The CAESAR Study

CAESARean section surgical techniques: a randomised factorial trial

AMENDED PROTOCOL

VERSION 3

DECEMBER 2003
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INTRODUCTION

This protocol is for a pragmatic, factorial design, multicentre randomised controlled trial to evaluate two alternative approaches to three aspects of the technique of caesarean section.

HYPOTHESIS TO BE TESTED

This trial will assess the following null hypotheses: In women undergoing delivery by caesarean section, no differences will be detected with respect to infectious morbidity when comparing the following three pairs of alternative surgical techniques:

(a) single versus double layer closure of the uterus

(b) closure versus non-closure of the pelvic peritoneum

(c) restricted versus liberal use of a sub-sheath drain.

BACKGROUND

Over 20% of women in the United Kingdom undergo delivery by either elective or emergency caesarean section® and this is the most common major surgical procedure conducted in the United States². Rates around the world vary between 5% to over 20% of all deliveries³.

Surgical techniques vary from surgeon to surgeon, and only a small number of these techniques have been evaluated in randomised controlled trials. Although it is likely that variations in surgical technique will produce relatively modest differences in outcome, the operation is conducted so frequently that any difference in morbidity is likely to have significant cost and community effects.

Systematic reviews of trials of different techniques for caesarean section

In the Cochrane Database of Systematic Reviews contained within the Cochrane Library the following overviews of trials are present: “Single versus two layer closure of uterine incision at caesarean section”, “Peritoneal non-closure at caesarean section”, “Manual removal of placenta at caesarean section”, “Uterine exteriorization versus intraperitoneal repair at caesarean section”, “Lateral tilt for caesarean section” and “Absorbable staples for uterine incision at caesarean section”.⁴⁻⁹

Additional reviews published on the now obsolete Cochrane Pregnancy and Childbirth Database include “Wound edge infiltration with local anaesthetic at caesarean section”¹⁰, “Closed suction wound drainage at Caesarean section”¹¹ and “Closure of Camper fascia at Caesarean section”.¹² These reviews have not been updated for several years.

A recent review summarised the evidence from both RCTs and observational studies of the effects of caesarean section surgical techniques on maternal health.¹³ This review included both Cochrane reviews and further RCTs that had not yet been incorporated, but did not perform meta-analyses to combine the results of different trials.
Other RCTs of caesarean section surgical techniques

A substantial number of trials that have not yet been incorporated into systematic reviews now exists (Table 1). Most of the reviews in the Cochrane Library were last updated in 1994 or 1995, so trials published since then have not been included.

Most of these trials have a relatively small sample size and rely on surrogate outcome measures such as duration of operation rather than substantive outcome measures such as febrile morbidity, pain, hospital stay and the outcome of subsequent pregnancies. Moreover, many have methodological shortcomings, such as poor methods of random allocation and exclusion of randomised women from the analysis, and may therefore be subject to bias.

There have been only two published long-term follow-up studies of trials of caesarean section surgical techniques. The first reported outcomes at the time of women’s next pregnancy in 70 women who had one layer uterine closure and 75 who had 2 layer closure (out of 906 originally randomised). No differences were found between the groups, but the study was small and only followed a small proportion of the women originally recruited. The second was a follow-up study to a trial of nonclosure versus closure of the peritoneum, and has been reported as an abstract only. 1544 of the 280 women randomised were included, and the study did not find any differences in outcome. There is therefore very little information about the long-term effects of different surgical techniques.

Table 1. Summary of randomised controlled trials of caesarean section surgical techniques.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Comparison</th>
<th>Systematic Review?</th>
<th>No. of RCTs</th>
<th>Total No. of Participants</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal incision</td>
<td>Pfannenstiel v Maylard</td>
<td>No</td>
<td>2</td>
<td>194</td>
<td>16, 17</td>
</tr>
<tr>
<td></td>
<td>Joel-Cohen v Pfannenstiel</td>
<td>No</td>
<td>3</td>
<td>679</td>
<td>18, 19, 20</td>
</tr>
<tr>
<td>Uterine incision</td>
<td>Absorbable staples</td>
<td>Yes</td>
<td>4</td>
<td>526</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Blunt v sharp expansion</td>
<td>No</td>
<td>2</td>
<td>1231</td>
<td>21, 22</td>
</tr>
<tr>
<td>Delivery of fetus</td>
<td>Vacuum v forceps v manual</td>
<td>No</td>
<td>1</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>Removal of placenta</td>
<td>Manual v controlled cord traction</td>
<td>Yes</td>
<td>7</td>
<td>1859</td>
<td>6, 24, 25, 26</td>
</tr>
<tr>
<td></td>
<td>Drainage v cord traction</td>
<td>No</td>
<td>1</td>
<td>148</td>
<td>27</td>
</tr>
<tr>
<td>Uterine exteriorisation</td>
<td>Exteriorisation v intraperitoneal repair</td>
<td>Yes</td>
<td>5</td>
<td>1280</td>
<td>7, 24, 28, 29</td>
</tr>
<tr>
<td>Uterine closure</td>
<td>1 layer v 2 layer</td>
<td>Yes</td>
<td>4</td>
<td>1249</td>
<td>4, 30, 31</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>Nonclosure v closure</td>
<td>Yes</td>
<td>11</td>
<td>2193</td>
<td>5, 32, 33, 34, 35, 36, 37, 38</td>
</tr>
<tr>
<td>Fat layer</td>
<td>Nonclosure v closure</td>
<td>No</td>
<td>2</td>
<td>683</td>
<td>39, 40</td>
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<tr>
<td>Skin closure</td>
<td>Percutaneous v intracutaneous suture</td>
<td>No</td>
<td>1</td>
<td>89</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Staples v subcuticular suture</td>
<td>No</td>
<td>1</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Blunt-tipped v sharp-tipped needles</td>
<td>No</td>
<td>1</td>
<td>204</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Cyanoacrilate v silk/nylon</td>
<td>No</td>
<td>1</td>
<td>74</td>
<td>44</td>
</tr>
<tr>
<td>Wound drain</td>
<td>Drain v no drain</td>
<td>No</td>
<td>7</td>
<td>2501</td>
<td>11, 45, 46, 47, 48, 49</td>
</tr>
<tr>
<td>Misgav-Ladach technique</td>
<td>Misgav-Ladach v standard</td>
<td>No</td>
<td>9</td>
<td>2357</td>
<td>50, 51, 52, 53, 54, 55, 56, 57, 58</td>
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</tbody>
</table>
Outcomes for trials assessing caesarean section technique

Appropriate outcomes for evaluating different techniques of caesarean section are not simple to specify. Short term maternal morbidity is important and outcome measures such as febrile morbidity, antibiotic use, wound complications, pain and length of stay in hospital are appropriate to measure this. Surrogate measures for maternal morbidity, such as duration of operation, however, are less appropriate, as they assume a correlation between maternal morbidity and the outcome measured. This relationship may not hold true. Although operation time may be longer, for example, it may be associated with a lower incidence of maternal morbidity because the technique being used causes less tissue damage or introduces a smaller amount of foreign material into the wound. Operating time is the most often recorded outcome for trials of different caesarean section techniques because it is easy to collect and, because it is expressed as a continuous variable, it will need a smaller sample size in order to demonstrate a given difference. It does not, however, represent maternal morbidity and may be actively misleading.

Evaluation of surgical techniques for caesarean section should also include an assessment of their long term effects on the functional integrity of the uterine and abdominal scar. This can only be assessed by measuring subsequent morbidity associated with the scars, for example the incidence of clinically recognised scar dehiscence, hernia formation and repeat caesarean section for scar dehiscence. The presence of adhesions at repeat caesarean section is not an appropriate outcome measure if they produce no symptoms or pose no problems at operation. Symptoms of adhesions may include secondary infertility, pain or dyspareunia. Information on substantive outcome measures associated with long term morbidity is more difficult to collect and requires relatively large numbers of women. It is unlikely that meaningful differences could be sought less than five years after the current trial. This trial, however, will provide a randomised cohort of women and our aim is to revisit the cohort in separate future studies to assess longer term outcomes.

Survey of practice

As part of this study a national survey of practice was undertaken amongst obstetricians in the UK to determine (a) current practice with respect to the techniques used at caesarean section, and (b) what aspects of the operation clinicians would like to see evaluated in a randomised controlled trial. The results of this survey have two main uses. First, they allow us to describe the context of current practice within which the trial results will be implemented. Second, they allowed practitioners in the UK to determine the interventions being compared ensuring (a) that the questions are relevant to the clinical community because they have nominated them and (b) that the results of the trial should be promptly adopted into practice because clinicians in the UK will have some ‘ownership’ of the trial findings.

A factorial design

Factorial trials maximise the efficiency of a trial by including more than one trial question into a single trial population. Instead of having one trial which compares, for example, single versus double layer closure of the uterine incision and another trial comparing closure versus non-closure of the peritoneum, both comparisons can be combined into one trial using only the number of women necessary to answer one of these questions in isolation. In the CAESAR study, three comparisons will be carried out in one trial, using a 2x2x2 or 2x2 factorial design. Such a design has rarely been used, but is appropriate for evaluation of several procedures which will be used together in clinical practice.
A factorial design compares two pairs of interventions A versus B and C versus D. Eligible subjects are allocated one of four potential alternatives:

<table>
<thead>
<tr>
<th>A plus C</th>
<th>B plus C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A plus D</td>
<td>B plus D</td>
</tr>
</tbody>
</table>

The analysis of this trial would compare all those allocated A with all those allocated B i.e. the columns of the above box. Similarly all those allocated C would be compared with all those allocated D i.e. the rows.

In the proposed trial of different caesarean section techniques, using three pairs of possible allocated interventions (A versus B, C versus D, E versus F), subjects can receive one of eight possible alternatives:

<table>
<thead>
<tr>
<th>A plus C plus E</th>
<th>B plus C plus E</th>
</tr>
</thead>
<tbody>
<tr>
<td>A plus C plus F</td>
<td>B plus C plus F</td>
</tr>
<tr>
<td>A plus D plus E</td>
<td>B plus D plus E</td>
</tr>
<tr>
<td>A plus D plus F</td>
<td>B plus D plus F</td>
</tr>
</tbody>
</table>

If centres choose to take part in two of the comparisons only (e.g. uterine closure and peritoneal...
closure) then subjects will receive one of four potential alternatives - as in the first example in the previous table.

During the analysis of a factorial trial the same process is used for a 2x2x2 factorial design as for a 2x2 factorial design. All those allocated A are compared with all those allocated B regardless of what other interventions were allocated. This assumes that there is no ‘interaction’ between the various interventions.

The presence of an interaction means that the effects of the interventions are not simply additive. This is best illustrated by an example. Consider a 2x2 factorial trial comparing the effects of two different drugs (A and B) on red blood cell count. Each drug is compared with a matching placebo, so there are four groups in the trial:

<table>
<thead>
<tr>
<th></th>
<th>Column 1</th>
<th>Column 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Row 1</td>
<td>Active A + active B</td>
<td>Active A + placebo B</td>
</tr>
<tr>
<td>Row 2</td>
<td>Placebo A + active B</td>
<td>Placebo A + placebo B</td>
</tr>
</tbody>
</table>

Each drug will cause a certain increase in red blood cell count, which will be the differences between the cells of column 2 (for drug A) and between the cells of row 2 (for drug B). If there is no interaction between the two interventions, the effect of both drugs together (the difference between row 1 column 1 and row 2 column 2) will be the sum of the effects of the individual drugs. If there is an interaction, the effect of the two drugs together will be different from their effects in isolation. This means that the effect of drug A will depend on whether or not drug B is also given.

Interactions appear to be uncommon but a factorial trial is the most efficient design for detecting them if they are present. A 2x2x2 factorial trial is slightly more likely to be compromised by interactions than a 2x2 factorial trial in that there is a further comparison for the interaction to be present in. However, this only represents a small increase in an uncommon event and is unlikely to seriously affect the interpretation of such a trial.

In addition, factorial trials are the most appropriate study design for evaluating several interventions that are expected to be used together as they allow all possible interactions to be assessed. These interactions would be missed if the interventions were tested in isolation, and unexpected effects might be found if they were then used together in clinical practice.
Summary

This trial will evaluate two alternatives of three techniques used at caesarean section to determine whether any particular technique is associated with a lower incidence of infectious morbidity or other short term markers of maternal morbidity.

Centres will be allowed to choose to take part in all three interventions or to take part in two.

A full scale follow-up to the CAESAR trial is planned, which will contact all participating women at least five years after CAESAR has finished and identify any long term effects of the surgical techniques being compared. This will allow as many as possible of the participating women to have had subsequent pregnancies.

However, until this follow-up study of all women recruited to CAESAR can be conducted, we will collect data from participating women who have a subsequent caesarean section or abdominal surgery. This will allow early identification of any association between morbidity at subsequent surgery and the trial’s interventions. Identification of major unexpected morbidity occurring during subsequent surgery can therefore be identified as soon as it happens, without needing to wait for a full follow-up study that may not be conducted until several years later.

TRIAL DESIGN

Trial eligibility

Women will be eligible for trial entry if:

(a) they are undergoing delivery by their first lower segment caesarean section and
(b) there is no clear indication for any particular surgical technique to be used and
(c) they are aged 16 years or over.

Trial entry

As approximately 8% of women undergo delivery by their first caesarean section, information about the trial will be made available during the antenatal period. Each participating centre, with advice from their local research ethics committee, will decide how best to achieve this.

It is expected that the majority of women will be aware of the trial during their antenatal visits to the unit, although some centres may wish to reinforce this information when women are admitted to the delivery suite. Information leaflets will be made available to local centres which explain the justification for the trial, the process of trial entry and follow up.

Once a woman becomes eligible the trial should be discussed with her (and her partner as appropriate). Although it is important that women undergoing intrapartum caesarean section are included in the trial, due consideration should be given to the clinical situation at the time a woman becomes eligible. If an intrapartum caesarean section is being undertaken for severe fetal distress or cord prolapse, for example, discussion of the trial is clearly inappropriate. If a woman has received opiate analgesia during labour she may be unable to give informed consent. The recruiting clinician should use their discretion in deciding which women can be approached during labour for discussion about the trial. All women will be required to sign a
formal consent form if they agree to participate in the trial. If there is no objection to trial entry, a few brief details will then be recorded on the trial data collection form. This information is collected for four reasons:

(a) to check eligibility
(b) to allow comparison of baseline characteristics of the randomised groups
(c) to enable later description of the women studied
(d) to assist follow-up

Treatment allocation

At the time of the caesarean section a telephone call will be made to a 24 hours a day, 7 days a week randomisation service. Details of the woman's eligibility and trial entry data will be recorded during the telephone call.

Minimisation

Provided that sufficient details are given over the telephone and that the woman is eligible, a random allocation will then be made by the randomisation service. The randomisation service computer will use minimisation to ensure comparability between women allocated to the interventions in respect of three prognostic variables:

(a) participating centre
(b) 'in-labour' or not 'in-labour' caesarean section
(c) single or multiple pregnancy

The allocation will be to three repair options. This will be to one or other of the interventions for each repair option. For example, the randomisation service may allocate:

“Repair uterus in a single layer; do not repair the pelvic peritoneum; use a sub-sheath drain”

The person making the telephone call from the participating centre will record the allocation on specifically designed data collection forms which facilitate the accurate recording of this information therefore minimising the likelihood of women receiving interventions which they were not allocated.

Clinical management

Interventions:

1. Uterine closure

(a) Double layer uterine closure
This is the standard approach to uterine closure used in the UK. The uterine incision is closed with two layers of sutures. Each layer may be continuous, continuous locking, interrupted or any other accepted technique. The first layer opposes the endometrial aspect of the uterine muscle layer and the second layer of sutures bring together the serosal layer ensuring haemostasis and complete apposition of the incision.

There are no restrictions on the type of suture material or needles used.

Haemostasis of the incision can be effected by using additional single or ‘figure of eight’ sutures as judged necessary by the surgeon.

(b) Single layer uterine closure
This technique involves bringing both edges of the uterine incision together with a single layer of sutures. This may be a continuous, continuous locking or an interrupted layer of sutures.

Haemostasis of the incision can be effected by using additional single or ‘figure of eight’ sutures as judged necessary by the surgeon. There are no restrictions on the suture material used or any other aspects of the techniques used to effect single layer closure.

2. Closure or non-closure of the pelvic peritoneum

Women allocated closure of the pelvic peritoneum should have this performed unless there are overwhelming reasons not to effect closure. The techniques of closure, including the suture material used, will be at the discretion of the clinician.

In women allocated non-closure, closure can be performed if there are overwhelming reasons to do so. In either case, haemostasis should be effected as usual including, where necessary, the use of haemostatic sutures.

3. Liberal or restricted use of a sub-sheath drain

Women allocated liberal use of a drain should have a drain inserted unless there are overwhelming reasons why it is felt unnecessary by the surgeon. This may occur, for example, if the wound is particularly “dry”. The choice of drain used and the duration of use will be determined by local unit policy.

Women allocated restricted use of a drain should not have a drain inserted unless the surgeon feels that a drain is definitely indicated. This could occur, for example, where there is oozing of the wound which does not respond to local treatment such as diathermy or the placement of haemostatic sutures. Similarly, if oozing is thought to be occurring because of coagulation problems not identified at the time of trial entry, then the surgeon may decide to insert a drain. All other aspects of the operation will be determined by the attending surgeon including the choice of suture materials and the techniques for repair used.

Compliance with the allocated intervention

Clinical circumstances may change during the course of the surgical procedure after a particular intervention has been allocated. If the clinician performing the caesarean section is certain that a non-allocated intervention is necessary then this should be performed and the reasons for not
complying with the allocated intervention recorded on the data collection form.

**Training in surgical techniques**

Each participating unit will initiate and maintain a training and accreditation programme which ensures that all personnel involved in the undertaking of caesarean sections are familiar with the techniques being compared before they can enter women into the trial.

The only technique not in common usage in the UK which is to be evaluated in this trial is single layer closure of the uterus. In order to ensure that obstetricians taking part in the trial are competent in this technique, the following procedures will be set in place for those centres participating in the comparison of single layer closure with double layer closure of the uterus:

- Each participating centre will identify an experienced operator who is able to train other staff in single layer closure of the uterus. This person is the unit’s designated ‘trainer’. It may be convenient to have more than one person acting as a trainer in each centre.

- For units where there is no senior obstetrician experienced in single layer closure of the uterus, training in this technique will be organised with the assistance of the CAESAR co-ordinating centre.

- The designated trainers will train other members of staff in single layer closure of the uterus. The trainers will decide when other members of staff have reached at least Level 4 competency in single layer uterine closure. This is defined in the RCOG log book as: ‘Indirect Supervision, performs the entire activity in question with indirect supervision of a senior colleague’.

- Staff who have reached Level 4 competency in single layer closure can then be registered as operators. The trainer will sign a CAESAR training log for the operator and send it to the CAESAR co-ordinating centre. The co-ordinating centre will issue the unique ‘operator number’ and enter it into the database supplied to the randomisation service.

- Registrar equivalent staff who are already competent in single layer closure can be issued with an operator number without further training, with the approval of the designated trainer.

- Operators in centres not participating in the single layer comparison can be issued with an operator number without further surgical training.

- The randomisation service will require the operator number during randomisation; if it is not in their database randomisation will not proceed.

**Other obstetric management**

Women participating in the trial will be managed in whatever way seems best for them. Participation in the trial does not restrict the use of any other therapeutic or diagnostic procedures judged necessary by the attending clinician. This applies particularly to the use of perioperative antibiotics or thromboprophylaxis. Current unit practice should be continued, regardless of participation in the trial.
**Measures of outcome**

**Primary outcome measure:**

(a) Maternal infectious morbidity

This will include women who have one or more of the following:

(i) Antibiotic use for maternal febrile morbidity during postnatal hospital stay.

*This is any antibiotics prescribed as treatment for maternal fever (temperature \( \geq 39^\circ C \) on any occasion or \( \geq 38^\circ C \) on two or more successive days). Antibiotics prescribed for prophylaxis such as those given for Group B streptococcus carriage will not be included.*

(ii) Endometritis

*This is any clinical diagnosis of endometritis made in hospital, which is treated with antibiotics within six weeks of the caesarean section.*

(iii) Wound infection treated with antibiotics

*This is any antibiotics prescribed specifically for a wound infection; the severity of the wound infection will not be recorded separately unless the wound requires further surgical therapy.*

**Secondary outcomes – short term:**

(b) Antibiotic use for maternal febrile morbidity during postnatal hospital stay

*This is any antibiotics prescribed as treatment for maternal fever (temperature \( \geq 39^\circ C \) on any occasion or \( \geq 38^\circ C \) on two or more successive days). Antibiotics prescribed for prophylaxis such as those given for Group B streptococcus carriage will not be included.*

(c) Endometritis

*This is any clinical diagnosis of endometritis made in hospital, which is treated with antibiotics within six weeks of the caesarean section.*

(d) Wound infection treated with antibiotics

*This is any antibiotics prescribed specifically for a wound infection. The severity of the wound infection will not be recorded separately unless the wound requires further surgical therapy.*

(e) Operative procedures on wound

*This will include any procedures on the wound because of infection, dehiscence or haematoma.*

(f) Pain

*This will be assessed by analgesic use, other than that usually prescribed, on day three following the caesarean section; discharge home with analgesia other than that usually prescribed; subjective assessment of post-operative pain by the women at the time of hospital discharge and at six weeks.*
Blood transfusion - intrapartum
- postnatal

Breastfeeding at hospital discharge

Other severe or unexpected maternal morbidity

This will include events such as deep venous thromboses, which may be associated with wound infections.

Secondary outcomes – long term:

Uterine rupture
Uterine scar dehiscence
Placenta percreta
Placenta accreta
Adhesions (none, mild, moderate, severe)
Distortion of pelvic anatomy
Bladder adherent to uterus
Fibrosis of anterior abdominal wall (none, mild, moderate, severe)
Method of closure of anterior abdominal wall

Health Service Utilisation:

Duration of caesarean section operation
Duration of postnatal hospital stay
Re-admission to hospital within 6 weeks of the caesarean section

Data collection

Information will be collected at the following times:

• trial entry and randomisation
• immediately following the operation
• at discharge from hospital
• at six weeks after delivery
• at the time of subsequent caesarean section or abdominal surgery

Short-term outcomes

The surgeon will complete details of the caesarean section immediately after the operation. Outcomes up until discharge from hospital will be described from hospital records onto the trial data collection forms and women will be asked to complete a short questionnaire immediately before they are discharged.

All women will be contacted at six weeks postpartum to determine whether they have been re-admitted to hospital or prescribed antibiotics. If they have been admitted, their case notes will be examined to determine whether their re-admission was for any of the trial outcomes.

Long-term outcomes

Shortly after they are discharged home, all women participating in CAESAR will be sent a letter
explaining that we would like to collect data from trial participants who have subsequent abdominal surgery or caesarean section. Along with this letter they will be sent:

(a) a card to be completed and returned to the CAESAR Co-ordinating Centre if they become pregnant or need to have abdominal surgery. This requests consent for follow-up data to be collected and information on the hospital and doctor who will be caring for the woman.

(b) a card detailing their participation in CAESAR, to be given to the woman’s doctor, midwife or nurse if she is pregnant or due to have abdominal surgery. It asks the health professional to contact the CAESAR Co-ordinating Centre, who will then ask the woman for consent for follow-up data collection.

If consent for data collection is given, the hospital will be asked to complete the follow-up questionnaire after the surgery. The questionnaire asks for details of any surgery that has been performed, and any morbidity that could be related to the first caesarean section.

**Future follow-up**

Sufficient descriptive information will be collected about the women participating in the trial to allow a full follow-up study of all participating women in the future. Of particular interest is the effect that operative techniques may have on future pregnancies, specifically problems with conception, antenatal complications such as the incidence of abruption, mode of delivery especially ‘in-labour’ caesarean sections, and subsequent wound complications. To allow as many of possible of the participants to have had further pregnancies, it is likely that this follow-up study will be undertaken five years or more after CAESAR is completed. To facilitate follow-up, women will be flagged at the NHS Central Register.

**Analysis**

The analysis of this trial will be by ‘intention-to-treat’, therefore women will be analysed by the groups into which they were randomised regardless of what interventions they received.

Statistical analysis will use standard methods to calculate the risk of an outcome occurring in each group compared with the risk in the other group for each technique along with the 95% confidence interval. For secondary analyses, 99% confidence intervals will be calculated in order to take account of the number of comparisons. Where appropriate, \( \chi^2 \) tests of significance will be performed and presented as p-values.

The factorial design of this trial allows interactions between the different interventions to be estimated. This is particularly important for interventions that will be used together in clinical practice. The presence of interactions may affect the power of the analyses: if there is a negative interaction between two interventions or “subadditivity” (i.e. the effect of two interventions together is less than the sum of each in isolation) the power will generally be reduced. Likewise, with a positive interaction (“superadditivity”), power will be enhanced.

In addition, pre-defined subgroup analysis will be performed based on the principal outcomes stratified by:

(a) ‘in-labour’ or not ‘in-labour’ caesarean section

(b) single and multiple pregnancy
For the secondary long-term outcomes, data will not be collected at this stage for all of the women recruited to the trial, but only from those who have subsequent surgery and inform the Co-ordinating Centre. It will therefore not be possible to calculate the absolute risks of outcomes. Because the data for each group will be incomplete to an unknown extent (we will not know how many of each group had a subsequent pregnancy or surgery, but only the minimum number), full intention to treat analysis will not be possible and all analyses will be regarded as exploratory. However, these analyses will alert the investigators to a substantial imbalance in morbidity between the groups, which may justify commencing a full follow-up study.

Further exploratory analysis will be performed to generate hypotheses for future testing. This will include the effect of other interventions and techniques used during the operation and the effect these have on the outcomes. The additional analyses will include an exploration of the effect of different suture materials and the use of other peripartum interventions such as thromboprophylaxis and antibiotic prophylaxis.

**Interim analyses: the Data Monitoring Committee**

For the trial a Data Monitoring Committee (DMC) has been established. This is independent of the trial organisers. During the period of recruitment to the trial, interim analyses will be supplied, in strict confidence, to the DMC, together with any other analyses the DMC may request. The data will be supplied to the Chair of the DMC as frequently as she requests. Meetings of the committee will be arranged periodically, as considered appropriate by the Chair.

In the light of interim data, and other evidence from relevant studies (including updated overviews of the relevant randomised controlled trials), the DMC will inform the Steering Committee, if in their view, i) there is proof beyond reasonable doubt that the data indicate that any part of the protocol under investigation is either clearly indicated or contra-indicated, either for all women or for a particular subgroup of trial participants or ii) it is evident that no clear outcome will be obtained. Decision to inform the Steering Group in either of these circumstances will in part be based on statistical considerations. Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard deviations in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed.\(^{63}\)

Unless modification or cessation of the protocol is recommended by the DMC, the Steering Committee, collaborators and administrative staff (except those who supply the confidential information) will remain ignorant of the results of the interim analysis. Collaborators and all others associated with the study, may write through the study co-ordinating centre to the DMC, to draw attention to any concern they may have about the possibility of harm arising from the treatment under study, or about any other matters that may be relevant.

If sufficient follow-up data (secondary long-term outcomes) have been collected before CAESAR recruitment has finished, interim analyses of the accumulating follow-up data will be undertaken at the time of meetings of the DMC. These will be presented to the DMC in confidence and will inform their recommendations about continuation of recruitment.

Members of the DMC: Professor Janet Darbyshire (Trialist and Chair), Dr Susan Bewley (Obstetrician), Mr Zarko Alfirevic (Obstetrician), Dr Jon Deeks (Statistician).

**Sample size and feasibility**
In a meta-analysis of 68 randomised controlled trials of antibiotic prophylaxis at caesarean section involving over 10,000 women, the incidence of febrile morbidity/endometritis in the placebo/no prophylaxis group was 31% and the incidence in the antibiotic prophylaxis group was 13%. Although antibiotic prophylaxis is not used by all centres in the UK we have estimated that the incidence of antibiotic use for infectious morbidity will be approximately 12%. A sample size of 3500 women for each comparison will be necessary to demonstrate a decrease in the incidence of antibiotic use for infectious morbidity from 12% to 9% with 80% power (confidence 95%, relative risk reduction 25%). If the relative risk reduction is greater than this the trial will have greater power to detect such a difference.

**Sample size**

<table>
<thead>
<tr>
<th>Total number of women required</th>
<th>Difference in event rate</th>
<th>90% Power</th>
<th>80% Power</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome:</strong></td>
<td>12% - 9%</td>
<td>4516</td>
<td>3408</td>
</tr>
</tbody>
</table>

**Feasibility**

First caesarean sections occur in approximately 12% of deliveries in England and Wales. If 25% of eligible women consent to join the trial, 20 average sized hospitals of 3000 deliveries per year would be necessary to complete recruitment in two years. A recruitment target of 3,500 therefore appears feasible.

**Publication policy**

To safeguard the scientific integrity of the trial, data from this study should not be presented in public or submitted for publication without requesting comments from the Trial Steering Committee (see Organisation below). The success of the trial depends on the collaboration of a number of doctors and midwives. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all who have wholeheartedly collaborated in the study.

**Organisation**

**Trial Steering Committee**

The Trial Steering Committee comprises:

Felicity Ashworth, Obstetrician (Chair)
Pauline Hurley, Obstetrician
Jo Anthony, Obstetrician
Alison Chevassut, Midwife
Debbie Chippington-Derrick, Consumer Representative
Peter Brocklehurst, Epidemiologist
Simon Gates, Statistician
Ursula Bowler, Trials Co-ordinator

The specific tasks of the Steering Committee will be:

(a) to approve the main study protocol
(b) to approve necessary changes in the protocol based on considerations of feasibility
Within the Trial Steering Committee a small group will continue to work closely on a day-to-day basis to enable the smooth and efficient running of the trial. This will be the Project Management Group and will include: Peter Brocklehurst (Epidemiologist), Ursula Bowler (Trials Co-ordinator), Simon Gates (Trials Statistician), Sarah Ayers (Computing Co-ordinator), Elizabeth Anderson (Clinical Research Fellow), Ruth Davis (Trial Co-ordinator) and Madalena Marques (Trial Data Manager).

The responsibilities of the Project Management Group include:

(a) recruitment of participating centres
(b) distribution and supply of data collection forms and other appropriate documentation for the trial
(c) data collection and management
(d) data entry and cleaning
(e) data analysis
(f) collection of adverse event data
(g) organising and providing information for the Data Monitoring Committee.

Local co-ordination

Each participating centre will identify a local medical co-ordinator and a local midwife co-ordinator.

The responsibility of the local co-ordinators will be to:

(a) be familiar with the trial
(b) liaise with the Trial Co-ordinating centre in Oxford
(c) ensure that all medical and midwifery staff involved in the care of pregnant women are informed about the trial
(d) ensure that mechanisms for recruitment of eligible women (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible women with relevant staff
(e) ensure that supplies of data collection forms are always available, that they are completed and returned to the Trial Co-ordinating centre promptly, and to deal with any queries arising
(f) notify the trial co-ordinating centre of any serious adverse events
(g) facilitate other aspects of local collaboration as appropriate
(h) make all data available for verification, audit and inspection purposes as necessary
(i) ensure that the confidentiality of all information about trial participants is respected by all persons

Handling of records and confidentiality

For each randomised woman a data collection form will be completed by the local clinical team. If serious adverse events occur, a full written report will be produced by the local medical co-ordinator immediately if possible, and in no case more than 15 days later.

It is desirable that the names and addresses of the trial participants be recorded on the data
collection forms in addition to the allocated trial number. This will allow the Trial Co-ordinating centre to assist local clinicians in follow-up. Data will be stored in compliance with the Data Protection Act 1998.

The investigators and local medical co-ordinators will ensure conservation of records in areas to which access is restricted.

REFERENCES


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