Antibiotic prophylaxis for elective hysterectomy (Protocol)

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[Intervention Protocol]

Antibiotic prophylaxis for elective hysterectomy

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

Our primary objectives are to determine to what extent antibiotic prophylaxis reduces the risk of postoperative infection in women having an elective total or subtotal hysterectomy by any route or technique, to establish which (if any) antibiotic regimen is most effective and to assess the risk of adverse effects.

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BACKGROUND

Hysterectomy is one of the most commonly performed operations, particularly in the USA, where nearly one in three women will have undergone hysterectomy by the age of 65 (Pokras 1989). Most hysterectomies are elective (non-urgent) procedures for benign gynaecological conditions, the commonest in the USA being leiomyoma (fibroids). Other common indications are endometriosis, heavy menstrual bleeding, uterovaginal prolapse and pelvic inflammatory disease. The surgery can be performed abdominally, laparoscopically or vaginally, with or without laparoscopic assistance (Farquhar 2002).

Even with the best surgical and postoperative care, hysterectomy is unavoidably associated with a high infection risk because the surgery breaches the genital tract, an area commonly colonised by a wide variety and large number of micro-organisms. In addition, most women undergoing hysterectomy require an indwelling urinary catheter for the first 24 hours, which increases the risk of urinary tract infection. Common sites of infection after hysterectomy are the bladder, the pelvic floor, the cuff of tissue at the top of the vagina (vaginal vault) and the abdominal wound, while related complications include pelvic abscess, infected hematoma (accumulation of blood from the wound), septicaemia (infection of the blood) and pneumonia (Duff 1980; Faro 2001). Such infections are usually caused by a mixture of bacteria from the woman's own vaginal or urethral tissues, both Gram-positive and Gram-negative and both aerobic and anaerobic (these terms refer to the staining techniques used in identification and whether the bacteria are oxygen-dependent). The susceptibility to infection of the individual woman depends upon the effectiveness of her immune system, the virulence of the bacteria present, and the degree of tissue trauma and fluid collection resulting from surgery (Duff 1980).

'Antibiotic prophylaxis' refers to the administration of antibiotics to prevent infection: it has been used in surgery since antibiotics were introduced in the 1950s, in an attempt to reduce the rate of postoperative infections. Such infections not only cause patient morbidity but also result in additional costs, extended hospital stay and increased antibiotic use, which promotes the emergence of antimicrobial resistant organisms (Dellinger 1994). Prophylaxis works by briefly bolstering tissue defence mechanisms to promote the rapid restoration of normal immune responses after the trauma of surgery. Antibiotic prophylaxis for hysterectomy has been extensively studied and has been estimated to more than halve the rate of postoperative infections, which otherwise affect about 40% to 50% of women after vaginal hysterectomy and over 20% after abdominal hysterectomy (Duff 1980; Mittendorf 1993). Antibiotic prophylaxis is now recommended in national guidelines for all types of hysterectomy (Dellinger 1994; RCOG 1999; SIGN 2000), although in practice the application of such guidelines is variable (Gorecki 1999).

Although various antibiotic regimens and routes of delivery have been used, currently the most frequent practice is for a single dose of antibiotic to be given intravenously within two hours of the surgical incision, in order to facilitate optimum serum antibiotic levels during the operation (DiPiro 1984; Classen 1992). A single dose has been reported to be as effective as multiple doses, though some authors have suggested repeating the dose if the surgery is long or blood loss is high (DiPiro 1986; Tanos 1994). If prophylaxis is continued postoperatively, it is recommended that the duration of therapy does not exceed 24 hours (Dellinger 1994).

The type of antibiotic most commonly used is one that is active against a wide range of bacteria (broad-spectrum), such as amoxicillin/clavulanic acid (Augmentin) or a cephalosporin. Cephalosporins are grouped into generations according to their antimicrobial properties, with the oldest type being termed *first generation*. Subsequent generations of these drugs have progressively widened their antibacterial coverage against Gram negative organisms, but there has been a concurrent reduction in their effectiveness against Gram positive organisms. The wide use of very broad spectrum antibiotics greatly increases the risk of drug-resistant bacteria emerging (BNF 2002). It is generally recommended that first or second generation cephalosporins should be used for prophylaxis, as they appear to be equally effective for this purpose, less expensive and less likely to favour drug resistance (Tanos 1994; Fukatsu 1997; Weed 2003).

There is a large body of evidence on prophylactic antibiotics for hysterectomy, involving hundreds of clinical trials. However there has been no systematic review on the topic. There have been three previous meta-analyses of trials of antibiotic prophylaxis for abdominal hysterectomy, as follows:

- Wttewaall-Evelaar (1990) meta-analysed 17 randomised blinded placebo-controlled trials of prophylaxis for elective abdominal hysterectomy, all published between 1986 and 1988.In most cases the antibiotics used were cephalosporins. The author concluded that prophylaxis significantly reduced levels of infection (p = <0.001; no odds ratio reported) and that further placebo-controlled trials were not warranted.

- Mittendorf (1993) meta-analysed 31 randomised controlled trials published in English from 1972 to 1986 and concluded that antibiotic prophylaxis reduced the rate of serious infections after abdominal hysterectomy from 21.1% to 9% (p = 0.00001; no odds ratio reported in text). The author pooled trials which used different routes of administration and differing prophylaxis regimens, varying from a single dose to five days' duration.

- Tanos (1994) meta-analysed 17 "controlled or comparative" trials conducted between 1978 and 1990 investigating single or one-day prophylactic regimens of intravenous or intramuscular cephalosporins for abdominal hysterectomy. It is unclear whether all the included trials were randomised, and some trials included oncology patients among their participants. Again the results clearly favoured the use of prophylaxis (odds ration (OR) 0.35, 95% confidence interval (CI) 0.3 to 0.4).

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Although evidence firmly suggests that antibiotic prophylaxis is beneficial,this has not been tested recently nor in a systematic way. Mittendorf 1993 and Tanos 1994 combined the results from studies that included very different participants or interventions. Wttewaall-Evelaar 1990 was more rigorous but the study does not include any of the many studies carried out from 1986 to the present. Changes during this period include the introduction of laparoscopic techniques, which may influence the risk of infection.There has been no meta-analysis of trials involving routes other than abdominal.

There are three Cochrane reviews of prophylactic antibiotics for elective surgery. Two are on the topic of caesarean section: one evaluates the use of antibiotic prophylaxis for women undergoing caesarean delivery (Smaill 2003) and the other considers which prophylactic antibiotic regimen is most effective (Hopkins 2003). The reviewers conclude that the use of routine antibiotic prophylaxis for elective caesarean section is justified by the resulting reduction in endometritis and wound infections, and that first generation cephalosporins and ampicillin are equally effective for this purpose. In contrast, a review of antibiotic prophylaxis for elective open inguinal hernia repair finds no clear evidence that it reduces infection rates (Sanchez-Manuel 2003). The present systematic review aims to assess the benefits and potential harms of antibiotic prophylaxis for elective hysterectomy, and to determine which,if any,prophylactic drug regimen is best.

OBJECTIVES

Our primary objectives are to determine to what extent antibiotic prophylaxis reduces the risk of postoperative infection in women having an elective total or subtotal hysterectomy by any route or technique, to establish which (if any) antibiotic regimen is most effective and to assess the risk of adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of women having an elective total or subtotal hysterectomy by any route, comparing prophylactic antibiotics versus a placebo or versus a different type, route or timing of antibiotic. Trials will be at least double blinded (i.e. participants and clinicians blinded). We will not include quasi-total or subtotal randomised trials (for example trials that allocate treatment by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study).

We will exclude studies that have not analysed at least 80% of women randomised for at least one outcome. Where trials have analysed at least 80% of participants for some outcomes but analysed less than 80% of participants for other outcomes, we will only include outcomes that include at least 80% of participants. The rationale for excluding trials with high numbers of withdrawals is that attrition is unlikely to be equally distributed between trial arms: women who do not develop infection are more likely to be lost to follow up than those who do.

Types of participants

Women of any age without serious comorbidity (such as cancer) having an elective total or subtotal abdominal, vaginal, laparoscopic or laparoscopically assisted hysterectomy, with or without oophorectomy, for a benign gynaecological condition such as fibroids, endometriosis, uterovaginal prolapse or heavy menstrual bleeding.

Types of interventions

Prophylactic antibiotics versus placebo or a different type or regimen of antibiotics.
Terms are defined as follows:
Prophylactic: Antibiotics given where there are no signs or symptoms of infection, where no antibiotics have been taken within the previous 48 hours, and where the first dose is given up to 24 hours preoperatively and the last dose is given not more than 24 hours postoperatively.

Type of antibiotic:
We will classify antibiotics as follows:
(1) Cephalosporins

- *First generation* (for example cefazolin, cephradine, cephazolin, cephalexin, cefadroxil)
- *Second generation* (for example cefoxitin, cefuroxime, cephamandole, cefaclor, cefprozil, loracarbef)
- *Third generation* (for example cefotaxime, cefotetan, ceftazidime, ceftriaxone, cefixime, cefpodoxime proxetil, ceftibuten, cefdinir, cephoperazone,ceftizoxime)
- *Fourth generation* (for example cefepime)

(2) Penicillins (for example penicillin, amoxicillin)
(3) Macrolides (for example erythromycin, calrithromycin, azithromycin)
(4) Fluoroquinolones (for example metronidazoe, ciprofloxacillin, levofloxacin, oxfloxacin)
(5) Sulfonamides (for example co-trimoxazole, trimethoprim)
(6) Tetracyclines (for example tetracycline, doxycycline)
(7) Aminogylocosides (for example gentamycin, tobramycin)
(8) Glycopeptides (for example vancomycin)
(9) Antiprotozoals (for example metronidazole)
(10) Combination drugs:

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- *Augmentin* (amoxycillin and clavulanic acid)
- *Other combinations of drugs* (will be considered individually)

Antibiotic regimen includes the following:

- Route: any systemicregimen will be included, irrespective of the route of administration (for example intravenous, intramuscular, oral, rectal)
- Number of doses (for example single versus repeated doses)

Types of outcome measures

We will consider trials that report any one of the following clinical outcomes,

Primary outcomes

(1) Infection:

Measured as the proportion of women who develop one of the following (according tothe study definition) within eight weeks of surgery:

- Any postoperative infection
- Abdominal wound infection (for example wound cellulitis, abscess, dehiscence)
- Pelvic infection (including vaginal cuff (vault) infection, pelvic inflammatory disease, pelvic abscess, infected haematoma)
- Urinary tract infection
- Other serious infection or infectious complication, such as septicaemia, septic shock, distant infections (for example pneumonia)
- Postoperative fever of > 38 degrees on at least two occasions more than four hours apart, excluding the day of surgery

(2) Morbidity (for example allergic reaction, diarrhoea, bacterial resistance or as defined by the study) and mortality (infection-related and all-cause)

Primary outcomes will be classified as either early (before discharge from hospital or within seven days of surgery), late (at follow up: within eight weeks of surgery), or total (early and late).

Secondary outcomes:

(1) Asymptomatic infection, diagnosed solely by lab test with no clinical signs or symptoms (e.g. asymptomatic bacteriuria), either early (before discharge from hospital or within seven days of surgery), late (at follow up: within eight weeks of surgery) or total (early and late).

(2) Any requirement for systemic antibiotics, either early (before discharge from hospital or within seven days of surgery), late (at follow up: within eight weeks of surgery) or total (early and late).

(3) Length of hospital stay

(4) Readmission to hospital

(5) Cost (including both public and private costs)

(6) Quality of life

Search methods for identification of studies

We will search the following for all reports which describe (or might describe) randomised controlled trials of antibiotic prophylaxis: the specialised register of the Cochrane Menstrual Disorders and Subfertility Group, the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library ongoing), MEDLINE (1966 to ongoing), EMBASE (1980 to ongoing), Current Contents (1993 to ongoing), Biological Abstracts (1969 to ongoing) and reference lists of articles. We will also search the National Research Register and the metaRegister of Controlled Trials for ongoing trials and will contact pharmaceutical companies and experts in the field. We will use the search strategy developed by the Menstrual Disorders and Subfertility Group (see Review Group details for more information). See Appendix 1.

Data collection and analysis

Two reviewers will select trials for inclusion in the review from the results of the search outlined above. These reviewers will discuss uncertainty over eligibility, and where there is no consensus, the third reviewer will make the final decision.

IWe will analyse included trials for the following quality criteria and methodological details:

TRIAL CHARACTERISTICS

(1) Method of randomisation

(2) Quality of allocation concealment

(3) Presence or absence of blinding of participants, clinicians and outcome assessors to treatment allocation

(4) Number of women randomised

(5) Number of withdrawals (women excluded from analysis or lost to follow up) and reasons why.

(6) Whether an intention to treat analysis was done: intention to treat analysis is defined for the purpose of this review as the analysis of all women randomised, in the groups to which they were randomised

(7) Whether a power calculation was done

(8) Duration, timing and location of the study

CHARACTERISTICS OF THE STUDY PARTICIPANTS

(1) Type of elective hysterectomy undergone (total or subtotal vaginal, laparoscopically assisted vaginal or abdominal)

(2) Inclusion criteria

(3) Exclusion criteria

(4) Other characteristics of study participants (e.g. age, body mass index)

(5) Whether the groups of participants were well balanced with regard to prognostic factors

INTERVENTION USED

(1) Type of antibiotic used

(2) Dose

(3) Route

(4) Single or multiple doses given

(5) Duration of course of antibiotics

(6) Timing of doses

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NATURE OF COMPARISON
(1) Placebo or antibiotic: if antibiotic, what type?
(2) Route of administration
(3) Drug regimen
OUTCOMES
(1) Methods used to measure infection
(2) Methods used to measure fever
(3) Methods used to evaluate adverse effects
(4) Methods used to evaluate resource and patient costs
(5) Methods used to measure quality of life
Two reviewers will independently assess the quality of the trials and data extraction using forms designed according to Cochrane guidelines. We will request further information from authors whose trials appear to meet eligibility criteria if aspects of methodology are unclear, or where the data are in a form unsuitable for meta-analysis.
We will grade the quality of allocation concealment as adequate (A), unclear (B) or inadequate (C), following the detailed descriptions of these categories provided by the Menstrual Disorders and Subfertility Review Group.
STATISTICAL ANALYSIS
We will analyse statistics in accordance with the guidelines in the Cochrane Reviewers' Handbook and pool the outcomes statistically, where possible.
For dichotomous data (for example, proportion of participants developing an infection), results for each study will be expressed as a relative risk (RR) with 95% confidence intervals. Although odds ratios have commonly been used for meta-analyses, relative risk is easier to interpret, especially where high event rates and large treatment effects can be anticipated in the included studies, as pertains in this case (Clarke 2003; Sinclair 1994). Relative risks of individual studies will be combined for meta-analysis with Review Manager software using the Peto-modified Mantel-Haenszel method. Since there is no consensus about whether fixed or random effects models should be used for meta-analysis, we will use both. This might be viewed as a sensitivity analysis to assess the impact of the choice of model on the results of the analysis. Unless the results are robust to both models, they should be treated with caution. We plan to publish graphs displaying the results of the fixed effects approach. Where appropriate the results will also be expressed as a number needed to treat,as absolute measures can be more informative than relative measures (Clarke 2003).
Differences between groups in the meta-analysis of continuous outcomes (such as length of hospital stay) will be shown as a weighted mean difference (WMD) and 95% confidence interval. Meta-analytic methods for continuous data assume that the underlying distribution of the measurements is normal. The ratio of the mean to its standard deviation gives a crude method of assessing skew: if this ratio is less than 1.65 for any group in a trial, the results will not be pooled but will be reported in text in the Other Data section of the review, unless the original data is not available for log transformation. Results will also be reported in Other Data where data are clearly skewed and results are reported in the publication as median and range with non-parametric tests of significance.
Any heterogeneity (variation) between the results of different studies will be detected by inspecting the scatter in the data points on the graphs and the overlap in their confidence intervals and, more formally, by checking the results of the chi squared tests. A p value of 0.05 will be used for the chi squared tests, rather than the more conservative 0.1, since we anticipate that there will be many studies in the meta-analysis and in such a situation the test has high power to detect a small amount of heterogeneity that may be clinically unimportant. (Clarke 2003). If statistical heterogeneity is detected, and provided there are sufficient trials (> 10), we plan to conduct sensitivity analyses to examine the possible contribution of other clinical or methodological differences between the trials, specifically:
(1) Trials with adequate methodology versus those whose methodology is poor (for example unequal groups at baseline)
(2) Trials which appeared to differ from the others in their clinical criteria for defining infection and postoperative fever
We plan to conduct subgroup analysis according to
(1) The surgical route used (abdominal, vaginal, or laparoscopically assisted vaginal)
(2) The type of antibiotic used
(3) The antibiotic regimen used
If other possible sources of heterogeneity become evident during the preparation of the review; we may perform further subgroup or sensitivity analyses. The results of any such post hoc analyses need to be interpreted with great caution.
Publication bias is a strong possibility, particularly since it is likely that many of the studies will have been funded by industry. We will use a funnel plot to assess such bias.
TIMELINE
We intend to publish the full review will be published within a year of the publication of the protocol. We plan to search for new RCTs every two years and to update the review accordingly.

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* *Indicates the major publication for the study*

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APPENDICES

Appendix 1. SEARCH STRATEGY

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomized controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt.
9. exp clinical trials/
10. (clin$ adj5 trial$).ti,ab,sh.
11. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
12. placebos/
13. placebo$.ti,ab,sh.
14.random$.ti,ab,sh.
15. Research design/
16. or/8-15
17. animal/ not (human/ and animal/)
18. 7or 16
19. 18 not 17
20. exp HYSTERECTOMY/
21 hysterectomy.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
22. hysterectom$.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
23. or/20-22
24. ANTIBIOTICS/
25. antibiotic?.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
26. antimicrobial?.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
27. exp ANTIBIOTIC PROPHYLAXIS/
28. prophyla$.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
29. or/24-28
30. 19 and 23 and 29

The search string for EMBASE will be as follows:

1. Controlled study/ or randomised controlled trial/
2. double blind procedure/
3. double blind procedure.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. single blind procedure/
5. single blind procedure.mp.
6. crossover procedure/
7. drug comparison/
8. placebo/
9. random$.ti,ab,hw,tn,mf.
10. latin square.ti,ab,hw,tn,mf.
11. crossover.ti,ab,hw,tn,mf.
12. cross-over.ti,ab,hw,tn,mf.
13. placebo$.ti,ab,hw,tn,mf.
14. ((doubl$ or singl$ or tripl$ or treb$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf.
15. (clinical adj5 trial$).ti,ab,hw,tn,mf.
16. or/1-15

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17. nonhuman/
18. animal/ not (human/ and animal/)
19. or/17-18
20. 16 not 19
21. exp hysterectomy/
22. hysterectomy.mp
23. hysterectom$.mp.
24. or/21-23
25. antibiotics.mp. or Antibiotic Agent/
26. antimicrobial.mp.
27. prophylaxis.mp.
28. ANTIBIOTIC PROPHYLAXIS/
29. exp ANTIBIOTIC PROPHYLAXIS/
30. prophyla$.mp.
31. or/25-30
32. 20 and 24 and 31

WHAT'S NEW

Date	Event	Description
6 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2004

CONTRIBUTIONS OF AUTHORS

Jane Marjoribanks wrote the protocol and developed the search strategy.

Vanessa Jordan commented on the protocol and contributed to the methods section.

Karim Calis reviewed drafts of the protocol.

DECLARATIONS OF INTEREST

None known

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SOURCES OF SUPPORT

Internal sources

- University of Auckland, School of Medicine, Auckland, New Zealand.

External sources

- Ministry of Health, New Zealand.

NOTES

This protocol is a completely rewritten version of the protocol originally published by the Menstrual Disorders and Subfertility Group in Issue 2, 1999. It was withdrawn from the Cochrane Library in Issue 3, 2000. The original reference was: Martin-Hirsch P L, Papadimitriou D, Kitchener H. Antibiotic prophylaxis for major gynaecological surgery.

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