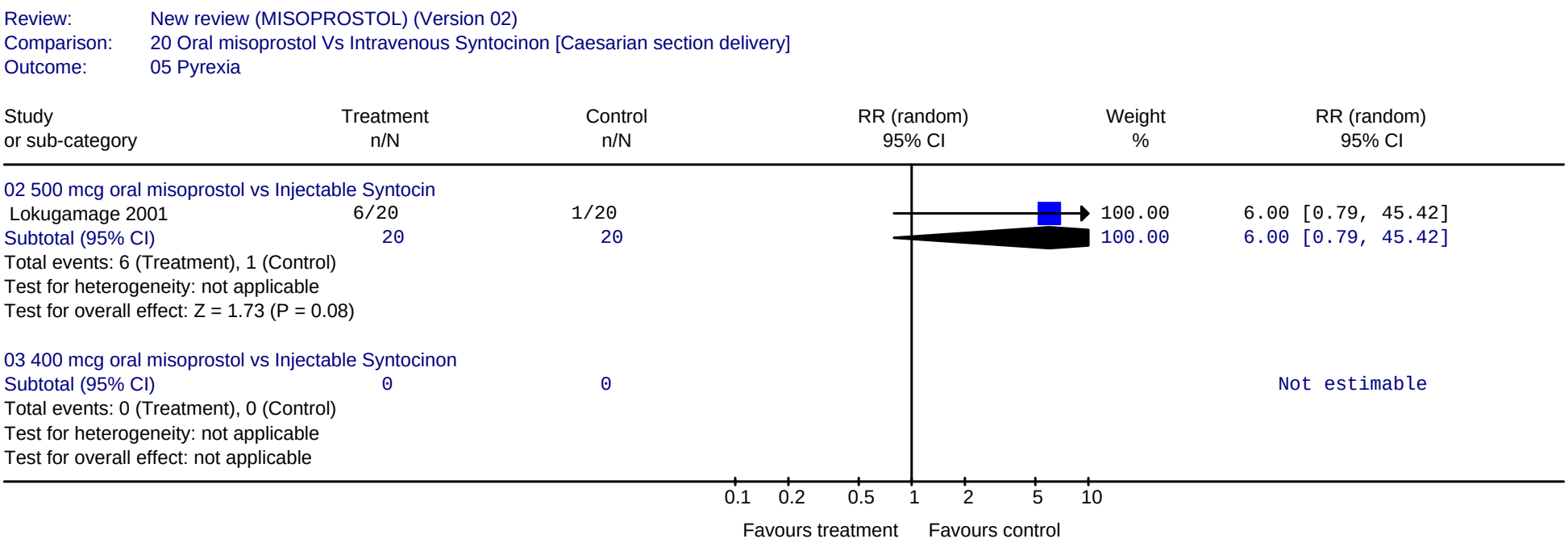


Figure 9.5e Oral misoprostol vs intravenous syntocinon (caesarian section delivery); Outcome: Pyrexia

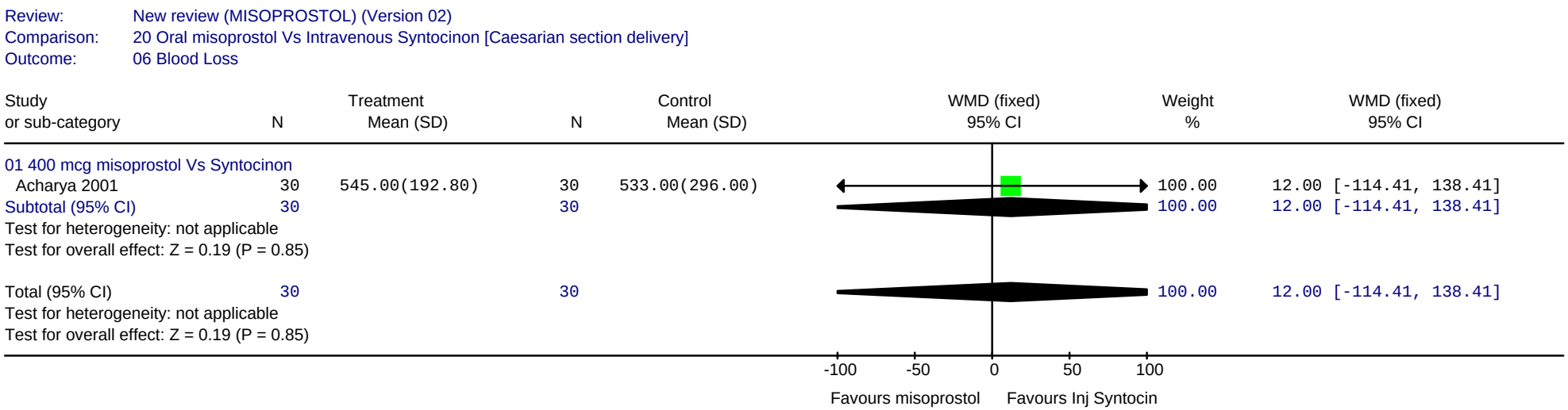


Figure 9.5f Oral misoprostol vs intravenous syntocinon (caesarian section delivery); Outcome: Blood loss

Table 9.6 Excluded studies (4 studies)

Study	Methods	Participants	Interventions	Comments
Zhao et al 1998 [Chinese language]	Random allocation. Sealed, opaque envelopes. Surgical team blinded to treatment group but not anaesthetist; nonidentical placebo tablets.	182 women undergoing caesarean section. No mention of risk status. China	Oral tablet misoprostol 600 µg versus oral tablet misoprostol 600 µg plus intramyometrial oxytocin 20 IU versus intramyometrial oxytocin 20 IU plus i/v oxytocin 20 IU	Blood loss within 2 hours of delivery measured. Mean blood loss in misoprostol group was 212 ± 56.0 mL, in misoprostol and oxytocin group was 208 ± 55.4 mL, and 345 ± 64.7 mL in oxytocin group. Excluded because data not presented in a form that can be extracted for meta-analysis.
Daly S et al 1999	Random allocation Double-blinded, identical placebo.	265 women expecting vaginal delivery. No mention of risk status.	Oral tablet misoprostol 400 µg versus i/v oxytocin 20 IU infusion	Management of third stage: uterotonics given after delivery of the placenta. 35 women excluded because of forceps or caesarean delivery. Measurement of blood loss: weighing of blood loss at delivery and for 24 hours after delivery. The reported rate of PPH was unusually high (78/115 in misoprostol group, 74/115 in the oxytocin group). Excluded because and the figures in the abstract did not tally (e.g. 78/115 reported as 51%).

Lokugamage et al 2001	Random allocation Sealed, opaque envelopes. Outcome assessment not blinded.	64 women with primary postpartum haemorrhage due to uterine atony. South Africa	Rectal misoprostol 800 µg versus i/m syntometrine 1 mL stat plus oxytocin 10 IU in 500 mL normal saline infusion.	There was a 28.1% difference between misoprostol and combined syntometrine/oxytocin therapy (p=0.01) favoring misoprostol. Excluded because this study assessed treatment of and not prophylaxis for postpartum haemorrhage. Primary outcome measure was whether haemorrhage ceased within 20 min of therapy.
Lumbiganon et al 2002	Random, block allocation, stratified. Identical treatment packs drawn from a dispenser; identical double placebos. Double-blinded.	1686 women after vaginal delivery; subset of WHO Misoprostol multicentre trial. No mention of risk status. Nigeria and Thailand.	Oral tablet misoprostol 600 µg versus i/m or i/v oxytocin 10 IU	Women who received misoprostol had more shivering and pyrexia in the first hour (RR 6.4, 95% CI 3.9-10.4; RR 2.8, 95% CI 1.4-5.3 respectively), and 2-6 hours following delivery (RR 4.7, 95% CI 1.9-11.2; RR 6.3, 95% CI 3.7-10.8 respectively). Excluded because this was a subset of the WHO Misoprostol multicentre trial already included in the meta-analysis.

Discussion

The existing evidence comparing oral and rectal tablet misoprostol against placebo or no treatment is inconclusive. Four trials [Bamigboye et al 1998; Hofmeyr et al 1998; Surbek et al 1999; Hofmeyr et al 2001] showed a non-significant protective effect against postpartum haemorrhage, while one unpublished study [Hofmeyr et al 1998a] showed a significantly increased risk of postpartum haemorrhage. The overall treatment effect was not significantly increased or decreased. There is place for a large well-conducted RCT to further test the hypothesis that misoprostol is more effective than placebo in preventing postpartum haemorrhage. Unfortunately, it will be difficult to ethically conduct any placebo-controlled trials for the third stage of labour as there is good evidence that conventional uterotonic agents can reduce the incidence of postpartum haemorrhage [Prendiville et al 2003].

The majority of the RCTs conducted to compare misoprostol against injectable uterotonic agents were not adequately powered to prove equivalence or non-inferiority. Only the WHO study [Gulmezoglu et al 2001a] was adequately powered with clear sample calculation done a priori. As a consequence, the results of the trials were mostly not statistically significant. However, except for two studies [Lumbiganon et al 1999; Bugalho et al 2001], they showed that the risk of postpartum haemorrhage was increased with misoprostol. Two studies [Cook et al 1999; Gulmezoglu et al 2001a], including the very large WHO multcentre trial proved that misoprostol significantly increased the risk of postpartum haemorrhage. The overall treatment effect was thus in favour of injectable uterotonic agents. On the basis of the current evidence, we can conclude that oral tablet misoprostol 400

μg to 600 μg is less effective than conventional injectable uterotonic agents. There is no need for further trials to compare oral tablet misoprostol against injectable uterotonic agents for use in the third stage of labour. We can also conclude that rectal tablet misoprostol is probably less effective than injectable uterotonic agents at preventing postpartum haemorrhage although further trials may help clarify the situation.

Unfortunately, the majority of the trials used misoprostol administered either as an oral or rectal tablet. Both these routes of administration result in a substantial delay in the onset of the uterotonic action of misoprostol relative to conventional injectable uterotonic agents. It is thus not surprising that this meta-analysis has concluded that injectable uterotonics are significantly more effective that misoprostol in preventing postpartum haemorrhage.

There were only two trials using oral solution misoprostol and both showed no significant difference between oral solution misoprostol and intramuscular oxytocin 10 IU in preventing postpartum haemorrhage and the use of additional uterotonics. These two trials were well conducted but lacked the power to prove equivalence or non-inferiority. The two studies comparing oral tablet misoprostol against intravenous oxytocin for use during caesarean deliveries were too small to reach any conclusions about the effectiveness of misoprostol against oxytocin.

Unlike the clinical efficacy of misoprostol, there is little uncertainty that misoprostol significantly increases the risks of shivering and pyrexia after delivery. When compared to placebo or no treatment, misoprostol significantly increased both

the risks of shivering and pyrexia. The magnitude of the risk was dose-related. Compared to injectable uterotonics, misoprostol also significantly increased the risk of shivering at 400 μg to 600 μg in a dose-related manner. However, the risk of pyrexia was only significantly increased with doses of misoprostol above 500 μg.

The two systematic reviews written by the authors of the WHO multicentre randomised trial [Gulmezoglu et al 2003; Villar et al 2002a] included the same RCTs and had similar conclusions. The date of their latest search was March 1, 2002. The reviewers concluded that conventional injectable uterotonics were more effective and had less side effects than misoprostol in the active management of the third stage of labour. They also recommended that there was no need for further trials comparing misoprostol with injectable uterotonics except, perhaps, the role of higher doses of misoprostol given by different routes in the treatment of postpartum haemorrhage. The most recent published systematic review by Joy and colleagues [Joy et al 2003] covered a similar period, and included 15 of the 16 studies reviewed in the earlier systematic reviews. Joy and colleagues reviewed data from two studies [Daly et al 1999; Benchimol et al 2001] not previously included, and did not include unpublished data from one study [Hofmeyr et al 1998a]. Their conclusion was that misoprostol was inferior to conventional injectable uterotonics, but that misoprostol reduced the need for additional uterotonics compared to placebo. They suggested that there may be a role for misoprostol in less developed countries where parenteral uterotonic drugs may not be easily available. They also recommended that further RCTs examine more objective outcome measures than the ones documented in the existing studies.

Our systematic review included all the RCTs reviewed by the above three systematic reviews, as well as an additional four RCTs [Caliskan et al 2002; Karkanis et al 2002; Caliskan et al 2003; Oboro & Tabowei 2003]. We separated out studies using oral tablet and oral solution misoprostol, and examined the different routes by which misoprostol was administered. We also examined the role of misoprostol for use in caesarean delivery. The results of the later RCTs that we included favoured conventional injectable uterotonic agents over misoprostol for use in the third stage of labour. It is thus not surprising that the our review lends support to the Cochrane review in finding misoprostol inferior to conventional uterotonics for routine prevention of postpartum haemorrhage in the third stage of labour.

Conclusions

Currently, there is no evidence that misoprostol, given by any route, is a more effective uterotonic agent than placebo or no treatment. Compared to injectable uterotonics, oral tablet misoprostol 600 μg is significantly less effective in preventing postpartum haemorrhage (≥ 500 mL) and the use of additional uterotonics. Rectal misoprostol 400 μg was less effective than injectable uterotonics in preventing the use of additional uterotonics. The role of misoprostol for caesarean delivery remains uncertain. There is good evidence that misoprostol, given by any route and at 400-600 μg, increases the risk of shivering. Doses of misoprostol above 400 μg also significantly increases the risk of pyrexia.

Recommendations

Based on the current evidence, and the findings of our studies, we recommend that no further trials be undertaken to compare the effectiveness of oral tablet misoprostol single therapy against parenteral uterotonic agents for the routine prevention of postpartum haemorrhage. Oral tablet or rectal misoprostol could be tested as adjunct therapy along with other drugs with a faster onset of action but will probably not be appropriate for routine use alone. On the other hand, studies are required to determine whether there is a place for misoprostol administered bucally or as an oral solution to shorten its onset of action. To avoid excessive side effects, we recommend that low doses of misoprostol be used. However, clinical trials testing these therapies should be adequately powered to prove equivalence or non-inferiority.

Chapter 10

CONCLUSION

The efficacy and safety of misoprostol as a uterotonic agent for preventing postpartum haemorrhage

Introduction

Excessive bleeding at or after childbirth accounts for almost half of all the postpartum maternal mortalities in developing countries, and is the single most important cause of maternal death worldwide. Postpartum haemorrhage can lead to irreversible shock and death within a short time and is a true obstetric emergency that demands fast vigorous treatment and proactive preventive management strategies. The introduction of the concept of active management of the third stage of labour and, in particular, the prophylactic use of oxytocics has led to a significant decrease in the incidence of postpartum haemorrhage in many countries. However, active management of the third stage of labour is not practiced universally. One of the unfortunate reasons for this is the unavailability of uterotonic agents that are suitable for use by traditional birth attendants for deliveries outside hospitals. Most uterotonic agents used for the prevention of postpartum haemorrhage are given by injection intramuscularly or intravenously and require sterile needles and syringes as well as proper storage conditions. There is thus a need for a uterotonic agent that is inexpensive, can be administered orally, vaginally or rectally, and is stable and easily stored. One such agent is misoprostol, a prostaglandin E1 analogue.

My hypothesis is that misoprostol, given in the correct dose and by the correct route, should produce a similar uterotonic effect to other uterotonic agents commonly used in the prophylaxis of postpartum haemorrhage.

The current management of the third stage of labour

Despite evidence that active management of the third stage of labour reduces the incidence of postpartum haemorrhage, it is not universally practised. Factors accounting for this situation include the unavailability of conventional uterotonic agents, the desire for a more natural experience of childbirth, the philosophy that active management is unnecessary in low risk women, and avoidance of the adverse effects of conventional uterotonic agents. I evaluated the evidence for the various strategies and uterotonic agents currently used for the prevention of primary postpartum haemorrhage.

Earlier studies explored various strategies for the management of the third stage of labour. Since publication of the first systematic review comparing active versus expectant management in 1988, active management of the third stage using oxytocics has become increasingly adopted. Recent surveys, however, show that there are still wide variations in practice around the world. Much interest has been focused recently on the use of misoprostol for the prevention of postpartum haemorrhage.

There is good evidence from Cochrane systematic reviews that active management of the third stage of labour is superior to expectant management in terms of blood loss, postpartum haemorrhage, and other serious complications, but is associated with unpleasant side effects and hypertension when ergometrine is included. Intramuscular oxytocin has less side effects. Of the remaining uterotonic agents evaluated, carbetocin, an oxytocin analogue, and misoprostol appear the most promising.

Misoprostol: the accidental uterotonic agent

Misoprostol is a prostaglandin E1 analogue originally developed for use in preventing NSAID-induced gastric ulcers. However, because of its cervical ripening and uterotonic properties, misoprostol has become one of the most useful drugs in obstetric and gynaecologic practice.

Misoprostol has proven to be a very convenient and adaptable drug because of its formulation as a tablet that is stable and that can be administered orally, rectally, vaginally and by the sublingual route. Beginning with its abuse for illegal abortion in the late 1980s, misoprostol has quickly become established as one of the most effective drugs for terminating pregnancies in the first and second trimesters, as well as for inducing labour in the third trimester. Its use in the third stage of labour has also recently become a subject of great interest.

Despite the large body of medical evidence about its efficacy and relative safety, the use of misoprostol in pregnant women remained off-label until the spring of 2002 when it was finally approved by the FDA for obstetric and gynaecologic use.

Measuring the uterotonic effect of oxytocics

The gold standard for the assessment of any intervention in the third stage of labour for preventing postpartum haemorrhage is the quantitative measurement of blood loss. Unfortunately, like most reference standards, the objective measurement of blood loss in the third stage is impractical and difficult to achieve with any precision.

Even if a convenient method is found for accurately measuring the blood loss in the third stage of labour, it should be borne in mind that if the intervention being assessed is a uterotonic agent, then blood loss may not truly reflect the efficacy of the therapy. Blood loss in the third stage does not only come from the placental bed. Blood is also lost from episiotomy wounds, lacerations, and other trauma to the birth canal. The type of vaginal delivery performed and the skill of the accoucheur, all influence the amount of blood lost from sites outside the uterus.

However, any uterotonic agent being used can only influence the blood loss by inducing contraction and retraction of the uterine muscles and, hence, occluding the open vessels in the placental bed. Interventions that influence more than one aspect of the third stage, such as comparing active versus expectant management, or non-uterotonic drugs such as tranexamic acid are still best assessed by measuring blood loss. But for uterotonic drugs, the key factor that should be assessed is the uterotonic effect they induce, as they do not affect blood loss from other factors.

We tested the reliability of catheter-tip transducers for the measurement of intrauterine pressure in the postpartum uterus. To demonstrate the reliability of the Gaeltec catheter-tip pressure transducers for measuring postpartum uterine activity, catheter-tip transducers were used in 20 women randomly allocated into two groups of 10. In each case in the first group, two catheters were tied together and introduced transcervically into the uterine cavity after delivery of the placenta. In the second group, the two catheters were inserted independently into the same uterine cavity. The active pressures recorded from the pairs of catheters within each uterine cavity

were compared. Comparison of individual active pressure readings from separate transducers revealed good agreement whether the catheters were tied together or were separate. We therefore concluded that intrauterine catheter-tip transducers can be used reliably to measure uterine activity in the postpartum uterus although there may be minor contraction by contraction differences in recordings of individual active pressures.

Determining the optimum dose of oral tablet misoprostol using intramuscular syntometrine for comparison

The use of oral misoprostol 500 μg for preventing postpartum haemorrhage was first described in an observational study in The Lancet in 1996 [El-Refaey et al 1996]. At this time, the optimum dose and route for administering misoprostol for the prophylaxis of postpartum haemorrhage was still undetermined, and its side effects in the immediate postpartum period were unknown. My studies were commenced in 1997 to address these issues.

To investigate the effect of oral misoprostol in dosages varying from 200 μg to 800 μg on postpartum uterine contractility and to document their side effects, we performed a prospective descriptive study in 57 women who delivered vaginally after spontaneous, unaugmented labours. These women were assigned to receive either oral tablet misoprostol 200 μg, 400 μg, 500 μg, 600 μg, 800 μg, or intramuscular Syntometrine 1 ml (a standard oxytocic used to prevent postpartum haemorrhage).

Within 5 minutes of delivery of the placenta, a calibrated Gaeltec® catheter with an intrauterine pressure transducer at its tip was inserted transcervically into the uterine cavity. Cumulative uterine activity was documented for 30 minutes in each woman before administering the oral misoprostol tablets and continued for a further 90 minutes after its administration. Thus each woman acted as her own control regarding changes in uterine contractility. Uterine activity was measured by a Sonicaid® Meridian fetal monitor, which measures active contraction area automatically. The incidence of side effects was also documented.

There was no statistical difference (p=0.887) in the adjusted mean difference in cumulative uterine activity following all the doses of oral misoprostol compared to intramuscular Syntometrine, the largest difference being seen in oral misoprostol 200 μg (adjusted mean difference –2282 kPas sec, 95% CI –7954 to 3390 kPas sec). The mean onset of action of oral misoprostol (6.1, SD 2.1 min) was significantly slower than that of intramuscular Syntometrine (3.2, SD 1.5 min) (p=0.002), but their durations of action were similar (p=0.637). In the misoprostol group, the commonest side effects were shivering (36%) and a rise in body temperature above 38°C (40%).

The results of this study show that oral misoprostol has a definite uterotonic effect on the postpartum uterus. At doses of 200 μg to 400 μg, oral misoprostol produced a similar uterotonic effect to intramuscular Syntometrine. Higher doses of oral misoprostol were associated with significantly more side effects. Hence, we decided to proceed to determine the optimum route for administering misoprostol 400 μg in terms of uteoronic effect and side effects.

Determining the optimum route of administration for misoprostol

To compare the postpartum uterotonic effect and side effects of misoprostol administered by different routes, we performed a prospective, descriptive study in which 50 women were given misoprostol 400μg either by the oral solution, oral tablet, rectal or vaginal route, or intramuscular Syntometrine 1mL after spontaneous vaginal delivery. Pre- and post-treatment uterine activity were measured with intrauterine pressure catheters.

The uterine activity produced by oral solution misoprostol 400μg was significantly higher than that of oral tablet, rectal and vaginal misoprostol ($p=0.045$, $p=0.004$, $p=0.002$ respectively). Onset of action after oral solution misoprostol was faster than by the oral tablet ($p=0.01$), rectal ($p<0.001$) and vaginal ($p<0.001$) routes. Unfortunately, shivering and pyrexia were also most common with oral solution misoprostol. Maximum body temperature recorded was significantly higher with oral solution misoprostol than with oral tablet, rectal and vaginal misoprostol ($p=0.005$, $p=0.009$, $p=0.001$ respectively).

Different routes of administering misoprostol greatly influence the effects achieved. Oral solution misoprostol produces the fastest and strongest uterotonic effect, with the most side effects.

The side effects of shivering and pyrexia when oral misoprostol is administered in the immediate postpartum period

As mentioned in Chapter 2, oral misoprostol, a prostaglandin E1 analogue, has been used for the prevention of nonsteroidal anti-inflammatory drug-induced

gastric ulcers since the 1980s and the induction of abortions and labour since the 1990s. No significant side effects had been reported in the early studies with normally prescribed doses of misoprostol up to 800 μg, with only two reports of misoprostol toxicity involving large overdosages. We describe a case of severe hyperthermia in a patient after an 800 μg oral dose of misoprostol in the immediate postpartum period.

A 20-year-old multiparous woman was given 800μg of misoprostol orally after an uneventful vaginal delivery as part of a clinical trial. She developed severe hyperthermia with a core temperature of 41.9°C one and a half hours later. Despite vigorous treatment, her body temperature only returned to normal three and a half hours later. Serum creatinine phosphokinase was raised to 4715 IU/L but there was no myoglobinuria. The patient recovered with no deleterious effects and was discharged three days later.

Oral misoprostol, even in routinely-prescribed doses, may cause severe shivering and hyperthermia that requires vigorous treatment. This was the first time the side effects of shivering and pyrexia have been reported with non-excessive doses of misoprostol.

Relationship of side effects with dose of misoprostol, uterine workload produced, and route of administration

My studies suggested that the safe dose of misoprostol for use in the third stage would be 200 to 400 μg. Oral solution misoprostol, while producing the fastest

onset of action and strongest uterine activity, unfortunately also produced the most side effects.

We examined the relationship between the side effects of misoprostol and the dose given, route of administration, and uterine activity produced. Based on the findings of our dose and route studies, we concluded that the dose of misoprostol and the route by which it is administered after vaginal delivery are both significantly associated with its side effects of shivering and pyrexia, while uterine activity produced was not.

Since misoprostol 400 μg given as an aqueous oral solution produced the fastest and strongest uterotonic effect but also the most side effects, we decided to test if a lower dose of misoprostol (200 μg) given as an oral solution would result in less side effects while maintaining a good level of uterine activity.

Comparing the uterotonic effect and side effects of oral tablet and oral solution misoprostol 200 μg and 400 μg

To compare the postpartum uterotonic effect and side effects of oral solution misoprostol 200 μg and 400 μg, and intramuscular syntometrine 1mL, we performed a prospective, descriptive study in which 30 women were given either oral solution misoprostol 200 μg or 400 μg, or intramuscular Syntometrine 1mL after spontaneous vaginal delivery. Pre- and post-treatment uterine activity were measured with intrauterine pressure catheters.

Uterine activity produced by oral solution misoprostol 200 μg was not significantly different from that of misoprostol 400 μg (p=0.758) or intramuscular syntometrine (p=0.623). There was no significant difference in onset of action among the three groups (p=0.132). Shivering and pyrexia occurred less frequently (20% versus 50%, p=0.350; 10% versus 80%, p=0.005 respectively), and maximum body temperature recorded was significantly lower (p=0.001) with 200 μg compared to 400 μg oral solution misoprostol.

Oral solution misoprostol 200 μg produced uterotonic effects that were not significantly different from that of oral solution 400 μg or intramuscular Syntometrine 1mL, with significantly less side effects. We recommend that further studies be performed in a clinical setting to determine if oral solution misoprostol 200 μg may be used as alternative to conventional oxytocics.

The use of misoprostol administered by different routes in the third stage of labour to prevent postpartum haemorrhage: a systematic review

The work for this thesis was commenced directly after the first report was made in 1996 of the use of oral misoprostol for the prevention of postpartum haemorrhage in the third stage of labour. By 1998, the first randomised controlled trial (RCT) was published, and over the next five years, another 24 RCTs were reported. Most were small to medium sized trials ranging from 40 to 2058 subjects. The largest single study was that by the WHO Collaborative Group, with 18530 subjects, published in 2001.

The WHO Misoprostol multicentre trial concluded that oral tablet misoprostol 600 μg given in the third stage of labour was associated with a higher risk of severe postpartum haemorrhage, need for additional uterotonics, shivering, and pyrexia compared to intramuscular or intravenous oxytocin 10 IU. Until this study, none of the RCTs had proven conclusively that misoprostol was either more or less effective than injectable uterotonics in preventing postpartum haemorrhage or the need for additional uterotonics. As expected, the results of the large WHO study overwhelmed the existing evidence, and the resulting Cochrane systematic review that followed concluded that conventional injectable oxytocics were preferable to misoprostol for the routine prevention of postpartum haemorrhage.

Based on our own observations (Chapter 5), we feel that misoprostol given orally as a tablet may not be the optimal method of administering this drug for the purpose of preventing postpartum haemorrhage. Pharmacokinetic studies have shown that the peak plasma concentration of misoprostol acid with oral tablet administration after delivery is around 18 to 20 minutes. From our intrauterine pressure measurement studies, we have found that the onset of uterotonic action after swallowing misoprostol tablets is 6 minutes (Chapter 5). This compares with a peak plasma concentration of oxytocin within 3 minutes of intramuscular injection, and onset of uterotonic action by 2.5 minutes. These few minutes difference in onset of action is of great clinical significance as delay in uterine contraction in the third stage can lead to a large volume of blood loss within a very short period of time. The delay in onset of action for rectal misoprostol is even greater, with peak plasma levels at 40.5 minutes, and onset of uterotonic activity at 11 minutes (Chapter 5). Hence, we feel that the current RCTs, which have either used misoprostol as oral

tablets, or as rectal suppositories (for which most misoprostol tablets were not formulated), will not show misoprostol to be an effective uterotonic agent for the purpose of preventing postpartum haemorrhage in the third stage. We separated out the two trials using oral solution misoprostol from those using oral tablet misoprostol as we feel that this method of administration may result in quicker absorption and greater uterotonic efficacy.

The purpose of this systematic review was to determine the effectiveness and safety of routine administration of misoprostol by different routes for the prevention of postpartum haemorrhage after vaginal delivery compared to no treatment or treatment with injectable uterotonics. Electronic databases were searched to identify randomised trials that compared misoprostol administered by different routes. Eligibility and trial quality were assessed by selected criteria which were determined *a priori*. Primary outcomes were chosen to address clinical effectiveness (severe postpartum haemorrhage ≥ 1000 mL, postpartum haemorrhage ≥ 500 mL, and the use of additional uterotonics) and safety (side effects of "any shivering", and pyrexia > 38ºC). Data were extracted and analysed using RevMan 4.2 software. All meta-analyses were based on the intention-to-treat principle. Overall treatment effects were expressed as relative risk (95% confidence intervals). Where there was result heterogeneity a random effects model was used. To explore the dose-response relationship a sub-group analysis was done. The date of the latest search was July 1, 2003.

Five studies (2,367 women) compared oral tablet misoprostol with placebo. There were no statistically significant differences in the risks of severe PPH (≥

1000ml), PPH (≥ 500 ml), and use of additional uterotonics. Eight studies (25,402 women) assessed oral tablet misoprostol against injectable uterotonics. Oral tablet misoprostol 600 µg was significantly less effective than injectable oxytocics in preventing PPH (RR 1.27, 95% CI 1.01-1.58), and use of additional uterotonics (RR 1.30, 95% CI 1.03-1.65). Two trials (897 women) compared oral solution misoprostol with intramuscular oxytocin for the third stage of labour, and two studies (100 women) compared oral misoprostol against intravenous oxytocin for preventing PPH during caesarean delivery. There were no statistically significant differences in the primary outcomes for these four trials as they were underpowered statistically. Rectal misoprostol was studied in six trials (3,975 women). Rectal misoprostol 400mcg was less effective than injectable uterotonics in preventing use of additional uterotonics (RR 1.63, 95% CI 1.16-2.30). There was an increased risk of having shivering and pyrexia with all concentrations of misoprostol compared to placebo and injectable uterotonics.

There is currently no evidence that misoprostol, given by any route, is more effective than placebo. Compared to injectable uterotonics, oral tablet misoprostol 600 µg was less effective in preventing PPH and the use of additional uterotonics. Rectal misoprostol 400 µg was less effective than injectable uterotonics in preventing the use of additional uterotonics. Misoprostol, given by any route, increases the risk of shivering and pyrexia.

We recommend that tablet misoprostol, given orally or rectally, should not be used alone for the routine prevention of postpartum haemorrhage in the third

stage of labour if injectable uterotonics are available. Care givers and patients should be aware of the dose-related side effects of misoprostol.

Conclusion

Misoprostol is capable of producing contractions in the postpartum uterus similar to those induced by intramuscular Syntometrine, a standard oxytocic used for preventing postpartum haemorrhage. The uterotonic action of misoprostol is significantly influenced by the dose administered and the route of administration. The route of administration that produces the fastest onset of action as well as the greatest uterine activity is an oral aqueous solution. This is followed in descending order by misoprostol administered as oral tablets, rectally, and vaginally.
There was a trend towards stronger uterotonic activity with increasing doses of oral tablet misoprostol from 200 μg to 600 μg. Unfortunately, with doses of oral tablet misoprostol above 400 μg, the side effects of shivering and pyrexia was significantly increased. We therefore proceeded with doses of misoprostol 200 to 400 μg in our studies.

With the increased speed of onset as well as strength of uterine activity produced by misoprostol 400 μg given as an oral solution, there were also more side effects. However, misoprostol 200 μg given as an oral solution produced good uterotonic activity with significantly less side effects.

A systematic review of the randomized controlled trials using misoprostol administered by different routes for the prevention of postpartum haemorrhage showed that conventional injectable oxytocics are more effective and have less side

effects. The two randomised trials using oral solution misoprostol were underpowered statistically to prove the effectiveness of misoprostol but did confirm the increased risk for shivering and pyrexia with doses of 400 μg and 600 μg.

From my studies, I conclude that my hypothesis that misoprostol, given in the correct dose and by the correct route, is able to produce a similar uterotonic effect to intramuscular Syntometrine is true. However, it can only be achieved with the production of the troublesome and potentially dangerous side effects of shivering and pyrexia. From large clinical trials, it has been shown conclusively that misoprostol administered as oral tablets or rectally are not as effective as conventional uterotonic agents and produce more side effects.

I therefore recommend that tablet misoprostol, given orally or rectally, should not be used alone for the routine prevention of postpartum haemorrhage in the third stage of labour if injectable uterotonics are available. Care givers and patients should also be aware of the dose-related side effects of misoprostol. In a trial setting, misoprostol 200 μg administered as an aqueous oral solution may be studied for the prevention of postpartum haemorrhage in low risk deliveries. Oral solution misoprostol may also be studied for the treatment of established postpartum haemorrhage.

Chapter 11

REFERENCES

Abdel-Aleem H, Villar J, Gulmezoglu AM, Mostafa SA, Youssef AA, Shokry M, Watzer B. The pharmacokinetics of the prostaglandin E1 analogue misoprostol in plasma and colostrums after postpartum oral administration. Eur J Obstet Gynecol Reprod Biol 2003; 108: 25-8.

Acharya G, Al-Sammarai MT, Patel N, Al-Habib A, Kiserud T. A randomized, controlled trial comparing effect of oral misoprostol and intravenous syntocinon on intra-operative blood loss during cesarean section. Acta Obstet Gynecol Scand 2001; 80: 245-50.

Adair CD, Weeks JW, Barrilleaux S, Edwards M, Burlison K, Lewis DF. Oral or vaginal misoprostol administration for induction of labor: a randomized, double-blind trial. Obstet Gynecol 1998; 92: 810-3.

Agrawal NM, Saffouri B, Kruss DM, Callison DA, Dajani EZ. Healing of benign gastric ulcer. A placebo-controlled comparison of two dosage regimens of misoprostol, a synthetic analog of prostaglandin E1. Dig Dis Sci. 1985 Nov; 30(11 Suppl):164S-170S.

Akdamar K, Agrawal N, Ertan A. Inhibition of nocturnal gastric secretion in normal human volunteers by misoprostol: a synthetic prostaglandin E1 methyl ester analog. Am J Gastroenterol 1982; 77: 902-4.

Amant F, Spitz B, Timmerman D, Corremans A, Van Assche FA. Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial. Br J Obstet Gynaecol 1999; 106: 1066-70.

American College of Obstetricians and Gynecologists. Induction of labor with misoprostol. ACOG Committee Opinion 228. Washington, DC: ACOG; 1999.

American College of Obstetricians and Gynecologists. Induction of labor. ACOG Practice Bulletin 10. Washington, DC: ACOG; 1999a.

American College of Obstetricians and Gynecologists: Response to Searle's drug warning on misoprostol. ACOG Committee Opinion 248. Washington, DC: ACOG; 2000.

American College of Obstetricians and Gynecologists. New U.S. Food and Drug Administration Labeling on Cytotec (Misoprostol) Use and Pregnancy. ACOG Committee Opinion 283. Washington, DC: ACOG; 2003.

Andersen B, Andersen LL, Sorensen T. Methylergometrine during the early puerperium; a prospective randomized double blind study. Acta Obstet Gynecol Scand 1998;77(1):54-7.

Arulkumaran S, Chua S, Ratnam SS. Symptoms and signs with scar rupture- value of uterine activity measurements. Aust N Z J Obstet Gynaecol 1992; 32(3): 208-12.

Ashok PW, Templeton A. Nonsurgical mid-trimester termination of pregnancy: a review of 500 consecutive cases. Br J Obstet Gynaecol 1999; 106: 706-10.

Athavale RD, Nerurkar NM, Dalvi SA, Bhattacharya MS. Umbilical vein oxytocin in the management of third stage of labour. J Postgrad Med. 1991; 37(4):219-20.

Atke A, Vilhardt H. Uterotonic activity and myometrial receptor affinity of 1-deamino-1-carba-2-tyrosine(O-methyl)-oxytocin. Acta Endocrinol (Copenh) 1987;115(1):155-60.

Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol 1998; 179: 1043-6.

Bamigboye AA, Merrell DA, Hofmeyr GJ, Mitchell R. Randomized comparison of rectal misoprostol with Syntometrine for management of third stage of labor. Acta Obstet Gynecol Scand 1998a; 77: 178-81.

Barbaro CA, Smith GO. Clinical trial of SE505 - a new oxytocic mixture. Aust NZ J Obstet Gynaecol 1961; 1:147-50.

Barbosa BM, Arilha M. The Brazilian experience with Cytotec. Stud Fam Plann 1993; 24: 236-40.

Bauer RF: Misoprostol preclinical pharmacology. Dig Dis Sci 1985; 30: 118S-123S.

Begley CM. A comparison of 'active' and 'physiological' management of the third stage of labour. Midwifery 1990; 6: 3-17.

Benchimol M, Gondry J, Mention JE, Gagneur O, Boulanger JC. Place du misoprostol dans la direction de la deliverance. (Placement of misoprostol in the direction of the delivery.) J Gynecol Obstet Biol Reprod 2001; 30: 576-83.

Bennett BB. Uterine rupture during induction of labor at term with intravaginal misoprostol. Obstet Gynecol 1997; 89: 832-3.

Bider D, Zolti M, Menashe Y, Dulitzky M, Mashiach S, Ben-Rafael Z. Oxytocin or saline injected intra-umbilically did not influence the third stage of labor. Acta Obstet Gynecol Scand. 1991; 70(4-5): 321-3.

Bider D, Ben-Rafael Z, Dulitzky M, Menashe Y, Mashiach S, Barkai G. Effect of intraumbilical prostaglandin F2 alpha injection on the third stage of labor. J Reprod Med 1992 Apr; 37(4): 317-9.

Bique C, Bugalho A, Bergstrom S. Labor induction by vaginal misoprostol in grand multiparous women. Acta Obstet Gynecol Scand. 1999 Mar;78(3):198-201.

Bjornerem A, Acharya G, Oian P, Maltau JM. Postpartum hemorrhage--prophylaxis and treatment in Norway. Tidsskr Nor Laegeforen 2002 Oct 30;122(26):2536-7.

Bond G R, Van Zee A. Overdosage of misoprostol in pregnancy. Am J Obstet Gynecol 1994; 171: 561-2.

Bonham DG. Intramuscular oxytocics and cord traction in third stage of labour. BMJ 1963; 2: 1620-3.

Boucher M, Horbay GL, Griffin P, Deschamps Y, Desjardins C, Schulz M, Wassenaar W. Double-blind, randomized comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing cesarean section. J Perinatol 1998; 18(3):202-7.

Brant HA. Precise estimation of postpartum haemorrhage: difficulties and importance. Br Med J 1967; i: 398-400.

Brucker MC. Management of the third stage of labor: an evidence-based approach. J Midwifery Womens Health 2001; 46(6): 381-92.

Bugalho A, Bique C, Almeida L, Faundes A. The effectiveness of intravaginal misoprostol (Cytotec) in inducing abortion after eleven weeks of pregnancy. Stud Fam Plann 1993; 24: 319-23.

Bugalho A, Bique C, Almeida L, Bergstrom S. Application of vaginal misoprostol before cervical dilatation to facilitate first-trimester pregnancy interruption. Obstet gynecol 1994; 83: 729-31.

Bugalho A, Faunders A, Jamisse L, Usfa M, Maria E, Bigue C. Evaluation of the effectiveness of vaginal misoprostol to induce first trimester abortion. Contraception 1996; 53: 243-6.

Bugalho A, Daniel A, Faundes A, Cunha M. Misoprostol for prevention of postpartum hemorrhage. Int J Gynaecol Obstet 2001; 73: 1-6.

Bullough CH, Msuku RS, Karonde L. Early suckling and postpartum haemorrhage: controlled trial in deliveries by traditional birth attendants. Lancet 1989; **ii**: 522-5.

Bygdeman M, Swahn ML. Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. Contraception. 1985; 32: 45-51.

Caliskan E, Meydanli MM, Dilbaz B, Aykan B, Sonmezer M, Haberal A. Is rectal misoprostol really effective in the treatment of third stage of labor? A randomized controlled trial. Am J Obstet Gynecol 2002; 187: 1038-45.

Caliskan E, Dilbaz B, Meydanli MM, Ozturk N, Narin MA, Haberal A. Oral misoprostol for the third stage of labor: a randomized controlled trial. Obstet Gynecol 2003; 101: 921-8.

Calkins LA. Factors governing blood loss in the third stage of labor. Am J Obstet Gynecol 1929; 17: 578-82.

Carbonell JL, Varela L, Velazco A, Fernandez C. The use of misoprostol for termination of early pregnancy. Contraception 1997; 55: 165-8.

Carbonell JL, Varela L, Velazco A, Tanda R, Barambio S, Chami S. Vaginal misoprostol 600 microg for early abortion. Eur J Contracept Reprod Health Care 2000; 5: 46-51.

Carbonell JL, Velazco A, Rodriguez Y, Tanda R, Sanchez C, Barambio S, Valera L, Chami S, Valero F, Aragon S, Mari J. Oral versus vaginal misoprostol for cervical priming in first-trimester abortion: a randomized trial. Eur J Contracept Reprod Health Care 2001; 6: 134-40.

Carbonell JL, Rodriguez J, Aragon S, Velazco A, Tanda R, Sanchez C, Barambio S, Chami S, Valero F. Vaginal misoprostol 1000 microg for early abortion. Contraception 2001a; 63: 131-6.

Carlan SJ, Bouldin S, O'Brien WF. Extemporaneous preparation of misoprostol gel for cervical ripening: a randomized trial. Obstet Gynecol 1997; 90(6): 911-5.

Carroli G, Bergel E. Umbilical vein injection for management of retained placenta (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

Chestnut DH, Wilcox LL. Influence of umbilical vein administration of oxytocin on the third stage of labor: a randomized, double-blind, placebo-controlled study. Am J Obstet Gynecol. 1987;157(1):160-2.

Chong YS, Chua S, Arulkumaran S. Severe hyperthermia following oral misoprostol in the immediate postpartum period. Obstet Gynecol 1997; 90; 2: 703-4.

Chong Y S, Chua S, Arulkumaran S. Can oral misoprostol be used as an alternative to parenteral oxytocics in the active management of labour? A preliminary study of its effect on the postpartum uterus. Published abstract in The Royal Australian and Royal New Zealand Colleges of Obstetricians and Gynaecologists 1997 Combined Scientific Meeting Handbook, 28 April-2 May 1997a: page 61.

Chong YS, Chua S, El-Refaey H, Choo WL, Chanrachakul B, Tai BC, et al. Postpartum intrauterine pressure studies of the uterotonic effect of oral misoprostol and intramuscular syntometrine. BJOG 2001; 108: 41-7.

Chong Y S, Chua S, Arulkumaran S. Sublingual misoprostol for first trimester termination of pregnancy: safety concerns. Hum Reprod 2002; 17: 2777-8.

Chong YS, Chua S, Shen L, Arulkumaran S. Does the route of administration of misoprostol make a difference? The uterotonic effect and side effects of misoprostol given by different routes after vaginal delivery. Eur J Obstet Gynecol Reprod Biol 2004; 113: 191-8.

Choo WL, Chua S, Chong YS, Vanaja K, Oei PL, Ho LM, Roy AC, Arulkumaran S. Correlation of change in uterine activity to blood loss in the third stage of labour. Gynecol Obstet Invest. 1998; 46: 178-80.

Choy CM, Lau WC, Tam WH, Yuen PM. A randomised controlled trial of intramuscular syntometrine and intravenous oxytocin in the management of the third stage of labour. BJOG. 2002;109(2):173-7.

Chua S, Arulkumaran S, Yang M, Ratnam SS, Steer PJ. The accuracy of catheter-tip pressure transducers for the measurement of intrauterine pressure in labour. Br J Obstet Gynaecol 1992; 99: 186-9.

Chua S, Arulkumaran S, Adaikan G, Ratnam SS. The effect of oxytocins stored at high temperature on postpartum uterine activity. Br J Obstet Gynaecol 1993; 100: 813-4.

Chua S, Arulkumaran S, Lim I, Selamat N, Ratnam SS. Influence of breastfeeding and nipple stimulation on postpartum uterine activity. Br J Obstet Gynaecol 1994; 101: 804-5.

Chua S, Chew SL, Yeoh CL, Roy AC, Ho LM, Selamat N, Arulkumaran S, Ratnam SS. A randomized controlled study of prostaglandin 15-methyl F2 alpha compared with syntometrine for prophylactic use in the third stage of labour. Aust N Z J Obstet Gynaecol 1995; 35(4): 413-6.

Chua S, Lee M, Chong YS, Vanaja K, Nordstrom L, Arulkumaran S. The reliability of catheter-tip transducers for the measurement of intrauterine pressure in the third stage of labour. Br J Obstet Gynaecol 1998; 105: 352-6.

Chua SPK. Measurement of postpartum uterine activity and blood loss to evaluate the efficacy of different drugs and techniques used for the active management of third stage of labour. PhD thesis, NUS 1998.

Chung TKH, Lee DTS, Cheung LP, Haines CJ, Chang AM. Spontaneous abortion: A randomized, controlled trial comparing surgical evacuation with conservative management using misoprostol. Fertil Steril 1999; 71: 1054-9.

Clarke M, Oxman AD, eds. Cochrane reviewers' handbook 4.0. Oxford, United Kingdom: The Cochrane Collaboration, 1999.

Coelho HL, Teixeira AC, Santos AP, Forte EB, Morais SM, La Vecchia C, Tognoni G, Herxheimer A. Misoprostol and illegal abortion in Fortaleza, Brazil. Lancet 1993; 341: 1486.

Colton DG, Driskill DR, Phillips EL, et al. Effect of SC-29333, an inhibitor of gastric secretion, on canine gastric mucosal blood flow and serum gastrin levels. Arch Int Pharmacodyn Ther 1978; 236: 86-95.

Cook CM, Spurrett B, Murray H. A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour. Aust N Z J Obstet Gynaecol 1999; 39: 414-9.

Costa SH, Vessey MP. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. Lancet 1993; 341: 1258-61.

Costa SH. Commercial availability of misoprostol and induced abortion in Brazil. Int J Gynaecol Obstet 1998; 63 Suppl 1: S131-9.

Creinin MD, Darney PD. Methotrexate and misoprostol for early abortion. Contraception 1993; 48: 339-48.

Creinin MD, Vittinghoff E. Methotrexate and misoprostol alone for early abortion. A randomized controlled trial. JAMA 1994; 272 (15): 1190-5.

Creinin MD, Vittinghoff E, Galbraith S, Klaisle C. A randomized controlled trial comparing misoprostol three and seven days after methotrexate for early abortion. Am J Obstet Gynecol 1995; 173: 1578-84.

Creinin MD, Vittinghoff E, Keder L, Darney PD, Tiller G. Methotrexate and misoprostol for early abortion: a multicenter trial. I Safety and efficacy. Contraception 1996; 53: 321-7.

Creinin MD, Vittinghoff E, Schaff E, Klaisle C, Darney PD, Dean C. Medical abortion with oral methotraxate and vaginal misoprostol. Obstet Gynaecol 1997; 90: 611-6.

Creinin MD. Medical abortion with methotrexate 75mg intramuscularly and vaginal misoprostol. Contraception 1997a; 56: 367-71.

Creinin MD, Moyer R, Guido R. Misoprostol for medical evacuation of early pregnancy failure. Obstet Gynecol 1997b; 89: 768-72.

Crowshaw K. Comparison of the pharmacological properties of ONO-802 (Cervagem) and the naturally occurring prostaglandins. In: Karim SMM, ed. Cervagem: a new prostaglandin in obstetrics and gynaecology. Lancaster: MTP Press Limited, 1983: 1-14.

Cunningham FG, MacDonald PC, Gant NF. Abnormalities of the third stage of labor. In: Cunningham FG, MacDonald PC, Gant NF, eds. Williams Obstetrics. Connecticut: Appleton & Lange, 1989: 415-24.

Dahiya P, Puri M, Rathee S. Influence of intraumbilical oxytocin on the third stage of labour. Indian J Med Sci. 1995; 49(2):23-27.

Dajani EZ, Driskill DR, Bianchi RG, et al. SC-29333: A potent inhibitor of canine gastric secretion. Am J Dig Dis 1976; 21: 1049-1057.

Daly S, Andolina K, Tolosa JE, Roberts N, Wapner R. A randomized controlled trial of misoprostol versus oxytocin in preventing postpartum blood loss. Am J Obstet Gynecol 1999; 180: S68.

Danielsson KG, Marions L, Rodriguez A, Spur BW, Wong PY, Bygdeman M. Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol 1999; 93: 275-80.

Dansereau J, Joshi AK, Helewa ME, Doran TA, Lange IR, Luther ER, Farine D, Schulz ML, Horbay GL, Griffin P, Wassenaar W. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. Am J Obstet Gynecol. 1999;180(3 Pt 1): 670-6.

Darney PD. Misoprostol: a boon to safe motherhood…or not? Lancet 2001; 358: 682-3.

Data sheet compendium. ABPI Data Sheet Compendium. London: Datapharm Publications Ltd, 1993.

De Groot AN, Vree TB, Hekster YA, Pesman GJ, Sweep FC, Van Dongen PG, Van Roosmalen J. Bioavailability and pharmacokinetics of sublingual oxytocin in male volunteers. J Pharm Pharmacol 1995; 47(7): 571-5.

De Groot AN, van Roosmalen J, van Dongen PW. Survey of the management of third stage of labour in The Netherlands. Eur J Obstet Gynecol Reprod Biol 1996; 66(1): 39-40.

De Groot AN, Van Roosmalen J, Van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta Obstetricia et Gynecologica Scandinavica 1996a; 75: 464-8.

De Groot AN, van Dongen PW, Vree TB, Hekster YA, van Roosmalen J. Ergot alkaloids. Current status and review of clinical pharmacology and therapeutic use compared with other oxytocics in obstetrics and gynaecology. Drugs. 1998 Oct;56(4): 523-35.

Delmas PD: Non-steroidal anti-inflammatory drugs and renal function. British Journal of Rheumatology 1995; vol. 34 (suppl. 1): 25-8.

Dickinson JE, Godfrey M, Evans SF. Efficacy of intravaginal misoprostol in second-trimester pregnancy termination: a randomized controlled trial. J Matern Fetal Med 1998; 7: 115-9.

Diro M, Adra A, Gilles JM, Nassar A, Rodriguez A, Salamat SM, Beydoun SN, O'Sullivan MJ, Yasin SY, Burkett G. A double-blind randomized trial of two dose regimens of misoprostol for cervical ripening and labor induction. J Matern Fetal Med 1999; 8(3): 114-8.

Dumoulin JG. A reappraisal of the use of ergometrine. J Obstet Gynaecol 1981;1:178-81.

Duthie SJ, Ven D, Yung GL, Guang DZ, Chan SY, Ma HK. Discrepancy between laboratory determination and visual estimation of blood loss during normal delivery. Eur J Obstet Gynaecol Reprod Biol 1991; 38: 119-24.

Elbourne DR, Prendiville WJ, Carroli G, Wood J, McDonald S. Prophylactic use of oxytocin in the third stage of labour (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

El-Refaey H, Templeton A. Early abortion induction by a combination of mifepristone and oral misoprostol: a comparison between two dose regimens of misoprostol and their effect on blood pressure. Br J Obstet Gynaecol 1994; 101: 792-6.

El-Refaey H, Calder L, Wheatley D N, Templeton A. Cervical priming with prostaglandin E1 analogues, misoprostol and gemeprost. Lancet 1994a; 343: 1207-9.

El-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Introduction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. N Engl J Med 1995; 332: 983-7.

El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Misoprostol for third stage of labour. Lancet 1996; 347: 1257.

El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997, 104; 336-9.

El-Refaey H, Nooh R, O'Brien P, Abdalla M, Geary M, Walder J, Rodeck C. The misoprostol third stage of labour study: a randomized controlled comparison between orally administered misoprostol and standard management. BJOG 2000; 107: 1104-10.

El-Refaey H. Use of misoprostol in third stage of labour. Lancet 2002; 359: 707-8.

Elsheikh A, Antsaklis A, Mesogitis S, Papantoniou N, Rodolakis A, Vogas E, Michalas S. Use of misoprostol for the termination of second trimester pregnancies. Arch Gynecol Obstet 2001; 265: 204-6.

Express scripts. Clinical News August 2002: 2.

Facts in Brief: Induced Abortion Worldwide, 2003 Alan Guttmacher Institute.

Farah LA, Sanchez-Ramos L, Rosa C, Del Valle GO, Gaudier FL, Delke I, Kaunitz AM. Randomized trial of two doses of the prostaglandin E1 analog misoprostol for labor induction. Am J Obstet Gynecol 1997;177:364-9; discussion 369-71.

Festin MR, Lumbiganon P, Tolosa JE, Finney KA, Ba-Thike K, Chipato T, Gaitan H, Xu L, Limpongsanurak S, Mittal S, Peedicayil A, Pramono N, Purwar M, Shenoy

S, Daly S. International survey on variations in practice of the management of the third stage of labour. Bull World Health Organ. 2003;81(4):286-91. Epub 2003 May 16.

Fletcher HM, Mitchell S, Siemon D, Frederick J, Brown D. Intravaginal misoprostol as a cervical ripening agent. Br J Obstet Gynaecol 1993; 100(7): 641-4.

Fonseca W, Misago C, Correia LL, Parente JA, Oliveira FC. Determinats of induced abortion among poor women admitted to hospitals in a locality of northeastern Brazil. Rev Saude Publica 1996; 30: 13-8.

Foote EF, Lee DR, Karim A, Keane WF, Halstenson CE. Disposition of misoprostol and its active metabolite in patients with normal and impaired renal function. J Clin Pharmacol 1995; 35: 384-9.

Forman A, Gandrup P, Andersson KE, Ulmsten U. Effects of nifedipine on oxytocin and prostaglandin F2 alpha induced activity in the postpartum uterus. Am J Obstet Gynecol 1982; 144: 665-70.

Forman A, Gandrup P, Andersson KE, Ulmsten U. Effects of nifedipine on spontaneous and methylergometrine-induced activity postpartum. Am J Obstet Gynecol 1982a; 144: 442-8.

Francis HH, Miller JM, Porteous CR. Clinical trial of an oxytocin-ergometrine mixture. Journal of Obstetrics and Gynaecology 1965; 5:47-51.

Friedman MA. Manufacturer's warning regarding unapproved uses of misoprostol. N Engl J Med 2001; 344: 61

Fugo NW, Dieckmann WJ. A comparison of oxytocic drugs in the management of the placental stage. American Journal of Obstetrics and Gynecology 1958; 76:141-6.

Garcia J, Garforth S. Labour and delivery routines in English consultant maternity units. Midwifery 1989 Dec; 5(4): 155-62.

GD Searle & Co. Stability report on Cytotec® 200 μg tablets. Product Information Cytotec® 1991.

Gerstenfeld TS, Wing DA. Rectal misoprostol versus intravenous oxytocin for the prevention of postpartum hemorrhage after vaginal delivery. Am J Obstet Gynecol 2001; 185: 878-82.

Ghorab MN, El Helw BA. Second-trimester termination of pregnancy by extra-amniotic prostaglandin F2alpha or endocervical misoprostol. A comparative study. Acta Obstet Gynecol Scand 1998; 77: 429-32.

Gibbens D, Boyd NRH, Crocker S, Baumber S, Chard T. The circulating levels of oxytocin following intravenous and intramuscular administration of Syntometrine. J Obstet Gynaecol Br Commonw 1972; 79: 644-6.

Gilbert A, Reid R. A randomised trial of oral versus vaginal administration of misoprostol for the purpose of mid-trimester termination of pregnancy. Aust N Z J Obstet Gynaecol 2001; 41: 407-10.

Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. N Engl J Med 2001; 344(1): 38-47.

Gonzalez CH, Vargas FR, Perez AB, Kim CA, Brunoni D, Marques-Dias MJ, Leone CR, Correa Neto J, Llerena Junior JC, de Almeida JC. Limb deficiency with or without Mobius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. Am J Med Genet 1993; 47: 59-64.

Gonzalez CH, Marques-Dias MJ, Kim CA, Sugayama SM, Da Paz JA, Huson SM, Holmes LB. Congenital abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. Lancet 1998; 351: 1624-7.

Graber D J, Meier K H. Acute misoprostol toxicity. Ann Emerg Med 1991; 20: 549-51.

Gulmezoglu AM. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev 2000;(2):CD000494.

Gulmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev 2001; (4): CD000494.

Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001a; 358: 689-95.

Gulmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for prevention of postpartum haemorrhage (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.

Hale RW, Zinberg S. Use of misoprostol in pregnancy. N Engl J Med 2001; 344: 59-60.

Harding JE, Elbourne DR, Prendiville WJ. Views of mothers and midwives participating in the Bristol randomized, controlled trial of active management of the third stage of labor. Birth 1989 Mar;16(1):1-6.

Hendricks CH, Eskes TKAB, Saameli K. Uterine contractility at delivery and in the puerperium. Am J Obstet Gynecol 1962; 83: 890-906.

Henshaw RC, Cooper K, El-Refaey H, Smith NC, Templeton AA. Medical management of miscarriage: Non-surgical uterine evacuation of incomplete and inevitable spontaneous abortion. BMJ 1993; 306: 894-5.

Herabutya Y, O-Prasertsawat P. Misoprostol in the management of missed abortion. Int J Gynaecol Obstet 1997; 56: 263-6.

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 Gynaecol 1998; 105: 971-5.

Hofmeyr GJ, Nikoderm C, de Jager M, Drakely A, Gilbert B. Oral misoprostol for labour third stage management: randomised assessment of side effects (part 2). Proceedings of the 17th Conference on Priorities in Perinatal Care in South Africa, 1998a: 53-54.

Hofmeyr GJ. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy (Cochrane review). In: The Cochrane Library, Issue 4. Oxford: Update Software, 1999.

Hofmeyr GJ, Gulmezoglu AM, Alfirevic Z. Misoprostol for induction of labour: A systematic review. Br J Obstet Gynaecol 1999a; 106: 798-803.

Hofmeyr GJ, Nikodem VC, de Jager M, Drakely A. Side-effects of oral misoprostol in the third stage of labour- a randomised placebo-controlled trial. S Afr Med J 2001; 91: 432-435.

Hogerzeil HV, Walker GJA, de Goeje MJ. Stability of injectable oxytocics in tropical climates. Geneva: World Health Organisation, 1993.

Howard WF, McFadden PR, Keettel WC. Oxytocic drugs in fourth stage of labor. JAMA 1964; 189: 411-3.

Hunt JN, Smith JL, Jiang CL, et al. Effect of synthetic prostaglandin E1 analog on aspirin-induced gastric bleeding and secretion. Dig Dis Sci 1983; 28(10): 897-902.

Hunter DJ, Schulz P, Wassenaar W. Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clin Pharmacol Ther 1992 Jul;52(1):60-7.

Ilancheran A, Ratnam SS. Effect of oxytocics on prostaglandin levels in the third stage of labour. Gynecologic and Obstetric Investigation 1990;29:177-80.

Ingemarsson I, Arulkumaran S, Wide-Swensson D, Forman A, Andersson KE, Ratnam SS. Effects of isradipine, a new calcium antagonist on postpartum uterine activity. Acta Obstet Gynecol Scand 1989; 68: 725-30.

Irons DW, Sriskandabalan, Bullough CHW. A simple alternative to parenteral oxytocics for the third stage of labor. Int J Gynecol Obstet 1994; 46: 15-8.

Jackson KW Jr, Allbert JR, Schemmer GK, Elliot M, Humphrey A, Taylor J. A randomized controlled trial comparing oxytocin administration before and after placental delivery in the prevention of postpartum hemorrhage. Am J Obstet Gynecol. 2001 Oct; 185(4):873-7.

Joy SD, Sanchez-Ramos L, Kaunitz AM. Misoprostol use during the third stage of labor. Int J Gynecol Obstet 2003; 82: 143-52.

Kane TT, El-Kady AA, Saleh S, Hage M, Stanback J, Potter L. Maternal mortality in Giza, Egypt: magnitude, causes, and prevention. Stud Fam Planning 1992; 23: 45-57.

Karim A. Antiulcer prostaglandin misoprostol: single and multiple dose pharmacokinetic profile. Prostaglandins 1987; 33 (suppl): 40-50.

Karim SMM. Once a month vaginal administration of postaglandin E2 and F2α for fertility control. Contraception 1971; 3: 173-83.

Karkanis SG, Caloia D, Salenieks ME, Kingdom J, Walker M, Meffe F, et al. Randomized controlled trial of rectal misoprostol versus oxytocin in third stage management. J Obstet Gynaecol Can 2002; 24: 149-54.

Karlsson S. A contribution to the methods of recording human motility. Acta Obstet Gynecol Scand 1944; 24 (suppl 4).

Kelly JV, Schleifer O. A new method for assessment of uterine contractions. Surg Gynecol Obstet 1962; 114: 389-92.

Khan GQ, John IS, Chan T, Wani S, Hughes AO, Stirrat GM. Abu Dhabi third stage trial: oxytocin versus Syntometrine in the active management of the third stage of labour. Eur J Obstet Gynaecol and Reprod Biol 1995; 58:147-51.

Khan GQ, John LS, Wani, S, Doherty T, Sibai BM. Controlled cord traction versus minimal intervention techniques in delivery of the placenta: a randomized controlled trial. Am J Obstet Gynecol 1997; 77: 770-4.

Khan R, Sharma S. Use of misoprostol in third stage of labour. Lancet 2002; 359: 708-9.

Khan RU, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. Obstet Gynecol 2003; 101: 968-74.

Klitsch M. Antiprogestins and the abortion controversy: a progress report. Fam Plann Perspect 1991; 23: 275-82.

Koopersmith TR, Mishell DR. The use of misoprostol for termination of early pregnancy. Contraception 1996; 53: 237-42.

Kovavisarach E, Rojsangruang S. Effect of umbilical vein oxytocin injection on the third stage of labor: a randomized controlled study. J Med Assoc Thai 1998 Sep; 81(9): 693-7.

Kundodyiwa TW, Majoko F, Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. Int J Gynaecol Obstet 2001; 75: 235-41.

Kwast B. Post partum haemorrhage: its contribution to maternal mortality. Midwifery 1991; 7: 64-7.

Lamont RF, Morgan DJ, Logue M, Gordon H. A prospective randomised trial to compare the efficacy and safety of hemabate and syntometrine for the prevention of primary postpartum haemorrhage. Prostaglandins Other Lipid Mediat. 2001 Oct; 66(3): 203-10.

Lavery JP, Staten-McCormick M. Management of moderate to severe trauma in pregnancy. Obstet Gynecol Nth Am 1995; 22: 69-90.

le Roux PA, Olarogun JO, Penny J, Anthony J. Oral and vaginal misoprostol compared with dinoprostone for induction of labor: a randomized controlled trial. Obstet Gynecol 2002; 99: 201-5.

Li XF, Fortney JA, Kotelchuck M, Glover LH. The postpartum period: the key to maternal mortality. Int J Gynecol Obstet 1996; 54: 1-10.

Liu HS, Chu TY, Chang YK, Yu MH, Chen WH. Intracervical misoprostol as an effective method of labor induction at term. Int J Gynaecol Obstet 1999; 64: 49-53.

Lokugamage AU, Sullivan KR, Niculescu I, Tigere P, Onyangunga F, El-Refaey H, et al. A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. Acta Obstet Gynecol Scand 2001; 80: 835-9.

Lokugamge AU, Paine M, Bassaw-Balroop, Sullivan KR, El-Refaey H, Rodeck CH. Active management of the third stage at caesarean section: a randomised controlled trial of misoprostol versus syntocinon. Aust N Z J Obstet Gynaecol 2001a; 41: 411-4.

Longland P, Roebottom PC. Stability at room temperature of medicines normally recommended for cold storage. Pharmaceut J 1987; 288: 147-51.

Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour. WHO collaborative trial of misoprostol in the management of the third stage of labour. Br J Obstet Gynaecol 1999; 106: 304-8.

Lumbiganon P, Villar J, Piaggio G, Gulmezoglu AM, Adetoro L, Carroli G. Side effects of oral misoprostol during the first 24 hours after administration in the third stage of labour. BJOG 2002; 109: 1222-6.

Mackowiak P, LeMaistre C. Drug fever: a critical appraisal of conventional concepts. Ann Intern Med 1987; 106: 728-33.

Majoko F, Nystrom L, Lindmark G. No benefit, but increased harm from high dose (100microg) misoprostol for induction of labour: a randomized trial of high vs low (50 microg) dose misoprostol. J Obstet Gynaecol 2002; 22(6): 614-7.

McCormick ML, Sanghi HCG, Kinzie B, McIntosh N. Preventing postpartum hemorrhage in low-resource settings. Int J Gynecol Obstet 2002; 77: 267-75.

McDonald SJ, Prendiville W, Blair E. Randomised controlled trial of oxytocin alone versus oxytocin and ergometrine in active management of the third stage of labour. BMJ 1993; 307: 1167-71.

McDonald S, Prendiville WJ, Elbourne D. Prophylactic syntometrine versus oxytocin for delivery of the placenta (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

McGinty LB. A study of the vasopressor effects of oxytocics when used intravenously in the third stage of labour. Western Journal of Surgery 1956; 64:22-8.

Meydanli MM, Caliskan E, Burak F, Narin MA, Atmaca R. Labour induction post-term with 25 micrograms vs 50 micrograms of intravaginal misoprostol. Int J Gynaecol Obstet 2003; 81(3): 249-55.

Millar HD, Baker LE. A stable ultraminature catheter-tip pressure transducer. Med Biol Eng 1973; 11: 86.

Mitchell GG, Elbourne DR. The Salford third stage trial: oxytocin plus ergometrine versus oxytocin alone in the active management of the third stage of labour. Online J Curr Clin Trials 1993; 2: Doc 83.

Moir JC. The action of ergot preparation on the puerperal uterus. BMJ 1932; 1: 1119-22.

Moir JC. The history of present day use of ergot. Can Med Assoc J 1955; 72: 727-34.

Monda M, Amaro S, Sullo A, De Luca B. Posterior hypothalamic activity and cortical control during the PGE1 hyperthermia. Neuroreport 1994; 6: 135-9.

Munthali J, Moodley J. The use of misoprostol for mid-trimester therapeutic termination of pregnancy. Trop Doct 2001; 31: 157-61.

Murdoch R. Third-stage bowl. Lancet 1958; 2: 731-2.

Newton M, Mosey LM, Egli GE, Gifford WB, Hull CT. Blood loss during and immediately after delivery. Obstetrics and Gynecology 1961;17:9-18.

Newton J, Barnard G, Collins W. A rapid method for measuring menstrual blood loss using automatic extraction. Contraception 1977; 16: 269-82.

Ng PS, Chan AS, Sin WK, Tang LC, Cheung KB, Yuen PM. A multicentre randomized controlled trial of oral misoprostol and i.m. syntometrine in the management of the third stage of labour. Hum Reprod 2001; 16: 31-5.

Ngai SW, Yeung KC, Lao T, Ho PC. Oral misoprostol versus vaginal gemeprost for cervical dilatation prior to vacuum aspiration in women in the sixth to twelfth week of gestation. Contraception 1995; 51: 347-50.

Ngai SW, To WK, Lao T, Ho PC. Cervical priming with oral misoprostol in pre-labor rupture of membranes at term. Obstet Gynecol 1996; 87: 923-6.

Ngai SW, Tang OS, Ho PC. Randomized comparison of vaginal (200 microg every 3 h) and oral (400 microg every 3h) misoprostol when combined with mifepristone in termination of second trimester pregnancy. Hum Reprod 2000; 15: 2205-8.

Nieminen U, Jarvinen PA. A comparative study of different medical treatments of the third stage of labour. Ann Chir Gynaecol Fenn 1963; 53: 424-9.

Nopdonrattakoon L. A comparison between intravaginal and oral misoprostol for labour induction: a randomized controlled trial. J Obstet Gynaecol Red 2003; 29(2): 87-91.

Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. Br J Obstet Gynaecol 1997; 104: 781-6.

Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. Lancet 1991; 338: 1233-6.

Nuutila M, Toivonen J, Ylikorkala O, Halmesmaki E. A comparison between 2 doses of intravaginal misoprostol and gemeprost for induction of second-trimester abortion. Obstet Gynecol 1997; 90: 896-900.

O'Brien WF, Cefalo RC. Labour and delivery.In: Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: normal and problem pregnancies. 3rd Ed. Churchill Livingstone; 1996, pp 388.

O'Brien P, Lokugamage AU, Guillebaud J, Rodeck CH. Use of misoprostol in third stage of labour. Lancet 2002; 359: 708.

Oboro VO, Tabowei TO. A randomised controlled trial of misoprostol versus oxytocin in the active management of the third stage of labour. J Obstet Gynaecol 2003; 23: 13-6.

Orioli IM, Castilla EE. Epidemiological assessment of misoprostol teratogenicity. Br J Obstet Gynaecol 2000; 107: 519-23.

Ozcan T, Sahin G, Senoz S. The effect of intraumbilical oxytocin on the third stage of labour. Aust N Z J Obstet Gynaecol. 1996 Feb; 36(1):9-11.

Parott R F, Vellucci S V, Forsling M L, Goode J A. Hyperthermic and endocrine effects of intravenous prostaglandin administration in the pig. Domest Anim Endocrinol 1995; 12: 197-205.

Pastuszak AL, Schuler L, Speck-Martins CE, et al. Use of misoprostol during pregnancy and Mobius syndrome in infants. N Engl J Med 1998; 338: 1881-5.

Perry KG Jr, Rinehart BK, Terrone DA, Martin RW, May WL, Roberts WE. Second-trimester uterine evacuation: A comparison of intra-amniotic (15S)-15-methyl-prostaglandin F2α and intravaginal misoprostol. Obstet Gynecol 1999; 181: 1057-61.

Peyron R, Aubeny E, Targosz V, Silvestre L, Renault M, Elkik F et al. Early termination of pregnancy with mifepristone (RU486) and the orally active prostaglandin misoprostol. N Engl J Med 1993; 328: 1509-13.

Phillips CA, Kinch RA. Management of the third stage of labor: a survey of practice among Texas obstetricians. Tex Med 1994 Dec; 90(12): 44-7.

Pierre F, Mesnard L, Body G. For a systematic policy of iv oxytocin inducted placenta deliveries in a unit where a fairly active management of third stage of labour is yet applied: results of a controlled trial. European Journal of Obstetrics, Gynecology and Reproductive Biology 1992; 43: 131-5.

Plaut MM, Schwartz ML, Lubarsky SL. Uterine rupture associated with the use of misoprostol in the gravid patient with a previous caesarean section. Am J Obstet Gynecol 1999; 180: 1535-42.

Poeschmann RP, Doesburg WH, Eskes TKAB. A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour. British Journal of Obstetrics and Gynaecology 1991; 98: 528-30.

Pongsatha S, Morakot N, Tongsong T. Demographic charactersitics of women with self use of misoprostol for pregnancy interruption attending Maharaj Nakorn Chiang Mai Hospital. J Med Assoc Thai 2002; 85: 1074-80.

Porter KB, O'Brien WF, Collins MK, Givens P, Knuppel R, Bruskivage L. A randomized comparison of umbilical vein and intravenous oxytocin during the puerperium. Obstet Gynecol. 1991; 78: 254-6.

Prendiville W, Elbourne D, Chalmers I. The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. Br J Obstet Gynaecol. 1988; 95: 3-16.

Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active vs physiological management of the third stage of labour. BMJ 1988a; 297:1295-1300.

Prendiville W, Elbourne D. Care during the third stage of labour. In: Effective care in pregnancy and childbirth Vol 2. I Chalmers, M Enkin, MJNC Keirse (eds) Oxford University Press 1990. pp 1145-69.

Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

Rabe T, Basse H, Thuro H, Kiesel l, Runnebaum B. Effect of the PGE1 methyl analog misoprostol on the pregnant uterus in the first trimester. Geburtshilfe Frauenheilkd. 1987; 47: 324-31. German.

Ramin KD, Ogburn PL, Danilenko DR, Ramsey PA. High-dose oral misoprostol for mid-trimester pregnancy interruption. Gynecol Obstet Invest. 2002; 54: 176-9.

Razvi K, Chua S, Arulkumaran S, Ratnam SS. A comparison between visual estimation and laboratory determination of blood loss during the third stage of labour. Aust NZ J Obstet Gynaecol 1996; 36: 152-4.

Reddy VV, Carey JC. Effect of umbilical vein oxytocin on puerperal blood loss and length of the third stage of labor. Am J Obstet Gynecol. 1989; 160: 206-8.

Reichev R, Dimitrov N, Raicheva R. Provocation of labor activity by oral administration of methylergobasine (methergine) by Merger's method (R. Merger). Akush Ginekol (Sofiia). 1972; 11: 388-92.

Report of Technical Working Group. The prevention and management of post partum haemorrhage. Geneva: World Health Organisation, 1990. (WHO/MCH/90.7.)

Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active vs expectant management of the third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet 1998; 351: 693-9.

Sanchez-Ramos L, Kaunitz A M, Del-Valle G O, Delke I, Schroeder P A, Briones D K. Labor induction with the prostaglandin E1 methyl analogue misoprostol versus oxytocin: a randomized trial. Obstet Gynecol 1993; 81: 332-6.

Sanchez-Ramos L, Chen AH, Kaunitz AM, Gaudier FL, Delke I. Labor induction with intravaginal misoprostol in term premature rupture of membranes: A randomized study. Obstet Gynecol 1997; 89: 909-12.

Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction: a meta-analysis. Obstet Gynecol 1997a; 89: 633-42.

Saxena P, Salhan S, Sarda N. Role of sublingual misoprostol for cervical ripening prior to vacuum aspiration in first trimester interruption of pregnancy. Contraception 2003; 67: 213-7.

Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low dose mifepristone 200mg and vaginal misoprostol for abortion. Contraception 1999; 59: 1-6.

Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. Contraception 2001; 64: 81-5.

Schuler L, Pastuszak A, Sanseverino TV, Orioli IM, Brunoni D, Ashton-Prolla P, Silva da Costa F, Giugliani R, Couto AM, Brandao SB, Koren G. Pregnancy outcome after exposure to misoprostol in Brazil: a prospective, controlled study. Reprod Toxicol 1999; 13: 147-51.

Searle: Cytotec (misoprostol). (information package) G.D. Searle & Co., 1995.

Shannon C, Winikoff B. Use of misoprostol in third stage of labour. Lancet 2002; 359: 709.

Shetty A, Mackie L, Danielian P, Rice P, Templeton A. Sublingual compared with oral misoprostol in term labour induction: a randomized controlled trial. BJOG 2002; 109: 645-50.

Shetty A, Dalielian P, Templeton A. Sublingual misoprostol for the induction of labour at term. Am J Obstet Gynecol 2002a; 186: 72-6.

Shetty A, Stewart K, Stewart G, Rice P, Danielian P, Templeton A. Active management of term prelabour rupture of membranes with oral misoprostol. BJOG 2002b; 109: 1354-8.

Shield MJ: Novel applications of misoprostol. Pharmacological Theory 1995; vol. 65: 125-47.

Singh K, Fong YF, Dong F. A viable alternative to surgical vacuum aspiration: repeated doses of intravaginal misoprostol over 9 hours for medical termination of pregnancies up to eight weeks. BJOG 2003; 110: 175-80.

Smith RP. A brief history of intrauterine pressure measurement. Acta Obstet Gynecol Scand 1984; suppl 129: 4-24.

Soiva K, Koistinen O. Clinical experience with simultaneous intramuscular injection of oxytocin and methylergometrine. Annales Chirurgiae et Gynaecologiae 1964; 53: 173-86.

Sorbe B. Active pharmacologic management of the third stage of labor. A comparison of oxytocin and ergometrine. Obstetrics and Gynecology 1978; 52: 694-7.

Srisomboon J, Tongsong T, Tosiri V. Preinduction cervical ripening with intravaginal prostaglandin E1 methyl analogue misoprostol: a randomized controlled trial. J Obstet Gynaecol Res 1996; 22: 119-24.

Steer PJ, Carter MC, Gordon AJ. The use of catheter-tip pressure transducers for the measurement of intrauterine pressure in labour. Br J Obstet Gynaecol 1978; 85: 561-6.

Steiner JA. Misoprostol clinical pharmacology: establishment of activity in man. Dig Dis Sci 1985; 30: 136S-141S.

Still DK. Postpartum hemorrhage and other problems of the third stage. In: James DK, Steer PJ, Weiner CP, Gonik B, eds. High risk pregnancy - management options. London: WB Saunders Company Ltd, 1994: 1167-81.

Surbek DV, Fehr PM, Hosli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. Obstet Gynecol 1999; 94: 255-8.

Swahn ML, Cekan S, Wang G, Lujndstrom V, Bygdeman M. Pharmacokinetic and clinical studies of RU 486 for fertility regulation. In: Baulieu EE, Siegel S, editors. The antiprogestin steroid RU 486 and human fertility control. New York: Kluwer Academic / Plenum Publishers; 1985. P. 249-58.

Tang OS, Wong KS, Tang LCH, Ho PC. Pilot study on the use of repeated doses of misoprostol in termination of pregnancy at less than 9 weeks of gestation. Adv Contracept 1999; 15: 211-6.

Tang OS, Ho PC. Pilot study on the use of sublingual misoprostol for medical abortion. Contraception 2001; 64: 315-7.

Tang OS, Miao BY, Lee SW, Ho PC. Pilot study on the use of repeated doses of sublingual misoprostol in termination of pregnancy up to 12 weeks gestation: efficacy and acceptability. Hum Reprod 2002; 17: 654-8.

Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod 2002a; 17: 332-6.

Thilaganathan B, Cutner A, Latimer J, Beard R. Management of the third stage of labour in women at low risk of postpartum haemorrhage. Eur J Obstet Gynecol Reprod Biol 1993; 48:19-22.

Thong KJ, Baird DT. Induction of abortion with mifepristone and misoprostol in early pregnancy. Br J Obstet Gynaecol 1992; 99: 1004-7.

Toppozada MK, Anwar MY, Hassan HA, el-Gazaerly WS. Oral or vaginal misoprostol for induction of labour. Int J Gynaecol Obstet 1997; 56: 135-9.

Tsu VD. Postpartum haemorrhage in Zimbabwee: a risk factor analysis. Br J Obstet Gynaecol 1993; 100: 327-33.

Ulmsten U, Andersson KE. Multichannel intrauterine pressure recording by means of microtransducers. Acta Obstet Gynecol Scand 1979; 58: 115-20.

United States Food and Drug Administration. "Off-label" and investigational use of marketed drugs, biologics, and medical devices. Guidance for institutional review boards and clinical investigators 1998 update.]

Urban R, Lemancewicz A, Urban J, Skotnicki MZ, Kretowska M. Misoprostol and dinoprostone therapy for labor induction: a Doppler comparison of uterine and fetal hemodynamic effects. Eur J Obstet gynecol Reprod Biol 2003; 10: 106.

van Dongen PW, Verbruggen MM, de Groot AN, van Roosmalen J, Sporken JM, Schulz M. Ascending dose tolerance study of intramuscular carbetocin administered after normal vaginal birth. Eur J Obstet Gynecol Reprod Biol. 1998 Apr; 77(2): 181-7.

Villar J, Gulmezoglu AM, Hofmeyr GJ, Cheng L, Elbourne D. Use of misoprostol in third stage of labour. Lancet 2002; 359: 709-10.

Villar J, Gulmezoglu AM, Hofmeyr GJ, Forna F. Systematic review of randomized controlled trials of misoprostol to prevent postpartum hemorrhage. Obstet Gynecol 2002a; 100: 1301-12.

Vimala N, Mittal S, Kumar S. Sublingual misoprostol for preabortion cervical ripening in first –trimester pregnancy termination. Contraception 2003; 67: 295-7.

Wakabayashi M, Tretiak M, Kosasa T, Sharma S, Aeby T, Kamemoto L, Diniega L. Intravaginal misoprostol for medical evacuation of first trimester missed abortion. Prim. Care Update Ob Gyns 1998; 5: 176.

Walker GJA, Hogerzeil HV, Hillgren U. Potency of ergometrine in tropical countries. Lancet 1988; **ii**: 393.

Walley RL, Wilson JB, Crane JM, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. BJOG 2000; 107: 1111-5.

Weinblatt ME, Germain BF, Kremer JM, Wall BA, Weisman MH, Maier AL, Coblyn JS: Lack of a renal-protective effect of misoprostol in rheumatoid arthritis patients receiving cyclosporin A. Results of a randomized, placebo-controlled trial. Arthritis Rheum. 1994; vol. 37: 1321-5.

Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for pre-induction cervical ripening and labor induction. Am J Obstet Gynecol 1996; 175: 158-64.

Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labor induction. Am J Obstet Gynecol 1997; 176: 1423.

Wing DA, Lovett K, Paul RH. Disruption of prior uterine incision following misoprostol for labor induction in women with previous caesarean delivery. Obstet Gynecol 1998; 91(5 Pt 2): 828-30.

Wing DA, Tran S, Paul RH. Factors affecting the likelihood of successful induction after intravaginal misoprostol application for cervical ripening and labor induction. Am J Obstet Gynecol 2002; 186(6): 1237-40.

Wong F, Massie D, Hsu P, Dudley F: The effect of misoprostol on indomethacin-induced renal dysfunction in well-compensated cirrhosis. Journal of Hepatology 1995: vol. 23: 1-7.

Wong KS, Ngai CS, Wong AY, Tang LC, Ho PC. Vaginal misoprostol compared with vaginal gemeprost in termination of second trimester pregnancy. A randomised trial. Contraception 1998; 58: 207-10.

Wong KS, Ngai CSW, Yeo ELK, Tang LCH, Ho PC. A comparison of two regimens of intravaginal misoprostol for termination of second trimester pregnancy: a randomized comparative trial. Hum Reprod 2000; 15: 709-12.

World Health Organisation. Maternal mortality and global fact book. Geneva: World Health Organisation, 1991: 3-16.

Xu J, Chen H, Ma T, Wu X. Termination of early pregnancy in the scarred uterus with mifepristone and misoprostol. Int J Gynaecol Obstet 2001; 72: 245-51.

Young SB, Martelly PD, Greb L, Considine G, Coustan DR. The effect of intraumbilical oxytocin on the third stage of labor. Obstet Gynecol. 1988 May; 71: 736-8.

Yuen PM, Chan NST, Yim SF, Chang AMZ. A randomised double blind comparison of Syntometrine® and Syntocinon® in the management of the third stage of labour. Br J Obstet Gynaecol 1995; 102: 377-80.

Zhao Y, Li X, Peng Y. Clinical study on reduction of postpartum bleeding in cesarean section by misoprostol. Zhonghua Fu Chan Ke Za Zhi 1998; 33: 403-5.

Zieman M, Fong SK, Benowitz NL, Banskten D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997; 90: 88-92.

Chapter 12

PUBLICATIONS ARISING FROM THE THESIS

Chapter 1

1. Chong YS, Su LL, Arulkumaran S. Current strategies for the prevention of postpartum haemorrhage in the third stage of labour. *Curr Opin Obstet Gynecol* 2004; 16: 143-50.

Chapter 2

1. Chong YS, Su LL, Arulkumaran S. Misoprostol: a quarter century of use, abuse, and creative misuse. *Obstet Gynecol Surv* 2004; 59: 128-40.

Chapter 3

1. Chua S, Lee M, Vanaja K, Chong YS, Nordstrom L. Arulkumaran S. The reliability of catheter-tip transducers for the measurement of intrauterine pressure in the third stage of labour. *Br J Obstet Gynaecol* 1998; 105 (3): 352-6.

2. Choo WL, Chua S, Chong YS, Vanaja K, Oei P L, Ho L M, Roy A C, Arulkumaran S. Correlation of change in uterine activity to blood loss in the third stage of labour. *Gynecol Obstet Invest* 1998; 46: 178-80.

Chapter 4

1. Chong YS, Chua S, Arulkumaran S. Can oral misoprostol be used as an alternative to parenteral oxytocics in the active management of labour? A preliminary study of its effect on the postpartum uterus. Published abstract in

The Royal Australian and Royal New Zealand Colleges of Obstetricians and Gynaecologists 1997 Combined Scientific Meeting *Handbook*, 28 April-2 May 1997: page 61. Recipient of the ***Royal Australian and Royal New Zealand Colleges of Obstetricians and Gynaecologists Young Investigator Award 1997*** for the best research study presented by a young member of the college at their 1997 Combined Scientific Meeting.

2. Chong YS, Chua S, El-Refaey H, Choo WL, Chanrachakul B, Tai BC, Rodeck C, Arulkumaran S. Postpartum intrauterine pressure studies of the uterotonic effect of oral misoprostol and intramuscular syntometrine. *BJOG* 2001; 108: 41-7.

Chapter 5

1. Chong YS, Chua S, Shen L, Arulkumaran S. The uterotonic effect and side effects of misoprostol given by different routes after vaginal delivery. 7th NUS-NUH Annual Scientific Meeting, October 2-3, 2003. *Handbook* page 94.

2. Chong YS, Chua S, Shen L, Arulkumaran S. Does the route of administration of misoprostol make a difference for the routine prevention of postpartum haemorrhage? The uterotonic effect and side effects of misoprostol given by different routes after vaginal delivery. *Ann Acad Med Singapore* 2003 Sep; 32(5 Suppl): S119.

3. Chong YS, Chua S, Shen L, Arulkumaran S. Does the route of administration of misoprostol make a difference? The uterotonic effect and side effects of misoprostol given by different routes after vaginal delivery. *Eur J Obstet Gynecol Reprod Biol* 2004; 113: 191-8.

Chapter 6

1. Chong YS, Chua S, Arulkumaran S. Severe hyperthermia following oral misoprostol in the immediate postpartum period. *Obstet Gynecol* 1997; 90: 703-4.

Chapter 7

1. Chong YS, Chua S, Arulkumaran S. Sublingual misoprostol for first trimester termination of pregnancy: safety concerns. *Hum Reprod* 2002; 17: 2777-8.

Chapter 8

1. Chong YS, Chua S, Shen L, Arulkumaran S. Low dose oral misoprostol should be tested as a uterotonic agent to prevent postpartum haemorrhage. 7th NUS-NUH Annual Scientific Meeting, October 2-3, 2003. *Handbook* page 95.

2. Chong YS, Chua S, Shen L, Arulkumaran S. Can low dose oral solution misoprostol be used as a uterotonic agent to prevent postpartum haemorrhage? *Ann Acad Med Singapore* 2003 Sep; 32(5 Suppl): S119.

Chapter 9

1. Chong YS, Su LL, Samuel M. The Use of Misoprostol Administered by Different Routes to Prevent Postpartum Haemorrhage: A Systematic Review. International Conference on Evidence-Based Medicine 2003, 18-19 October 2003: *Handbook*. Recipient of the ***Best Free Paper Oral Presentation Award***.

2. Chong YS, Samuel M, Su LL, Arulkumaran S. Prevention and management of postpartum haemorrhage: is the first choice oxytocin or misoprostol? **Invited lecture** given at the Asian Pacific Congress on Controversies in Obstetrics and Infertility, Bangkok, 25th-28th November 2004: Congress Handbook & CD-ROM.