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Obstetric use of misoprostol: innovations, evidence, controversy and global health perspectives

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand,

in fulfillment of the requirements for the degree

of

Doctor of Science in Medicine.

East London, 2012

"More is not necessarily better" - Charles Schultz

Declaration

I declare that:

A. My role in each of the 40 submitted publications is as listed below.

Lead role:

Concept, writing: 1,3, 34, 35;

Originator of technique, concept, analysis, design, writing: 4, 5;

Originator of generic protocol concept, writing: 6;

Concept, design, meta-analysis, writing: 7, 8, 9, 10,11, 31, 32, 38, 40;

Concept, design, analysis, writing: 15, 16, 17, 20, 23, 24, 26;

Originator of technique, concept, design, analysis, writing, supervision of junior doctor: 29, 30;

Substantial collaboration:

Writing: 2;

Concept, design, analysis, writing, supervision of junior member of staff: 13;

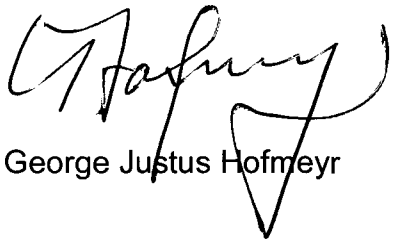
Concept, design, analysis, writing: 12, 14, 18, 19, 21, 22, 25, 27, 28;

Concept, design, writing: 36, 37;

Concept, design, meta-analysis, writing:.33, 39.

12,14 were from a PhD thesis by my postgraduate student which I conceptualised and supervised.

B. I have not submitted the work in this thesis to any University for any degree.

Signature 

George Justus Hofmeyr Date: 22 December 2012

Dedication

To my beloved wife Carol

Abstract.

In the late 1980's it became apparent that misoprostol, a prostaglandin E1 analogue tablet marketed for gastric ulcer care, could be used to stimulate contractions of a pregnant woman's uterus. The manufacturing company distanced themselves from any research or use of misoprostol during pregnancy. It therefore entered clinical use in a haphazard and uncontrolled way.

The 40 papers which constitute the scientific basis of this thesis document a research program over the last 15 years which has focused on the obstetric use of misoprostol. These include a series of studies to determine the effectiveness and appropriate dosage and route of administration in two clinical settings: labour induction; and the prevention and treatment of haemorrhage after childbirth. The main methodology has been randomized clinical trials, and systematic reviews of randomized trials, with an emphasis on safety.

In the case of labour induction, use of misoprostol even in relatively small dosages from time to time resulted in excessive contractions of the uterus, causing asphyxiation of the baby or rupture of the mother's uterus. A limiting factor was the lack of a tablet with sufficiently small dosage for safe use. The author developed a novel method of administration called 'titrated oral misoprostol solution' which allowed accurate administration of very small dosages. The papers document a series of randomized trials and systematic reviews showing that only in extremely small dosages was the safety of misoprostol similar to that of alternative prostaglandins registered for use for labour induction. The 'titrated oral misoprostol solution' method is now widely used internationally.

The papers also document development of a new methodology for organizing the systematic review of multiple interventions such as for labour induction, using a generic protocol for a series of reviews, and organizing the comparisons covered by each review by means of a hierarchical listing of the numerous interventions studied.

Regarding the use of misoprostol after childbirth, the papers document the first randomized trials to be published using misoprostol for the prevention of postpartum haemorrhage, and also the first for the treatment of postpartum haemorrhage. Evaluation of the relative benefits and risks of misoprostol, based on randomized trials and systematic reviews, led to recommendations for a lower dosage than that recommended by the majority of workers in the field.

Another original line of thought which the papers document, is the concept that whereas misoprostol reduces blood loss after childbirth, which is conventionally accepted as a proxy for a reduction in maternal deaths, effects on other organ systems might in fact increase the risk of death when used in excessive dosages. The research presented documents that 11 deaths have been recorded in women receiving misoprostol 600 micrograms or more in randomized trials, compared with 4 deaths in women receiving placebo or other uterotonics.

The thesis argues that the data presented in the papers is sufficiently compelling to justify limitation of the misoprostol dosage used after childbirth to 400 micrograms.

The thesis narrative supplements the strictly quantitative methodology of the submitted papers with discussions ranging from the thought processes, associations and serendipity which generate innovation, to political and advocacy

issues which influence the global research agenda and the interpretation and implementation of research findings.

The unifying theme of the thesis is the often underestimated potential for medical interventions to do more harm than good, because of the natural tendency of researchers and practitioners to give more attention to beneficial than to potential harmful effects of what they do.

Acknowledgements

For many years my freedom to pursue a career in clinical healthcare and research was thanks to the generosity of my wife, Carol Baker, who restricted her own career to take primary care of our children. I have the responsibility for limiting the extent to which the world has been able to benefit from her remarkable abilities.

I have been privileged to have learned from many gifted and inspiring teachers (I have also learned a great deal from some very bad teachers). I am acutely aware that the majority of my contemporaries in South Africa did not have this privilege. My commitment is to try to pass on as much of what I know as I am able to, in my lifetime.

The focus of my work has been innovation and rigorous testing of the effectiveness and risks of health interventions. In 1982 Alec Turnbull noticed my interest in the value of randomized clinical trial methods to assess the effects of interventions, and put me in touch with Iain Chalmers. The world owes a debt to Iain Chalmers for his realisation that if patients were to benefit from the evidence generated by randomized trials, a global collaborative effort was required to create a framework within which people such as me could function. This is now called the Cochrane Collaboration. Mark Starr shared this philosophy, and gave us the tools of the trade. Jini Hetherington, Sonja Henderson and their teams provided inspired organisational support.

When South Africa miraculously emerged from scientific isolation in the 1990's, I was fortunate to come into contact with a network of like-minded clinical researchers who believed in the need for collaborative research to generate robust evidence to improve the health of women and babies in low-income countries. These include Guillermo Carroli (Argentina), Pisake Lumbiganon (Thailand), Hany Abdel-Aleem (Egypt), Kassam Mahomed (Zimbabwe), Linan Cheng (China), Manorama Purwar (India), Nelly Zavaleta (Peru), Lekan Adetoro (Nigeria), Nguyen Ngoc (Vietnam), Gijs Walraven (The Gambia), Zahida Quereshi (Kenya), and Bukola Fawole (Nigeria).

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Colleagues from the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction at the Department of Reproductive Health and Research, WHO, have shown me considerable kindness and support: Metin Gülmezoglu, Oluwole Akande, Davy Chikamata, Mike Mbizvo, Catherine D'Arcangues, Paul van Look, Mario Merialdi, Lale Say, Gilda Piaggio, Heli Bathija, Ana Pilar Lazaga Betran, Mariana Widmer, and Helena von Hertzen.

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Members of our research team have maintained the levels of attention to detail and honesty on which credible research depend: Mandisa Singata, Cheryl Nikodem, Marinda Taha, Lindeka Mangesi, Nolundi Mshweshwe, Princess Jafta, Xoliswa Williams, Angel Phuti, Patience Moloi, Zukiswa Jafta, Zonke Mlokoti and Babalwa Maholwana.

Peter Cleaton Jones, as mentor for this thesis, generously shared his expertise.

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1 Introduction

After more than 30 years of confining myself to objective scientific writing (including the 40 papers which constitute the scientific basis of this DSc submission), I have decided to write this commentary from a personal, narrative and philosophical perspective. My reason is to add a dimension to the work which may provide insight into the relationship between personality and scientific discovery, and the often quirky and apparently unconnected chains of ideas which lead to innovation. It may serve to illustrate how working at the clinical coalface, particularly in an under-resourced setting, may expose one to experiences and predicaments which generate innovative ideas. I will also explore ways in which our human instincts, beliefs and natures may influence our scientific judgement, and the extent to which personal perspectives colour the global scientific debate.

Two listings of references are used in the text of this thesis. Numbers in brackets e.g.(12) refer to one of the 40 attached publications submitted as the scientific basis for the DSc degree (these are listed in sections in the thesis in which they first appear, boxed, with a brief synopsis where needed). References in the Harvard Style e.g. (Coutsoudis, Coovadia & Wilfert, 2008) are references to support a concept in the thesis. These are listed in the reference list at the end of the thesis.

A defining characteristic of my clinical and research endeavours has been an intuitive focus on the potential of health care to have unexpected and often unidentifiable harmful effects. This makes me something of an outlier in the health

profession, which is characterised by a greater sense of confidence in our collective effectiveness than is my nature.

Where did this scepticism originate?

An early experience which impressed on me the potential for the medical environment itself to have adverse effects occurred in 1977 when my wife Carol and I worked as Medical officers at Holy Cross Hospital in Eastern Pondoland in the so-called independent Transkei. One day a young woman gave birth to her first child at the hospital. A few days after birth the apparently healthy baby died. It turned out that the mother had never fed the baby. When asked why not, she explained that no-one had said she may feed the baby. This tragic event illustrates the extreme degree of disempowerment patients, particularly those from already disempowered backgrounds, experience in a clinical setting, and how dangerous this may be. In hospitals, patients become isolated from their families and dependent on hospital staff, who may or may not have the time or the insight to attend to their needs. Those who are not by nature assertive or by position in society influential are at greatest risk. An objective observer will identify many bad outcomes in our hospitals which would not have occurred had the victim been at home in the care of their family.

A second concern is the possibility of direct adverse effects of medical interventions, most of which are and will remain, unknown. A corollary of the acceptance of this concept is that no treatment, however apparently safe, should be used unless there is robust evidence that it is effective. Then at least there is

the possibility that beneficial effects will outweigh harms. This principle is central to the work outlined in this commentary.

One way in which our collective optimism and enthusiasm for medical interventions may endanger patients is by the selective use of scientific evidence. The first level at which this occurs is reliance on 'evidence' from observation of the effects of a medicine or other intervention. Most medical conditions improve over time. In many cases, improvement is promoted further by interactions such as care from an interested professional and the patient's belief that something positive is being done. Our view of the effectiveness of what we do is thus inherently biased by spontaneous recovery and effects of interactions over and above the medication.

The best method we have available to reduce this bias, is by means of the double blind, randomized clinical trial. Patients who stand to benefit from the purported cure are assigned in a random sequence to receive the medication or an identical-looking bland substance ('placebo'), in such a way that neither the patients nor the scientists know who received the placebo and who received the real thing. The outcomes in the two groups are compared, and if the treatment group do significantly better, there is some level of certainty that the treatment is effective.

Even this approach is subject to bias. Because we are dealing with variable responses and measurements, every trial is an approximation of the true result, with some degree of over- or underestimation. Thus if an intervention is

ineffective and enough trials are carried out, the overall balance of results will show no effect, but some trials will by chance show 'evidence' of a benefit. Human optimism is such that practitioners tend to choose the most optimistic trials on which to base their practice.

From the late 1970's onwards, Iain Chalmers, Murray Enkin, Adrian Grant, Marc Keirse and others began work on the Herculean task of putting into practice Archie Cochrane's recommendation that we systematically summarise the results of all known clinical trials to get to the best possible evidence of effects of interventions. Mark Starr provided the software to synthesize the results of multiple similar trials (meta-analysis).

Given my predisposition to avoiding harm from ineffective medicines, I needed no convincing about the value of this approach, and in 1983 joined what was then a minority view that evidence from systematic review of randomized trials should trump our clinical observations.

In general, the reaction to this approach from clinicians accustomed to unfettered use of their methods of personal choice was astoundingly negative, and at times, vicious. Thirty years on, there is widespread acknowledgement of the value of this approach and Iain Chalmers' vision of a worldwide collaboration of contributors from all walks of life has taken form as the Cochrane Collaboration.

Systematic reviews cannot entirely eliminate our tendency to over-estimate the effectiveness of our medical treatments. Given the fact that all trials will have some error in one or other direction, our human preference for good news dictates that scientists whose results err on the optimistic side are more likely to persist with the research and have it published, creating an inherent 'publication bias' in the results available to us in the medical literature.

Systematic reviews are the best we have, and we can improve their value by acknowledging their propensity to over-estimating effectiveness.

1.1 Interlude

On Monday 25 July, 2011, I arrived in Washington on the invitation of Mario Merialdi to participate in a WHO application for the USAID and partners 'Saving lives at birth' Grand Challenge for innovations finalists' meeting. It was an eventful 2 days. I met Jorges Odon, the Argentinian inventor of the device which had been entered in the competition, and Javier Schwartzman who had initiated clinical tests. The device was an elegant two layered plastic sleeve for assisting the birth of a baby.

In the lobby of the Fairfax Hotel, I was approached by Dr M A Quaiyum who told me that the government of Bangladesh in their 5 year health plan had approved to include misoprostol in the birth pack issued to all pregnant women in the country, to be taken after the birth. Based on my advice, they had chosen a dosage of 400

micrograms. The significant of this fleeting encounter will become apparent as we unravel the story of the obstetric use of misoprostol: innovations, evidence, controversy and global health perspectives.

1.2 Misoprostol

1.**Hofmeyr GJ,** Milos D, Nikodem VC, de Jager M. Limb reduction anomaly after failed misoprostol abortion. S Afr Med J. 1998; 88: 566-567

One day a great novel will be written about misoprostol. The story has all the elements of compelling literature. It is a story of human and scientific endeavour, of women's quest for rights, of political expediency, hidden agendas and vested interests, of conflicting philosophies and beliefs; but most of all, it is a story of life and death.

It is remarkable how long it can take the medical profession to cotton on to the blindingly obvious. This may be a function of our training. Often new ideas come from outside the health profession. Jorges Odon, the inventor of the Odon device to assist birth whom I referred to in the interlude above, is a car mechanic.

Prostaglandins are naturally-occurring hormones which have ubiquitous effects on the human body. These include smooth muscle contractility and thus the flow of

blood through blood vessels, inflammatory processes, and keeping open the ductus arteriosis, the shunt between pulmonary and systemic circulations which allows unborn babies to survive until the pulmonary circulation opens up after birth. They have an important role in human labour and birth, by softening the uterine cervix and stimulating uterine contractions.

Synthetic prostaglandins have been available for many years, and have been used for inducing labour, and for treating haemorrhage after childbirth. However, they could not be administered by mouth, and were too expensive for use in state services in low-income countries.

Misoprostol is a unique prostaglandin analogue which can be administered by mouth and was developed, registered and marketed for the treatment of stomach ulceration caused by anti-prostaglandin (anti-inflammatory) medicines. References to misoprostol appear in the medical literature from 1981, and another synthetic prostaglandin E1 analogue was reported to be effective in inducing abortion in 1980 (Nakano et al, 1980). The misoprostol package insert included a warning that it should not be taken during pregnancy as it may cause abortion. The number of years that this apparently obvious potential remained unexploited by the medical profession is astounding. The first reference to the use of misoprostol in pregnancy that I have found in the medical literature is a 1987 paper documenting abortion as a side-effect of misoprostol (Rabe et al, 1987). It is said that the first medical use of misoprostol in pregnancy was not by the

medical profession, but by women in Brazil who took the warning in the package insert seriously.

The news spread like wildfire. At last health workers (and the public) in low-income countries had their hands on an affordable medicine which gave them control over the initiation of labour. The sense of excitement and power was intoxicating. When one considers the mega-sums of advertising funds usually spent to launch a new product, that fact that the use of misoprostol spread exponentially (in spite of active discouragement from the manufacturers) is a measure of the avidity of health workers and women for such a product.

The manufacturer and patent holder publicly distanced themselves from the use of, or research into the use of misoprostol during pregnancy. There were even rumours that the medicine might be taken off the market. I remember discussions with colleagues about stockpiling misoprostol in deep freezers against such an eventuality. Such was our enthusiasm to have and retain access to this product.

This was a very dangerous situation. Across the globe, health workers and the public were experimenting with a drug for indications for which there were no guidelines regarding dosage or safety, because it had not gone through the normal regulatory process which includes strict and systematic scientific testing for effectiveness, safety and appropriate dosage.

As it turned out, use of misoprostol to terminate early pregnancy was extremely safe across a wide range of doses, up to 800 micrograms by mouth or vaginally (though failed abortion occasionally resulted in the birth of babies with missing limbs) (1). Use of very much smaller dosages to induce labour in late pregnancy sometimes produced disastrous results.

1.3 Misoprostol for inducing labour

2. Fawcus S, Mbombo N, **Hofmeyr GJ**. Trends in maternal deaths from Obstetric Haemorrhage in South Africa 2008 – 2010. Obstetrics and Gynaecology Forum 2012: 9-17

Tablets are in general manufactured with an amount of active ingredient to provide the correct adult dose with one or two tablets. Misoprostol was marketed as 200 microgram (mcg) tablets. Health workers started using one (or two) tablets by various routes to induce labour, and they worked wonderfully well. However, as with other prostaglandin preparations, the sensitivity of women's uteri in late pregnancy to misoprostol is exceptionally variable. Some women would not respond at all. Most would respond with good results, but every now and then, this dose would work too well, and the woman's uterus would contract with such force that it would burst, or rupture, and one of three things would happen: the baby might be born precipitously, and the bleeding from the rent in the uterus might be little enough to go undiagnosed, and the woman recover uneventfully; or the baby might be expelled from the torn uterus into the mother's abdominal cavity, and its lifeless body be retrieved by an abdominal operation; or the mother might die from

haemorrhage with or without the baby being born, and with or without anyone realising that the uterus had ruptured.

Since 1998 South Africa has had a national system of confidential enquiries into maternal deaths of which we can be proud, thanks to the dedicated work of a team led by Prof Jack Moodley. Between the first report for 1998 and the second report for 1999 to 2001, there were only two causes of maternal death which increased significantly: infections (mainly HIV), and ruptured uterus. Though misoprostol was not always documented as a contributory cause, there is little doubt it was responsible for more cases than were recorded, for reasons which will appear below.

The tragedy of this situation is that, had the use of misoprostol for labour induction followed the normal course of drug development, testing and marketing, the number of women with ruptured uterus would have been limited to one or two centres where the drug was being tested, and a safe dose would have been found before the drug became generally available, and supplied together with advice on the appropriate dosage.

Instead, the drug was 'tested' unofficially by countless individual health workers worldwide, and the lesson of the risk of uterine rupture was learned over and over to the cost of countless women. Despite recent concerted efforts by global organizations to distribute guidelines for the safe use of misoprostol, this lesson continues to be repeated to this day, because the dosage information is not part of

the drug packaging. Advice on dosage distributed by global organizations is unpersuasive to doctors who have used their own preferred dosage for years very successfully, and without any identified accidents.

One incident impressed on me the risk of uterine rupture even with a very small dose of misoprostol. Some years ago, when we were still using misoprostol administered by the vaginal route for labour induction, I was passing a young woman in the labour ward who was lying absolutely quietly, impassive and uncomplaining. I was about to pass by when I noticed a bead of perspiration on her forehead and a look in her eye which prompted me to ask her if she was alright. She said she was in excruciating pain. I examined her abdomen which was tender, and felt the baby lying outside the uterus, with no audible heartbeat. At operation we retrieved her stillborn baby and confirmed a rupture extending the whole length of one side of her uterus. She had received only one dose of one eighth of a misoprostol tablet vaginally. I shudder to think how many times this has happened worldwide, with the use of much larger doses over many years.

I must hasten to reassure colleagues who may be shocked at my apparent use of 'anecdotal' reporting (the bane of my scientific career), that the irony is intentional.

This incident and those I will report below are very emotive, but should not be confused with evidence. They are selected cases with bad outcomes. They don't tell us how many good outcomes there were, nor whether the bad outcomes would have been more or less frequent had another medication been used or no

medication at all. Penicillin and immunizations cause many deaths due to hypersensitivity, but we assume that the deaths prevented outnumber those caused.

On another occasion in our hospital service, a 25-year-old mother with two previous normal births had labour induced with low-dose misoprostol. After the birth of a live baby she developed postpartum haemorrhage, and died during resuscitation attempts. Had a post-mortem examination not been performed, the diagnosis of ruptured uterus would have been missed.

We stopped using misoprostol administered by the vaginal route for labour induction, but even low dose oral administration is not without risk. One evening recently I was called to the labour ward. A young women with two previous pregnancy losses had had labour induced with low-dose misoprostol. All had seemed fine when suddenly the baby's heartbeat had disappeared and her abdomen had become tense and tender. With these typical signs, placental abruption (bleeding between the placenta and the wall of the uterus) had been diagnosed. I was called in to confirm with ultrasound that the baby's heartbeat was indeed no longer present, and was distracted from further clinical examination by the need to console the distraught parents. I accepted the diagnosis of placental abruption, and expected rapid progress to delivery to occur. I was phoned in the early hours of the morning by the medical officer who reported that the baby was not yet born. In that instant I realised that we had missed the

diagnosis of ruptured uterus. The operative findings were very similar to the case above, a torn uterus and the dead baby lying among the abdominal organs.

I mention these cases as they are very unusual with such a low dose of misoprostol – the vast majority of cases of uterine rupture are due to excessive dosages. But such is the variability in uterine sensitivity to stimulants that in exceptional cases even a very low dose may be too much.

The most recent confidential enquiry into maternal deaths in South Africa (2008 to 2010) again emphasizes the abnormally high rate of rupture of unscarred uteri (2). The paper cited was largely the work of Sue Fawcus. The statistically significant increased incidence of ruptured uterus referred to above in 1999 to 2001 compared with the previous report, has been sustained. The deaths from haemorrhage in institutions numbered 25 per 100 000 live births (slightly up from 19 in the previous 3 years). Of 688 such deaths, 108 were identified as due to ruptured uterus, including 61 women with no previous caesarean section. This may be an underestimate as post-mortem examinations were seldom undertaken and in 128 deaths due to haemorrhage no cause was reported. Inappropriate use of misoprostol, including doses as high as 400 mcg, was highlighted as a contributory factor to these alarmingly high figures. In one example cited in the report, a 40-year-old mother of 4 carrying a dead baby received misoprostol 100 mcg vaginally at 17h00. At 02h00 she was found dead, with a ruptured uterus.

Recently (during 2012) a young woman was referred to us from a peripheral hospital. She had developed jaundice and her baby had died. Labour had been induced with misoprostol 200mcg vaginally. She delivered very quickly, followed by a postpartum haemorrhage. Shortly after reaching our hospital she died. Postmortem examination confirmed that the cause for the haemorrhage was a torn uterine cervix. A recent randomized trial has confirmed that the risk of postpartum complications such as cervical and vaginal tears is more common when labour is induced with 50 than with 25mcg misoprostol vaginally (Loto et al, 2012).

The reason for the continued use of these high doses in women with an unborn dead baby is tragically simple. The most common adverse effect of misoprostol is excessive uterine contractions causing asphyxiation of the baby. When the baby is dead, health workers assume that it is no longer necessary to use a small dosage.

The unusually high frequency of uterine ruptures continues unabated.

1.4 Concealing the evidence

The second factor which makes this situation even more perilous for women relates to the 'off-label' use of medication, the use for an indication not covered by the conditions for which it has been licensed. This is a common and necessary practice. Many life-saving drugs are used for conditions for which they have not been registered. The catch is that in the event of an adverse event, the responsibility lies with the practitioner rather than with the supplier. Health

workers sometimes use misoprostol for labour induction without recording this in the patient record, in order to avoid possible legal repercussions. Over the years, I and my colleagues have encountered many women whose labour has been induced with misoprostol without any record in their notes, and sometimes without their knowledge. All we find are the characteristic hexagonal white tablets which have been inserted during a vaginal examination.

On one occasion, a 25-year-old mother with one previous caesarean section, carrying a dead baby at 24 weeks of pregnancy, came to our hospital service with abdominal pain. We found 6 misoprostol tablets (1200 mcg) in her vagina, which she said a private doctor had inserted. She rapidly gave birth to an 840 gram stillborn baby, and fortunately was well thereafter.

One unusual case of a different nature that I encountered was of a young woman in early pregnancy who presented with a threatening miscarriage. On examination I found several misoprostol tablets in her vagina of which she had been unaware. It turned out that her estranged boyfriend had feigned reconciliation, and during sexual intercourse had surreptitiously inserted the misoprostol to induce an abortion.

In passing, the relatively low cost of misoprostol for labour induction is an aberration related to the fact that it was not marketed for this purpose. Had it been marketed for labour induction, it would probably have been marketed at a price similar to other labour induction prostaglandins, because each patient uses only a

small amount. Because it was marketed for long-term use for anti-prostaglandin-induced gastric ulceration, it had to be priced at a much lower level. I think that is how The Market works. (To be fair, the development costs to the company and the risk costs for use in pregnancy would have been higher as well).

This detailed discussion of the unusual circumstances surrounding the introduction of misoprostol to obstetric practice has been necessary to introduce the first theme of this dissertation: Labour induction with misoprostol: finding the right dose and route.

2. Labour induction with misoprostol: finding the right dose and route

3. **Hofmeyr GJ.** Misoprostol in obstetrics and gynaecology – unregistered, dangerous and essential. S Afr Med J 1998; 88: 535-536

Editorial outlining the dangers of using misoprostol for labour induction prior to establishment of safe regimens, as well as its use for postpartum haemorrhage prior to establishing evidence of effectiveness and safety.

Once the potential of misoprostol for labour induction was recognised, the field became something of a gold rush. The availability of an inexpensive and powerful prostaglandin was intoxicating to researchers and practitioners alike. In a 1998 editorial I cautioned against the use of misoprostol in clinical practice prior to the establishment of safe regimens (3).

The vast majority of reports followed the paradigm which had been successful for other prostaglandin products: a fixed, infrequent dose administered vaginally. The concept of administering the drug close to the cervix with the expectation of a direct effect on cervical ripening was intuitively an attractive one.

A minority of researchers chose the oral route – at either 4- or 6-hourly intervals.

2.1 A new paradigm

4. **Hofmeyr GJ**, Matonhodze BB, Alfirevic Z, Campbell E, de Jager M, Nikodem C. Titrated oral misoprostol solution--a new method of labour induction. S Afr Med J. 2000; 91: 775-6.

We pilot tested our novel, low-dose method in 25 women with various indications for induction of labour. Eighteen women (72%) delivered vaginally within 32

hours of induction and two women developed uterine hyperstimulation. The caesarean section rate was 20%.

I chose to approach the problem from a paradigm more closely aligned to that of oxytocin, in which a continuous intravenous infusion is used, starting at a low dose and titrating against the woman's individual response. Misoprostol is not available in intravenous form, but given its rapid absorption orally and relatively short half-life, I introduced the concept of using small, frequent (2-hourly) oral doses, and titrating (increasing or reducing) the dose according to the uterine contraction and labour progress response.

A major barrier to administering a small dose was that misoprostol was marketed as a 200 microgram tablet. It was common practice to break the tablet into 4 or 8 fragments, but it was impossible to be sure how much of the active ingredient was in the fragment administered.

I developed the idea of dissolving the 200microgram tablet in 200ml of water, shaking well, and measuring out an appropriate volume of the solution (eg 25ml = 25 micrograms), administered orally. I called this approach "titrated oral misoprostol solution", and it has stood the test of time, being used in many countries today (4).

2.2 Testing titrated oral misoprostol solution

5. **Hofmeyr GJ**, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. Br J Obstet Gynaecol. 2001; 108: 952-959.
Women due for labour induction were randomly allocated: 346 to titrated oral

misoprostol solution and 349 to vaginal dinoprostone. There were no significant differences in substantive outcomes. Vaginal delivery within 24 hours was not achieved in 38% of women in the oral misoprostol group and 36% in the vaginal dinoprostone group (RR 1.08; 95% CI 0.89-1.31). The caesarean section rates were 16% and 20%, respectively (RR 0.80; 95% CI 0.58-1.11). Hyperstimulation with fetal heart rate changes occurred in 4% and 3% respectively (RR 1.32, 95% CI 0.59-2.98). There were no differences in neonatal outcome between the two groups. This new approach to oral misoprostol administration was successful in minimising the risk of uterine hyperstimulation, which has been a feature of misoprostol use for induction of labour.

The annual 'Priorities in Perinatal Care in Southern Africa' conferences were initiated by Alan Rothberg in the 1980's, and are a unique forum for interaction between obstetricians, midwives, neonatologists and neonatal nurses as well as other professionals with an interest in the wellbeing of childbearing women and their babies in poor countries. At one such meeting in the Drakensberg, I discussed with Zarko Alfirevic setting up a multicentre trial between Coronation Hospital and Liverpool Womens' Hospital. For our initial work I had chosen a dosage of 20 micrograms, because it could easily be scaled down to 10 or even 5 micrograms. Zarko argued that 25 micrograms would 'sell' better as it fitted with the 200/100/50/25 microgram dosages which were familiar to most practitioners. We agreed on his dosage, and I'm sure he was right. The trial which followed confirmed our earlier work, and the effectiveness of the titrated oral misoprostol solution approach (5).

2.3 Order from chaos

6. **Hofmeyr GJ**, Alfirevic Z, Kelly T, Kavanagh J, Thomas J, Brocklehurst P, Neilson JP. Methods for cervical ripening and labour induction in late pregnancy: generic protocol (Protocol for a Cochrane Review). In: The Cochrane Library, 2000. Oxford: Update Software

The first generic protocol in the Cochrane Library – outlining a systematic strategy for reviewing data from multiple trials of labour induction, and serving as a template for the series of reviews.

Trials of misoprostol for labour induction proliferated at a remarkable rate. How were we to make sense of a multitude of trial results reported globally, using various dosages, different time intervals, different routes of administration and different comparisons?

As mentioned in the introduction, Iain Chalmers, Mark Starr and colleagues had given us the tools to synthesize the results of multiple similar randomized trials by meta-analysis. In the field of labour induction we were dealing with not only the multiplicity of variables involving misoprostol, but more than 20 methods of labour induction in a variety of clinical situations. A system was needed to give order to the task of summarising this complex mass of information.

I spent some time with Zarko Alfirevic in Liverpool to develop a strategy, and came up with two new concepts in the field of systematic reviews.

The first was what we called a 'generic' protocol which served as a template for a series of reviews of different methods of labour induction using the same methods

and outcome measures. This would provide uniformity, and greatly speed up the process of synthesizing the huge volume of experimental work (6).

Because any of the multiple methods of labour induction might be compared in a randomized trial with any other, the comparison of method A with method B would be duplicated in the reviews both of method A and of method B. To eliminate this duplication, we came up with a simple system of ranking all the methods from number 1 to number 25, and for each individual review comparing the particular method only with methods above it on the list. We allocated placebo number 1 so that all reviews would include a placebo comparison, and then ranked the methods roughly from the most conventional and well-established to the least conventional and recent. Thus in general, reviews of newer methods would include comparisons with more established 'gold standards'.

These innovations have proved very useful in bringing order to what would have been a chaotic multiplicity of reviews of labour induction, and have been adopted for other series of reviews involving multiple methods. The huge workload of completing and updating all these reviews was shared between a team of collaborators, with particular support from the UK National Institute for Clinical Excellence (NICE).

2.4 Systematic reviews and dosage

7. **Hofmeyr GJ**, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev. 2010; 10:CD000941

First published in 1998 and updated regularly since then.

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

9. **Hofmeyr GJ**. Induction of labour with misoprostol. Curr Opin Obstet Gynecol. 2001; 13: 577-81

10. **Hofmeyr GJ**, Gulmezoglu AM. 25µg misoprostol is less effective than 50 µg for induction of labour, but has lower risks – meta-analysis (commentary). Evidence-based Obstetrics and Gynaecology 2002; 4: 211-212.
Commentary on a North American meta-analysis showing greater safety with the lower dose.

11. **Hofmeyr GJ**. Induction of labour with an unfavourable cervix. Best Practice & Research Clinical Obstetrics & Gynaecology 2003; 17: 777-794

7 – 11: Series of systematic reviews progressively updating the world literature to provide up to date guidance for clinicians and policy-makers.

The value of Cochrane systematic reviews in general, and of our methodical approach to reviews of labour induction in particular, is well illustrated by the efficiency with which continuously updated systematic reviews were able to bring together results from a torrent of uncoordinated trials worldwide and produce rational guidance within a short time-frame (7-11).

However, the value of systematic reviews was not universally acknowledged.

The question of dosage became something of an international football.

On 7-8 May 2001 a global meeting was called at the Population Council headquarters in New York entitled Misoprostol: An emerging technology for women's health. At the time, the American College of Obstetricians and

Gynecologists recommended a dose of 50 micrograms of misoprostol vaginally, 4-hourly, to induce labour. Metin Gülmezoglu and I were invited to present the results of the Cochrane review which showed that 25 micrograms was a safer and almost as effective dose. Some North American delegates were totally dismissive of our data, arguing that their personal experience of large numbers of labour inductions with the 50 mcg dose convinced them of the safety of that dose. The interactions highlighted the tensions which exist between an evidence-based approach and that guided by clinical experience. A contemporary review concluded that "there is strong and consistent evidence to support the use of misoprostol for induction in the third trimester" (Goldberg Greenberg & Darney, 2001). We left New York frustrated, but fairly certain that sooner or later proponents of the 50mcg dose would recognise the greater safety of the smaller dose and the ACOG would amend the guidelines, which has happened (ACOG, 2009).

2.5 Which route for labour induction?

12. Matonhodze BB, **Hofmeyr GJ**, Levin J. Labour induction at term--a randomised trial comparing Foley catheter plus titrated oral misoprostol solution, titrated oral misoprostol solution alone, and dinoprostone. S Afr Med J. 2003; 93: 375-379.

Women due for labour induction were randomly allocated to extra-amniotic Foley catheter followed by titrated oral misoprostol solution, titrated oral misoprostol solution alone, or vaginal dinoprostone. Misoprostol was dissolved in water and 20 - 40 g was given 2-hourly. In the Foley catheter group, misoprostol was required in all but 1 case. Failure to deliver vaginally within 24 hours was similar

for the three groups (79/174 v. 70/176 v. 70/176 respectively). Labour augmentation, caesarean section and instrumental delivery were used somewhat more frequently in the Foley/misoprostol group than in the misoprostol alone group, but these differences were not statistically significant. More analgesia was used in the Foley catheter/misoprostol group than in the misoprostol group (64/172 v. 46/175). Side effects and neonatal complications were similar for the three groups. Use of extra-amniotic Foley catheter placement showed no measurable benefits over the use of oral misoprostol alone, or vaginal dinoprostone.

The next counter-intuitive evidence which our system of ongoing systematic review produced was the fact that although clinicians intuitively preferred the vaginal route of administration, and the great majority of trials investigated the vaginal route, a steady trickle of trials using the oral route, including ours, over time produced cumulative evidence to show that the oral route was as effective as the vaginal route, with less uterine hyperstimulation.

There was yet another turn of the wheel which emanated from the systematic review process, and brought us full circle in our search for a safe, affordable method of labour induction. Before prostaglandins were available, we had used a balloon catheter (such as a Foley catheter) inserted through the uterine cervix and held under tension, to induce labour in the presence of an unfavourable cervix. With the advent of expensive vaginal prostaglandin preparations, actively promoted by the manufacturers, these were assumed to be a more sophisticated and superior option, and the balloon catheter assumed the position of a second best approach when prostaglandins were unaffordable. With the advent of

misoprostol as an affordable prostaglandin, the balloon catheter was considered more or less obsolete. I had encouraged one of the PhD students I supervised, Dr Baron Matonhoze, to include the Foley catheter as one of three arms in a randomized trial of labour induction, and the results had in fact been disappointing (12). In retrospect, it may be that we did not apply sufficient traction to the Foley catheter.

However, the occasional trial of the balloon catheter continued to appear, and in time the relevant Cochrane systematic review accumulated sufficient evidence to show that the balloon catheter was in fact safer than either purpose-designed prostaglandin preparations or misoprostol.

What can account for the fact that the prostaglandin preparations (mainly dinoprostone) developed for labour induction comprehensively replaced an existing method (the balloon catheter) which subsequently turned out to be the safer method? The answer is simply: advertising. Pharmaceutical companies have an extremely important role to play in healthcare, as they have the capacity to develop and distribute new drugs and devices which contribute to on-going improvements in health. However, they are businesses, not charitable institutions. They would not spend huge amounts of their hard-earned profits on advertising if they did not have pretty solid evidence that advertising had a major effect on the use of drugs by doctors. Thus prostaglandins replaced the balloon catheter because they were actively promoted by their manufacturers, whereas the balloon catheter was not promoted for labour induction at all, as it was marketed for entirely different purposes. There is also the greater simplicity and comfort of the gel preparation, and the innate preference of professionals for a pharmacological medication over a simple, mechanical method. The uptake of misoprostol was

unusual in that it was driven by the enthusiasm of health providers, lobby groups and women rather than advertising efforts of the manufacturer.

The method of titrated oral misoprostol solution for labour induction that I devised in the 1990's has been incorporated into the South African National Essential Drugs List Committee guidelines, and is used in many countries across the globe. With the evolving evidence from the systematic reviews we have adjusted our own practice to use the balloon catheter as a first line method of labour induction, reserving titrated oral misoprostol solution for cases where rapid induction is critical, and those where the balloon catheter method is unsuccessful.

2.6 Misoprostol and meconium

13. **Mitri F**, Hofmeyr G J & Van Gelderen C J. Meconium during labour: self-medication and other associations. S. Afr. Med. J 1987; 71: 431-433.
In an observational study we found a trend to increased use of 'isihlambezo' in women with meconium-stained amniotic fluid.

14. Matonhodze BB, Katsoulis LC, **Hofmeyr GJ**. Labor induction and meconium: in vitro effects of oxytocin, dinoprostone and misoprostol on rat ileum relative to myometrium. J Perinat Med. 2002; 30: 405-10.
The contractile activity of dinoprostone, misoprostol and oxytocin was tested on isolated rat uterus and ileum mounted in Tyrode's solution. Uterine contractions were stimulated by all three drugs, whereas ileal contractions were stimulated only by dinoprostone and misoprostol.

Our series of systematic reviews was also the first to identify robust evidence that use of misoprostol was associated with an increase in meconium staining of the amniotic fluid. One of the many marvellous features of the physiology of the unborn baby is that passage of meconium (stool) is normally suppressed until after the birth. Stool passage before birth can be a life-threatening complication as the meconium may be inhaled by the baby causing chemical inflammation of the lungs (meconium aspiration syndrome), which carries a high mortality.

In the 1980's, we had been struck by the frequency of meconium staining of the amniotic fluid at Baragwanath Hospital. I encouraged one of our registrars, Dr Faouzi Mitri, to conduct an observational study to see whether there was a relationship between herbal and other remedies taken by women in Soweto, and meconium passage by the unborn baby. We found a significant association of meconium staining with ingestion of castor oil, and a trend to increased meconium passage with ishlambezo (13), a herbal remedy widely used in Southern Africa. We went on to show, with our colleagues from the pharmacology department, that isihlambezo contained plant alkaloids which cause contraction of both uterine and bowel smooth muscle (Katsoulis, Veale & Hofmeyr, 2000). Prior to this, it was thought that meconium passage was usually a baby's response to stress. We developed the hypothesis that in addition, meconium passage might be caused by smooth muscle stimulants crossing the placenta and directly stimulating the baby's bowel. This was of importance because it meant that meconium passage might not necessarily be an indication of distress, and interventions such as caesarean section might not always be appropriate. This did not mean that meconium could be ignored. Whatever the cause of the meconium passage, the risk of it being breathed in by the baby, particularly at the time of birth, remains.

In another facet of Dr Matonhodze's PhD work referred to previously, we repeated these in vitro studies, and found a similarity between misoprostol and ishlambezo: whereas oxytocin (the human hormone associated with uterine contractions in labour) stimulated rat uterine muscle but not bowel, misoprostol, like isihlambezo, stimulated both the uterus and the bowel (14). We put forward the hypothesis that misoprostol might cause meconium passage by crossing the placenta and directly stimulating the baby's bowel.

Before closing this chapter, I would like to pay tribute to the optimism, tenacity and perseverance against all odds of the PhD student, Baron Matonhodze, to whose work I referred above. During the clinical work at Coronation Hospital and the laboratory work in the department of Pharmacology, he underwent major surgery and radiation therapy for cancer. In January 2001 he was due to come down to East London to complete the PhD write-up when he sustained a major head injury in a motor vehicle accident. Recovery took more than a year, but he persisted, and graduated in 2005.

Our and others' evidence of the need to use very low dosages of misoprostol for labour induction has been widely acknowledged, but as illustrated above, the use of higher doses continues to inflate the maternal mortality rates in South Africa. The situation is certainly improving, but we need to reflect on whether the benefits of misoprostol used in appropriate dosage will ever outweigh the cumulative cost in loss of mothers' and babies' lives from over dosage?

2.7 Misoprostol and preterm birth

One January, we noticed that our high-care nursery was more crowded than usual. One of our nurses remarked, as if it were a matter of common knowledge, that this was because the new school year was about to start, and schoolgirls would not be allowed to enrol if they were pregnant.

In accordance with South African law we provide a free pregnancy termination service on request up to 13 weeks, and for medical or psycho-social reasons (including poverty), up to 20 weeks. This includes just about everyone. But not after 20 weeks. This is where entrepreneurs fill the gap.

Our patients tell us that the way it works in East London is that one calls a cellphone number found on one of many posters which adorn the street poles in Oxford street, advertising 'safe, painless abortion'. One is met by the practitioner who provides several misoprostol tablets for about R800 (about 100 US dollars), a plastic bag to put the baby into when born, and a number to call for the bag to be collected and disposed of. No examination or estimation of the duration of the pregnancy takes place.

Others simply sell misoprostol tablets as a business. One such businesswoman said in a newspaper interview that she buys 60 misoprostol tablets a week for R350 from pharmacy staff who steal them, and sells them at R200 for 4. The business model is nothing of not entrepreneurial.

Occasionally women using these parallel services arrive at the hospital in apparently spontaneous preterm labour or having given birth to a small baby at home. Unknowingly, we do everything we can to reverse the process. We give medication to suppress the contractions of the uterus; we give steroids to mature

the baby's lungs; after the birth, we resuscitate the baby, admit him or her to our already overcrowded high care unit; administer surfactant, continuous positive airways pressure, and all the care our limited resources allow us to, in an attempt to save the baby's life. Many of the babies are very small indeed, and don't survive. They appear on our records as neonatal deaths from spontaneous preterm birth, and contribute to our ever diminishing chance of achieving the Millennium Development Goals' objective to reduce deaths of babies and children.

Generally, fear of repercussions would prevent women from confiding in us that the preterm labour was not spontaneous, but now and then they do.

To try to get an idea of how often this was happening, I asked Sibongile Mandondo, one of our registrars in training, to conduct an observational study. Over 6 months, she came to know of 18 women who had taken misoprostol to induce early labour. The dosages ranged from 400 to 1200mcg. The gestational ages ranged from 24 to 39 weeks. Eleven babies were born alive, and one survived. One baby remained unborn, the mother presenting because of fear that the baby may have been harmed by the failed attempt. One mother with previous caesarean section sustained a ruptured uterus which we repaired, and one developed shock from severe infection.

This is likely to be the tip of the iceberg.

I mention this issue not to be in any way judgemental, but to illustrate the complexity of providing care for women in an environment which precludes openness in our interactions, and of assessing the quality of perinatal care against an unmeasurable background of purposeful perinatal deaths.

3. Misoprostol after childbirth

3.1 How do new ideas come about?

It is remarkable, given the cumulative extent of global intelligence, how long it sometimes takes for new ideas to surface, which in retrospect appear obvious. It seems obvious now that the most stable way to pull a suitcase on wheels is on its side, to provide a wide wheelbase. For many years, wheels were placed at the bottom with the suitcase in the upright carrying position, with a wheelbase so narrow that the smallest bump would unbalance it. Before the advent of wheels on suitcases, suitcases had been carried in an upright position, and the first people who put wheels on suitcases worked within this entrenched paradigm. Who was the first person to think of tipping the case on its side to position the wheels more widely apart? And why did it take so long?

My observation is that new ideas are often serendipitous, the results of apparently unrelated trains of thought, and often occur to someone outside the field of study (those in the field are too locked into the prevailing thought paradigms).

For myself, when I am unable to solve a problem, I need to dissociate my thoughts from the conventional paradigm by going running. More often than not, after several kilometres when I seem to be thinking about nothing in particular, the solution will pop up for no apparent reason.

Haemorrhage after childbirth (postpartum haemorrhage) is one of the main causes of maternal deaths, particularly in low-resource settings. For decades it has been known that drugs which cause contraction of the uterus (such as ergometrine, oxytocin and prostaglandins), reduce the bleeding. Today, the notion that misoprostol should be an ideal drug for preventing and treating postpartum

haemorrhage seems obvious, and it has become the focus of global efforts to reduce maternal deaths from postpartum haemorrhage in low-resource settings.

Misoprostol has been known to be an orally active prostaglandin analogue for decades, and was reported to be a powerful stimulant of the pregnant uterus as early as 1988 (Mariani Neto Delbin & do Val Junior, 1988). The thought of using misoprostol for preventing postpartum haemorrhage occurred to me only in 1995, and I can find no record or mention of its use for this purpose before this time. I first discussed the idea with colleagues from London at the 27th British Congress of Obstetrics and Gynaecology in Dublin in July 1995. The sequence of thought processes which gave rise to the idea are interesting to analyze.

I have outlined above our work on the possible relationship between the use of the herbal remedy isihlambezo and passage of meconium by the unborn baby. By wrestling with the problem of how to discourage the use of isihlambezo during pregnancy without being disrespectful of a cultural practice, I came up with the idea of encouraging women to use isihlambezo after, rather than before the birth. This would avoid the risks to the baby, and the stimulant effect on uterine muscle might help to reduce postpartum haemorrhage. I think it was this train of thought which resurfaced years later as the idea to use misoprostol after childbirth. As discussed in the chapter on labour induction above, there are many similarities between isihlambezo and misoprostol.

As is often the case, the idea of using misoprostol for preventing postpartum haemorrhage probably occurred to several people independently around the same time. The first publication I can find was a report of cases published in May 1996 (el-Refaey, 1996).

3.2 The concept

There are in our lives moments of intense emotion, positive or negative, which are burned in our consciousness and remain with us forever. I remember as if it were yesterday the sense of excitement when the thought first occurred to me that misoprostol might be the global answer to the scourge of postpartum haemorrhage. For someone who had committed years of work to seeking ways to reduce maternal deaths globally, it was like catching a glimpse of the Holy Grail. Misoprostol had all the qualities we had been searching for. It was inexpensive, a powerful stimulant of uterine muscle, and most importantly, whereas other uterine stimulants such as oxytocin or ergometrine were dependent on a health provider for administration by injection, it could be taken by mouth. Given the fact that a large proportion of women globally have no access to skilled attendance during childbirth, the potential to supply these tablets to women to take themselves after the birth of the baby opened a whole new paradigm for the elimination of unnecessary deaths from postpartum haemorrhage.

3.3 The testing: a new route of administration

15. **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: 971-975.

Women in labour were randomly allocated to receive either misoprostol 400 mcg or placebo after the birth. A pilot study in 70 women using a novel route of administration, the buccal route, found no difference in haemorrhage. Thus for

the main trial, the oral route was used. Conventional oxytocics were given immediately if blood loss was thought to be more than usual. Measured blood loss > or = 1000 ml occurred in 15/250 (6%) after misoprostol and 23/250 (9%) after placebo (relative risk 0.65; 95% confidence interval 0.35-1.22). The difference may have been reduced by the greater use of conventional oxytocics in the placebo group, which was statistically significant for intravenous oxytocin infusion (2.8% vs 8.4%, relative risk 0.33, 95% confidence interval 0.14-0.77). Shivering was more common in the misoprostol group (19% vs 5%, relative risk 3.69; 95% confidence interval 2.05-6.64).

16. **Hofmeyr GJ**, Gülmezoglu AM. Misoprostol for the prevention and treatment of postpartum haemorrhage. Best Pract Res Clin Obstet Gynaecol. 2008; 22: 1025-41.

A review of pharmacokinetic, physiological and clinical research to determine the effectiveness and risks, and optimal dosage and routes of administration of misoprostol after childbirth.

All that was needed was proof that misoprostol was effective for reducing postpartum haemorrhage in the clinical setting, which seemed a formality. The drug was in every way so perfect for the purpose. We set out to confirm effectiveness scientifically in the appropriate way: by conducting a double blind, placebo-controlled randomized clinical trial (15). After receiving ethical approval, we started counselling pregnant women about the trial, and to those who volunteered to participate we gave two tablets which might be misoprostol or placebo to take after birth. Because of the need for rapid action, we introduced a novel method of administering the misoprostol buccally, on the assumption that

absorption from the buccal/sublingual mucosa would be more rapid than from the stomach. To assess whether this novel method was effective we conducted a randomized pilot study of just 70 cases. We found no difference in the blood loss between misoprostol and placebo. So sure were we that misoprostol would be highly effective, that we assumed that the lack of effect was due to inadequate absorption from the buccal route, possibly due to lack of an acid environment to convert misoprostol to the acive metabolite, misoprostol acid, and we reverted to the oral route in our ongoing randomized trial. Ironically, our subsequent review of pharmacokinetic, physiological and clinical studies (16) showed excellent absorption from the buccal/sublingual route, and it has become a widely used method.

Though we were the first to report use of this route of administration, we made the wrong inference because of our excessive enthusiasm for and belief in the effectiveness of misoprostol. The next report of the use of sublingual misoprostol following our 1998 publication was in November 2001 (Tang & Ho, 2001).

3.4 The poor man's placebos

Because the company marketing misoprostol had distanced themselves from any research on misoprostol during pregnancy (or even after pregnancy), we were unable to obtain identical placebos. We improvised a method in which misoprostol or placebo tablets of similar size but not identical in appearance were concealed in an opaque test tube. The woman was asked to open the tube and tip the tablets directly into her mouth without them being seen. This rather simplistic innovation, though clearly less reliable as a form of blinding, worked very well in practice.

3.5 Measuring blood loss

Most previous trials of methods of preventing postpartum haemorrhage had used the traditional method of estimating blood loss after the birth. This is of course an extremely inaccurate method (often under-estimating by as much as 50%), and subject to considerable bias. We decided to measure the blood loss, and came up with a novel method of slipping a low-profile plastic 'fracture bedpan' (used by orthopaedic surgeons to slip under the buttocks of immobilised orthopaedic patients) under the woman's buttocks after the birth. It worked unexpectedly well. It was comfortable for the woman, very efficient at collecting all the blood loss, and the nursing staff were delighted not to be dealing with blood-soaked bed linen.

3.6 The results

17. **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. SAMJ 2001; 91: 432-435; S A J Obstet Gynaecol 2001; 7: 41-43.
Women in labour were randomly allocated to receive either misoprostol 600 mcg or placebo orally after birth. Conventional oxytocics were given immediately if blood loss was thought to be more than usual. Misoprostol use was associated with more shivering (44% versus 11%, relative risk (RR) 4.03, 95% confidence irlterval (CI) 2.85 - 5.70) and pyrexia ~ 37.8°C (38% v. 6%, RR 6.23, CI 3.89 - 9.97). There was no difference in blood loss > 1 000 ml. Possible effects on blood loss may have been obscured by the lesser use of additional oxytocics in the misoprostol group (14% v. 18%, RR 0.78, CI 0.54 - 1.13).

We randomly compared misoprostol 400mcg after birth with placebo (15). The trial showed a trend to reduced haemorrhage with misoprostol, but nothing like the impressive effect we had expected. This was the first published randomized trial of oral misoprostol used in the third stage of labour, and also the first to prove an association of misoprostol with shivering. We realised then that we would need to balance the beneficial effects of misoprostol with possible adverse effects.

We subsequently compared misoprostol 600 micrograms with placebo (17). We recruited only 600 women, again expecting misoprostol to be very much more effective than placebo. The result was a resounding disappointment. There was no significant reduction in blood loss with misoprostol. There were very high rates of shivering and pyrexia.

3.7 Another new route of administration

18. Bamigboye A, Merrell DA, Mitchel R, **Hofmeyr GJ**. Randomised comparison of misoprostol with syntometrine for management of third stage of labor. Acta Obstet Gynecol Scand 1998; 77: 178-182

Low risk women in labor were randomly allocated to receive either misoprostol 400 mcg rectally or Syntometrine 1 ampuole intramuscularly. Duration of third stage of labor, estimated blood loss postpartum and hemoglobin estimation post-partum were all similar. Postpartum diastolic hypertension was more common in the Syntometrine group. No other apparent side effect was noted in either group.

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

179: 1043-1046.

Women were randomly allocated to receive 400 mcg misoprostol or nonidentical placebo rectally after birth. Any excessive bleeding was actively managed with conventional oxytocic agents. Blood loss was measured directly. Blood loss of 1000 mL or more occurred in 4.8% (13/270) of the misoprostol group and 7% (19/272) of the placebo group (not significant). Additional oxytocic therapy was required by 3.3% and 4.7%, respectively. No predominance of side effects, particularly shivering, was noted in the misoprostol group. The early active management of excessive bleeding with conventional oxytocic agents may have reduced the potential of the study to detect differences between the groups.

I wish to acknowledge Dr Derek Merrell, consultant obstetrician at Natalspruit Hospital, for pioneering the rectal route of administration of misoprostol. We designed a randomized trial comparing misoprostol with oxytocin-ergometrine, conducted mainly by Dr Anthony Bamigboye, a registrar at Natalspruit hospital, which was to my knowledge the first report of misoprostol administered rectally (18). Blood loss was similar between groups, and shivering was not seen as a major side-effect. The rectal route has since become extremely popular for treatment of postpartum haemorrhage, though without robust evidence of its effectiveness.

With the same team we conducted a second study at Natalspruit hospital comparing rectally administered misoprostol with placebo (19). The reduction in blood loss with misoprostol was not statistically significant.

3.8 Side-effects

20. **Hofmeyr GJ**, Nikodem C, de Jager M, Drakely A, Gilbart 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; South Africa*. 1998: 53-4.

Women in labour were randomly allocated to receive misoprostol 400mcg or 600mcg or placebo orally after the birth of the baby. Conventional oxytocics were given immediately if blood loss was thought to be more than usual. The rate of shivering in the 3 groups was 81/199; 65/199; 30/199; pyrexia: 53/200; 28/200, 5/200. Blood loss >1000ml: 17/200, 16/200, 6/200.

21. Lumbiganon P, **Hofmeyr J**, Gulmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour. Br J Obstet Gynaecol 1999; 106: 304-308

In a randomized pilot study comparing misoprostol 600mcg vs 400 mcg vs oxytocin, the rates of shivering were 56/199 vs 38/198 vs 25/200, and pyrexia >38 degC 15/199 vs 4/195 vs 6/199.

We conducted another study of oral misoprostol to see whether the side-effects were dose-related, comparing 600 micrograms versus 400 micrograms versus placebo, and confirmed that indeed the side-effects with 400 micrograms were fewer (20). Together with international colleagues, we subsequently confirmed this finding as part of our large World Health Organization trial (21). The data on blood loss in our trial (20) were even more disappointing. The rates of postpartum haemorrhage were 17/200 (8.5%) for 600 micrograms, 16/200 (8%) for 400

micrograms, and for placebo 6/200 % (3%)! As we did the analysis, we couldn't believe what we were seeing. We went over the data time and time again, convinced that we had made some error, but nothing changed. The lesson, of course, is a very important one in clinical research. In studies with relatively small numbers of outcomes, even if perfectly randomized, there is considerable scope for variation in the results due to chance. If the same small trial is repeated over and over, the results will tend to cluster around the 'true' result, but every now and then there will be a chance aberration which falls far away from the 'true' result in one or other direction. This trial is an example of an extreme outlier. One other trial of similar size conducted in France also showed a trend to more haemorrhage with misoprostol than with placebo (Benchimol et al, 2001). This chance variation in the results of small trials is the cause of a fundamental limitation of meta-analysis: publication bias.

3.9 Chance variation and publication bias

The randomized trial is the most reliable way of getting information close to the 'true' effectiveness of an intervention, but there will always be some variation in the result, due to the play of chance. The smaller the number of cases with the outcome, the greater the degree of variation. If all the randomized trials conducted on the same intervention are synthesised by meta-analysis, the variations in each direction will cancel each other out and give a summary result close to the 'true' effect.

To illustrate this principle in the research methods courses we run, I ask the class to each flip 2 coins at the same time, 10 times, and write down the number of times they get 2 heads. The results are all over the place, usually from 0/10 to about 7/10. We then enter all the results into a meta-analysis program, and as the

numbers build up, the summary effect always moves closer and closer, and ends up uncannily close to the 'true' result: 25%.

The Achilles heel of meta-analysis in is that we don't have access to all the trials of an intervention which have been conducted. If we had access to a random sample of the trials that would also be fine, but in effect we have access to a biased sample of trials. What happens in real life is that not all the small trials of an intervention which are conducted, are published. All the trials represent the chance variation in the results ranging from more positive than the 'true' result to less positive. Those with more positive results are more likely to be published. Investigators getting less positive results tend to be discouraged, feel the results are not worth publishing, or their submissions are less likely to be accepted because they are not newsworthy. The literature available on which we base our policies and our practice is thus inherently skewed by this 'publication bias'. How should we deal with it?

Firstly, we fortunately know that publication bias is invariably in the direction of over-estimating the effectiveness of an intervention. If meta-analysis of a new intervention shows no beneficial effect, we can safely conclude that the intervention is not effective.

If meta-analysis of a number of small trials shows a beneficial effect, we need to keep in mind the possibility of publication bias, and the best solution is to use the meta-analysis as an hypothesis-generating exercise, and proceed to conduct a large, high-profile, international, multicentre 'mega-trial'. The mega-trial will invariably give a lower estimate of the effect of the intervention than the meta-analysis of small trials, and will be a more reliable estimate of the true effect (Scifres et al, 2009). There are many examples of this principle, such as our WHO

multicentre trial of calcium supplementation to reduce pre-eclampsia (Villar et al, 2006) which found a far smaller effect than our preceding meta-analysis (Hofmeyr Atallah & Duley, 1998), and our WHO misoprostol trial to which I shall refer below.

I have given some time to the issue of publication bias as it is not a generally well-acknowledged phenomenon, and is crucial to an understanding of the controversy surrounding misoprostol and postpartum haemorrhage which will emerge below.

3.10 The WHO misoprostol for preventing postpartum haemorrhage trial

22. Gülmezoglu AM, Villar J, Ngoc NN, Piaggio G, Carroli G, Adetoro L, Abdel-Aleem H, Cheng L, **Hofmeyr GJ**, Lumbiganon P, Unger C, Prendiville W, Pinol A, Elbourne D, El-Refaey H, Schulz KF, *for the WHO Collaborative Group To Evaluate Misoprostol in the Management of the Third Stage of Labour.* The WHO multicentre double-blind randomized controlled trial to evaluate the use of misoprostol in the management of the third stage of labour. Lancet 2001; 358: 689-695.

Measured blood loss of 1000 mL or more occurred in 366/927 women with misopropstol versus 263/9232 women with injectables (RR 1.39, 95%CI 1.19 to 1.63). Misoprostol use was associated with 3.5 times more shivering and 7 times more raised body temperature.

23. **Hofmeyr GJ**, Gülmezoglu AM, Villar J, Lumbiganon P, Piaggio G. Effects of misoprostol on profuse blood loss after birth: an exploratory study of data from the WHO Randomised Trial of Misoprostol in the Third Stage of Labour (unpublished).

In the face of extremely erratic results of several smaller randomized trials, including those from our unit to which I have referred above, our network of researchers from low-income countries led by Metin Gülmezoglu from the World Health Organization decided to mount a mega-trial to determine the effectiveness or otherwise of misoprostol (22). We chose 600 mcg orally as the largest reasonable dose to use for 'proof of concept' (to minimize the risk of failing to detect an effect by choosing a sub-optimal dose). So high were our expectations that misoprostol would prove to be the solution to postpartum haemorrhage we were all searching for, that we set this up as an equivalence trial. We expected to prove, through enrolment of very large numbers of women, that misoprostol was more or less as effective as oxytocin. The results from recruitment of more than 18 000 women were another resounding disappointment. Misoprostol was considerably less effective than injectables. This left us with a monumental gap in our knowledge. We knew that misoprostol was less effective than injectables, but not having had a placebo group, we did not know how effective it was in absolute terms, or whether it was effective at all. To this day our evidence on the absolute effectiveness of misoprostol is based on data from a number of placebo controlled trials very much smaller than the WHO trial, with a wide range of results, and subject to the possibility of publication bias.

Ironically, although this was essentially a negative result, because of the enormous scale of the trial, which numerically overwhelmed all other randomized trials in the area, 600 mcg became entrenched in the collective psyche as the 'WHO trial dosage'.

My contention is that this fundamental disappointment in the less than expected level of effectiveness of misoprostol even at this high dosage, instinctively discourages

researchers and advocates from entertaining the use of a smaller dose. The 600mcg used in the WHO trial became the benchmark for subsequent trials which have influenced global practice.

An interesting anomaly in the WHO trial data was that despite a 40% higher number of women who lost 1000ml or more of blood, there was a trend to fewer blood transfusions in the misoprostol group than the oxytocin group. To determine whether this might be due to a reduction in massive blood loss, I developed a protocol and we conducted a post hoc analysis of higher levels of blood loss (23). We confirmed that for volumes of blood loss above 1750ml there was a trend to slightly fewer cases with misoprostol than with oxytocin.

This was odd. Perhaps it was due to greater use of 'rescue' oxytocin in women in the misoprostol group who continued to bleed, or perhaps there was something about the action of misoprostol over time we did not yet understand.

A very recent trial from India comparing powdered misoprostol 400mcg sublingually with oxytocin, found exactly the opposite effect as the large WHO trial: a 66% reduction in blood loss >500ml (Bellad et al, 2012). This discrepancy is very difficult to understand. Either it was yet another chance finding, or the oxytocin was less effective than that used in the WHO trial, or for some reason we don't yet fully understand, 400mcg sublingually is more effective than the 600mcg orally used in the WHO trial.

3.11 Different effects in different settings?

Most trials of misoprostol for preventing postpartum haemorrhage have been conducted in hospital settings. In 2005 and 2006 three trials were reported from a

primary care setting in Guinea-Bissua (Hoj et al, 2005) or community settings in India (Derman et al, 2006) and Gambia (Walraven et al, 2005), comparing misoprostol 600mcg sublingually or orally with placebo or (in Gambia) with oral ergometrine, which is considered to have negligible effect. In contrast to the inconsistent results of studies in hospital settings, these trails showed a consistent reduction in severe postpartum haemorrhage which was statistically significant for the Guinea-Bissau and the India trials. The findings in a subsequent community-based trial in Pakistan (Mobeen et al, 2011) were similar. The question arises whether misoprostol may be uniquely effective in community settings? It is plausible that in hospital settings, the availability of 'rescue' treatment with oxytocin may mask the benefits of misoprostol compared with placebo. Data from these trials were the basis for the WHO to recommend the use of misoprostol in community settings where oxytocin was not available. The dose recommended was 600mcg, as there were no community based trials of lower dosages to guide recommendations.

3.12 The effect of misoprostol over and above oxytocin

24. **Hofmeyr GJ**, Fawole B, Mugerwa K, Godi NP, Blignaut Q, Mangesi L, Singata M, Brady L, Blum J. Administration of 400 µg of misoprostol to augment routine active management of the third stage of labor. Int J Gynaecol Obstet. 2011; 112: 98-102.

Blood loss of 500 mL or more was not significantly reduced by sublingual misoprostol 400 µg versus placebo, in addition to standard oxytocin. (misoprostol 22/546 [4.0%] versus placebo 35/553 [6.3%]; relative risk, 0.64; 95% confidence

interval, 0.38–1.07). Shivering and pyrexia occurred more frequently in the misoprostol group.

25. Fawole AO, Sotiloye OS, Hunyinbo KI, Umezulike AC, Okunlola MA, Adekanle DA, Osamor J, Adeyanju O, Olowookere OO, Adekunle AO, Singata M, Mangesi L, **Hofmeyr GJ**. A double-blind, randomized, placebo-controlled trial of misoprostol and routine uterotonics for the prevention of postpartum hemorrhage. Int J Gynaecol Obstet. 2011;112: 107-11.

Blood loss of 500 mL or more was not significantly reduced by sublingual misoprostol 400 µg versus placebo, in addition to standard oxytocin (40/658 [6.1%] vs 42/660 [6.4%], relative risk [RR] 0.96; 95% confidence interval [CI], 0.63–1.45); nor was blood loss of at least 1000 mL (4/658 [0.61%] vs 8/660 [1.2%], RR 0.50; 95% CI, 0.15–1.66). Misoprostol was associated with pyrexia and moderate/severe shivering.

Having shown conclusively that oral misoprostol 600mcg was much less effective than oxytocin (if effective at all), the next important question was: what about both together?

For the past 12 years we have run an annual research methods course, funded by WHO and the Eastern Cape Department of health. About 30 prospective researchers from all over the continent come to East London for hands on training in randomized trial and systematic review methodology. We encourage them to develop a project and offer mentoring. One year, participants from Eastern Cape, Mpumalanga, Uganda and Nigeria agreed to tackle a trial of oxytocin plus misoprostol versus oxytocin plus placebo (24,25) . Part of the exercise was to show that with committed staff and capacity-building for decentralized data

collection, high quality trials could be conducted without huge expenditure. Neither trial alone showed significantly reduced blood loss. However, when combined by meta-analysis with one previous study from Turkey using 400 mcg (orally), they added to the body of data showing an overall significant reduction of postpartum haemorrhage of about 30% when misoprostol 400mcg was added to the oxytocin regimen.

3.13 Observational studies and clinical experience

26. **Hofmeyr GJ**, Ferreira S, Nikodem VC, Mangesi L, Singata M, Jafta Z, Maholwana B, Mlokoti Z, Walraven G, Gulmezoglu AM, Misoprostol for treating postpartum haemorrhage: a randomized controlled trial [ISRCTN72263357]. BMC Pregnancy and Childbirth 2004; 4: 16.

Women with postpartum haemorrhage received routine treatment with injectable uterotonics, and in addition misoprostol (200mcg orally, 400mcg sublingually and 400mcg rectally) versus placebo. With misoprostol there was a trend to reduced blood loss ≥500 ml (6/117 vs 11/120, relative risk 0.56; 95% confidence interval 0.21 to 1.46). Side-effects were increased, namely shivering (63/116 vs 30/118; 2.14, 1.50 to 3.04) and pyrexia > 38.5°C (11/114 vs 2/118; 5.69, 1.29 to 25). In the misoprostol group 3 women underwent hysterectomy of whom 1 died, and there were 2 further maternal deaths.

27. Walraven G, Dampha Y, Bittaye B, Sowe M, **Hofmeyr J**. Misoprostol in the treatment of postpartum haemorrhage in addition to routine management: a placebo randomised controlled trial. BJOG. 2004; 111: 1014-7.

Women with postpartum haemorrhage received routine treatment with injectable

uterotonics, and in addition misoprostol (200mcg orally and 400mcg sublingually) versus placebo. With misoprostol there was a trend to reduced blood loss ≥500 ml: 13/79 (16.5%) 23/81 (28.4%) RR 0.58 95% CI 0.32 to 1.06

28. Widmer M, Blum J, **Hofmeyr GJ**, Carroli G, Abdel-Aleem H, Lumbiganon P, Nguyen TN, Wojdyla D, Thinkhamrop J, Singata M, Mignini LE, Abdel-Aleem MA, Tran ST, Winikoff B. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. Lancet. 2010; 375: 1808-13.

Women with postpartum haemorrhage received routine treatment with injectable uterotonics, and in addition misoprostol 600 µg sublingually versus placebo. Blood loss of 500 mL or more after enrolment was similar between the misoprostol group (100/705 [14%]) and the placebo group (100/717 [14%]; relative risk 1.02, 95% CI 0.79 to 1.32). In the first 60 min, an increased proportion of women on misoprostol versus placebo, had shivering (455/704 [65%] vs 230/717 [32%]; 2.01, 1.79 to 2.27) and body temperature of 38°C or higher (303/704 [43%] vs 107/717 [15%]; 2.88, 2.37 to 2.50).

Around this time, in contrast to the disappointing results of our early randomized trials on postpartum haemorrhage prevention, a number of observational studies were published which showed remarkable benefits from misoprostol used to treat postpartum haemorrhage in a variety of doses and by various routes of administration. In about 95% of cases reported, misoprostol given to women with postpartum haemorrhage was followed by almost immediate cessation of bleeding. The fact that in many cases the bleeding stopped before the

misoprostol could have been absorbed into the system did not deter clinicians from ascribing these dramatic effects to the misoprostol.

The phenomenon of cessation of bleeding following misoprostol administration was experienced by doctors and midwives globally, and the clinical conviction entered the collective psyche of health professionals that misoprostol was a spectacularly effective treatment for postpartum haemorrhage.

We set out to conduct the first ever placebo-controlled randomized trials of misoprostol for the treatment of postpartum haemorrhage. Gijs Walraven from the Reproductive Health Program of the MRC Research Laboratories in The Gambia visited us in East London, and together we planned similar protocols for trials to be run in South Africa (237 women) (26) and Gambia (160 women) (27). Most of the observational reports had used doses up 1000 mcg by various routes, mainly the rectal route. We decided to use a large dose including the rectal route to be sure not miss a beneficial effect through under dosing. We also hoped that using various routes, with differing rates of absorption, would reduce side-effects. In East London we chose to use 200 mcg orally plus 400 mcg sublingually plus 400 mcg rectally. Gijs Walraven chose to use, based on what was acceptable and feasible in the Gambian context, 200 mcg orally plus 400 mcg sublingually. We compared the effect of misoprostol with placebo, over and above the effect of routine treatment which all women received. The trials showed remarkably similar results – a reduction in additional blood loss after enrolment which was not statistically significant, but became significant when the data from the two trials were combined by meta-analysis. A recent similar small trial conducted in Pakistan using misoprostol 600 mcg sublingually produced similar results (Zuberi, 2008).

As before with prevention of postpartum haemorrhage, there was the need to confirm the results of small trials with a mega-trial, and once again we worked with our network of colleagues, co-ordinated by Metin Gülmezoglu at the World Health Organization, to repeat our studies, this time using 600 mcg sublingually. Yet another profound disappointment. After using conventional treatment, misoprostol had absolutely no additional measurable effect compared with placebo (28).

What was the truth? The effects ranging from modest to zero shown by our three randomized trials, or the dramatic effects experienced in clinical practice in the treatment of postpartum haemorrhage?

The crux of this common dissonance between clinical experience and randomized clinical trials lies in the question: "What would have happened in clinical practice had placebo been given instead of misoprostol?"

Medical practice is a very satisfying field in which to work, much more so than, say, repairing motor cars. Generally, people consult a doctor when they are unwell. Most illnesses are self-limiting. It is inevitable that health professionals are exposed to an unrealistically favourable impression of the effectiveness of what they do. Cars seldom recover without somebody doing something effective.

One may say, "So what?" The patient is better, the doctor feels good, what does it matter whether the recovery was assisted by the medication or not?

3.14 "At least it does no harm"

Once upon a time, doctors developed a new treatment for women at risk of miscarriage (mainly women who had previously suffered miscarriage). In contrast to their previous history of miscarriage, more than 9 out of 10 women who received the new treatment had a successful pregnancy. These results were

wonderful, and the treatment became widely practiced as standard care. Unlike many other impressively effective interventions which are part of our everyday practice, this treatment was tested in a randomized trial. The trial confirmed that more than 9 of 10 women who received the treatment had a successful pregnancy. What was unexpected, was that women who were randomly allocated to receive an identical-looking placebo (blank) tablet had identically good outcomes. The treatment itself had absolutely no beneficial effect.

The results of this trial were presented at a meeting of the American College of Obstetricians and Gynecologists. In the published discussion following the presentation, proponents of the treatment stated that their personal results with the treatment were so good that they were unconvinced by the trial findings, and would continue to use the treatment. Over the next 2 decades, over 2 million women received this treatment, which was known to be ineffective. Such is the power of the personal conviction of clinicians. The good thing was that there appeared to be no adverse effects. The doctors were happy, and the women were happy with the excellent pregnancy outcomes. Why be bothered?

Time passed and a strange thing happened. A few young women in the Boston area developed cancer of the vagina. Had they developed breast cancer, the event would have passed unnoticed. But vaginal cancer was exceptionally rare, and doctors started searching for an explanation. It came to light that the mothers of these women had received the treatment to prevent miscarriage. Panic ensued. The offspring of women enrolled in the original trial were tracked down and asked to undergo health checks. Fortunately the incidence of vaginal cancer was very low, but compared with the offspring of women who had received the placebo tablets, these young men and women had an excess of multiple health

problems, including vaginal adenosis, abnormally shaped uteri, recurrent miscarriages, testicular hypotrophy, infertility and psychiatric illness.

None of these adverse effects would have come to light had it not been for the sheer fluke that one of the side-effects (vaginal cancer) was so extremely unusual that it elicited the interest of the astute pathologists who dealt with some of the cases. Theirs is the credit that, unlike many other medicines of unproven effectiveness, the hormone diethylstilboestrol (DES) is no longer given to pregnant women on the basis of "well, it doesn't do any harm" (that we know of).

3.15 Back to misoprostol

What does this have to do with misoprostol? The enthusiasm with which misoprostol was embraced by clinicians as a treatment for postpartum haemorrhage, based on striking personal experience, was out of all proportion to the evidence overall from randomized trials that misoprostol has little if any benefit over and above oxytocin. The most recent report on Confidential Enquiries into Maternal Deaths in South Africa, to which I have referred previously with respect to ruptured uteri following labour induction with misoprostol, highlighted the fact that in the face of life-threatening postpartum haemorrhage following treatment with oxytocin, clinicians all too often chose to use rectal misoprostol rather than the recommended second line treatment, ergometrine (2).

We need to analyse the clinical context in which misoprostol is used for treatment of postpartum haemorrhage. This is a particularly terrifying condition with which to be faced. I know only too well the sense of impending doom when the bleeding is profuse and relentless and seems incompatible with survival of the mother. Our instinct is to use any method which may possibly help to arrest the bleeding. It is

quite understandable that even doctors who are aware of the evidence that once injectable uterotonics have been given, misoprostol has no proven additional benefit, and may cause harm, in this situation argue "she is dying, we have to do something".

Similarly, at a public health policy level, faced with the ongoing global maternal mortality from haemorrhage, the compelling argument is "Women are dying every day, we have to do something now" (Potts & Hemmerling, 2006).

Instinctively, when faced with possible disaster, we want to do something.

3.16 The global debate

Early on, the issue of misoprostol after childbirth became an issue of considerable, and unfortunately heated, global debate. Misoprostol represented a ray of hope for a way of overcoming our appalling lack of progress in reducing maternal mortality in poor countries, despite the rhetoric of the Millenium Development Goals. There was intense pressure from global agencies and advocates to implement large-scale programs using misoprostol routinely after childbirth to prevent postpartum haemorrhage.

On the surface, the arguments regarding rapidly upscaling misoprostol programs were as follows:

Con: we need more trials to be sure that misoprostol does more good than harm.

Pro: we can't wait for more trials while women are dying.

In several years' time we would probably have more certainty as to whether misoprostol does more good than harm. If we implemented programs and it turned out to be harmful, we would be responsible for causing harm through an inadequately tested intervention. If we did not implement its use and it turned out

to be effective, we would be responsible for withholding a lifesaving intervention while women died. Damned if you do and damned if you don't. It was an impossible choice which decision-makers had to make, and be prepared to face the consequences.

Rationally, if we don't yet know whether the intervention will do more good than harm, we know that doing nothing may in fact save lives. However, our human instinct is such that faced with impending death or deaths, doing something with the possibility of improving outcomes is at an emotional level a more attractive proposition than doing nothing, with the possibility of avoiding more harm.

It is perhaps because of his knowledge of human nature that Hippocrates found it necessary to counteract this tendency with the specific injunction: "First, do no harm."

3.17 New drugs versus drugs already on the market

The fact that the dilemma arose at all was due to the fact that misoprostol was already widely available for other indications. Had it been a new drug being developed for use after childbirth, it would not have been allowed to be distributed before there was a large and systematic body of evidence of both safety and effectiveness. This process usually takes a drug company 10 to 20 years and multiple millions of dollars to complete. Misoprostol had the potential to skip this process, and there was enormous pressure for it to do so, with the attendant risks.

For reasons which will become apparent, I was opposed to widespread use of misoprostol after childbirth in the dosage being recommended (600 mcg) without more evidence of safety. My personal evaluation of the total body of scientific evidence available was that at a dosage of 600 mcg or more there was a real

possibility of doing more harm than good, whereas at 400 mcg or less, the risk of harm was considerably less, and the balance of probability was in favour of benefit over harm.

Time and again in international meetings and expert committees I argued for caution and use of a smaller dosage, against an overwhelming lobby of global organizations pushing for immediate implementation at the higher dose. Debates often became heated, but for the most part I failed to convince any of the advocates of implementation of my point of view. It is not an easy proposition to sell, because it is essentially counter-intuitive. One important aspect is a fatal flaw in the argument for misoprostol: the use of a proxy outcome.

3.18 How proxy outcomes may be misleading

In clinical research, when the health outcome of concern cannot be measured directly, we may make use of a 'proxy' outcome – a measurable outcome which serves as a substitute for the more critical outcome.

The primary purpose of using misoprostol after childbirth is to reduce maternal deaths from haemorrhage. The argument appears compelling:

1. Haemorrhage is a major cause of maternal death

2. Misoprostol reduces haemorrhage after childbirth

3. Therefore use of misoprostol will reduce maternal deaths

My argument, which was far less persuasive, was as follows:

1. Misoprostol reduces blood loss modestly, but also has powerful effects on multiple organ systems including the cardiovascular system.

2. It is possible that adverse effects on other homeostatic mechanisms might cause more deaths than those prevented by reduced blood loss, particularly when used in large dosages (the data which suggested this possibility will emerge below).

In 'misoprostol' circles, this was an exceptionally unpopular heresy. I remember after suggested this possibility during an international presentation (Hofmeyr, 2006), one of my colleagues from a global agency approached me in great distress and said "You just can't say that!" It was so undermining of what everyone was working for that it could not even be contemplated.

Yet there are examples of just such counter-intuitive dissonance between a proxy outcome and the primary outcome of concern. A good example is the use of certain antiarrhythmic agents following myocardial infarction. The proposition was:

1. Arrhythmias (ventricular premature depolarizations) are a common cause of death following myocardial infarction

2. Anti-arrhythmic agents reduce arrhythmias (proxy outcome) following myocardial infarction

3. Therefore anti-arrhythmic agents should reduce deaths

On this basis, anti-arrhythmic agents were widely used to reduce death following myocardial infarction. However, a randomized trial large enough to measure death rather than the proxy outcome of reduced arrhythmias was conducted by the CAST group (Epstein et al, 1993). Men and women (3549 of them) who had suffered myocardial infarction with left ventricular dysfunction were randomly assigned to receive ant-arrhythmic agents or placebo. Death within 1 year was significantly more common in those who receive the anti-arrhythmic agents (10%)

than those who received placebo (5%). It has been estimated that tens of thousands of men and women were killed by the well-meaning use of anti-arrhythmic agents, based on a logical extrapolation from a proxy outcome.

The same might conceivably apply to the apparently logical use of misoprostol following childbirth, but a trial large enough to measure death as an outcome is unlikely to be feasible, so the truth will be more difficult to discern.

Another example of an apparently logical intervention which did more harm than good was formula feeding for women with HIV infection living in low-resource settings. It seemed self-evident that avoiding the risk of HIV infection via breast milk would improve the babies' chances of survival. A small group of researchers in South Africa opposed this policy on the basis that the risks of formula feeding in this setting probably outweighed the benefits. In time, evidence emerged that in this setting more babies died from complications of formula feeding than contracted HIV from breastfeeding, but it took years and considerable loss of life before the policy was changed (Coutsoudis Coovadia & Wilfert, 2008).

3.19 Postpartum haemorrhage as the Trojan horse

There was another layer to the misoprostol for postpartum haemorrhage issue which I never heard mentioned in public, but which I now understand contributed to the vehemence with which my call for caution in implementing misoprostol for postpartum haemorrhage was met. The unspoken issue was abortion. The one context in which misoprostol is undeniably life-saving is as a method of safe abortion. Widespread distribution of misoprostol ostensibly for use after childbirth, clearly makes misoprostol available in the community for use for safe abortion. As

abortion is illegal in many countries, postpartum haemorrhage was seen as a politically persuasive alternative for distribution of the medication.

Although I never heard the abortion issue mentioned, it was the only explanation I could give for the seemingly excessive diligence with which the misoprostol for postpartum haemorrhage agenda was promoted. Only in 2011 was my assumption confirmed in a Family Care International report entitled "Mapping Misoprostol for Postpartum Hemorrhage: Organizational activities, Challenges and Opportunities". Over 30 organizations were surveyed. One of the summary points was: "Rather than hiding misoprostol's abortion indication to avoid controversy, this indication should be presented as one of many ways misoprostol can potentially save women's lives." Quotes from respondents included: "*Because misoprostol for postpartum haemorrhage is less controversial than misoprostol for safe abortion, it is a "door-opener";*" and another: "*Go under the radar. Introduce misoprostol for noncontroversial uses, such as postpartum haemorrhage, with the tacit understanding that it may also be used for abortion.*"

Ironically, advocates of misoprostol distribution assumed that my reason for caution regarding misoprostol distribution was that I must be anti-abortion (I was informed by a representative of a global agency that this was a widely held opinion). This is an understandable projection: those following an undisclosed agenda will assume that others are as well.

3.20 Abortion

Because the abortion agenda has distorted the misoprostol after childbirth debate so profoundly, it is important that I declare any potential conflict of interest and place on record my personal standpoint on abortion.

This has two aspects: equity, and personal experience.

On the grounds of equity, my view is that any restriction placed on women's access to safe abortion is unenforceable against women with wealth and therefore fundamentally unjust. In South Africa when abortion was restricted (prior to 1995), wealthy women travelled to Swaziland or London for safe unspecified 'gynaecological procedures', while those of us working in state hospitals dealt with the indescribable misery, mutilation and death following the 'backstreet' abortion attempts of those less affluent. We did all we could by way of treatment, blood transfusion, removing rotten uteri, ventilation in ICU, but all too frequently the young women died.

Because I have the technical ability to provide safe abortions and I work in the public sector with women without access to private care, I regard it as my duty to do everything in my power to ensure that our clients have the same access to safe abortion as their wealthy counterparts. One might call this the Dr Larch principle (from 'Ciderhouse Rules'). It is not a question of right or wrong or moral or immoral; it is a question of equity between rich and poor. I have also done as much as I can to promote access to quality family planning services so that fewer women are faced with this painful dilemma.

The second issue is personal. Over almost 40 years of clinical practice I have sat face to face and counselled countless women requesting abortion. I do not recall a single case in which my human instinct was not to support the woman in the painful choice she had made. The dilemma faced by women requesting abortion is well illustrated by a response from a participant in one of our research projects relating to abortion: "I love this baby, but I know that if I keep the baby I will lose my job and not be able to feed the child I already have".

If abortionists do end up in Hell, I will have thoroughly earned my place there.

3.21 The Journal of the Royal Society of Medicine review

There has recently been a further twist to the misoprostol for postpartum haemorrhage saga. A review in the JRSM argued that the evidence for the use of misoprostol in home and community settings in low- and middle income countries was weak and inconclusive, and called on the WHO to rethink their inclusion of misoprostol in the Essential Medicines List (Chu Brhlikova & Pollock, 2012). I personally found the review scientifically unconvincing, but that is beside the point. What is interesting is the ideological undertones which emerged in the subsequent correspondence published in the Journal.

Malcolm Potts and co-authors wrote: "Their paper is a sad example of workers in an elite setting advocating policies with the potential to endanger the lives of thousands of vulnerable women in low resource settings."

Nancy L Kerr wrote: "I write due to concern that persons who wish to restrict misoprostol from the women of the world, because of personal biases, might attempt to use this article to influence policy."

Richard Derman wrote: "..there is no excuse for the lack of awareness of the methodologically stringent review and meta-analysis, (Sloan et al, 2010) which clearly demonstrates that methodologically sound studies find a substantial and highly significant benefit in the provision of misoprostol for postpartum haemorrhage prevention."

Two of the authors of the original paper responded to Derman's letter and concluded: "On the basis of current evidence the WHO should rescind its recent

decision to add misoprostol to the EML. An investigation into the organisations, networks and motives including potential conflicts of interests behind the promotion and research into misoprostol use is long overdue."

3.22 Misoprostol dosage: abortion and postpartum haemorrhage

Another unfortunate influence which may originate from the abortion agenda, relates to the dosage of misoprostol used for prevention and treatment of postpartum haemorrhage. As mentioned, I have for many years put forward, based on a systematic review of the literature, what I regard as a scientifically sound recommendation that the dosage of misoprostol used for prevention (and probably treatment) of postpartum haemorrhage should not exceed 400mcg. I will give full details of the research below. I have found it difficult to understand why my colleagues have been so reluctant to take my proposals seriously. It is only recently, in the light of understanding that the abortion and postpartum haemorrhage issues are intertwined, that it has occurred to me that researchers and advocates approaching the postpartum haemorrhage issue from an abortion perspective, would intuitively favour a dosage which was also appropriate for abortion (600 to 800 mcg). It is also understandable that those with long experience in the abortion field, where these doses have been well shown in a huge body of research to be effective and safe for abortion, should expect such doses also to be safe after childbirth.

3.23 Misoprostol dosage after childbirth

It will have become clear in the previous discussion of misoprostol for labour induction, that the dosage of misoprostol at different stages of pregnancy differs

enormously, and is an important issue. Prior to 20 weeks of pregnancy, a woman's uterus is relatively resistant to misoprostol, and fairly large doses are needed to stimulate uterine activity. Doses of misoprostol around 600 to 800 mcg are required for abortion, and are extremely safe. Towards the end of pregnancy, the uterus becomes exquisitely sensitive to misoprostol: doses as low as 25 mcg carry a measurable risk of causing hyperstimulation of the uterus and distress in the baby, and occasionally catastrophic rupture of the uterus.

After childbirth, there is no biological reason to expect that the sensitivity of the uterine muscle to misoprostol would suddenly and dramatically decline. However, when I and my colleagues around the world started to research this field, we decided, in keeping with sound scientific principles, that for the purpose of 'proof of concept', we should start our research with the highest dose considered safe. If this was effective, we could reduce the dosage to find the lowest effective dose. As, after birth of the baby, the main known risks (fetal distress and ruptured uterus) were removed (barring in the event of an undiagnosed, unborn second twin), we considered around 600 mcg to be a safe upper limit dosage with which to begin. Our mistake was to assume that the risks were limited to fetal distress and uterine rupture.

3.24 Misoprostol does more than contract the uterus

In 1996 I met Y S Chong, a young registrar from Singapore, at the Third International Scientific Meeting of the Royal College of Obstetricians and Gynaecologists in New Delhi. He presented an elegant study in which he and colleagues had measured intrauterine pressure after childbirth in healthy women volunteers treated with oxytocin-ergometrine or oral misoprostol 200, 400, 500, 600 or 800 mcg (Chong Chua & Arulkumaran, 1997; Chong et al, 2001). The onset of

increased uterine activity was significantly slower with misoprostol than with oxytocin-ergometrine. There was no statistically significant difference in the measured pressures between the five misoprostol dosages. The 7th woman to receive misoprostol 800 mcg developed life-threatening hyperpyrexia requiring life-support in ICU. She pulled through, but it is difficult to imagine the anxiety of researchers facing the situation of a previously healthy volunteer fighting for her life following a purely physiological experiment of no benefit to her. This severity of side-effect had never, to my knowledge, been described amongst hundreds of thousands of women receiving the same dose of misoprostol for abortion. This was the first intimation that after childbirth, women might be uniquely vulnerable to the multiple hormonal effects of misoprostol (other than effects on the uterus). In retrospect, this is biologically not surprising.

The period immediately before and after childbirth is one of profound physiological instability, with release of high levels of endogenous hormones such as oxytocin, prostaglandins, prolactin and catecholamines, and profound cardiovascular readjustment following the birth. The possibility that a powerful prostaglandin analogue with ubiquitous effects on multiple organ systems, including thermoregulation, coagulation, the gastrointestinal system and vascular tone, might interact with these turbulent homoeostatic processes in a unique and dangerous way, is far from implausible.

The mistake we made, and which is still being made today, was to view misoprostol in a one-dimensional way, in terms of its effects on the uterus, and with insufficient attention to its many other effects on human physiology. We viewed misoprostol simplistically as an alternative uterotonic to oxytocin, failing to recognize that whereas oxytoxin has very specific effects on a limited number of tissues such as the

uterine muscle and the breast myoepithelial cells, prostaglandin receptors are present throughout the human body. A simple example of this dichotomy was our finding referred to in the chapter on labour induction, that misoprostol stimulated both rat ileal and uterine smooth muscle, whereas the oxytocin effect was specific to uterine muscle (14).

That misoprostol might have dangerous side-effects should not be unexpected. Sulprostone, a prostaglandin E2 analogue has been registered for the treatment of postpartum haemorrhage in France for many years. There have been several reports of serious side-effects including cardiac arrest (Cheng Koh & Chong, 1998) and hyperpyrexia with neurological symptoms (Cellier et al, 2012).

It is my contention that the potential risks of high dose misoprostol after childbirth continue to be underplayed in the context of the global imperative to improve outcomes for women by promoting widespread distribution of misoprostol.

It is most unfortunate that the adversarial climate engendered by the abortion issue, has created a situation in which well-intentioned proponents of misoprostol need to play down the risks in order to minimize the ammunition available to the anti-misoprostol lobby.

Chong and colleagues' finding of no difference in the effect of misoprostol on uterine contractions after childbirth in dosages from 200mcg upwards has been confirmed in a randomized study showing no difference in postpartum uterine contractions between sublingual misoprostol 200, 400 and 600 mcg (Elati et al, 2011). The rate of hyperpyrexia >39 degrees C increased from 8.3% with the lower dosages to 45% with 600mcg.

3.25 What else causes reluctance to lower the recommended dosage of misoprostol following childbirth?

I have suggested above that the link with abortion has primed researchers and advocates with a long experience of abortion to perceive 600 to 800 mcg as a 'safe and effective' dose, and one which allows convenient translation from the postpartum to the abortion indication.

However, I wish to suggest that there is another human factor which evokes an instinctive reluctance to lower the dosage of misoprostol used after childbirth. This relates to the disappointing degree of effectiveness of misoprostol for preventing or treating postpartum haemorrhage. Because of an intuitive link between dosage and effect, we are reluctant to consider reducing the dosage of a compound which even in high dosage is less effective that we had hoped it would be.

3.26 A new method of measuring postpartum intra-uterine pressure

29. Pipingas A, **Hofmeyr GJ**, Sesel KR (1993). Umbilical vessel oxytocin administration for retained placenta: in vitro study of various infusion techniques. Am J Obstet Gynecol 168: 793

Contrast medium was injected into the umbilical vessels of 25 freshly delivered placentas and sequential x-ray films were taken. Capillary filling was inconsistent after injection of 20 ml of solution into the umbilical vein without or with "milking" of the cord (1/5 and 2/5, respectively). These were the techniques most commonly used in reported controlled clinical studies. Injection via an infant mucus aspiration catheter introduced along the umbilical vein to 5 cm from the placental insertion demonstrated a cotyledonary pattern in three of five cases

after 20 ml and in all 5 after 30 ml.

30. Bamigboye A A, **Hofmeyr GJ**, Nikodem VC. Measuring postpartum uterine contractions during the third stage of labour: a pilot study, using a novel minimally invasive technique. Open Journal of Obstetrics and Gynecology 2011; 1: 128-130

The study showed that postpartum intra-uterine pressure could be measured non-invasively with a pressure catheter inserted via the umbilical vein into the placenta.

I mentioned above the work of Chong and colleagues on the physiological effects of various dosages of misoprostol on contractions of the uterus after birth (Chong et al, 2001). Contractions were measured with a pressure-tip catheter inserted into the uterus after birth of the baby. This is the 'gold standard' method of measuring postpartum intrauterine pressure, but exposes the mother to the risk of introducing infection from the birth canal to the uterus. I came up with an idea for a less invasive method, by introducing the pressure tip catheter through the umbilical vein into the placenta, and thus measuring pressure in the uterus while the placenta was still inside the uterus, without the catheter coming into contact with the mother's tissues.

The idea probably originated from a problem I had had to solve some time previously: At the time, there was global interest in a non-invasive method of assisting the birth of a retained placenta (one which had not separated from the inside of the mother's uterus), by injecting oxytocin into the umbilical vein (misoprostol was also tried). The idea was that the oxytocin would diffuse from the placenta to the uterine muscle causing contraction of the muscle and thus shearing off the placenta. However, there was no evidence as to whether the injected

oxytocin reached the placenta. I had the idea of delivering the oxytocin more directly to the placenta by injecting it through a long catheter introduced along the umbilical vein to the placenta itself, rather than injecting peripherally into the vein as had been done up to this time. To test the effectiveness of this method, I developed an in vitro model whereby radio-opaque dye was injected via the catheter into a freshly-delivered placenta under Xray screening. I supervised one of our registrars at Baragwanath Hospital, Dr A Pipingas, to carry out a series of tests, and showed that provided at least 30ml of dye was injected via the catheter, the dye perfused to the periphery of the placental cotyledons (29). I mentioned the work to Iain Chalmers who was guest speaker at the 8th Priorities in Perinatal Care conference at Mpekweni in 1989. His National Perinatal Epidemiology Unit in Oxford was embarking on a large trial in collaboration with Memo Carroli of the Centro Rosario de Estudios Perinatales in Argentina, and they were able to at the last minute, incorporate the technique into their trial (Carroli et al, 1998). The method was also used in a subsequent large multicentre trial (Weeks et al, 2010). Injecting oxytocin into the placenta has not proved to be a useful method for removing a retained placenta, but the idea of accessing the placenta with a long catheter via the umbilical vein remained.

When searching for a non-invasive method of measuring postpartum intra-uterine pressure, this previous innovation probably acted as a catalyst for the idea of again using the umbilical vein for access to the placenta within the uterus. I supervised one of our registrars at Coronation Hospital, Dr Anthony Bamigboye, to conduce a series of experiments which showed it to be a feasible method (30).

3.27 Reviews of misoprostol for preventing or treating postpartum haemorrhage

31. **Hofmeyr GJ**, Gulmezoglu AM. Misoprostol in the third stage of labour and maternal mortality: a review. BMJ 2006. Rapid response to: Høj L, Cardoso P, Nielsen BB, Hvidman L, Nielsen J, Peter Aaby P. Effect of sublingual misoprostol on severe postpartum haemorrhagein a primary health centre in Guinea-Bissau: randomised double blind clinical trial BMJ 2005; 331: 723

32. **Hofmeyr GJ**, Walraven G, Gulmezoglu AM, Maholwana B, Alfirevic Z, Villar J. Misoprostol to treat postpartum haemorrhage: a systematic review. BJOG. 2005; 112: 547-53.

33. Gulmezoglu A, Forna F, Villar J, **Hofmeyr G**. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2007. 18; CD000494

34. **Hofmeyr GJ**. Medical treatment of postpartum haemorrhage. O&G Forum 2010, 20

One of the dilemmas facing researchers, clinicians, policymakers and advocates for women's health, is the fact that the results of scores of randomized trials using variable dosages and routes of administration in thousands of women under variable circumstances are exceptionally variable and contradictory. It is clear from the debate surrounding the Journal of the Royal Society of Medicine review discussed above, that different reviewers interpret the same information quite differently. We have, over the years published several reviews, all founded in the well-established methodology used for Cochrane systematic reviews (31-34). For the purposes if this dissertation, I will focus only on the extensive WHO Bulletin review referred to below.

3.28 Are there any other options?

35. **Hofmeyr GJ**, Abdel-Aleem H. Prevention of postpartum hemorrhage in the absence of uterotonics. Int J Gynaecol Obstet. 2006; 94 Suppl 2:S124-5

We highlight the potential role of uterine massage for preventing postpartum haemorrhage, particularly in setting with no access to pharmaceutical uterotonics, and call for relevant research.

36. Abdel-Aleem H, **Hofmeyr GJ**, Shokry M, El-Sonoosy E. Uterine massage and postpartum blood loss. Int J Gynaecol Obstet. 2006; 93: 238-239

All women received oxytocin. Blood loss >500ml with uterine massage occurred in 4/98 versus 8/102 without (RR 0.52, 95% CI 0.16 to 1.67). Additional uterotonics were used in 5/98 versus 26.102 respectively (RR 0.20, 95% CI 0.08 to 0.50).

37. Abdel-Aleem H, Singata M, Abdel-Aleem M, Mshweshwe N, Williams X, **Hofmeyr GJ.** Uterine massage to reduce postpartum hemorrhage after vaginal delivery. Int J Gynaecol Obstet. 2010; 111: 32-6

Three groups were compared. Uterine massage alone was less effective than oxytocin alone. The comparison of uterine massage plus oxytocin versus oxytocin alone was inconsistent between sites.

38. **Hofmeyr GJ**, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2008. 16; CD006431.

The review found insufficient evidence and called for more research.

39. Novikova N, **Hofmeyr GJ**. Tranexamic acid for preventing postpartum

haemorrhage. Cochrane Database Syst Rev. 2010: CD007872.

Blood loss greater than 400 ml was less common in women who received tranexamic acid after vaginal birth or caesarean section in the dosage of 1 g or 0.5 g intravenously (risk ratio (RR) 0.51; 95% confidence interval (CI) 0.36 to 0.72; two studies, 453 women).

A standard element of management of postpartum haemorrhage is to "rub up" the uterus. This is based on the clinical observation that the uterus responds to manual stimulation by palpably contracting, and this appears to reduce blood loss. The presumed mechanism is that mechanical stimulation releases endogenous uterotonic hormones, mainly prostaglandins, causing contraction of the uterus. This is analogous to stimulation of the lower uterine segment manually or with a Foley catheter bulb which has been proved to promote labour induction (as discussed in the section on labour induction).

Why not use uterine massage prophylactically to prevent postpartum haemorrhage? Uterine massage has long been used as part of the package 'Active management of the third stage of labour', but remarkably little attention has been given to testing whether it is effective or not. If uterine massage were indeed effective, it would be the ideal method, as it could be practiced anywhere, without dependence on supply of medications, and would be free of pharmacological side-effects (35). We collaborated with our colleagues in Assuit University to conduct 3 small randomized trials, the first in Egypt (36), and two simultaneously in Egypt and South Africa (37). The results were inconsistent, and may have been distorted by the concomitant use of oxytocin, and the fact that uterine massage might artificially increase measured

blood loss by expelling blood which would otherwise have pooled in the uterus. In a Cochrane systematic review of the subject, we emphasized the need for more research, particularly in settings with no access to uterotonic agents, where any benefits of uterine massage would be easier to demonstrate (38).

It is striking that in comparison to the hundreds of research papers on misoprostol, there have been no other trials on the effectiveness or otherwise of uterine massage. This highlights again the bias of medical research towards drug-based research, and is analogous to the relative lack of research on the Foley catheter for labour induction discussed previously.

An indication of the unusual enthusiasm for misoprostol is given by the fact that our review of tranexamic acid, another promising medication for treating postpartum haemorrhage, included only two studies (39).

3.29 Outvoted in Bellagio

In 2006 Helena von Hertzen from WHO arranged an ad hoc working group who met in Bellagio to develop guidance for the use of misoprostol. The guidance produced was published in a series of papers in the international Journal of Gynaecology and Obstetrics. I was the lead author on the paper on Misoprostol for treatment of postpartum haemorrhage and a co-author on the paper on misoprostol for prevention of postpartum haemorrhage. I tried very hard to convince my colleagues that a lower dose would be a safer option, but unsuccessfully, and the consensus was to recommend 600 mcg for both purposes. Rather that have my name associated with a recommendation I considered not the safest option, I withdrew from authorship of both papers (Alfirevic et al, 2007, Blum et al, 2007).

3.30 Balancing benefits and risks, and the dosage of misoprostol after childbirth

The line of thought which I have tried (unsuccessfully for the most part), through multiple publications, presentations and expert meetings, to persuade my colleagues to follow, is as follows:

1. The plausible benefits of misoprostol after childbirth are limited to improved contraction of the uterus which might reduce blood loss and thus the risk of death.

2. Physiological and clinical studies have shown no significantly greater effect of doses of 600 mcg or more over that of 400mcg.

3. The known and measurable side-effects (mainly pyrexia and shivering) are clearly dose-related.

4. More importantly, as with any potent medication, there is the possibility of other, unknown adverse effects which are also likely to be dose-related. In general, beneficial effects of drugs plateau at a certain dosage. When it comes to poisoning, there is no upper limit to the increase in harm.

5. In the context of routine, prophylactic use of a medication in all childbearing women, most of whom would not have developed postpartum haemorrhage and therefore would not benefit from the medication, the greatest emphasis should be on safety.

6. For these reasons, programs to distribute misoprostol widely for use by women following childbirth should use a higher dose only if there is robust evidence that such a dose is more effective than a lower dose.

7. Currently, there is no evidence that 600 mcg is more effective than 400 mcg.

3.31 Misoprostol after childbirth and the risk of death

40. **Hofmeyr GJ**, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organisation 2009; 87: 666-77

We analyzed 46 trials with more than 40 000 participants. Of 11 deaths reported in 5 trials, 8 occurred in women receiving 600 µg or more of misoprostol (Peto odds ratio, OR: 2.49; 95% CI: 0.76 to 8.13). Meta-analysis of direct and adjusted indirect comparisons of the results of randomized trials showed no evidence that 600 µg are more effective than 400 µg for preventing blood loss ≥1000 ml (RR: 1.02; 95% CI: 0.71 to1.48). Pyrexia was more common among women who received ≥600 µg rather than 400 µg of misoprostol (RR: 2.53; 95% CI: 1.78 to 3.60).

I have mentioned above that the current widespread use of misoprostol after childbirth is based on certain evidence of reduction in the proxy outcome: blood loss after birth; and the assumption that reduced blood loss will translate to reduced maternal death. One limitation of randomized trials is that they give information only on outcomes selected to be measured, and these usually focus on the perceived benefits and any known adverse effects of the intervention. In the case of misoprostol after childbirth, we focussed on blood loss and the obvious

side-effects, shivering and pyrexia. No-one measured other potential side-effects such as effects on cardiovascular dynamics, and there are bound to be others which have not even been thought of.

None of the trials have been large enough to assess the risk of death, but of course when deaths occurred in the trials, they were recorded. Because the intervention aimed to reduce deaths from haemorrhage, there is an intuitive (though quite illogical) expectation that if there were an adverse effect on deaths, these would also be related to haemorrhage. The idea that misoprostol might cause deaths unrelated to haemorrhage is not intuitive, and not easy to accept.

However, when a death was reported in a trial in Guinea-Bissau in 2005 (Hoj et al, 2005), subsequent correspondence in the British Medical Journal pointed out that any death in a trial should be regarded as a serious adverse event potentially linked to the study drug, and called for a randomized trial of misoprostol with death as the end-point (Sloan Winikoff & Blum, 2005).

With colleagues, I conducted a systematic review of all randomized trials of misoprostol after childbirth, focussing on deaths and effectiveness/side effects in relation to dosage (44). Because there were insufficient numbers for robust comparison of risk of postpartum haemorrhage from direct comparisons between 400 and 600 mcg, we used a statistical technique called adjusted indirect comparison (Bucher et al, 1997). In simple terms, randomized trials comparing either 400 or 600mcg with a common comparator (injectable oxytocic or placebo) were used to extrapolate the relative risks for 400 versus 600 mcg. Both direct and adjusted indirect comparisons found no difference in effectiveness between the two dosages. We validated the method by applying it to another outcome, pyrexia, for which there were much bigger numbers, and therefore robust

estimates from the direct comparisons. The indirect method proved to give very similar results to the direct method.

What about adverse effects? With misoprostol 600 mcg about 20% of women develop shivering which is severe in 2% of cases, and about 7% develop pyrexia, more rarely hyperpyrexia (fever above 40 degrees C, sometimes accompanied by delirium). The thermogenic response appears to be geographically related, with a rate of hyperpyrexia (>40 degrees C) as high as 36% following misoprostol 800 mcg sublingually and 16% following 600 mcg sublingually in Ecuador (León et al, 2012). The impact of these side-effects on women have, in my opinion, been undervalued, usually by presenting them as a small price to pay for avoiding death, for example:. "Although more women in the misoprostol group had shivering, in a low-resource setting, this may be acceptable and clearly preferable to excessive haemorrhage." (Derman et al, 2006). However, shivering and pyrexia are at the least, unpleasant experiences at a time of intense emotion and joy, when a woman wants to focus on her newborn baby. There is good evidence that disruption of early mother-child interaction may have long-term harmful effects. The discomfort and distress caused by these side-effects alone should be reason to avoid the higher dose without good evidence that it is more effective than a lower dose.

This is a classic case of 'where does the burden of proof lie?' Proponents of the higher dose want more proof that the lower dose is as effective. My approach is that in view of dose-related side-effects, the higher dose should be used only if there is proof that it is more effective than the lower dose.

What about death? To date, among all the randomized trials of misoprostol after childbirth involving more than 40 000 women, 15 deaths have been reported.

Four of these occurred in the comparison groups (injectable oxytocic or placebo), and 11 in the misoprostol groups, all of whom received misoprostol 600 mcg or more. This difference is not quite statistically significant. What the figures mean is that we can be 95% certain that the true effect of misoprostol in the dosages studied on maternal death lies somewhere between a small reduction and a large increase. These numbers are too small for certainty, but the balance of probability is that in doses of 600mcg or more, the adverse effects of misoprostol on post-childbirth homoeostatic mechanisms may cause more deaths than are prevented by the beneficial effects on uterine contraction. My contention is that even if increased death with the higher dose were a remote possibility, this would be a compelling reason not to use a higher dose without robust evidence that it is more effective than a lower dose.

I have presented these figures in formal presentations at international meetings in Washington and Entebbe (2006), Buenos Aires (2007), Luanda (2008), Seattle (2009), and Adelaide (2010), in many expert panel meetings, and we have published them in the WHO bulletin in 2009 (40). The figures have never been challenged, but they have been comprehensively ignored, and almost never quoted. My assumption is that in the context of a global imperative to roll out programs routinely using misoprostol 600 mcg after childbirth, the possibility that this dosage may cause more deaths than it prevents is too horrifying to contemplate. Blocking out that with which we are unable to cope is a human survival mechanism, and we are all human.

My efforts, and those of a few colleagues, to persuade the international health community that until we have more evidence, 400 mcg would be a safer dose to routinely expose large numbers of women in low-resource setting to, have been

spectacularly unsuccessful. Which is why the interchange in the foyer of the Fairfax Hotel to which I referred in the introductory interlude to this commentary, meant so much to me. One person was listening.

3.32 Close

A central theme of this thesis has been the dissonance between my assessment of the evidence and balance of possible benefits and harms from misoprostol used for specific purposes at specific doses, versus those of the majority of my colleagues. I have offered possible explanations for the differences between my perspective and that of the majority. I do believe that with time caution will prevail.

Misoprostol is a unique molecule which probably has the potential to reduce maternal mortality worldwide. It also causes many deaths from uterine overstimulation and rupture With respect to its use after childbirth, I believe that there is a real possibility that the current use of doses above 400mcg may cause more deaths than they prevent. From the bottom of my heart, I hope that I am wrong.

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