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A study comparing three medicines used for the active management of the third stage of labour (to help deliver the placenta after your baby has been born)

Submission date
19/02/2018

Recruitment status
No longer recruiting

Registration date
06/03/2018

Overall study status
Completed

Last Edited
28/05/2020

Condition category
Pregnancy and Childbirth

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Excessive bleeding after giving birth is a major complication of pregnancy globally. Bleeding after delivery is known as postpartum haemorrhage (PPH). PPH can result from a failure of the uterus (womb) to contract properly following birth. In the UK PPH occurs in 10% of births and additional treatments are needed to control the bleeding. This can include surgical removal of the womb, blood transfusion and prolonged hospital stay. Research has shown that women who experience PPH are less likely to want another child and 60% of those who have another pregnancy experience anxiety.
The current method of preventing PPH involves using a uterotonic drug to help the womb contract following delivery. The use of a uterotonic drug along with cutting of the umbilical cord and delivery of the placenta by controlled traction of the cord is known as Active Management of the Third Stage of Labour (AMTSL). AMTSL reduces the risk of PPH by 66%. Two thirds of pregnant women who experience PPH have no risk factors, so AMTSL is currently offered to all pregnant women. In the UK Syntometrine and Syntocinon are the two most commonly uterotonic drugs used in AMTSL. Both of these drugs mimic the natural hormone in the body that causes the uterus to contract. Syntometrine contains ergometrine which makes its affects last longer. However, this medication is associated with nausea, vomiting, and high blood pressure, and in some rare cases it has been linked to stroke which has been fatal. Syntometrine is known to be better at preventing moderate blood loss but not severe blood loss. Currently international guidelines recommend Syntocinon as the medicine of choice for AMTSL. At Southmead Hospital in Bristol a telephone survey of all consultant-lead maternity units in the UK was conducted to find out whether the guidelines for AMTSL were being followed. It was found that 71.4% of consultant-lead units still use Syntometrine as their first choice of uterotonic instead of Syntocinon as recommended. Many units reported that they had changed to Syntocinon following the publication of the guidelines but changed back to Syntometrine as they were concerned that their PPH rates had increased with Syntocinon. There is therefore a concern that women are being given a medicine (Syntometrine) that can cause potentially dangerous high blood pressure, and is contrary to national recommendations. A newer

uterotonic called Carbetocin is offered for management of the third stage of labour after birth by caesarean section. This medication is not licenced for use in vaginal births. Studies have shown that Carbetocin is more effective at preventing bleeding following birth than Syntometrine. It also has fewer side effects than Syntometrine. Studies comparing Carbetocin and Syntocinon have shown that there is no significant difference in the risk of women bleeding heavily. Furthermore, Carbetocin reduces the need to have additional medication to aid the contraction of the womb. To date there have been no studies directly comparing Syntometrine, Syntocinon and Carbetocin for management of AMTSL in vaginal births. The aim of this study is to compare the effectiveness, side effects and cost of Syntocinon, Syntometrine and Carbetocin in AMTSL in vaginal births.

Who can participate?
Women aged 18 and over with a single pregnancy who are planning to have a vaginal birth

What does the study involve?
Participants are randomly allocated to receive a single dose of either Syntocinon, Syntometrine or Carbetocin, given as an injection into the leg muscle after the vaginal birth of their baby and after the cord has been clamped. All participants are followed up until day 14 after giving birth. The proportion of women requiring additional uterotonic drugs to treat or prevent PPH is measured, along with incidence of PPH, blood transfusion, side effects, health-related quality of life, and cost.

What are the possible benefits and risks of participating?
Carbetocin may cause less nausea, vomiting and high blood pressure than Syntometrine, and Syntocinon causes less of these side effects than Syntometrine. Women who are allocated to either Carbetocin or Syntocinon may have a better overall birth experience because having fewer side effects may allow them to bond with their baby during the first few hours after birth. Not all participants will benefit from taking part in the study but their participation might be helpful to the NHS and to women giving birth in the future. All three drugs are currently used in routine care therefore no serious side effects are expected.

Where is the study run from?
1. Southmead Hospital, North Bristol NHS Trust (UK)
2. St Michael's Hospital, University Hospitals NHS Foundation Trust (UK)
3. Royal United Hospital Bath NHS Trust (UK)
4. Gloucestershire Hospitals NHS Foundation Trust (UK)
5. Nottingham University Hospitals NHS Trust of City Hospital (UK)
6. The Great Western Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
February 2014 to August 2019

Who is funding the study?
Ferring Pharmaceuticals

Who is the main contact?
Michelle Mayer

Contact information

Type(s)

Scientific

Contact name
Ms Michelle Mayer

Contact details
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Additional identifiers

ClinicalTrials.gov (NCT)
NCT02216383

Clinical Trials Information System (CTIS)
2014-001948-37

Protocol serial number
17677

Study information

Scientific Title
Intramuscular oxytocics: a multi-centre randomised comparison study of intramuscular carbetocin, syntocinon and syntometrine for the third stage of labour following vaginal birth

Acronym
IMox

Study objectives
A quarter of all global pregnancy-related deaths occur due to excessive bleeding after childbirth, or “post partum haemorrhage” (PPH). Active Management of the Third Stage of Labour (AMTSL) after vaginal birth, which includes use of a preventative uterotonic drug, reduces the risk of PPH by 66%.

Syntometrine is most commonly used for this purpose in the UK. Syntocinon is the drug which national guidelines recommend first-line. This is because Syntocinon is less likely to cause nausea , vomiting and transient high blood pressure, and is just as effective as Syntometrine at preventing PPH >1000ml. However, Syntometrine is more effective at preventing PPH of 500-1000ml. This is why maternity units still choose to use it, despite the nausea and vomiting experienced by ~25% of patients.

Carbetocin, a newer uterotonic drug already used during caesarean section, is more expensive but potentially more effective. Previous studies suggest that patients receiving Carbetocin may

need fewer additional drugs to treat and prevent PPH than those receiving Syntocinon. Compared with Syntometrine, patients receiving Carbetocin lose less blood and experience fewer side effects. No studies have directly compared these three drugs.

The aim of the study is to compare carbetocin, syntometrine and syntocinon when administered intramuscularly after vaginal birth to prevent primary postpartum haemorrhage, in order to directly compare the:
1. Clinical effectiveness of each drug
2. Maternal side effects experienced with the use of each drug
3. Overall cost of each intervention

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee South Central - Oxford B, 28/10/2014, ref: 14/SC/1312

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Reproductive health and childbirth, Primary sub-specialty: Reproductive and Sexual Medicine; UKCRC code/ Disease: Reproductive Health and Childbirth/ Complications of labour and delivery

Interventions
Patients are randomised to receive Carbetocin, Syntometrine or Syntocinon during the third stage of labour. The intervention is a single dose of intramuscular injection of the randomly allocated study drug (10iU Syntocinon, 500µg/5iU Syntometrine or 100µg Carbetocin) given after vaginal birth of the baby, once the cord has been clamped. Study participants are followed up until day 14 postnatal. Standard intrapartum care will be adopted leading up to, and after, this single-dosed intervention. The primary outcome measure will be the proportion of women requiring additional uterotonic drugs to treat or prevent PPH. Secondary outcomes will include incidence of PPH, blood transfusion, maternal side effects, health-related quality of life, and cost.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Carbetocin, Syntometrine, Syntocinon

Primary outcome(s)

Requirement for additional uterotonic drugs. This is defined as the administration, following the administration of Imox IMP and prior to discharge from Delivery Suite (and not more than 24 hours after delivery), of any of the following: Syntocinon (IM/IV), Syntometrine (IM), Carboprost (IM), Carbetocin (IM/IV), Misoprostol (PO/PV/PR). This information is taken from the participant' s medical notes or the maternal database where the information is recorded routinely.

Key secondary outcome(s)

Current secondary outcome measures as of 27/06/2018:
Secondary clinical outcomes
1. Number and type of additional uterotonic drugs required within 24 hours of delivery
2. Estimated weighed blood loss following delivery until 24 hours after delivery
3. Transfusion of blood products (type and number of units given)
4. Volume of own blood returned to participant (if cell salvage used)
5. Use of prophylactic oxytocin infusion to reduce the risk of haemorrhage before a diagnosis of PPH was made
6. Manual removal of placenta in theatre
7. Requirement for surgical intervention to manage PPH (examination under anaesthetic in theatre/intrauterine balloon tamponade/uterine compression sutures/hysterectomy)
8. Maternal hypertension in first two postnatal hours following administration of study drug, defined as either:
8.1. Postpartum systolic BP >140 mmHg on any occasion in first two postnatal hours
8.2. Postpartum diastolic BP >90 mmHg on any occasion in first two postnatal hours
9. Maternal hypotension (BP <90/60) in first two postnatal hours
10. Maternally-reported health-related quality of life, measured using EQ-5D-5L questionnaire at day 1 and day 14 postpartum

Patient reported secondary outcomes:
1. Abdominal pain in the first two postnatal hours, recorded in Case Report Form (CRF) by midwife
2. Postpartum vomiting in first two postnatal hours
3. Need for antiemetic in first two postnatal hours
4. Headache in the first two postnatal hours, recorded in CRF by midwife

Previous secondary outcome measures:
1. Blood transfusion requirement is measured as the need to have a blood transfusion (including number of units given) following delivery (within 24 hours), at day 1 postnatal and at any point from day 1 to day 14 postnatal
2. Volume of own blood returned to participant (if Cell Salvage used) (ml). Method is this a yes or no documented in the notes. If yes, volume returned within 24 hours of birth
3. Requirement for any other blood products including fresh frozen plasma, cryoprecipitate, Factor VII (number of units of each given) Method is this a yes or no documented in the notes. If yes, number of units within 24 hours of birth
4. Estimated blood loss at delivery (including estimated total blood loss (ml or L) until transfer from Delivery Suite i.e. if there is excessively heavy lochia within 24 hours of birth (ml)
5. Use of prophylactic Syntocinon infusion to reduce the risk of hemorrhage before a diagnosis of PPH; was prophylactic Syntocinon infusion given immediately after birth, yes or no
6. Whether or not a Syntocinon infusion was used to either augment or induce labour. Was Syntocinon infusion given during labour? Yes or no
7. Whether terbutaline 0.25 mg was given subcutaneously to reduce uterine hypercontractility during the 2nd stage of labour. Yes or no

8. Duration of third stage of labour (mins)
9. Need for manual removal of placenta in theatre – yes or no, within 24 hours following birth
10. Need for examination under anaesthetic in theatre - yes or no, within 24 hours following birth
11. Use of interuterine balloon tamponade/uterine compression sutures/hysterectomy to control PPH, yes or no, within 24 hours following birth
12. Maternal hypertension in first two postnatal hours, following administration of study drug. Blood pressure readings taken at 1 hour and 2 hours following drug administration
13. Postpartum systolic BP >140 mmHg on any occasion in first two postnatal hours (and maximum systolic BP in first two postnatal hours). Blood pressure readings taken at 1 hour and 2 hours following drug administration
14. Postpartum diastolic BP >90 mmHg on any occasion in first two postnatal hours (and maximum diastolic BP in first two postnatal hours). Blood pressure readings taken at 1 hour and 2 hours following drug administration
15. Maternal hypotension (BP <90/60) in first two postnatal hours. Blood pressure readings taken at 1 hour and 2 hours following drug administration
16. Intrapartum vomiting – yes or no for vomiting during labour
17. Post-partum vomiting in first two postnatal hours - yes or no for vomiting during two hours postnatal
18. Need for antiemetics in first two postnatal hours - yes or no for for antimetics given during two hours postnatal
19. Time from delivery to discharge from Delivery Suite (either to postnatal ward or home) (mins)
20. Time spent in recovery (mins)
21. Maternal side effects including hypertension, nausea and vomiting, headache, abdominal pain and dizziness will be captured using a maternal questionnaire at 2 hours postnatal. Participants are asked to score their experiences as either none, mild, moderate, severe or severe
22. Health-related quality of life, measured using EQ5D- 5L questionnaire antenatally from 20 weeks gestation, at 1 day postnatal, and day 14 postnatal
23. Cost per patient – length of hospital stay following birth and cost of additional uterotonics

Completion date
30/09/2018

Eligibility

Key inclusion criteria
Current inclusion criteria as of 27/06/2018:
1. ≥18 years of age at time of delivery
2. Vaginal birth
3. Live, singleton pregnancy
4. >24 weeks gestation

Previous inclusion criteria:
1. ≥18 years of age at time of baby's birth
2. Planning to have a vaginal birth (spontaneous and instrumental)
3. Singleton pregnancy
4. Any gestational age

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Female

Total final enrolment
5717

Key exclusion criteria
Current exclusion criteria as of 27/06/2018:
1. Significant antepartum haemorrhage (>50ml) or suspected or proven placenta abruption
2. Maternal coagulation disorder
3. Women who would decline blood products if required
4. Known or suspected hypertensive disorders
5. Peripheral, hepatic or cardiac disease
6. Epilepsy
7. Patients with an allergy or hypersensitivity to any of the active ingredients of the study drugs

Previous exclusion criteria:
1. Significant antepartum haemorrhage (>50ml) or suspected or proven placenta abruption
2. Maternal coagulation disorder
3. Multiple pregnancy (twins or higher order)
4. Intrauterine fetal death
5. Patients who would decline blood products if required (i.e., Jehovah's Witnesses - clinicians may have a lower threshold for administering additional prophylactic uterotonic drugs to these patients)
6. Known or suspected hypertensive disorders, including pre-eclampsia,
pregnancy induced hypertension, essential hypertension (even if blood pressure well controlled), and patients with hypertension in labour
7. Patients with peripheral, hepatic or cardiac disease
8. Patients with an allergy or hypersensitivity to any of the active ingredients in Carbetocin, Syntometrine or Syntocinon

Date of first enrolment
13/02/2015

Date of final enrolment
31/07/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Southmead Hospital (lead site)
Southmead Road
Westbury-on-Trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Royal United Hospital Bath NHS Trust
Obstetric/Anaesthetic Research Office
1st Floor PAW
Zone D (by D10)
RUH Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Gloucestershire Hospitals NHS Foundation Trust
Trust HQ
1 College Lawn
Cheltenham
United Kingdom
GL53 7AG

Study participating centre
Nottingham University Hospitals NHS Trust
City Hospital
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Nottingham
United Kingdom
NG5 1PB

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Trust Headquarters
Marlborough Street
Bristol

United Kingdom
BS1 3NU

Study participating centre
The Great Western Hospital NHS Foundation Trust
Marlborough Road
Swindon
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SN3 6BB

Sponsor information

Organisation
North Bristol NHS Trust

ROR
https://ror.org/036x6gt55

Funder(s)

Funder type
Industry

Funder Name
Ferring Pharmaceuticals

Alternative Name(s)
Ferring

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan

Anonymised participant-level data will be publicly available for free access within the University of Bristol Research Data Management Depository (https://data.bris.ac.uk/data/group/health-sciences) for 5 years after the end of the study. The specific DOI will be made available in the publication of results.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	03/01/2019		Yes	No
Basic results			28/05/2020	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version V5	05/03/2018	06/03/2018	No	Yes