Protocol

SUTURE VERSUS STAPLES IN SKIN CLOSURE AFTER CAESAREAN SECTION AND OTHER ABDOMINAL SURGERY: SYSTEMATIC REVIEW WITH META-ANALYSES AND TRIAL SEQUENTIAL ANALYSES OF RANDOMISED CLINICAL TRIALS.

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Background

Caesarean section is one of the most common major abdominal operations performed on women in the world. WHO has recommended that the proportions of Caesarean section should be kept under 10%-15% of the total number of births in developed countries (Anderson 2004). Today the proportion exceeds 15% in many countries (Gunnervik 2000; Rasmussen 2000; Smith 2008; Joseph 2003). When a caesarean section is performed several structures has to be opened before delivering the baby through an abdominal incision. These structures include skin, fat, muscle, peritoneum and uterus. Other abdominal surgery includes the same structures except the uterus.

There are many different ways of entering and closing these abdominal structures, but we lack firm knowledge of how the different techniques impact maternal outcomes. Today most skin incisions for, e.g., caesarean section are made through a low transverse incision just above os pubis. The surgeon may then enter the next layers with a knife, scissor, or blunt dissection. The techniques used to perform an abdominal section depend on many factors. These are, among other, the clinical situation, equipment at hand, and the preference of the operator.

In 2002 Tully (Tully 2002) made a national survey about different techniques used during caesarean section among obstetricians in the UK. This survey showed great differences in both which structures were closed and what material was used. When closing the skin, which is the subject of this review, 73.9% chose sub-cuticular stitch, 7.7% chose interrupted stitch, and 18.4% chose other methods. Regarding closure of the subcutaneous layer, 41.0% answered that they never close, 21.0% always closed, 8.0% closed when the layer is thin, and 27.0% closed when the layer is fat. The Oxford Textbook of Surgery (Morris 2001), states that techniques for caesarean section are many and are best learned from an experienced obstetrician. Furthermore it states that choosing the best suture material is a question of personal preference of the surgeon.

A Cochrane review from 2008 (Hofmeyr 2008) provided an overview of techniques, indications, and postoperative complications in regards to caesarean section. The review recommended the following concerning closure of structures including the skin:

- Lack of evidence regarding one or two layer closure of the uterus.
- No closure of both peritoneal layers.
- No evidence regarding closure of the fascie.
- Closure of the subcutaneous layer reduces wound haematoma and seroma
- No routine drainage of subcutis.
- Skin closure with suture, staples, or tissue glue. No final recommendation possible.

Potential wound complications are infection, oedema, or haematoma, which may lead to ischaemic necrosis, rupture of the wound, hernia, keloid (hard prominent and irregular scar tissue), or persisting pain in the wound. Ideally, therefore, the closure of the skin and the material used should eliminate these complications. In addition the materials chosen must be economical, easy to use, and yield a successful cosmetic result. Today there are many options when choosing suture
technique and materials, and many factors are in play. The tension of the skin around the incision, length and depth of the wound are just some of the factors.

**Suture**
Suture material, currently available, are natural or synthetic, absorbable (further divided into fast or slow) or non-absorbable, monofilament or braided.

**Fast absorbable suture:**
Catgut is usually made of intestines from sheep. They persist in the tissue for about 15 days. Due to the fast loss of tension and possible allergic reaction catgut is now considered almost obsolete in obstetrics (Scheidel 1987).

Polyglycolic acid (Dexon) and polyglactin (Vicryl) are synthetic, monofilament. They persist for about 20 and 80 days, respectively.

**Slow absorbable suture:**
Polydioxanone (PDS) and polyglyconate (Maxon) are synthetic monofilament that persist for about 180 days.

The absorbable have the advantage of not persisting in the tissue so they cannot be used as a hiding place for bacteria. However, they could potentially lose their strength before wound healing is completed.

**Non-absorbable suture:**
Nylon, polypropylene, polyethylene and polyamide are all synthetic monofilaments, they persist permanently in the tissue if they are not removed. There are potential benefits and disadvantages regarding all of the sutures.

The skin can be closed with continues stitch in the subcutis layer, immediately below the skin, or single/continuous stitches thru the skin. Potential risks when using single stitch is that the strength of the suture are localised to the loops, and are these to tight on the skin there are risk of necrosis of the tissue. In theory the continues stitch below the skin provides less risk of infection, because the suture does not lead bacteria from the skin into the tissue.

Many studies have tried to find the perfect suture for wound closure after abdominal surgery (Cedelli 2005, Weiland 1998, Murtha 2006, Riet 2002, Lindholt 1994, Waard 2006). When comparing the conclusions of these studies they suggest the use of a synthetic slow absorbable continues stitch as being superior for abdominal wound closure.

**Staples**
The use of staples provides, in theory, less risk of infection by eliminating bacterial migration into the wound (Scheidel 1987). Furthermore they result in less damage of the skin barrier than sutures (Johnson 1981). In both animal and patient studies staples have shown to both provide less and increased risk of wound infection (Shetty 2004; Pineros-fernandez 2006; Fick 2005).

Several studies (Frishman 1997; Meiring 1982; Lubowski 1985) have shown that perhaps the main benefit of staples is speed. None of the above mentioned studies are in consensus when it comes to the cosmetic result when using staples.
Currently there are both absorbable and non-absorbable staples in use. They are especially used in abdominal-, vascular-, and urology- surgery (Burkett 1989) and in obstetric surgery in the US. In the textbook Clinical Surgery (Thompson 2001) staples are described as having their place when operating on high-risk patient because they eliminate the risk of needle prick accidents.

In 2003 a Cochrane review looked at techniques and materials for skin closure in Caesarian section (Alderdice 2008). They found only one small trial eligible for inclusion and could therefore not conclude a superior technique for skin closure. In 2009 a narrative study was done in regards to skin closure techniques after Pfannenstiel incisions (Altman 2009).

This systematic review will compare the possible benefit and harm when using staples versus sutures in skin closure of abdominal surgical wounds. Abdominal surgeons rarely use the transverse supra pubic skin incision commonly used in caesarian section, and their patients are therefore likely to have different traction on their skin edges. Women undergoing caesarian section is usually considered healthy and the operation is therefore relatively clean. Abdominal patients may sometimes differ from this.

**Objectives**

To compare the possible benefit and harm when using staples versus suture in skin closure after abdominal surgery, with incision in both cutis, subcutis, and peritoneum.

**Criteria for considering studies for this review**

**Types of studies**

All randomised comparisons of staples versus sutures in skin closure after caesarean section and after other abdominal, urogenietal, or gynaecological surgery with an abdominal incision.

**Types of participants**

Women, who undergo a caesarean section, (elective or emergency, first or repeat).

Men and women, who undergo any abdominal surgery where an incision is made in both cutis, subcutis, and the peritoneum.

**Types of intervention**

Staples compared with any type of suture material, using any technique for skin closure.

**Types of outcome measures**
Complications: pain (analgesia use, VAS score); infection (temperature greater than 38 degrees centigrade, presence of redness, presence of swelling); presence of haematoma; scar dehiscence (breakdown): sheath dehiscence and skin dehiscence; scar cosmetics; hernia formation.

Time: isolated time used for skin closure as well as time used for entire surgery.

Cost/benefit analysis.

**Search methods for identification of studies**

See: Cochrane Pregnancy and Childbirth Group methods used in reviews.

We will search the Cochrane Pregnancy and Childbirth Group trials register.

The Cochrane Pregnancy and Childbirth Group’s trials register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies’ section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

We also searched the Cochrane Wounds Group as well as the Cochrane Colorectal Cancer Group (Nov. 2009).

We will performed a MeSH search in PubMed and EMBASE.

**Search words:**
- staples
- suture
- caesarean section
- wound closure
- skin
- abdominal surgery

**Methods of the review**
Trial identification
Two authors will independently select the trials and evaluate whether the trials fulfill the inclusion criteria. Disagreement will be resolved by discussion. Excluded trials will be listed with the reason for exclusion.

Data extraction
Two authors will extract the data. Disagreement will be resolved by discussion.

We will extract the following characteristics from each trial:
Primary author, number of patients randomized, patient inclusion and exclusion criteria, methodological quality, follow-up (number and reason for withdrawal), intention-to-treat analysis, sample size calculation, intervention regimens, mean age, proportion of females and males, types of abdominal surgery performed, type of incision used, number and type of outcomes, number and types of adverse events in all groups, time to follow-up.

Primary authors will be contacted for additional information if outcome measures or generation of allocation sequence are not included in the published trial reports.

We will perform the data analyses according to the recommendations of The Cochrane Collaboration, and we used the software package RevMan 5 provided by The Cochrane Collaboration (RevMan 2008).

Assessment of methodological quality
Methodological quality will be defined as the confidence that the design and the report of the randomized clinical trial would restrict bias in comparison of the intervention (Moher 1998).

The methodological quality assessment of the included trials in this review will be conducted by two authors, following the recommendations given by the Cochrane Handbook for Systematic Reviews of Interventions (Higgs 2008), using the following definitions:

(1) Generation of the allocation sequence (checking for possible selection bias)

- YES (low risk of bias), if random number table, computer random-number generator, coin toss, shuffling cards or similar methods are used.
- Unclear (uncertain risk of bias), if a trial is described as randomised, but the method used for the allocation sequence generation was not described.
- NO (high risk of bias), if any non random process, e.g. odd or even date of birth, hospital or clinic record number are used. These trials are known as quasi-randomised. These trials will not be included in our primary analysis, but will be included in our sub-group analysis.

(2) Allocation concealment (checking for possible selection bias)

- YES, if telephone or web-based central randomisation, consecutively numbered sealed opaque envelopes, sequentially numbered suture or staples of identical appearance are used.
- Unclear, if the method used to conceal the allocation was not described.
- NO, if open random allocation such as unsealed or non-opaque envelopes,
alternation, date of birth are used. These trials will not be included in our primary analysis, but will be included in our sub-group analysis.

(3) Blinding (checking for possible performance bias)

- YES, if blinding of participants and the personal conducting the outcomes are ensured. If outcome assessment was blinded and the non-blinding of others are unlikely to introduce bias
- Unclear, if the trial did not address blinding or provided insufficient information to decide YES or NO.
- NO, if no blinding or incomplete blinding is likely to influence outcome measures. If blinding could have been broken.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- YES, if no outcome data are missing. Missing data have been imputed using appropriate methods. If missing outcome data is equally balanced across intervention groups with similar reasons for missing data, and if numbers and reasons for missing data are described.
- Unclear, if the trial did not address this or provided insufficient information to decide YES or NO.
- NO, if the proportion of missing outcomes is likely to induce clinically relevant bias in intervention effect estimate or observed effect size. If numbers and reasons for missing data are not described and if missing data have been inappropriately imputed.

(5) Selective reporting bias

- YES, where it is clear that all of the trials pre-specified outcomes and all expected outcomes of interest to the review have been reported.
- Unclear, if the trial did not address reporting bias or provided insufficient information to decide YES or NO.
- NO, where not all the trials pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used. Trials fails to include results of a key outcome that would have been expected to have been reported.

(6) Other sources of bias

This includes potential sources of bias, related to, for example, extreme baseline imbalance, whether the trial was stopped early, academic bias, publication bias and other potential risk of bias.

- YES, the trial appears to be free of other sources of bias.

- Unclear. There may be a risk of bias but there are insufficient information to assess whether an important risk of bias exist or if the identified problem will introduce
bias.
• NO, the trial has at least one of the above described risk of bias.

Furthermore, we will extract information on whether sample-size and intention-to-treat analysis are performed in the trials.

To assess and adjust for the risks of random errors in our meta-analyses we will perform trial sequential analyses (TSA). TSA in a cumulative meta-analysis corresponds to group analysis of a single trial (Wetterslev 2008, Ashari 2007). The TSAs will be calculated using a control event proportion based on interpretation of the data obtained in our meta-analyses and an a priori effect size of 60% RR reduction. A type I error of 5% and a type II error of 20% will be applied. We will calculate the required information size as well as the alpha spending monitoring boundaries with the TSA program version 0.8 of The Copenhagen Trial Unit.

Measures of treatment effect

**Dichotomous data**
Dichotomous data will be expressed as relative risks (RR) with 95% confidence intervals.

**Continuous data**
Continuous data will be expressed in mean difference (MD) with 95% confidence intervals when outcomes are reported in the same scale and the mean difference can be used. If this not the case, data will be expressed in standardized mean difference (SMD) with 95% confidence intervals. If a trial only reports a mean value and not a standard deviation (SD) we will calculate the SD from the data reported. If a range is not given for the mean we will use the 95% confidence interval as the range. We will use the following formula for estimation of the SD (Hozo 2005):

\[ S = \frac{1}{12}((a-2m+b)^2/4+(b-a)^2). \]
(a representing lowest value, b the high value and m is the mean value)

**Data synthesis**
For all analysis we will use both random-effects model (DerSimonian 1986) and a fixed- effect model (DeMets 1987). These analyses will provide us with a combined estimate of the relative risk and a corresponding 95% CI for each outcome measure. In case of discrepancy between the two models (sign of possible heterogeneity) we will report both results, otherwise we will only report results from the fixed-effect model.

**Assessment of heterogeneity**
To address possible heterogeneity between studies we will perform a Chi-squared test (P-value of 0.10 will be considered statistically significant), and the quantity of heterogeneity will be measured by I-squared statistic (Higgins 2002). This will give us an indication of how much the percentage of the variability in effect estimates is due to heterogeneity rather than to sampling error (chance). A I-squared of 50%-75% will be considered to represent substantial heterogeneity.
Sources of heterogeneity will be assessed in the pre-specified sub-group analysis.

**Subgroup analysis and investigation of heterogeneity**

The following sub-group analysis will be considered and performed when feasible.

- **Risk of bias:** the intervention effect of trials that are assessed to be at low risk of bias will be compared to the intervention effect of trials with unclear or high risk of bias.
- **Participants:** trials with both sexes versus trials with only women. trials who use per-operative antibiotics versus trials where antibiotic use is not recorded or not used.
- **Surgery:** general abdominal surgery versus caesarean section. vertical versus horizontal incisions. elective versus emergency abdominal surgery. first versus repeat surgery
- **Intervention:** removal of material for skin closure before and after 1 week. differences in time to follow up. blinded versus non-blinded cosmetic results.

Subgroups will be interpreted as potentially different if the 95% confidence intervals did not overlap. Furthermore, the P-values in the respective subgroups were disregarded in the subgroup analysis.

**Dealing with missing data**

For trials with missing data we will assess the adequacy of the methods used to deal with the missing data. We will extract both the results based on the missing data methods (if reported) as well as the crude results, and all meta-analysis will be performed with both.

If patients are lost to follow-up and missing data methods are not applied, data will be analysed according to the intention to treat (ITT) principle. ITT will be performed in the four possible extremes:

- Assuming poor outcome for both suture and staples group. Dropouts from both groups will be considered as failures, using the total number of participants as the denominator.
- Assuming good outcome for both suture and staples group. Dropouts from both groups will be considered as successes, using the total number of participants as the denominator.
- Assuming good outcome in the suture group, and assuming poor outcome in the staples group.
- Assuming good outcome in the staples group, and assuming poor outcome in the suture group.

In the discussion section we will addressed the potential impact of missing data on the
findings of the review.

**Sensitivity analysis**  
Suitable sensitivity analysis will be identified during the review process.

**Declaration of interest**  
None known

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**Contribution to authorship**  
Mie Larsen (ML): initiated the review, drafted the protocol, will perform literature search, data extraction, statistical analyses, and will draft the review.  
Morten Hedegaard (MH): initiated the review, will perform data extraction, and revise the review.  
Christian Gluud (CG): revised the protocol, act as arbiter for disagreements, and will revise the final review.
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