

Antibiotic prophylaxis for hysterectomy, a prospective cohort study: cefuroxime, metronidazole, or both?

THI Brummer,^a A-M Heikkinen,^b J Jalkanen,^c J Fraser,^d J Mäkinen,^e E Tomás,^f T Seppälä,^g J Sjöberg,^a P Härkki^a

^a Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland ^b Department of Obstetrics and Gynaecology, Kuopio University Hospital, Kuopio, Finland ^c Department of Obstetrics and Gynaecology, Central Finland Central Hospital, Jyväskylä, Finland ^d Department of Obstetrics and Gynaecology, North Karelia Central Hospital, Joensuu, Finland ^e Department of Obstetrics and Gynaecology, Turku University Hospital, Turku, Finland ^f Department of Obstetrics and Gynaecology, Tampere University Hospital, Tampere, Finland ^g Department of Information and Service Management, Aalto University School of Economics, Helsinki, Finland

Correspondence: Dr THI Brummer, Department of Obstetrics and Gynaecology, Helsinki University and Helsinki University Central Hospital, PO Box 140, 00029 HUS, Helsinki, Finland. Email tea.brummer@hus.fi

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Objective To evaluate cefuroxime and metronidazole antibiotic prophylaxis.

Design Observational nonrandomised 1-year prospective cohort study.

Setting Fifty-three hospitals in Finland.

Population A total of 5279 women undergoing hysterectomy for benign indications, with cefuroxime given to 4301 and metronidazole given to 2855. Excluding other antibiotics, cefuroxime alone was given to 2019, metronidazole alone was given to 518, and they were administered in combination to 2252 women.

Methods Data on 1115 abdominal hysterectomies (AHs), 1541 laparoscopic hysterectomies (LHs), and 2133 vaginal hysterectomies (VHs) were analysed using logistic regression adjusted for confounding factors.

Main outcome measures Postoperative infections.

Results Cefuroxime had a risk-reductive effect for total infections (adjusted odds ratio, OR, 0.29; 95% confidence interval, 95% CI, 0.22–0.39), but the independent effect of metronidazole and the interaction effect of cefuroxime and metronidazole were

nonsignificant. In subgroup analyses of AHs, LHs, and VHs involving those receiving the two main antibiotics only, the effect of cefuroxime alone nonsignificantly differed from that of cefuroxime and metronidazole in combination for all types of infection. The absence of cefuroxime, assessed by comparing metronidazole alone with cefuroxime and metronidazole in combination, led to an increased risk for total infections in AHs (adjusted OR 3.63; 95% CI 1.99–6.65), in LHs (OR 3.53; 95% CI 1.74–7.18), and in VHs (OR 4.05; 95% CI 2.30–7.13), and also increased risks for febrile events in all categories (AHs, OR 2.86; 95% CI 1.09–7.46; LHs, OR 13.19; 95% CI 3.66–47.49; VHs, OR 12.74; 95% CI 3.01–53.95), wound infections in AHs (OR 6.88; 95% CI 1.09–7.49), and pelvic infections in VHs (OR 4.26; 95% CI 1.76–10.31).

Conclusions In this study, cefuroxime appeared to be effective in prophylaxis against infections. Metronidazole appeared to be ineffective, with no additional risk-reductive effect when combined with cefuroxime.

Keywords Antibiotic prophylaxis, cefuroxime, hysterectomy, metronidazole.

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Introduction

Infections are responsible for a significant proportion of postoperative morbidity. Hysterectomy is a clean-contaminated operation, and postoperative infections are polymicrobial, as vaginal bacteria inoculate the surgical site.¹ In

vaginal hysterectomy (VH), evidence supporting antibiotic prophylaxis (AP) was established over three decades ago,² and controversies regarding the benefits of AP in abdominal hysterectomy (AH) eventually diminished.^{3–6} Infections are more than halved with AP, and so placebo-controlled studies are no longer justifiable.^{2,6}

Guidelines on AP vary considerably. The National Institute for Health and Clinical Excellence (NICE) in 2008 stated that, for clean-contaminated surgery, AP is preferable. Nevertheless, these UK guidelines provide no recommendations separately for VH, and for AH they state, 'There is insufficient evidence that prophylactic administration of antibiotics results in fewer surgical site infections.'⁷ In 2008, the Scottish Intercollegiate Guidelines Network (SIGN) recommended AP for both AH and VH, but did not suggest which antibiotics should be used.⁸

In a large meta-analysis of placebo-controlled and comparative studies of antibiotics, Hemsell included 18 and 34 studies, respectively, involving VH, and 19 and 21 studies involving AH.⁵ On the basis of the findings of this meta-analysis, Hemsell proposed a prophylactic regime with a first-generation cephalosporin, cefazolin 1 or 2 g, administered intravenously in the operating room before anaesthesia, for both types of hysterectomy. These recommendations from two decades ago seem to be the basis for the current American College of Obstetricians and Gynecologists (ACOG) guidelines. In 2006, for hysterectomy the ACOG recommended preoperative single-dose intravenous AP consisting of cefazolin 1 or 2 g, or cefoxitin 2 g. Metronidazole 1 g is recommended for those with hypersensitivity to penicillin.⁹ In the 2009 update, the recommended alternative to cefazolin was metronidazole or clindamycin, each combined with gentamicin or a quinolone.¹⁰ In Denmark, national guidelines for hysterectomy AP recommend the use of cefuroxime plus metronidazole.¹¹

The majority of postoperative pelvic infections involve anaerobic bacteria.¹ This is the basis for prophylaxis directed against anaerobes. Metronidazole is a common treatment for bacterial vaginosis (BV), in which the vaginal flora is altered, with increasing concentrations of *Gardnerella vaginalis* and anaerobes. Although the bacteria involved are fairly apathogenic, BV is associated with post-hysterectomy infection, increasing the risk of pelvic infection by three-fold or more.^{12,13} This is important because of the high prevalence of BV, which ranges from 15 to 30%.^{13,14}

Additional anaerobic coverage is recommended in AP for colorectal surgery,¹⁵ but its role has not been clarified with hysterectomy. As a national quality assessment, the frequency and type of AP were analysed in a 1-year cohort study: the FINHYST study. The aim of this evaluation of AP in hysterectomy was to analyse the independent effects of cefuroxime and metronidazole. Of particular interest was the evaluation of whether additional anaerobic coverage with metronidazole was beneficial, in combination with cefuroxime.

Methods

Data were prospectively collected from 1 January to 31 December 2006 in 53 hospitals, and represent 79.4% of

hysterectomies performed for benign causes in Finland in 2006. Surgical data and data on complications for this study, FINHYST, have appeared in detail previously.^{16,17} To summarise, hysterectomies were performed using three main approaches: AH ($n = 1255$; 24%), laparoscopic hysterectomy (LH; $n = 1679$; 32%), and VH ($n = 2345$; 44%); only 1.7% of the operations were subtotal, i.e. were performed without opening the vagina. The 'VH' category includes operations with (55%) or without concomitant colpoperineoplasty. Conversions from LH (5.2%) and VH (0.6%) were included in the analysis, and were grouped as intention-to-treat by the type of hysterectomy initially chosen.

A study form for each patient was completed at discharge by her gynaecological surgeon. In addition, infections following discharge were documented on a separate form at the outpatient clinics, provided at the same hospitals in which the operation took place. The definition of wound infection was antibiotic usage or drainage being necessary, the definition of urinary tract infection (UTI) was a single bacterial growth exceeding 10^5 bacteria/ml, and the definition of a febrile event was a clinically relevant fever for unknown reason with axillary temperature $\geq 38^\circ\text{C}$. Late-onset complications also included pelvic infections, defined as an infected haematoma or abscess. Total infections represent the number of patients affected; some may have had more than one infection. In total, 20% of UTIs, 22% of febrile events, and 63% of wound infections were of late onset.

There were 5279 hysterectomies performed in FINHYST in total. For each patient, the administration of AP was individually reported by her surgeon. Data on AP were available for 5240 operations, with 39 forms left incomplete. AP was given to 5111 women (97.5%). No method was used to randomise or allocate patients to different groups; the choice of antibiotic(s) was made according to local hospital policy, or according to the preference of the individual gynaecological surgeon. Cefuroxime was given to 4301 women and metronidazole was given to 2855 women. Cefuroxime alone was given to 2019 women (38.5%), metronidazole alone was given to 518 women (9.9%), and metronidazole in combination with cefuroxime was given to 2252 women (43.0%). Other combinations were used for 106 patients (2.0%), and other antibiotics alone were given to 78 patients (1.5%), the AP was left unspecified for 138 patients (2.6%), and 129 patients (2.5%) received no AP. By hysterectomy method, cefuroxime was given in a total of 945 AH, 1455 LH, and 1901 VH operations, and metronidazole was given in 732 AH, 920 LH, and 1203 VH operations. These data are presented in Table 1, excluding patients given other antibiotics.

The common dosages were intravenous cefuroxime 1.5 g and metronidazole 0.5 g at induction. The exact cefuroxime dosage was reported for 38% of patients (for 1647 of the 4301 receiving cefuroxime), with the vast

Table 1. Infection complications by antibiotic prophylaxis

	Total	Total infections	Febrile event	Wound infection	Pelvic infection	Urinary tract infection
Abdominal hysterectomy						
Combination of cefuroxime and metronidazole	532	31 (5.8)	14 (2.6)	6 (1.1)	2 (0.4)	10 (1.9)
Cefuroxime alone	405	28 (6.9)	6 (1.5)	7 (1.7)	6 (1.5)	10 (2.5)
Metronidazole alone	178	27 (15.2)	9 (5.1)	10 (5.6)	2 (1.1)	7 (3.9)
Laparoscopic hysterectomy						
Combination of cefuroxime and metronidazole	806	50 (6.2)	8 (1.0)	15 (1.9)	22 (2.7)	5 (0.6)
Cefuroxime alone	645	37 (5.7)	6 (0.9)	7 (1.1)	22 (3.4)	2 (0.3)
Metronidazole alone	90	13 (14.4)	6 (6.7)	1 (1.1)	4 (4.4)	2 (2.2)
Vaginal hysterectomy						
Combination of cefuroxime and metronidazole	914	35 (3.8)	4 (0.4)	5 (0.5)	13 (1.4)	14 (1.5)
Cefuroxime alone	969	38 (3.9)	5 (0.5)	8 (0.8)	15 (1.5)	12 (1.2)
Metronidazole alone	250	31 (12.4)	9 (3.6)	3 (1.2)	15 (6.0)	6 (2.4)

Total infections refer to the number of patients having at least one complication; a patient may have had more than one infection.
All values are *n* (%).

majority reported to have been given a preoperative single 1.5-g intravenous dose. Extended prophylaxis was rare: in three cases one and in 11 cases two extra doses were given. Miscellaneous dosages, such as 750 mg, 1 g, and 2 g were rare (eight in total). The exact metronidazole dosage was reported for 24% of patients (680 of the 2855 receiving metronidazole), usually 0.5 g intravenously at induction, but eight patients received a 1-g intravenous dose. Oral (64; 2.2%) and vaginal (42; 1.5%) administration on the previous evening was rare, most commonly with doses of 2 and 0.5 g. Thus, in 95% of operations the gynaecological surgeons indicated the antimicrobial agent(s), but seldom provided the exact dosage. It is likely that particularly uncommon dosages or routes for metronidazole administration other than intravenously were reported, but that the standard regime was left unreported. As a consequence of the missing data no subgrouping was attempted, and all uses of cefuroxime or metronidazole, irrespective of dosage, were analysed together.

Univariate data analysis preceded logistic regression in the analysis of complications. The analyses were adjusted for hospital type (university, central, local, or private hospital), the experience of the gynaecological surgeon (<30 or ≥ 30 such hysterectomies ever performed), patient characteristics (body mass index, BMI [linear], and age [<45 , $45\text{--}54$, or ≥ 55 years]), indication for hysterectomy (myomas, menorrhagia, dysmenorrhoea, endometriosis, uterine prolapse, adnexal mass, or other), operation time (minutes), haemorrhage (ml), concomitant surgery (yes or no), adhesiolysis, and uterine weight (g). The model was also adjusted for type of hysterectomy (AH, LH, or VH) in the analysis of all hysterectomies together. $P < 0.05$ was considered to be statistically significant, and adjusted odds ratios (aORs, the exponential of the B-coefficient) are presented

with 95% confidence intervals (95% CIs). Analyses were conducted with SPSS 17.0 (Chicago, IL, USA).

We analysed, using logistic regression, the separate and interactive effects of cefuroxime and metronidazole on total infections. In addition to the other control variables, the model was also adjusted for the use of other miscellaneous antibiotics. If AP was unspecified, the patient was excluded from the analysis. The reference for use of cefuroxime AP was no cefuroxime given; similarly, for metronidazole AP, the reference was no metronidazole given. In the additional analyses for the categorised individual infections, cefuroxime or metronidazole antibiotics given alone were compared with their use in combination; in these analyses, we excluded all users of other miscellaneous antibiotics. Cefuroxime, irrespective of dosage, and metronidazole, irrespective of dosage and route, were analysed as yes/no indicator variables (1, yes; 0, no).

The effect of the duration of LH on risk of infection was illustrated for cefuroxime, metronidazole, and both given in combination (Figure 1). This curve presents the effect for a common LH case, with mean values and the most common categorical variable responses applied: a patient aged 45–54 years, operated on for myomas in a university hospital, with no concomitant surgery or adhesiolysis performed, with a mean BMI (26.1 m²/kg), haemorrhage (270 ml), and uterine size (211 g), and given thrombosis prophylaxis. The graph presents a duration range of 23–305 minutes, covering all of the surgeries excepting a single extreme duration involving an iliac vessel injury.

Results

Incidence of postoperative infections by type of hysterectomy and by cefuroxime and metronidazole AP are

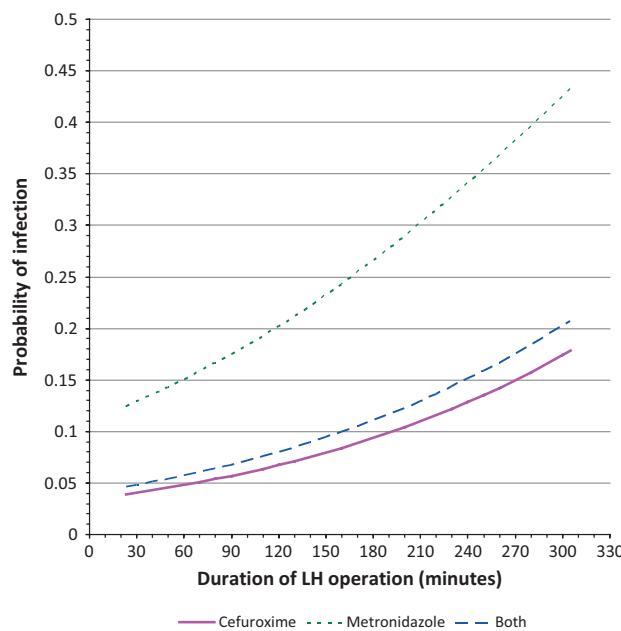


Figure 1. Effect on probability of infection according to duration of operation. Estimated probabilities of infection for the effect of cefuroxime or metronidazole alone, and for the effect of both given in combination, are shown as a function of the duration of the laparoscopic hysterectomy (LH) operation, from a logistic regression analysis adjusted for confounding factors.

Table 2. Independent effects of cefuroxime and metronidazole prophylaxis for total infections

	Cefuroxime	Metronidazole
All hysterectomies	0.29 (0.22–0.39)	0.95 (0.72–1.24)
Abdominal hysterectomy	0.33 (0.20–0.56)	0.97 (0.58–1.62)
Laparoscopic hysterectomy	0.34 (0.19–0.63)	1.21 (0.73–1.99)
Vaginal hysterectomy	0.21 (0.13–0.33)	0.75 (0.47–1.19)

Logistic regression analyses, adjusted for the group of other miscellaneous prophylactic antibiotics, hospital type, experience of the gynaecological surgeon, use of thrombosis prophylaxis, age, BMI, indication for hysterectomy, duration of surgery, haemorrhage, concomitant surgery, adhesiolysis, and weight of the uterus. When all hysterectomies were analysed together, the model was also adjusted for type of hysterectomy. The interaction of cefuroxime and metronidazole was nonsignificant for all analyses. Values are adjusted odds ratios (95% confidence intervals), with statistically significant results set in bold.

presented in Table 1. In the logistic regression analysis adjusted for confounding factors, cefuroxime had a risk-reductive effect for total infections versus no cefuroxime given (Table 2). The independent effect of metronidazole and the interaction effect of cefuroxime and metronidazole were both nonsignificant; results were similar for all types

of hysterectomy (Table 2). Therefore, although the lowest absolute rate of infections occurred with a combination of cefuroxime and metronidazole for AH and VH (Table 1), we found no statistically significant additional risk-reductive effect with metronidazole.

These results were supported by the subgroup analyses performed for cefuroxime or metronidazole antibiotics given alone, compared with their combined use, for total infections and also for the individual infection complications (Table 3). Those given miscellaneous other antibiotics were excluded from the analyses. For all types of infection, the effect of cefuroxime alone was nonsignificantly different from that of cefuroxime and metronidazole in combination. In contrast, when metronidazole was given alone compared with its use in combination with cefuroxime, an increased risk for total infections and febrile events was evident with all hysterectomy types. The same result was obtained for wound infections in AH and pelvic infections in VH (Table 3).

The duration of the operation was associated independently with the appearance of infections. In AH, the odds of wound infection rose by an average of 13.3% per 10 minutes (95% CI 0.1–28.3%; $P = 0.048$). The risk for total infections rose by 6.1% per 10 minutes (95% CI 0.4–12.1%; $P = 0.042$) for LH only, in which the strongest effect was for febrile events, with the risk rising by 12.5% per 10 minutes (95% CI 0.4–26.0%; $P = 0.042$). The effect on total infections for LH according to duration of surgery is illustrated in Figure 1 for cefuroxime, metronidazole, and for both in combination. The mean duration of LH was 108 minutes.¹⁷ Thus, for cefuroxime, compared with the estimated infection rate for an operation with a mean duration (6.3%), the estimated rate at 180 minutes was 1.5 times higher (9.4%), and at 240 minutes it was more than double (12.9%) (Figure 1). The difference between cefuroxime alone and cefuroxime and metronidazole in combination (Figure 1) was found to be nonsignificant.

Discussion

Cefuroxime had an independent risk-reductive effect for total infections in all three types of hysterectomy. Moreover, compared with metronidazole alone, cefuroxime combined with metronidazole had a risk-reductive effect for total infections and for febrile events in every hysterectomy type, and also for wound infections after AH and for pelvic infections after VH. Metronidazole in combination or alone was used in as many as 54% of operations, but appeared to be ineffective: the independent effect of metronidazole in reducing the risk of total infections was nonsignificant, and analyses of its use in combination with cefuroxime showed no significant benefits versus cefuroxime alone.

Table 3. Effect of cefuroxime and metronidazole antibiotic prophylaxis for various infections

	Abdominal hysterectomy	Laparoscopic hysterectomy	Vaginal hysterectomy
Infections total			
Cefuroxime alone	1.38 (0.74–2.57)	1.00 (0.57–1.76)	1.11 (0.65–1.92)
Metronidazole alone	3.63 (1.99–6.65)	3.53 (1.74–7.18)	4.05 (2.30–7.13)
Febrile events			
Cefuroxime alone	0.61 (0.19–1.96)	1.39 (0.32–5.98)	1.28 (0.28–5.97)
Metronidazole alone	2.86 (1.09–7.49)	13.19 (3.66–47.49)	12.74 (3.01–53.95)
Wound infections			
Cefuroxime alone	2.68 (0.71–10.16)	1.01 (0.32–3.17)	2.23 (0.62–8.09)
Metronidazole alone	6.88 (2.12–22.30)	0.84 (0.10–6.79)	3.99 (0.83–19.10)
Pelvic infection			
Cefuroxime alone	3.18 (0.53–18.95)	1.07 (0.49–2.34)	1.32 (0.53–3.28)
Metronidazole alone	2.67 (0.35–20.29)	2.13 (0.67–6.81)	4.26 (1.76–10.31)
Urinary tract infection			
Cefuroxime alone	1.13 (0.42–3.02)	0.51 (0.07–3.91)	0.69 (0.29–1.63)
Metronidazole alone	2.20 (0.79–6.16)	5.65 (0.68–47.14)	1.79 (0.65–4.96)

Logistic regression analyses, adjusted for hospital type, experience of the gynaecological surgeon, use of thrombosis prophylaxis, age, BMI, indication for hysterectomy, duration of surgery, haemorrhage, concomitant surgery, adhesiolysis, and weight of the uterus. Women given other antibiotics or not given antibiotic prophylaxis were excluded from the analysis. The reference for the use of individual antibiotics is the combination of cefuroxime and metronidazole. Consequently, the risk effect for metronidazole is observed as the effect of not giving cefuroxime, and vice versa. Values are adjusted odds ratios (95% confidence intervals), with statistically significant results set in bold.

A limitation of our evaluation is the lack of randomisation. We were unable to affect the power or the sample sizes realised. Therefore, unintentional bias may have occurred: a single-drug regime may have been chosen for the less challenging cases, for example patients with no co-morbidities, such as diabetes. Nevertheless, in the analysis we controlled for many important factors affecting infection morbidity, such as age,^{17–20} obesity,^{17,20–22} and haemorrhage.²³ The reasons why drug choice for some patients was widened to cover the anti-aerobic spectrum, with a combination involving metronidazole in preference to cefuroxime alone, also remain unknown. A great deal of postoperative morbidity arises from the vaginal flora, which places hysterectomy in the category of clean-contaminated surgery. In most cases, regular clean-contaminated surgery was carried out: only ten of the 5279 operations performed were for pelvic inflammatory disease (PID), and could be categorised as contaminated. Sporadic cases involving the opening of the gastrointestinal tract were also included in our unselected cohort: ten intraoperatively detected bowel injuries and 50 concomitant appendectomies, in addition to 13 other bowel resections.

FINHYST is a large national observational study, for which infectious morbidity data were collected prospectively; in addition, data on complications occurring after discharge were collected at hospital outpatient clinics, where most postoperative complaints are dealt with. Mild infections, however, may have been treated by general prac-

titioners outside the hospitals, and therefore may be unknown to FINHYST. We believe that this may apply particularly to UTIs.

The initiation of AP should be preoperative²⁴: high tissue concentrations should be present at the time at which contamination is most likely to occur. One large review observed pelvic infections in 25% of patients after VH, but in only 10% after AH; with AP, both these percentages fell to 5%.³ In AH and LH, the vagina is opened at the end of the procedure, and the period of exposure to vaginal bacteria is brief, in comparison with that in VH, in which there may be a greater colonisation of the surgical site. However, the duration of surgery has been found to be associated with increasing risk of infection in both AH and VH.¹⁸ For the first time we observed the same association for LH; less invasive surgery did not protect patients from this phenomenon.

One placebo-controlled meta-analysis on AH grouped cephalosporins according to whether they were first, second, or third generation. Infection rates were found to decrease significantly with each group: 10.8% (OR 0.35) for the first generation; 9.7% (OR 0.29) for the second; and 7.4% (OR 0.26) for the third. The intravenous route was superior, and a single dose was more efficient than multiple doses.²⁵ No studies of cefuroxime were included in the analysis. To our knowledge, the only study of AP with LH prior to ours retrospectively analysed cefazolin in single versus multiple doses, with no change in prophylactic effect being found.²⁶

Metronidazole has long been the drug of choice in Finland, probably as a consequence of the positive results of a Finnish placebo-controlled trial.²⁷ The vast majority of studies on AP have not involved metronidazole: four large reviews, evaluating over 200 studies,^{2,4–6} found only eight that involved metronidazole, with a beneficial effect in three; all were AH studies against a placebo.^{27–29} Only one placebo-controlled metronidazole study has been carried out since. This largest evaluation (to date) enrolled 258 patients with AHs: postoperative wound infections fell from 12 to 6% with the use of metronidazole.³⁰ Metronidazole may be more effective than placebo, but, from the few small comparative studies with other antimicrobial agents, support for the superiority of metronidazole is lacking.^{31–33}

Compared with the first-generation cephalosporins, cefuroxime, as a second-generation drug, has a wider spectrum extending from Gram-positive cocci to Gram-negative rods.^{34,35} Second-generation cephalosporins also show coverage against some anaerobes, such as the Gram-positive peptostreptococci and the Gram-variable *Mobiluncus* rods,^{36,37} which are abundant in women with BV. Obviously, cefuroxime also has a wider spectrum than metronidazole, the classic antimicrobial agent against anaerobes. *Gardnerella vaginalis* is exceptional in the sense that, although aerobic,^{1,38} it is susceptible to metronidazole. In the treatment of BV, a narrow spectrum is advantageous, as metronidazole has no effect on lactobacilli. Cefuroxime, however, with its broad spectrum, is also effective against *G. vaginalis*.³⁸ Thus, against the microbes involved in BV, cefuroxime appears to be a sufficient prophylactic agent.

Clostridium difficile infections (CDIs) have been linked to AP with cephalosporins, but a single-dose regimen seems safe, whereas the risk has been found to increase with the number of prophylactic doses.³⁹ In elective surgery, CDI was found to occur in 1% of patients receiving AP with a second-generation cephalosporin, but, if this was combined with any other antibacterial agent, the rate was as high as 7.2%.^{40,41} Our data, however, included only a single case of CDI.¹⁷ The unnecessary routine use of an antibiotic with no demonstrated effect is, in the expanding global struggle against resistance, unjustified. Since the year 2000, failure rates of metronidazole therapy for CDIs have risen.⁴² In the treatment of pelvic abscesses, however, the use of metronidazole or other antimicrobial agents potent against anaerobes is essential.¹ Many anaerobic bacteria involved in such infections, such as the *Prevotella* species and the *Bacteroides fragilis* group, produce β -lactamase, an enzyme that renders them resistant to penicillin and to many cephalosporins.^{34–36} Our study, however, examined prophylactic use. Either anaerobic bacteria resistant to cefuroxime are a minor issue or the eradication of other bacteria is sufficient

to prevent infections: anaerobic bacteria seem to require the presence of other pathogenic bacteria to initiate infection.⁴³ Notably, even in VH the risk of pelvic infection, defined as haematoma or abscess, for metronidazole alone was over four times greater than for its combined use with cefuroxime, and the combination of these two drugs provided no benefit exceeding that of cefuroxime alone.

Cefuroxime AP in hysterectomy has never been compared with a first-generation intravenous cephalosporin, such as cefazolin or cefalotin. In AP for caesarean section, cefazolin plus metronidazole was superior to cefazolin alone.⁴⁴ Also, whether the first-generation cephalosporins are as effective as cefuroxime in the prevention of infections with hysterectomy, arising from the anaerobic polymicrobial flora, remains uncertain.

Conclusion

The prospective FINHYST study is the first evaluation of different AP agents on such a large scale for current methods of hysterectomy. In this study, cefuroxime seemed to be effective in prophylaxis against postoperative infections, but metronidazole appeared ineffective, with no additional risk-reductive effect when combined with cefuroxime. A randomised controlled trial would be the best way to confirm these results of our national prospective cohort study.

Disclosure of interests

All authors have completed the ICMJE Unified Competing Interest form and declare no financial relationship with any companies with a relationship to the submitted work, and no relationships or activities that may have influenced the submitted work. No author has received support from companies for the submitted work. P.H. has lectured at one educational endometriosis event with lecturer payments from Bayer and Abbott, and attended one endometriosis congress with economic support from Bayer and Abbott.

Contribution to authorship

All the authors participated in the design of the study. TB, JF, AH, JJ, JM, JS, ET, and PH also participated in the acquisition of data. Advice on statistical data analysis was provided by TS, and analyses were conducted by TS and by TB, who is the guarantor of the study. TB drafted the article. All authors contributed to the critical revision of the article and provided substantial input into the study. The final version was approved by all of the authors.

Details of ethics approval

The study plan was approved by the ethics committees at the hospitals and by the Ministry of Social Affairs and Health in Finland, and was included in the ClinicalTrials.gov

protocol. Written consent was obtained from each patient. Data were collected by the operating gynaecological surgeons, who received no financial compensation for completing the forms. Trial registration: ClinicalTrials.gov protocol (NCT00744172).

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References

- 1 Hager D. Postoperative infections: prevention and management. In: Rock J, Jones H, editors. *Te Linde's Operative Gynecology*, 9th edn. Lippincott: Williams and Wilkins; 2003. pp. 195–207.
- 2 Duff P, Park R. Antibiotic prophylaxis in vaginal hysterectomy: a review. *Obstet Gynecol* 1980;55:1935–2025.
- 3 Hirsch H. Prophylactic antibiotics in obstetrics and gynecology. *Am J Med* 1985;78:170–6.
- 4 Cartwright P, Pittaway D, Jones H, Entman S. The use of prophylactic antibiotics in obstetrics and gynecology. A review. *Obstet Gynecol Surv* 1984;39:537–54.
- 5 Hemmell D. Prophylactic antibiotics in gynecologic and obstetric surgery. *Rev Infect Dis* 1991;13 (Suppl 10):S821–41.
- 6 Mittendorf R, Aronson MP, Berry RE, Williams MA, Kupelnick B, Klickstein A, et al. Avoiding serious infections associated with abdominal hysterectomy: a meta-analysis of antibiotic prophylaxis. *Am J Obstet Gynecol* 1993;169:1119–24.
- 7 National Institute for Health and Clinical Excellence, NICE. Clinical guideline 74. Surgical site infection. Prevention and treatment of surgical site infection. 2008 Cited May 1st 2011, [www.nice.org.uk/CG74]. Accessed 1 May 2011.
- 8 The Scottish Intercollegiate Guidelines Network (SIGN) 104 Antibiotic prophylaxis in surgery. A national clinical guideline. 2008 Cited May 1st 2011, [www.sign.ac.uk/pdf/sign104.pdf]. Accessed 1 May 2011.
- 9 ACOG Practice bulletin 74. Antibiotic prophylaxis for gynecologic procedures. *Obstet Gynecol* 2006;108:225–34.
- 10 ACOG practice bulletin 104. Antibiotic prophylaxis for gynecologic procedures. *Obstet Gynecol* 2009;113:1180–9.
- 11 Hansen CT, Møller C, Daugbjerg J, Kehlet H, Ottesen B. Establishment of a national Danish hysterectomy database: preliminary report on the first 13 425 hysterectomies. *Acta Obstet Gynecol Scand* 2008;87:546–57.
- 12 Soper D, Bump R, Hurt G. Bacterial vaginosis and trichomoniasis vaginitis are risk factors for cuff cellulitis after abdominal hysterectomy. *Am J Obstet Gynecol* 1990;163:1016–23.
- 13 Persson E, Bergström M, Larsson PG, Moberg P, Platz-Christensen JJ, Schedvin K, et al. Infections after hysterectomy. A prospective nation-wide Swedish study. The study group on infectious diseases in obstetrics and gynecology within the Swedish Society of obstetrics and gynecology. *Acta Obstet Gynecol Scand* 1996;75:757–61.
- 14 Holzman C, Leventhal J, Qiu H, Jones N, Wang J, the BV Study Group. Factors linked to bacterial vaginosis in nonpregnant women. *Am J Public Health* 2001;91:1664–70.
- 15 Nelson RL, Glenny AM, Song F. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev* 2009. Art. No.: CD001181. DOI: 10.1002/14651858.CD001181.pub3.
- 16 Brummer TH, Jalkanen J, Fraser J, Heikkilä A, Kauko M, Mäkinen J, et al. FINHYST 2006 - National prospective 1-year survey of 5 279 hysterectomies. *Hum Reprod* 2009;24:2515–22.
- 17 Brummer T, Jalkanen J, Fraser J, Heikkilä A, Kauko M, Mäkinen J, et al. FINHYST, a prospective study of 5 279 hysterectomies: complications and their risk factors. *Hum Reprod* 2011;26:1741–51.
- 18 Shapiro M, Muñoz A, Tager I, Schoenbaum S, Polk F. Risk factors for infection at the operative site after abdominal or vaginal hysterectomy. *N Eng J Med* 1982;307:1661–6.
- 19 Spilsbury K, Hammond I, Bulsara M, Semmens JB. Morbidity outcomes of 78 577 hysterectomies for benign reasons over 23 years. *BJOG* 2008;115:1473–83.
- 20 Löfgren M, Poromaa I, Stjernholm J, Renström B. Postoperative infections and antibiotic prophylaxis in Sweden: a study by the Swedish National Register for Gynecologic Surgery. *Acta Obstet Gynecol Scand* 2004;83:1202–7.
- 21 David-Montefiore E, Rouzier R, Chapron C, Darai E, the Collégiale d'Obstétrique et Gynécologie de Paris-Ile de France. Surgical routes and complications of hysterectomy for benign disorders: a prospective observational study in French university hospitals. *Hum Reprod* 2007;22:260–5.
- 22 Kjølhede P, Halil S, Löfgren M. Vaginal cleansing and postoperative infections morbidity in vaginal hysterectomy. A register study from the Swedish National Register for Gynecological Surgery. *Acta Obstet Gynecol Scand* 2011;90:63–71.
- 23 Peipert J, Weitzner S, Cruickshank C, Story E, Ethridge D, Lapane K. Risk factors for febrile morbidity after hysterectomy. *Obstet Gynecol* 2004;103:86–91.
- 24 Classen D, Evans S, Pestotnik S, Horn S, Menlove R, Burke J. The timing of prophylactic administration of antibiotics and the risk of surgical wound infection. *N Eng J Med* 1992;326:281–6.
- 25 Tanos V, Rojansky N. Prophylactic antibiotics in abdominal hysterectomy. *J Am Coll Surg* 1994;179:593–600.
- 26 Chang WC, Lee MC, Yeh LS, Hung YC, Lin CC, Lin LY. Quality-initiated antibiotic use in laparoscopic-assisted vaginal hysterectomy. *Aust N Z J Obstet Gynaecol* 2008;48:592–5.
- 27 Kauppila A, Rautiainen H, Tuimala R. Prevention on posthysterectomy infection with a combination of preoperative vaginal and perioperative intravenous administration of metronidazole. *Ann Chir Gynaecol* 1983;72:214–7.
- 28 Appelbaum PC, Moodley J, Chatterton SA, Cowan DB, Africa CW. Metronidazole in the prophylaxis and treatment of anaerobic infection. *S Afr Med J* 1978;54:703–6.
- 29 Poulsen HK, Borel J, Olsen H. Prophylactic metronidazole or suction drainage in abdominal hysterectomy. *Obstet Gynecol* 1984;63:291–4.
- 30 Henriksson L, Collins-Saltin A, Frick G, Kullander S, Sandholm L, Ursing J, et al. Metronidazole prophylaxis to prevent infections after total abdominal hysterectomy. *Acta Obstet Gynecol Scand* 1998;77:116–9.
- 31 Hamod K, Spence M, Rosenshein N, Dillon M. Single –dose and multidose prophylaxis in vaginal hysterectomy: a comparison of sodium cephalothin and metronidazole. *Am J Obstet Gynecol* 1980;136:976–9.
- 32 Houang E, Watson C, Howell R, Chapman M. Ampicillin combined with sulbactam or metronidazole for single dose chemoprophylaxis in major gynaecological surgery. *J Antimicrob Chemother* 1984;14:529–35.

33 Kauer F, Wijma J, Manson W. Vaginal hysterectomy: cefuroxime, metronidazole or both? *Pharm Weekbl Sci* 1990;12:284–8.

34 Rang H, Dale M, Ritter J, Flower R. *Rang and Dale's Pharmacology*, 6th edn. Churchill Livingstone: Elsevier, 2007.

35 Brooks GF, Carroll KC, Butel JS, Morse SA. *Jawetz, Melnick & Adelberg's Medical Microbiology*, 24th edn. New York: The McGraw-Hill Companies, 2007.

36 Murray P, Rosenthal K, Pfaller M. *Medical Microbiology*, 6th edn. Mosby: Elsevier, 2009.

37 Bahar H, Torun M, Öcer F, Kocazeybek B. *Mobiluncus* species in gynaecologic and obstetric infections: antimicrobial resistance and prevalence in a Turkish population. *Int J Antimicrob Agents* 2005;25: 268–71.

38 Martens M, Faro S, Maccato M, Riddle G, Hammill H. Susceptibility of female pelvic pathogens to oral antibiotic agents in patients who develop postpartum endometritis. *Am J Obstet Gynecol* 1991;164: 1383–6.

39 Mukhtar S, Shaker H, Basarab A, Byrne JP. Prophylactic antibiotics and *Clostridium difficile* infection. *J Hosp Infect* 2006;64:93–4.

40 Al-Obaydi W, Smith CD, Foguet P. Changing prophylactic antibiotic protocol for reducing *Clostridium difficile*-associated diarrhoeal infections. *J Orthop Surg* 2010;18:320–3.

41 Carignan A, Allard C, Pépin J, Cossette B, Nault V, Valiquette L. Risk of *Clostridium difficile* infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. *Clin Infect Dis* 2008;46:1838–43.

42 Kelly C, LaMont T. *Clostridium difficile* – More difficult than ever. *N Eng J Med* 2008;359:1932–40.

43 McDonald PJ, O'Loughlin JA. Prophylactic antibiotics and prevention of surgical sepsis. *Baillieres Clin Obstet Gynaecol* 1993;7: 219–36.

44 Meyer NL, Hosier KV, Scott K, Lipscomb G. Cefazolin versus cefazolin plus metronidazole for antibiotic prophylaxis at cesarian section. *South Med J* 2003;96:992–5.