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Control of Blood Loss at Caesarean Section

A dissertation submitted to the University of Dublin
for the Degree of Doctor of Philosophy

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Trinity College Dublin, April 2011
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Supervisor: Professor Deirdre J. Murphy

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Summary

Introduction

Caesarean section is one of the most commonly performed major operations in women throughout the world. Operative morbidity includes haemorrhage, anaemia, blood transfusion and in severe cases, maternal death. The value of routine oxytocics in the third stage of vaginal birth has been well established and it has been assumed that these benefits apply to caesarean delivery as well. There is very limited evidence to guide practice.

Aim

The aim of this project was to assess the control of blood loss at caesarean section.

Methods

This thesis reports four components of the research: 1) a Cochrane systematic review of medical methods to prevent blood loss at caesarean section, 2) a survey of guideline implementation across Ireland and the United Kingdom (UK) examining the medications used by obstetricians and anaesthetists to control blood loss at caesarean section, 3) a randomised controlled trial (RCT) to evaluate the role of an oxytocin infusion in addition to bolus oxytocin on the control of blood loss at elective caesarean section, and 4) a prospective cohort study assessing the methods of measuring blood loss and the risk factors for major obstetric haemorrhage (MOH).

Results

The Cochrane systematic review found no evidence of sufficient magnitude or quality to recommend any particular uterotonic agent over another to prevent haemorrhage at caesarean section. The survey of guideline implementation found poor compliance with guidelines and huge variations in clinical practice. The RCT recruited 2069 women and demonstrated that an additional oxytocin infusion reduced the need for an additional uterotonic agent but had no effect on the high rates of MOH. The cohort study found that there was little correlation between methods of measuring blood loss and failed to identify a "gold

standard" method. Maternal obesity, older maternal age and an inexperienced operator were identified as risk factors for MOH.

Conclusions

Previous studies assessing control of blood loss at caesarean section have failed to provide definitive evidence for using one uterotonic agent over another. Oxytocin is the most commonly used agent, but variations in practice exist. The ECSSIT (Elective Caesarean Section Syntocinon Infusion Trial) RCT, the largest study to date, found that the use of an oxytocin infusion in addition to bolus oxytocin, reduced the need for an additional uterotonic agent but had no effect on overall rates of MOH. For inexperienced obstetricians however, the risk of MOH was almost halved with the additional oxytocin infusion. The routine use of this infusion is supported by the finding that an inexperienced obstetrician is an independent risk factor for MOH. Precise measurement of blood loss remains a concern and further research is required to find a "gold standard" method that will allow valid comparisons between different studies in different settings.

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LIST OF ABBREVIATIONS

AJOG	American Journal of Obstetrics and Gynecology
BMC	BioMed Central
BMI	Body mass index
BMJ	British Medical Journal
BNF	Birth Notification Form
CCT	Controlled cord traction
CI	Confidence interval
CS	Caesarean Section
DMEC	Data monitoring Committee
EBV	Estimated blood volume
ECSSIT	Elective Caesarean Section Syntocinon Infusion Trial
ESRI	Economic and Social Research Institute
FIGO	Federation of International of Gynaecologists and Obstetricians
Hb	Haemoglobin
HCT	Haematocrit
HRB	Health Research Board
ICM	International Confederation of Midwives
IMB	Irish Medicines Board
IQR	Interquartile range
KPI	Key performance indicator
MDG	Millennium Development Goal
MOH	Major obstetric haemorrhage (blood loss > 1000 ml)
NICE	National Institute for Clinical Excellence
NPRS	National Perinatal Reporting System
OECD	Organisation for Economic Cooperation and Development
OR	Odds ratio
PPH	Postpartum Haemorrhage

RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RR	Risk ratio
SD	Standard deviation
SOP	Standard operating procedure
TCD	Trinity College Dublin
TTN	Transient tachypnoea of the newborn
UNICEF	United Nations Children's Fund (formerly United Nations International Children's Emergency Fund)
WHO	World Health Organisation

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CHAPTER 1. INTRODUCTION

1.1 Introduction

Every minute, a mother dies somewhere in the world as a result of pregnancy-related haemorrhage. Although caesarean section saves lives, it increases the risk of haemorrhage compared to vaginal delivery. Over the past four decades, rates of caesarean section have soared globally and this rise has created one of the most concerning dilemmas in modern obstetrics.

This thesis documents a programme of work examining the control of blood loss at elective caesarean section with four distinct but linked elements: 1) a Cochrane systematic review was undertaken to evaluate all medical methods used for the prevention of blood loss at caesarean section, 2) a review of guideline implementation and survey of practice across Ireland and the United Kingdom was undertaken that examined the medications used by obstetricians and anaesthetists to control blood loss at caesarean section, 3) a multi-centre randomised controlled trial (RCT) was performed to assess whether an oxytocin infusion in addition to an oxytocin bolus would reduce blood loss at elective caesarean section, 4) a prospective cohort study, embedded within the RCT, was performed to compare methods used to estimate blood loss and to identify risk factors for haemorrhage at caesarean section.

1.2 Background

1.2.1 History of caesarean section

The description of infants being delivered through an opening in the mother's abdomen dates back to ancient times, performed mostly peri- or post-mortem.[1] The first reported successful caesarean section, one in which both mother and baby survived, was performed in 1500 by a Swiss sow gelder, Jacob Nufer, on his wife. She allegedly lived to 77 years of age and bore several more children.[2] Despite her survival, mortality at that time was close to 100%, with bleeding and infection the main causes, resulting from non-closure of the uterine incision. Thankfully, much has changed since 1500. There are now many possible approaches to performing a caesarean section, the aim being to achieve safe delivery of the infant with a minimum of maternal morbidity. Caesarean section is

now one of the most commonly performed major operations in women throughout the world.

1.2.2 Epidemiology of caesarean section

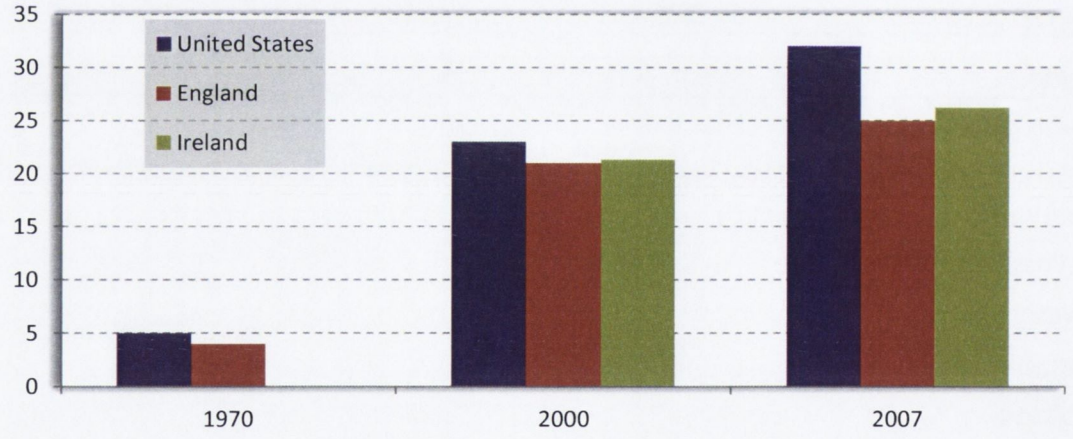
The rate of caesarean section may be defined as the number of caesarean deliveries divided by the total number of live births, and is expressed as a percentage. Many argue that it should be possible in theory to calculate an optimal caesarean section rate which would minimise maternal and perinatal adverse outcomes. However, this has not proven possible.[3] Attempts to calculate an "ideal" rate have been met with sharp criticism, the argument being that such an exercise may be interesting but of no value to the obstetrician making decisions on the labour ward.[3] In 1985 the World Health Organisation (WHO) recommended that the optimum caesarean section rate was between 10 and 15%, with no additional benefit associated with a higher rate.[4] Concerns were raised over the validity of this recommendation based on admittedly poor quality data, causing global controversy.[5] This recommendation was updated in 1997 by UNICEF and the WHO, recommending a rate of between 5 and 15%.[6] Few countries have achieved such rates, with marked variation in rates between developed and developing countries.

The increase in rates observed in many developed and middle-income countries contrasts sharply with the very low rates in numerous resource-poor settings. In the developed world, higher rates have been associated with increased maternal morbidity and mortality, problems for future pregnancies and have huge resource implications.[7 8] On the other hand, it is the lack of resources in the developing world and the resulting underuse of caesarean section that has contributed to high maternal and perinatal morbidity and mortality.[9] An analysis of global caesarean section rates by Betrán and colleagues found the lowest rates in Western Africa (1.9%) and the highest rates in Eastern Asia (40.5%).[10] A Global Survey on Maternal and Perinatal Health, conducted by the WHO in Latin America, Africa and Asia from 2004 to 2005, found the overall caesarean section rate was 35.4%.[11-13] More recent data from the National Vital Statistics System in the United States revealed that almost one-third (32%) of all births in the United States in 2007 were caesarean deliveries.[14]

1.2.3 Worldwide caesarean section trends

Accurate determination of global caesarean section rates can be very difficult as national estimates in many countries are unreliable and often not available.[15 16] It is not just the actual rates of caesarean section that have caused concern, it is more the dramatic escalation in these rates that has generated considerable alarm. Over the past four decades, rates have risen dramatically.[7 8 17] (Figure 1-1) In developed countries in the early 1970s, rates were estimated at about 5%,[18-20] but by the late 1990s, some regions of the world were reporting rates in excess of 50%.[21] This worrying trend has continued.

The rate of caesarean deliveries in the United States was 5% in 1970, increasing to 23% in 2000, and rising to an all-time high of 32% in 2007.[22 23] In England a similar trend has been reported, 4% in 1970, rising to 21% 30 years later, with a further jump to 25% by 2007.[7 24] In Ireland, we have seen an escalation similar to that seen throughout the world and it will be discussed further in the following section.



* Irish data not available for 1970

Figure 1-1 Global rise in rates of caesarean section

1.3 The Irish situation

1.3.1 Sources of Irish data

Data on rates of caesarean section within Ireland may be obtained from a variety of sources including:

- National Perinatal Reporting System (NPRS)
  The NPRS is the main source of data on perinatal events in Ireland, collected and processed by the Economic and Social Research Institute (ESRI) since 1999. This contains information on all births in the Republic of Ireland. Births are registered and notified on a standard Birth Notification Form (BNF) which is completed where the birth takes place, either at the hospital or by the attending midwife. In 2009, Brick and Layte produced an analysis of recent Irish caesarean section trends, on behalf of the ESRI.[25]

- Annual Reports produced by the three main Dublin maternity hospitals
  The three main maternity hospitals in Dublin are located within a 5 km radius of the city centre in the Greater Dublin Area. An annual audit of the activity of the relevant year is produced by each of these hospitals in the form of an Annual Report. These reports are presented and externally assessed every November at the Annual Reports Meeting, held at the Royal College of Physicians of Ireland. Heated debates have been known to ensue, often centred around the varying caesarean section rates seen within the three units.

- Irish Childbirth Trust (Cuidiú)
  Cuidiú is a voluntary organisation that provides support to parents across the country. In 2005, they collated data on national caesarean section rates.

1.3.2 Caesarean section rates in Ireland

The rising trends seen globally have been mirrored within the Irish setting also and are the source of considerable concern.[26] The analysis of recent Irish caesarean section trends referred to above by Brick and Layte on behalf of the ESRI

demonstrated a 58% increase in caesarean sections from 1993 to 1999, which has continued to rise.[25] (Figure 1-2)

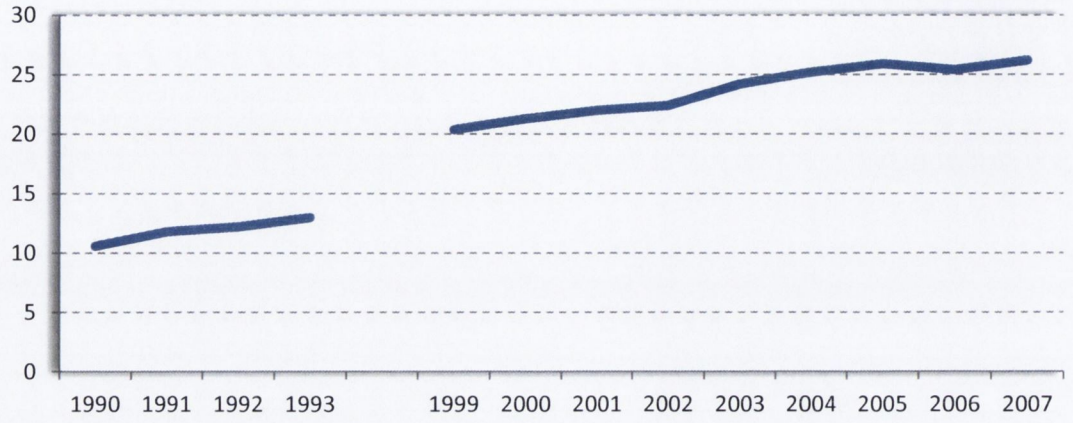


Figure 1-2 Rates of caesarean sections in Ireland 1999 – 2008

(Data obtained from NPRS - data not available for 1994-1998)

Even within the 5 km radius of the greater Dublin area, significant variation persists. (Figure 1-3)

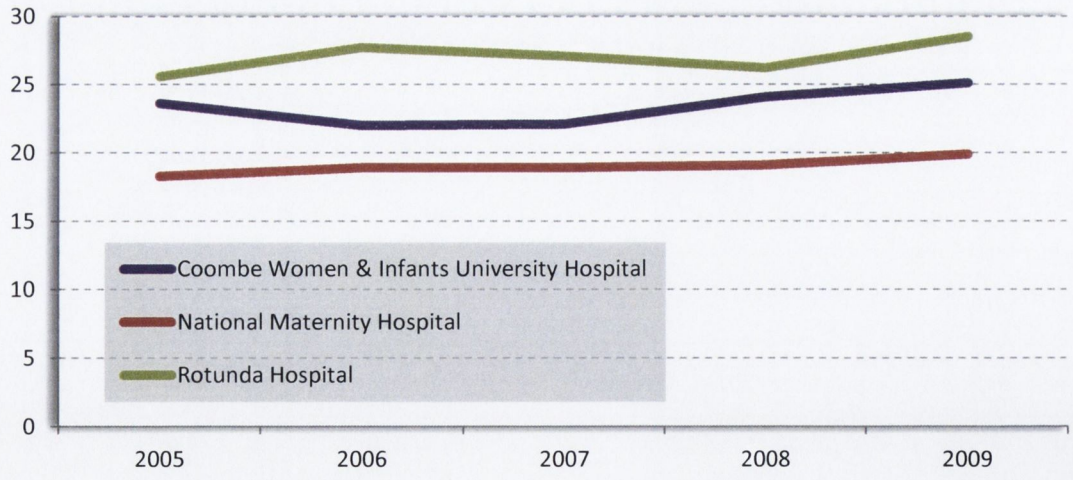


Figure 1-3 Rates of Caesarean Section in the three Dublin Maternity Hospitals (2005-2009)

(data obtained from annual hospital reports)

Considerable differences are also seen across all of the maternity centres within Ireland. (Figure 1-4)

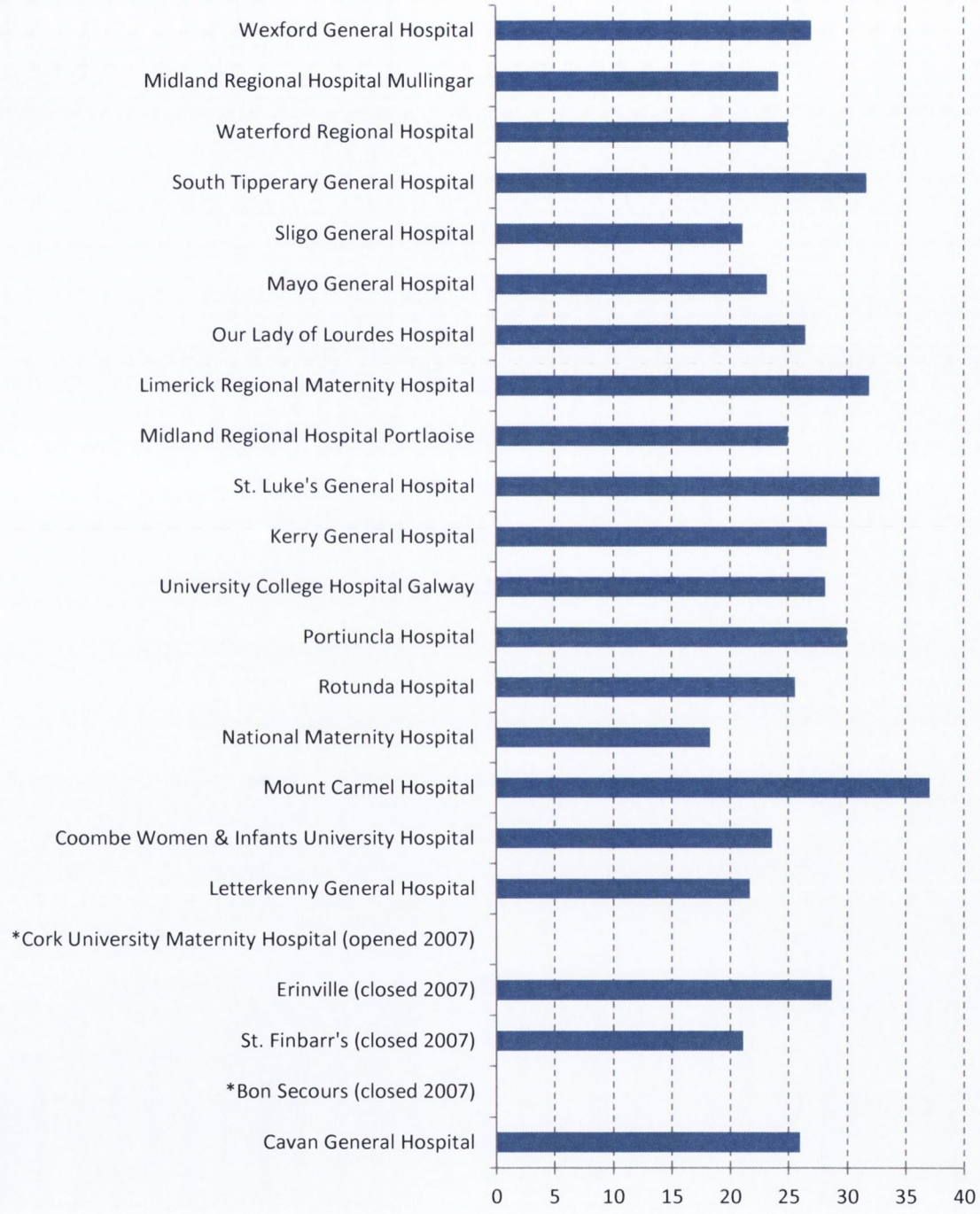


Figure 1-4: Caesarean section rates in Irish Maternity Units (2005)

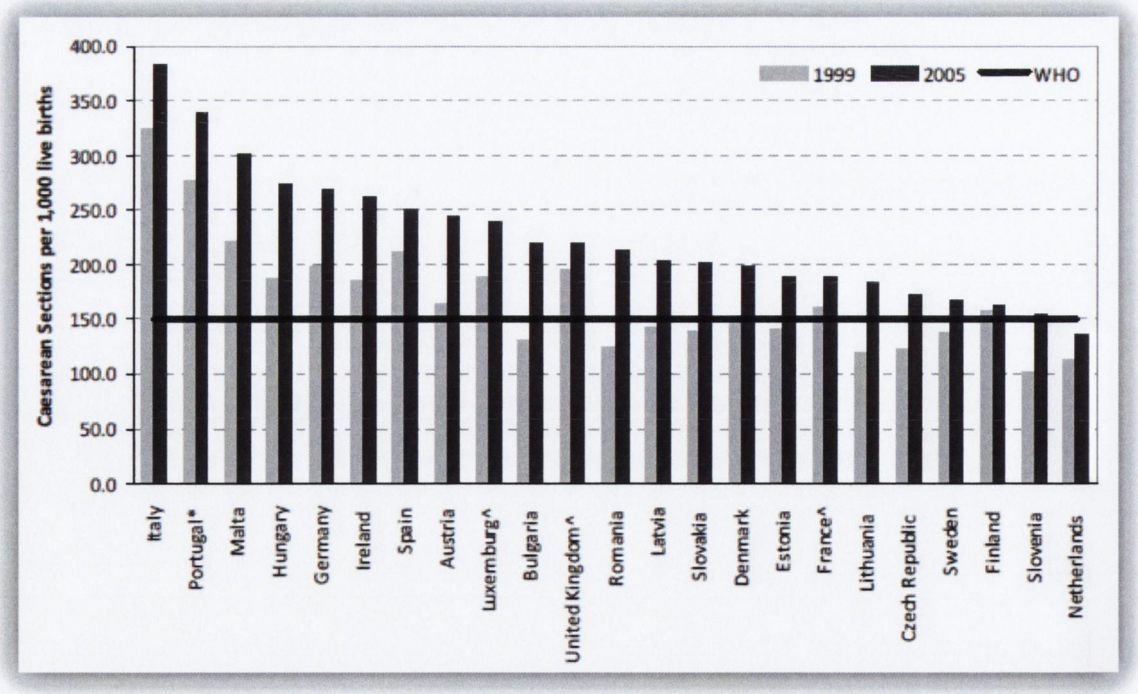
(data obtained from www.cuidiu-ict.ie) *no data available

1.3.3 *Political interest*

The Department of Health and Children and the Health Service Executive (HSE) is acutely concerned by this global trend and has made caesarean section a priority topic. The HSE's Programme of Obstetrics and Gynaecology has focused on reducing the caesarean section rate in first-time mothers (primary caesarean). The caesarean section rate has been identified as a key performance indicator (KPI) by the Department. A national "normal" caesarean section range per maternity unit has been developed and has recently been distributed to the programme's local implementation boards for their consideration. Hospitals outside this "normal" range will be asked to review their practices. The local and national audit of caesarean sections is intended to be an ongoing audit. It aims to reduce the wide variations in practice that are seen across the country by continually reviewing practice, with the ultimate objective of improving quality of care and patient safety.

1.3.4 *Ireland within the global context*

Figures on European rates of caesarean section produced by the WHO in 2009 placed Ireland sixth highest, much higher than the WHO's recommended target of 15%. (Figure 1-5)



(data obtained from the WHO Regional Office for Europe 2009)

* 1999 data not available for Portugal, data from 2000 is substituted

ˆ 2005 data not available for Luxembourg, United Kingdom and France, data from 2004 is substituted.

Data not available for Cyprus, Poland or Greece for both years

Figure 1-5 European rates of caesarean section for 1999 and 2005 compared to the WHO recommended rate of 15%.

Figure 1-6 demonstrates where Ireland is placed within the global setting.

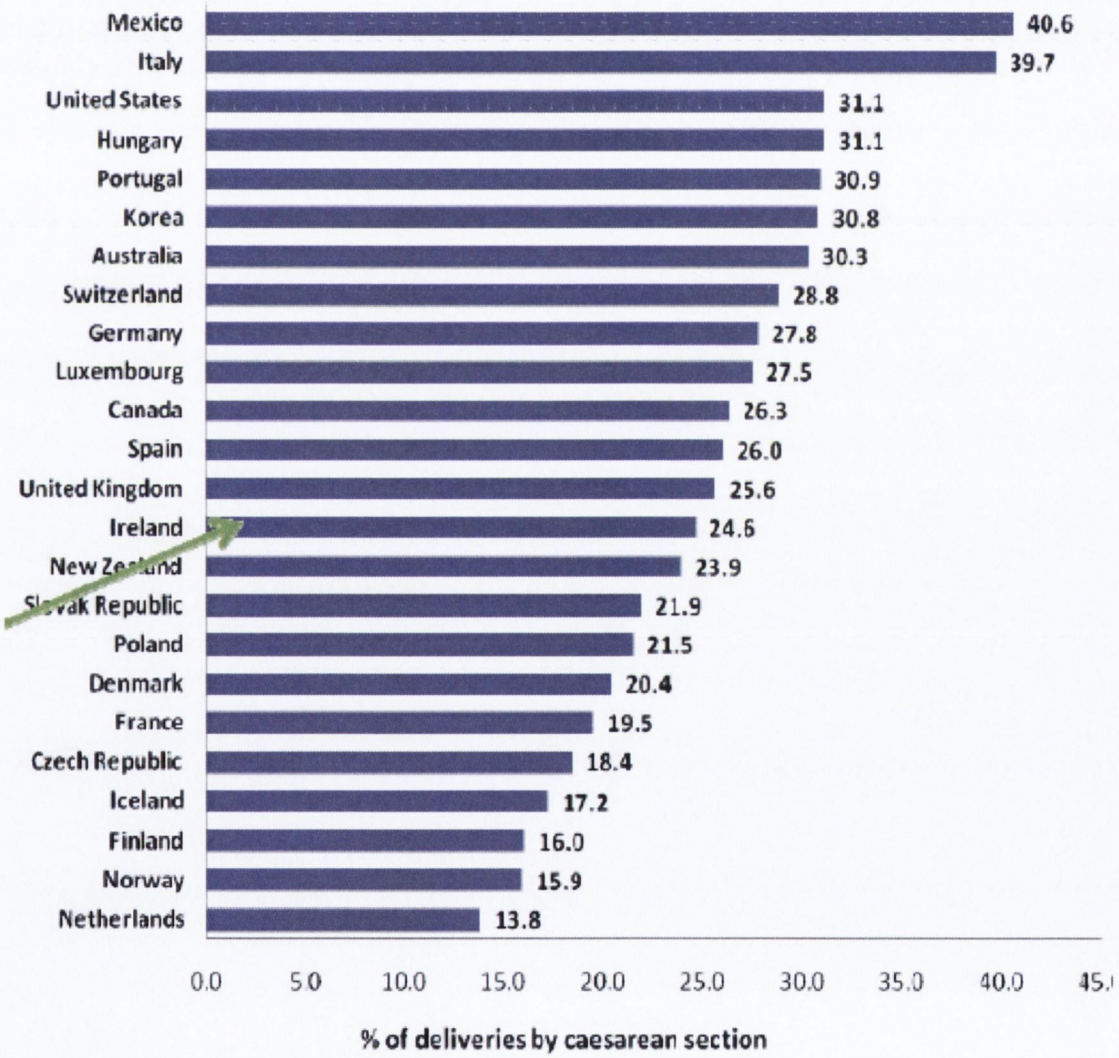


Figure 1-6 Caesarean section rates among Organisation for Economic Cooperation and Development Countries (OECD), 2006

(data obtained from the OECD)

1.4 Understanding the current trends

Understanding the reasons behind the rise in caesarean section rates has proved challenging. The indications for caesarean are often not reliably documented making comparisons difficult. We have moved a great distance from the original use of caesarean delivery as a "last resort" to an acknowledgement in current practice that this operation can save lives and reduce maternal and neonatal harm in certain circumstances. The improved safety of the procedure may explain a proportion of the rise together with advancements in anaesthesia, antibiotic prophylaxis, availability of blood and blood products for transfusion, and improvements in neonatal intensive care. Where the likelihood of harm from vaginal delivery is high, caesarean section is clearly indicated, for example placenta praevia, transverse lie, cord prolapse or vasa praevia. Other indications may not be as clear cut and have led to considerable debate.

1.4.1 UK National Sentinel Caesarean Section Audit

In 2001, the National Sentinel Caesarean Section Audit was published in the United Kingdom.[7] This audit was performed in response to growing concerns over the variation in caesarean section rates and a lack of good quality maternity data across England, Wales and Northern Ireland. The aims were to explore what type of women were undergoing caesarean section and why. It also surveyed obstetricians' views towards caesarean section. It found that more than one in five (21.5%) of births in England and Wales were by caesarean section. In Northern Ireland the rate was 23.9%. Most worryingly, caesarean section rates had increased over the preceding decade by one per cent a year in England and Wales. Just over half (51%) of the obstetricians surveyed believed that the caesarean section rate in their unit was too high, and that the average rate was also excessive.[7] Overall, the most common indications for caesarean section were: fetal distress (22%), failure to progress (20%), previous caesarean section (14%), breech presentation (11%) and maternal request (no medical reason) (7%). When subdivided, for women having their first (primary) caesarean section, the most common indications were: fetal distress (28%), failure to progress (25%) and breech presentation (14%). For women having a repeat caesarean section, the most common indications were: previous caesarean section (44%), maternal request (12%), failure to progress (10%), fetal distress (9%) and breech presentation (3%).[7]

As the overall rate of caesarean section had increased, it was no surprise to see that the indication with the greatest relative increase was previous caesarean section. The authors concluded that the escalation in rates was not the result of changes in obstetric management, but rather secondary to a lowering of the threshold at which the decision to perform a caesarean section was made.[7] This view mirrored that of the obstetricians surveyed. A subsequent survey of clinical directors in the UK found fear of litigation to be the most common reason for the increasing caesarean section rates.[27] Other reasons included maternal request, reduced obstetric skills and a sharp decline in the number of vaginal breech deliveries.[27]

In essence, two main groups of reasons for the escalation in caesarean section rates have been suggested: 1) demographic differences, and 2) changing clinical practice.[25]

1.4.2 Demographic contributors

The clinical indicators (including fetal distress, failure to progress, previous caesarean section and breech) may be influenced by changing trends in fetal and maternal characteristics. There is a substantial body of evidence to suggest that much of the observed increase in caesarean section rates seen over the past four decades is due to changes in reproductive behaviour and corpulence.

In a population-based study of more than 127,000 births in Nova Scotia, adjustment for maternal characteristics reduced the temporal increase in primary caesarean section rates from 21% to 2% between 1988-1991 and 1998-2000.[28] The authors suggested that almost all of the increase in caesarean rates over the time period from 1998 to 2000 could be attributed to changes in maternal age, parity and weight.

Using nationally collected Scottish data from 1980 to 2005, Smith and colleagues demonstrated that a substantial proportion of the rise in emergency primary caesarean sections could be attributed to delaying first childbirth.[29] The authors postulated that the association between increased caesarean section rates and advanced maternal age was likely to have a biological basis.

A recent systematic review and meta-analysis of published cohort studies has shown that the risk of caesarean delivery in overweight women increases by 50% and is more than double in obese women when compared to women with a normal BMI.[30]

In essence, advancing maternal age,[28 29 31-34] obesity,[28 30 35-39] and smaller parity[28 29 34 40-42] have all been identified as independent risk factors for caesarean section.

1.4.3 Changing clinical practice

Changes in the preferences and behaviours of pregnant women and maternity healthcare providers have occurred.[28] Higher rates of labour induction,[43 44] electronic fetal monitoring,[45] fetal blood sampling,[45] and a reduction in obstetrical skills[28] are often blamed for the rising caesarean section rates.

Women's preferences and maternal request as an indication for caesarean section are more contentious issues. Current guidance from the National Institute for Clinical Excellence in the UK and the Royal College of Obstetricians and Gynaecologists suggests that maternal request alone should not be considered sufficient indication for caesarean section.[8] We have already seen however that 7% of caesarean sections were performed in the UK for this very reason.[7] Similar rates have been seen elsewhere. In the United States, a population-based study of caesarean section trends found that the incidence of caesarean section with no medical indication almost doubled from 3.7% in 1996 to 6.9% in 2003.[46] The Public Health Agency of Canada conducted a telephone survey of more than 6000 women who had recently delivered to learn more about their maternity care experiences and found that 8.1% of women had requested a caesarean section without any medical indication.[47] Rates appear to be higher in private hospitals in Ireland (see Figure 4), and women delivering in private hospitals are more likely to have an elective caesarean delivery.[25] Similar trends have been described in other countries.[12 48 49] Maternal request has been proposed as a likely explanation. Many of the studies however, comparing rates in public and private hospitals do not explore the specific indications for caesarean section.[12 25 48 49] A recent analysis of variation in caesarean section rates across English NHS trusts suggests that maternal request is unlikely to make any substantial contribution to the overall increased rates.[40]

1.4.4 Classification of caesarean section

Upon reviewing the literature, the most striking challenge in understanding the fundamental reasons behind the dramatic change in caesarean section rates lies in the lack of uniformity in coding of indications for the procedure. More useful insights into the cause of these changing trends will hopefully be gained from the widespread adoption of a robust system for documenting the indication for the procedure, allowing comparisons to be made within a unit itself and across other units.

Caesarean sections are often divided into the two broad categories of "elective" and "emergency". An elective caesarean section is often defined as any caesarean section planned more than 24 hours in advance. A recent paper by Berghella et al. has criticised this categorisation, suggesting that it lacks specificity.[50] They have suggested that clear documentation of the indication for delivery would be more beneficial and have proposed eliminating the expression "elective" from obstetric practice. It is however a widely used and understood expression, but there is no doubt that a more detailed classification system would add significant value to interpretation and comparison of data.

Dr Michael Robson, current Master of the National Maternity Hospital, Holles Street, Dublin proposed a classification system for caesarean sections, the Robson Ten Group Classification System.[51] It is a mutually exclusive, totally inclusive, prospectively determined classification system.[51] [52] The characteristics of a woman's pregnancy, rather than the reason for caesarean section, form the basis for the classifications. It has been adopted not only by the National Maternity Hospital, but also by national registries and more recently by international agenies.[53-57] As more units report using this classification system, it should facilitate understanding of the groups of women globally in whom the caesarean section rate is rising. The characteristics of the pregnancy used for the 10-group classification are: (i) single or multiple pregnancy; (ii) nulliparous, multiparous or multiparous with a previous CS; (iii) cephalic, breech presentation or other lies; (iv) spontaneous or induced labour and (v) term or preterm births. Robson's belief is that it is not the actual number of caesarean sections that is important, rather the reasons for the caesarean section. A recent systematic review of all classification systems for caesarean section has suggested that Robson's classification is the most suitable system to meet the current global needs.[58]

1.5 Caesarean section-related morbidity

As caesarean section rates continue to rise both locally and globally, it is important to highlight the impact such a procedure can have on the health outcomes of mothers and babies.

1.5.1 Maternal morbidity

The caesarean section guideline issued by NICE [8] and the more recently published RCOG consent advice for caesarean section[59] outline several conditions that are more likely to affect the mother after caesarean section compared with vaginal delivery. Table 1 highlights the maternal risks associated with caesarean section and has been adapted from these documents. A wide range of negative social and emotional consequences of caesarean section have also been cited, including poor birth experience, less early contact with the baby and poor overall mental health.[60]

The haemorrhagic morbidity associated with caesarean section will be discussed in more detail later in this chapter.

Table 1-1 Frequent and serious occurring risks of caesarean section

Frequent risks	Frequency
Increased risk of repeat caesarean section in subsequent pregnancies	1 / 4
Persistent wound and abdominal discomfort for the first few months after surgery	9 / 100
Infection	6 / 100
Haemorrhage	5 / 100
Readmission to hospital	5 / 100
Blood transfusion	Risk not quoted

Serious risks	Frequency
Thromboembolic disease	4-16 / 10000
Admission to ICU	9 / 1000
Emergency hysterectomy	7-8 / 1000
Increased risk of placenta praevia and placenta accreta in subsequent pregnancies	4-8 / 1000
Need for further surgery at a later date (including curettage)	5 / 1000
Increased risk of uterine rupture in subsequent pregnancies	2-7 / 1000
Bladder injury	1 / 1000
Ureteric injury	1 / 10000
Death	1 / 12000

1.5.2 Perinatal morbidity

In addition to the increased risks for the mother, there are notable increased risks from caesarean delivery for the baby. Respiratory distress syndrome and transient tachypnoea of the newborn (TTN) are both significantly increased after delivery by caesarean section and especially when the woman has not laboured. The risk is even greater if delivery occurs before 39 weeks or if there is uncertainty about the due date.[8 61] Although usually not life-threatening, unanticipated admission to the neonatal unit can be very distressing for the mother and also has significant resource implications.[62] Accidental surgical cuts[60 63] and increased breastfeeding difficulties[60 64] have also been described. Rates of unexplained infant mortality among primiparous women in a US study were found to be 56% higher for caesarean deliveries compared to vaginal ones. For multiparous women, the infant mortality rates for caesarean deliveries were more than twice that for vaginal deliveries.[65] Apart from the short-term adverse outcomes for the baby, caesarean section has also been associated with risks to long-term health. Meta-analyses indicate that infants delivered by caesarean section have a 20% increase in the odds of developing asthma and type 1 Diabetes Mellitus in childhood or adulthood.[66 67] Links to the occurrence of food allergies and obesity have also been suggested.[68]

1.6 Economics of caesarean section

In the current economic climate, the cost implications of rising caesarean section rates cannot be ignored. In 1997, the Audit Commission in the UK reported that a 1% rise in the caesarean section rate costs the NHS £5 million per year.[69] In 2002, a study examining Scottish data explored the costs of alternative modes of delivery during the first two months postpartum. The authors found that the initial hospitalisation costs for caesarean section were more than twice those for spontaneous vaginal delivery. When further expenses, including hospital readmissions, midwifery care, GP care and health visitor support, were added, caesarean deliveries were found to cost 1.8 times as much as spontaneous vaginal deliveries.[70] Henderson and colleagues conducted a systematic review between 1990 and 1999 of the economic aspects of alternative modes of delivery, confirming that caesarean section is far more costly than vaginal delivery.[71] Increased staffing requirements, theatre time and extended in-patient hospitalisation account for the higher costs.

1.7 Postpartum haemorrhage

1.7.1 Definition of postpartum haemorrhage

Postpartum haemorrhage (PPH) is traditionally defined as blood loss in excess of 500 ml from the genital tract following delivery. Primary postpartum haemorrhage refers to haemorrhage within the first 24 hours, whereas secondary describes bleeding from 24 hours to 42 days.

1.7.2 Epidemiology

An estimated 500,000 women die from pregnancy-related complications every year.[72] Postpartum haemorrhage is thought to account for up to one quarter of these deaths and remains a leading cause of maternal mortality and severe maternal morbidity.[73-76] It is estimated that one women dies every four minutes from PPH.[77] The risk of dying from PPH depends not only on the amount of blood lost but also on the pre-existing health status of the woman.[78] PPH occurs in approximately 5% of all deliveries.[78] Poverty and malnutrition, endemic in low-resource settings, compound the problem.

1.7.3 Global concern

The shocking statistics about haemorrhagic morbidity and mortality are undoubtedly a source of great concern globally. The United Nations Millennium Development Goals (MDGs) are eight goals that all 191 UN member states have agreed to try to achieve by the year 2015. They are derived from the United Nations Millennium Declaration, signed in September 2000. Millennium Development Goal 5 is aimed at improving maternal health, with a target of reducing maternal mortality by 75 percent. Many international bodies have added their support to achieve MDG 5. In October 2003, at the XVII World Congress of the International Federation of Gynaecology and Obstetrics (FIGO) held in Santiago, Chile, FIGO launched an international effort with the International Confederation of Midwives (ICM) and other partners and donors to develop strategies to prevent PPH and to identify effective medical and surgical treatments in situations where it still occurred.[79] Given the statistics described earlier in this chapter, strategies aimed at reducing postpartum haemorrhage are clearly essential if the target of MDG 5 is to be achieved.

1.7.4 Pathophysiology

Throughout pregnancy, maternal blood volume increases by almost 50% (from 4 L to 6 L) and the red cell volume increases by 25%.[80] The perfusion demands of the low-resistance uteroplacental unit are fulfilled by the increase in blood volume and a reserve for the blood loss that occurs at delivery is secured.[81] At term, the estimated blood flow to the uterus is 500–800 ml / min, constituting approximately 10-15% of cardiac output. The uterine blood vessels that supply the placental site traverse a weave of myometrial fibres. As these fibres contract following delivery, myometrial retraction occurs. Control of haemorrhage from the uterus after delivery is orchestrated by two mechanisms: vasoconstriction provoked by myometrial contraction and retraction, the more important physiological actions in haemostasis, aided by intravascular thrombosis in the placental bed induced by platelet adhesion, aggregation, and formation of fibrin.[82] Uterine atony is defined as failure of the uterus to contract adequately following delivery.[83]

One of the greatest challenges to both the immediate management of the patient and to research in this area is the notorious inaccuracy associated with measuring blood loss. A gold standard method is lacking and traditionally it is

underestimated. The signs of hypovolemic shock are more subtle in pregnancy due to physiological adaptation putting the patient at risk of late intervention.

1.7.5 Aetiology

The causes of postpartum haemorrhage are traditionally referred to as the 4 T's: tone (70%), tissue (10%), trauma (20%) and thrombin (1%).[84]

Tone

Uterine atony is the leading cause of PPH and can lead to rapid and severe haemorrhage and hypovolaemic shock. It can occur after spontaneous vaginal delivery, instrumental delivery or caesarean section.

Tissue

Uterine contraction and retraction leads to detachment and expulsion of the placenta. This permits continued retraction and optimal occlusion of the blood vessels. Most retained placentas can be removed manually, but abnormal placentation may occur and the placenta may become morbidly adherent, e.g. placenta accreta or percreta.

Trauma

Genital tract trauma may occur at the time of delivery and include cervical, vaginal or labial injuries. Other forms of trauma include uterine rupture or trauma to the broad ligament.

Thrombin

Disorders of the clotting cascade and platelet dysfunction may also result in PPH, but are much less common. Abnormalities may be inherited or acquired. If a bleeding disorder is suspected, haematological consultation is essential.

1.7.6 Prevention

The majority of deaths from PPH occur within four hours of delivery, suggesting they are a consequence of the third stage of labour.[85 86] The third stage of labour is defined as the period from delivery of the baby until the delivery of the placenta and its membranes. Active management of the third stage of labour has three components: use of a prophylactic uterotonic agent, early umbilical cord

clamping and controlled cord traction.[87] Expectant (or physiological) management involves waiting for the signs of placental separation and allowing the placenta to deliver spontaneously or aided by gravity or nipple stimulation.[88] Active management has been proven to work[87 89-91] and the prevalence rate of PPH has been shown to be approximately 5% when active management is used compared to 13% when expectant management is used. The overall aim is to prevent uterine atony.

The WHO has made the following recommendations to minimise maternal morbidity and mortality rates:[92]

1. Active management should be offered to all women by skilled care providers
2. Skilled attendants should offer uterotonics to prevent PPH. Uterotonics include oxytocin, ergometrine, misoprostol, carboprost and carbetocin. Oxytocin is the recommended agent.
3. Early cord clamping is recommended only when the newborn needs to be resuscitated.
4. Despite the lack of evidence to support cord traction, this practice should be continued as part of active management.

Each of the uterotonic agents will be discussed in more detail later in this chapter.

1.7.7 Treatment

The initial goal of treatment is to determine the cause of the haemorrhage while instituting resuscitative measures. Assessment of uterine tone and a complete inspection of the lower genital tract are required. The goal of resuscitative measures is to maintain haemodynamic stability and oxygen perfusion of the tissues. Local guidelines for the management of PPH and major obstetric haemorrhage (MOH) should be in place and should be followed.

Former president of the Royal College of Obstetricians and Gynaecologists, Professor Sabaratnam Arulkumaran, and his colleague, Dr. Chandraharan, have proposed the following mnemonic "HAEMOSTASIS" describing a management plan for the effective control of PPH:[93]

H	Get **H**elp
A	**A**ssess (haemodynamic status and blood loss) and resuscitate
E	**E**stablish a**e**tiology, **e**cbolics, **e**nsure availability of blood
M	**M**assage the uterus
O	**O**xytocin infusion / prostaglandins
S	**S**hift to theatre
T	**T**amponade (balloon) or uterine packing
A	**A**pply compression sutures
S	**S**ystematic pelvic devascularisation
I	**I**nterventional radiology, if appropriate
S	**S**ubtotal or total hysterectomy

1.8 Caesarean section and postpartum haemorrhage

Bleeding at caesarean section can arise from the incised edges of the uterus, the placental bed or as a result of uterine atony. Of these three mechanisms, uterine atony has been identified as the most common cause of haemorrhage at caesarean section.[94]

Much attention has been focused on the third stage of vaginal birth to reduce PPH, whereas the third stage of caesarean section has received little attention to date. It has been assumed that the benefits seen with active management apply to caesarean delivery as well. Limiting the focus on PPH to vaginal delivery was entirely appropriate while rates of caesarean section were very low. However, as these rates have soared, it is now incumbent on the obstetric profession to shift our attention, and to focus specifically on caesarean section as a separate entity.

The average blood loss at vaginal delivery is estimated at 300 -400 ml[95], whereas the average blood loss at caesarean section is approximately 700 – 1000 ml.[96] An elective caesarean section has been shown to double the risk of PPH (blood loss greater than 500ml) compared to vaginal delivery.[96] An emergency caesarean section, one which is unplanned either before or after labour has commenced, has been shown to quadruple this risk.[97] Massive obstetric haemorrhage (blood loss >1 litre) has been reported to occur in 7.3% of caesarean sections.[98] As major obstetric haemorrhage (MOH) remains a leading cause of maternal death, early and accurate recognition are essential to reduce adverse outcomes.[97]

Severe anaemia affects approximately 11% of all women with a primary PPH.[77] It can result in disabling fatigue and reduce a woman's capacity to care for herself and her child, and to work.[99] Approximately 1% of women will require transfusion following spontaneous vaginal delivery, whereas this figure increases to 5-6% for women with caesarean sections.[100] The risk of infection from transfusion with blood products is undoubtedly higher in developing world countries without screening guidelines, whereas in countries of the developed world, the risks arise from adverse reactions.[101]

1.9 Risk factors for postpartum haemorrhage at caesarean section

There is an extensive body of literature examining risk factors for haemorrhage following delivery, but the vast majority have focussed on vaginal delivery rather than caesarean delivery. Definitions of PPH vary across the studies, with some describing it as blood loss in excess of 1000 ml and others using a cut-off of 1500 ml. Methods of measuring blood loss also differ from one study to another, some using gravimetric methods and others using haemoglobin and haematocrit changes. The lack of uniformity makes it difficult to draw any meaningful comparisons.

1.9.1 Maternal factors

Obesity predisposes women to inefficient uterine contractility in labour and was identified earlier in this chapter as an independent risk factor for caesarean section. It has also been shown, most likely by the same mechanism, to be associated with PPH at caesarean section. In an Australian study of more than 4800 caesarean deliveries, obesity was a risk factor for PPH following emergency deliveries, but not for elective ones (OR 2.28, 95% CI 1.17 to 4.16).[102] Similar findings also emerged from a more recent Norwegian case-control study.[103]

Ethnicity also appears to play a role with Hispanic and North American races more likely to experience PPH following caesarean section.[104] [105] However little explanation has been offered for this finding.

Pre-eclampsia was identified as a risk for PPH in two US studies of more than 4600 women.[104] [105] In vaginal deliveries, it has previously been shown to be one of the most important predictors of PPH, most likely contributing to uterine atony.[78]

Intrapartum disorders,[105] including bleeding,[102] prolonged labour,[104] dystocia[102] [104] and caesarean section at full dilatation[103] were all noted to be independent risk factors for PPH. Unsurprisingly, similar findings have been seen for vaginal deliveries.[78]

1.9.2 Surgical and anaesthetic factors

Despite emerging evidence, there is still no widely accepted technique for performing caesarean sections. There is wide variation in surgical approaches and techniques vary from obstetrician to obstetrician.[106]

Skin incision

A transverse suprapubic skin incision is widely accepted as preferable to a midline incision and a recent Cochrane review found that the Joel-Cohen technique was associated with less bleeding than other incisions (weighted mean difference -58.00, 95% CI -108.51 to - 7.49 ml; 101 women, one trial).[107]

Uterine incision

As for the skin incision, a transverse uterine incision is recommended and associated with less haemorrhage. Blunt extension of this incision has been associated with less bleeding compared to sharp extension.[108] [109] Interestingly, a recent trial compared the direction of expansion, medial- lateral versus cephalad-caudad, and found less bleeding with the latter.[110]

Placental delivery

In 2008, a Cochrane systematic review found that manual removal of the placenta was associated with increased rates of major obstetric haemorrhage (blood loss > 1000 ml) (RR 1.81, 95% CI 1.44 to 2.28; 872 women, two trials) compared to spontaneous delivery and controlled cord traction.[111] It was also associated with greater blood loss and endometritis.

Closure of the uterine incision

Closure of the uterine incision has been a contentious issue over the past few years. Two aspects have given rise to debate: the site of the repair (intrabdominal or extraabdominal) and the method of closure (single layer or double layer). A recent meta-analysis of 11 RCTs found no difference in complications in women according to the site of repair.[112] Estimated blood loss and duration of surgery were similar between the two groups. In 2008 a Cochrane review of techniques for uterine closure compared 10 RCTs.[108] While single-layer closure was associated with significant reductions in blood loss, there has been much debate over the subsequent risk of uterine rupture. Significantly higher rates of uterine rupture in subsequent pregnancies of women whose uterine was repaired with single layer closure have been seen in two large retrospective studies.[113 114]

General anaesthesia

Whilst the majority of caesarean sections in the developed world are performed with regional anaesthesia, general anaesthesia is still used routinely in some parts of the world. In a large case-control study of over 3000 caesarean deliveries, general anaesthesia almost trebled the risk of PPH (OR 2.94, 95% CI 1.94 to 4.46).[104] The association with general anaesthesia had also been described in a previous study which demonstrated an increased risk of haemorrhage when halogenated inhalation anaesthesia was used, predisposing to uterine atony.[115]

1.9.3 Uterine atony

As with vaginal delivery, uterine atony is the predominant underlying mechanism which results in haemorrhage at caesarean section.[94] Of the few studies looking at risk factors associated with caesarean section, some have looked at PPH and others have looked more specifically at PPH secondary to uterine atony. The studies examining risk factors for PPH make reference to uterine atony resulting in PPH but they include women with a PPH rather than specifically uterine atony, an important distinction.

Specifically looking at uterine atony as a cause of PPH, a large cohort study of over 23,000 women undergoing primary caesarean section found an incidence of six percent.[116] Seventeen percent of the women with uterine atony required a blood transfusion. Several risk factors were independently associated with uterine

atony including, multiple gestation (OR 2.40, 95% CI 1.95-2.93), maternal Hispanic race (OR 2.21, 95% CI 1.90-2.57), induced labour or augmented labour for > 18 hours (OR 2.23, 95% CI 1.92-2.60), birth weight > 4.5 kg (OR 2.05, 95% CI 1.53-2.69) and clinically diagnosed chorioamnionitis (OR 1.80, 95% CI 1.55-2.09).

In summary, it would appear that a variety of factors may result in the failure of the myometrium to contract adequately and limit blood loss at caesarean section. The scheduling of the surgery appears to be associated with a difference in risk profile. Awareness and anticipation will prove essential if inroads are to be made into reducing PPH. As uterine atony has been confirmed as the most common underlying mechanism of excessive bleeding at caesarean section,[94] much attention has now focussed on strategies to firstly prevent it and secondly to treat it.

1.10 Uterotonic agents

Uterotonic agents form the mainstay of the prevention and treatment of uterine atony. The value of routine uterotonics in the third stage of vaginal birth has been well established[90 117] and it has been assumed that these benefits apply to caesarean delivery as well.[118 119] Worldwide, oxytocin is the most commonly used uterotonic agent.[118 120]

Descriptions of oxytocin and other alternative uterotonic agents, including ergometrine, carbetocin, carboprost will now be outlined. A haemostatic agent used for the treatment of PPH, tranexamic acid, will also be described. The use of these agents for the prevention of haemorrhage at caesarean section will be explored in Chapter 2.

1.10.1 Oxytocin

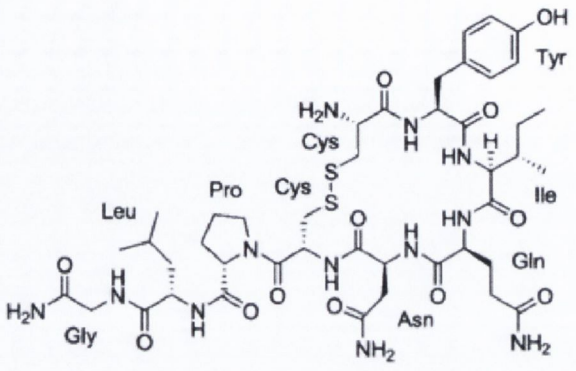


Figure 1-7: Oxytocin

Sir Henry Dale first discovered oxytocin, a nonapeptide, and it was the first polypeptide hormone ever synthesised, by Du Vigneaud in 1953.[121] Synthesised by the posterior pituitary gland, it binds to a G-protein on the surface of the uterine myocyte. Prostaglandin synthesis and calcium release result from this binding, with further prostaglandin synthesis resulting from an additional interaction. As gestation advances, the concentration of myometrial receptors increase, augmenting sensitivity to oxytocin.[121] It has numerous physiological effects including uterine contraction with subsequent relaxation, cardiovascular regulation, effects on the breast and lactation, sexual and maternal behaviour, memory and the regulation of dietary intake.[121]

Oxytocin stimulates the upper uterine segment to contract in a rhythmic fashion.[122] The onset of action of intravenous oxytocin is almost immediate (within 45 seconds), and its concentration plateaus after 30 minutes. A slower onset of action occurs with intramuscular injection (3-7 minutes), but this method of administration has the advantage of a sustained clinical effect, lasting up to 60 minutes.[122]

When compared to other uterotonic agents, the main advantages of oxytocin are its speed of onset of action and the fact that it does not increase blood pressure. However, it has been linked with various adverse outcomes when given in large doses or as a rapid intravenous bolus injection. These include hypotension,

cardiac arrhythmias, flushing and occasional nausea, vomiting, chest pain, headache, water intoxication and myocardial ischaemia.[123] The magnitude of the side effects caused by oxytocin are thought to be dose-related.[123]

Syntocinon® is a pharmacologically manufactured synthetic form of the posterior pituitary hormone oxytocin. In Ireland, it is manufactured by Novartis Pharmaceuticals and is available in 5 IU and 10 IU ampoules. It is an inexpensive, readily available medication, costing less than one euro per 10 IU ampoule. Licensed for use in obstetric practice, its clinical applications are in the induction and augmentation of labour, and during the third stage of labour for the prevention and treatment of postpartum haemorrhage. The product information leaflet for this drug recommends that is should be administered as either an intramuscular injection (5-10 IU) or a slow bolus intravenous injection (5 IU) for the third stage of labour. It specifies that 5 IU should be administered after caesarean section by slow bolus intravenous injection or infusion. It is stable at temperatures up to 25^{0}C but refrigeration does prolong its shelf-life.

The RCOG, United Kingdom, Guideline on caesarean section recommends a slow intravenous bolus dose of 5 IU of oxytocin following delivery of the infant[8], in keeping with practice across most of Europe and Australia.[124] Various approaches have been tested and it is possible that smaller bolus doses (0.3 – 5 IU) may be sufficient for elective caesarean section.[125] [126] This is a lower dose than used previously by many obstetric anaesthetists (10-20 IU)[127] and is based on concerns about side effects such as maternal hypotension.[128] Conversely, a conservative approach to the use of oxytocin may increase the risk of haemorrhage. In the United States however, an oxytocin infusion is recommended instead of a bolus dose,[129] with the potential advantage of an infusion at caesarean section maintaining uterine contractility for a longer period.

Oxytocin is by no means the only uterotonic agent available for use in the third stage of labour. Whilst it is the most commonly used uterotonic agent, alternative agents also exist and have been evaluated in randomised controlled trials.[120] [130-134] Alternative uterotonic agents include the ergot alkaloids, prostaglandins, oxytocin receptor analogues and tranexamic acid.[131] [135] [136] Their mechanisms of preventing PPH are different and will be explored.

1.10.2 Ergot alkaloids

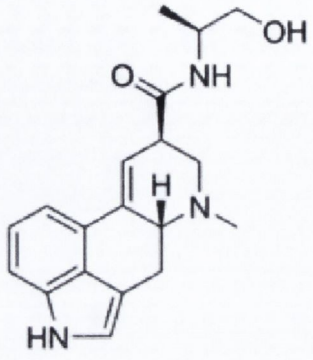


Figure 1-8: Ergometrine

Ergometrine is the most common type of ergot alkaloid and is derived from the fungus *Claviceps Purpurea*. The use of ergot alkaloids in the treatment of PPH dates back to as early as 1582 when in Germany, Adam Loncier, noted a relationship with uterine contractions.[137] By 1822, its popularity had ended due to associations with stillbirth, uterine rupture and maternal death, secondary to inaccurate dosages and ergotism (gangrene and convulsions).[135 137] In 1932 ergometrine was isolated by Dale and Moir which proved to have more beneficial obstetric effects with fewer adverse effects.[138]

A specific uterotonic action through adrenergic receptors with less vasoconstriction has been described, leading to the prevention of PPH. Unlike oxytocin, it results in a sustained tonic uterine contraction, and both upper and lower uterine segments are stimulated.[139] These contractions are produced in the inner zone of the myometrium through calcium channel mechanisms and actin-myosin interaction resulting in a shearing effect on placental separation and ultimately less blood loss; maternal side-effects are described however including hypertension, nausea and vomiting.[135 140-144] Intramuscular ergometrine acts within 2-5 minutes and the mean plasma half-life is 30 minutes. However, the clinical effect actually persists for three hours. Intravenous ergometrine administration should be given over 1 minute with careful monitoring of pulse and blood pressure. It increases both the frequency of uterine contractions and the basal

tone with a decrease in amplitude lasting at least 30 minutes and maintained for up to 90 minutes, whereas the effect of oral administration is less predictable.[145-147] Hypertension can occur as a result of its action on alpha-adrenergic receptors. Contraindications to its use therefore include hypertension, pre-eclampsia, heart disease and peripheral disease. It is sensitive to both heat and light, requiring storage at temperatures below 8^{0}C and away from light.

Syntometrine, a combination of 5 IU oxytocin and 0.5 mg ergometrine, has been designed to utilise the rapid onset of oxytocin with the longer action of ergometrine. The disadvantages however of both oxytocin and ergometrine are the requirements for trained personnel for administration.[92 148-150]

1.10.3 Prostaglandins

Prostaglandins have strong uterotonic properties and have been used widely in obstetrics and gynaecology for cervical ripening and induction of labour. Preparations are available in injectable, tablet and gel forms depending on their indications for use.[149] These agents do not cause hypertension and their use has been predominantly limited to the treatment of intractable PPH.[149]

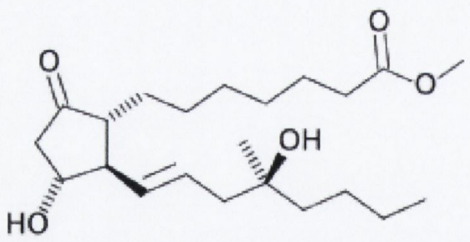


Figure 1-9: Misoprostol

Misoprostol is a synthetic analogue of prostaglandin E1 and is manufactured in Ireland by Pharmacia. Its original license in 1988 was for the prevention and treatment of gastric ulcers associated with the use of non-steroidal anti-inflammatory drugs. Its effects on uterine contractions and cervical ripening were quickly noted and a wide-range of "off-label" uses were reported. The first

documented use of misoprostol for the prevention of PPH was in 1996 in a prospective uncontrolled study.[151]

Misoprostol binds selectively to myometrial EP-2/EP-3 prostanoid receptors. It can be administered by oral, rectal, vaginal and sublingual routes. The onset of action, time to peak concentration and bioavailability all vary enormously depending on the dose and route of administration. High rates of side effects including shivering, hyperpyrexia and diarrhoea have been described.[149 152 153] Misoprostol has the advantages of being thermostable, light-stable, inexpensive. It also has no requirements for sterile needles or syringes. It has a shelf-life of several years.

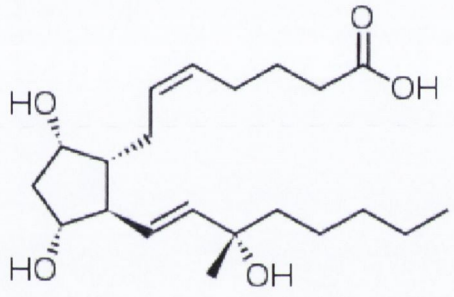


Figure 1-10: Carboprost / Haemabate

Prostaglandin 15-methyl F2a (Carboprost, Haemabate) works as a smooth muscle stimulant. It is a PGF2a analogue with a longer duration of action than its parent compound. Routes of administration include deep intramuscular injection or intramyometrial injection. The latter route has been attributed with a quicker onset of action.[154 155] Peak concentrations occur 15 minutes after intramuscular injection compared to 5 minutes with the intramyometrial route. The dose of 0.25 mg can be repeated up to a maximum of 2 mg every 15 minutes (8 doses total). It is expensive and profuse diarrhoea has been described as an adverse effect.[156 157] Other adverse effects include nausea, vomiting, pyrexia and bronchospasm. It is contraindicated in patients with cardiac or respiratory disease. Similar to ergometrine, it is both light- and heat-sensitive.

1.10.4 Oxytocin receptor analogues

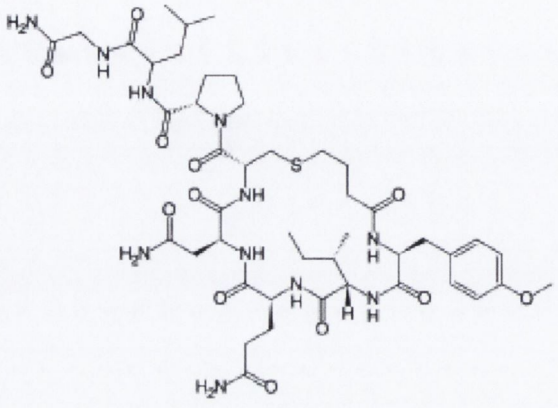


Figure 1-11: Carbetocin

Carbetocin, a long-acting oxytocin receptor analogue, was first described in 1987.[158] Intramuscular injection has been shown to produce tetanic uterine contractions in less than two minutes, lasting for approximately 11 minutes, and followed by rhythmic contractions for an additional two hours. The duration of activity after intravenous administration is significantly less.[159] It is well-tolerated, with a side effect profile similar to oxytocin. Its major disadvantage is its high price. It costs approximately 27 euro per 100 ug (single dose), at least 27 times the price of a dose of oxytocin.[131 132]

1.10.5 Tranexamic acid

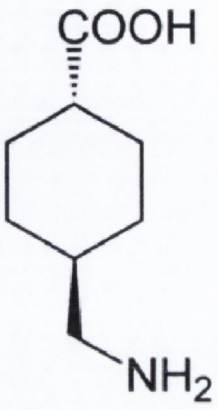


Figure 1-12: Tranexamic acid

While tranexamic acid is a haemostatic agent rather than a uterotonic agent, it is included here as part of the armamentarium used to control postpartum haemorrhage. It is an anti-fibrinolytic that competitively inhibits the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin.[160] Fibrin is the basic framework for the formation of a blood clot in haemostasis. It is a synthetic derivative of the amino acid lysine and exerts its anti-fibrinolytic effect through the reversible blockade of lysine-binding sites on plasminogen molecules.[160] It inhibits endometrial plasminogen activator and thus prevents fibrinolysis and the breakdown of blood clots. Side effects are uncommon. While prolonged treatment may heighten the risk of an increased thrombotic tendency, such as deep vein thrombosis, large scale studies reveal the incidence of thrombosis in women treated by tranexamic acid is no different from the spontaneous incidence of thrombosis in untreated women.[160] Tranexamic acid has been shown to significantly reduce blood loss in women with menorrhagia. NICE recommends using it as a treatment for intractable postpartum haemorrhage.[161]

A systematic review of the literature relating to the use of all of these agents at caesarean section follows in Chapter 2.

1.11 Aims and objectives

The overall aim of this research was to assess the control of blood loss at elective caesarean section. It examined the existing evidence, explored clinical practice, benchmarking this against clinical guidelines, assessed whether an inexpensive and widely used drug could be employed in a more optimal way to reduce the haemorrhagic morbidity associated with caesarean section and examined methods of measuring blood loss and identification of risk factors for haemorrhage.

A review of all of the medical methods for preventing blood loss at caesarean section was undertaken in the form of a Cochrane systematic review. A survey of practice and assessment of the implementation of existing clinical guidelines relating to the prevention and treatment of haemorrhage at caesarean section was performed throughout Ireland and the United Kingdom. The effect of an oxytocin infusion on blood loss at elective caesarean section was assessed by means of a multi-centre double blind randomised controlled trial. A prospective cohort study was performed to examine the methods used to estimate blood loss at caesarean section and to identify the risk factors for major obstetric haemorrhage.

There were four specific components of the project:

a) Cochrane systematic review

The aim of this review was to compare the use of prophylactic drug treatments administered in order to minimise blood loss at the time of caesarean section on the outcomes of maternal blood loss, the need for additional medication or treatment to control haemorrhage, and maternal side effects or complications.

b) Survey of guideline implementation

This survey was conducted to determine whether the variation in approach to blood loss at caesarean section was universal across the individual countries of Great Britain and Ireland and whether this reflected differences in the interpretation and implementation of clinical practice guidelines.

c) Randomised controlled trial

The aim of the randomised controlled trial was to compare the effects of an intravenous slow bolus of oxytocin (5 IU) and placebo infusion (500ml 0.9% saline) with an intravenous slow bolus of oxytocin (5 IU) and oxytocin infusion (40 IU in 500ml 0.9% saline over 4 hours) at elective caesarean section in a double blind randomised trial. This would address the question whether an inexpensive and widely used drug can be employed in a more optimal way to prevent haemorrhage at caesarean section.

d) Prospective Cohort Study

The aim of the prospective cohort study was to examine the methods used to estimate blood loss at caesarean section and to identify the risk factors for major obstetric haemorrhage.

1.12 Thesis outline

The remaining chapters in this thesis will report the work conducted to meet the objectives outlined above. Chapter 2 reviews international studies examining the medical methods used to control blood loss at caesarean section. Oxytocin was identified as the most commonly used uterotonic agent. Difficulties in accurately determining blood loss were highlighted across the range of studies reviewed.

The survey of guideline implementation across Ireland and Great Britain is reported in Chapter 3. Oxytocin was identified as the most commonly used uterotonic agent. The difficulties recognised in estimating blood loss were again highlighted in this survey.

These findings were used to inform the design of the randomised controlled trial reported in Chapters 4 - 6 and the prospective cohort study described in Chapter 7.

The thesis is summarised and implications for future research and patient care are highlighted in the concluding chapter.

CHAPTER 2. COCHRANE SYSTEMATIC REVIEW

MEDICAL METHODS FOR PREVENTING BLOOD LOSS AT CAESAREAN SECTION

2.1 Introduction

This chapter provides a systematic review of the published literature with the aim of contextualising the subsequent chapters of this thesis. The effects of key uterotonic medications used at caesarean section, which were described in the previous chapter, will be evaluated.

The Cochrane Collaboration is an international network, which aims to prepare, maintain and disseminate systematic reviews of effects of healthcare. Each year applications are invited by the Health Research Board of Ireland for the Cochrane Training Fellowships. I applied and was awarded this fellowship which commenced in December 2008. (Appendix 1) The first step in publishing a Cochrane Systematic Review is to register a title. The title most appropriate to my thesis had already been registered by an Australian group in 2007. In keeping with the Cochrane spirit of international collaboration, I approached the Australian group and asked if Prof Deirdre Murphy (my supervisor) and I could join them as co-reviewers. They kindly accepted our offer and informed the Cochrane Collaboration that we had joined their team. The Australian group, Dr Jennie Connell and Prof Kassam Mahomed had prepared the review protocol by the time we joined them as co-reviewers. Both Prof Murphy and I reviewed their protocol prior to submission and suggested some amendments. It was agreed at our first teleconference call that I would take the lead on the comparisons evaluating oxytocin, given that we had already secured funding to conduct the randomised controlled trial described in Chapters 4 - 6 and in order to fulfil the requirements of the HRB Cochrane Training Fellowship. The protocol was submitted to Cochrane in December 2008, and published in January 2009.

2.2 The Cochrane Collaboration

The Cochrane Collaboration is an international organisation named after a Scottish medical researcher, Archie Cochrane. He wrote the book "Effectiveness and Efficiency: Random Reflections on Health Services" which was published in 1972,[162] and he is renowned for his extensive contributions to the development of epidemiology as a science. In this book, he highlighted the importance of using

evidence from randomised controlled trials (RCTs), stressing that they were far more likely to provide reliable evidence than other types of studies. In 1987, the year before he died, he referred to a systematic review of randomised controlled trials of maternity related care as "a real milestone in the history of randomised trials and in the evaluation of care".[163]

In 1992, the first Cochrane centre opened in Oxford and the Cochrane Collaboration was founded in 1993, in his honour. In its mission statement the Cochrane Collaboration states that it is an "international organisation that aims to help people make well-informed decisions about health care by preparing, maintaining, and promoting the accessibility of systematic reviews of the effects of healthcare interventions". The logo is a diagram that shows the results of a systematic review of RCTs of antenatal corticosteroids performed by Professor Patricia Crowley,[164] currently a Professor of Obstetrics and Gynaecology at Trinity College Dublin, the Coombe Women and Infants University Hospital and Tallaght Hospital. This systematic review demonstrated that corticosteroids administered prior to preterm birth were effective in preventing respiratory distress syndrome and neonatal mortality. Antenatal corticosteroid treatment was also associated with a significant reduction in the risk of intraventricular haemorrhage. There is little doubt that the findings of this review revolutionised the care of preterm neonates.

2.3 Systematic review as a form of evaluation

The aim of a systematic review is to gather all the evidence that fulfils pre-specified eligibility criteria to answer a specific research question. The key characteristics of a systematic review are:[165]

- A clearly stated set of objectives with pre-defined eligibility criteria for studies
- An explicit, reproducible methodology
- A systematic search that attempts to identify all studies that would meet the eligibility criteria
- An assessment of the validity of the findings of the included studies

- A systematic presentation, and synthesis, of the characteristics and findings of the included studies.

Meta-analyses are often contained within systematic reviews. A meta-analysis is the use of statistical methods to summarise the results of independent studies.[166] The results often provide a more precise estimate of the effects of an intervention compared to the results of an individual study.

2.4 Objectives

The objectives were to determine, from the best evidence available, the effectiveness of different uterotonic agents used to control blood loss at caesarean section. Comparisons between specific regimens were included in the review.

2.5 Methods

2.5.1 Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), quasi-randomised controlled trials and cluster randomised controlled trials were to be included in the review.

Types of participants

All women undergoing caesarean section, both elective and non-elective, were included in the review.

Types of interventions

Trials were considered if they compared any uterotonic agent administered at caesarean section with another uterotonic agent, placebo or no treatment for the prevention of haemorrhage due to uterine atony. Studies comparing different agents, dosages and methods of administration were included.

Types of outcome measures

Primary outcomes

1. Major obstetric haemorrhage (greater than 1000 ml) which may be clinically estimated or formally calculated. It is expected that most trials will provide a clinical estimate of blood loss, but formal empirical methods of blood loss calculation would be desirable.
2. Need for additional uterotonic agents.

Secondary outcomes

1. Mean blood loss at caesarean section in millilitres (ml).
2. Need for transfusion.
3. Greater than 10% difference in pre-operative and postoperative (24 to 48 hours) haemoglobin or haematocrit.
4. Maternal side effects after delivery, including nausea, vomiting, shivering, headache.
5. Maternal complications including: infection or endometritis, ECG (electrocardiogram) changes, hypotension or hypertension, admission to intensive care unit or maternal death.
6. Use of additional non pharmacological measures to control haemorrhage, such as: double layer closure of lower uterine segment where this was not planned, intrauterine balloon tamponade systems; extrauterine suture compression techniques; caesarean hysterectomy, internal iliac artery ligation or uterine artery embolisation.
7. Use of additional haemostatic agents or coagulation factors including: fresh frozen plasma; factor VII.
8. Duration of operative procedure.
9. Duration of hospitalisation.
10. Secondary postpartum haemorrhage.
11. Neonatal outcomes including initiation of breastfeeding, breastfeeding upon discharge, neonatal jaundice or admission to special care nursery.

2.5.2 *Search methods for identification of studies*

This review draws on the search strategy developed for the Pregnancy and Childbirth Group of the Cochrane Collaboration. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Coordinator and contains trials identified from:

1. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. Weekly searches of MEDLINE;
3. Hand-searches of 30 journals and the proceedings of major conferences;
4. Weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of hand-searched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the "Specialized Register" section within the editorial information about the Cochrane Pregnancy and Childbirth Group. Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Coordinator searches the register for each review using the topic list rather than keywords. Reference lists of trials and other review articles were also searched. No language restrictions were applied.

2.5.3 *Data collection and analysis*

The methodology for data collection and analysis was based on the Cochrane Handbook of Systematic Reviews of Interventions.[167]

Selection of studies

All potentially eligible trials identified by the search strategy were obtained as full-text papers, and one additional review author (Dr Jennie Connell, JC) and I assessed each study for potential inclusion. It did not prove necessary to consult with a third review author to resolve any disagreement. Five papers required translation. Missing information and clarification were sought from nine authors and five replies were received.

Data extraction and management

I designed a data extraction form to standardise and assist with data extraction and piloted it on a number of published studies. (Appendix 2) The data extraction form was subsequently reviewed by the co-reviewers and amended accordingly. Two review authors (JC and I) planned to independently extract data from the original publications using the agreed form. Following difficulties experienced maintaining contact with Dr Connell, Professor Deirdre Murphy agreed to independently extract data from all of the original publications. Discrepancies were resolved through discussion, and a third party was not required. Authorship was not blinded. The Cochrane Review Manager software (RevMan 2008) was used to enter all data, which was checked independently.[168]

Assessment of risk of bias in included studies

Professor Murphy and I independently assessed risk of bias as a measure of methodological quality of included studies using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[167] When information regarding any of the criteria was unclear, the authors of the original reports were contacted to provide further details. Where these data were unobtainable, and the missing data were thought to introduce serious bias, the impact of including such studies in the overall assessment of results by sensitivity analysis was explored. The following criteria were used in the assessment of bias.

(1) Sequence generation (randomisation)

The quality of method of randomisation was assessed using the following headings:

- Adequate generation – random-number table, computer generated random numbers;
- Inadequate generation – systematic non-random approach, e.g. use of dates of birth, hospital numbers, days of the week;
- Unclear.

(2) Allocation concealment (selection bias)

The quality of allocation concealment was assessed under the following headings:

- Adequate concealment – central or telephone randomisation, consecutively numbered sealed, opaque envelopes;
- Inadequate concealment – open list of random-number tables, alternation or rotation;
- Unclear.

(3) Blinding (checking for possible performance bias)

The methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received, were described. Information was also provided on whether the blinding was effective. Blinding was assessed under the following headings:

- Adequate blinding
- Inadequate blinding
- Unclear.

(4) Incomplete data collection (checking for possible attrition bias through withdrawals, dropouts, protocol violations)

For each included study and for each outcome, the completeness of data was described, including attrition and exclusions from the analysis. Studies were assessed as:

- Reasonably complete data – less than 10% attrition at any stage, or 10 %-15% attrition in small sections of data, equal in both groups;
- Incomplete data – more than 20% attrition, or more than 15% exclusion at any stage when the reason for missing data was likely to be unrelated to the true outcomes;
- Unclear.

(5) Selective reporting bias

Each included study was examined for the possibility of selective outcome reporting bias and the methods for this were described. Reporting methods were assessed as:

- Adequate – where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest were reported;
- Inadequate – where not all the study's pre-specified outcomes were reported; one or more primary outcomes were not pre-specified; outcomes of interest were incompletely reported and so could not be used; study failed to include a key outcome that would be expected to have been reported;
- Unclear.

(6) Other sources of bias

Any important concerns about other possible sources of bias were assessed and described (e.g. specific study design, trial stopped early, extreme baseline imbalances). Studies were assessed as:

- Free from other problems;
- Not free from other problems (problems detailed);
- Unclear.

(7) Overall risk of bias

Explicit judgements were made about whether or not studies were at high risk of bias, according to the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions with reference to (1) to (6) above.[167] As necessary, the impact of the level of bias was explored by undertaking sensitivity analyses.

2.5.4 Measures of treatment effect

Statistical analysis was conducted using the Review Manager software, RevMan 2008.[168]

Dichotomous data

For dichotomous data, results are presented as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, results are presented as the mean difference if outcomes were measured in the same way between trials. The standardised mean difference was used to combine trials that measured the same outcome, but used different scales.

2.5.5 Unit of analysis issues

Cluster-randomised trials

No cluster-randomised trials were identified in this review.

Quasi-randomised trials

No quasi-randomised trials were identified in this review.

2.5.6 Dealing with missing data

Data were analysed on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If, in the original reports, participants were not analysed in the group to which they were randomised, and there was sufficient information in the trial report or in information obtained from the trial authors, the plan was to restore them to the correct group and analyse accordingly (i.e. intention-to-treat analysis). No studies required re-analysis in this manner. The denominators were determined from the number of women randomised minus the number of women known to have missing data.

2.5.7 Assessment of heterogeneity

The degree of heterogeneity was assessed by using the Chi^2 test and the I^2 statistic.[165] The Chi^2 test is known to be poor at detecting true heterogeneity among studies; while a statistically significant result indicates heterogeneity, a

non-significant result is not evidence of no heterogeneity. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance. The values of the I^2 statistic lie between 0% and 100%. For the current meta-analysis, a simplified categorisation of the I^2 statistic was used as follows: if significant heterogeneity (I^2 statistic > 50%) was found, a random-effects model was used and if low heterogeneity (I^2 statistic < 50%) was found, a fixed-effect model was used.

2.5.8 Assessment of reporting biases

If there had been 10 or more studies in the meta-analysis, reporting biases (such as publication bias) would have been investigated using funnel plots. Funnel plot asymmetry would have been assessed visually, and formal tests for funnel plot asymmetry would have been used. For continuous outcomes, the test proposed by Egger would have been used,[169] and for dichotomous outcomes, the test proposed by Harbord would have been used.[170] If asymmetry had been detected in any of these tests or was suggested by a visual assessment, exploratory analyses would have been performed to investigate it.

2.5.9 Data synthesis

Data were analysed using a fixed-effect model in cases of low heterogeneity (I^2 statistic < 50%) and a random-effects model in cases of moderate to high heterogeneity between studies (I^2 statistic > 50%).

2.5.10 Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were planned:

1. According to the risk of postpartum haemorrhage – low risk versus high risk
2. According to the dose effect of the medication. For oxytocin bolus, low dose was considered ≤ 5 IU and high dose > 5 IU.
   Other subgroup analyses were planned according to gestation, dose of uterotonic agent or route of administration if data were available.

2.5.11 Sensitivity analysis

Sensitivity analyses were performed based on trial quality, separating high-quality trials from trials of lower quality. "High quality", for the purposes of sensitivity analysis, was defined as a trial having adequate sequence generation, allocation concealment and an attrition rate of less than 20%, given the stated importance of attrition as a quality measure.[171]

2.6 Results

Overall, 58 studies were identified and considered for inclusion in this review (Figure 1, Tables 2-1 to 2-3). The Cochrane Collaboration kindly translated six studies and the remainder were in English. Nine authors were contacted for further information, four of whom replied very helpfully.[133 172-174]

2.6.1 Description of the studies

Included studies

Of the 58 studies, a total of 35 studies involving 5600 women were included in the review. Characteristics of the included studies are shown in Table 2-1.

Location

Included studies had been conducted in a variety of countries spanning all continents with the exception of Africa: fourteen trials were conducted in Europe,[118-120 130 134 173 175-182] 11 trials were conducted across the Americas, [126 131 132 172 183-189] nine in Asia,[133 174 190-196] one in Australia.[197] All studies were in hospital settings.

Ethics approval

Approval by ethics committee or institutional review board was granted for the majority of studies (26/35, 74.3%). There was no mention of approval in nine studies.[132 174 181 183 185 189-192]

Participants

The trials varied largely in size, seven had fewer than 50 participants,[118 176 177 183 184 186 187] 12 had between 50 and 100 participants,[120 126 130 131 133 173 178 181 191 194 195 197], 14 had between 101 and 500 participants,[119 134 172 174 175 179 182 185 188-190 192 193 196] and two had between 501 and 750 participants.[132 180] The largest trial had 720 participants.[180]

All participants were healthy pregnant women undergoing caesarean section. Twenty studies included only women classified as being at low risk of postpartum haemorrhage (PPH),[119 126 131-134 173 175-177 180 183 184 186 187 189 193-195 197] three studies included only women classified as being at high risk of postpartum haemorrhage,[179 188 190] and three studies included women irrespective of their risk of bleeding.[130 172 178] No reference was made to the woman's risk of PPH in nine studies.[118 120 174 181 182 185 191 192 196] Caesarean sections were classified as "elective" only in 16 studies,[120 126 130-132 173 175-177 180 182 184 185 187 196 197] as "emergency" only in three studies,[119 186 191] as both in 10 studies,[118 133 134 172 178 179 188 193-195] and not classified in six studies.[174 181 183 189 190 192]

Type of anaesthesia

In the majority of trials, caesarean sections were performed under regional anaesthesia (20/35, 57.1%). In two trials, general anaesthesia was used for all participants,[133 180] and in five trials both forms of anaesthesia were used.[119 130 172 183 188] No description of the type of anaesthesia was given for eight trials.[174 179 181 185 189-192]

Type of intervention

i. Oxytocin

Overall, oxytocin formed part of the intervention in 34 (97%) trials. A total of 12 studies examined the effects of oxytocin only. Of these, two trials compared a bolus only with an infusion only,[177 196] two compared a bolus only with a bolus and infusion,[175 180] and two compared an infusion only with a bolus and infusion.[126 188] Different bolus doses of oxytocin were compared in two studies, each comparing

a 5 IU bolus with a 10 IU bolus.[176 182] Alternative doses of oxytocin infusions were also assessed in two other studies.[119 184] A further two studies compared the effects of different bolus doses of oxytocin used in conjunction with oxytocin infusions.[126 197] Only one study examined alternative routes of oxytocin administration, comparing intravenous and intramyometrial routes.[187] No studies compared oxytocin to placebo only.

Alternative uterotonic agents were also compared to oxytocin, including misoprostol, ergometrine, carboprost, carbetocin and tranexamic acid. Many studies of the alternative uterotonic agents compared each agent either alone or in combination with oxytocin. Only one study compared a uterotonic agent with placebo only.[185]

ii. Misoprostol

Misoprostol only was compared with oxytocin only in seven studies.[118 120 133 191-193 195] In five studies, misoprostol was used in combination with oxytocin and compared to oxytocin only.[172 174 178 189 192] Misoprostol only was compared to misoprostol and oxytocin in a single study.[192]

iii. Ergometrine

Ergometrine only was compared with oxytocin only in one study.[196] It was used in combination with oxytocin and compared to oxytocin in two studies.[181 186]

iv. Carboprost (15-methyl-prostaglandin F2a)

Two studies examined the effects of carboprost only compared to oxytocin only.[130 190] Two studies examined the effects of carboprost and oxytocin compared to oxytocin only.[183 190] A single study compared carboprost only to carboprost and oxytocin.[190]

v. Carbetocin

Carbetocin only was compared with oxytocin only in five trials.[131 132 134 173 179] One trial compared it to placebo.[185] No trials assessed it in combination with oxytocin.

vi. Tranexamic acid

Unlike the other uterotonic agents, no trial compared the use of this agent only with oxytocin only. It was assessed however in one trial which compared it in combination with oxytocin to oxytocin only.[194]

Timing of intervention

In 25 trials (71.1%), the intervention was administered before placental delivery,[118-120 126 130 133 134 172 173 175-178 180 182 184 186 188 191-197] and after placental delivery in five trials.[131 179 181 183 187] In two trials, some patients received the intervention before while others received it after the placenta had delivered.[132 189] The timing of administration was not described in two studies.[174 185 190]

Outcomes

Just over half of the studies reported a clearly focused primary outcome (19/35, 54.3%).

i. Blood loss assessment and Major Obstetric Haemorrhage (blood loss > 1000 ml)

The most frequently reported outcome was estimated blood loss, presented as mean and standard deviation or range and interquartile range. Of the 35 included studies, 28 (80.0%) assessed mean estimated blood loss. Major obstetric haemorrhage (MOH) was reported as an outcome in only eight studies (22.9%).

Comparisons of these outcomes were complicated by inconsistent measurement and reporting across the included studies. Thirteen trials did not describe any method for measuring blood loss.[118 119 130 133 174 177 181 182 190-192 196 197] Four trials used a visual estimate of blood loss.[120 134 172 188] Change in haemoglobin or haematocrit were used to calculate the estimated blood loss in three trials.[175 180 186] Gravimetric methods were used in six trials,[126 178 184 193-195] with three of these making an adjustment for liquor volume.[178 193 194] Only two trials used colorimetric methods to assess blood loss.[131 179] Differing timeframes for measurement further complicated interpretation and comparison of results.

ii. Need for additional uterotonic agents

Of the 35 studies, 31 (88.6%) assessed the need for additional uterotonic agents. The studies varied in their reporting of need for additional uterotonic agents. Some reported requirements within the first hour after caesarean section, whereas others reported up to 24 hours post-operatively. Thresholds for the use of additional uterotonic agents varied between studies as did the particular agents used.

Excluded studies

Overall 19 studies were excluded. Characteristics of these studies are shown in Table 2-2. Three studies were dose-finding studies and had no comparative data.[125 198 199] Four studies were not randomised controlled trials.[200-203] One study was a randomised controlled trial of spinal anaesthesia and was not relevant to the review.[204] One study compared delayed cord clamping rather than any uterotonic agent and was thus excluded.[205] One study includes patients undergoing either vaginal delivery or caesarean delivery. It was not possible to ascertain data specific to caesarean section from the paper.[206] Seven studies were excluded as they contained no relevant data.[207-213] One study was excluded as the data were found to be unreliable.[214] The last study was excluded as it investigated the role of a uterotonic agent used postoperatively to prevent infection and thus did not fit the inclusion criteria.[215]

Registered studies

Including the randomised controlled trial that will be described in Chapters 4-6,[216] four studies were registered with trial registries when the initial search was conducted.(Table 2-3) Three are still on-going and the randomised controlled trial conducted as part of my thesis is now complete. The findings of this completed randomised controlled trial will be discussed in Chapter 6 and a further meta-analysis will be presented within the chapter.

2.6.2 *Risk of bias in included studies*

i. Randomisation

Adequate sequence generation was described in 15 studies.[118 119 126 132 134 174 175 178 180 182 184 186-188 195] However, it was not clear in the remaining 20 studies.[120 131 133 172 173 176 177 179 181-183 185 189-194 196 197]

ii. Allocation

Allocation concealment was adequate in 18 studies.[118-120 126 130 132 134 172 174-176 182 186 188 189 193 195 197] and was unclear in 17 studies.[131 133 173 177-181 183-185 187 190-192 194 196]

iii. Blinding

Adequate blinding was described in 21 studies.[118 119 126 130-132 134 172 175 176 178 180 182-184 186-189 193 197] It was inadequate in five studies,[120 174 177 179 195] and unclear in nine studies.[133 173 181 185 190-192 194 196]

iv. Incomplete reporting

Data were fully detailed in 33 studies and in the remaining two studies[133 174] details of attrition and exclusions from the analysis were unavailable.

v. Selective reporting

Reporting was assessed as adequate in 19 studies,[118 120 126 130-132 134 172 174-176 180 182 186-188 193 195 197] and unclear in 16 studies.[119 133 173 177-179 181 183-185 189-192 194 196]

vi. Other potential sources of bias

Fourteen studies were assessed as having no other potential sources of bias,[118 119 126 131 132 172 176 178 182 187 188 193 195 197] and in 19 studies, this was unclear.[130 134 173-175 177 179-181 183-186 189-192 194 196] Two studies were deemed to be at high risk of bias, one due to imbalances in surgical procedures between both groups,[120] and the other as a result of numerous discrepancies in the data, and a lack of information about study design.[133]

2.6.3 *Effects of the interventions*

Primary and secondary outcomes are presented together in light of the large number of interventions.

Oxytocin only trials (12 trials)

i. *Oxytocin bolus only versus oxytocin infusion only (2 trials)*

Two trials compared oxytocin bolus only with oxytocin infusion only.[177] [196] In one study, an oxytocin bolus of 5 IU was used and a 10 IU bolus was used in the other study. The trial that used an oxytocin 10 IU bolus was a four-arm trial, comparing oxytocin bolus versus oxytocin infusion over five minutes versus oxytocin infusion over 15 minutes versus ergometrine.[196] Three of these groups were used for this comparison, combining the two infusion groups. Comparing oxytocin bolus to infusion, mean blood loss was similar between both groups with a very wide confidence interval (mean difference 80 ml, 95% CI -229.27 to 389.27). No difference was found in the need for additional uterotonic agents (RR 1.01, 95% CI 0.65 to 1.58, 2 trials, 130 participants). One study measured the need for blood transfusion but no patients in either group required a transfusion.[196] Neither study measured side effects.

ii. *Oxytocin bolus only versus oxytocin bolus and infusion (2 trials)*

Two trials compared an oxytocin bolus to an oxytocin bolus and infusion.[175] [180] One of these trials was the pilot study[175] of the RCT described in Chapters 4 – 6. Both trials compared a 5 IU oxytocin bolus with a 5 IU oxytocin bolus and a 30 IU oxytocin infusion. Interestingly both studies used the same methods for assessing blood loss based on haematocrit calculations.[217] The pilot study randomised 110 women (all with regional anaesthesia) and found no difference in rates of blood loss of either > 500 ml or > 1000 ml. A larger study randomised 720 women, all of whom had general anaesthesia, and found an increase in the rate of blood loss > 1000 ml in the bolus only group (RR 2.86, 95% CI 1.59 to 5.00). When combined, there was no difference in the rate of MOH between the

groups (RR 1.87, 95% CI 0.88 to 3.98). Mean estimated blood loss was increased in the bolus group in both studies (mean difference 77.26, 95% CI 45.02 to 109.50, 830 participants). Both studies described increased need for additional uterotonic agents in the bolus only group (combined RR 2.43, 95% CI 1.63 to 3.60, 830 participants). The need for blood transfusion was also increased in the bolus only group (RR 8.00, 95% CI 1.01 to 63.63, 2 trials, 830 participants). Side effects were similar in both groups (RR 0.75, 95% CI 0.45 to 1.26). Lengths of time in theatre and in hospital were similar in both groups.

iii. Oxytocin infusion only versus oxytocin bolus and infusion (2 trials)

Two studies compared an oxytocin infusion only with a combination of a bolus and infusion.[126 188] One of these studies was a five-arm study, with four of the arms being relevant for this comparison.[126] A variety of bolus doses were used, ranging from 0.5 IU to 5 IU. Mean blood loss was increased in the infusion only group (mean difference 93.65, 95% CI 17.80 to 169.51, 2 trials, 173 participants). The need for additional uterotonic agents was similar in both groups (RR 2.04, 95% CI 0.85 to 4.92), as was the need for blood transfusion (RR 2.88, 95% CI 0.31 to 27.00, 1 trial, 143 participants). Hypotension was significantly reduced in the infusion only group compared to the bolus and infusion group (RR 0.43, 95% CI 0.22 to 0.81, 2 trials, 173 participants). No differences between the groups were seen for any other side effects.

iv. Oxytocin bolus 5 IU versus oxytocin bolus 10 IU (2 trials)

A 5 IU oxytocin bolus was classified as "low dose", with a 10 IU bolus being classified as "high dose". Two trials compared low dose versus high dose boluses of oxytocin.[176 182] Estimated blood loss was similar in both groups (mean difference 45 ml, 95% CI -109.40 to 199.40, 1 trial, 103 participants). Both trials assessed the need for additional uterotonic agents and when combined significantly fewer participants receiving the "high dose" bolus required an additional uterotonic agent (RR 17.35, 95% CI 2.18 to 137.83, 137 participants). Neither study assessed side effects.

v. *Lower dose oxytocin infusion versus higher dose oxytocin infusion (2 trials)*

The dose of oxytocin infusion was classified into "lower dose" if the dose of oxytocin infusion was 350 mU/min or less, and "higher dose" if the dose was greater than 350 mU/min. Two studies compared alternative doses of oxytocin infusion. One trial compared the use of a 333 mU/min oxytocin infusion and a 2667 mU/min oxytocin infusion for 30 minutes.[119] A second trial, was a four-arm trial comparing four different infusion doses: 125 mU/min, 250 mU/min, 375 mU/min and 500mU/min for 40 minutes.[184] Mean estimated blood loss was similar when comparing "low dose" infusion with "high dose" infusion (mean difference 20.00 ml, 95% CI -13.63 to 53.63, 2 trials, 351 participants). There was significantly more need for additional uterotonic agents in the "lower dose" infusion (RR 2.07, 95% CI 1.42 to 3.01, 1 trial, 321 participants). Side effects were not measured in either of the two trials.

vi. *"Very low dose" oxytocin bolus and infusion versus "low dose" oxytocin bolus and infusion (2 trials)*

Two trials compared different doses of oxytocin bolus and infusion.[126 197] Oxytocin bolus dose was categorised into "very low dose" of less than 5 IU and "low dose" of between 5 IU and 10 IU. No differences were seen in the need for additional uterotonic agents between the groups (RR 1.01, 95% CI 0.45 to 2.25, 2 trials, 139 participants). Nausea was reduced in the "very low dose" bolus and infusion group compared to the "low dose" group (RR 0.15, 95% CI 0.04 to 0.64, 2 trials, 139 participants), however other side effects were similar in both groups.

vii. *Intravenous oxytocin versus intramyometrial oxytocin (1 trial)*

Only one trial compared intravenous oxytocin with intramyometrial oxytocin.[187] This trial described a mean fall in haemoglobin of 1.12 g/dl in the intravenous group compared to 1.16 g/dl in the intramyometrial group. Duration of hospital stay was also similar in both groups (mean difference 4.30, 95% CI -2.04 to 10.64, 39 participants).

viii. *Oxytocin before placental delivery versus oxytocin after placental delivery (no trials)*

No trials compared the administration of oxytocin before placental delivery with the administration of oxytocin after placental delivery.

Misoprostol trials (11 trials)

i. *Misoprostol only versus oxytocin only (seven trials)*

Oral misoprostol was used in four trials,[118 120 191 192] sublingual in two trials,[133 195] and rectal in one trial.[193] One of the oral misoprostol trials was a three-arm trial with a misoprostol only arm, an oxytocin only arm and a combined misoprostol and oxytocin arm.[192] Mean blood loss was estimated in all seven trials (688 participants) and was greater in the oxytocin only group (mean difference 82.50, 95% CI 74.68 to 90.33). There was no difference in the need for additional uterotonic agents between the two groups. Three trials measured blood loss > 500 ml (330 participants) and four trials measured blood loss > 1000 ml (390 participants). No difference in either outcome was noted. Compared to oxytocin only, misoprostol had no effect on the need for blood transfusion (RR 1.67, 95% CI 0.23 to 12.50, two trials, 100 participants). Shivering was significantly less likely in the oxytocin only group (RR 0.36, 95% CI 0.21 to 0.63, four trials, 390 participants). Significant differences were not seen for other side effects including vomiting, pyrexia/fever, headache, giddiness or metallic taste. Duration of surgery was longer in the oxytocin only group (mean difference 3.63 min, 95% CI 3.07 to 4.18, three trials, 260 participants).

ii. *Misoprostol and oxytocin versus oxytocin only (5 trials)*

Two trials used oral misoprostol (including the three-arm trial described above), one used the buccal route, one used the sublingual route and one placed the misoprostol tablets into the uterine cavity. Three trials measured estimated blood loss (530 participants). Blood loss was increased in the oxytocin only group compared to misoprostol and

oxytocin (mean difference 101 ml, 95% CI 82.04 to 119.92). No studies measured blood loss > 500 ml or > 1000 ml. The addition of misoprostol to oxytocin had no effect on the need for additional uterotonic agents (RR 0.76, 95% CI 0.47 to 1.25, four trials, 819 participants). There was no difference in the need for blood transfusion between the two groups (RR 0.96, 95% CI 0.49 to1.91, three trials, 619 participants). Pyrexia/fever and shivering were reduced in the oxytocin only group. Other side effects were similar in both groups. The durations of surgery and hospital stay were also similar.

iii. *Misoprostol and oxytocin versus misoprostol only (1 trial)*

The only trial to compare misoprostol and oxytocin to misoprostol only used oral misoprostol.[192] This was the three-arm trial described above. 600 mcg oral misoprostol was used at the time of peritoneal incision in this trial in addition to intramyometrial oxytocin. The only outcome measured was mean estimated blood loss which was similar in both groups (mean difference -4 ml, 95% CI -23.62 to 15.62, 124 participants).

Ergometrine trials (3 trials)

i. *Ergometrine only versus oxytocin only regimens (1 trial)*

This trial was a four-arm trial of ergometrine versus oxytocin bolus versus a short oxytocin infusion versus a longer oxytocin infusion.[196] Comparing the ergometrine only to oxytocin only, the need for additional uterotonic agents was similar (RR 0.71, 95% CI 0.45 to 1.11, 136 participants). Other outcomes evaluated in this study were not statistically different.

ii. *Ergometrine and oxytocin versus oxytocin only (2 trials)*

Two trials compared ergometrine and oxytocin to oxytocin only.[181] [186] Estimated blood loss was increased in the oxytocin only group (mean difference 70.07 ml, 95% CI 35.57 to 104.58, 103 participants). The need for additional uterotonic agents was also increased in the oxytocin only group (RR 2.14, 95% CI 1.07 to 4.30, 1 trial, 48 participants). Less nausea

was described in the oxytocin only group (RR 0.20, 95% CI 0.05 to 0.82), no differences were seen for other side effects. One trial reported the need for blood transfusion, however no patients required such intervention.[186]

iii. Ergometrine only versus ergometrine and oxytocin (no trials)

No trials compared ergometrine only to ergometrine and oxytocin.

Carboprost trials (3 trials)

i. Carboprost only versus oxytocin only (2 trials)

Two trials compared carboprost only to oxytocin only.[130 190] One of these trials was a three-arm trial comparing carboprost only versus carboprost and oxytocin versus oxytocin only.[190] Carboprost only was associated with significantly less blood loss compared to oxytocin only (mean difference -91.47, 95% CI -156.19 to 26.76, two trials, 337 participants). There was no difference in the need for additional uterotonic agents between the groups (RR 1.18, 95% CI 0.39 to 3.57, two trials, 337 participants). Side effects and the need for blood transfusion were similar in both groups.

ii. Carboprost and oxytocin versus oxytocin only (2 trials)

The three-arm trial described in the previous section was also included in this comparison.[190] The combination of carboprost and oxytocin was associated with a reduction in blood loss compared to oxytocin only (mean difference -180.00 ml, 95% CI -240.17 to -119.83, two trials, 344 participants). Need for additional uterotonic agents and blood transfusion were similar in both groups.

iii. Carboprost and oxytocin versus carboprost only (2 trial)

As for the two previous comparisons of carboprost, the trial with three-arms was evaluated for this comparison.[190] There was a trend towards a reduction in blood loss in the combined carboprost and oxytocin arm however this was not significant (mean difference -57.00 ml, 95% CI -117.58 to 3.58, 1 trial, 317 participants). No patients required blood transfusion in

either group. Requirements for additional uterotonic agents were similar in both groups (RR 0.26, 95% CI 0.05 to 1.32).

Carbetocin trials (6 trials)

i. *Carbetocin only versus oxytocin only (5 trials)*

Five trials compared carbetocin only to oxytocin only.[131 132 134 173 179] Rates of blood loss > 500 ml were reduced in the carbetocin only group (RR 0.52, 95% CI 0.29 to 0.93, 1 trial, 104 participants), but there was no difference in rates of blood loss >1000 ml between the two groups (RR 1.02, 95% CI 0.41 to 2.5, 1 trial, 375 participants). Carbetocin reduced the need for additional uterotonic agents compared to oxytocin (RR 0.63, 95% CI 0.44 to 0.88, 4 trials, 1173 participants). Side effects were similar in both groups.

ii. *Carbetocin and oxytocin versus oxytocin only (no trials)*

No trials compared the combination of carbetocin and oxytocin with oxytocin only.

iii. *Carbetocin and oxytocin versus carbetocin only (no trials)*

No trials compared the combination of carbetocin and oxytocin with carbetocin only.

iv. *Carbetocin only versus placebo (1 trial)*

One trial (published abstract only) compared carbetocin with placebo.[185] This trial demonstrated a reduction in the need for additional uterotonic agents with carbetocin compared to placebo (RR 0.10, 95% CI 0.09 to 0.35, 119 participants). The author reported that carbetocin produced transient tachycardia and a decrease in diastolic blood pressure compared with placebo, data for these outcomes however were not presented. Other adverse events were reported as similar between both groups but no data were presented.

Tranexamic acid trials (1 trial)

i. *Tranexamic acid only versus oxytocin only (no trials)*
No trials compared tranexamic acid only with oxytocin only.

ii. *Tranexamic acid and oxytocin and ergometrine versus oxytocin and ergometrine (1 trial)*
One trial compared the effects of a combination of tranexamic acid, oxytocin and ergometrine with oxytocin and ergometrine.[194] The combination of tranexamic acid, oxytocin and ergometrine reduced the rate of blood loss > 500 ml when compared with oxytocin and ergometrine (RR 0.35, 95% CI 0.13 to 0.92, 100 participants). The estimated blood loss was also reduced with this combination of three agents (mean difference -40.55, 95% CI -52.38, 28.72).

iii. *Tranexamic acid and oxytocin versus tranexamic acid only (no trials)*
No trials compared the combination of tranexamic acid and oxytocin with tranexamic acid only.

2.7 Discussion

2.7.1 Summary of main findings

Uterotonic agents

This systematic review includes comparisons of all uterotonic agents used to control blood loss at caesarean section: oxytocin, misoprostol, ergometrine, carboprost, carbetocin and tranexamic acid. Of the 35 trials included in the review, only one trial had a "no uterotonic arm". Oxytocin was administered as a bolus dose, as an infusion or as a combination of both. It was also used in combination with other uterotonic agents. Misoprostol was administered via the oral, sublingual, buccal, rectal or intrauterine routes while the other prostaglandin investigated, Carboprost, was used intramuscularly or intramyometrially. All trials took place within hospital settings. There was wide variation in the timing of administration of the uterotonic agent, either before or after placental delivery.

Most of the trials had only small numbers of participants, the largest randomising 720 women. In terms of outcomes, major obstetric haemorrhage and the use of additional uterotonic agents were considered to be the most clinically relevant primary outcomes.

Major obstetric haemorrhage

Major obstetric haemorrhage (MOH) was reported as an outcome in only eight studies (1947 participants).(Table 2-4) The addition of an oxytocin infusion to a bolus dose, compared with bolus alone had no effect on the rate of MOH.(Figure 2-2) When oxytocin was combined with misoprostol and compared with oxytocin only, no differences in rates of MOH were seen.(Figure 2-3) Similarly, when oxytocin was compared to either misoprostol or carbetocin, rates of MOH were not affected.(Figures 2-4 and 2-5) None of the other comparisons assessed reported rates of MOH.

Need for additional uterotonic agents

A total of 31 trials (5557 participants) assessed the need for additional uterotonic agents.(Table 2-5, Figures 2-6 to 2-21) The need for additional uterotonic agents was significantly reduced by the combination of an oxytocin bolus and infusion compared to bolus only. Reassuringly, side effects were not increased by this intervention. Not surprisingly, higher bolus doses and higher infusion doses also reduced the need for additional uterotonic agents when compared with lower doses. Unfortunately, the side effect profiles could not be balanced against this benefit as they were not recorded in these trials. When oxytocin was used in conjunction with ergometrine, the need for additional uterotonic agents was also reduced when compared to oxytocin by itself. For this ergometrine study, higher rates of nausea were described compared to oxytocin alone although other adverse effects were not increased. The need for additional uterotonic agents was reduced when carbetocin was compared to oxytocin and reassuringly side effects were similar in both groups. Not surprisingly, when carbetocin was compared to no uterotonic, the need for additional uterotonic agents was also reduced but adverse effects were not measured. The combination of an oxytocin bolus and infusion when compared to infusion only had no effect on the need for additional uterotonic agents. There was less hypotension when an

oxytocin infusion was used by alone, however other side effect profiles were similar in these groups.

Blood transfusion

The need for blood transfusion was reported in 17 trials (3399 participants).(Table 2-6) The relative risk was not estimable in many of the trials. The combination of an oxytocin infusion and an oxytocin bolus when compared to a bolus only reduced the need for blood transfusion, but with wide confidence intervals. Interestingly when this same combination was compared to an infusion only, the need for blood transfusion was similar in both groups. When oxytocin was compared with misoprostol, carboprost or carbetocin, no differences in the need for blood transfusion were found.

Other outcomes of interest were specific side effects including nausea, vomiting, pyrexia/fever and hypotension. The results of these meta-analyses can be seen in tables 2-6 to 2-10.

2.7.2 Quality of the evidence

The significant heterogeneity evident across the studies included in the systematic review and meta-analysis is an indication of the varying approaches to the control of blood loss at caesarean section. Widespread variation in the methods used to measure blood loss and the timing of administration of the interventions certainly account for much of the heterogeneity found. It may also be explained by significant differences in the populations of pregnant women in the included studies, with geographical diversity, varying degrees of risk for postpartum haemorrhage and alternative types of anaesthesia. It was deemed reasonable to carry out a meta-analysis despite the substantial degree of heterogeneity in the included studies in order to give some quantitative indication of whether administration of uterotonic agents reduces blood loss at caesarean section.

Variable reporting of factors that may be important confounders of the relationship between uterotonic agents and control of blood loss made it difficult to account for these factors in meta-analyses. The meta-analysis has been hampered by the varying definitions of postpartum haemorrhage used in different studies. It is also possible that biases inherent in trials performed with unblinded assessment of outcomes, may have affected the overall conclusions. For these reasons, the results of the meta-analysis should be regarded as hypothesis generating, requiring further testing in adequately designed future studies.

2.7.3 Future work

Ideally randomised controlled trials should be used to compare the effects of each uterotonic agent versus no uterotonic agent, however there would be important ethical and practical difficulties in randomising women to an arm without any uterotonic agent. It is acknowledged that much of the use of uterotonic agents at caesarean section is simply derived from knowledge of the benefits seen at vaginal delivery. As they have crept into widespread use however, it would be extremely difficult to recruit to a trial where patients may not receive one at all. Clinicians are unlikely to be willing to allow patients to participate in such a trial and our experience of the regulatory authorities in the UK and Ireland when designing the RCT in chapter 4 suggests that this would not be approved. Only one trial in this review (a published abstract) did employ such a study design, however the need for additional uterotonic agents was extremely high in the no uterotonic arm (41/57, 71.9%).[185]

The true effects of alternative uterotonic agents on the reduction of significant haemorrhage at caesarean section may have been missed in the meta-analyses as the majority of included studies were inadequately powered to detect clinically significant differences in this outcome. If more data become available for a future update of this review, it may be possible to determine the beneficial effects of each of the uterotonic agents.

2.8 Conclusions

This systematic review and meta-analysis has not found evidence of sufficient magnitude or quality to recommend any particular uterotonic agent over another for the control of blood loss at caesarean section. The most commonly used uterotonic agent for the control of blood loss at caesarean section was found to be oxytocin. Oxytocin formed part of the intervention in 34 (97%) trials. It is a widely used, inexpensive, well-tolerated, safe medication. There did appear to be a reduction in the need for additional uterotonic agents with the use of a combination of oxytocin bolus and infusion compared to oxytocin bolus alone. Encouragingly there was no difference in side effects between the two groups. Studies using higher doses of oxytocin have also shown a reduction in need for additional uterotonic agents. Concern however, has previously been raised over the safety of higher doses, and none of the trials in this review adequately addressed these concerns.

Most striking was the variation within each trial. Rather than replicating interventions used, the majority of trials used different interventions, either varying the dose, method of administration or timing of the intervention. Study design was often poorly described and the risk of bias was high in many trials. Few trials were sufficiently powered to detect any significant outcomes. The quality of outcome reporting differed across the range of studies, making interpretation very difficult. Large high quality randomised controlled trials are required to address the question of which uterotonic regimen should be recommended to prevent haemorrhage at caesarean section. It is anticipated that the randomised controlled trial described in Chapters 4, 5 and 6 will have an important contribution to make to the evidence-base.

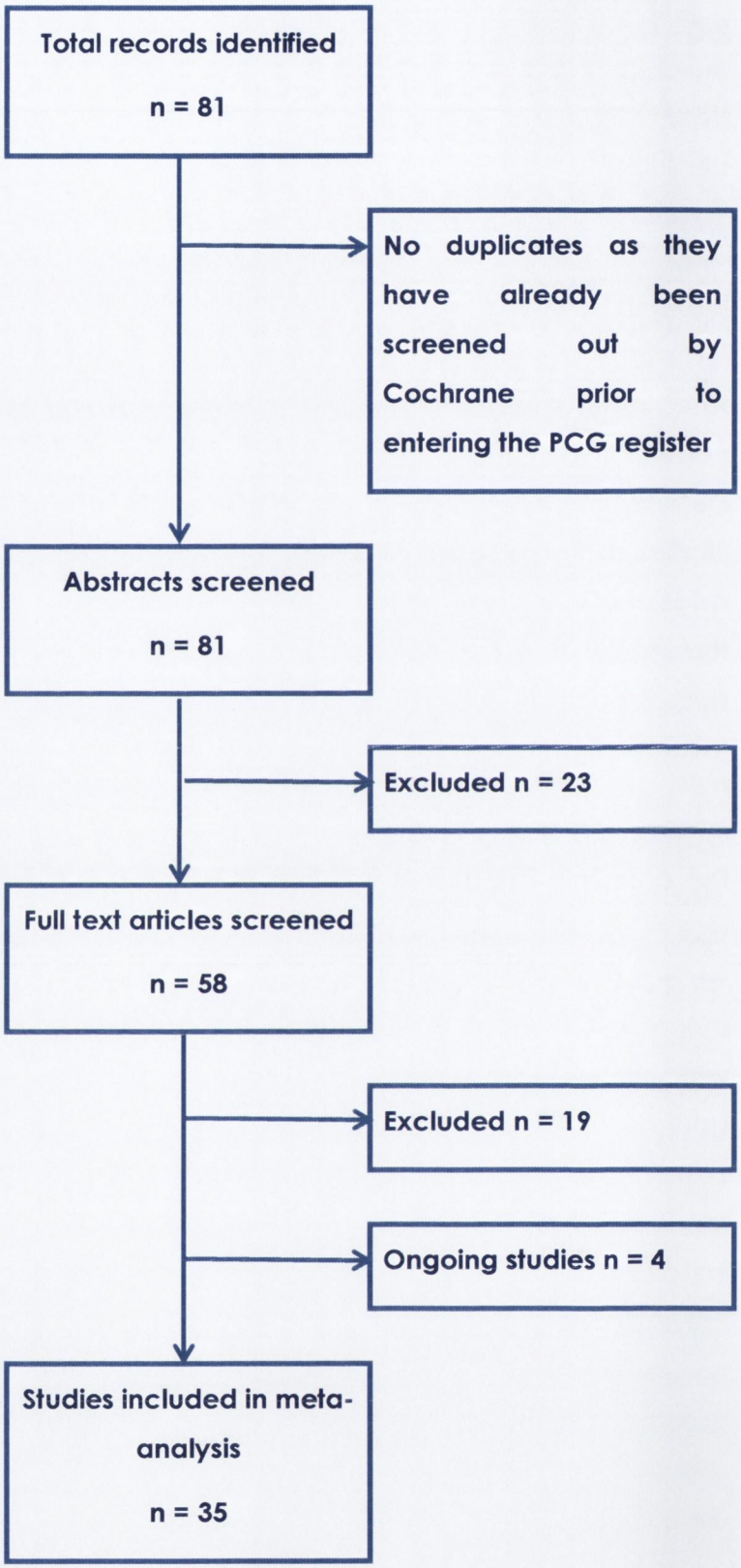


Figure 2-1 Flow diagram of literature search

Table 2-1 Details of studies included in the review

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Acharya 2001	RCT – open Harlow, UK No mention of ethics	Before placental delivery	60 women: 30/30 Elective c-section Regional anaesthesia Visual estimate ? risk	Misoprostol 400 mcg PO versus oxytocin bolus 10 IU IV	1- Intraoperative blood loss 2 – duration of surgery, side effects, mean change in Hb and HCT Biases – uterus exteriorised, TL, twins
Attilakos 2010	RCT – double-blind Bristol, UK Ethics approval	Before placental delivery	377 women: I-188, C-189 Elective & emergency c-section Regional anaesthesia Visual estimate Low risk	Carbetocin 100 ug IV versus oxytocin bolus 5 IU IV	1 - Add uterotonic 2 – EBL, s/e, side effects, change in Hb, uterine tone, blood transfusion, change in vital signs.

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Balki 2008	RCT – double-blind Toronto Ethics approval	Before placental delivery	48 women: 24/24 c-section for labour arrest Regional anaesthesia HCT calculation Low risk	Oxytocin infusion 20 IU in 1 L Ringer's lactate + ergometrine 0.25 mg versus oxytocin infusion 20 IU in 1L	1 -EBL (HCT calculation) 2 - Uterine tone, additional uterotonic agents, blood transfusion, side effects
Barton 1996	RCT – double-blind Utah No mention of ethics	?timing	119 women: I-62, C-57 Elective caesarean section ? anaesthesia ? risk	Carbetocin 100 ug IV versus placebo ? any oxytocin given	1 - Additional uterotonics 2 - uterine contraction s/e
Borruto 2009	RCT – unclear re blinding ?Italy or Monaco Ethics approval	After placental delivery	104 women: 52/52 Elective & emergency c-section Colorimetric method ≥ 1 risk factor for PPH	Carbetocin 100 IV versus oxytocin infusion 10 IU over 2 hours	1- Add uterotonic Mean blood loss

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Boucher 1998	RCT – double-blind Montreal Ethics approval	After placental delivery	57 women : I-29, C-28 Elective c-section Regional anaesthesia Colorimetric method Low risk	Carbetocin 100 ug IV versus oxytocin bolus 2.5 IU IV and oxytocin infusion over 16 hours	All had MROP Intra-op- blood loss Uterine tone
Butwick 2010	RCT – double-blind Stanford, CA Ethics approval	Bolus Before placental delivery Infusion after placental delivery	74 women, 5 groups: 15/15/15/15/15 Elective c-section Regional anaesthesia Gravimetric Low risk	Oxytocin 0 IU + oxytocin infusion 10 IU versus oxytocin 0.5 IU + oxytocin infusion 10 IU versus oxytocin 1 IU + oxytocin infusion 10 IU versus oxytocin 3 IU + oxytocin infusion 10 IU versus oxytocin 5 IU bolus over 15 sec + oxytocin infusion 10 IU	All had MROP Some had uterine massage 1 -Uterine tone 2 – Intra-op blood loss s/e Change HCT before and 30 min postop

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Catanzarite 1990	RCT – double-blind Arkansas No mention of ethics	After placental delivery	46 women: I-25, C-21 "routine" c-section Regional and general anaesthesia Low risk	Carboprost tromethamine 125 ug intramyometrially + oxytocin infusion 20 IU versus oxytocin 20 IU intramyometrially + oxytocin infusion 20 IU	Unclear re 1 and 2 Uterine tone Hb and HCT change (day 3) Transfusion (included classical incisions and GA)
Chaudhuri 2010	RCT – double-blind India Ethics approval	Before placental delivery	200 women: I-96, C-94 Elective & emergency c-section Regional anaesthesia Gravimetric, adjusted for liquor Low risk	Misoprostol 800 ug PR after incising uv fold and placebo infusion versus placebo PR and oxytocin infusion IV	1 - EBL intra-op and 8 hours postop Add uterotonics s/e transfusion

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Chou 1994	RCT – double-blind Oxford Ethics approval	Before placental delivery	60 women: 30/30 Elective c-section Regional and general anaesthesia "standard" assessment All risks	Carboprost (15-methyl PGF2a) 125 ug intramyometrially + placebo bolus IV + placebo infusion versus placebo intramyometrially + oxytocin bolus 5 IU IV + oxytocin infusion 15 IU	1 -Blood loss Hb and HCT deficit (24 hours) Transfusion Add uterotonics Hospitalisation
Dansereau 1999 (linked to Gambling 1994 and 1994a)	RCT – double-blind Canada No mention of ethics	Before (87%) and after (13%) placental delivery	694 women: I-348, C-346 Elective c-section Regional anaesthesia Low risk	Carbetocin 100ug IV bolus + placebo infusion versus oxytocin bolus 5 IU IV + oxytocin infusion 20 IU	1- Add uterotonics 2 - Fundal height Tone Lochia Vital signs Hb change s/e

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Dennehy 1998	RCT – double-blind Canada Ethics approval	After placental delivery	40 women: IV-20, IMY-19 Elective c-section Regional anaesthesia Low risk	Oxytocin intramyometrially 2 ml (10 IU ml^{-1}) + placebo bolus IV versus placebo intramyometrially + Oxytocin bolus 0.5 ml (10 IU ml^{-1}) IV	Mean drop BP Uterine contractility Change Hb
Eftekhari 2009 Emailed author re data discrepancies. Responded stating that text was correct rather than tables	RCT – open India Ethics approval	Before placental delivery	100 women: 50/50, Then 50/34 Elective & emergency c-section General anaesthesia Low risk	Misoprostol 400 ug SL versus oxytocin infusion 20 IU until "full contraction of the uterus"	Mean blood loss Change in Hb (20 hours postop) Side effects Surgery duration

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Gohel Mayur 2007	RCT – India Ethics approval		100 women: 50/50 Elective & emergency c-section Regional anaesthesia Low risk	20 min before skin incision, Tranexamic acid 1 g slowly IV over 5 minutes and after delivery of the neonate, oxytocin infusion 10 IU in 1 pint dextrose normal saline IV over 30 min and 0.4mg methylergometrine IV versus after delivery of the neonate, oxytocin infusion 10 IU in 1 pint dextrose normal saline IV over 30 min and 0.4mg methylergometrine IV	Mean blood loss (gravimetric – suction volume for AFI) (end or surgery and 2 hours postop) Hb day 3 Heart rate, respiratory rate, blood pressure, uterine contractility, placental separation, neonatal manifestations, side effects

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Gungorduk 2010	RCT- double-blind Turkey Ethics approval	Before placental delivery	720 women: 360/360 Elective c-section General anaesthesia HCT calculation Low risk except for GA	Oxytocin bolus 5 IU iv + oxytocin infusion 30 IU versus oxytocin bolus 5 IU IV + placebo infusion	1 - PPH> 1L 2 - EBL Change HB. HCT Transfusion Add uterotonics s/e postnatal stay
Hamm 2005 **Author replied**	RCT – double-blind Florida Ethics approval	At cord clamping and at placental delivery	352 women: I-173, C-179 Elective & emergency c-sections Regional anaesthesia bar one Visual estimate All risks	Misoprostol 200 ug buccal at cord clamping + oxytocin infusion 20 IU at placental delivery versus placebo buccal + oxytocin infusion 20 IU at placental delivery	1 - Add uterotonics Uterine atony Haemorrhage (all subjective) s/e

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Hong 2007	RCT - ? blinding Korea No mention of ethics	? timing	214 women: I-96, C-118 ? all c-sections ? anaesthesia ? risk	Misoprostol 200 ug PR + oxytocin 20 IU infusion versus placebo PR + oxytocin 20 IU infusion	Change in Hb and HCT day 1 Add uterotonics Transfusion s/e
Jonsson 2010	RCT – double-blind Sweden Ethics approval	Before placental delivery	103 women: 5-52, 10-51 Elective c-section Regional anaesthesia ?risk	Oxytocin bolus 5 IU IV versus oxytocin bolus 10 IU IV	1 - ST depression Chest symptoms Troponin MAP HR Blood loss Add uterotonics
Kikutani 2006	RCT - ? blinding Japan Translated by Cochrane Ethics approval	Before placental delivery	136 women 4 groups: 34/34/34/34 Elective c-section Regional anaesthesia but later sedated ? assessment of blood loss ? risk	4 groups; Oxytocin bolus 10 IU versus oxytocin infusion 10 IU over 5 min versus oxytocin infusion 10 IU over 15 min versus methylergometrine 0.2mg	Blood loss Lochia Change Hb Add uterotonics

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
King 2010 **(same as Wong, Douglas)**	RCT – double-blind British Colombia Ethics approval	Before placental delivery	143 women Bolus – 70, placebo - 73 Elective & emergency c-section Regional and general anaesthesia visual estimate ≥ 1 risk factor for PPH	Oxytocin bolus 5 IU + oxytocin infusion 40 IU then 20 IU versus placebo bolus + oxytocin infusion 40 IU then 20 IU	1- Add uterotonics Uterine tone EBL s/e transfusion time from bolus to placental delivery
Kumru 2005	RCT - Turkey Translated by Cochrane No mention of ethics	After placental delivery	55 women: Oxy-35, ergo-20 No mention of risk factors Singleton pregnancy	Oxytocin bolus 10 IU IV + oxytocin infusion versus oxytocin bolus 10 IU + methylergonovine maleate 0.2mg IV + oxytocin infusion + methylergonovine repeated 8 hourly	Change in Hb and HCT Lochia Surgery duration

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Lapaire 2006	RCT – double-blind Switzerland Ethics approval	Before placental delivery	56 women: 28/28 Elective and emergency c-section Regional anaesthesia Gravimetric, adjusted for liquor All risks	Oxytocin bolus 5 IU IV + misoprostol 800 ug PO + placebo infusion over 8 hours versus oxytocin bolus 5 IU IV + placebo PO + oxytocin infusion 20 IU over 8 hours	1 - EBL intra- and post-op s/e 2 - Hb, HCT change Add uterotonics
Lokugamage 2001	RCT – double-blind London No mention of ethics	Before placental delivery	40 women: 20/20 Elective & emergency c-section Regional anaesthesia ? risk	Placebo bolus IV + misoprostol 500 ug PO versus oxytocin bolus 10 IU IV + placebo PO	EBL Hb drop Add uterotonics s/e
Moertl 2008 **Author replied** **Unpublished data**	Submitted for publication RCT – double-blind Austria Ethics approval	Before placental delivery	56 women : 28/28 Elective c-section Regional anaesthesia Low risk	Oxytocin bolus 5 IU vs. carbetocin 100 ug IV	HR BP

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Munn 2001	RCT – double-blind Alabama Ethics approval	Before placental delivery	321 women: I-163, C-158 Emergency c-section Regional & general anaesthesia Low risk	Oxytocin 10 IU infusion versus oxytocin 80 IU infusion	1 - Add uterotonics Hypotension Mean blood loss HCT change
Murphy 2009	RCT – double-blind Scotland Ethics approval	Before placental delivery	110 women: I-56, C-54 Elective c-section Regional anaesthesia HCT calculation and gravimetric Low risk	Oxytocin bolus 5 IU + oxytocin infusion 30 IU versus oxytocin bolus 5 IU + placebo infusion 30 IU	1 - EBL > 1L 2 - Mean blood loss Add uterotonics Hb, HCT change s/e postnatal stay transfusion
Pinder 2002	RCT – double-blind Leeds, UK Ethics approval	Before placental delivery	34 women: 17/17 Elective c-section Regional anaesthesia Low risk	Oxytocin 5 IU bolus versus oxytocin 10 IU bolus	1 - Maternal haemodynamics MAP, HR, Cardiac output Add uterotonic

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Quiroga Diaz 2009	RCT - double-blind Mexico Translated by Cochrane No mention of ethics	Before and after placental delivery	200 women: 100/100 c-section ?elective or emergency low risk	Oxytocin + misoprostol 800 ug in cavity versus oxytocin + manogen	Hb, HCT change s/e
Sarna 1997	RCT – double-blind Boston Ethics approval	Before placental delivery	40 women: 4 groups: 10/10/10/10 Elective c-section Regional anaesthesia Low risk	4 groups; Oxytocin infusion 5 IU versus oxytocin infusion 10 IU versus oxytocin infusion 15 IU versus oxytocin infusion 20 IU	Uterine tone EBL Hb, HCT change (day 1 and 2)
Sartain 2008	RCT – double-blind Cairns, Australia Ethics approval	Before placental delivery	80 women: 40/40 Elective c-section Regional anaesthesia Low risk	Oxytocin bolus 2 IU + oxytocin infusion 40 IU over 4 hours versus oxytocin bolus 5 IU + oxytocin infusion 40 IU over 4 hours	1- Maternal haemodynamics s/e blood loss add uterotonics

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Thomas 2007 (same as Cooper 2004)	RCT – single-blind Birmingham Ethics approval	Before placental delivery	30 women: 14/14 Elective c-section Regional anaesthesia "estimated" loss- no specifics Low risk	Oxytocin bolus 5 IU IV over 1 minute versus oxytocin infusion 5 IU over 5 minutes	MAP EBL Add uterotonic
Vimala 2006	RCT – open India Ethics approval	Before placental delivery	100 women: 50/50 Elective & emergency c-section Regional anaesthesia Gravimetric Low risk	Misoprostol 400 ug SL versus oxytocin infusion 20 IU over 6 hours	1 - Hb change EBL Add uterotonics s/e transfusion major complication
Wu 2007	RCT Beijing Translated by Cochrane No mention of ethics	?timing	469 women: 3 groups: O-152, O+H-192, H-125 c-section ? anaesthesia High risk	3 groups: Oxytocin 20 IU intrauterine + oxytocin 20 IU IV versus oxytocin 20 IU IV + Hemabate 250 ug intrauterine versus Hemabate 250 ug intrauterine	EBL (2 hours post op) Other haemostatic measures Side effects

Study	Methods	Timing of exposure	Participants	Interventions	Outcomes and comments
Xu 2003	RCT China Translated by Cochrane No mention of ethics	Before placental delivery	80 women: 40/40 Emergency c-section (failed induction) ? anaesthesia ?risk	Misoprostol 400 ug PO when peritoneum incised versus oxytocin 20 IU intramyometrially	EBL (2 hours postop) Fetal outcomes ??
Zhao 1998	RCT China Translated by Cochrane No mention of ethics	Before placental delivery	182 women: 3 groups: O-58, M+O-64, M-60 ? anaesthesia ? risk	3 groups: Misoprostol 600 ug when peritoneum incised versus Misoprostol + oxytocin intramyometrially versus oxytocin 20 IU intramyometrially + oxytocin 20 IU bolus after delivery of infant	EBL (2 hours postop)

Table 2-2 Details of excluded studies

Study	Reason for exclusion
Balki 2006	Dose-finding, not comparative
Carvalho 2004	Dose-finding, not comparative
Cappiello 2006	No relevant data
Dweck 2000	Uterotonic agent administered postoperatively
Erkkola 1984	Not uterotonic agent
George 2010	Dose-finding, not comparative
Kalinka 2009	Not RCT
Langastaeter 2009	Observational study within RCT
Lourens 2007	Not RCT
Langastaeter 2009	Not relevant. RCT of spinal anaesthesia
Ozalp 2010	Combines vaginal and caesarean delivery
Mollitt 2009	Haemodynamic changes only
Van den Enden 2009	No relevant data provided. Haemodynamics
Perdiou 2009	No relevant data
Kikutani 2003	Pharmacokinetics only

Study	Reason for exclusion
Kikutani 2003a	No relevant data
Sekhavat 2009	Unreliable data
Svanstrom 2008	No relevant data
Zarzur 1998	Not an RCT

Table 2-3 Registered studies

Study	Trial status
Razali 2010	Ongoing
Wallace 2008	Ongoing
Yilidirim 2009	Ongoing
Murphy 2009	Complete

Table 2-4 Major obstetric haemorrhage (blood loss > 1000 ml)

Intervention	Studies	Participants	Relative risk (95% CI)
Oxytocin bolus only versus oxytocin bolus & infusion	2	830	1.87 (0.88, 3.98)
Misoprostol only versus oxytocin only	4	390	0.54 (0.27, 1.10)
Misoprostol and oxytocin versus oxytocin only	1	352	1.12 (0.66, 1.92)
Carbetocin only versus oxytocin only	1	375	1.02 (0.41, 2.50)

Table 2-5 Need for additional uterotonic agents

Intervention	Studies	Participants	Relative risk (95% CI)
Oxytocin bolus versus infusion	2	130	1.01 (0.65, 1.58)
Oxytocin bolus only versus oxytocin bolus and infusion	2	830	2.43 (1.63, 3.60)
Oxytocin infusion only versus oxytocin bolus and infusion	2	217	2.04 (0.85, 4.92)
Low dose oxytocin bolus versus high dose oxytocin bolus	2	137	17.35 (2.18, 137.83)
Low dose oxytocin infusion versus high dose infusion	1	321	2.07 (1.42, 3.01)

Intervention	Studies	Participants	Relative risk (95% CI)
Very low dose oxytocin bolus and infusion versus low dose oxytocin bolus and infusion	2	139	1.01(0.45, 2.25)
Misoprostol only versus oxytocin only	5	490	0.80 (0.56, 1.15)
Misoprostol and oxytocin versus oxytocin only	4	819	0.76 (0.47, 1.25)
Ergometrine only versus oxytocin only	1	136	1.41 (0.90, 2.22)
Ergometrine and oxytocin versus oxytocin only	1	48	0.47 (0.23, 0.93)
Carboprost only versus oxytocin only	2	337	1.18 (0.39, 3.57)
Carboprost and oxytocin versus oxytocin only	1	344	0.32 (0.06, 1.61)
Carboprost and oxytocin versus carboprost only	1	317	0.26 (0.05, 1.32)
Carbetocin only versus oxytocin only	4	1173	0.63 (0.44, 0.88)
Carbetocin only versus placebo	1	119	0.18 (0.09, 0.35)

Table 2-6 Need for blood transfusion

Intervention	Studies	Participants	Relative risk (95% CI)
Oxytocin bolus only versus infusion only	1	102	Not estimable
Oxytocin bolus only versus oxytocin bolus and infusion	2	830	8.00 (1.01, 63.63)
Oxytocin infusion only versus bolus & infusion	1	143	2.88 (0.31, 27.00)
Misoprostol only versus oxytocin only	2	100	1.67 (0.23, 12.50)
Misoprostol and oxytocin versus oxytocin only	3	619	1.04 (0.52, 2.04)
Ergometrine only versus oxytocin only	1	136	Not estimable
Ergometrine and oxytocin versus oxytocin only	1	48	Not estimable
Carboprost only versus oxytocin only	2	337	1.35 (0.34, 5.26)
Carboprost and oxytocin versus oxytocin only	2	390	1.23 (0.21, 7.14)
Carboprost and oxytocin versus carboprost only	1	317	Not estimable
Carbetocin only versus oxytocin only	1	377	0.81 (0.22, 2.94)

Table 2-7 Nausea

Intervention	Studies	Participants	Relative risk (95% CI)
Oxytocin infusion only versus oxytocin bolus and infusion	2	217	5.32 (0.63, 44.82)
Very low dose oxytocin bolus & infusion versus low dose oxytocin bolus and infusion	2	139	0.15 (0.04, 0.64)
Misoprostol and oxytocin versus oxytocin only	2	253	1.54 (0.41, 5.56)
Ergometrine and oxytocin versus oxytocin only	1	48	5.00 (1.22, 20.00)
Carbetocin only versus oxytocin only	4	1149	0.93 (0.74, 1.16)

Table 2-8 Vomiting

Intervention	Studies	Participants	Relative risk (95% CI)
Oxytocin infusion only versus oxytocin bolus and infusion	2	217	Not estimable
Very low dose oxytocin bolus & infusion versus low dose oxytocin bolus and infusion	2	139	0.17 (0.02, 1.32)
Misoprostol only versus oxytocin only	3	350	1.10 (0.47, 2.56)
Misoprostol and oxytocin versus oxytocin only	1	200	1.00 (0.21, 4.76)
Ergometrine and oxytocin versus oxytocin only	1	48	5.88 (0.78, 50.00)
Carboprost only versus oxytocin only	1	60	7.14 (0.38, 100.00)
Carbetocin only versus oxytocin only	3	1093	0.90 (0.59, 1.39)

Table 2-9 Pyrexia / fever

Intervention	Studies	Participants	Relative risk (95% CI)
Misoprostol only versus oxytocin only	2	140	1.00 (0.15, 6.67)
Misoprostol and oxytocin versus oxytocin only	2	414	2.22 (1.03, 4.76)
Carboprost only versus oxytocin only	1	60	0.50 (0.05, 5.26)

Table 2-10 Hypotension

Intervention	Studies	Participants	Relative risk (95% CI)
Oxytocin infusion only versus oxytocin bolus & infusion	2	217	0.44 (0.23, 0.87)
Very low dose oxytocin bolus & infusion versus low dose oxytocin bolus and infusion	1	59	0.54 (0.25, 1.13)
Misoprostol only versus oxytocin only	1	40	Not estimable
Ergometrine and oxytocin versus oxytocin only	1	48	0.83 (0.29, 2.38)
Carbetocin only versus oxytocin only	2	481	1.08 (0.56, 2.08)

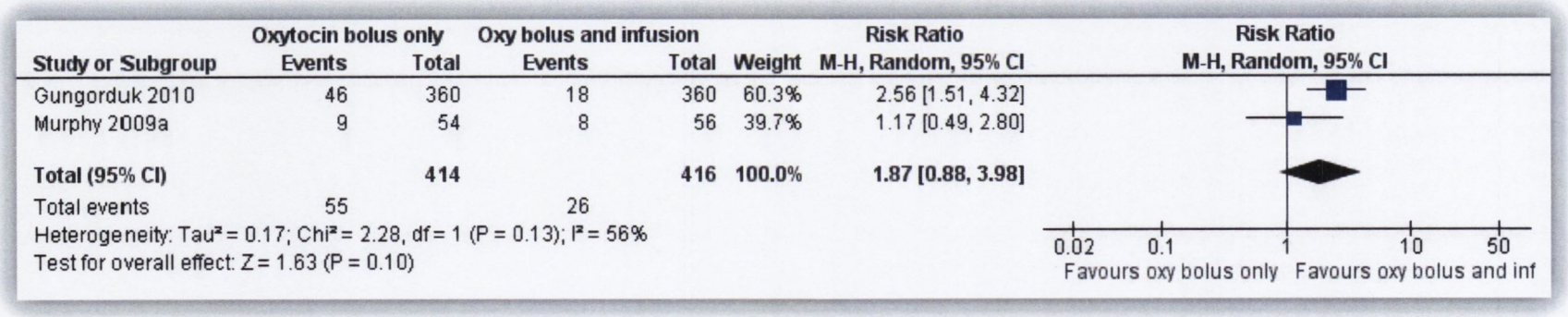


Figure 2-2 Forest plot of comparison: Oxytocin bolus only versus oxytocin bolus and oxytocin infusion, outcome: Blood loss > 1000 ml.

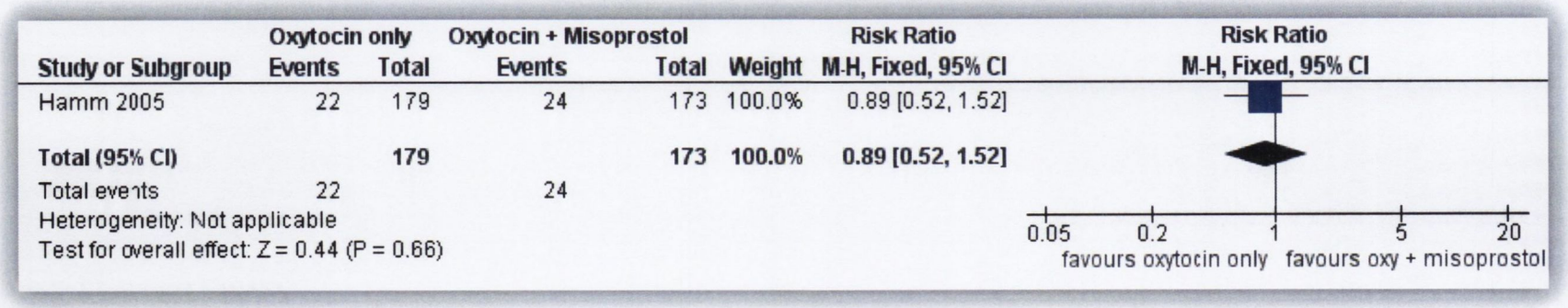


Figure 2-3 Forest plot of comparison: Oxytocin only versus oxytocin and misoprostol, outcome: Blood loss > 1000 ml.

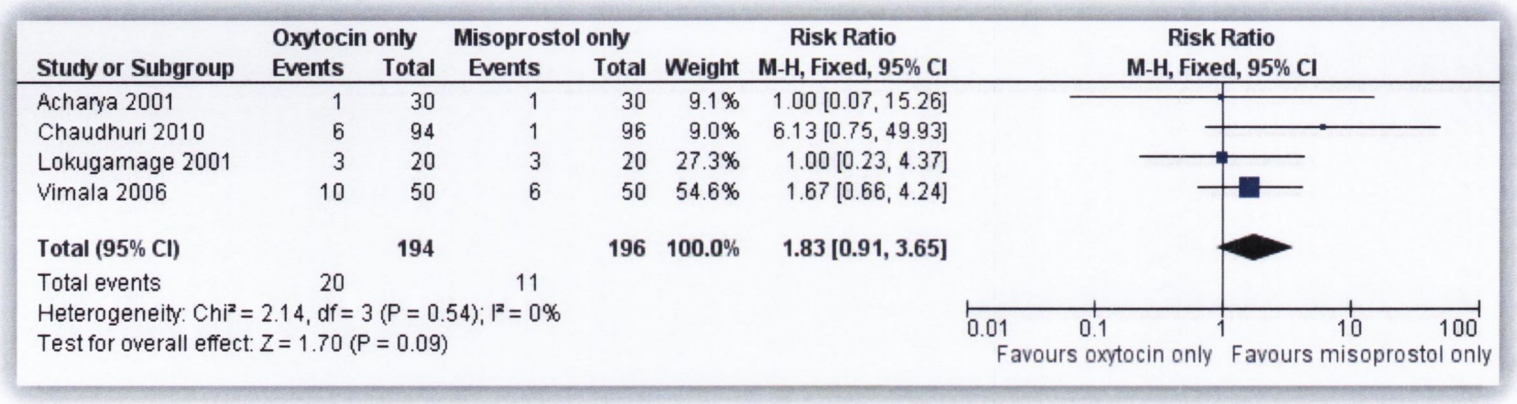


Figure 2-4 Forest plot of comparison: Oxytocin only versus misoprostol only, outcome: Blood loss > 1000 ml.

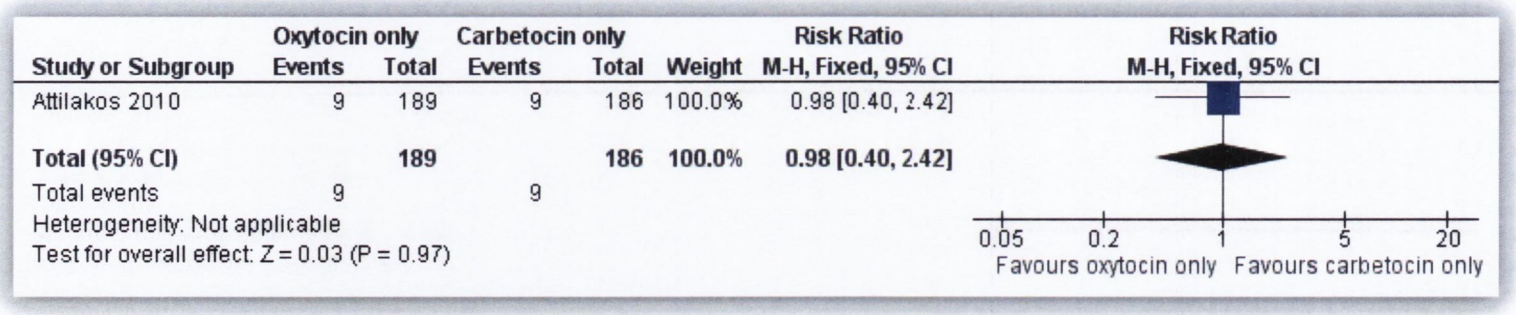


Figure 2-5 Forest plot of comparison: Oxytocin only versus carbetocin only, outcome: Blood loss > 1000 ml.

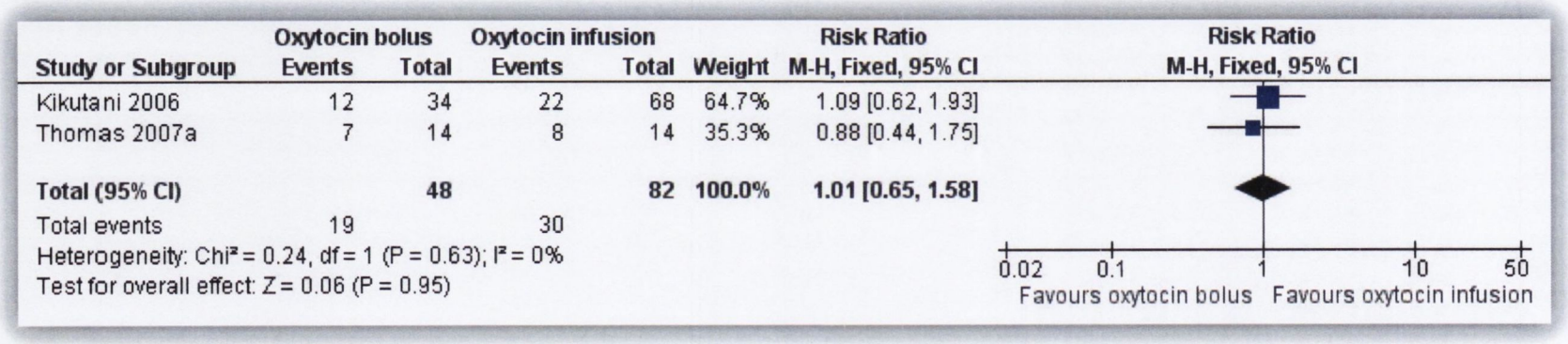


Figure 2-6 Forest plot of comparison: Oxytocin bolus versus oxytocin infusion, outcome: Need for additional uterotonic agents.

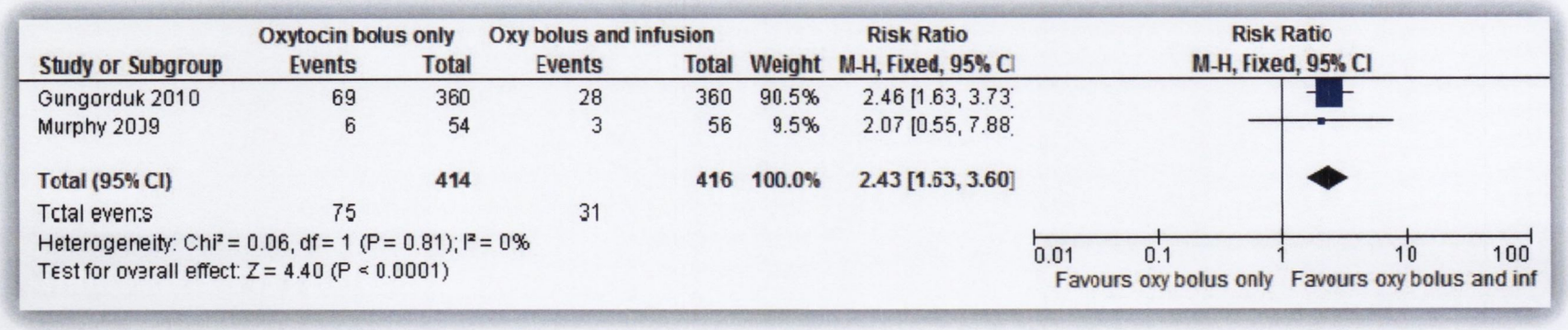


Figure 2-7 Forest plot of comparison: Oxytocin bolus only versus oxytocin bolus and oxytocin infusion, outcome: Need for additional uterotonic agents.

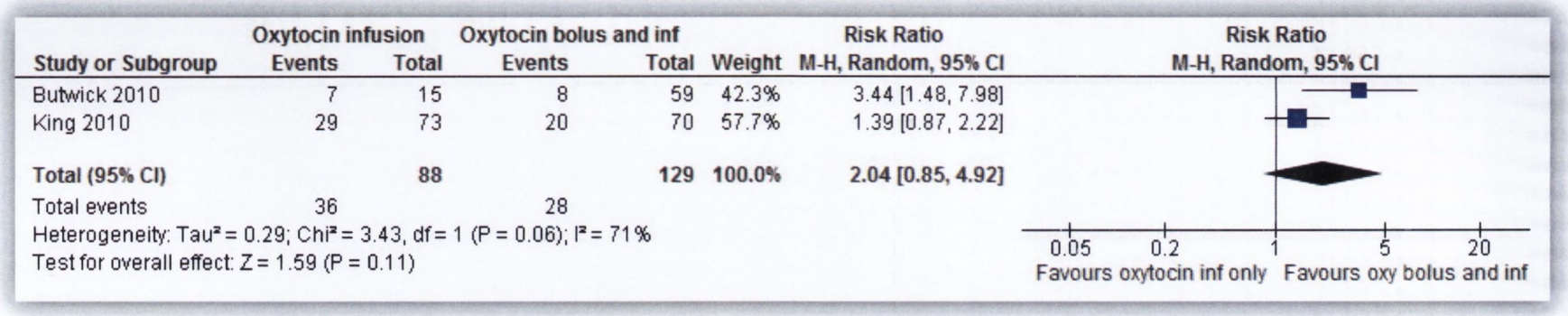


Figure 2-8 Forest plot of comparison: Oxytocin infusion only versus oxytocin bolus and infusion, outcome: Need for additional uterotonic agents.

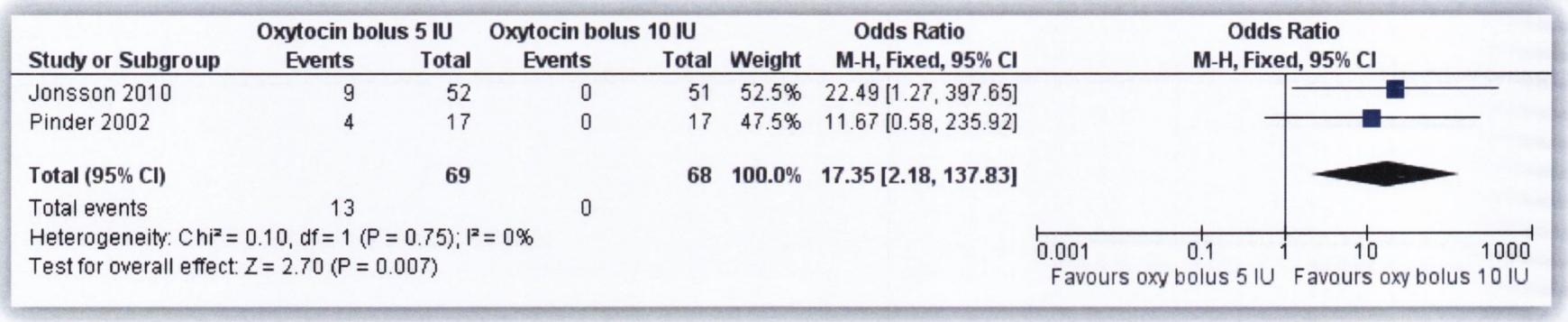


Figure 2-9 Forest plot of comparison: Low dose oxytocin bolus versus high dose oxytocin bolus, outcome: Need for additional uterotonic agents.

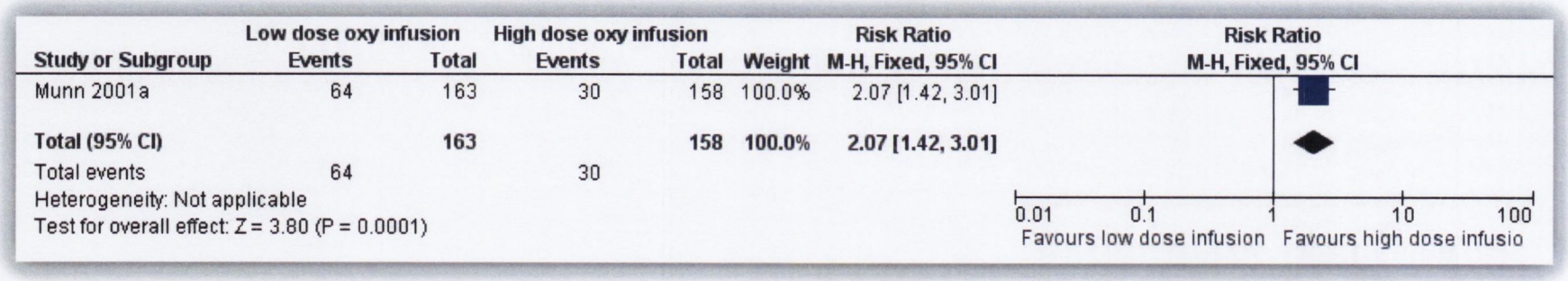


Figure 2-10 Forest plot of comparison: Low dose oxytocin infusion versus high dose oxytocin infusion, outcome: Need for additional uterotonic agents.

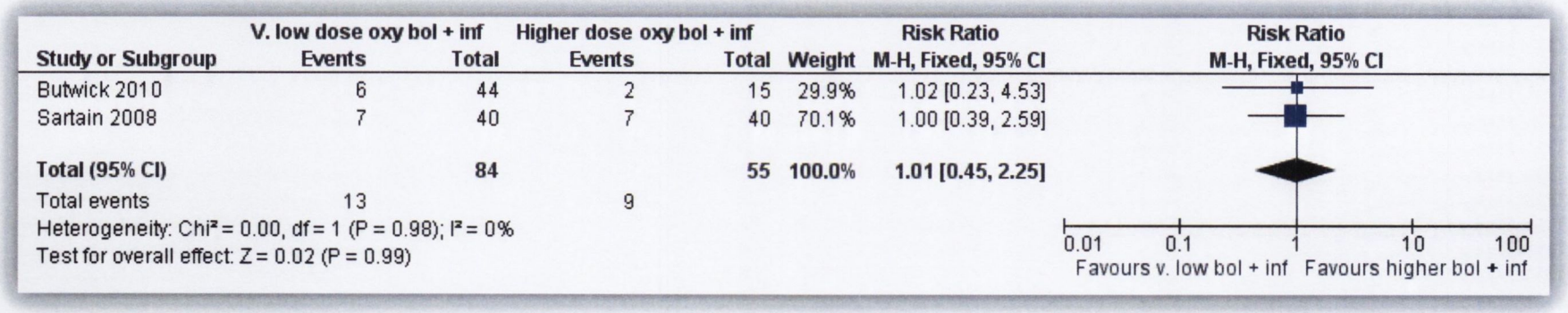


Figure 2-11 Forest plot of comparison: Very Low dose oxytocin bolus and infusion versus higher dose oxytocin bolus and infusion, outcome: Need for additional uterotonic agents.

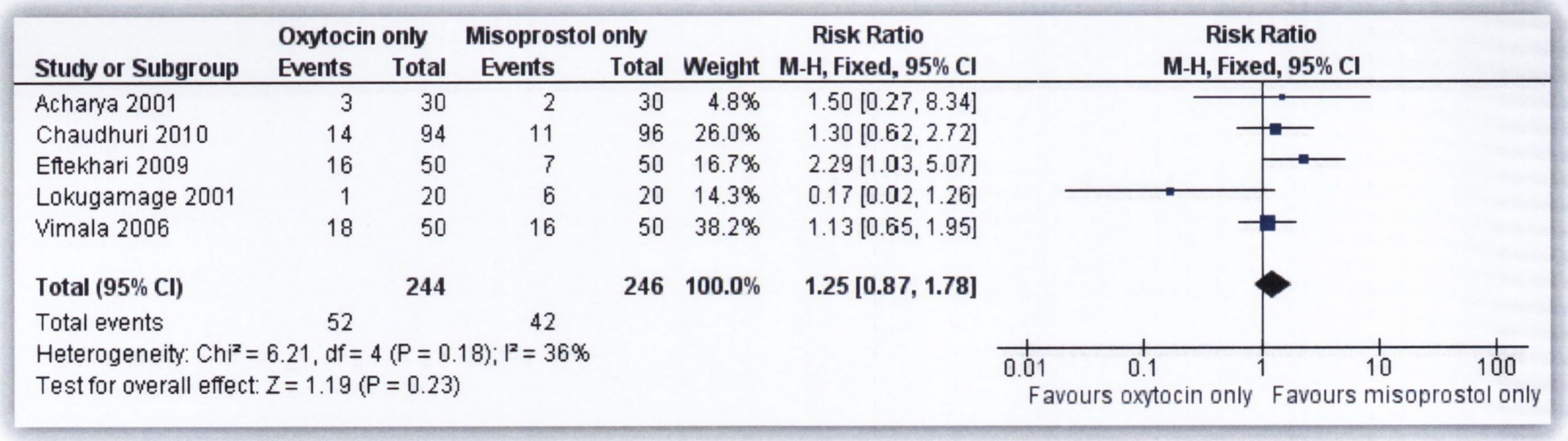


Figure 2-12 Forest plot of comparison: Oxytocin only versus misoprostol only, outcome: Need for additional uterotonic agents.

Study or Subgroup	Oxytocin only Events	Total	Oxytocin + Misoprostol Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hamm 2005	76	179	45	173	48.7%	1.63 [1.20, 2.21]
Hong 2007	31	118	28	96	40.7%	0.90 [0.58, 1.39]
Lapaire 2006	0	25	0	28		Not estimable
Quiroga 2009	6	100	3	100	10.6%	2.00 [0.51, 7.78]
Total (95% CI)		**422**		**397**	**100.0%**	**1.31 [0.80, 2.13]**
Total events	113		76			

Heterogeneity: Tau² = 0.10; Chi² = 5.16, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 1.08 (P = 0.28)

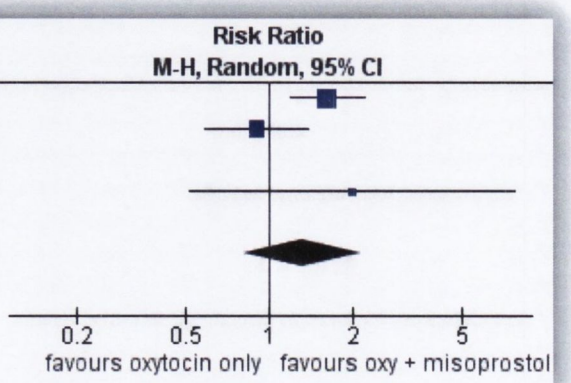


Figure 2-13 Forest plot of comparison: Oxytocin only versus oxytocin and misoprostol, outcome: Need for additional uterotonic agents.

Study or Subgroup	Oxytocin only Events	Total	Ergometrine only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kikutani 2006	34	102	16	34	100.0%	0.71 [0.45, 1.11]
Total (95% CI)		**102**		**34**	**100.0%**	**0.71 [0.45, 1.11]**
Total events	34		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)

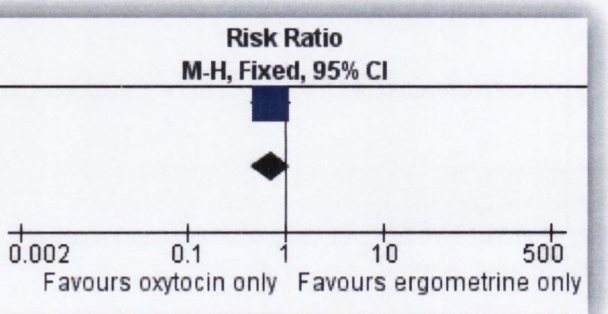


Figure 2-14 Forest plot of comparison: Oxytocin only versus ergometrine only, outcome: Need for additional uterotonic agents.

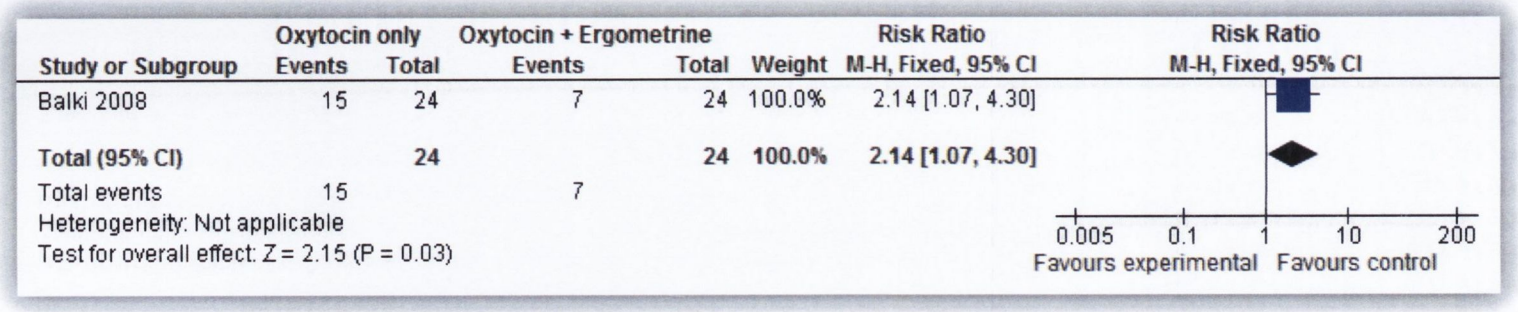


Figure 2-15 Forest plot of comparison: Oxytocin only versus oxytocin and ergometrine, outcome: Need for additional uterotonic agents.

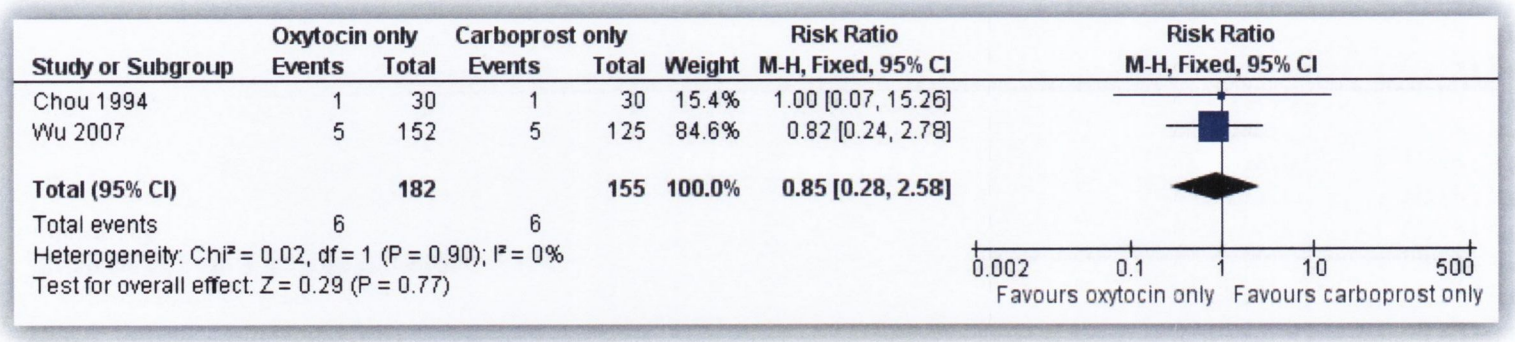


Figure 2-16 Forest plot of comparison: Oxytocin only versus carboprost only, outcome: Need for additional uterotonic agents.

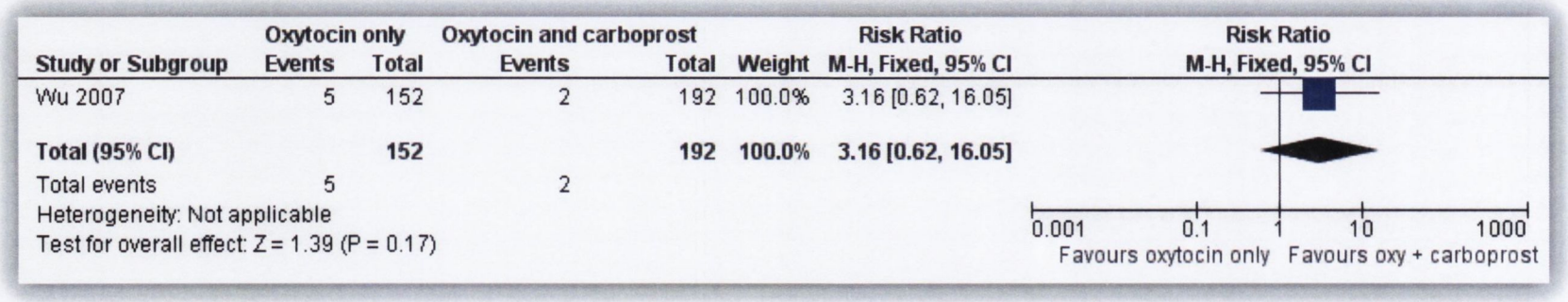


Figure 2-17 Forest plot of comparison: Oxytocin only versus oxytocin and carboprost, outcome: Need for additional uterotonic agents.

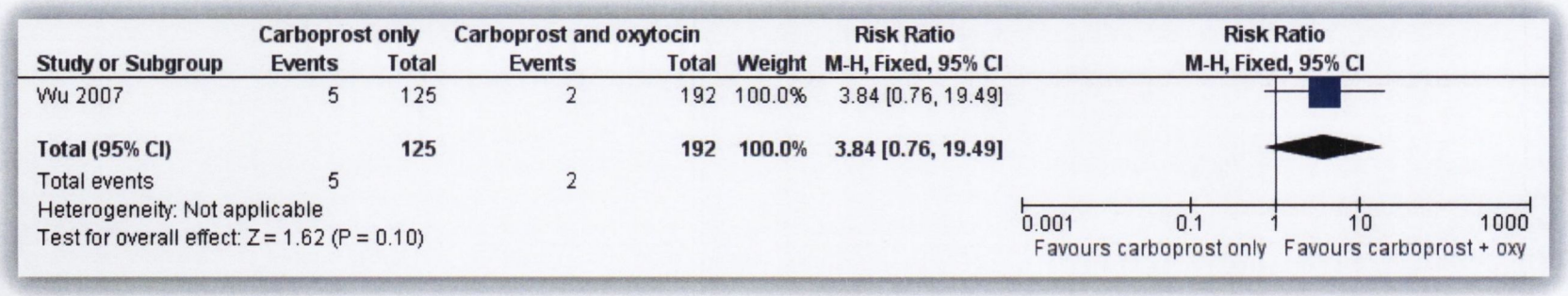


Figure 2-18 Forest plot of comparison: Carboprost only versus carboprost and oxytocin, outcome: Need for additional uterotonic agents.

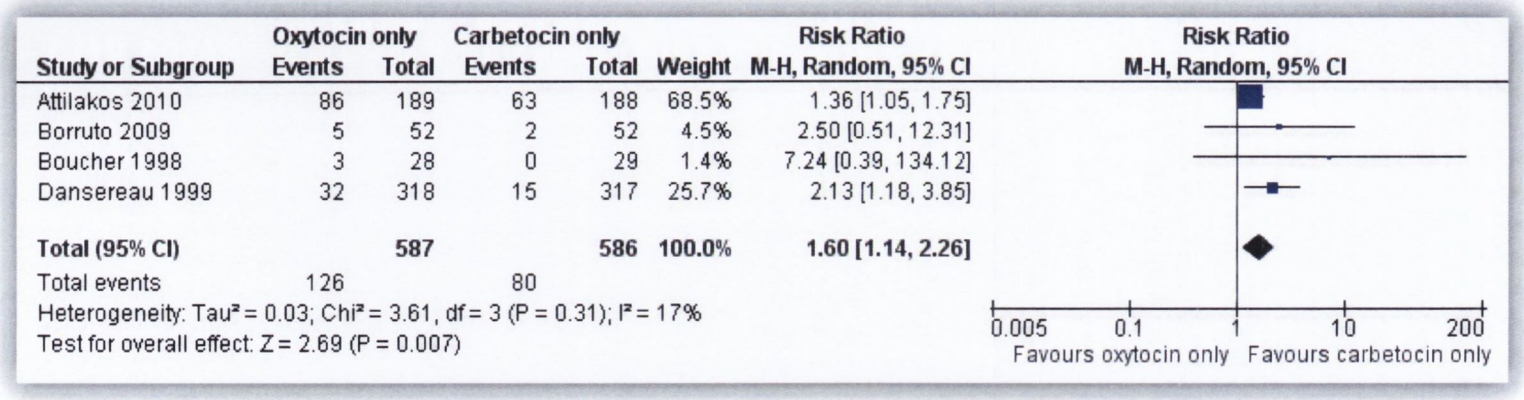


Figure 2-19 Forest plot of comparison: Oxytocin only versus carbetocin only, outcome: Need for additional uterotonic agents.

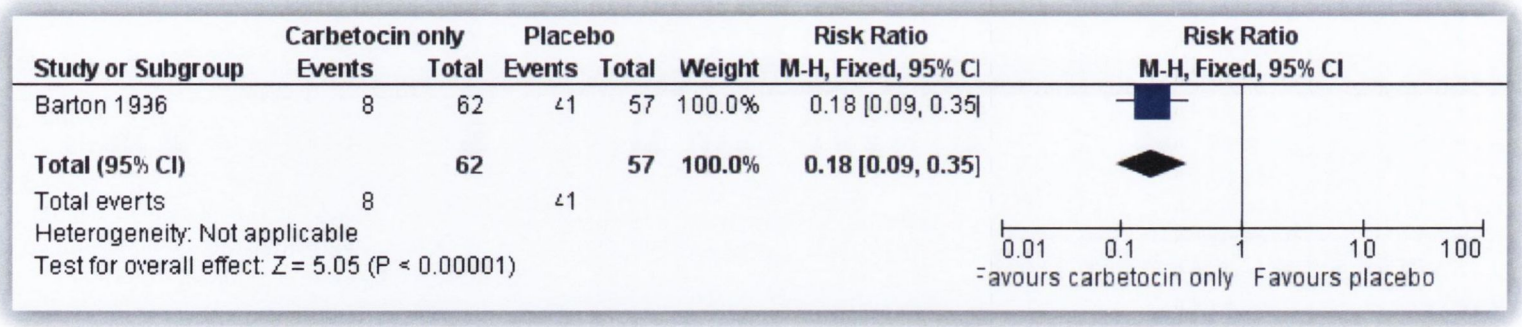


Figure 2-20 Forest plot of comparison: Carbetocin only versus placebo, outcome: Need for additional uterotonic agents.

CHAPTER 3. SURVEY OF GUIDELINE IMPLEMENTATION ON THE USE OF MEASURES TO PREVENT AND TREAT BLOOD LOSS AT CAESAREAN SECTION IN IRELAND AND GREAT BRITAIN

3.1 Introduction

As outlined in Chapter 1, this survey was set within the context of rising caesarean section rates and increasing haemorrhagic morbidity. There is a wealth of information and guidance on the management of the third stage of vaginal birth, with the assumption that the benefits apply to caesarean delivery also. The evidence presented in Chapter 2 has highlighted the paucity of good quality data in relation to the prevention of haemorrhage at caesarean section. Despite the lack of robust evidence, various clinical guidelines, readily accessible to clinicians, address the use of oxytocin at the time of caesarean section.[8 84] The aim of this study was to benchmark current clinical practice against recommended practice across the five countries of the Republic of Ireland, Northern Ireland, England, Scotland and Wales. It explored whether variations in approach were universal across the individual countries of the United Kingdom and Ireland and whether these variations reflected differences in the interpretation and implementation of clinical practice guidelines. It was performed within the context of the randomised controlled trial (RCT) to evaluate the role of an oxytocin infusion on the control of blood loss at elective caesarean section, described in detail in Chapters 4 – 6.

Essentially this study would determine the extent to which clinicians across the countries of Ireland and Great Britain had implemented the recommendations of published clinical guidelines and if and where variations in practice existed.

3.2 Materials and methods

3.2.1 Survey as a form of evaluation

A questionnaire survey is considered to be an objective method of gathering information about an individual's knowledge, beliefs, attitudes and behaviours.[218] It is a cost effective means of collecting data and ideal for large study populations or when the study population extends over a broad geographical location. The possibility of interviewer bias is removed as there is no interviewer. Limitations do exist however with this study method, and may include poor response rates, low quality data that is not generalisable and inflexibility.[218] Bearing in mind these potential pitfalls, a questionnaire survey was chosen as the most effective means

of gathering information about current practice. A well designed survey will increase response rates and improve the quality of information collated.[218 219]

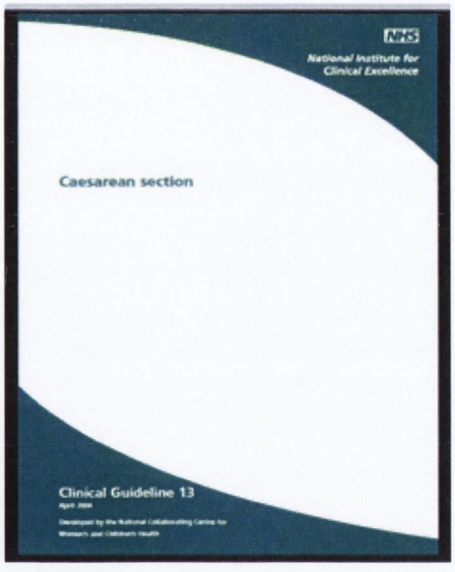
3.2.2 Developing the survey

A questionnaire was developed addressing the management of blood loss at caesarean section. (Appendix 3) It comprised a series of closed answer questions. Free-text options were also included to explore additional issues raised by individual clinicians. Use of oxytocin at caesarean section, perceived frequency of side effects, methods of estimating blood loss and the incidence of postpartum haemorrhage (> 500 ml) were investigated. Clinicians were asked to describe the dosage used for both oxytocin boluses and infusions. The indications for use of a prophylactic oxytocin infusion were also explored. Side effects, including hypotension, nausea, vomiting, headache, flushing and other serious adverse reactions, were described in terms of frequency of occurrence. Clinicians were asked to estimate the average blood loss at both an elective and an emergency caesarean section. Categorical responses ranging from 0-5% up to greater than 20% were included to gather information on the reported incidence of postpartum haemorrhage (defined as > 500 ml) at both an elective and emergency caesarean section. The questionnaire was piloted on all obstetricians and anaesthetists within a single maternity hospital and was finalised and distributed following final editing of errors and inconsistencies.

From the website www.cuidiu-ict.ie, 20 maternity units were identified in the Republic of Ireland. Each unit was then telephoned to ascertain or confirm contact details for each lead labour ward consultant obstetrician and anaesthetist. The questionnaire was distributed to all lead labour ward consultant obstetricians and anaesthetists in each unit. Stamped addressed envelopes were enclosed to assist response. Six weeks after initial contact, a reminder letter and questionnaire were sent to non-responders. These data were collected in August 2008 and added to pre-collected data for the 217 maternity units across England, Scotland, Wales and Northern Ireland.[220] The UK data had been collected by members of our research group in February 2006. The different time periods were not likely to pose a problem as there had been no change in guidelines during this time. The original analysis of the UK data addressed variation in clinical practice and the new extended analyses addressed implementation of guidelines.

3.2.3 *Current guidelines*

Existing clinical guidelines available at the time of the survey were used to benchmark reported practice against recommended practice for the management of blood loss at caesarean section. The National Collaborating Centre for Women's and Children's Health issued a clinical guideline on "Caesarean section" in 2004 recommending a slow intravenous bolus of 5 IU oxytocin following delivery of the infant at caesarean section.[8](see Figure 3-1) This guideline was supported by the National Institute for Health and Clinical Excellence (NICE) and the Royal College of Obstetricians and Gynaecologists (RCOG).(see Figure 3-2) NICE Guidelines specifically target practice within England, Wales and Northern Ireland but are readily accessible to practitioners within Scotland and the Republic of Ireland via the RCOG web-based link. The Advanced Life Support in Obstetrics (ALSO) manual (2000) also recommends a 5 IU bolus dose and clinicians from all six countries attend ALSO training courses.[84] (see Figure 3-3)



"Oxytocin 5 IU by slow intravenous injection should be used to encourage contraction of the uterus and to decrease blood loss"

Figure 3-1 NICE Caesarean Section Clinical Guideline

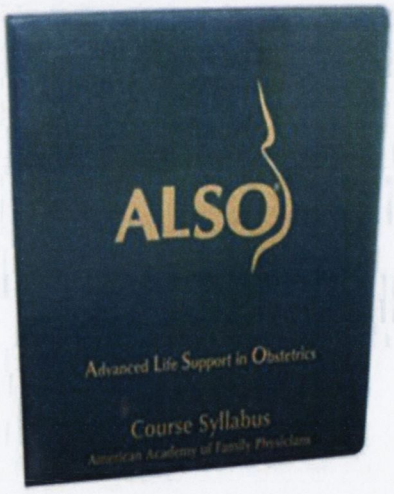
Royal College of Obstetricians and Gynaecologists

Green-top Guideline No. 52

PREVENTION AND MANAGEMENT OF POSTPARTUM HAEMORRHAGE

"For women delivering by caesarean section, oxytocin (5 IU by slow intravenous injection) should be used to encourage contraction of the uterus and to decrease blood loss"

Figure 3-2 RCOG Prevention and Management of Postpartum Haemorrhage, Green-top Guideline



"oxytocin 5 IU by slow intravenous injection"

Figure 3-3 Advanced Life Support in Obstetrics Course Manual

There is no specific guidance provided on the use of an oxytocin infusion for the prevention of haemorrhage. In the event of a postpartum haemorrhage at caesarean section, NICE recommends using a 30 IU oxytocin infusion whereas ALSO recommends a 40 IU infusion. Specific guidelines for the management of

caesarean section have not been issued to date in Scotland, Northern Ireland and the Republic of Ireland.

3.3 Results

Of the 40 questionnaires sent, 31 clinicians replied with a response rate of 78%. No clinician indicated that the questionnaire was inapplicable to their practice. Of the 31 responders, 14 (45%) were obstetricians and 17 (55%) were anaesthetists. When combined with the data available from the U.K, a total of 474 questionnaires had been sent. Of the 474 clinicians that were surveyed, 391 (82%) replied. No clinician indicated that the questionnaire was inapplicable to their practice. Of the 391 responders, 194 (49.6%) were obstetricians and 197 (50.4%) anaesthetists. Results are presented as the proportion of those responding to each question. There were occasional instances where respondents did not answer all of the questions or gave more than one answer, thus accounting for minor variation in denominators between questions. The results are presented as numbers and proportions. No formal statistical analyses between the groups have been performed as it was felt that analyses between and within the 5 groups would appear confusing and that the overall message would be more striking presented in a simple but transparent descriptive format.

Annual birth rates overall ranged from 200 to 8700 with a median of 3000 (interquartile range (IQR) 1800). Caesarean section rates ranged from 12% to 34% with a median of 23% (IQR 4). Use of a slow bolus of 5 IU intravenous oxytocin after delivery of the infant in keeping with recommended practice was reported by 346 responders overall (85-95% for individual countries), with a slow bolus of 10 IU oxytocin reported by 14% of responders in England and none in Wales (Table 3-1). The routine use of an oxytocin infusion varied greatly between countries (11% to 55%), with highest use in Ireland (Table 3-2). Marked variations in choice of oxytocin regimens were noted. There were 38 different regimens used to administer an oxytocin infusion. Doses of 30 IU or 40 IU over 4 hours were reported most frequently in keeping with the NICE and ALSO recommendations with additional regimens of 10 IU, 15 IU, 20 IU, 25 IU, 50 IU or 80 IU infusions. Volumes of infusion from 20 ml up to 1 litre were reported, with use of a syringe driver for smaller volume infusions. Normal saline was the preferred solution for oxytocin

administration. The timescale over which the infusion was given ranged from 1 hour to 8 hours according to the volume of infusion. The rate at which oxytocin infused varied from 3.33 IU/h to 20 IU/hr with 10 IU/hr being the mode. Overall, an infusion of 40 IU oxytocin over 4 hours was the most popular regimen. The ALSO guidance on infusion protocol was preferred in the Republic of Ireland and the NICE guidance in the North of Ireland with a more divided approach in England, Wales and Scotland.

More than half of the clinicians (52.4%) made a global estimate of blood loss (visual estimate) without objective measurement (Table 3-2). Average estimated blood loss reported for elective caesarean section ranged from 150 ml to 1000 ml (median 500 ml, IQR 100), while for emergency caesarean section, the estimated loss ranged from 200 ml to 1500 ml (median 600 ml, IQR 250). There were small differences between the reported approach of obstetricians and anaesthetists within individual countries with the only notable consistency in Wales where neither obstetricians nor anaesthetists ever use a 10 IU bolus oxytocin in keeping with recommended practice (Table 3-3).

3.4 Discussion

3.4.1 Summary of main findings

There appeared to be general consistency in the use of a bolus dose of oxytocin at caesarean section, with the majority of clinicians preferring to use a slow 5 IU intravenous bolus dose of oxytocin for the prevention of haemorrhage in keeping with existing clinical guidelines. Use of a 10 IU bolus dose was far less popular most likely reflecting published concerns of a link with such doses and maternal hypotension, arrhythmias and death.[127] However, in England, up to 14 % of clinicians used a 10 IU bolus of oxytocin despite recommendations against this compared to Wales where no clinicians use a 10 IU bolus and both countries should be implementing NICE guidance.

The dose of oxytocin used for infusions varied greatly, with the majority using either 30 IU or 40 IU over 4 hours in keeping with the two recommended approaches. Numerous other doses were described however, using a variety of alternative

solutions and alternative time regimens. When benchmarked against the country-specific recommendation, there were marked variations in choice of oxytocin regimens noted. An example of this was that only 122 clinicians (40%) in England and Wales used a 30 IU oxytocin infusion over 4 hours despite its recommended use by NICE which covered these two countries.

The majority of clinicians (79%) reported selective use of an additional oxytocin infusion. Ireland however, had the highest rate of routine infusion use (36% Republic of Ireland, 55% Northern Ireland). This may be related to a heightened awareness of the risk of (potentially avoidable) hysterectomy at the time of caesarean delivery due to a high profile Hospital enquiry.[221]

3.4.2 Strengths and weaknesses

A high response rate was achieved, representing a wide spectrum of obstetricians and anaesthetists throughout Great Britain and Ireland. There did not appear to be any difficulty in completing the questionnaire and there were very few inconsistencies in the responses within questionnaires. The free text responses enhanced the quality of information provided and suggested that this was a subject of particular interest and relevance to the respondents. Although the clinicians in the Republic of Ireland were surveyed more recently this would not be expected to introduce bias as the published guidelines had not been updated during the study time period. Clearly with any survey of this type there is a possibility that the non-responders may hold views that are at strong variance with the study findings.

3.4.3 Comparison with the literature

The evidence that active management of the third stage of labour reduces postpartum haemorrhage has led to clinicians prescribing prophylactic oxytocin routinely at caesarean section. Recent dose-finding studies have suggested that very low doses of oxytocin (1-2 IU) may be sufficient to prevent haemorrhage at caesarean section and therefore further questions the need to use a 10 IU bolus.[125 198]

3.4.4 Practice implications

The variation in practice exposes trainees in particular to the potential for drug errors when rotating from centre to centre and responding to major haemorrhage in the emergency setting.[222 223]

Overall, global estimation was the most widely used method of documenting blood loss (54%). There was marked variation in the individual clinician's perception of average blood loss at caesarean section and rates of postpartum haemorrhage at elective or emergency caesarean section.

3.4.5 Future work

Some of the variation seen reflects a lack of robust evidence and the need for future research in this area. It is hoped that ECSSIT – Elective Caesarean Section Syntocinon Infusion Trial (Chapter 4 - 6) will address some of the uncertainty that surrounds the prevention of postpartum haemorrhage at caesarean section described within the current study and to see this implemented within future clinical guidelines.

It is widely accepted that clinicians underestimate blood loss and hence this practice of estimation remains of great concern.[224] Given the importance of recognising and responding to excess blood loss, a defined approach to measuring blood loss (weighing swabs and measuring suction volume, with or without adjustment for liquor volume) should be addressed by future guidelines.

3.5 Conclusions

This survey found that clinicians' approach to use of oxytocin at the time of caesarean delivery varied between countries and while there was good consensus about the 5 IU bolus dose, both the use and dose of infusion varied greatly reflecting the limited guidance available at present. Even in countries with on-site visits to ensure guideline implementation (e.g. Clinical Negligence Scheme for Trusts in England), marked deviations from guideline recommendations existed.

The evidence-base for the development of clear clinical guidelines in this area is sparse. Large high-quality randomised controlled trials are essential to form the

basis of such guidelines. Procedures for ensuring guideline implementation also need to be explored.

Table 3-1 Use of oxytocin at the time of caesarean section

	Rep of Ireland (n=34) (%)	England (n=287) (%)	Scotland (n=29) (%)	Wales (n=19) (%)	Northern Ireland (n=22) (%)
Slow bolus 5 IU oxytocin	29 (85)	254 (89)	26 (90)	18 (95)	19 (90)
Slow bolus 10 IU oxytocin	3 (9)	40 (14)	3 (10)	0 (0)	1 (5)
Routine use of oxytocin infusion	12 (36)	50 (17)	5 (17)	2 (11)	12 (55)
Selective use of oxytocin infusion	22 (67)	234 (82)	24 (83)	17 (89)	9 (43)
30 IU infusion over 4 hours	1 (3)	116 (41)	16 (55)	6 (32)	15 (75)
40 IU infusion over 4 hours	23 (68)	160 (56)	12 (41)	13 (68)	4 (18)

Percentages refer to complete responses

Table 3-2 Estimate blood loss (EBL) at the time of caesarean section

	Rep of Ireland (n=34) (%)	England (n=287) (%)	Scotland (n=29) (%)	Wales (n=19) (%)	Northern Ireland (n=22) (%)
Global estimate of blood loss	18 (53)	150 (54)	9 (32)	11 (58)	17 (77)
Measured blood loss (no adjustment for liquor)	2 (6)	31 (11)	1 (4)	0 (0)	2 (9)
Measured blood loss (adjusted for liquor)	15 (44)	132 (47)	18 (64)	11 (58)	6 (27)
PPH (EBL > 500ml) frequency > 20% for elective caesarean section	3 (9)	46 (17)	3 (11)	1 (6)	3 (14)
PPH (EBL > 500ml) frequency > 20% for emergency caesarean section	4 (12)	75 (29)	6 (22)	4 (22)	5 (24)
EBL median (IQR) and range for elective caesarean section	500 (200), 200 – 1000	500 (100), 150 – 1000	500 (200), 250 – 750	400 (200), 200 – 700	500 (338), 300 – 900
EBL median (IQR) and range for emergency caesarean section	600 (237.5), 200 – 1000	600 (250), 200 – 1500	600 (313), 300 – 1100	500 (125), 200 – 1000	500 (325), 300 – 1000

Percentages refer to completed responses – some respondents reported more than one method of estimating blood loss

PPH: postpartum haemorrhage – includes haemorrhage at the time of caesarean section

Table 3-3 Use of oxytocin bolus and infusion by obstetricians and anaesthetists

	Rep of Ireland	England	Scotland	Wales	Northern Ireland
5 IU BOLUS OVER 1 MIN					
Obstetricians	13 (81%)	118 (84%)	16 (94%)	7 (100%)	11 (92%)
Anaesthetists	16 (94%)	136 (94%)	10 (83%)	11 (92%)	8 (89%)
10 IU BOLUS OVER 1 MIN					
Obstetricians	2 (13%)	26 (19%)	1 (6%)	0 (0%)	1 (8%)
Anaesthetists	1 (6%)	14 (10%)	2 (17%)	0 (0%)	0 (0%)
30 IU INFUSION OVER 4 HOURS					
Obstetricians	1 (6%)	61 (44%)	10 (59%)	2 (33%)	10 (77%)
Anaesthetists	0 (0%)	55 (38%)	6 (50%)	4 (36%)	5 (56%)
40 IU INFUSION OVER 4 HOURS					
Obstetricians	12 (75%)	75 (54%)	7 (41%)	5 (72%)	2 (17%)
Anaesthetists	11 (61%)	85 (59%)	5 (42%)	8 (67%)	2 (25%)

Percentages refer to complete responses

CHAPTER 4. ELECTIVE CAESAREAN SECTION SYNTOCINON INFUSION TRIAL (ECSSIT) – STUDY DESIGN

4.1 Introduction

The dramatic increase in caesarean section rates over the last four decades has now focussed attention on the associated morbidity, and in particular, the associated haemorrhagic morbidity. The systematic review and meta-analysis presented in Chapter 2 found no evidence of sufficient magnitude or quality to recommend any particular uterotonic agent over another for the control of blood loss at caesarean section. In the RCTs, oxytocin was clearly identified as the most commonly used uterotonic agent. In clinical practice across Ireland and the UK, this is also true, with oxytocin being the most widely used uterotonic agent. The majority of clinicians surveyed reported using a 5 IU oxytocin bolus for the prevention of haemorrhage at caesarean section. The use of an additional oxytocin infusion varied, as too did the regimens described, with 30 IU and 40 IU over four hours being the most popular.

A multi-centre RCT was designed to address the clear need for large high quality RCTs in this field. It was hoped that this would advance the understanding of which uterotonic regimen should be recommended to prevent haemorrhage at caesarean section. Based on the findings described in Chapters 2 and 3, we chose oxytocin as the uterotonic agent of interest and evaluated the role of an additional oxytocin infusion. It was postulated that an infusion would maintain uterine contractility during surgery and in the immediate post-operative period, when bleeding is most likely to occur. Women were randomised to receive a 5 IU oxytocin bolus and placebo infusion (bolus only group) or a 5 IU oxytocin bolus and 40 IU oxytocin infusion (bolus and infusion group).

Only women booked for elective caesarean section were recruited to the trial. "Elective" caesarean section was defined as any caesarean section planned more than 24 hours in advance, without any signs of labour. This pragmatic approach avoided the difficulties of ethics and consent that can be associated with recruiting patients in an emergency situation, and particularly intrapartum.

This chapter details the study design of this RCT. It includes descriptions of the trial setting and eligibility criteria. It also explains the methods used for recruitment, randomisation, interventions and data collection. Details of the outcome measures, sample size calculation, statistical analyses and study set-up are provided.

The results of the RCT will be presented in Chapter 5. The meta-analysis conducted in Chapter 2 of oxytocin bolus only versus oxytocin bolus and infusion will be performed again to include the results of the RCT and will be presented in this discussion chapter. This will be done as a means of interpreting the overall findings of the thesis rather than just the RCT. Chapter 6 will involve a discussion of the trial.

A pragmatic double-blind, placebo-controlled randomised trial was performed. The hypothesis was that an oxytocin infusion used in addition to an oxytocin bolus at elective caesarean section would reduce the risk of major obstetric haemorrhage.

4.2 Methods

4.2.1 A randomised controlled trial as a form of evaluation

The effect of a single intervention is most accurately assessed by a randomised controlled trial (RCT). Traditionally it is renowned as the "gold standard" of research. The double-blind randomised controlled trial is accepted as objective scientific methodology. The ideal RCT produces knowledge untainted by bias. As Ted Kaptchuk said, it "seeks to confer the ideal of scientific exactitude onto clinical experimentation in an effort to attain the objectivity of the laboratory model.[225] Random error is mathematically estimated, while systematic error is minimised by the rigorous application of methodological safeguards, notably randomisation and blinding. The randomisation process avoids selection bias. Blinding reduces observer bias, eliminating the influences of pre-conceived ideas of both professionals and patients.

4.2.2 Setting

Recruitment was planned to take place in three Dublin maternity hospitals: Coombe Women & Infants University Hospital, National Maternity Hospital (Holles Street) and the Rotunda Hospital. Each of the three Dublin maternity hospitals is a university teaching hospital and delivers in excess of 8500 women annually. Recruitment commenced at each centre in February 2008.

The graph in figure 4-1 demonstrates recruitment over the first half of the trial, from February 2008 to April 2009. For a period of six months, from September 2008 to March 2009, no recruitment took place at the National Maternity Hospital as we had no research midwife at this site. In the early months of recruitment, it became apparent that in order to reach the recruitment target of 2112 women by the summer of 2010, recruitment would need to be extended to additional centres. Mount Carmel Hospital in Dublin and Our Lady our Lourdes Hospital in Drogheda were identified as suitable centres and approached. Mount Carmel Hospital is a private hospital and has in the region of 2500 deliveries per annum; Our Lady our Lourdes Hospital is a university teaching hospital, north of Dublin and delivers approximately 4000 women each year. Recruitment commenced at Mount Carmel in April 2009 and in Our Lady of Lourdes in July 2009. The projected timeline of recruitment for the second half of the trial is shown in Figure 4-2, with actual recruitment for this period demonstrated in Figure 4-3.

Recruitment concluded in March 2010 in four centres due to financial restraints and research midwifery availability, continuing through to June 2010 in the Coombe Women & Infants University Hospital to achieve the recruitment target.

4.2.3 Recruitment procedure

The antenatal clinic midwife or research midwife/fellow approached potentially eligible women and offered information about the study when initial arrangements were being made for an elective caesarean section. (Appendix 4) Women returned on the day of surgery and spent a number of hours on the day ward or antenatal ward prior to surgery. At that point the woman's interest in participation in the study was confirmed; an opportunity to ask additional questions was provided and informed written consent completed. (Appendix 5)

4.2.4 Eligibility

Eligibility was established by the research midwife/fellow after reviewing the woman's maternity chart and as a result of discussion with the woman prior to recruitment.

Inclusion criteria

The study was limited to healthy women at term (>36 weeks) with singleton pregnancies who were booked for elective caesarean section.

Exclusion criteria

Women with placenta praevia, thrombocytopenia, coagulopathies, previous major obstetric haemorrhage (> 1000 ml), known fibroids, polyhydramnios, or receiving anti-coagulant therapy were excluded, as were women who did not understand English and women under the age of 18 years. Women with known uterine anomalies or any contraindications to oxytocin use were also excluded. Women undergoing general anaesthesia were also excluded. Other patients were excluded at the clinician's discretion if a major haemorrhage was anticipated, in keeping with the recommendations of the research ethics committee.

4.2.5 Allocation procedure

When comparing outcomes in two treatment groups, any observed difference may be due to: treatment, chance or bias. Bias may be defined as any factor or process that tends to deviate the results or conclusions of a trial systematically away from the truth. Two major potential sources of bias are:

- The method of allocation of patients to each treatment
- The knowledge of patients, health care professionals and investigators of the treatment allocation of the subject.

To minimise potential bias from these sources, random allocation to treatment group and blinding (also known as masking) are employed to ensure that treatment allocation is unknown. Even when randomisation has been used, it is crucial to conceal the randomisation schedule from those recruiting trial participants. Schulz et al found a 41% increase in estimated effects in favour of active treatments in trials where inadequate concealment was used.[226] The importance of this issue is highlighted by the fact that many items in the CONSORT checklist for trial reporting relate to the method of concealment of randomization so that the "purity" of the randomization can be judged by the reader.[227]

The randomisation was performed after the patient consented to the study. This procedure ensured allocation concealment. Randomisation was performed using an automated web-based randomisation system hosted by the Bristol Randomised Trials Collaboration, a UKCRN-registered trials unit. (Appendix 6) Allocation was stratified by centre and previous caesarean section (no/yes), and blocked using random permuted blocks of varying size. Each woman's GP was also informed of her participation in the study by means of a standard letter (Appendix 7).

4.2.6 Treatment regimen

Women were randomised to receive either an intravenous slow bolus of oxytocin 5 IU and 0.9% saline solution 500 ml over four hours (bolus only group) or oxytocin bolus 5 IU and 40 IU oxytocin in 500 ml 0.9% saline solution over four hours (bolus and infusion group). The active or placebo infusion was prepared by the research fellow/midwife. This was done in the pharmacy department, away from theatre and was labelled as "Trial drug – Placebo or 40 IU oxytocin". (Appendix 8) This ensured blinding of everyone except the research fellow who made up the infusion, who played no role in the management of the patient, or the measurement of outcomes. Having the research fellow blinded in all centres was not possible for two reasons. Firstly, it was not possible to pre-prepare the infusions due to a lack of knowledge of the stability of oxytocin. Secondly, it was not possible to obtain identically matched placebo ampoules. In one recruitment centre, the Rotunda Hospital, the pharmacist randomised the patient via the web system and prepared the infusion, thus ensuring blinding of the research midwife. This was not feasible in any of the other centres. In each of the other centres, upon obtaining the allocation from the web, the research midwife prepared the infusion. Outcome data was not calculated or recorded by any members of the research team, neither were they involved in any aspects of the patients' care or management.

4.2.7 Surgical and anaesthetic protocols

In any trial, the two groups should be identical with the exception of the treatment assigned. For clinical trials many factors may interfere with this "ideal". As a result of this, specific protocols and procedures must be devised and followed. Where the protocol is not followed, it must be documented and the protocol deviation

noted. In ECSSIT, both surgical and anaesthetic techniques were standardised with all deviations from protocol recorded.

Grade of obstetrician/anaesthetist was defined as junior and senior, with junior having three years or less specialist training. Both surgical techniques and anaesthesia were standardised. Obstetricians were asked to operate to a standard procedure that specified controlled cord traction for delivery of the placenta after administration of the oxytocin bolus, two layer closure of the uterine incision, and to avoid delivering the uterus for suturing unless clinically indicated. Deviations from the standard procedure were recorded. If the uterus remained atonic despite the trial intervention, the obstetrician/anaesthetist was permitted to use an additional uterotonic agent, either replacing the trial infusion with a known oxytocin infusion and/or use of other additional agents. An algorithm for use of additional uterotonic agents is shown in Figure 4-4.

Measurement of operative blood loss was standardised. Disposable waterproof drapes were in use with pockets that captured all body fluids. The suction volume was measured and all swabs were weighed to measure additional blood loss. A more objective measure of blood loss was calculated using pre- and post-operative haematocrit (see outcome measures below).

Anaesthesia was also standardised. An intravenous bolus of 500ml crystalloid was given to all patients prior to spinal anaesthesia. A size 25G pencil-point needle was used at a suitable lumbar interspace. The patient could be sitting or in the left lateral position for spinal anaesthesia. The anaesthetic solution consisted of 2ml 0.5% hypertonic bupivocaine (2.2ml in the sitting position), 10-20μg fentanyl and 0.1mg preservative free morphine. Anaesthesia was to the level of T5, as assessed by touch. The patient was tilted 15^0 to the left of supine and standard monitoring used as per the AAGBI guidelines. The sphygmomanometer cuff was placed on the left arm. Haemodynamic monitoring was performed before spinal anaesthesia, every minute until 10 minutes after delivery, every 15 minutes during the first postoperative hour then every 30 minutes for four hours. For the purpose of this study, baseline hemodynamic variables were regarded as those immediately after clamping of the cord and before administration of oxytocin 5 IU. Intravenous crystalloids were continued at 1 L every 8 hours until the morning after surgery, unless the patient was unable to tolerate oral fluids. It was accepted that

individual anaesthetists may deviate from this protocol according to clinical needs. This was acceptable and was documented on the case report form.

Intraoperative hypotension was treated with intravenous boluses of phenylephrine 50μg. If the heart rate fell below 60/min, intravenous boluses ephedrine 6mg was substituted. The anaesthetist aimed to maintain blood pressure at preoperative values. After delivery, the operating table tilt was removed and the patient placed in the full supine position. Blood loss at operation was replaced with colloid infusion or blood as deemed necessary by the anaesthetist. Postoperative pain relief consisted of regular non-steroidal analgesia combined with paracetamol. Opiates in the form of oxycodone could be used with caution considering the use of intrathecal opiates. Again it was acceptable for the local administrator to use any form of analgesia as per local practice and to document it on the case report form.

4.2.8 Data from medical records

Information about each woman's medical and obstetric history was collected from antenatal clinical records at the time of recruitment. Details of the caesarean section and postnatal recovery were collected from theatre, midwifery, anaesthetic, obstetric and paediatric notes. (Appendices 9 and 10) Theatre staff were asked to complete a specific "Theatre/Recovery" form which documented surgery times and measured blood loss. (Appendix 11)

4.2.9 Data entry and checking

As data were received, they were entered onto a password protected Microsoft Access database by members of the research team. Validation rules were established within the database to assist accurate data entry. All data were double-checked for quality. Erroneous values were verified against source data and corrected as appropriate.

4.3 Baseline characteristics

Baseline assessment includes initial patient characteristics. This documents socio-demographic characteristics and self-reported health. Whilst it may be tempting

to collect as much information as possible, it is important to focus on relevant information. It is essential to ensure all prognostic factors and end points are included. While block randomisation controls possible imbalance in group size that may arise by chance, it does not control possible imbalance in the characteristics at baseline of the groups. It is often said that the purpose of randomisation is to ensure equality between the groups in terms of prognostic factors that may affect outcome; this however is misleading. It is more accurate to say that randomisation ensures that any inequality between the groups in terms of prognostic factors is due to chance. For all randomisations, the two groups are equal however, in any one trial it is extremely unlikely that the groups will be exactly balanced. While a substantial imbalance is unlikely to occur in a very large trial, small trials may well be subject to sufficient imbalance in prognostic factors to affect the overall result of the trial. It is therefore important to assess and report the baseline characteristics of the treatment groups, with particular reference to potential prognostic factors. This is useful general information to help the reader assess the comparability of the treatment groups, as well as providing general information to help the reader assess the trial's external validity. However, the common practice of undertaking significance tests of baseline characteristics is not appropriate.

Socio-demographic, past medical and obstetric history information was collected in order to characterise participants at trial entry. Socio-economic status was classified according to the Central Statistics Office classifications (Appendix 12). Marital status was defined as married, single supported, single unsupported or unknown. Participants' date of birth was used to calculate their age on the day of caesarean section. Maternal weight, height and BMI were routinely recorded at the booking visit in each of the five centres and these values were collected. Gestational age at booking was also recorded. The following information concerning each participant's obstetric history was recorded: parity, previous caesarean section, history of postpartum haemorrhage, previous pelvic surgery, previous pelvic infection, indication for this caesarean section. Information relating to any past medical or surgical history was also gathered. Each participant's smoking status, alcohol intake and drug use was also recorded.

4.4 Outcome measures

Outcome measurement is the means of gauging the effectiveness of an intervention in a trial. It is central to the interpretation of results and the conclusions that can be drawn. As it impacts on the study design in terms of sample size, it requires precise pre-specification in the study protocol to ensure it is accurate and consistent. Trials may have many outcomes. It is important though to appreciate that a trial is powered to detect a primary outcome rather than all other outcomes.

There were two primary outcomes, both binary: (1) major obstetric haemorrhage and (2) use of an additional uterotonic agent. Major obstetric haemorrhage (MOH) was defined as "calculated" blood loss >1000 ml. This was chosen as a quantitative objective measure in preference to other methods estimating major haemorrhage since it is widely accepted that clinicians underestimate rather than overestimate blood loss, and that gravimetric methods include liquor in addition to blood, limiting accuracy.[224] This estimate was based on the difference between the pre-operative and post-operative haematocrit (HCT) calculated as follows:[125 217]

$$EBL_{calc} = EBV \times \frac{\text{(Pre-op HCT – Post-op HCT)}}{\text{Pre-op HCT}}$$

EBL_{calc} = Calculated estimated blood loss

EBV estimated blood volume = Booking weight in kg x 85

Use of an additional uterotonic agent was also chosen as a primary outcome as obstetricians are likely to intervene in the event of uterine atony and use an additional uterotonic agent to prevent haemorrhage.

As a secondary outcome, blood loss was assessed gravimetrically, by measuring the suction volume and weighing all swabs. Disposable waterproof drapes were used with pockets that captured blood and liquor. While this approach is subject to technical and observer error, it is considered more accurate than clinicians' subjective estimations of blood loss. Additionally, routine pre- and post- operative

haematocrit testing is not performed in many countries. Other secondary outcomes included early lochial loss, change in haemoglobin (Hb) and haematocrit, significant anaemia (Hb fall ≥ 20%) 48 hours after delivery, need for blood transfusion, side effects (including vomiting and hypotension), breastfeeding at hospital discharge and length of postnatal stay in the operating room/recovery area and in hospital. Hypotension was defined as a fall in blood pressure of more than 30% below the pre-operative blood pressure and/or use of ephedrine.

4.5 Testing the success of blinding

Although description of the mechanism used for blinding may provide such assurance, the success of blinding can sometimes be evaluated directly by asking participants, caregivers, or outcome assessors which treatment they think was received. In principle, if blinding is successful, the ability of participants to accurately guess their group assignment should be no better than chance. In practice, however, if participants do successfully identify their assigned intervention more often than expected by chance, it may not mean that blinding was unsuccessful. Although adverse effects in particular may offer strong clues as to which intervention was received, especially in studies of pharmacological agents, the clinical outcome may also provide clues. Thus, clinicians are likely to assume, not always correctly, that a patient who had a favourable outcome was more likely to have received the active intervention rather than control. If the active intervention is indeed beneficial, their "guesses" would be likely to be better than those produced by chance.

It is recommended that authors should report any failure of the blinding procedure, such as placebo and active preparations that were not identical in appearance, as a lack of blinding is associated with bias.[228-231] Patients who know they are in the "new treatment" group may react differently to those in the "standard treatment" group. The impact will depend on the nature of the condition being treated and on the treatment. As well as their response in terms of outcomes, patient compliance may also vary if treatment allocation is known. Patients on a "new" treatment may be observed more closely and be given

enhanced care compared to those on "standard" or "placebo" treatment. This may affect treatment and patient attitude.

When assessing outcomes, if the assessor is aware of the patient's treatment group, there is the danger that they will err to record more favourable responses on the new treatment; after all, most trials are conducted in the hope that the new treatment will appear superior to the existing treatment, to the likely benefit of the investigators and/or their sponsors. Such ascertainment bias is most likely where outcomes are dependent on clinical judgment, but even "objective" measures can be affected since there are always borderline judgments to be made (e.g. rounding errors in blood loss measurement). Placebos are specifically used in trials where now comparable alternative treatment exists, so that patients, health professionals and assessors are unaware of treatment allocation. Wherever possible, a blinded design should be used, in which neither the patient, nor those responsible for care and assessment know which treatment the patient is receiving. In many cases, this may not be possible, but one should endeavour to blind assessors and data analysts. A meta-analysis of studies of bias found that trials described as "double-blind" in trial reports revealed 14% lower treatment effects, on average, compared to similar trials not described as "double-blind".[228]

The success of blinding was evaluated within a cohort of patients recruited to ECSSIT over a 5-month period. Prior to discharge, participants and clinicians were asked to complete a simple questionnaire to assess blinding. (Appendix 13) They were asked which study intervention they believed was received – 40 IU oxytocin infusion or placebo infusion. The questionnaire will comprise of yes/no/don't know categories. Reasons for these answers were sought.

The degree of agreement between the actual intervention and the presumed intervention was assessed and the reasons for presuming one intervention over another were also evaluated.

4.6 Sample size calculation

The pilot study estimated that approximately 14% of the study participants in the placebo group had a major obstetric haemorrhage[175], and that a relative

reduction of between 20-50% was feasible and would be clinically important. The sample size and power calculations were performed (80% power and 5% two-sided alpha) and are shown in Table 4-1.

Table 4-1 Sample size calculations for ECSSIT RCT

Incidence of EBL_{calc} >1000 ml in control group	Assume 30% relative reduction with oxytocin infusion	Sample size (≥ 80% power, 2-sided α = 0.05)
10%	6.4%	2000 (1000 each arm)
15%	10.7%	2000 (1000 each arm)

With an estimated incidence in the placebo group of 14%, 80% power and 5% two-sided alpha, a total N for analysis of 1000 per group was required to detect a between-group difference of 4.2 percentage points, equivalent to an odds ratio of 0.67.

Based on the hospital statistics in the Dublin Maternity units for 2004 we estimated that there would be approximately 2500 elective caesarean sections at term each year between the centres. Over the course of 30 months we aimed to recruit 2112 patients representing almost 34% of the available population (2112/6250) – this conservative estimate took account of eligibility criteria and non-English speaking women. The target sample size to be recruited was inflated to allow for a 3% rate of missing primary outcome data (blood test not performed or at the wrong time point).

4.7 Statistical analysis

Data analyses and reporting proceeded according to CONSORT guidelines for randomised controlled trials[232], and was conducted blinded to group status by me and checked by the trial statistician, Alan Montgomery. Analyses were conducted on all randomised patients as assigned to one of the two treatment groups (oxytocin bolus and placebo infusion or oxytocin bolus and oxytocin infusion)

applying the principles of intention-to-treat (ITT). All analyses were conducted blinded to treatment allocation using SPSS 16 and Stata 11.

Appropriate descriptive statistics were used to assess comparability of the trial arms at baseline. The primary between-group comparisons for both primary (binary) outcomes were conducted using multivariable logistic regression models with adjustment for stratification variables. The effects on the primary analyses of further adjustment for any variables displaying marked imbalance between the arms at baseline were then investigated. Secondary outcomes were analysed in a similar way using appropriate (that is, logistic or linear) regression models depending on outcome type. Results from all regression models were presented as point estimates (odds ratios or differences in means), 95% confidence intervals and p values. A series of planned subgroup analyses were conducted by including appropriate interaction terms in the regression models to ascertain any differential effects in relation to repeat caesarean section (0, 1, ≥ 2), adherence to anaesthetic and surgical protocols (no/yes), and operator experience (junior/senior). Success of blinding was evaluated within a sub-sample of recruited cases already described, where patients, obstetricians and anaesthetists were asked to identify which infusion they thought had been administered. Cohen's kappa co-efficient, which examines the level of agreement beyond that expected by chance, was used. Agreement ranges from values "< 0" implying no agreement to "> 0.81" implying almost perfect agreement.

The meta-analysis described in Chapter 2 was updated to include the results of the trial. As before, the methodology was based on the Cochrane Handbook of Systematic Reviews.[165] Data were analysed using a fixed-effect model in cases of low heterogeneity (I^2 statistic < 50%) and a random-effects model in cases of moderate to high heterogeneity between studies (I^2 statistic > 50%). For dichotomous data, results are presented as a summary risk ratio with 95% confidence intervals. Results for continuous data are presented as the mean difference with 95% confidence intervals. Statistical analysis was conducted using the Review Manager Software, RevMan 2008.[168]

4.8 Timetable

Total 36 months: Commencing 01.12.07 - Estimated completion date 31.11.10

Month 0-2: Validate datasets; Raise study awareness; Finalise recruitment procedures

Month 3-33: Recruit participants and complete documentation and follow-up

Month 34-36: Analysis; Final report; Peer-review publications; Presentations.

4.9 Study set-up

4.9.1 Funding

This study was funded by a Research Project Grant from the Health Research Board of Ireland with supplementary funding from the Coombe Women & Infants University Hospital. (Appendix 14) Annual reports were submitted to both the Health Research Board and the Master of the Coombe Women & Infants University Hospital. The funding sources had no involvement in any aspects of trial design, writing of the trial reports, or the decision to submit the paper for publication. There was no pharmaceutical sponsorship.

4.9.2 Ethics committee approvals

Research ethics approval for the study was received from the Central Clinical Trials Ethics Committee, located at the National Maternity Hospital. (Appendix 15) Each of the local research ethics committees also granted approval for the study. Annual reports were submitted to each of the research ethics committees.

4.9.3 Irish Medicines Board approval

Approval from the Irish Medicines Board was obtained in March 2007 (Appendix 16), and annual reports were submitted.

4.9.4 Trial registration

The trial was registered at controlled-trials.com and was assigned the registration number: ISRCTN17813715. (Appendix 17)

4.9.5 *Research team*

Research midwife positions were advertised in each of the participating centres and interviews were held. A part-time research midwife was appointed to each of the centres. I worked as a full-time research fellow, acting as trial co-ordinator at each of the centres, but with responsibility for recruitment predominantly at the Coombe centre.

4.9.6 *Trial Steering Committee (TSC)*

The trial steering committee met quarterly. Meetings took place at the Coombe Women & Infants University Hospital, with teleconferencing facilities for those overseas. Miss Bryony Strachan was appointed as the independent Chair of the Committee. Members of the ECSSIT study team are shown in Table 4-1. Contributions of each of the members are highlighted in Table 4-2.

4.9.7 *Data Monitoring Committee (DMEC) (see table 4-3)*

An independent Data Monitoring Committee was established and reviewed recruitment and safety data after 1000 patients had been recruited. A charter was drawn up for this committee (Appendix 18), with Dr Andrew Weeks as Chair. Dr Andrew Weeks is a consultant in Liverpool Women's Hospital and has extensive experience both clinically and academically. He has recently conducted a large multi-centre randomised controlled trial of intraumbilical injection of oxytocin to reduce retained placenta. Dr Louise Kenny is a consultant obstetrician and gynaecologist at University College Cork, Cork University Maternity Hospital. She also has significant clinical and trial experience. Dr Ed Juszczak is a statistician, and works at the National Perinatal Epidemiology Centre, Oxford. He has been involved with clinical trials for several years.

4.9.8 *Protocol publication*

The trial protocol was submitted originally to the Lancet for publication. The time from the original date of submission to the date of rejection was almost eight months. It was rejected on the basis that the Lancet recommended only one method of measuring blood loss for the primary outcome. The initial protocol submission had described using two methods to calculate blood loss, a gravimetric method and a calculated method. Taking this advice into consideration, it was agreed by the Trial Steering Committee that the study

protocol would be amended and that the calculated method would be used to calculate the primary outcome. Unfortunately when the Lancet was advised that their advice had been taken on board and that the protocol had been duly amended, the study protocol was rejected for publication. The Lancet rejected the protocol on the basis that it is editorial policy not to accept appeals to protocol rejections. Despite initial disappointment, it was acknowledged that the eight-month long interaction with the journal had been invaluable and that the trial protocol was undoubtedly an improved, more robust template as a result of the extensive peer-review process and reflection.

It was accepted for publication by BioMed Central Pregnancy and Childbirth and published in 2009.[216] (Appendix 19)

4.9.9 Study promotion

This study was publicised to all relevant hospital staff groups: obstetricians, anaesthetists, midwives, nurses and pharmacists. Oral presentations and written information were provided to these groups on a regular basis. Information leaflets were displayed in the antenatal clinics of participating hospitals to alert staff and potential participants to the study. Prior to recruitment, letters were sent out to all consultant obstetricians and anaesthetists in each of the recruitment centres advising them of the trial and requesting their permission to include their patients in the trial. Signed agreements were received from each consultant and filed away. Regular trial updates were distributed in the form of a newsletter "The ECSSIT Poll". (Appendix 20). The study was also reported on the Trinity College Dublin School of Medicine website, as part of the "E-bulletin".

4.10 Summary

This chapter has described in detail the study design of the RCT. The results of this trial will now be presented in the following chapter.

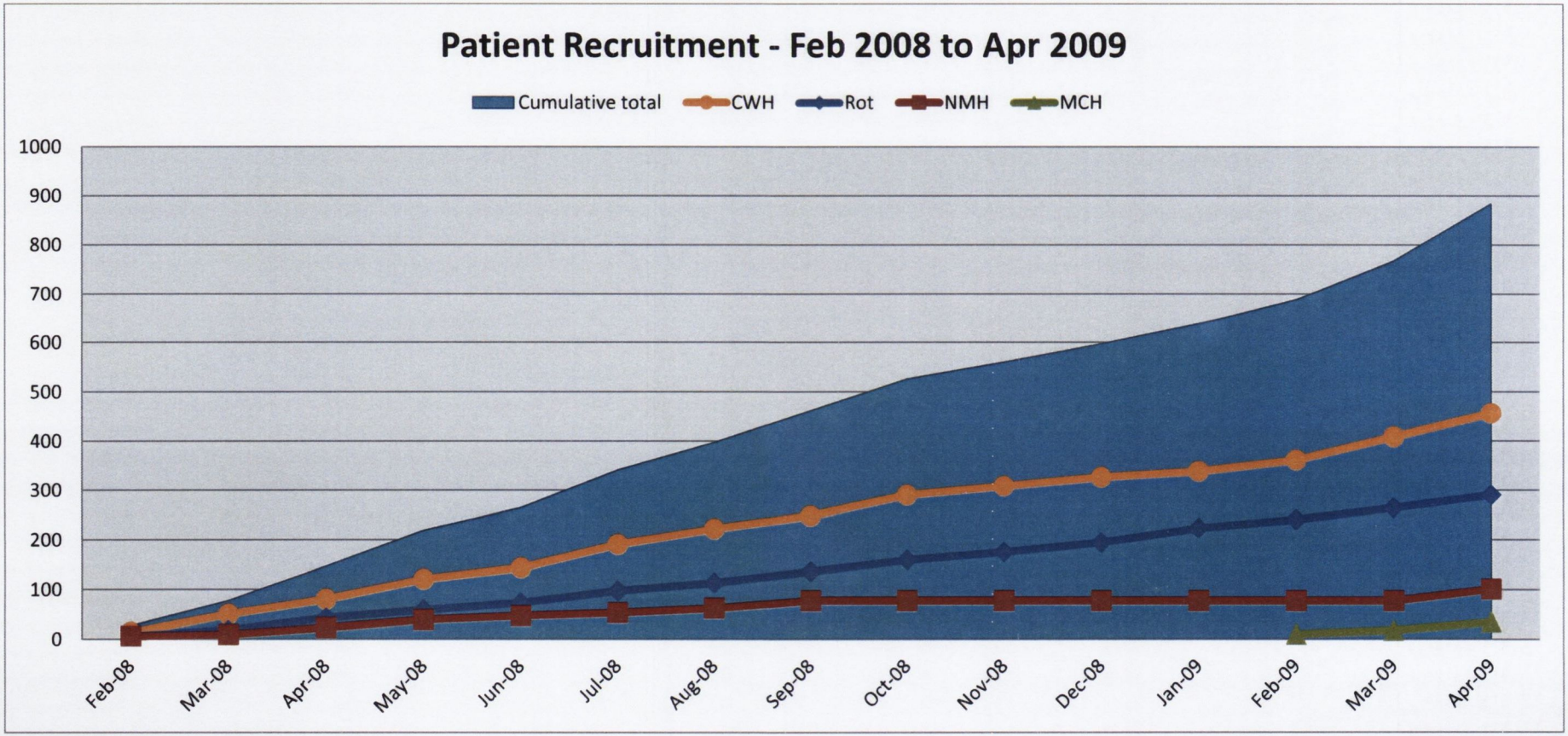


Figure 4-1 Recruitment from February 2008 – April 2009 (inclusive)

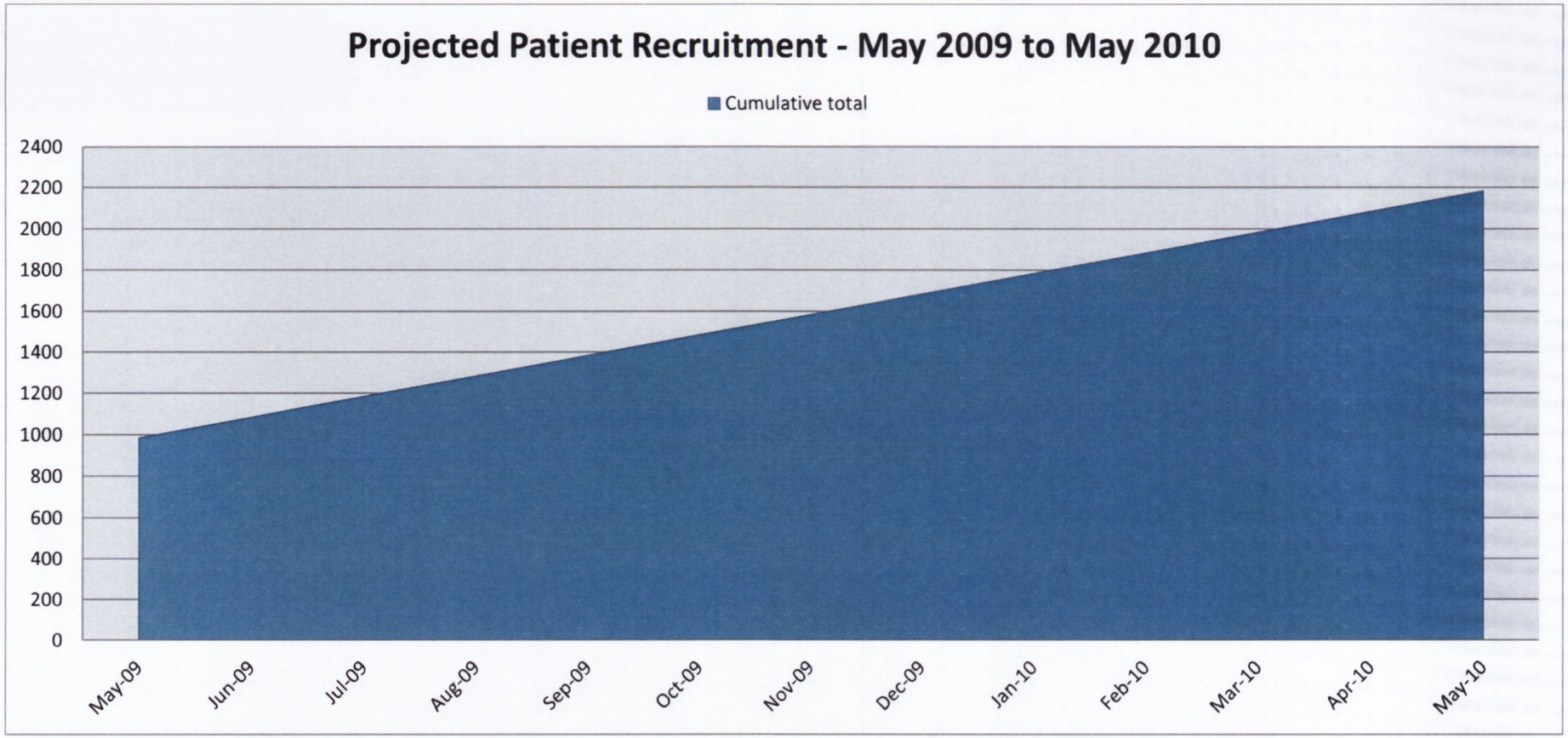


Figure 4-2 Projected timeline of recruitment from May 2009 to May 2010 (inclusive)

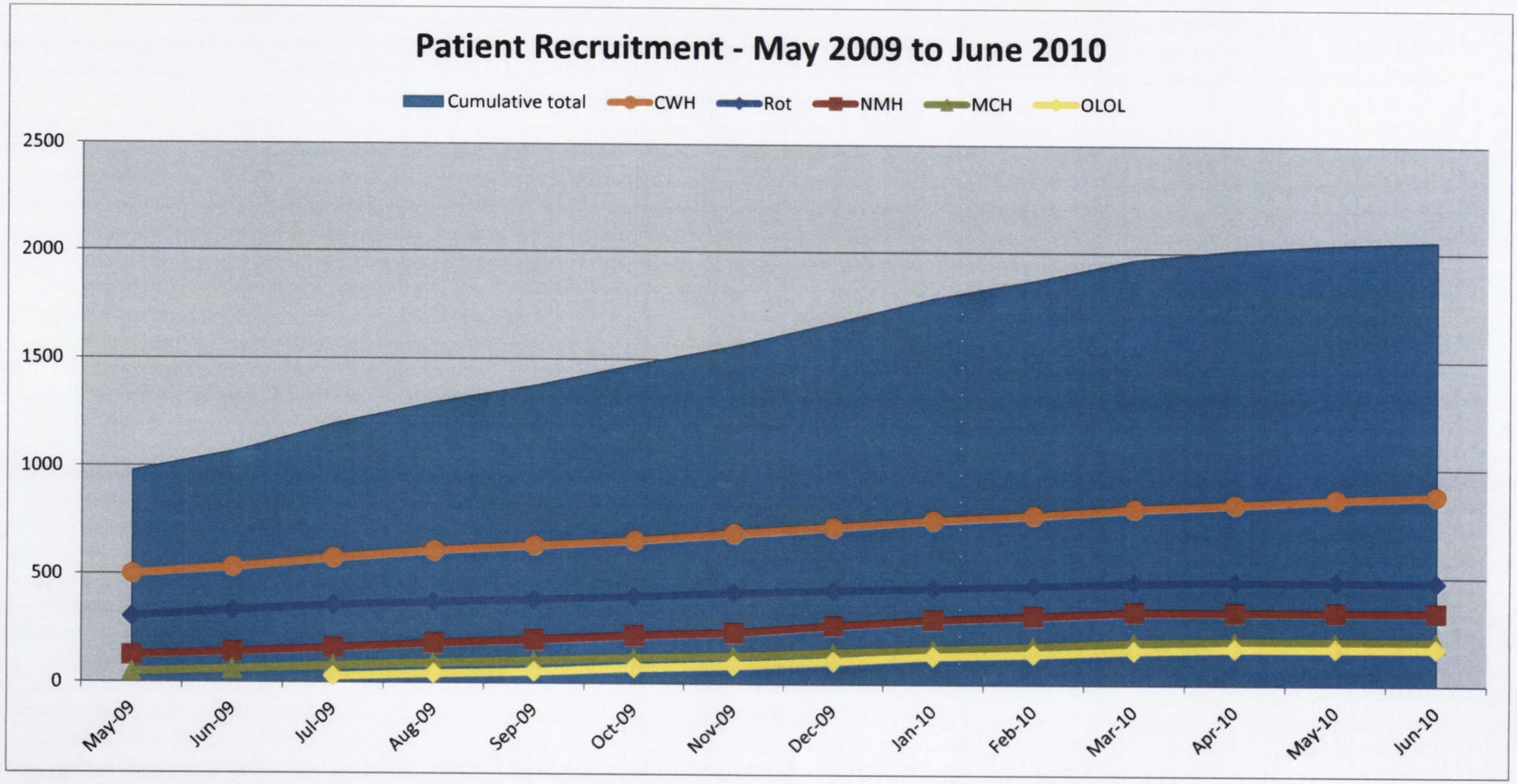


Figure 4-3 Recruitment from May 2009 to June 2010 (inclusive)

- **Replace trial infusion with a known oxytocin infusion**

  (40 IU oxytocin in 500 ml 0.9% normal saline at 125 ml/hour)

- **Oxytocin bolus 5 IU slowly IV (may have a repeat dose)**

- **Ergometrine 0.5 mg IM or syntometrine 1ml IM**

- **Misoprostol 1 mg PR (5 × 200 micrograms tablets)**

- **15-methyl-prostaglandin F2α 0.25 mg IM**

  (may be repeated every 15 minutes to a maximum of 8 doses)

* adapted from the Royal College of Obstetricians and Gynaecologists. *Prevention and management of postpartum haemorrhage.* Green-top Guideline no. 52. London RCOG; 2009

† Each unit has its own local guidelines and each obstetrician may have their preferred agent

Figure 4-4 Algorithm for use of additional uterotonic agents*†

Table 4-2 Members of the ECSSIT Study Group

Name	Initials	Job Title	Location during trial
Michael Carey	MC	Director of Peri-operative Medicine	Coombe Women & Infants University Hospital
Sharon Cooley	SC	Fetal medicine sub-specialty trainee	Rotunda Hospital
Ann Marie Connor	AMC	Research Midwife	Our Lady of Lourdes Hospital, Drogheda
Michelle D'Arcy	MDA	Research Midwife	Rotunda Hospital
Clare Dunney	CD	Research Midwife	Coombe Women & Infants University Hospital
Maeve Eogan	ME	Consultant Obstetrician & Gynaecologist	Rotunda Hospital
Michael Geary	MG	Master and Consultant Obstetrician & Gynaecologist	Rotunda Hospital
Hilary Gilligan	HG	Research Midwife	Coombe Women & Infants University Hospital
Ronan Gleeson	RG	Consultant Obstetrician & Gynaecologist	Rotunda Hospital
Fionnuala McAuliffe	FMA	Associate Professor of Obstetrics & Gynaecology	University College Dublin and National Maternity Hospital, Holles Street
Alan Montgomery	AM	Reader in Health Services Research	University of Bristol
Deirdre Murphy	DM	Professor of Obstetrics and Head of Department (Principal Investigator)	Trinity College Dublin and Coombe Women & Infants University Hospital
Ruth O'Connor	ROC	Research Midwife	Mount Carmel Hospital
Hassan Rajab	HR	Registrar in Obstetrics & Gynaecology	Rotunda Hospital
Sharon Sheehan	SS	Research Fellow (Trial Coordinator)	Trinity College Dublin and Coombe Women & Infants University Hospital
Eleanor Woods	EW	Research Midwife	National Maternity Hospital, Holles Street

Table 4-3 Contributions of ECSSIT study group members

Note: My contribution is highlighted in red

Task	Major Contribution	Supporting or Supervisory Contribution
Initial idea for study	DM	
Developing the study protocol	DM, AM, MC, SS	FMA, RG, ME
Obtaining funding	DM, AM, MC	
Obtaining IMB approval	DM	
Obtaining ethics approval	DM, SS	
Conducting pilot study	Scotland: DM Ireland: SS	DM
Organising Trial Steering Committee Meetings	SS	DM
Establishing Data Monitoring Committee	SS	DM
Recruiting research midwives	SS	DM
Recruiting to ECSSIT	SS, MDA, ME, HG, HR, CD, ROC, AMC, EW	DM, FMA, MG, ME
Producing newsletters "The ECSSIT Poll"	SS	DM
Producing annual reports: Health Research Board of Ireland, Irish Medicines Board, Ethics Committees	SS	DM
Data collection	SS, MDA, ME, HG, CD, ROC, AMC, EW	DM
Data entry	SS, HG, CD, EW	DM
Data checking	CD	SS
Statistical analysis	SS, AM	DM
Writing study publications	SS	DM, AM, ME, RG, MG, FMA, MC

Table 4-4 Members of the Data Monitoring Committee

Position	Name	Institution
Chair	Andrew Weeks	Liverpool Women's Hospital, UK
Member	Louise Kenny	Cork University Maternity Hospital, Ireland
Member	Ed Juszczak	National Perinatal Epidemiology Unit, Oxford, UK

CHAPTER 5. ELECTIVE CAESAREAN SECTION SYNTOCINON INFUSION TRIAL (ECSSIT) – RESULTS

5.1 Introduction

This chapter will describe the results of the RCT discussed in the previous chapter. It will initially provide details of the study population, including participant flow and characteristics of trial participants at baseline. Data relating to the primary and secondary outcomes are then reported using descriptive statistics and multivariable regression analyses where appropriate. The results of the subgroup analyses are also described. Finally a meta-analysis will be presented updating the results of the meta-analysis in Chapter 2 to include the findings from the ECSSIT trial.

5.2 Study population

Participant flow is shown in Figure 5-1. Across all recruitments centres from February 2008 to June 2010, 5592 women were booked for elective caesarean section. Of these, 1617 (28.9%) were not approached as there was no researcher available. The eligibility of these 1617 women was thus unknown. The research midwives worked part-time and thus were not available to approach all patients. The remaining 3975 women were assessed for eligibility, with 2574 (64.8%) of these determined to be eligible. The main reasons for ineligibility were: multiple pregnancy (n=301), clinician concern re. haemorrhage (n=210), pregnancy complications (n=192), previous severe PPH (n=155), previous uterine surgery/uterine anomaly (n=149), language barriers (n=128), coagulation disorders/anti-coagulated (n=93), preterm (n=71), cardiac problems (n=39), general anaesthesia (n=31) and other reasons (n=32). A total of 504 (19.6%) eligible women did not consent to take part in the study. Reasons cited by the women who refused consent included: "not interested" (n=317), "too anxious" (n=134), "no reason" (n=46) and other reasons (n=7). The remaining 2070 women were consented. One of these women was not randomised as the pharmacy department at that recruitment centre was closed. A total of 2069 women were randomised to the trial. Figure 5-2 shows the number of women randomised at each recruitment centre.

5.3 Allocation

Of the 2069 women randomised, 1032 were allocated to the bolus only group and 1037 were allocated to the bolus and infusion group. Post-randomisation, 11 women were deemed to be ineligible as their caesarean sections were cancelled, leaving 2058 women suitable for inclusion, 1025 in the bolus only group and 1033 in the bolus and infusion group. The trial infusion was received as allocated in 961 participants in the bolus only group and 982 participants in the bolus and infusion group. Reasons for not receiving the allocated infusion are shown in Figure 5-1.

5.4 Data management

Primary outcome data were collected for 97% (MOH) and 100% (use of additional uterotonic agent) of participants respectively. For the primary outcome of major obstetric haemorrhage, data from 2001 patients were included, 994 in the placebo group and 1007 in the oxytocin group. Missing data were the result of no booking weight (n=4), no pre-operative haematocrit (n=5) and no post-operative haematocrit (n=49). One woman was missing both pre- and post-operative blood results. For the primary outcome of additional uterotonic agent, there was complete ascertainment of data. The allocated trial infusion was discontinued in 216 women (10.5%); 129 women (12.6%) in the bolus only group compared to 87 women (8.4%) in the bolus and infusion group (p=0.002), mostly for increased bleeding (39%) and uterine atony (36%).

5.5 Baseline characteristics

Table 5-1 lists characteristics of the trial participants at baseline. The mean age of women at delivery was 33.2 years and the median parity was 1 (IQR 1). More than one in five of the women were obese (BMI ≥ 30). The gestational age was greater than or equal to 39 weeks in the majority of women (1443, 70.1%). Of the 2058 women, 712 (34.6%) had no prior caesarean section. Overall the main indications for caesarean section were previous caesarean section (1069, 51.9%) and breech (434, 21.1%), with similar proportions in each group. The rate of pre-operative

anaemia (Hb < 10.5g/dL) was high, 14.8%. Junior obstetricians performed 42.1% of the caesarean sections; 40.3% in the bolus only group and 43.9% in the bolus and infusion group. A total of 1943 (94.4%) received the intervention as intended.

5.6 Departures from protocol

The anaesthetic protocol was adhered to in the majority of patients (2023, 98.3%), with similar proportions in each group, however there was less adherence to the surgical protocol (1620, 78.7%). The most common surgical protocol deviations included uterine exteriorisation (230, 11.2%), peritoneal closure (224, 10.8%) and manual removal of placenta (110, 5.3%). Obstetricians often deviated by more than one factor. More adherence to this protocol was seen in the bolus only group compared to the bolus and infusion group, 80.7% versus 76.8% respectively (p=0.02).

5.7 Analysis of primary outcomes

Overall, almost one in six women in the study had a MOH, with a similar proportion requiring an additional uterotonic agent (Table 5-2). There was no evidence of any difference in MOH between the groups (15.7% v.16.0%), and the 95% confidence intervals rule out any clinically meaningful difference. There was evidence that women in the bolus and infusion group were less likely to require an additional uterotonic agent (12.2% v.18.4%). A known oxytocin infusion was the most commonly chosen additional uterotonic agent used. Other uterotonics used included misoprostol (4.7%), oxytocin bolus (1.0%), carboprost (0.5%), syntometrine (0.4%) and ergometrine (0.3%).

5.8 Analysis of secondary outcomes

There was no evidence of any significant differences in any of the secondary outcomes between the groups (Table 5-3). Only a 4 ml difference (95% CI -38 to 47) in blood loss was found between the two groups using the "calculated

method", and a 19 ml difference (95% CI -65 to 29) using the "measured method". The rates of post-operative anaemia (Hb < 10.0 g/dL) and significant anaemia (≥ 20% fall in haemoglobin) were high overall (31.9% and 8.7% respectively), but did not differ between the groups. Blood transfusion rates however were low (0.8%), and similar in both groups. Less than half of all women recruited to the trial were breastfeeding at the time of hospital discharge (1013, 49.2%), and no difference was seen between the two groups (bolus only, 50.4% vs. bolus and infusion, 47.5%, p=0.18). Early lochial loss was not possible to assess with any consistency or accuracy due to varying use of sanitary pads and incontinence pads, and is therefore not presented.

The allocated trial infusion was discontinued in 216 women (10.5%); 129 women (12.6%) in the bolus only group compared to 87 women (8.4%) in the bolus and infusion group (p=0.002), mostly for increased bleeding (39%) and uterine atony (36%).

5.9 Subgroup analysis

MOH occurred more frequently among women delivered by junior obstetricians than senior obstetricians (19.6% v. 13.1%). Women were less likely to have a MOH in the bolus and infusion group compared with bolus only if the obstetrician was junior rather than senior (OR 0.57, 95% CI 0.35 to 0.92, p=0.02) (Table 5-4). There was no evidence that the effects of bolus and infusion on either primary outcome differed for any of the other subgroup variables investigated. (Tables 5-4 – 5-6)

5.10 Analysis of baseline imbalance

Despite less adherence to the surgical protocol in the oxytocin arm, there was no evidence of any differential effects on either MOH (OR 0.81, 95% CI 0.46 to 1.44, p=0.48) or need for an additional uterotonic agent in relation to this (OR 1.16, 95% CI 0.63 to 2.15, p=0.63).

5.11 The success of blinding

Between 6th January 2010 and 13th May 2010, 109 patients were recruited to this study at the Coombe Women and Infants University Hospital recruitment centre. Of these 109 patients, information was collected by anaesthetists for 104 patients, by obstetricians for 105 patients, and by the patients themselves for 107 patients (327 responses). Table 5-5 demonstrates the responses for anaesthetists, obstetricians and patients.

The majority of respondents answered equivocally (207, 63%) unable to identify the infusion, and were thus blinded. Of the anaesthetists that thought they could identify the infusion, 57% were correct. This result was similar for both obstetricians and patients, with the correct solution being identified in 56% and 58% respectively. Table 5-6 shows the accuracy of responses for each group when the equivocal responses were excluded.

Overall, blinding was successfully maintained in the women and clinicians, with neither group able to identify the trial infusion with any accuracy beyond chance (overall 207 "don't know", 62 correct, 47 incorrect, 11 no response, kappa = 0.15).

5.12 Meta-analysis

When the results of ECSSIT were included in the meta-analysis of trials comparing oxytocin bolus only with oxytocin bolus and infusion, described in Chapter 2, the use of additional uterotonic agents remained significantly reduced in the oxytocin bolus and infusion group (RR 0.54, 95% CI 0.36 to 0.79). As before, there was no difference in rates of MOH between the two groups (RR 0.70, 95% CI 0.36 to 1.33). There was no longer however any difference in the need for blood transfusion between the two groups (RR 1.26, 95% CI 0.64 to 2.47). In a similar change, the reduction in mean blood loss that was described in the meta-analysis of the two earlier studies in the oxytocin bolus and infusion group was no longer significant (mean difference -41.19 ml, 95% CI -107.01, 24.63). Other outcomes were not altered by the addition of the ECSSIT trial to the meta-analysis. Side effects in both groups remained similar (RR 1.14, 95% CI 0.96 to 1.35). No differences were seen between the groups in relation to duration of surgery or hospital stay. All outcomes

for the updated meta-analysis are detailed in Table 5-7 and forest plots are shown in Figures 5-3 to 5-14.

5.13 Summary

This chapter has presented the full results of the RCT with a meta-analysis to complete the findings of the systematic review in Chapter 2. The following chapter will now discuss these findings in depth and compare them with the published literature. Strengths and limitations of the trial will be identified and recommendations for a practical application of the results will be offered. Future research directions will also be discussed.

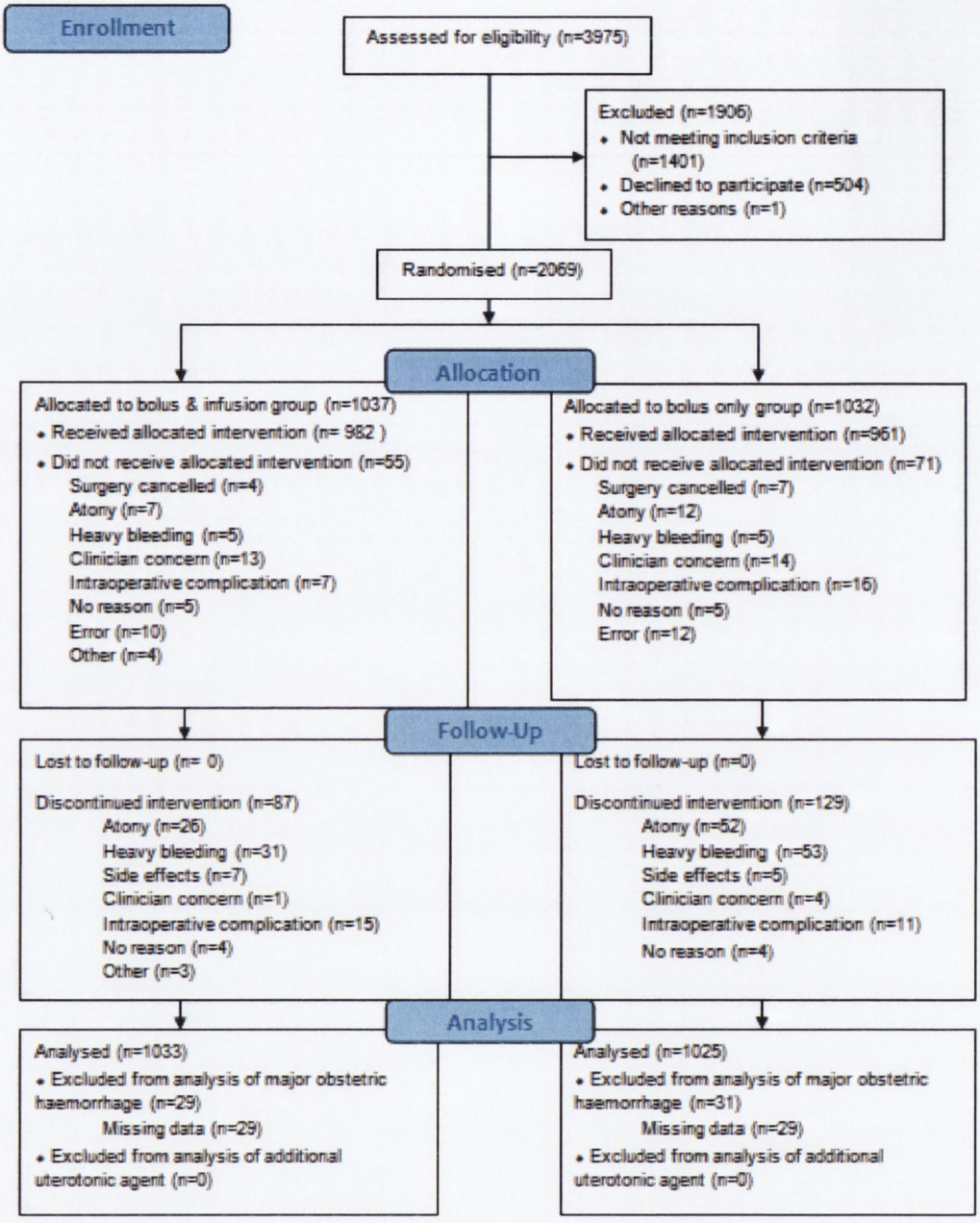


Figure 5-1 Participant Flow

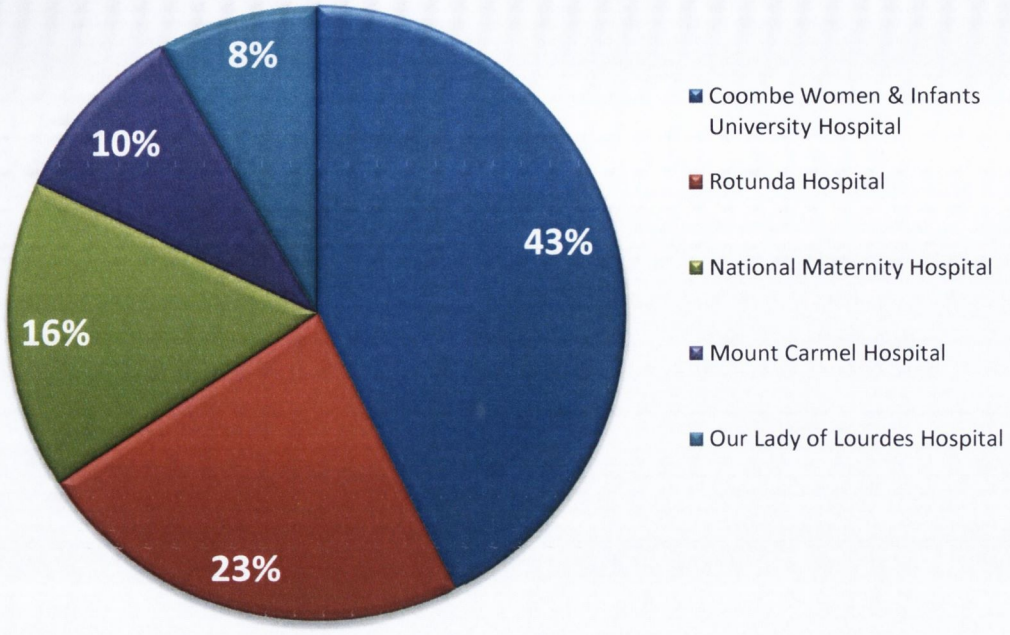


Figure 5-2 Percentage of participants recruited at each centre

Table 5-1 Baseline characteristics and operative variables of trial participants

	Bolus only N=1025	Bolus & infusion N=1033
Mean maternal age (SD)	33.2 (4.9)	33.2 (4.9)
Maternal age ≥ 35 years (%)	431 (42.0)	423 (40.9)
Mean BMI (SD)*	26.2 (5.0)	26.6 (5.4)
Overweight (BMI 25.0 – 29.9) (%)	338 (33.0)	305 (29.6)
Obese (BMI ≥ 30.0) (%)	210 (20.5)	241 (23.4)
Chronic medical disorder (%)†	126 (12.3)	137 (13.3)
Cigarette smoker (%)	105 (10.2)	92 (8.9)
Alcohol (moderate/heavy) (%)	57 (6.2)	57 (5.6)
Parity ≥ 2 (%)	330 (32.2)	338 (32.7)
Previous c-section (%)	668 (65.2)	678 (65.6)
≥ 2 previous c-sections (%)	234 (22.8)	218 (21.1)
Previous PPH (> 500 ml) (%) ‡	9 (0.9)	10 (1.0)
Previous pelvic surgery (%)	44 (4.3)	46 (4.5)
Mean pre-op Hb (SD)	11.7 (1.2)	11.8 (1.2)
Hb < 10.5g/dL pre-op (%) §	155 (15.2)	147 (14.3)
Mean pre-op HCT (SD) ‖	0.351 (0.032)	0.351 (0.032)
Gestational age ≥ 39 weeks (%)	689 (67.2)	754 (73.0)
Infant gender male (%)	559 (54.8)	553 (53.7)
Birth weight ≥ 4.0 kg (%)	160 (15.6)	191 (18.5))
Junior obstetrician (%) ¶	413 (40.3)	453 (43.9)
Junior anaesthetist (%)	452 (44.1)	463 (44.9)
Vascular lower segment (%)	11 (1.1)	14 (1.4)
Scarring/adhesions (%)	92 (9.0)	96 (9.3)
Surgical protocol adherence (%)	827 (80.7)	793 (76.8))
Anaesthetic protocol adherence (%)	1004 (98.0)	1019 (98.6)

* BMI, body mass index is the weight in kilograms divided by the square of the height in metres

† Chronic medical disorder, diabetes, endocrine disease, cardiac disease, hypertension, renal disease, inflammatory bowel disease

‡ PPH, postpartum haemorrhage

§ Hb, haemoglobin

‖ HCT, haematocrit

¶ Junior obstetrician/anaesthetist – three or less years of specialist training

Table 5-2 Primary outcomes

	Bolus only N (%)	Bolus & infusion N (%)	Adjusted OR* (95% CI)	p value	NNT‡(95% CI)
Major obstetric haemorrhage (MOH, blood loss > 1000ml)†	159/994 (16.0)	158/1007 (15.7)	0.98 (0.77, 1.25)	0.86	
Additional uterotonic agent ll	189/1025 (18.4)	126/1033 (12.2)	0.61 (0.48, 0.78)	<0.001	16 (11, 32)

* ORs are calculated from models adjusted for centre and previous caesarean section

† Blood loss calculation:

EBV x (Pre HCT- Post HCT)/ Pre HCT, where EBV estimated blood volume = booking weight in kilograms x 85

HCT, haematocrit

‡ NNT, number needed to treat

ll Oxytocin infusion, oxytocin bolus, misoprostol, carboprost, ergometrine or syntometrine

Table 5-3 Secondary outcomes

	Bolus only N=1025	Bolus & infusion N=1033	OR (95% CI)	p value
Mean "calculated" loss ml (SD)*	583 (489)	587 (505)	4 (-38, 47)*	0.83
Mean "measured" loss ml (SD)*	843 (487)	824 (622)	-19 (-65, 29)*	0.45
Mean fall in Hb (SD)*	1.19 (0.94)	1.21 (0.95)	0.02 (-0.06, 0.11)*	0.56
Mean fall in HCT (SD)*	0.035 (0.029)	0.034 (0.029)	-0.001 (-0.003, 0.002)	0.83
Post-op Hb < 10.5 g/dL (%)	473 (47.4)	463 (45.8)	0.93 (0.78, 1.12)	0.45
Post-op Hb < 10.0 g/dL (%)	330 (33.1)	311 (30.7)	0.90 (0.74, 1.08)	0.25
Significant anaemia (fall Hb ≥ 20%) (%)	95 (9.6)	80 (7.9)	0.82 (0.60, 1.11)	0.20
Transfusion (%)	7 (0.7)	9 (0.9)	1.28 (0.48, 3.46)	0.63
Side effects to oxytocin (%) †	185 (18.0)	208 (20.1)	1.16 (0.92, 1.45)	0.21
Nausea	87 (8.5)	100 (9.7)	0.87 (0.64, 1.17)	0.35
Vomiting	58 (5.7)	52 (5.0)	1.13 (0.77, 1.66)	0.53
Hypotension	108 (10.5)	132 (12.8)	0.80 (0.61, 1.05)	0.11
Mean duration of surgery (min) (SD)*	30.0 (11.6)	30.4 (11.6)	0.4 (-0.61, 1.14)*	0.44
Mean length of stay in theatre/recovery (min) (SD)*	112.6 (46.8)	116.6 (56.0)	4 (-0.50, 8.44)*	0.08
Prolonged hospitalisation (> 5 days) (%)	54 (5.3)	57 (5.7)	1.05 (0.72, 1.55)	0.79

Percentages refer to completed responses

* Absolute difference in means (95% CI)

† Oxytocin side effects – may include more than one side effect

Table 5-4 Subgroup analysis of major obstetric haemorrhage (MOH) and additional uterotonic agent by experience of obstetrician

	JUNIOR OBSTETRICIAN		SENIOR OBSTETRICIAN		OR (95% CI)	p value
	MOH n (%)	No MOH n (%)	MOH n (%)	No MOH n (%)		
Bolus & infusion	76 (17.3)	363 (82.7)	82 (14.4)	486 (85.6)	0.57	0.02
Bolus only	88 (22.2)	308 (77.8)	71 (11.9)	527 (88.1)	(0.35, 0.92)	
	Add. Uterotonic n (%)	No add. uterotonic n (%)	Add. uterotonic n (%)	No add. uterotonic n (%)		
Bolus & infusion	56 (12.4)	397 (87.6)	70 (12.1)	510 (87.9)	0.95	0.84
Bolus only	80 (19.4)	333 (80.6)	109 (17.8)	503 (82.2)	(0.58, 1.56)	

Table 5-5 Subgroup analysis of major obstetric haemorrhage (MOH) and additional uterotonic agent by choice of anaesthetic

	ADHERENCE TO ANAESTHETIC PROTOCOL		NON ADHERENCE TO ANAESTHETIC PROTOCOL		OR (95% CI)	p value
	MOH n (%)	No MOH n (%)	MOH n (%)	No MOH n (%)		
Bolus & infusion	156 (15.7)	837 (84.3)	2 (15.4)	11 (84.6)	1.59	0.63
Bolus only	155 (15.9)	819 (84.1)	4 (20.0)	16 (80.0)	(0.24, 10.48)	
	Add. uterotonic n (%)	No add. uterotonic n (%)	Add. uterotonic n (%)	No add. uterotonic n (%)		
Bolus & infusion	124 (12.2)	895 (87.8)	2 (15.4)	11 (84.6)	1.40	0.71
Bolus only	183 (18.2)	821 (81.8)	6 (28.6)	15 (71.4)	(0.23, 8.55)	

Table 5-6 Subgroup analysis of major obstetric haemorrhage (MOH) and additional uterotonic agent by previous caesarean section

	0 PREVIOUS C-SECTIONS		1 PREVIOUS C-SECTION		≥2 PREVIOUS C-SECTIONS		OR (95% CI)	p value
	MOH n (%)	No MOH n (%)	MOH n (%)	No MOH n (%)	MOH n (%)	No MOH n (%)		
Bolus & infusion	65 (19.0)	278 (81.0)	63 (14.0)	388 (86.0)	30 (14.1)	183 (85.9)	0.86	0.35
Bolus only	58 (16.7)	290 (83.3)	65 (15.6)	353 (84.4)	36 (15.8)	192 (84.2)	(0.62, 1.18)	
	Add. uterotonic n (%)	No add. Uterotonic n (%)	Add. uterotonic n (%)	No add. uterotonic n (%)	Add. uterotonic n (%)	No add. uterotonic n (%)		
Bolus & infusion	52 (14.6)	303 (85.4)	48 (10.4)	412 (89.6)	26 (11.9)	192 (88.1)	0.76	0.10
Bolus only	63 (17.6)	294 (82.4)	72 (16.6)	362 (83.4)	54 (23.1)	180 (76.9)	(0.55, 1.05)	

Table 5-7 Responses by anaesthetists, obstetricians and patients

	Bolus only	Bolus and infusion	Don't know
Obstetricians (n=105)	13	23	69
Anaesthetists (n=104)	24	18	62
Patients (n=107)	11	20	76

Table 5-8 Accuracy of responses for each group (excluding equivocal responses)

	Anaesthetist n=42 (%)	Obstetrician n=36 (%)	Patient n=31 (%)
Correct	24 (57.1)	20 (55.6)	18 (58.1)
Incorrect	18 (42.9)	16 (44.4)	13 (41.9)

Table 5-9 Oxytocin bolus & infusion versus oxytocin bolus only: Outcomes

Outcome	Studies	Participants	Statistical Method	Effect Estimate
Blood loss > 1000 ml	3	2831	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.36, 1.33]
Need for additional uterotonic agents	3	2888	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.36, 0.79]
Side effects	3	2888	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.96, 1.35]
Blood transfusion	3	2888	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.64, 2.47]
Estimated mean blood loss	3	2831	Mean Difference (IV, Random, 95% CI)	-41.19 [-107.01, 24.63]
Blood loss > 500 ml	2	2111	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.09]
Prolonged hospital stay	2	2168	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.69, 1.38]
Duration of hospital stay	2	2778	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.06]
Prolonged surgery (> 40 min)	2	2159	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.47, 1.54]
Duration of surgery	2	2769	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.33, 0.20]
Mean fall in Hb	22	2114	Mean Difference (IV, Fixed, 95% CI)	1.01 [0.93, 1.09]
Mean fall in HCT	1	2004	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.03, 0.02]

Study or Subgroup	Oxytocin bolus & infusion Events	Total	Oxytocin bolus only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gungorduk 2010	18	360	46	360	33.9%	0.39 [0.23, 0.66]
Murphy 2009a	8	56	9	54	24.3%	0.86 [0.36, 2.06]
Sheehan 2011	158	1007	159	994	41.7%	0.98 [0.80, 1.20]
Total (95% CI)		**1423**		**1408**	**100.0%**	**0.70 [0.36, 1.33]**
Total events	184		214			

Heterogeneity: Tau² = 0.25; Chi² = 10.32, df = 2 (P = 0.006); I² = 81%
Test for overall effect: Z = 1.09 (P = 0.27)

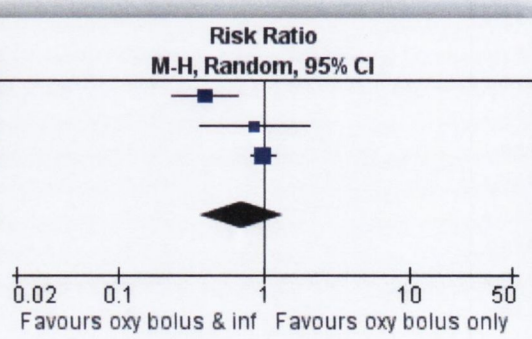


Figure 5-3 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Blood loss > 1000 ml

Study or Subgroup	Oxytocin bolus & infusion Events	Total	Oxytocin bolus only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gungorduk 2010	28	360	69	360	37.5%	0.41 [0.27, 0.61]
Murphy 2009a	3	56	6	54	7.5%	0.48 [0.13, 1.83]
Sheehan 2011	126	1033	189	1025	54.9%	0.66 [0.54, 0.81]
Total (95% CI)		**1449**		**1439**	**100.0%**	**0.54 [0.36, 0.79]**
Total events	157		264			

Heterogeneity: Tau² = 0.06; Chi² = 4.38, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 3.12 (P = 0.002)

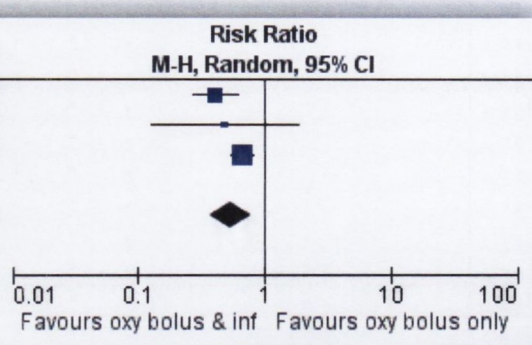


Figure 5-4 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Need for additional uterotonic agents.

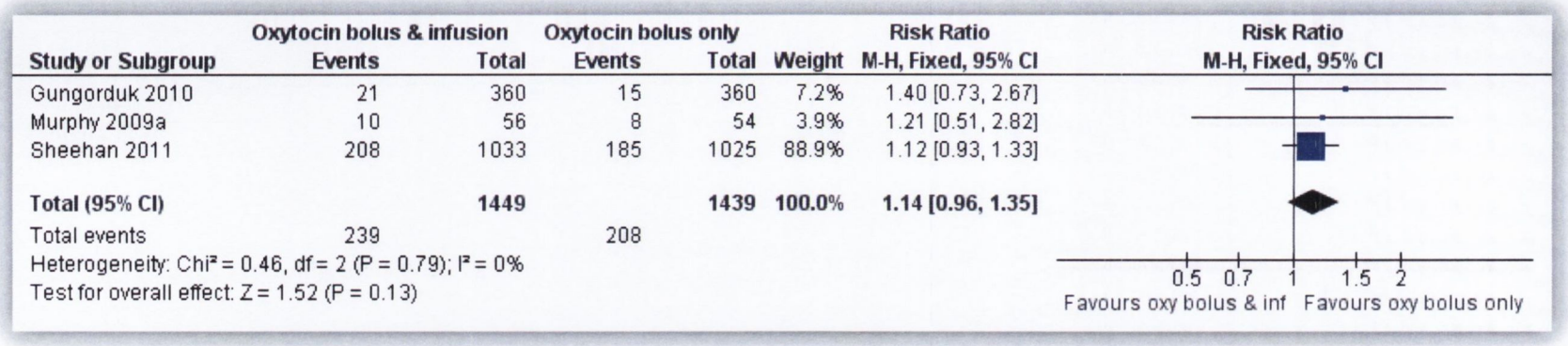


Figure 5-5 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Side effects.

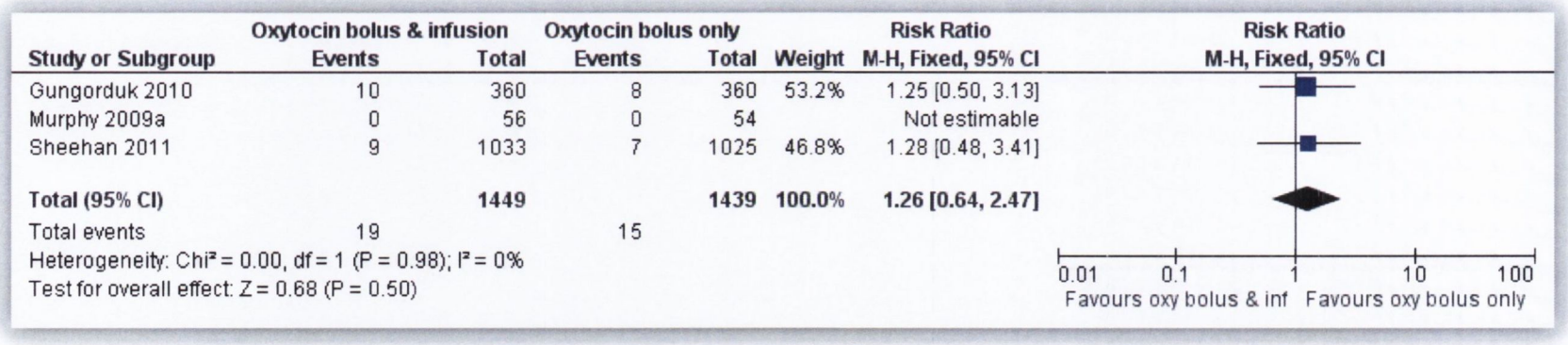


Figure 5-6 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Blood transfusion

Study or Subgroup	Oxytocin bolus & infusion Mean	SD	Total	Oxytocin bolus only Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Gungorduk 2010	609.63	208.52	360	686.89	232.28	360	44.1%	-77.26 [-109.50, -45.02]
Murphy 2009a	567	328	56	624	413	54	15.3%	-57.00 [-196.69, 82.69]
Sheehan 2011	587	505	1007	583	489	994	40.6%	4.00 [-39.55, 47.55]
Total (95% CI)			**1423**			**1408**	**100.0%**	**-41.19 [-107.01, 24.63]**

Heterogeneity: Tau² = 2285.89; Chi² = 8.65, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 1.23 (P = 0.22)

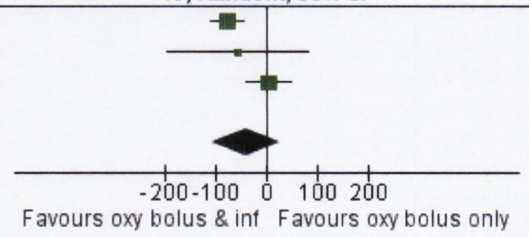


Figure 5-7 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Estimated mean blood loss.

Study or Subgroup	Oxytocin bolus & infusion Events	Total	Oxytocin bolus only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Murphy 2009a	3	56	7	54	11.6%	0.41 [0.11, 1.52]
Sheehan 2011	57	1033	54	1025	88.4%	1.05 [0.73, 1.50]
Total (95% CI)		**1089**		**1079**	**100.0%**	**0.97 [0.69, 1.38]**
Total events	60		61			

Heterogeneity: Chi² = 1.83, df = 1 (P = 0.18); I² = 45%
Test for overall effect: Z = 0.15 (P = 0.88)

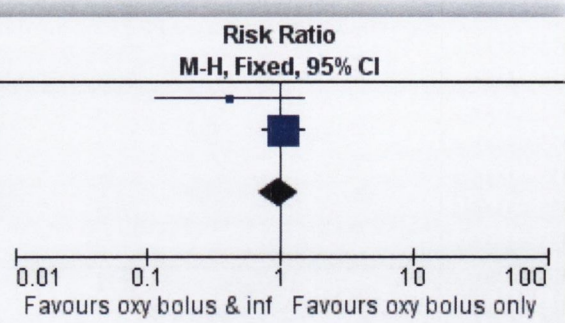


Figure 5-8 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Prolonged hospital stay (> 3 days).

Study or Subgroup	Oxytocin bolus & infusion Events	Total	Oxytocin bolus only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Murphy 2009a	12	56	20	54	38.9%	0.58 [0.31, 1.07]
Sheehan 2011	165	1027	152	1022	61.1%	1.08 [0.88, 1.32]
Total (95% CI)		**1083**		**1076**	**100.0%**	**0.85 [0.47, 1.54]**
Total events	177		172			

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 3.62$, df = 1 (P = 0.06); $I^2 = 72\%$
Test for overall effect: Z = 0.54 (P = 0.59)

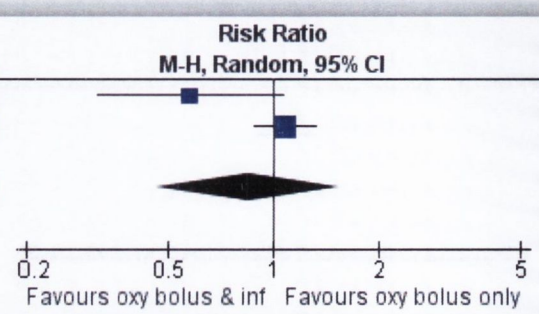


Figure 5-9 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Prolonged surgery (>40min).

Study or Subgroup	Oxytocin bolus & infusion Mean	SD	Total	Oxytocin bolus only Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Gungorduk 2010	2	0.2	360	2	0.1	360	57.0%	0.00 [-0.02, 0.02]
Sheehan 2011	4.15	1.07	1033	4.27	1.03	1025	43.0%	-0.12 [-0.21, -0.03]
Total (95% CI)			**1393**			**1385**	**100.0%**	**-0.05 [-0.17, 0.06]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.31$, df = 1 (P = 0.01); $I^2 = 84\%$
Test for overall effect: Z = 0.87 (P = 0.38)

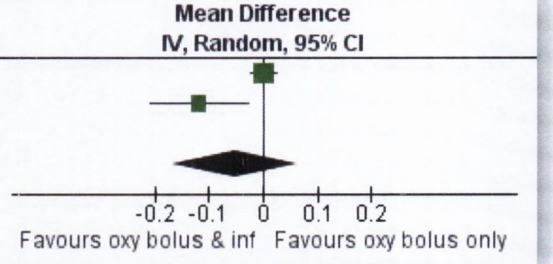


Figure 5-10 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Duration of hospital stay

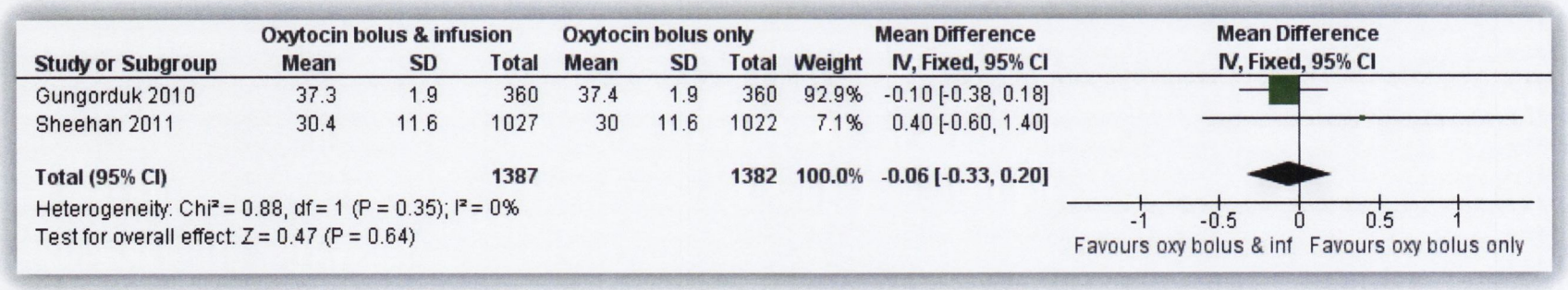


Figure 5-11 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Duration of surgery.

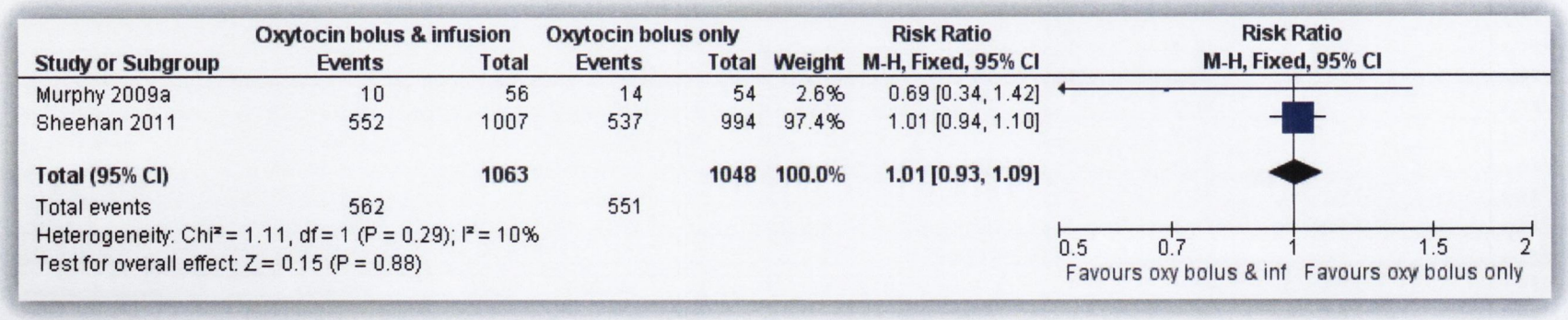


Figure 5-12 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Blood loss > 500 ml.

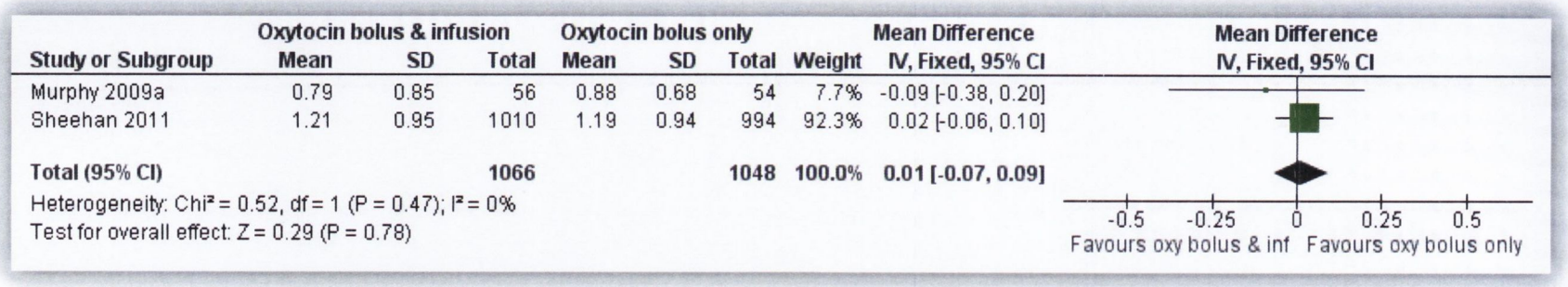


Figure 5-13 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Mean fall in Hb.

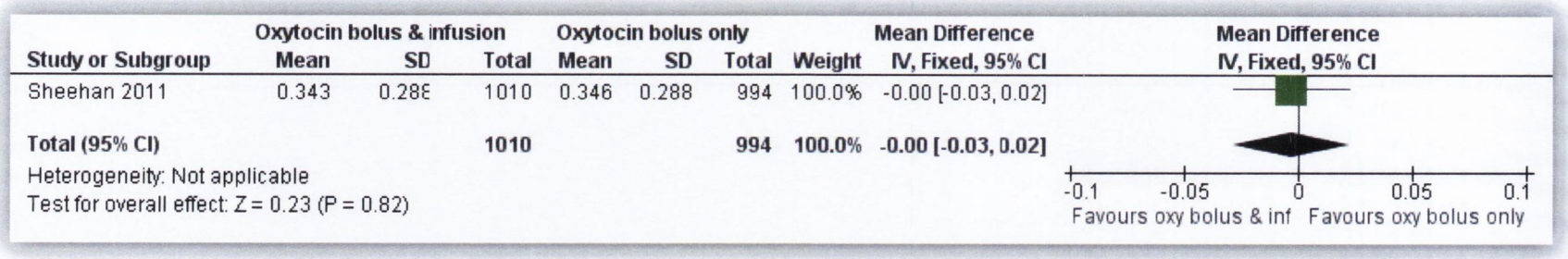


Figure 5-14 Forest plot of comparison: Oxytocin bolus & infusion versus infusion only, outcome: Mean fall in HCT.

CHAPTER 6. ELECTIVE CAESAREAN SECTION SYNTOCINON INFUSION TRIAL (ECSSIT) – DISCUSSION

6.1 Summary of findings

In this large multi-centre trial of women delivering by elective caesarean section, we found that an oxytocin infusion in addition to an oxytocin bolus had no effect on overall rates of MOH compared with oxytocin bolus and placebo infusion, but that the need for an additional uterotonic agent was reduced. MOH was reduced following use of oxytocin bolus and oxytocin infusion at caesarean section by inexperienced obstetricians compared to senior obstetricians. Side effects were not increased by use of an oxytocin infusion after an initial bolus. Blinding was successfully maintained.

6.2 Strengths and limitations

We conducted a large pragmatic clinical trial within five maternity centres in the Republic of Ireland. The population was carefully defined, with a range of indications for caesarean section and varying grades of operator. The results are generalisable to similar populations. Surgical techniques and anaesthesia were standardised. Data were collected by trained staff with theatre staff appropriately trained in the measurement of blood loss. Haematocrit levels were checked at 48 hours after delivery to provide an adequate interval for haemodynamic equilibrium.

Some limitations of our study warrant consideration. It could be argued that we should have included a third comparison group that reflected current US clinical practice – placebo bolus with an oxytocin infusion (infusion only). However this would have required a deviation from hospital protocols based on RCOG recommendations.[8] Whilst we gave this approach consideration, we felt that it would not have been acceptable in any of our recruitment centres, where oxytocin bolus is standard practice. [22] We chose to follow the UK guidelines, basing our decision on the benefits described in vaginal birth where a bolus dose of oxytocin has a proven role in prevention of postpartum haemorrhage.[90 91] The mechanisms of action of oxytocin bolus and infusion are thought to be different, with a bolus causing constriction of the venous sinuses, leading to placental separation and placental bed haemostasis, and an infusion maintaining uterine contractility.

We debated the choice of primary outcome and decided on two outcomes both reflecting uterine atony. MOH is the most relevant clinical outcome as it is a leading cause of maternal death worldwide. However, clinicians intervene in the event of uterine atony by administering an additional uterotonic agent. In itself, this would be an important outcome. We measured total blood loss at the time of caesarean section but chose a calculation based estimate based on pre- and post-operative haematocrit as a primary outcome in the interests of objectivity. The measured blood loss would be more relevant in resource-poor settings where blood tests are not routinely performed.

6.3 Comparison with the literature

Three trials (2888 participants) have now compared an oxytocin bolus and infusion to an oxytocin bolus only, with ECSSIT being the largest of these trials.[175 180] All three trials used the same method to estimate blood loss, based on the pre- and post-operative haematocrit calculation described in Chapter 4. Only "low risk" women booked for elective caesarean section were recruited to these studies. All women in two of the trials (ECSSIT and the Scottish pilot study for ECSSIT) had spinal anaesthesia whereas all women in the Turkish trial had general anaesthesia. While the results of the Turkish trial did report reductions in both the use of additional uterotonic agents and MOH, these findings are not generalisable as all caesarean sections were performed in a military hospital-setting with routine general anaesthesia. Regional anaesthetic techniques are standard at elective caesarean section in developed countries and use of general anaesthesia is uncommon. General anaesthesia is known to increase blood loss at the time of caesarean section as inhalational agents can reduce uterine contractility and increase atony.[104 115]

Two trials have investigated the effects of an oxytocin infusion only versus an oxytocin bolus and oxytocin infusion, and found no difference in the need for additional uterotonic agents after caesarean section.[126 188] These trials have relevance for US practice but not for European practice. One trial was limited to patients at high risk of uterine atony, with neither surgery nor anaesthesia standardised and oxytocin administered before placental delivery.[188] The other trial was limited to low-risk women.[126] In this trial, surgery was not standardised and

uterine massage was performed after manual removal of the placenta. By contrast we examined a very large sample of women undergoing elective caesarean section with regional anaesthesia, clearly defined surgical and anaesthetic protocols, and our results are more relevant to the general obstetric population.

Carbetocin, a synthetic oxytocin agonist, has a longer half-life than oxytocin and may be of value. A recent trial comparing oxytocin 5 IU bolus versus carbetocin 100ug demonstrated an increased use of additional uterotonic agents in the oxytocin arm.[134] Of concern however is the fact that in excess of one third of women in the carbetocin arm still required additional uterotonic agents. As in our trial, there was no change in mean blood loss between the two arms. Not only will the high cost of carbetocin prevent its use in countries where resources are scarce and indeed even in developed countries where cost-cutting is being implemented, but the high requirements for additional uterotonic agents will undoubtedly question its usefulness.

6.4 Critical discussion of the new meta-analysis findings

The findings of the RCT (ECSSIT) have now been added to the initial meta-analysis described in Chapter 2 of oxytocin bolus and infusion versus oxytocin bolus only, and the results updated. Essentially the results of the meta-analysis are consistent with the findings of the ECSSIT trial. The addition of an oxytocin infusion to an oxytocin bolus significantly reduces the need for additional uterotonic agents. No effect is seen on rates of MOH. Mean estimated blood loss and the need for blood transfusion are unchanged between the groups. Concerns over adverse effects in relation to the additional oxytocin should be allayed by the finding that they are not increased in this group.

Oxytocin remains the most commonly used uterotonic for the prevention of haemorrhage at caesarean section. Of the 36 trials now included in the review, oxytocin formed part of the intervention in 35 trials (97.2%).

Major obstetric haemorrhage was reported as an outcome in only 9 studies (3948 participants). Some individual trials did report reductions in MOH with a variety of

interventions, however when data were combined appropriately, these reductions were no longer significant.

The need for additional uterotonic agents, already discussed as an indicator of uterine atony, was reported in a far greater proportion of trials (32, 88.9%, 7615 participants). The combination of an oxytocin bolus and infusion as already described reduced this need when compared to bolus only but also when compared to infusion only. This combination had no effect on side effects but when ergometrine was used in conjunction with oxytocin, the rate of nausea was increased. Unfortunately other studies that demonstrated reductions in the use of uterotonics, including studies of higher doses of oxytocin boluses and infusions, did not report on side effects. Interestingly one agent used alone, carbetocin, did reduce the need for additional oxytocin agents when compared to oxytocin alone, with similar side effects in both groups. Predictably, when compared to placebo, a similar reduction in the need for additional uterotonic agents was seen.

ECSSIT is by far the largest of all of the studies included in the review, with more than double the number of participants compared to the largest trial in the initial meta-analysis. Oxytocin and carbetocin are certainly emerging as the agents with the most promise.

6.5 External peer-review comments

The randomised controlled trial, ECSSIT, was published in the British Medical Journal (BMJ). It was reviewed by the BMJ editorial committee and by three independent peer-reviewers. Their comments were particularly helpful and the manuscript of the trial has no doubt been improved. The process of external peer-review has helped me to clarify in my own mind why exactly this trial was performed, to determine the practice implications of the findings and to consider how I would improve it if I were starting all over again. I have included them here in a summarised form as I think they add great value to the discussion of the trial, highlighting the key findings and identifying key areas of future work.

6.5.1 *Justification of the chosen comparator groups*

A clearer justification of the chosen comparator groups was recommended.

Other suggested comparator groups included: 1) oxytocin versus placebo, 2) oxytocin bolus versus infusion or 3) immediate versus delayed oxytocin infusion in addition to a routine oxytocin bolus. The comparator groups for the RCT were given much consideration. We chose to compare the use of an additional oxytocin infusion to a routine oxytocin bolus at elective caesarean section. The survey of obstetricians and anaesthetists in the UK, performed in advance of the RCT, found that an oxytocin bolus was used as standard at caesarean section, although the dose of bolus varied between 5 IU and 10 IU. A routine oxytocin infusion, in addition to the oxytocin bolus, was used by 20% of obstetricians. When Irish obstetricians were surveyed, the results were similar. Obstetricians in the UK and Ireland would not consider it acceptable to perform a caesarean section with only placebo (no uterotonic agent) and would not have been willing to participate in a trial with one arm receiving only placebo. Equally, it would not have been possible to recruit 2000 women across five centres without a bolus oxytocin component. The argument for using an immediate infusion was based on the very short half-life of oxytocin (4-10 minutes) therefore the potential advantage of an oxytocin infusion would be in maintaining uterine contractility throughout the surgical procedure and immediate postpartum period, when most primary haemorrhage occurs.

6.5.2 *Justification for two primary outcomes*

Justification was sought for reporting two primary outcomes.

Both primary outcomes reflect uterine atony. MOH is undoubtedly the most important clinical outcome, contributing significantly to maternal morbidity and mortality worldwide. The need for additional uterotonic agents was used however as a surrogate marker of uterine atony, with clinicians likely to intervene if atony occurred. In itself this was therefore an important outcome, and appropriate as a co-primary outcome.

6.5.3 *Interpretation of subgroup analysis findings*

Caution was advised in interpreting subgroup analysis findings.

In our trial protocol, operator experience was pre-specified as a planned subgroup analysis. The cut-off of three years of specialist training was described based on Irish and UK specialist registrar training programmes and to make it interpretable within the US and other settings. The subgroup analysis revealed that women were less likely to have a MOH in the bolus and infusion group compared with bolus only if the obstetrician was junior rather than senior. This was not a primary outcome and should be interpreted with caution. It is however very important from a clinical perspective and warrants attention.

6.5.4 *Health economics evaluation*

The value of a health economics evaluation was highlighted.

This evaluation is currently being undertaken by our research group, led by a member of the Clinical Trials Unit at the University of Bristol, as part of a higher degree. The results of such an analysis will be invaluable in making a business case for the implementation of the trial findings into clinical practice. It would have been very helpful to have these results available for publication with the trial results.

6.6 Practice implications

We reported a high rate of MOH, greater than that reported in previous studies.[102] [103] The use of different methods of estimating blood loss however limits direct comparisons.[233] Although estimation of blood loss at caesarean section can be imprecise, MOH is common, even in apparently low-risk women. This begs the question whether a woman undergoing an elective caesarean section can ever really be termed "low-risk". Vigilance in monitoring blood loss and prompt management is essential if the associated morbidity and mortality is to be avoided.

Whilst we demonstrated a reduction in the use of additional uterotonic agents, but no difference in overall rates of MOH with use of oxytocin bolus and infusion,

we did show a lower rate of MOH amongst inexperienced operators. Of note we had a relatively high proportion of experienced operators reflecting private practice in Ireland. The proportion of inexperienced operators will be higher in UK training hospitals and certainly in parts of the world where access to trained personnel is limited. We need to consider how our findings could be implemented. One approach would be to recommend that all women undergoing elective caesarean section should receive an oxytocin bolus and infusion. This would eliminate the need for clinical judgement on when to use an additional uterotonic agent. The potential downside would be that some women would receive an unnecessary infusion. Alternatively, a more selective approach could be implemented. An oxytocin infusion could be recommended at all elective caesareans performed by inexperienced operators, whose judgement of when to use additional uterotonic agents may not be as reliable.

As rates of caesarean section continue to escalate, future research aimed at reducing MOH and haemorrhagic complications is essential. Further work is planned on the cost-effectiveness of introducing an additional infusion of oxytocin at elective caesarean section. Oxytocin is an inexpensive drug but the use of an infusion requires either a four hour period of monitoring or use of a controlled infusion pump. One could argue that a four hour interval of observation following a caesarean section is in the patient's best interests however delay in transferring patients to the postnatal ward affects case throughput and would need to be balanced with the risk of an unrecognised postpartum haemorrhage occurring on the ward.

6.7 Future studies

Establishing the cost-effectiveness of an additional oxytocin infusion is essential. A health economics evaluation is currently in progress. This research is being conducted by a research fellow in our Clinical Trials Unit.

As rates of caesarean section continue to escalate, future research aimed at reducing blood loss at these deliveries is essential. Previous work has shown that the risk of major obstetric haemorrhage is greater at emergency than at elective caesarean section.[102] ECSSIT was limited to women undergoing elective

caesarean section; future work addressing non-elective deliveries would be strongly recommended.

As outlined in Chapter 1, a potential side effect of oxytocin is water retention leading to intoxication. To date no studies have been performed examining this effect of oxytocin in patients following caesarean section. There is clearly a need to investigate this in future studies.

Many centres have started to introduce alternative uterotonic agents into practice based on the limited evidence from a few small studies. Carbetocin is the uterotonic agent that appears to have attracted most of the recent attention. I recently started working in a centre in the United Kingdom that changed local hospital guidelines approximately 8 months ago, moving away from a bolus of oxytocin 5 IU IV to a bolus of carbetocin 100 ug IV at caesarean section. My impression is that the time to placental expulsion does appear to be shortened but no trials have looked at this. A large RCT comparing carbetocin to an oxytocin bolus and infusion would examine the hypothesis as to whether this more expensive drug is more effective and at what cost, both in terms of the actual price of the medication and the need for additional uterotonic agents.

6.8 Conclusions

In conclusion, the trial findings and the updated meta-analysis demonstrate that the addition of an oxytocin infusion at elective caesarean section significantly reduces the need for an additional uterotonic agent, although it does not reduce overall rates of MOH. An oxytocin infusion is an inexpensive, well tolerated and relatively safe medication which when used routinely takes the uncertainty out of who should receive an additional uterotonic agent. Our findings support the use of an additional oxytocin infusion in terms of reducing MOH where the operator is inexperienced. We anticipate that this approach could be implemented safely and cheaply into current clinical practice and welcome the results of the health economics evaluation.

CHAPTER 7. ESTIMATION OF BLOOD LOSS AND IDENTIFICATION OF RISK FACTORS FOR MAJOR HAEMORRHAGE

7.1 Introduction

The importance of measuring blood loss accurately following delivery was highlighted by Williams as early as 1919.[234] The signs of hypovolemic shock are more subtle in pregnancy due to physiological adaptation putting the patient at risk of late intervention. Postpartum haemorrhage remains a leading cause of maternal death worldwide. It is widely accepted that blood loss following caesarean section is far greater than after vaginal delivery. Elective caesarean section has been shown to double the risk of haemorrhage (blood loss greater than 500 ml) compared to vaginal delivery, and emergency caesarean section to quadruple the risk.[97] The results of the RCT (ECSSIT), detailed in Chapter 5, have clearly demonstrated that the rate of major obstetric haemorrhage (MOH, blood loss greater than 1000 ml) at apparently low-risk elective caesarean sections is high.

Unfortunately, there is no consensus at present on the most appropriate method of measuring blood loss. Interpretation and comparison of results from studies included in the systematic review described in Chapter 2 were complicated by inconsistent measurement. Numerous methods of assessing blood loss at delivery have been described, including visual estimation,[224] weighing swabs and measuring suction volume[235], with or without adjustment for liquor volume,[178 184] calculating haemoglobin and haematocrit changes,[125 217 236 237] acid-haematin extraction[238] and radiolabeled red cell determination.[239] These methods can be unreliable, cumbersome, complicated and expensive.[95 240 241] Although the accurate determination of operative blood loss is desirable, it is particularly difficult in obstetric practice, when measurement at delivery is distorted by the presence of amniotic fluid and meconium.[242] As early and accurate recognition of excessive bleeding is essential to reduce adverse maternal outcomes, precisely estimating the amount of blood lost is vital. Future research will continue to be limited unless a "gold standard" method of measurement is identified.

Whilst recognition of excessive bleeding is important, anticipation could facilitate early and appropriate intervention. An awareness of risk factors for major obstetric haemorrhage at caesarean delivery could substantially reduce the haemorrhagic morbidity associated with this mode of delivery. These risk factors may be present antenatally but may also arise *de novo* during the delivery.

The aims of this study were twofold i) to evaluate alternative methods of estimating blood loss at elective caesarean section and ii) to identify risk factors for major obstetric haemorrhage at apparently uncomplicated procedures. The emphasis was on evaluating approaches potentially applicable on a global basis irrespective of available resources.

7.2 Materials and methods

7.2.1 Cohort

A prospective cohort study was conducted of 1973 women with a singleton, apparently uncomplicated, pregnancy of more than 36 completed weeks' gestation undergoing elective caesarean section. The study was nested within the RCT described in Chapters 4 – 6. These 1973 women had complete data and represented 96% of participants in the randomised controlled trial, with similar numbers in each trial arm. As outlined earlier, women with a history of previous major obstetric haemorrhage, placenta praevia, thrombocytopaenia, macrosomia, polyhydramnios, known fibroids or receiving anti-coagulant medication were excluded as each of these complications has previously been associated with major obstetric haemorrhage and warrants specific measures. Participants were randomised on a 1:1 basis to receive either a bolus of oxytocin 5 IU and a placebo infusion (bolus only group) or a bolus of oxytocin 5 IU and a 40 IU oxytocin infusion (bolus and infusion group) after delivery of the baby. The approach to anaesthesia and the surgical technique were specified in the study protocol (controlled cord traction for delivery of the placenta, non-exteriorisation of the uterus and two-layer uterine closure).[216] Deviations from the protocol were recorded. The comparator group for baseline characteristics was the hospital population of the Coombe Women & Infants University Hospital (control group), a large tertiary level maternity hospital in Dublin. This group of almost 61000 women comprised of all singleton births who delivered at greater than 24 completed weeks gestation for the period of 2000 – 2007.

7.2.2 Explanatory variables

Detailed data were extracted on maternal and infant characteristics, antenatal and intrapartum factors and the outcome measures of interest. Body mass index

(BMI) was measured as booking weight (kg) / height $(m)^2$. Pre-operative anaemia was defined as haemoglobin (Hb) less than 10.5 g / dl. Surgery was classified as prolonged if it exceeded 40 minutes. An inexperienced operator was defined as having three years or less of specialised obstetrical training in the Irish system (or equivalent). Antepartum, intra-operative and postpartum events up until first hospital discharge were recorded. Surgical complexities were defined as presence of a vascular lower segment, pelvic scarring or adhesions and previously undiagnosed fibroids.

7.2.3 Outcome measures

Major obstetric haemorrhage (MOH) was classified according to the Royal College of Obstetricians and Gynaecologists (RCOG) green top guideline: blood loss greater than 1000 ml, and further divided into moderate (1001 to 2000 ml) and severe (greater than 2000 ml).[97] Blood loss was estimated in four ways; total "measured loss" including liquor volume, "measured loss" with a 25% deduction for liquor volume, "measured loss" with a standard 300 ml deduction for liquor volume and "calculated loss" based on pre- and post- operative haematocrit. At the time of surgery, blood loss was measured by theatre staff and included the volume in a standard graduated suction bottle and the weight of used swabs recorded on a calibrated kitchen scales. This was reported as total "measured loss". Adjustments were made to this estimate for liquor volume, of a fixed percentage (25%) and a fixed volume (300 ml). The 25% deduction was based on a theoretical percentage of fluid lost at the time of caesarean section. The 300 ml deduction was chosen as it represents half the estimated 600 ml of liquor surrounding the fetus at 40 weeks' gestation, with allowances for spillage at the time of making the surgical incision in the lower uterine segment. "Calculated loss" was estimated based on the difference between pre-operative and post-operative haematocrit (HCT). Post-operative haematocrit was measured on the second post-operative day. If the patient required a transfusion however, the lowest haematocrit value was used.

The estimate was calculated as follows:[125 217]

$$\text{"Calculated" blood loss} = \text{EBV} \times \frac{\text{(Pre-op HCT} - \text{Post-op HCT)}}{\text{Pre-op HCT}}$$

Where EBV estimated blood volume = Booking weight in kg x 85

7.2.4 Statistical analysis

Statistical analysis with χ^2 test for proportions was used to compare the cohort with the hospital population. The degree of agreement between the "measured loss" and "calculated loss" assessments of blood loss was analysed by computing Cohen's kappa (k). This statistic (used to evaluate the success of blinding in Chapter 4) evaluates the level of agreement beyond that expected by chance. Using Cohen's kappa (k), overall agreement ranges from "<0" implying no agreement, to "0.81 – 1.00" implying almost perfect agreement. The hypothesis was that the "calculated loss" method would be the "gold standard" for each comparison as it was based on laboratory results, and thus objective. Clinical and operative variables were evaluated for a possible association with major obstetric haemorrhage (defined using the "calculated loss" method). All of these variables were then included in the multivariable logistic regression model. Trial arm was also included as a covariate in this multivariable model. Results are presented as odds ratios (OR) and 95% confidence intervals (CI). The statistical package SPSS version 16.0 was used for analysis.

7.3 Results

7.3.1 Baseline characteristics

Characteristics of women who were delivered by caesarean section were different to the control group. Notably, they were more likely to be older (maternal age ≥ 35 years), have a higher BMI (≥ 35), heavier infants (≥ 4 kg) and were less likely to be smokers (Table 7-1).

7.3.2 *Rates of postpartum haemorrhage*

More than half the cohort of women (1070, 54.2%) lost in excess of 500 ml of blood at delivery. Rates of haemorrhage estimated using the four different methods of assessing blood loss are shown in Table 7-2. The highest rates of haemorrhage were recorded using the total "measured loss" method. More than a quarter of women (27.4%) had a MOH (blood loss > 1000 ml) if this method was used compared with 12.4%, 13.4% and 15.9% using the 25% liquor deduction, 300 ml liquor deduction, and "calculated" methods of estimation respectively.

The Cohen's kappa (k) statistic for the degree of agreement between the total "measured loss" group and the "calculated loss" group was 0.13. This represents only "slight agreement". Similarly the k values were 0.13 and 0.14 for the "measured loss" with 25% and 300 ml deductions respectively, again representing only "slight agreement", (Tables 7-3 – 7-5).

There were some anomalous values with the calculated method, for example some values equated with no blood loss or even a gain in blood volume (196 women, 9.9%). This was clearly not feasible as all estimates were based on haematocrit values and none of these 196 women was transfused. Repeating the analyses without these 196 cases showed little change in overall rates of MOH: 27.9% total "measured" and 12.7%, 13.7% and 17.6% using the 25% liquor deduction, 300 ml liquor deduction, and "calculated" methods of estimation respectively.

7.3.3 *Risk factors for postpartum haemorrhage*

The risk factors we investigated for association with major obstetric haemorrhage are listed in Table 7-6. Strong univariable associations with MOH were found for BMI ≥ 35, surgery by an inexperienced operator, prolonged surgery, surgical complexity, exteriorisation of the uterus and infant birth weight ≥ 4 kg. Many of the variables were potentially interrelated and hence adjusted odds ratios are reported for multivariate analyses. Risk factors for MOH after adjustment for confounding included; maternal age ≥ 35 years (OR 1.42, 95% CI 1.09 to 1.86), BMI ≥ 35 (OR 3.97, 95% CI 2.72 to 5.79), surgery by an inexperienced operator (OR 1.48, 95% CI 1.13 to 1.93), prolonged surgery (OR 1.45, 95% CI 1.05 to 2.00) and surgical complexity (OR 2.32, 95% CI 1.69 to 2.95). Prior caesarean section was associated

with a reduced risk of MOH (OR 0.65, 95% CI 0.49 to 0.87). Of note, 16% of women were anaemic pre-operatively, but this showed no association with MOH.

7.4 Discussion

7.4.1 Summary of main findings

Major obstetric haemorrhage was common in this apparently low risk elective caesarean section cohort. There was poor agreement between the alternative methods of estimating blood loss with likely underestimation in as many as 10% of cases if the "calculated loss" method was used and likely over-estimation if total "measured loss" was used. Risk factors for MOH included older maternal age, obesity, an inexperienced operator, prolonged duration of surgery and surgical complexity.

7.4.2 Strengths and limitations of the study

This study included a large cohort of women undergoing elective caesarean section within five maternity centres in the Republic of Ireland. The population was carefully defined, with a range of indications for caesarean section and varying grades of operator. The results are generalisable to similar populations. All data were collected by trained research staff. Theatre staff were appropriately trained in the measurement of blood loss.

There are well recognised difficulties in accurately determining blood loss at caesarean section. The challenges include imprecise determination of pre-operative liquor volume and the inevitable spillage of blood and liquor despite best efforts with waterproof collecting drapes and suction. The haematocrit-based calculation is an appealing approach as it is objective and reflects continuing losses up to 48 hours postoperatively. However there are two important limitations; the underestimation of loss in almost 10% of cases and the estimate is not available until the second post-operative day limiting its practical use in the acute setting. It is clearly not suitable as a "gold standard". The approach that applies a 25% deduction for liquor volume is easy to calculate however while it is likely to be reasonably accurate for average blood loss it becomes unreliable for large volume blood losses where an inappropriately high deduction is made. The

approach that applies a standard 300 ml deduction overcomes this limitation but fails to take account of the natural variation in liquor volume at term and the variable degree of liquor spillage immediately following incision in the lower uterine segment.

7.4.3 Comparison with existing literature

We reported a high rate of major obstetric haemorrhage at elective caesarean section, similar to rates reported in the United Kingdom[175] but greater than other studies have reported in Australia[102] and the United States.[104] The use of different definitions and methods of estimating postpartum haemorrhage make it difficult however to compare reported rates.[233] In keeping with many other studies, there was poor agreement between the methods used to estimate blood loss.[237 243 244]

Obesity has previously been linked to postpartum haemorrhage.[245] In our study, maternal BMI ≥ 35 was associated with a nearly four-fold increase in MOH. Obesity poses an increasing challenge in obstetrics, with data suggesting the prevalence has doubled over the last ten years.[246] The increase in MOH with advanced maternal age, has also been confirmed in a number of earlier publications,[245 247] and highlights the downside of deferring pregnancy. Our study found that an inexperienced operator was a risk factor for major obstetric haemorrhage and supports the International PPH Collaborative Group who has highlighted training as a key element to reduce the severity of postpartum hemorrhage.[233] Prolonged duration and complexity of the surgery were also associated with major obstetric haemorrhage. Although we specifically recruited low risk cases, the rate of major obstetric haemorrhage was still high and begs the question of whether any caesarean section can be considered low risk. Obstetricians need to anticipate the potential for surgical complexity, prolonged duration of surgery and the risk of unexpected haemorrhage. We were surprised to find that prior caesarean delivery appeared to have a protective role.

7.4.4 Practice implications

Although estimation of blood loss at caesarean section can be imprecise major obstetric haemorrhage appears to be common. Vigilance in monitoring blood loss is essential if maternal haemorrhagic morbidity and mortality is to be avoided. Measuring blood loss by means of weighing swabs and recording suction volume

is safe, simple, timely and inexpensive, but the potential to overestimate blood loss must be remembered. Some adjustment for liquor volume may be helpful in overcoming this problem and further research is required to determine the optimal approach to take account of individual variation. It is far safer to over-estimate blood loss than to under-estimate it. The "measured loss" approach is readily applicable in low income settings and may be all that is available. In resource rich settings, pre and post-operative haematocrit estimates are readily available and allow a more objective estimate of blood loss, but do not provide any practical value in the immediate setting. They are best employed as a research tool. With over 54% of patients losing in excess of 500 ml blood at caesarean delivery, the prevention and management of anaemia remains a fundamental aspect of good antenatal care. As rates of caesarean section continue to rise, future research aimed at reducing blood loss at these deliveries is essential.

Clinicians must be aware of the risk factors for major obstetric haemorrhage in apparently uncomplicated cases and appropriate training and supervision needs to be available to inexperienced operators to minimise the risk of avoidable haemorrhage. The results of the RCT (ECSSIT) clearly demonstrated a reduction in the risk of MOH with the use of an additional oxytocin infusion when the operator was inexperienced. This finding coupled with the identification of an inexperienced operator as an independent risk factor for MOH, provides a far stronger argument in favour of a routine oxytocin infusion after delivery.

7.5 Conclusions

The search for a "gold standard" measurement of blood loss at caesarean section continues. In the interim, gravimetric measurements appear to be the safest and simplest methods available.

Obesity, older maternal age and inexperienced operators increase the risk of MOH at caesarean section. Obesity and older maternal age continue to pose challenges as they are not easily reversible factors within a population: an additional oxytocin infusion has been shown however, to almost half the rate of MOH when used by inexperienced operators. It is simple, safe, inexpensive and effective.

Table 7-1 Baseline characteristics of women delivered by elective caesarean section compared to the control group

	Elective Caesarean section N=1973 (%)	Hospital births 2000-2007 N=60991	p value
Maternal age ≥ 35 years	816 (41.4)	13459 (22.1%)	< 0.001
BMI ≥ 35	145 (7.4)	1167 (5.7%)*	0.002
Cigarette smoker	188 (9.5)	13677 (22.4%)	< 0.001
Parity ≥ 2	636 (32.2)	15919 (26.1%)	< 0.001
Gestational age ≥ 39 weeks	1379 (69.9)	48488 (79.5%)	< 0.001
Infant male gender	1069 (54.2)	31116 (51.0%)	0.006
Infant birth weight ≥ 4 kg	338 (17.1)	9271 (15.2%)	0.02
Previous caesarean section	1294 (65.6)	—	
≥ 2 previous c-sections	430 (21.8)	—	
Previous pelvic surgery	85 (4.3)	—	
Pre-operative anaemia (Hb < 10.5g/dl)	290 (14.7)	—	

* Denominator data refers to 2005-2007 when women were routinely weighed at the booking visit

Table 7-2 Estimated blood loss for women delivered by elective caesarean section using different methods of estimation

	Total "measured loss"*	"Measured loss" with a 25% deduction for liquor volume	"Measured loss" with a 300 ml deduction for liquor volume	"Calculated loss" †
	n=1973 (%)	n=1973 (%)	n=1973 (%)	n=1973 (%)
≤ 1000ml	1432 (72.6)	1728 (87.6)	1708 (86.6)	1660 (84.1)
1001 – 2000ml	486 (24.6)	234 (11.9)	240 (12.2)	288 (14.6)
> 2000ml	55 (2.8)	11 (0.6)	25 (1.3)	25 (1.3)

* "Measured loss" – swabs weighed and suction volume measured

†"Calculated loss"[125 217]– based on pre-operative and 48 hours post-operative haematocrit (HCT)

$$= \text{EBV} \times \frac{\text{(Pre-op HCT – Post-op HCT)}}{\text{Pre-op HCT}}$$

Where EBV estimated blood volume = Booking weight in kg x 85

Table 7-3 Agreement between total "measured loss" and "calculated loss"

	Total "measured loss"		
"Calculated loss"	≤ 1000 ml	1001 – 2000 ml	>2000 ml
≤ 1000 ml	1256	364	40
1001 – 2000 ml	166	110	12
> 2000 ml	10	12	3

Kappa correlation coefficient = 0.13, represents "slight agreement"

MOH sensitivity 176/313 = 56.2%

specificity 1256/1660 = 75.7%

Table 7-4 Agreement between "measured loss" with a 25% deduction for liquor volume and "calculated loss"

	"Measured loss" with a 25% deduction for liquor volume"		
"Calculated loss"	≤ 1000 ml	1001 – 2000 ml	>2000 ml
≤ 1000 ml	1489	165	6
1001 – 2000 ml	222	62	4
> 2000 ml	17	7	1

Kappa correlation coefficient = 0.13, represents "slight" agreement

MOH sensitivity 239/313 = 76.4%

specificity 1489/1660 = 89.7%

Table 7-5 Agreement between "measured loss" with a 300 ml deduction for liquor volume and "calculated loss"

	"Measured loss" with a 300 ml deduction for liquor volume		
"Calculated loss"	≤ 1000 ml	1001 – 2000 ml	>2000 ml
≤ 1000 ml	1475	168	17
1001 – 2000 ml	216	66	6
> 2000 ml	17	6	2

Kappa correlation coefficient = 0.14, represents "slight" agreement

MOH sensitivity 233/313 = 74.4%

specificity 1475/1661 = 88.9%

Table 7-6 Risk factors for major obstetric haemorrhage (MOH)

	MOH n=313 (%)	No MOH n=1660 (%)	Unadjusted OR	95% CI	Adjusted OR§	95% CI
Maternal age ≥ 35 years	138 (44.1)	678 (40.8)	1.14	(0.90, 1.46)	1.42	(1.09, 1.86)
BMI ≥ 35	58 (18.5)	87 (5.2)	4.11	(2.87, 5.88)	3.97	(2.72, 5.79)
Previous caesarean section	190 (60.7)	1104 (66.5)	0.78	(0.61, 1.0)	0.65	(0.49, 0.87)
≥ 2 previous c-sections	63 (20.1)	367 (22.1)	0.89	(0.66, 1.20)	0.87	(0.62, 1.24)
Pre-operative anaemia (Hb < 10.5g/dl)	37 (11.8)	253 (15.2)	0.75	(0.52, 1.08)	0.78	(0.53, 1.15)
Inexperienced operator*	163 (52.1)	662 (39.9)	1.64	(1.29, 2.09)	1.48	(1.13, 1.93)
Prolonged surgery (surgery onset–completion time > 40 min)	77 (24.6)	229 (13.8)	2.04	(1.52, 2.73)	1.45	(1.05, 2.00)
Birth weight ≥ 4000 g	70 (22.4)	268 (16.1)	1.50	(1.11, 2.01)	1.33	(0.96, 1.83)
Gestational age ≥ 39 weeks	222 (70.9)	1157 (69.7)	1.06	(0.81, 1.38)	0.97	(0.73, 1.29)
Male infant gender	177 (56.5)	892 (53.7)	1.12	(0.88, 1.43)	1.16	(0.90, 1.50)
40 IU oxytocin infusion†	157 (50..2)	839 (50.5)	0.99	(0.77, 1.25)	0.92	(0.71, 1.19)
Surgical complexities‡	115 (36.7)	317 (19.1)	2.46	(1.90, 3.19)	2.32	(1.75, 3.09)
Surgical protocol adherence	238 (76.0)	1307 (78.7)	0.86	(0.65, 1.14)	1.25	(0.73, 2.14)

	MOH n=313 (%)	No MOH n=1660 (%)	Unadjusted OR	95% CI	Adjusted OR§	95% CI
Deviations from surgical protocol:						
Single layer closure	1 (0.3)	17 (1.0)	0.31	(0.04, 2.34)	0.54	(0.07, 4.41)
Manual removal of placenta	17 (5.4)	89 (5.4)	1.01	(0.60, 1.73)	1.04	(0.53, 2.03)
Uterus exteriorised	48 (15.3)	176 (10.6)	1.53	(1.08, 2.16)	1.76	(0.98, 3.16)

All measurements are based on "calculated loss"

*Inexperienced operator –3 years or less specialised obstetrical training

† Trial arm

‡ Surgical complexities - vascular lower segment, pelvic scarring/adhesions, fibroids

§ Adjusted for all variables

CHAPTER 8. Summary and Conclusions

8.1 Summary of the thesis

The aim of this thesis was to assess the control of blood loss at caesarean section. This chapter summarises the findings of the four elements of the research project designed to address this aim and highlights the clinical and research implications of the thesis as a whole.

The systematic review of the medical methods used to control blood loss at caesarean section highlighted the existence of poor quality data, heterogeneity in study design and inconsistency in the results between studies. Oxytocin was the most studied of all the uterotonic agents, but the majority of studies were small and underpowered. There is clearly an overwhelming need for high quality randomised controlled trials in this area of clinical practice.

The review of guideline implementation and survey of practice reinforced the findings of the systematic review and meta-analysis. A lack of good quality data has resulted in limited guidance with inevitable variations in clinical practice. It did identify oxytocin as the most commonly used uterotonic agent for control of blood loss at caesarean section. Clinicians' approaches to the use of oxytocin however varied both within countries and between countries. While there was good consensus about the 5 IU bolus dose, both the use and dose of infusion varied greatly reflecting the limited guidance available at the time. Even in countries with on-site visits to ensure guideline implementation (e.g. Clinical Negligence Scheme for Trusts in England), marked deviations from guideline recommendations existed. This study reinforces the need for high quality evidence on which to base practice recommendations.

To address the urgent need for improved evidence that had been highlighted by both the systematic review and the review of guideline implementation, a large, multi-centre randomised trial was performed. This RCT, ECSSIT, found that an oxytocin infusion in addition to an oxytocin bolus had no effect on overall rates of MOH at elective caesarean section compared with oxytocin bolus only, but that the need for an additional uterotonic agent was reduced. MOH was reduced following use of oxytocin bolus and oxytocin infusion by inexperienced obstetricians compared to senior obstetricians. Importantly, side effects were not increased by use of this additional oxytocin infusion.

Putting this into context of the general obstetric population, the prospective cohort study demonstrated that MOH was common in an apparently low risk elective caesarean section cohort. Risk factors for MOH included older maternal age, obesity, an inexperienced operator, prolonged duration of surgery and surgical complexity. Accurately determining blood loss remains a challenge. It had been hoped that a calculation of blood loss based on pre- and post-operative haematocrit would prove to be the "gold standard", both exact and reliable. Unfortunately however, there was poor agreement between the alternative methods of estimating blood loss with likely underestimation in as many as 10% of cases if this calculated method was used. Conversely, gravimetric methods resulted in likely over-estimation. Precise measurement of blood loss remains a challenge to the practicing obstetrician.

8.2 Practice implications

Some of the variation seen in the use of uterotonic agents to prevent postpartum haemorrhage at caesarean section reflects a lack of robust evidence and the need for future research in this area. It was hoped that the RCT (ECSSIT – Elective Caesarean Section Syntocinon Infusion Trial) would address some of the uncertainty that surrounds the prevention of postpartum haemorrhage at caesarean section and the results would inform future clinical guidelines.

The RCT (ECSSIT) has demonstrated a reduction in the use of additional uterotonic agents, but no difference in overall rates of MOH with use of a routine oxytocin infusion. A lower rate of MOH amongst inexperienced operators was shown however. Consideration must be given to how these findings could be implemented. One approach would be to recommend that all women undergoing elective caesarean section should receive a routine additional oxytocin infusion. This would eliminate the need for clinical judgement on when to use an additional uterotonic agent. The potential downside would be that some women would receive an unnecessary infusion. Alternatively, a more selective approach could be implemented. An oxytocin infusion could be recommended at all elective caesareans performed by inexperienced operators, whose judgement of when to use additional uterotonic agents may not be as reliable. To put this RCT into context, Ireland is somewhat unique in the structure of its

healthcare service where public and private care is co-located in most hospitals. This results in extensive consultant presence on the labour ward and in theatre. Approximately 30% of all deliveries in the four university teaching hospitals involved in recruitment and 100% of all deliveries in the private hospital, were performed by consultant obstetricians. Globally, this percentage of senior operators is unlikely to be so high. Instead, it is far more likely that more inexperienced operators would be performing the overwhelming majority of caesarean sections. This would make the finding of a significant reduction in MOH for inexperienced operators using an additional oxytocin infusion all the more pertinent.

Although estimation of blood loss at caesarean section can be imprecise, major obstetric haemorrhage appears to be common. Vigilance in monitoring blood loss is essential if maternal haemorrhagic morbidity and mortality is to be avoided. Measuring blood loss by means of weighing swabs and recording suction volume is safe, simple, timely and inexpensive, but the potential to overestimate blood loss must be remembered. Some adjustment for liquor volume may be helpful in overcoming this problem and further research is required to determine the optimal approach to take account of individual variation. It is far safer to over-estimate blood loss than to under-estimate it. The "measured loss" approach is readily applicable in low income settings and may be all that is available. In resource rich settings, pre and post-operative haematocrit estimates are readily available and allow a more objective estimate of blood loss, but do not provide any practical value in the immediate setting. They are best employed as a research tool. With over 54% of patients losing in excess of 500 ml blood at caesarean delivery, the prevention and management of anaemia remains a fundamental aspect of good antenatal care.

Clinicians must be aware of the risk factors for major obstetric haemorrhage in apparently uncomplicated cases and appropriate training and supervision needs to be available to inexperienced operators to minimise the risk of avoidable haemorrhage.

The key to translating evidence into practice is the adoption and implementation of appropriate clinical guidelines. Clinical guidelines are regularly developed and updated. As mentioned in Chapter 1, the HSE has prioritised two main areas – the development of national guidelines for Ireland and caesarean section. It is

incumbent on our research team to raise awareness of the results of the RCT, the systematic review and the cohort study, by both publication of the data and direct correspondence with guideline authors and policy makers. The RCOG and NICE regularly update their guidelines and we will write to the Clinical Guidelines Committees. It would be short-sighted to focus solely at a local level, as the problem of PPH following caesarean section is far worse globally. The WHO should also be advised of the results of this research, as they have responsibility for making global recommendations for this aspect of obstetrical care if Millennium Development Goal 5 is to be achieved.

8.3 Research implications

As rates of caesarean section continue to escalate, future research aimed at reducing MOH and haemorrhagic complications is essential. Previous work has shown that the risk of MOH is greater at emergency than at elective caesarean section.[102] The Randomised Controlled Trial (ECSSIT) was limited to women undergoing elective caesarean section; future work addressing non-elective deliveries would be strongly recommended.

There are well recognised difficulties in accurately determining blood loss at caesarean section. As rates of caesarean section continue to rise, future research aimed at accurately calculating and reducing blood loss at these deliveries is essential.

8.4 Conclusions

This thesis reports on a body of research that addressed the control of blood loss at caesarean section. Uterine atony is the most common cause of excessive bleeding following caesarean section and oxytocin was identified as the most commonly used uterotonic agent used. This work has demonstrated that major obstetric haemorrhage was common in a low risk elective caesarean section cohort of patients. Methods of estimating blood loss were unreliable, with poor agreement between alternative methods. Risk factors for MOH included older

women, high BMI, an inexperienced operator, prolonged duration of surgery and surgical complexity.

A routine oxytocin infusion at elective caesarean section significantly reduces the need for an additional uterotonic agent, although it does not reduce overall rates of MOH. An oxytocin infusion is an inexpensive, well tolerated and relatively safe medication which when used routinely takes the uncertainty out of who should receive an additional uterotonic agent.

Recommendations for clinical practice and future research from this research have been highlighted. Implementation of these recommendations could reduce the haemorrhagic morbidity associated with caesarean section worldwide, but particularly in countries where resources are scarce.

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APPENDICES

Appendix 1: HRB Cochrane Training Fellowship

HRB
Health Research Board

An Bord Taighde Sláinte
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Dr Sharon Sheehan
Dept. of Obstetrics & Gynaecology
Coombe Women's Hospital
Dolphin's Barn
Dublin 8

15 September 2008

Re: Cochrane Fellowships 2008 (CTF/2008/2)

Dear Dr Sheehan

Thank you for your application for the above award. After careful consideration by the Evaluation Panel, your application has been judged successful. May we offer you our congratulations on your success in this highly competitive fellowship scheme.

We will be in touch in the coming weeks regarding detailed administrative and funding arrangements and the terms and conditions of the award.

In the meantime if you need any further information please do not hesitate to contact us.

Yours sincerely

Annalisa Montesanti PhD
Research Programme Manager
Research Management Unit

Appendix 2: Data Extraction Form

Data Extraction

Medical methods for preventing blood loss at caesarean section

Review ID:	Study ID:	Reference ID:
Person extracting data:	Date of date extraction:	Year of study publication:
Title:		
Author:		
Reference:		

Study design

Type of study design (cluster RCT; block randomisation; stratified randomisation; multi-arm; factorial etc):

Unit of randomisation:

Participants and setting

Describe setting:

Inclusion criteria:

Exclusion criteria:

Intervention

Experimental intervention:

Comparison

Control/Comparison intervention:

Outcomes:

Outcomes:

Study methods
Risk of bias

Adequate sequence generation Was the allocation sequence adequately generated?	Yes / Unclear / No Describe:
Allocation concealment Was allocation concealment adequate?	Yes / Unclear / No Describe:
Blinding Was knowledge of the allocated intervention adequately prevented during the study?	Participant: Yes / Unclear / No Clinician: Yes / Unclear / No Outcome assessor: Yes / Unclear / No Describe:
Incomplete outcome data addressed Were complete outcome data adequately addressed?	Yes / Unclear / No Describe any loss of participants to follow-up at each data collection point: Describe any exclusion of participants after randomisation: Was the analysis intention to treat? If not has the data been able to be re-included?
Free of selective reporting bias Are reports of study free of suggestions of	Yes / Unclear / No Describe:

selective reporting bias?	
Free of other bias Was the study apparently free of other problems that could put it at high risk of bias?	Yes / Unclear / No If the study was stopped early, explain the reasons: Describe any baseline imbalance: Describe any differential diagnosis:

Additional information requested

Outcomes for main analysis

	Outcome Measures	Total number of participants in study =			
		Intervention group total no. in study =		Control / other group Total no. in study =	
		events	Total	events	total
	Primary:				
1	Mean blood loss mls(continuous) _____				
2	Primary postpartum haemorrhage -				
	≥ or > 500ml Y / N				
	≥ or > 1000ml Y / N				
	≥ or > 1500ml Y / N				
	Estimated Y / N				
	Measured Y / N How?				
	Adjusted for liquor Y / N How?				
3	> 10% Δ pre- and post-op Hb or HCT				
4	Blood transfusion				

	Secondary:				
1	Uterine atony				
2	Single additional uterotonic agent Which? _____				
3	Multiple additional uterotonic agents Which? _____				
4	Non pharmacological interventions for control of haemorrhage What ?_____				
5	Additional haemostatic agents or coagulation factors				
6	Maternal side effects –				
	Nausea Y / N				
	Vomiting Y / N				
	Shivering Y / N				
	Headache Y / N				
	Other, please state _____				
7	Maternal complications –				
	Infection Y / N				
	Endometritis Y / N				
	ECG changes Y / N				
	Hypotension Y / N				
	Hypertension Y / N				
	ICU admission Y / N				
	Death Y / N				
	Other, please state _____				
	Secondary postpartum haemorrhage				
	Neonatal outcomes –				
	Initiation of breastfeeding Y / N				
	Breastfeeding on discharge Y/N				
	Neonatal jaundice Y / N				
	NICU / SCBU admission Y /N				
	Other, please state _____				
	Duration of operation (mins) (continuous)				
	Duration of hospitalisation days) (continuous)				
	Other				

Outcomes for sub-group analyses

Risk of PPH	Low		High
Dose of Syntocinon	Low	Mid	High
Gestation	_____		
Alternative agents and dose	_____	_____	
Route of administration	_____		

Notes on sub-group analyses

General conclusions

Very brief summary of study authors main findings/conclusions:

Notes

Exclusion after data extraction

Reasons for exclusion: (study design? participants? interventions/ outcomes? attrition? bias?)

Dates & Details:

	Date	Reviewer (JC, SS, KM, DJM)
RevMan		
Checked		
Editorial base		

USE of OXYTOCIN to prevent BLOOD LOSS at CAESAREAN SECTION - QUESTIONNAIRE

Study Number ☐

Please provide the following background information:

Clinical specialty: Obstetrics ☐ Anaesthetics ☐

Number of deliveries per year in your unit: _____

Caesarean section rate in your unit: (total elective and emergency) _____

PART ONE - Oxytocin

1. With regard to use of oxytocin for the third stage at caesarean section, do you use:

	Yes	No
i) a slow bolus intravenous 5IU oxytocin (syntocinon) after delivery of the infant?	☐	☐
ii) a slow bolus intravenous 10IU oxytocin (syntocinon) after delivery of the infant?	☐	☐
iii) an alternative dose of oxytocin? Please state dose used. _____	☐	☐
iv) any additional doses of oxytocin? Please describe. _____	☐	☐

2. With regard to use of oxytocin for the third stage at caesarean section, do you use an additional infusion of intravenous oxytocin:

	Yes	No
i) routinely for all caesarean sections?	☐	☐
ii) not at all?	☐	☐
iii) selectively for caesarean sections in certain circumstances?	☐	☐

If you answered yes to iii) please complete question 3, otherwise move to question 4.

3. If you use an intravenous infusion of oxytocin selectively do you use it under the following circumstances: Please tick any that apply.

	Yes	No
i) Intrapartum haemorrhage?	☐	☐
ii) Emergency caesarean section?	☐	☐
iii) Prolonged labour?	☐	☐
iv) Placenta praevia?	☐	☐
v) Multiple pregnancy?	☐	☐
vi) Previous PPH?	☐	☐
vii) Maternal medical disorder? Please state. _____	☐	☐
viii) Other indication? Please state. _____	☐	☐

4. If you use an additional infusion of oxytocin do you use:

		Yes	No
i) 30IU oxytocin in 500ml normal saline solution?		☐	☐
i) 40IU oxytocin in 500ml normal saline solution?		☐	☐
ii) An alternative solution? Please state	_____	☐	☐
iii) An alternative regimen? Please state	_____	☐	☐

5. In relation to maternal adverse effects following a **bolus** dose of oxytocin at caesarean section, please describe the frequency with which you deal with the following complications

	Always	Frequently	Rarely	Never
i) Hypotension	☐	☐	☐	☐
ii) Nausea	☐	☐	☐	☐
iii) Vomiting	☐	☐	☐	☐
iv) Headache	☐	☐	☐	☐
v) Flushing	☐	☐	☐	☐
vi) Tachycardia	☐	☐	☐	☐
vi) Serious adverse reaction/anaphylaxis	☐	☐	☐	☐
vii) Other? Please state	_____			

6. In relation to maternal adverse effects following an **infusion** of oxytocin at caesarean section, please describe the frequency with which you deal with the following complications

	Always	Frequently	Rarely	Never
i) Hypotension	☐	☐	☐	☐
ii) Nausea	☐	☐	☐	☐
iii)Vomiting	☐	☐	☐	☐
iv) Poor urinary output	☐	☐	☐	☐
v) Serious adverse reaction/anaphylaxis	☐	☐	☐	☐
vi) Other? Please state	_____			

PART TWO – Blood loss

7. Please describe how you estimate blood loss at caesarean section.

	Yes	No
i) A global estimate without objective measurement	☐	☐
ii) Measurement of collected blood loss with no adjustment for liquor volume	☐	☐
iii) Measurement of collected blood loss with adjustment for liquor volume	☐	☐

iv) Other? Please state _____

8. Please state what you would consider an average blood loss for a routine **elective** caesarean section, for example - a woman with a breech presentation at term?

_____ml

9. Please state what you would consider an average blood loss for a routine **emergency** caesarean section, for example - a woman with failure to progress in term spontaneous labour?

_____ml

10. How often do you think women in your unit experience a primary postpartum haemorrhage (> 500ml) at **elective** caesarean section?

0-5%	6-10%	11-15%	16-20%	>20%
☐	☐	☐	☐	☐

11. How often do you think women in your unit experience a primary postpartum haemorrhage (> 500ml) at **emergency** caesarean section?

0-5%	6-10%	11-15%	16-20%	>20%
☐	☐	☐	☐	☐

Please turn over

Thank you for your time and co-operation.

Should you have any further comments regarding this questionnaire please note them below.

.....

.....

.....

.....

.....

Elective Caesarean Section Syntocinon® Infusion Trial

ECSSIT

PATIENT INFORMATION SHEET

A randomised controlled trial of oxytocin (syntocinon®) 5iu versus oxytocin 5iu and 40iu infusion for the control of blood loss at elective caesarean section.

You are being invited to take part in a research study. Before you decide whether to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read this information carefully and discuss it with others. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

The purpose of the study is to evaluate two different approaches to reducing blood loss at an elective caesarean section. The two interventions, a slow intravenous injection of oxytocin (a drug that helps the uterus to contract) followed by a dummy infusion (no active agent) or a slow intravenous injection of oxytocin followed by an additional infusion of the oxytocin (active agent) are being compared. Both interventions are part of standard obstetric practice with variation in the preference of individual clinicians. The purpose of this study is to help us understand what is the best approach to preventing blood loss when performing an elective caesarean section.

Why have I been chosen?

We are carrying out the study in several maternity units in Dublin. We are trying to contact every woman booked for an elective caesarean section who has no specific complication that would prevent her participating in the trial (for example a known bleeding disorder). On average 10% of women (1 in 10) will require an elective caesarean section. Over the next three years we would hope to have around 2000 women like you taking part in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and asked to sign and return the enclosed consent form. After deciding to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive from your doctor or midwife in any way. If you decide not to take part, your delivery will be managed in the usual way through discussion with your obstetrician, anaesthetist and midwife.

The Research Ethics Committee, which has responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from Trinity College, University of Dublin and the Regulatory Authorities.

What will happen during the study?

We are trying to find the best approach to reducing blood loss at an elective caesarean section. In this study, we want to find out the best use of oxytocin, a routinely used agent for preventing blood loss at delivery.

Sometimes because we do not know which way of treating patients is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by a computer which has no information about the individual – i.e. by chance. Patients in each group then have a different treatment and these are compared. You would have an equal chance of receiving either one of the interventions and neither you nor the doctor treating you would know which intervention you have received (although, if your doctor needs to find out he/she can do so). The two groups will be compared at the end of the study to find out which one, if any, best helps women to make an uncomplicated recovery following delivery. If you consent to participate in the study, your participation would be confirmed again on the day of the caesarean section and it is at this point that you would be allocated to one of the interventions.

Depending on which group you are in, you may be managed with:
(1) **Bolus and placebo** - a slow intravenous dose of oxytocin followed by a dummy infusion (routine intravenous fluids) for four hours
(2) **Bolus and infusion** - a slow intravenous dose of oxytocin followed by an infusion of oxytocin (within routine intravenous fluids) for four hours.
In both groups, you will be reviewed in theatre, recovery and the postnatal ward to assess your health and well-being. You will require a blood test to check your blood count approximately 48 hours after delivery as part of routine clinical care.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. A researcher on the study will need to look at your hospital records for information about your pregnancy and delivery. All published information will have your name and address removed so that you cannot be recognised from it. We will ask for your consent to inform your GP that you are taking part in the study.

What will happen to the results of the study?

The study will last for approximately 3 years. We hope that the results will provide clear information for women and doctors about the safest approach to controlling blood loss at elective caesarean section. A report will be produced at the end of the study, and the main results will be published in medical journals. This can sometimes take up to about a year after the end of the study. If you would like us to send you a copy of the results, please let us know at some time during your involvement in the study.

Who is organising and funding the research?

The study is being organised jointly by Trinity College Dublin and the Coombe Women and Infants' University Hospital. The study is funded by the Health Research Board of Ireland.

What do I do now?
If you want to take part in this study, we would like you to bring the enclosed trial documents with you to the Coombe Women and Infants' University Hospital where we will have a chance to discuss the study in more detail and to answer any questions you may have. We would ask for your written consent at that point if you feel happy to participate in the study.

Contact for further information

If you have any other questions about the study in the interim you can contact

Dr. Sharon Sheehan	Prof Deirdre Murphy	Ms. Clare Dunney
Research fellow	Professor of Obstetrics and Gynaecology	Research Midwife

Elective Caesarean Section Syntocinon® Infusion Trial

ECSSIT

A randomised controlled trial of oxytocin(syntocinon®) 5iu versus oxytocin 5iu and 40iu infusion for the control of blood loss at elective caesarean section.

CONSENT FORM

NB. This form must be completed and signed by the research subject in the presence of someone with knowledge of the research designated by the Principal Investigator. This may be a doctor, nurse, clinical research assistant or other member of the research team who must countersign the form as witness to the subject's signature

Please tick (✓) appropriate box

Have you read and understood the Subject Information Sheet? Yes ☐ No ☐

Have you been given an opportunity to ask questions and further discuss this study? Yes ☐ No ☐

Have you received satisfactory answers to all of your questions? Yes ☐ No ☐

Have you now received enough information about this study? Yes ☐ No ☐

Who have you spoken to? Dr\Mr\Mrs\Miss .....

Do you understand that your participation is entirely voluntary? Yes ☐ No ☐

Do you understand that you are free to withdraw from this study:

At any time? Yes ☐ No ☐

Without having to give a reason for withdrawing? Yes☐ No ☐

Without this affecting your present or future medical care? Yes ☐ No ☐

Do you agree that your records in this research and supporting medical records be made available for inspection by monitors from:

Trinity College? Yes ☐ No ☐
Regulatory authorities? Yes ☐ No ☐

Do you agree to take part in this study? Yes ☐ No ☐

Do you agree to your family doctor (GP) being informed of your participation in this study? Yes ☐ No ☐

Subject's signature ..... Date .....

Subject's name in block capital letters .....

Telephone contact (Subject) .....(Home) .....(Work)

Signature witnessed by ..... Date .....

Witness name in block capital letters .....

Appendix 6: Pharmacy form

Elective Caesarean Section Syntocinon® Infusion Trial

PHARMACY FORM

NB. This form must be completed by the recruiter after consenting the patient. It must then be handed in to pharmacy prior to receiving allocation.

Patient surname _____

Forname(s) _____

Date of birth (dd/mm/yyyy) _____/_____/_____

Hospital number _____

Centre _____

Previous caesarean section **YES / NO**

Name of recruiter _____

Date (dd/mm/yyyy) _____/_____/_____

Time _____**(use 24 hour clock)**

Study ID Number _____**(received from pharmacy)**

Allocated treatment type _____**(received from pharmacy)**

Signature of pharmacy personnel issuing patient allocation _____

Appendix 7: GP letter

Elective Caesarean Section Syntocinon® Infusion Trial

ECSSIT

Randomised controlled trial of oxytocin (Syntocinon®) 5iu versus oxytocin 5iu and 40iu infusion for the control of blood loss at elective caesarean section

Dear

I am writing to inform you that _____has agreed to take part in a research study being conducted by Trinity College Dublin, the Coombe Women and Infants' University Hospital, the Rotunda Hospital and the National Maternity Hospital.

The objective of the study is to evaluate two different approaches to the use of uterotonic agents for the control of blood loss at elective caesarean section. The two interventions, slow intravenous bolus oxytocin 5iu, and slow intravenous bolus oxytocin 5iu and 40iu infusion are being compared. Both interventions are part of standard obstetric practice with variation in the preference of individual clinicians. The two approaches have had no formal evaluation by randomised controlled trial to date.

Women will be recruited in the third trimester at the time of discussing a planned elective caesarean section. An information sheet will be provided and written consent is required. The woman's consent to participate will again be confirmed on admission to the day ward, and she will be randomised at that point to one of the two possible interventions. We will evaluate the outcome for the mother immediately postpartum, at 24 hours after delivery, and prior to hospital discharge. Postnatal review will otherwise be as usually indicated. Women with a singleton term pregnancy will be included. Women with a placenta praevia, known coagulopathy, thrombocytopenia or receiving anti-coagulant therapy will be excluded.

We anticipate that any requests by women for additional appointments to discuss their caesarean section will be with the obstetric team at the Coombe Women and Infants' University Hospital. If you have anything that you would like to discuss, either about the study in general, or this patient in particular, please do not hesitate to contact me at the address/telephone number at the top of this letter.

Yours sincerely,

Dr. Sharon Sheehan

Study Co-ordinator

Appendix 8: Infusion label

ECSSIT TRIAL DRUG

Placebo or 40IU Oxytocin

Patient's Name: .....

Hospital No.: .....

Date: .....

Location: .....

Added by: .....

Checked by: .....

Elective Caesarean Section Syntocinon® Infusion Trial ECSSIT

PRIVATE AND CONFIDENTIAL

CASE REPORT FORM (CRF)

Study Number: _____ Patient Initials: _____

CHI Number: _____ Date of Delivery: _____ Time: _____

DEMOGRAPHIC DATA

1. Mother's age: _____
2. Mother's social class: ☐
3. Mother's ethnic origin: ☐
4. Mother's marital status: ☐

MATERNAL FACTORS

5. Infertility: ☐
6. Diabetes: ☐
7. Cardiac disease: ☐
8. Endocrine disease: ☐
9. Hypertension at time of booking: ☐
10. Renal disease: ☐
11. Inflammatory bowel disease ☐
12. Smoking: ☐
13. Alcohol: ☐
14. Drug abuse: ☐
15. Other ☐

PAST OBSTETRIC/GYNAE HISTORY

16. Parity: ☐ + ☐
17. Complications:
    - Previous LSCS ☐ No.___
    - Previous difficult vaginal delivery ☐
    - Previous PPH ☐
    - Previous pelvic surgery ☐
    - Previous pelvic infection ☐

PRE-DELIVERY DETAILS

18. Maternal weight at booking _____ Kg
19. Maternal height _____ cm
20. BMI _____ Kg/m^2
21. Pre-op Haemoglobin _____ g/dl
22. Pre-op Haematocrit _____
23. Indication for caesarean section ☐
24. Other issue, state _____

DELIVERY DETAILS

25. Time of anaesthetic _____
26. Knife to skin time _____
27. Onset of surgery – delivery interval _____ mins
28. Onset of surgery – surgery completed interval _____ mins
29. Anaesthetic protocol adhered to ☐
30. Deviations, Describe _____
31. Grade of anaesthetist performing anaesthetic ☐
32. Grade of supervising anaesthetist ☐
33. Caesarean section protocol adhered to ☐
34. Deviations, Describe _____
35. Grade of surgeon ☐
36. Grade of assistant ☐
37. Measured blood loss in theatre _____ ml

MATERNAL SIDE EFFECTS IN THEATRE

38. Maternal side effects to oxytocin ☐
    - Hypotension ☐
    - Nausea ☐
    - Vomiting ☐
    - Serious adverse reaction ☐
    - Other ☐
39. Trial infusion
    - Used ☐ If not, state reason _____
    - Discontinued ☐ If not, state reason _____

COMPLICATIONS

39. Use of additional…

			Dose	No.
Uterotonic agent	☐	Ergometrine	☐	___ ___
Oxytocin bolus	☐	Haemabate	☐	___ ___
Oxytocin infusion (replacement)	☐	Misoprostol	☐	___ ___
		Cervagem	☐	___ ___
		Other, state	_____	

40. Additional surgical procedure ☐

Repeat laparotomy	☐	Ligation uterine arteries	☐
B Lynch suture	☐	Interventional radiology	☐
Uterine tamponade balloon	☐	Pelvis packed	☐
Hysterectomy	☐	Tubal ligation	☐
Ligation internal iliac arteries	☐	Other, state	_____

41. Blood products received ☐

Red blood cells, total units	☐	Cryoprecipitate	☐
Fresh Frozen plasma, total units	☐	Other, state	_____
Platelets, adult doses	☐		

42. Operative complications ☐

Atonic uterus	☐	Fibroids	☐
Vascular lower segment	☐	Other	☐
Pelvic scarring/adhesions	☐		

43. Blood loss in recovery _____ ml

44. Total blood loss in theatre and recovery _____ ml

45. Interval from delivery to transfer to postnatal ward _____ mins

46. If delay, state reason _____

47. Transfer to ITU/HDU ☐

POST-OPERATIVE COURSE

48. Post-operative haemoglobin day 2, lowest if transfused _____ g/dl
49. Post-operative Hct day 2 or pre-transfusion _____
50. Post-delivery in-patient days _____
51. Post-operative heparin ☐
52. Placental bed complications ☐
    - Infection/ endometritis ☐
    - Retained products ☐
    - Antibiotics ☐
    - ERPC ☐
    - Other ☐

BABY DETAILS

53. Presentation ☐
54. Birthweight: _____ g
55. Gestation: _____ weeks
56. Sex: ☐
57. Apgar score at 1 min: _____
58. Apgar score at 5 min: _____
59. Cord gases done: ☐
    pH value: a/v ____ ____
    Base deficit value: a/v ____ ____
60. Admission to SCBU: ☐
61. Reason for SCBU admission ☐

STANDARD CODES

0 NO
1 YES
8 NOT DONE
9 NOT KNOWN

TIMES IN 24 HOUR CLOCK

CODES AND DEFINITIONS

DEMOGRAPHIC DATA

2. Mother's social class: as classified in OPCS
   0. Forces
   1. Professional
   2. Intermediate
   3. Skilled non-manual
   4. Skilled manual
   5. Partly skilled
   6. Unskilled
   7. Students
   8. Unemployed

3. Mother's ethnic origin:
   1. Caucasian
   2. Caribbean black
   3. African black
   4. Indian
   5. Pakistani
   6. Bangladeshi
   7. Chinese
   8. Other

4. Mother's marital status:
   1. Married
   2. Single supported
   3. Single unsupported
   4. Single unknown

MATERNAL FACTORS

5. Previous infertility
   0. None
   1. Donor semen/ Donor egg
   2. Clomiphene
   3. Pergonal
   4. In-vitro fertilisation/ ICSI
   Record that which requires greatest intervention

6. Diabetes:
   1. IDDM Type 1 or 2
   2. Gestational Diabetes in any previous pregnancy

7. Cardiac disease: present at the time of booking including corrected cardiac anomalies.

8. Endocrine disease: other than diabetes, present at the time of booking.

9. Hypertension at time of booking: BP >/= 140 or >/= 90 on two seperate occasions.

10. Renal disease:
    0. None
    1. Recurrent UTIs
    2. Structural abnormality
    3. Renal disease

11. Inflammatory bowel disease	0. None 1. Ulcerative colitis/Crohn's 2. Other
12. Smoking:	0. None 1. 1 - 10/day 2. 11 - 20/day 3. > 20/day
13. Alcohol:	0. None 1.Moderate 2. Heavy
14. Drug abuse	0. None 1. Non-IVDU 2. IVDU intravenous drug use
17. Previous difficult vaginal delivery	1. Shoulder dystocia 2. midcavity forceps/ Ventouse 3. 3° tear 4. PPH/ transfusion

PRE-DELIVERY DETAILS

23. Indication for caesarean section	1. Previous caesarean section 2. Breech presentation 3. Unstable lie 4. Previous traumatic delivery 5. Maternal medical indication 6. Fetal medical indication 7. Maternal request 8. Other, state
31, 32,35, 36. Grade of doctor	1. SHO 2. Senior SHO 3. SpR Year 1-3 4. SpR Year 4-5 5. Consultant 6. Staff grade/Associate specialist

COMPLICATIONS

45. Delay in transfer to postnatal ward	1. Beds 2. PPH 3. Other, state
52. Presentation	1. Cephalic 2. Breech 3. Transverse 4. Oblique
55.Sex:	1.Male 2.Female
59. Reason for SCBU admission	1. Tachypnoea/RDS 2. Hypoglycaemia 3. Other, state

Appendix 11: Theatre Data Form

Elective Caesarean Section Syntocinon® Infusion Trial

ECSSIT

THEATRE / RECOVERY DATA FORM

Study Number _____ Patient Initials _____

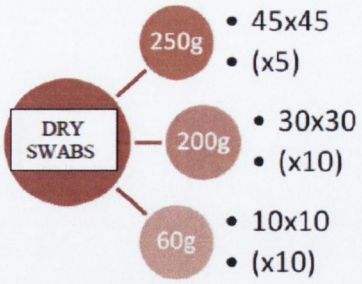
Hospital Number _____ Date of delivery _____

Times

1. Anaesthetic start: _____
2. Knife to skin: _____
3. Closure: _____
4. Transfer to postnatal ward: _____

   If delay, state reason _____

Blood loss



1. Weight of swabs: _____
2. Suction volume: _____

Total blood loss: _____

Detailed level of occupations used in the 2002 Census classification

Please use the LAST NUMBER

Social class

000 Gainfully occupied but occupation not stated Z Z Z 7 7 7

100 Senior managers in national government A A A 1 1 1

101 General managers in large companies A H A 2 2 2

102 Local government officers A A A 2 2 2

103 General administrators in national government A A A 2 2 2

110 Production and works managers A H A 2 2 2

111 Building managers A H A 2 2 2

120 Company financial managers A H A 2 2 2

121 Marketing managers A C A 2 2 2

122 Purchasing managers A H A 2 2 2

124 Personnel managers A H A 2 2 2

126 Computer systems managers A H A 2 2 2

130 Credit controllers A H A 2 2 2

131 Bank and building society managers A H A 2 2 2

132 Civil Service executive officers C C C 2 2 2

139 Other financial managers n.e.s. A H A 2 2 2

140 Transport managers A H A 2 2 2

141 Stores and warehousing managers A H A 2 2 2

150 Commissioned officers in armed forces A 2

152 Senior police and prison officers A 2

160 Farm owners and managers I I I 1-5 1-5 1-5

171 Garage managers and proprietors A H A 2 2 2

173 Hotel and accommodation managers A H A 2 2 2

174 Restaurant and catering managers A H A 3 3 2

175 Publicans, innkeepers and club managers A H A 2 2 2

176 Entertainment and sport managers A H A 3 3 2

177 Travel agency managers A H A 2 2 2

178 Managers and proprietors of butchers A H A 2 3 2

179 Managers and proprietors of shops A H A 2 2 2

191 Administrators of schools and colleges A A A 2 2 2

199 Other managers n.e.s. A H A 2 2 2

200 Chemists B B B 1 1 1

201 Biological scientists B B B 1 1 1

202 Physicists B B B 1 1 1

209 Other natural scientists n.e.s. B B B 1 1 1

210 Civil and mining engineers B B B 1 1 1

211 Mechanical engineers B B B 1 1 1

212 Electrical and electronic engineers B B B 1 1 1

214 Software engineers B B B 1 1 1

215 Chemical, production, planning and quality control engineers B B B 1 1 1

216 Design and development engineers B B B 1 1 1

219 Other engineers and technologists n.e.s. B B B 1 1 1

220 Medical practitioners B B B 1 1 1

221 Pharmacists, pharmacologists, ophthalmic and dispensing opticians B B B 1 1 1

223 Dental practitioners B B B 1 1 1

224 Veterinarians B B B 1 1 1

230 University, RTC and higher education teachers B B B 1 1 1

233 Secondary and vocational education teachers C C C 2 2 2

234 Primary and nursery education teachers C C C 2 2 2

239 Other teaching professionals n.e.s. C C C 2 2 2

240 Judges A A A 1 1 1

242 Barristers and solicitors B B B 1 1 1

250 Chartered and certified management accountants

(incl. taxation experts) B B B 1 1 1

252 Actuaries, economists, statisticians, management

consultants and business analysts B B B 1 1 1

260 Architects, town planners and surveyors B B B 1 1 1

270 Librarians, archivists and curators A A A 2 2 2

290 Psychologists and other social/behavioural scientists B B B 1 1 1

292 Clergy B B B 1 1 1

293 Social workers and probation officers B B B 1 1 1

300 Laboratory technicians C C C 2 2 2

301 Engineering technicians C C C 2 2 2

302 Electrical and electronic technicians C C C 2 2 2

303 Architectural, town planning, building and civil

engineering technicians C C C 2 2 2

309 Other scientific technicians n.e.s. C C C 2 2 2

310 Draughtspersons A H D 3 3 3

312 Building inspectors and quantity surveyors C C C 2 2 2

313 Marine, insurance and other surveyors C C C 2 2 2

320 Computer analyst programmers C C C 2 2 2

331 Aircraft officers, traffic planners and controllers A H C 2 2 2

332 Ship and hovercraft officers A H A 2 2 2

340 Nurses and midwives C C C 2 2 2

342 Medical radiographers C C C 2 2 2

343 Physiotherapists and chiropodists C C C 2 2 2

346 Medical technicians, dental auxiliaries and dental nurses C C C 2 2 2

347 Occupational and speech therapists, psychotherapists and other therapists n.e.s. C C C 2 2 2

349 Other health associate professionals n.e.s. C C C 2 2 2

350 Legal service and related occupations C C C 2 2 2

361 Underwriters, claims assessors, brokers and investment analysts A C C 2 2 2

363 Personnel, industrial relations and work study officers C C C 2 2 2

371 Matrons, houseparents, welfare, community and youth workers A H D 2 2 2

380 Authors, writers and journalists A C C 2 2 2

381 Artists, commercial/industrial artists, graphic and clothing designers A C C 2 2 2

384 Actors, musicians, entertainers, stage managers, producers and directors A C C 2 2 2

386 Photographers, camera, sound and video equipment operators A H D 3 3 3

387 Professional athletes and sport officials A H D 3 3 3

390 Information officers, careers advisers and vocational guidance specialists C C C 2 2 2

391 Vocational, industrial trainers and driving instructors A H C 3 3 2

394 Inspectors of factories, trading standards and other statutory inspectors C C C 2 2 2

396 Environmental health workers, occupational hygienists and safety officers C C C 2 2 2

399 Other associate professional and technical occupations n.e.s. C C C 2 2 2

400 Civil Service administrative officers and assistants D D D 3 3 3

401 Local government clerical officers and assistants D D D 3 3 3

410 Accounts and wages clerks, book-keepers and other financial clerks A H D 3 3 3

411 Cashiers, bank and counter clerks A H D 3 3 3

412 Debt, rent and other cash collectors A H D 3 3 3

430 Filing, computer, library and other clerks n.e.s. A H D 3 3 3

441 Storekeepers, warehousemen/women, despatch and production control clerks A H F 5 5 5

459 Secretaries, medical, legal; personal assistants, typists and word processor operators A H D 3 3 3

460 Receptionists and receptionist-telephonists D D D 3 3 3

462 Telephone operators, telegraph operators and other office communication system operators D D D 3 3 3

490 Computer operators, data processing operators and other office machine operators A H D 3 3 3

500 Bricklayers and masons A H E 4 4 4

501 Roofers, slaters, tilers, sheeters and cladders A H F 5 5 5

502 Plasterers A H E 4 4 4

503 Glaziers A H F 5 5 5

504 Builders and building contractors A H E 4 4 4

506 Floorers, floor coverers, carpet fitters and planners, floor and wall tilers A H E 4 4 4

507 Painters and decorators A H E 4 4 4

509 Scaffolders, riggers, steeplejacks and other construction trades n.e.s. A H F 5 5 5

515 Toolmakers A H E 4 4 4

516 Metal working production and maintenance fitters A H E 4 4 4

517 Precision instrument makers, goldsmiths, silversmiths

and precious stone workers A H E 4 4 4

519 Other machine tool setters and CNC setter-operators

n.e.s. A H E 4 4 4

521 Electricians and electrical maintenance fitters A H E 4 4 4

523 Telephone fitters A H E 4 4 4

524 Cable jointers and lines repairers A H E 4 4 4

525 Radio, TV and video engineers A H E 4 4 4

526 Computer engineers (installation and maintenance) A H E 4 4 4

529 Other electrical and electronic trades n.e.s. A H E 4 4 4

530 Smiths, forge/metal plate workers and shipwrights A H E 4 4 4

532 Plumbers, heating and ventilating engineers and

related trades A H E 4 4 4

533 Sheet metal workers A H E 4 4 4

537 Welders and steel erectors A H E 4 4 4

540 Motor mechanics, auto electricians, tyre and exhaust

fitters A H E 4 4 4

541 Vehicle body repairers, panel beaters and spray

painters A H E 4 4 4

550 Weavers, knitters, warp preparers, bleachers, dyers

and finishers A H E 4 4 4

553 Sewing machinists, menders, darners and

embroiderers

A H F 5 5 5

554 Coach trimmers, upholsterers and mattress makers A H E 4 4 4

555 Shoe repairers and other leather makers A H E 4 4 4

556 Tailors, dressmakers, clothing cutters, milliners and

furriers A H E 4 4 4

559 Other textiles, garments and related trades n.e.s. A H E 4 4 4

561 Printers, originators and compositors A H E 4 4 4

569 Bookbinders, print finishers and other printing trades n.e.s. A H E 4 4 4

570 Carpenters and joiners A H E 4 4 4

571 Cabinet makers A H E 4 4 4

579 Other woodworking trades n.e.s. A H E 4 4 4

580 Bakers and flour confectioners A H E 4 4 4

581 Butchers and meat cutters A H E 4 4 4

582 Fishmongers and poultry dressers A H E 4 4 4

590 Glass product and ceramics makers, finishers and other operatives A H E 4 4 4

594 Gardeners and groundsmen/women A H F 5 5 5

595 Horticultural trades A H J 5 5 5

599 Other craft and related occupations A H F 5 5 5

600 Soldiers (sergeant and below) D 3

610 Police officers (sergeant and below) D 3

611 Fire service officers D D D 3 3 3

612 Prison service officers D 5

615 Security guards and related occupations F F F 3 3 5

619 Other security and protective service occupations n.e.s. F F F 3 3 5

620 Chefs and cooks A H D 4 4 4

621 Waiters and waitresses D D D 5 5 5

622 Bar staff D D D 5 5 5

630 Travel and flight attendants D D D 4 4 4

640 Nurses' aids and ambulance staff C C C 2 2 2

644 Care assistants and attendants F F F 5 5 5

650 Childminders, nursery nurses and playgroup leaders A H D 4 4 4

652 Educational assistants A H D 4 4 3

660 Hairdressers, barbers and beauticians A H D 3 3 4

670 Housekeepers (domestic and non-domestic) D D D 4 4 4

672 Caretakers F F F 5 5 5

673 Launderers, dry cleaners and pressers A H F 5 5 5

690 Undertakers, bookmakers and other personal service workers n.e.s. A H F 4 4 5

700 Buyers and purchasing officers C C C 2 2 2

702 Importers, exporters, commodity and shipping brokers A H D 2 2 3

710 Technical and wholesale sales representatives A H D 3 3 3

719 Auctioneers, estimators, valuers and other sales representatives n.e.s. A H D 3 3 3

720 Sales assistants, check-out operators and petrol pump attendants A H D 2 2 3

731 Roundsmen/women and van salespersons A H E 4 4 4

732 Market/street traders and scrap dealers A H D 5 5 5

790 Merchandisers, window dressers, floral arrangers and telephone salespersons A H D 3 3 3

800 Bakery and confectionery process operatives A H E 4 4 4

802 Tobacco process operatives A H F 5 5 5

809 Other food and drink (incl. brewing) process operatives A H F 5 5 5

810 Tannery production operatives A H E 4 4 4

812 Spinners, doublers, twisters, winders and reelers A H F 5 5 5

814 Other textiles processing operatives A H F 5 5 5

820 Chemical, gas and petroleum process plant operatives A H F 5 5 5

821 Paper, wood and related process plant operatives A H E 4 4 4

824 Rubber process operatives, moulding machine operatives and tyre builders A H E 4 4 4

825 Plastics process operatives, moulders and extruders A H F 5 5 5

829 Synthetic fibre and other chemical, paper, plastics and related operatives A H F 5 5 5

830 Moulders and furnace operatives (metal) A H E 4 4 4

834 Electroplaters, galvanisers and colour coaters A H E 4 4 4

839 Other metal making and treating process operatives n.e.s. A H E 4 4 4

840 Machine tool operatives (incl. CNC machine tool operatives) A H F 5 5 5

841 Other automatic machine workers, metal polishers and dressing operatives A H F 5 5 5

850 Assemblers and lineworkers (electrical and electronic goods) A H F 5 5

851 Assemblers and lineworkers (metal goods and other goods) A H F 5 5 5

860 Inspectors, viewers and laboratory testers A H F 5 5 5

862 Packers, bottlers, canners, fillers, weighers, graders and sorters A H F 5 5 5

871 Bus and road transport depot inspectors E E E 4 4 4

872 Drivers of road goods vehicles A H E 4 4 4

873 Bus conductors and coach drivers A H E 4 4 4

874 Taxi/cab drivers, chauffeurs and couriers A H E 4 4 4

880 Seafarers (merchant navy), barge and boat operatives A H F 5 5 5

881 Railway station workers, supervisors and guards D D E 4 4 4

882 Rail engine drivers and other railway line operatives E E E 4 4 4

885 Mechanical plant drivers/operatives and crane drivers A H E 4 4 4

887 Fork lift truck drivers A H E 4 4 4

889 Other transport and machinery operatives n.e.s. A H E 4 4 4

892 Water and sewerage plant attendants G G G 6 6 6

893 Electrical, energy, boiler and related plant operatives and attendants F F F 5 5 5

895 Pipe layers/pipe jointers and related construction workers A H F 5 5 5

897 Woodworking machine operatives A H E 4 4 4

898 Mine (excluding coal) and quarry workers A H F 5 5 5

899 Other plant, machine and process operatives n.e.s. A H E 4 4 4

900 Farm workers J 6

901 Agricultural machinery drivers and other farming occupations J 6

903 Fishing and related workers A H F 5 5 5

904 Forestry workers J J J 5 5 5

913 Mates to metal, electrical and related fitters F F F 5 5 5

919 Labourers in engineering and other making/processing industries G G G 5 5 6

922 Rail construction and maintenance workers F F F 5 5 5

923 Road construction workers, paviors and kerb layers A H G 5 5 6

929 Other building and civil engineering labourers A H G 5 5 6

930 Stevedores and dockers A H G 5 5 6

931 Goods porters A H G 5 5 6

933 Refuse and salvage collectors A H G 6 6 6

934 Drivers' mates G G G 6 6 6

940 Postal workers and mail sorters F F F 5 5 5

951 Hotel porters and kitchen porters F F F 5 5 5

953 Counterhands and catering assistants D D D 5 5 5

955 Window cleaners and car park attendants A H G 6 6 6

958 Cleaners and domestics A H G 5 5 6

959 Other occupations in sales and services n.e.s. A H F 5 5 5

990 All other labourers and related workers A H G 5 5 6

999 All other gainful occupations n.e.s. Z Z Z 7 7

Appendix 13: Success of Blinding Questionnaire

Elective Caesarean Section Syntocinon® Infusion Trial

ECSSIT

Testing the success of blinding in ECSSIT

CLINICIAN VERSION

Study number _____ Patient Initials _____

Hospital number _____ Date of Delivery _____

Please tick (✓) appropriate box

1. Which intervention do you think the patient received?

a) Bolus and placebo infusion (dummy infusion) Yes ☐ No ☐

b) Bolus and oxytocin infusion Yes ☐ No ☐

c) Don't know Yes ☐ No ☐

2. Please state the reasons for your answer:-

_____

_____

_____

_____

ECSSIT

Testing the success of blinding in ECSSIT

PATIENT VERSION

Study number _____ Patient Initials _____

Hospital number _____ Date of Delivery _____

Please tick (✓) appropriate box

1. Which intervention do you think you received?

a) Bolus and placebo infusion (dummy infusion) Yes ☐ No ☐

b) Bolus and oxytocin infusion Yes ☐ No ☐

c) Don't know Yes ☐ No ☐

2. Please state the reasons for your answer:-

_____

_____

_____

_____

Health Research Board

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UNIVERSITY OF DUBLIN
TRINITY COLLEGE
11 JUL 2007
RECEIVED
TREASURER'S OFFICE

10 July 2007

RP/2007/171
Professor Deirdre Murphy
School of Obstetrics and Gynaecology
Trinity College Dublin
St James's Hospital

HRB Research Project Grants – General 2007
RP/2007/171 (Please quote this reference on all correspondence)

Dear Professor Murphy,

The Health Research Board (HRB) has agreed to award Trinity College Dublin, a Research Project Grant to enable you, to undertake the study entitled: 'A multi-centre randomised controlled trial of oxytocin 5 IU bolus and placebo infusion versus oxytocin 5 IU bolus and 40 IU infusion for the control of blood loss at elective caesarean section'.

The purpose of the Research Project Grants scheme is to support research for health and social gain, including health, biomedical and clinical sciences, public health, epidemiology, health service research, practice based research and translational research in Ireland.

Commencement and Duration

The Grant will commence on **1 October 2007** and will provide funding for a maximum period of three years. The HRB must be notified in writing of any changes to the start date using a 'Grant Amendment Form', available on the HRB website, http://www.hrb.ie/formsforgrantholders.

Amount of the Award

	Year 1 (€)	Year 2 (€)	Year 3 (€)
Salary	42,328.00	45,483.00	39,031.00
Employer's PRSI	4,550.00	4,890.00	4,196.00
Pension Contribution*	8,465.00	9,097.00	7,807.00
Student Stipend	0.00	0.00	0.00
Fees	0.00	0.00	0.00
Consumables	3,000.00	3,000.00	3,000.00
Other	18,000.00	14,000.00	22,000.00
Travel/Dissemination**	0.00	0.00	1,600.00
Overhead***	22,903.00	22,941.00	23,290.00
Start-up Cost****	5,000.00		
Equipment****	0.00	0.00	0.00
Total	104'246.00	99'411.00	100'924.00

The value of the grant is fixed for the duration of the grant.

Note: Please note amendments have been made to the budget with regard to 'Travel & Dissemination', 'Start-up' and 'Equipment' costs. See notes below for details

*Pension contribution is calculated at 20% of salary. This includes provision of 15% for employer's contribution and 5% for employee's contribution.
** All 'Travel & Dissemination' costs will be paid in Year 3 only
***Overhead payments are calculated on the basis of 30% of non-equipment costs excluding fees and should be used to support the indirect cost associated with the project.
**** 'Start-up' & 'Equipment' costs will be paid in October 2007.

Appendix 15: Ethics Approval – National Maternity Hospital

National Maternity Hospital
Founded in 1894
Holles Street, Dublin 2.
Telephone: (01) 6373800. Fax: 6766624. Web: www.nmh.ie

Master: Dr. Michael Robson

29th November 2007

Dr. Deirdre Murphy
Professor of Obstetrics
Head of Department of Obstetrics & Gynaecology
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

Re: A randomised trial of oxytocin bolus versus oxytocin bolus and infusion for the control of blood loss at elective caesarean section.

Dear Prof. Murphy,

I am writing to confirm that approval has been given for the above study.

Thanks for all your patience and help with the amendments.

Kind regards

Yours sincerely

Dr. John Murphy
Consultant Paediatrician
Chairman of Ethics Committee

Appendix 16: Irish Medicines Board Approval

IRISH MEDICINES BOARD

27th April 2007

Dr. Chris Fitzpatrick
Coombe Women's Hospital
Dublin 8

EUROPEAN COMMUNITIES (CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE) REGULATIONS, 2004

RE: CT number: CT 900/456/1 -Syntocinon
Case number: 2034912
EudraCT number: 2006-004799-11
Protocol number: 2006OB01
Title of trial: A randomised trial of oxytocin bolus versus oxytocin bolus and infusion for the control of blood loss at elective caesarean section

Dear Sirs,

The Irish Medicines Board has considered the application dated **12th March 2007** seeking authorisation to conduct the above clinical trial.

On the basis of the evidence available, the application is acceptable. Please note that the date of this letter is the date of authorisation of the trial.

Yours sincerely,

A person authorised in that behalf by the said Board

Irish Medicines Board,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2.

IRISH MEDICINES BOARD
BORD LEIGHEASRA NA HEIREANN

Bord Leigheasra na hEireann
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: 353-1-676 4971 Fax: 353-1-676 7836
Website: www.imb.ie

Appendix 17: Trial Registration

ISRCTN17813715 - A randomised controlled trial of oxytocin bolus versus oxytocin bolus and infusion for the control of blood loss at elective caesarean section

Dear All,

Our Accounts Department have confirmed your payment.

I am therefore pleased to inform you that the following ISRCTN has been assigned to your trial:

ISRCTN17813715 - http://www.controlled-trials.com/ISRCTN17813715

When quoting the ISRCTN, please make sure that no space is inserted between the ISRCTN and the actual number. Please refer to the link below for further guidance notes about how to use the ISRCTN.

http://www.controlled-trials.com/isrctn/sample_documentation.asp

I would also like to remind you that CCT's sister company, BioMed Central (http://www.biomedcentral.com), publishes a wide range of Open Access biomedical journals, in particular the journal Trials, dedicated to publishing protocols, results and other issues relevant to clinical trials. If you would like to publish your trial protocol and/or results papers in Open Access, please visit Trials for more information http://www.trialsjournal.com.

If you have any further questions about the use of the ISRCTN, please do not hesitate to contact me.

Best wishes,
Rebecca

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Elective Caesarean Section Syntocinon® Infusion Trial

Charter for the Data Monitoring Committee (DMC)

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1. Introduction

ECSSIT – Elective Caesarean Section Syntocinon Infusion Trial

A randomised controlled trial of oxytocin (syntocinon) bolus versus oxytocin bolus and infusion for the control of blood loss at elective caesarean section

Funding body: Health Research Board of Ireland RP/2007/171

Sponsor: Trinity College, University of Dublin

EudraCT number: 2006-004799-11

ISRCTN17813715

Objectives of the trial:

The objective of the study is to compare the effects of an intravenous slow bolus of oxytocin 5 IU and placebo infusion (500ml 0.9% saline) with an intravenous slow bolus of oxytocin 5 IU and oxytocin infusion (40 IU in 500ml 0.9% saline over 4 hours) at elective caesarean section in a double blind randomised trial.

The aims are as follows:

Primary outcomes

- To compare the incidence of major obstetric haemorrhage (≥1000ml) following oxytocin bolus compared with oxytocin bolus and infusion
- To compare the need for an additional uterotonic agent between the two groups

Major obstetric haemorrhage will be defined in two ways

i. Measured blood loss as calculated by theatre staff

ii. Measured blood loss as calculated from pre and post-operative haematocrit

Secondary outcomes

- To compare the estimated mean operative blood loss and early lochial loss following oxytocin bolus compared with oxytocin bolus and infusion
- To compare the objective change in haemoglobin and haematocrit before and 48 hours after delivery between the two groups
- To compare the incidence of severe anaemia (Hb≥20%) 48 hours after delivery between the two groups (or patients transfused)
- To compare the need for blood transfusion and/or blood products
- To compare the incidence of side effects (vomiting, hypotension)
- To compare the postnatal length of stay in theatre/recovery and in hospital

Cost effectiveness

- To compare the cost-effectiveness of an oxytocin bolus regimen versus oxytocin bolus and infusion (separate protocol)

The Charter for the DMC:

The purpose of this document is to describe the roles and responsibilities of the independent DMC for ECSSIT, including the timing of the meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.

2. Roles and Responsibilities

Aims:

"To protect and serve ECSSIT – Elective Caesarean Section Syntocinon Infusion Trial patients and to assist and advise the Principal Investigator so as to protect the validity and credibility of the trial."

Terms of Reference:

The DMC is an independent group of experts that advises the ECSSIT Trial Steering Committee. The DMC will receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The DMC will not make decisions about the trial, but rather will make recommendations to the Chair of the Trial Steering Committee.

Specific roles of DMC

The DMC will review updated figures on recruitment, baseline data, retention, adverse events and compliance. The DMC will not undertake any formal interim analyses for either safety or effectiveness and therefore there are not formal stopping rules. There is no evidence of adverse reactions associated with oxytocin infusion. Although adverse reactions have been shown to be associated with oxytocin 5 IU bolus, all trial participants will receive this bolus, and thus we do not anticipate any differences in rates of adverse events between the groups. However all adverse events will be reported to the DMC. Additionally, in the event of a postpartum haemorrhage, clinicians are permitted to discontinue the trial infusion and commence a known 40 IU oxytocin infusion.

- Assess data quality, including completeness (and by so doing encourage collection of high quality data)
- Monitor recruitment figures and losses to follow-up

- Monitor compliance with the protocol by participants and investigators
- Suggest additional data analyses
- Advise on protocol modifications
- Assess emerging evidence from other studies (to be included in report prepared for DMC)

3. Composition

The members of the DMC for this trial are:

1. Dr. Andrew Weeks (Chair of the DMC, Senior Lecturer in Obstetrics & Consultant Obstetrician, Liverpool Women's Hospital & University of Liverpool)
2. Dr. Louise Kenny (Senior Lecturer and Consultant Obstetrician and Gynaecologist, University College Cork & Cork University Maternity Hospital)
3. Dr. Ed Juszczak (Head of Trials, NPEU Clinical Trials Unit and University Research Lecturer, NPEU, Oxford)

The Trial Co-ordinator and Trial Statistician will prepare a comprehensive report for circulation to DMC members in advance of DMC meetings. This report will contain information on trial accrual rates, baseline data, data describing compliance with the intervention and outcome data (blinded to allocation group). The Principal Investigator, Trial Statistician or Trial Co-ordinator may be invited by the DMC Chair to attend part of the DMC meetings to present the data. If this is the case, the Principal Investigator, Trial Statistician or Trial Co-ordinator will withdraw from the meeting after presentation of the data.

4. Trial Steering Committee

Principal Investigator:

Deirdre J. Murphy, Professor of Obstetrics & Gynaecology (Trinity College Dublin and Coombe Women and Infants University Hospital)

Co-applicants:

Michael Carey, Director of Perioperative Medicine (Coombe Women and Infants University Hospital)

Alan A. Montgomery, Senior Lecturer in Primary Care Research (University of Bristol)

Trial Steering Committee Members:

Maeve Eogan, Consultant Obstetrician & Gynaecologist (Rotunda Hospital)

Ronan Gleeson, Senior Lecturer in Obstetrics & Gynaecology (Trinity College Dublin & Rotunda Hospital)

Fionnuala McAuliffe, Associate Professor of Obstetrics & Gynaecology (University College Dublin & National Maternity Hospital)

Trial Co-ordinator:

Sharon Sheehan, Research Fellow in Obstetrics (Trinity College Dublin & Coombe Women and Infants University Hospital)

Research Midwives:

Michelle D'Arcy (Rotunda Hospital)

Clare Dunney (Coombe Women and Infants University Hospital)

Hilary Gilligan (Coombe Women and Infants University Hospital & National Maternity Hospital)

Ruth O'Connor (Mount Carmel Hospital)

Eleanor Woods (National Maternity Hospital)

5. Organisation of DMC meetings

The DMC will meet twice during the trial, at yearly intervals. Meetings will be organised by the Trial Co-ordinator in consultation with the DMC members.

The meetings will be by teleconference. Teleconferencing facilities will be provided by the Trial Co-ordinator.

6. Trial documentation and confidentiality

All materials, discussions and proceedings of the DMC are completely confidential. Members and other participants in DMC meetings are expected to maintain confidentiality.

Accumulating information relating to recruitment and data quality will be presented. Side effect profiles will be presented and total numbers of events for the primary outcome measures and secondary outcome measures will be presented.

The DMC will remain blinded.

7. Decision making

Possible recommendations include:

- No action needed, trial continues as planned
- Sanctioning and/or proposing protocol changes
- Extending recruitment

There are no stopping rules. There are no planned interim analyses. (See Section 2)

8. Reporting

This should take the form of a letter to the Trial Steering Committee within 2 weeks of the meeting.

Minutes of the meeting should be made and kept by the Chair. The Chair will also sign off any minutes or notes.

If there is disagreement between the DMC and the Trial Steering Committee, a further committee may be convened to adjudicate.

9. After the trial

At the end of the trial there will be a meeting to allow the DMC to discuss the final data with the principal investigator and give advice about data interpretation. The DMC may wish to see a statement that the trial results will be published in a correct and timely manner.

DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings will be included in the body of this paper.

10. References

The following document was used in developing this charter:

Damocles Study Group, NHS Health Technology Assessment Programme. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005 Feb 19-25;365(9460):711-22.

Appendix 1. Competing Interest Form

Potential competing interests of Data Monitoring Committee members for ECSSIT – Elective Caesarean Section Syntocinon Infusion Trial

Table 1. Potential Competing Interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by the trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict, egg. Strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial products
- Investment (financial or intellectual) in competing products
- Involvement in this publication

Please complete the following section and return to the trial's office

□ No, I have no competing interests to declare

□ Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____
_____
_____

Name: _____

Signed: _____

Date: _____

Appendix 2. Illustrative report from DMC to TSC where recommendation is to continue the trial according to the protocol

[*Insert date*]

To: Chair of the Trial Steering Committee

Dear [*Chair of the Trial Steering Committee*]

The Data Monitoring Committee (DMC) for ECSSIT – Elective Caesarean Section Syntocinon Infusion Trial met on [*meeting date*] to review its progress and interim accumulating data. [*List members*] attended the meeting and reviewed the report.

The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol [*specify protocol version number and date*] with no changes.

We shall next review the progress and data [*provide approximate timing*].

Yours sincerely,

[*Name of meeting Chair*]

Chair of the Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:

1) Andrew Weeks
2) Louise Kenny
3) Ed Juszczak

Appendix 19: Published Protocol for ECSSIT RCT

BMC Pregnancy and Childbirth

BioMed Central

Study protocol

Open Access

Study Protocol. ECSSIT – Elective Caesarean Section Syntocinon® Infusion Trial. A multi-centre randomised controlled trial of oxytocin (Syntocinon®) 5 IU bolus and placebo infusion versus oxytocin 5 IU bolus and 40 IU infusion for the control of blood loss at elective caesarean section

Deirdre J Murphy[1], Michael Carey[2], Alan A Montgomery[3], Sharon R Sheehan*[4] and The ECSSIT Study Group[1,2,3,4]

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Abstract

Background: Caesarean section is one of the most commonly performed major operations in women throughout the world. Rates are escalating, with studies from the United States of America, the United Kingdom, China and the Republic of Ireland reporting rates between 20% and 25%. Operative morbidity includes haemorrhage, anaemia, blood transfusion and in severe cases, maternal death.

The value of routine oxytocics in the third stage of vaginal birth has been well established and it has been assumed that these benefits apply to caesarean delivery as well. A slow bolus dose of oxytocin is recommended following delivery of the baby at caesarean section. Some clinicians use an additional infusion of oxytocin for a further period following the procedure. Intravenous oxytocin has a very short half-life (4–10 minutes) therefore the potential advantage of an oxytocin infusion is that it maintains uterine contractility throughout the surgical procedure and immediate postpartum period, when most primary haemorrhages occur. The few trials to date addressing the optimal approach to preventing haemorrhage at caesarean section have been under-powered to evaluate clinically important outcomes. There has been no trial to date comparing the use of an intravenous slow bolus of oxytocin versus an oxytocin bolus and infusion.

Methods and design: A multi-centre randomised controlled trial is proposed. The study will take place in five large maternity units in Ireland with collaboration between academics and clinicians in the disciplines of obstetrics and anaesthetics. It will involve 2000 women undergoing elective

caesarean section after 36 weeks gestation. The main outcome measure will be major haemorrhage (blood loss >1000 ml). A study involving 2000 women will have 80% power to detect a 36% relative change in the risk of major haemorrhage with two-sided 5% alpha.

Discussion: It is both important and timely that we evaluate the optimal approach to the management of the third stage at elective caesarean section. Safe operative delivery is now a priority and a reality for many pregnant women. Obstetricians, obstetric anaesthetists, midwives and pregnant women need high quality evidence on which to base management approaches. The overall aim is to reduce maternal haemorrhagic morbidity and its attendant risks at elective caesarean section.

Trial registration: number: ISRCTN17813715

Background

Systematic review of literature

Caesarean section is one of the most commonly performed major operations in women throughout the world. Rates are escalating, with studies from the developed world reporting rates between 20% and 25%. [1-3] Rates vary considerably between centres within Ireland. [4]There are many possible approaches to performing a caesarean section, the aim being to achieve safe delivery of the infant with a minimum of maternal morbidity. Operative morbidity includes haemorrhage, anaemia, blood transfusion and the risks associated with receiving donor blood products. In severe cases it may result in hysterectomy, admission to an intensive care unit or death.

The active management of the third stage at caesarean section has received little attention to date. The value of routine oxytocics in the third stage of vaginal birth has been well established [5] and it has been assumed that these benefits apply to caesarean delivery as well. [6,7] The Royal College of Obstetricians and Gynaecologists (RCOG) Guideline on caesarean section recommends a slow intravenous bolus dose of 5 IU of oxytocin following delivery of the infant. [8] This is a lower dose than used previously by many obstetric anaesthetists (10–20 IU) [9] and is based on concerns about side effects such as maternal hypotension. [10] Conversely, a conservative approach to the use of oxytocin may increase the risk of haemorrhage.

Intravenous oxytocin has a very short half-life (4–10 minutes) therefore the potential advantage of an oxytocin infusion at caesarean section is that it maintains uterine contractility throughout the surgical procedure and immediate postpartum period, when most primary haemorrhages occur. Several randomised controlled trials have compared intravenous oxytocin with oral misoprostol, 15-methyl prostaglandin F2 alpha and carbetocin, reporting little evidence of benefit with the newer agents. [6,11-13] There has been no trial to date comparing the simpler approach of an intravenous slow bolus of oxytocin versus an oxytocin bolus and infusion. Both approaches are employed within current obstetric practice but there is great variation in the approach of individual clinicians and institution. There is very limited evidence to guide practice.

A search of Medline and Embase from 1965 to 2006 and of the Cochrane Library was undertaken, for relevant systematic reviews, meta-analyses, randomised controlled trials, and other clinical trials. The date of the last search was September 2006. We intend to update this as part of a Cochrane Systematic Review, but at the time of planning and starting the trial, there were no key changes since the search of September 2006. The main keywords used were: caesarean section, blood loss, haemorrhage, oxytocin, uterotonic agent, embolic agent, randomised controlled trial. In addition, when reviewing published reference lists, key articles cited were also retrieved and reviewed. The review of the literature has been divided into use of oxytocin at varying doses and comparative use of alternative uterotonic agents.

The literature relating to the use of oxytocin bolus doses at caesarean section is presented in Table 1. The current recommendation is to use a slow bolus of 5 IU intravenously after clamping of the cord. [8] Various approaches have been tested and it is possible that smaller doses (0.3 – 5 IU) may be sufficient for elective caesarean section. [14] Nonetheless we plan to use a 5 IU bolus of oxytocin within the trial in keeping with current recommended practice. Various alternative uterotonic agents have been evaluated in randomised controlled trials. (Table 2) Most published trials to date have had between 30 and 50 participants and have been under-powered to detect important clinical outcomes such as major haemorrhage and anaemia. The largest trial of over 500 women used "need for an additional uterotonic agent" as the primary outcome measure.

We propose to compare the simpler approach of oxytocin bolus versus oxytocin bolus and infusion. This will

Table 1: Published studies evaluating doses of oxytocin (syntocinon)

Author, citation	Study design	Exposures	Outcome measures	Results	Conclusions
Sarna MC et al Anesth Analg 1997 84:753–6.	RCT 40 women Elective CS/regional	Oxytocin after cord clamping 5 IU vs 10 IU vs 15 IU vs 20 IU	Linear analogue of uterine tone EBL ΔHCT (pre-op/post-op)	No difference in any outcomes	No benefit in doses exceeding 5 IU
Zarzur Anesth Analg 1998 86:1334.	Dose-finding 20 women Elective CS	Oxytocin dosing	Uterine contractility Side effects	3 IU oxytocin Satisfactory No side effects	Low dose 3 IU sufficient
Carvalho JC et al Obstet Gynecol 2004 104:1005–10.	Dose-finding RCT single blind 40 women Elective CS/regional	Titrating increments of 0.5 IU oxytocin bolus Infusion 2.4 IU/hr	Minimum effective dose ED Uterine contraction EBL (calculated)	ED_{90} at 0.35 IU 100% at 1.0 IU	Low dose bolus < 5 IU effective
Balki M et al Obstet Gynecol 2006 107:45–50.	Dose-finding RCT single blind 30 women CS for labor arrest	Titrating increments of 0.5 IU oxytocin bolus Infusion 2.4 IU/hr	Minimum effective dose ED Uterine contraction EBL (calculated)	ED_{90} at 3.0 IU	Much higher dose than for elective CS Suggest alternative agent for non-elective

address the question whether an inexpensive and widely used drug can be employed in a more optimal way to prevent haemorrhage at caesarean section. We will be able to establish the number needed to treat to prevent one case of major haemorrhage with reasonable confidence limits.

The hypothesis is that an oxytocin infusion used in addition to an oxytocin bolus at elective caesarean section will reduce the risk of major haemorrhage and anaemia.

National survey of current practice

Prior to undertaking this study it is important to establish current practice and the support for such a trial. A questionnaire was developed, composed of a series of closed answer questions with additional space for free text comments. The questionnaire focussed on the clinicians' use of oxytocin at caesarean section, perceived frequency of side effects, estimated average blood loss, rates of haemorrhage and willingness to participate in a future clinical

Table 2: Published studies comparing oxytocin (syntocinon) with alternative uterotonic agents

Author, citation	Study design	Exposures	Outcome measures	Results	Conclusions
Catanzarite VA et al Am J Perinatol 1990;7:39–42.	RCT double blind 46 women Elective CS	Oxytocin 20 IU iv bs $PGF_{2\alpha}$ 125 mcg im After placenta delivered	ΔHCT (EBL)	No difference in EBL	No benefit with carboprost
Chou MM et al Am J Obstet Gynecol 1994;171:1356–60.	RCT double blind 60 women Elective CS	Oxytocin 20 IU iv vs $PGF_{2\alpha}$ 125 mcg im	EBL ΔHCT, ΔHb Side effects (SE)	No significant differences	No benefit with carboprost
Boucher M et al J Perinatol 1998;18:202–7.	RCT double blind 57 women Elective CS	Oxytocin infusion 16 hr vs Carbetocin 100 mcg iv	EBL Side effects	Carbetocin as effective Lower EBL	Carbetocin as effective/ reliable
Dansereau J et al Am J Obstet Gynecol 1999;180:670–6.	RCT double blind 635 women Elective CS	Oxytocin infusion 8 hr vs Carbetocin 100 mcg iv	Need for additional uterotonic agent	Carbetocin more effective 10% vs 4.7%	Carbetocin more effective than infusion only
Acharya G et al Acta Obst Gyn Scand 2001;80:245–50.	RCT single blind 60 women Elective CS/regional	Oxytocin 10 IU iv vs Misoprostol 400 mcg po	EBL, HCT, Hb, Side effects	No difference No SE	Misoprostol as safe/ effective as 10 IU oxytocin
Lokugamage AU et al Aus NZ J Obst Gyne 2001;41:411–4.	RCT double blind 40 women Elective/Em CS	Oxytocin 10 IU iv vs Misoprostol 400 mcg po	EBL ΔHb Additional uterotonic	No difference	Misoprostol an alternative to 10 IU Need for large RCT

trial. The questionnaire was sent to the lead consultant obstetrician and lead obstetric anaesthetist in all consultant-led obstetric units in the United Kingdom. Analysis was performed using SPSS Version 13.0 for windows. The findings of this survey are reported in detail in the European Journal of Obstetrics & Gynaecology and Reproductive Biology. [15]

Of the 434 questionnaires sent, 365 clinicians replied (response rate 84%), with none indicating that the questionnaire was inapplicable to their practice. Among the responders, 49% were lead obstetric consultants and 51% were lead obstetric anaesthetists. The various approaches to the use of oxytocin at the time of caesarean section are presented in Table 3. A slow bolus of 5 IU oxytocin was the preferred approach of obstetricians and anaesthetists (153, 86% and 171, 92% respectively). Routine oxytocin infusions were used by 72 clinicians (20%), and selective infusions were used for particular clinical situations by 289 (80%). Most clinicians used either 30 IU (158, 43%) or 40 IU (192, 53%) infusions over 4 hours, with a total of 38 different regimens. The perceived risk of side effects with oxytocin was low, particularly for infusions. Estimated "average" blood loss varied (150–1500 ml) with 56 clinicians (17%) and 93 (28%) reporting a >20% risk of postpartum haemorrhage for elective and emergency caesarean sections, respectively.

This national survey of practice in the use of oxytocin for the prevention of blood loss at caesarean section found general consistency in the use of bolus oxytocin but a great deal of variation in the use of additional oxytocin infusions. The perceived risk of side effects with oxytocin was low, particularly for infusions. Obstetricians and anaesthetists reported a high rate of excess haemorrhage at caesarean section and more than half of the clinicians surveyed would participate in a randomised controlled trial comparing oxytocin bolus with bolus and infusion. There is wide variation in the approach to prevention of haemorrhage at caesarean section, reflecting a lack of robust evidence. This survey supports the need for further research into this important aspect of intrapartum care. The preferred approach was to use a 40 IU infusion of oxytocin in a solution of 0.9% saline in keeping with the recommendations of the Advanced Life Support in Obstetrics (ALSO) courses. This is the regimen we plan to use for the proposed trial.

The survey was carried out within the UK as the original plan (prior to relocation of the PI) was to conduct the study in Scotland. The practice of clinicians in Ireland is very similar to reported practice in the UK.

The hypothesis is that an oxytocin infusion used in addition to an oxytocin bolus at elective caesarean section will reduce the risk of major haemorrhage and anaemia.

Aims and objectives

The aim of this study is to compare the effects of an intravenous slow bolus of oxytocin (5 IU) and placebo infusion (500 ml 0.9% saline) with an intravenous slow bolus of oxytocin (5 IU) and oxytocin infusion (40 IU in 500 ml 0.9% saline over 4 hours) at elective caesarean section in a double blind randomised trial.

Specific objectives are as follows:

Primary outcomes

- to compare the incidence of major obstetric haemorrhage (≥ 1000 ml) following oxytocin bolus compared with oxytocin bolus and infusion

- to compare the need for an additional uterotonic agent between the two groups

Major obstetric haemorrhage will be defined by:

- measured blood loss as calculated from pre and post-operative haematocrit (see below)

Secondary outcomes

- to compare the estimated mean operative blood loss between the two groups (as measured by theatre staff)

- to compare early lochial loss following oxytocin bolus compared with oxytocin bolus and infusion

Table 3: Percentages refer to complete responses

	All n = 365 (%)	Obstetricians n = 179 (%)	Anaesthetists n = 186 (%)
Slow bolus 5 IU oxytocin	324 (89.5)	153 (86.4)	171 (92.4)
Slow bolus 10 IU oxytocin	44 (12.1)	28 (15.6)	16 (8.6)
Additional 5 IU bolus if clinically indicated	61 (17.0)	17 (9.5)	44 (23.5)
Routine use of oxytocin infusion	72 (19.8)	33 (18.4)	39 (21.1)
Selective use of oxytocin infusion	289 (79.8)	145 (81.0)	144 (78.7)
30 IU oxytocin infusion	158 (43.3)	83 (46.4)	76 (40.9)
40 IU oxytocin infusion	192 (53.3)	90 (50.8)	102 (55.0)

Approaches to the use of oxytocin at the time of caesarean section

- to compare the objective change in haemoglobin and haematocrit before and 48 hours after delivery between the two groups

- to compare the incidence of severe anaemia (Hb fall ≥ 20%) 48 hours after delivery between the two groups (or patient transfused).

- to compare the need for blood transfusion and/or blood products

- to compare the incidence of side effects (vomiting, hypotension)

- to compare the postnatal length of stay in theatre/recovery and in the hospital

Cost-effectiveness

- to compare the cost-effectiveness of an oxytocin bolus regimen versus oxytocin bolus and infusion (separate protocol).

Methods and design

Recruitment and allocation

Inclusion criteria

The study will be limited to healthy women at term (> 36 weeks) with singleton pregnancies who are booked for elective caesarean section.

Exclusion criteria

Women with placenta praevia, thrombocytopenia, coagulopathies, a previous major obstetric haemorrhage (≥ 1000 ml), known fibroids or receiving anti-coagulant therapy will be excluded as will women who do not understand English and women under the age of 18 years. Other patients may be excluded at the clinician's discretion if a major haemorrhage is anticipated.

Women will be recruited to the trial in the third trimester when initial arrangements are being made for a booked elective caesarean section. The antenatal clinic midwife or research midwife/fellow will approach eligible women and offer information about the study. Women return on the day of surgery and spend a number of hours on the day ward or antenatal ward prior to surgery. At that point the woman's interest in participation in the study will be confirmed, an opportunity to ask additional questions will be provided and informed written consent will be completed. Randomisation will be performed using an automated web-based randomisation system hosted by the Bristol Randomised Trials Collaboration, a UKCRN-registered trials unit. Allocation will be stratified by centre and previous caesarean section (no/yes), and blocked using random permuted blocks of varying size.

The active or placebo infusion will be prepared by the research fellow/midwife. This will be done in the pharmacy department, away from theatre and will be labelled as "Trial drug – Placebo or 40 IU oxytocin". This will ensure blinding of everyone except the research fellow who makes up the infusion, and they will have no role in the management of the patient. Having the research fellow blinded is not possible for two reasons. Firstly, it is not possible to pre-prepare the infusions due to a lack of knowledge of the stability of oxytocin. Secondly, it has not been possible to obtain identically matched placebo ampoules.

Intervention

Following written informed consent women will be randomised to receive either an intravenous slow bolus of oxytocin 5 IU and a placebo infusion (0.9% saline solution 500 ml over 4 hours), or oxytocin bolus 5 IU and oxytocin infusion (40 units in 500 ml 0.9% saline over 4 hours). Both the patient and the health care staff will be blinded to the intervention. The hospital pharmacist will produce numbered treatment kits containing either 1 × 5 IU ampoule or 1 × 5 IU ampoule and 4 × 10 IU ampoules. There will be labels and instructions for the research fellow to prepare the infusion so that the anaesthetist and other members of the investigator team remain blinded to the randomised treatment.

It is important that the surgical approach to caesarean section is standardised. Surgeons will be asked to operate to a standard procedure that specifies controlled cord traction for delivery of the placenta after administration of the oxytocin bolus, two layer closure of the uterine incision, and to avoid delivering the uterus for suturing unless clinically indicated. Deviations from the standard procedure will be recorded. Should the uterus remain atonic despite the trial intervention, the obstetrician/anaesthetist can use an additional uterotonic agent either replacing the trial infusion with a known infusion of oxytocin and/or use of a further agent.

Measurement of operative blood loss will be standardised. Disposable waterproof drapes are in use with pockets that capture all body fluids. The suction volume is measured. All swabs are weighed to measure additional blood loss. A more objective measure of blood loss will be calculated using pre- and post-operative haematocrit (see outcome measures below).

Anaesthesia will also be standardised. An intravenous bolus of 500 ml crystalloid should be given to all patients prior to spinal anaesthesia. A size 25G pencil-point needle should be used at a suitable lumbar interspace. The patient can be sitting or in the left lateral position for spi-

nal anaesthesia. The anaesthetic solution will consist of 2 ml 0.5% hypertonic bupivocaine (2.2 ml in the sitting position), 10–20 μg fentanyl and 0.1 mg preservative free morphine. Anaesthesia should be to the level of T5, as assessed by touch. The patient will be tilted 15° to the left of supine and standard monitoring used as per the AAGBI guidelines. The sphygmomanometer cuff should be placed on the left arm. Haemodynamic monitoring will be performed before spinal anaesthesia, every minute until 10 minutes after delivery, every 15 minutes during the first postoperative hour then every 30 minutes for 4 hours. For the purpose of this study, baseline haemodynamic variables will be regarded as those immediately after clamping of the cord and before administration of syntocinon 5 IU. The investigators accept that individual anaesthetists may deviate from this protocol according to clinical needs. This is acceptable and should be documented on the case report form.

Intraoperative hypotension will be treated with intravenous boluses of phenylephrine 50 μg. If the heart rate falls below 60/min, intravenous boluses ephedrine 6 mg will be substituted. The anaesthetist will aim to maintain blood pressure at preoperative values. After delivery, the operating table tilt will be removed and the patient placed in the full supine position. Blood loss at operation will be replaced with colloid infusion or blood as deemed necessary by the anaesthetist. Postoperative pain relief will consist of regular non-steroidal analgesia combined with paracetamol. Opiates in the form of oxynorm can be used with caution considering the use of intrathecal opiates. Again it is acceptable for the local administrator to use any form of analgesia as per local practice and to document it on the case report form.

Outcome measures

The primary outcome measures are major obstetric haemorrhage (estimated blood loss ≥ 1000 ml) and use of an additional uterotonic agent. Estimated blood loss of ≥1000 ml has been chosen to reflect major obstetric haemorrhage and it is widely accepted that clinicians underestimate rather than overestimate blood loss. This estimate will be based on the difference between pre-operative and post-operative haematocrit (EBL_{calc} – Calculated estimated blood loss). [14]

The estimate is calculated as follows:

$$EBL_{calc} = EBV \times \frac{(\text{Pre-op Hct} - \text{Post-op Hct})}{\text{Pre-op Hct}}$$

Where EBV estimated blood volume = Booking weight in kg × 85

Secondary outcomes include mean estimated blood loss (as measured by theatre staff), change in haemoglobin and haematocrit, significant anaemia (Hb fall = 20%) 48 hours after delivery, need for blood transfusion, side effects (including vomiting and hypotension) and length of postnatal stay in theatre/recovery and in hospital. Hypotension will be defined as a fall in blood pressure of more than 30% below the pre-operative blood pressure and/or use of ephedrine.

Follow-up

A routine full blood count will be performed 48 hours after delivery to assess haemoglobin and haematocrit. Clinical follow-up of the mother will be completed prior to hospital discharge.

Trial end

The trial will be considered complete after the final review of the last trial participant. The end of the trial will be notified to the Competent Authority and the Ethics Committee using the appropriate form.

Statistical analysis

Data analysis and reporting will proceed according to CONSORT guidelines for randomised controlled trials, and will be conducted blinded to group status by the trial statistician and researcher. The first stage of analysis will be to use descriptive statistics to describe recruited individuals in relation to those eligible, and to investigate comparability of the trial arms at baseline. The primary analyses will involve intention-to-treat comparisons between the two groups for the primary outcomes, with transformation as appropriate after examination of distributions, and adjusted for stratification variables. Secondary analyses will investigate the effects of further adjustment for any variables displaying marked imbalance between the arms at baseline. Secondary outcomes will be analysed in a similar way. All analyses will use appropriate (that is, logistic or linear) regression models, with results presented as point estimates (odds ratios or difference in means), 95% confidence intervals and p values. Further secondary analyses will involve planned subgroup analyses and will use multivariable regression models with appropriate interaction terms to ascertain any differential effects in relation to repeat caesarean section, choice of anaesthetic, and operator experience.

Pilot study results

We have completed an initial pilot study that has informed the study design allowing an estimate of appropriate sample size and likely recruitment, alongside an evaluation of outcome measures. The results of this study have been published by the European Journal of Obstetrics & Gynaecology and Reproductive Biology. [16] The pilot study represented a single centre randomised controlled trial of oxytocin 5 IU and placebo infusion versus oxytocin 5 IU bolus and oxytocin 30 IU infusion. We chose a 30 IU infusion as this was the approach recom-

mended in the NICE Guideline on induction of labour. We have changed the study design to a 40 IU infusion reflecting preferred practice within the national survey and the recommendation of emergency obstetrics training courses (ALSO). The pilot results therefore reflect a slightly lower oxytocin concentration than is planned for the multi-centre study.

Feasibility

The pilot study was conducted over an eight month period in a unit with 3400 deliveries a year. We received approval from the Edinburgh multi-centre research ethics committee (MREC) and approval of the UK MHRA in keeping with the requirements of the EU directive on Clinical Trials. The obstetricians, anaesthetists, midwives, theatre staff and hospital pharmacist were very supportive. We received a high level of support from women undergoing caesarean section, the majority of who were happy to participate in the trial. There were no serious unexpected adverse events. The recruitment is summarised in the Consort flow chart. (Figure 1)

Sample size

We estimate from the pilot study that 5–10% of study participants will have an estimated blood loss of > 1000 ml. The rate is around 15% for the calculated estimate (EBL_{calc}) and this is more likely to be an accurate reflection of actual blood loss. We found relative reductions of between 20–50% in the outcome measures on comparing infusion and placebo in the pilot study, but with wide 95% confidence intervals around these estimates. It is also possible that a pilot study will over or under estimate differences and we have therefore chosen conservative effect estimates for this multi-centre study.

With 1000 patients per group for analysis, the study will have 80% power at the 5% two-sided alpha level, to detect differences in the proportion of patients with clinician estimated blood loss >1000 ml of 15% vs. 10.7%, or 10% vs. 6.4%, equivalent to odds ratios of 0.62 and 0.68 respectively.

For the co-primary outcome of calculated blood loss, and estimated incidence in the control group of 14%, n = 1000 per group has 80% power to detect a difference 4.2%, equivalent to odds ratio of 0.67.

Based on the hospital statistics in the Dublin Maternity units for 2004 we estimate that there will be approximately 2500 elective caesarean sections at term each year between the five centres. Over the course of 30 months we would aim to recruit 2112 patients representing almost 34% of the available population (2112/6250) – this conservative estimate takes account of eligibility criteria and non-English speaking women. The sample size is slightly inflated from 2000 to allow for missing outcome data (full blood count not taken at the correct time or blood loss not measured).

Timetable

Total 36 months: Commencing 01.09.07 – Estimated completion date 31.03.10

Month 0–2: Validate datasets; Raise study awareness; Finalise recruitment procedures

Month 3–33: Recruit participants and complete documentation and follow-up

Month 34–36: Analysis; Final report; Peer-review publications; Presentations.

Governance issues

Ethical Committee Permission

Full ethical approval has previously been received for an eight- month local pilot study designed to develop the trial documentation and to test early feasibility issues.

05/MRE10/20 Approval date 16.03.05 MREC for Scotland

Ethical committee approval (Clinical Trials approved Committee) from the Coombe Women's Hospital, the National Maternity Hospital and the Rotunda Hospital, and approval of the Irish Medicines Board have been granted for this study.

IMB Application date 12.03.07 Approval date 27.04.07

Clinical trials approved committee Approval date 29.11.07

Data management

Data will be collected in duplicate on a case report form (CRF) at the time of recruitment by a trained researcher. The researcher will also be responsible for ensuring that the details of the delivery are recorded and the blood loss measured. The inpatient notes will be marked so that they can easily be recovered following discharge from hospital. After discharge the CRF will be collected by the local co-ordinator and the completeness of the data checked against the woman's notes. Any errors will be followed up at this time. The data will be entered into a computer database (password protected) at the Coombe Women's Hospital.

Trial Management Group (TMG)

This group will be in charge of the everyday running of the trial. The full group will meet 4-monthly and as required. Day-to-day decision making will be by Prof Murphy, Dr Michael Carey and the trial researcher.

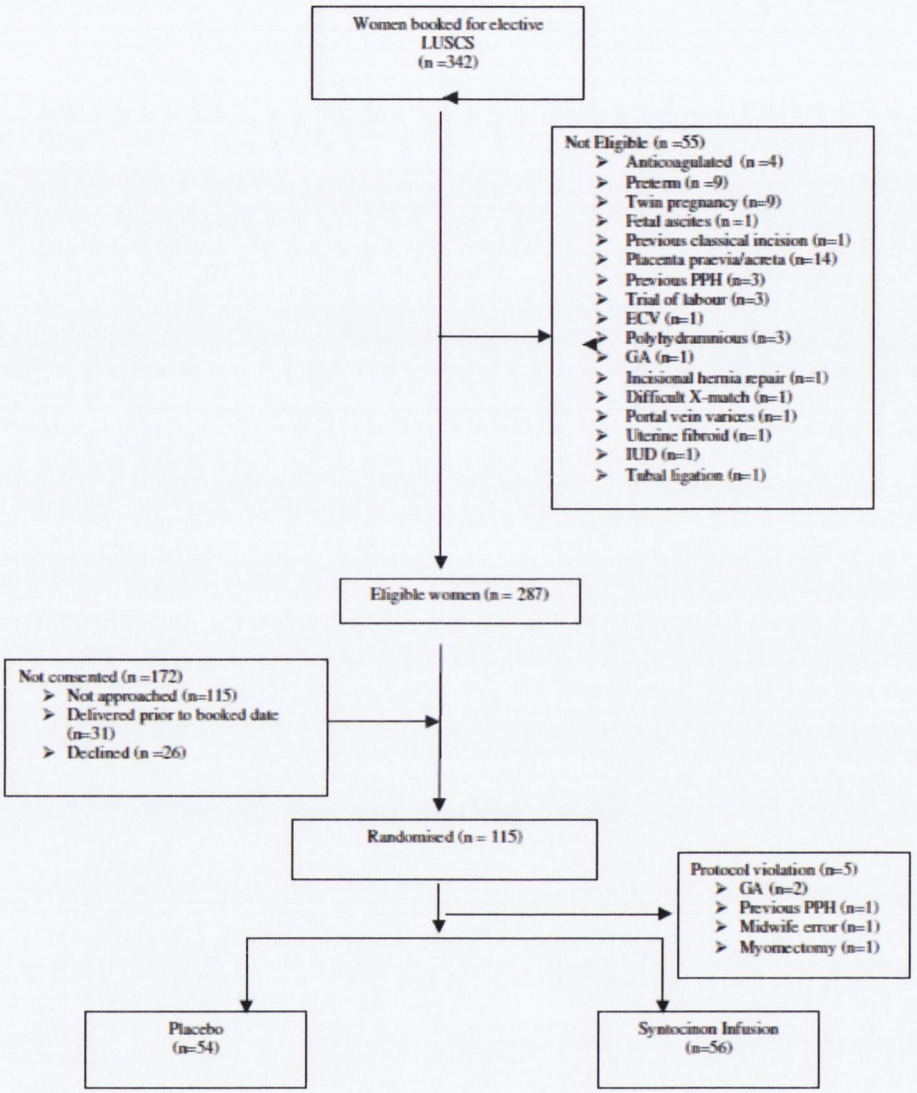

Figure 1
Oxytocin at Caesarean Section Pilot Study – CONSORT Flowchart.

Trial Steering Committee

A trial steering committee will be set up which will have overall supervision of the trial. It will meet prior to commencement of the trial and then at least 6 monthly until completion. A meeting of the TSC will be held within a month of every DMEC meeting to consider their recommendations. An independent Chair will be sought for the TSC.

Data monitoring and Ethics Committee (DMEC)

An independent safety and data monitoring committee will also be formed. They will meet yearly to examine recruitment figures, baseline data, retention and adverse events. The DMEC will not undertake any formal interim analyses for either safety or effectiveness and therefore there are no formal stopping rules. There is no evidence of adverse reactions associated with oxytocin infusion. Although adverse reactions have been shown to be associated with the 5 IU oxytocin bolus, all trial participants will receive a bolus, and thus we do not anticipate any differences in rates of adverse events between the groups. However all adverse events will be reported to the DMEC who will report these data to the Trial Steering Committee. Additionally, in the event of a postpartum haemorrhage, clinicians are permitted to discontinue the trial infusion and commence a known 40 IU oxytocin infusion.

Safety considerations

Serious or unexpected serious adverse reactions (SUSARs) will be recorded and reported using the IMB approved SUSAR form. SUSARs include maternal death, surgery (other than caesarean section) in the 2 weeks following randomisation, transfusion of over 4 units of blood, admission to intensive care unit or suspected drug reactions. In the event of a SUSAR the form will be completed by the local trial co-ordinator and faxed to the trial co-ordinating centre at the Coombe Women's Hospital within 72 hours. From there the copies of the form will be sent to the trial statistician for unblinding and the chair of the Data Monitoring and Ethics Committee (DMEC). The IMB, the trial sponsor and the Chair of the MREC will also be informed by the DMEC Chair if considered appropriate.

Discussion

Potential and Implementation of the findings

It is both important and timely that we evaluate the optimal approach to the management of the third stage at elective caesarean section. The caesarean section rate has risen dramatically over the last two decades and continues to rise. Safe operative delivery is now a priority and a reality for many pregnant women. Obstetricians, obstetric anaesthetists, midwives and pregnant women need high quality evidence on which to base management approaches. The use of oxytocin in this context is a poorly evaluated component of obstetric care. The overall aim is to reduce maternal haemorrhagic morbidity and its attendant risks at elective caesarean section. In addition we will develop a protocol establishing the economic implications and patient perspective of the two approaches.

Dissemination

We aim to raise awareness of this clinical question and our proposed research approach at both local and national meetings. A final report will be prepared for the funding body and papers will be prepared for peer-review publication and national/international dissemination.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DM, MC, AM and SS drafted the manuscript, with input from other members of the ECSSIT Study Group.

Acknowledgements

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The Elective Caesarean Section Syntocinon Infusion Trial (ECSSIT) Study Group comprises the following members:

Michael Carey, Ann Marie Connor, Michelle D'Arcy, Claire Dunney, Maeve Eogan, Michael Geary, Hilary Gilligan, Ronan Gleeson, Fionnuala McAuliffe, Alan Montgomery, Deirdre Murphy, Ruth O'Connor, Hassan Rajab, Sharon Sheehan, Bryony Strachan, Eleanor Woods.

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Appendix 20: The ECSSIT Poll

Elective Caesarean Section Syntocinon® Infusion Trial

Newsletter
Volume 1, Issue 1

May 2008

THE ECSSIT POLL

INSIDE THIS ISSUE:

What is ECSSIT?

When did it start?

Research Midwives

Appreciation

Continued support

Recruitment

HAVE YOU SEEN THIS SIGN?

What is ECSSIT?

It's a multi-centre randomised controlled trial comparing 2 different approaches to reduce blood loss at elective caesarean section.

It compares oxytocin bolus and oxytocin infusion with oxytocin bolus and placebo infusion.

When did it start?

The trial officially commenced in the 3 Dublin maternity hospitals on 12th February '08 :

Coombe Women and Infants University Hospital

National Maternity Hospital

Rotunda Hospital

Research Midwives

We'd like to welcome our 2 research midwives on board – Michelle D'Arcy and Hilary Gilligan. Both started in April and have been doing trojan work!

Appreciation

Many thanks to all who have been involved in the study thus far. The 3 pharmacy departments have played a huge role in facilitating the study. Theatre staff (nurses, midwives and anaesthetists) have been extremely helpful and without their help, the study wouldn't be possible.

Thanks also to the day ward staff who are plagued by the researchers – putting up with our loitering! The staff on the postnatal wards have been great and we really appreciate the day 2 FBCs!!

Continued Support

We need everyone's continued support to keep ECSSIT alive.

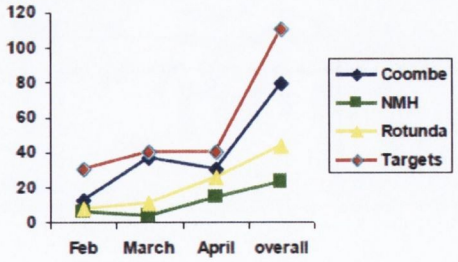
Target Participants:

1500

is the magic number!

(only 1355 to go!)

Recruitment – How are we doing?



If any queries about the trial, please contact one of the following:

Sharon Sheehan (Coombe)

Hilary Gilligan (Coombe & NMH)

Michelle D'Arcy (Rotunda)

Elective Caesarean Section Syntocinon® Infusion Trial

Newsletter
Volume 1, Issue 2

September 2008

THE ECSSIT POLL

INSIDE THIS ISSUE:

A reminder of ECSSIT

How are we calculating blood loss?

Coombe research symposium

Appreciation

Continued support

Recruitment

DOES THIS LOOK FAMILIAR?

A reminder of ECSSIT

It's a multi-centre randomised controlled trial comparing 2 different approaches to reduce blood loss at elective caesarean section.

It compares oxytocin bolus and oxytocin infusion with oxytocin bolus and placebo infusion.

How are we calculating blood loss?

Measured blood loss in theatre

(swab weight and total suction volume, including liquor)

AND

Pre- and post-op full blood count (FBC)

The post-op FBC is done **2 days** after surgery, ie. If the patient has her caesarean section on a Monday, then the FBC must be done on the Wednesday. For each patient who has the FBC done on the incorrect day, an additional patient will have to be recruited.

Coombe Research Symposium

On November 7th, a Research Symposium will be held at the Coombe Women and Infants University Hospital. The program will include a number of invited speakers and an opportunity for others to present their research. We're hoping to present some of the findings of the trial thus far.

All are welcome to attend.

Appreciation

An enormous thanks to all those who continue to make ECSSIT possible. In particular, we'd like to extend our gratitude to day ward staff for all their support, and to the pharmacy departments for their unending assistance. To all of the theatre staff—a huge thank-you for your tireless efforts in making ECSSIT run so smoothly. Many thanks also to all of the postnatal staff for their continued help with day 2 bloods.

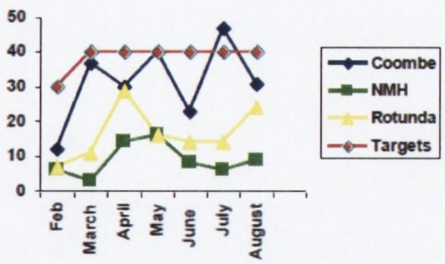
Continued Support

We need everyone's continued support to keep ECSSIT alive.

Recruitment to date:

397 participants!

Recruitment – How are we doing?



Local contacts:

If you have any queries, please contact our research staff in each centre:

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Elective Caesarean Section Syntocinon® Infusion Trial

THE ECSSIT POLL

ECSSIT

Newsletter
Volume 1, Issue 3
December 2008

INSIDE THIS ISSUE:

A reminder of ECSSIT
How are we calculating blood loss?
New centres
Appreciation
2009
Recruitment

MERRY CHRISTMAS

A reminder of ECSSIT

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It compares oxytocin bolus and oxytocin infusion with oxytocin bolus and placebo infusion.

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AND

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The post-op FBC is done 2 **days** after surgery, ie. If the patient has her caesarean section on a Monday, then the FBC must be done on the Wednesday. For each patient who has the FBC done on the incorrect day, an additional patient will have to be recruited.

New centres

We're delighted to announce that **Our Lady of Lourdes Hospital, Drogheda** and **Mount Carmel Hospital, Dublin**, will be joining us as recruitment centres from early January.

Appreciation

An enormous thanks to all those who continue to make ECSSIT possible. In particular, we'd like to extend our gratitude to day ward staff for all their support, and to the pharmacy departments for their unending assistance. To all of the theatre staff--a huge thank-you for your tireless efforts in making ECSSIT run so smoothly. Many thanks also to all of the postnatal staff for their continued help with day 2 bloods.

2009

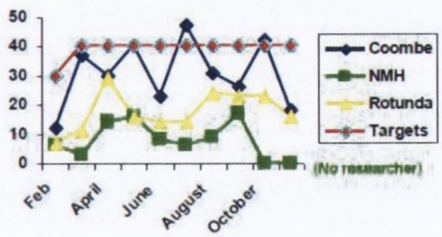
2009 promises to be a very exciting year. If you would like to get involved with the trial, please contact one of our researchers below.

Finally, we want to wish you all a very Merry Christmas and a Happy New Year.

Recruitment to date:

600 participants!

Recruitment – How are we doing?



Local contacts:

If you have any queries, please contact our research staff in each centre:

Sharon Sheehan (All centres)
sharon.sheehan@tcd.ie

Michelle D'Arcy (Rotunda)
ecssit@rotunda.ie

Professor Deirdre Murphy
Principal Investigator

Elective Caesarean Section Syntocinon® Infusion Trial

THE ECSSIT POLL

ECSSIT

Newsletter
Volume 2, Issue 1

Summer 2009

INSIDE THIS ISSUE:

A reminder of ECSSIT

How are we calculating blood loss?

New centre

New research midwives

Appreciation

Contact details

Interesting findings so far...

Recruitment to date:

880 participants!

Target end date:

Summer 2010

ONE YEAR ON...

A reminder of ECSSIT

It's a multi-centre randomised controlled trial comparing 2 different approaches to reduce blood loss at elective caesarean section.

It compares oxytocin bolus and oxytocin infusion with oxytocin bolus and placebo infusion.

How are we calculating blood loss?

Measured blood loss in theatre

(swab weight and total suction volume, including liquor)

AND

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The post-op FBC is done **2 days** after surgery, ie. If the patient has her caesarean section on a Monday, then the FBC must be done on the Wednesday. For each patient who has the FBC done on the incorrect day, an additional patient will have to be recruited.

New centre

Mount Carmel Hospital joined as a recruitment centre in March this year, much to our pleasure. We would like to thank all the staff who have embraced the trial there, in particular Dr. Valerie Donnelly and Ms. Dolores Tempany for their continued support.

New research midwives

We're delighted to welcome 3 new research midwives to the study– Clare Dunney (CWIUH), Ruth O'Connor (MCH) and Eleanor Woods (NMH). Since starting, all 3 are rapidly adding to the recruitment. Michelle D'Arcy, who has been with the trial since the beginning, continues her trojan work in the Rotunda.

Appreciation

An enormous thanks to all those who continue to make ECSSIT possible. In particular, we'd like to extend our gratitude to all the staff who look after the patients on the day of their surgery, day ward staff, labour ward staff and antenatal staff. To the pharmacy departments, thanks for your unending assistance. To all of the theatre staff–a huge thank-you for your tireless efforts in making ECSSIT run so smoothly. Many thanks also to all of the postnatal staff for their continued help with day 2 bloods.

Contact details:

If you have any queries, please contact our researchers in each centre:

Principal investigator:	Professor Deirdre Murphy
Trial Co-ordinator:	Sharon Sheehan (Speed dial 4565)
CWIUH:	Clare Dunney (Speed dial 4779)
MCH:	Ruth O'Connor (Bleep 797)
NMH:	Eleanor Woods (Bleep 203)
Rotunda:	Michelle D'Arcy (Bleep 409)

Interesting findings so far....

High rates of blood loss and anaemia are the most striking and concerning findings.

Major obstetric haemorrhage (calculated on pre- and post-op haematocrit)	15%
Pre-op anaemia	16%
Post-op anaemia	51%