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Preventing IUCD-related pelvic infection: the efficacy of prophylactic doxycycline at insertion

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Summary. Most of the small increased risk in pelvic inflammatory disease (PID) associated with the intrauterine contraceptive device (IUCD) appears to be caused by bacterial contamination of the endometrial cavity at the time of insertion. This randomized clinical trial of 1813 women in Nairobi, Kenya, assessed the effectiveness of 200 mg of doxycycline given orally at the time of insertion in reducing the occurrence of PID. The rate of this infection in the doxycycline-treated group was 31% lower than that in the placebo-treated group (1·3 and 1·9%, respectively; RR 0·69; 95% CI 0·32 to 1·5). The rate of an unplanned IUCD-related visit to the clinic was also 31% lower in the doxycycline-treated group (RR 0·69; 95% CI 0·52 to 0·91). Although the significance level ($P = 0·17$) for the reduction is PID does not meet the conventional standard of 0·05, the results may be suggestive of an effect. Moreover, the reduction in IUCD-related visits ($P = 0·004$) not only represents an important decrease in morbidity but also substantiates the reduction found for PID. Further studies are needed to corroborate these results. Consideration should be given to the prophylactic use of doxycycline at the time of IUCD insertion as an approach to preventing PID and other IUCD-related morbidity.

Most pelvic inflammatory disease (PID) associated with use of an intrauterine contraceptive device (IUCD) appears attributable to bacterial contamination of the endometrial cavity at the time of insertion. That contamination routinely occurs has been observed for over two decades

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(Mishell *et al.* 1966). Results from a number of studies (Vessey *et al.* 1981; Booth *et al.* 1980; O'Brien *et al.* 1983; Lee *et al.* 1983) have shown that the risk of PID was inversely related to the duration of IUCD use. In the largest and most detailed of these (Lee *et al.* 1983), the risk of PID (excluding women using the Dalkon Shield) was significantly elevated only during the first 4 months of use. The relative risk (RR) compared with women not using contraception was highest in the first month (RR = 3·8). The additional risk was lower at 2–4 months (RR = 1·7) and almost absent at ⩾5 months (RR = 1·1). Thus, both bacteriological and epidemiological studies implicate endometrial contamination at IUCD insertion in the development of PID. Since use of prophylactic antibiotics in women having an induced abortion appears to reduce the risk of subsequent infectious morbidity by about 50% (Grimes *et al.* 1984; Park *et al.* 1985), we conducted this randomized clinical trial to investigate whether use of prophylactic antibiotics at IUCD insertion would have an analogous protective effect.

Subjects and methods

From December 1984 to January 1986, all women requesting an IUCD at the Family Welfare Centre, Kenyatta National Hospital, who were menstruating regularly and who were between 20 and 44 years of age, were candidates for inclusion in the study. They were not admitted to the study if any of the following criteria were present: (1) a history of ectopic pregnancy, (2) pregnancy within the past 42 days, (3) leiomyomata of the uterus, (4) active PID, (5) a cervical or endometrial malignancy, (6) a known hypersensitivity to tetracyclines, (7) use of any antibiotics within the past 14 days or long-acting injectable penicillin, (8) an impaired response to infection, or (9) residence outside the city of Nairobi, insufficient address for follow-up, or unwillingness to return for follow-up. As a result, 470 women were excluded from the study, most due to exclusion criterion 9. Informed written consent was obtained before entry into the study; 75 women refused to participate, 57 because of time constraints on the day of insertion.

Trial design

The study was a double-blind, randomized clinical trial of the efficacy of a single oral dose of prophylactic doxycycline (Pfizer Limited, Sandwich, UK) versus placebo given at the time of IUCD insertion in preventing PID. The study was approved by the institutional review board. Women were randomized only after admission criteria were met on the day of the planned IUCD insertion, and eligibility had been assured by the physician. Women had an equal probability of assignment to the groups. The randomization code was developed using a computer random number generator to select random permuted blocks. The block lengths were 4, 8 and 10, varied randomly every 200 women (Friedman *et al.* 1984). No exclusions of women after randomization were allowed.

The doxycycline and placebo were in capsule form and identical in appearance. They were prepacked in bottles and consecutively numbered for each woman according to the randomization schedule. Each woman was assigned an order number and received the capsules in the corresponding prepacked bottle. This scheme effectively blinded the randomization process. Doxycycline was chosen for prophylaxis because of its broad spectrum, long half-life, excellent gastrointestinal absorption, selective concentration in the endometrium, and low cost (Grimes *et al.* 1984).

The randomization code was kept in the USA. Thus, all administration and assessments were done blinded to treatment assignment, and the investigators and patients were also blinded to the ongoing results of the study. The code was broken only after data collection had been completed.

Regimen

The doxycycline and placebo were both supplied as two capsules. The physician who administered the treatments at the time of randomization observed carefully that the capsules were ingested to assure compliance. The therapies were administered at least 1 h before IUCD insertion to allow for systemic absorption of the drug. The implementation of this trial within the clinic did not alter the choice of IUCD type. When the study began, the Lippes loop was used by most women, with the Copper T, Nova T, and Multiload being used less frequently. (Brand names are used for identification only and do not imply endorsement by the USPHS or any of its agencies.) IUCDs were inserted by clinic nurses as is the standard practice.

Withdrawals and deviations

The women who entered the trial remained in the allocated study group for analysis regardless of subsequent management. Antibiotics or other treatments for PID were not given at our study facility unless PID was diagnosed. However, women enrolled in the study were treated appropriately for other illnesses which occurred during the follow-up period.

Endocervical cultures

Endocervical specimens for culture of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were taken before insertion of the IUCD. For culture of *N. gonorrhoeae*, a cotton-tipped swab was used to inoculate Thayer-Martin medium. Plates were incubated at 35°C in candle jars and examined at 48 and 72 h. Colonies typical of *N. gonorrhoeae* were confirmed by Gram stain appearance and oxidase positivity. For culture of chlamydia, a second, dacron-tipped, metal or plastic swab was rotated in the endocervical canal for 5–10 s. The swab was placed into 2-SP transport media and held at 4°C until transported to the laboratory where it was kept at −80°C until inoculated on to cycloheximide-treated McCoy cells and centrifuged at 2800 *g* for 1 h. Cells were incubated for 72 h and stained with fluoresceinated monoclonal antibody (Syva Company, Palo Alto, CA, USA).

Measurement of outcome

The women were asked to return to the clinic 1 month after IUCD insertion. This extended occasionally to 6 weeks to allow for follow-up of women who had not returned when scheduled. Complete information, including an assessment for PID, was recorded at this 1-month visit for all women returning. Throughout the first month, all women were assessed for PID whenever they returned for an unscheduled IUCD-related visit.

PID was assessed clinically by the gynaecologists responsible for admitting and assessing all the women in the study. The primary outcome variable of interest was the frequency of PID during the first month after insertion. The important secondary outcome variable was the frequency of an unscheduled visit for an IUCD-related problem during the first month. The criteria used for diagnosis of PID were those suggested by the Infectious Disease Society for Obstetrics and Gynecology in the United States (Hager *et al.* 1983). A diagnosis of PID was made only if the following three tenderness criteria were identified: abdominal direct tenderness, tenderness with motion of cervix and uterus, and adnexal tenderness, together with at least one of the following five objective criteria (1) Gram-negative intracellular diplococci identified in endocervical swabs, (2) pyrexia >38°C, (3) leucocytosis >10 000 WBC/μl, (4) purulent material from peritoneal cavity obtained by culdocentesis, or (5) pelvic abscess or inflammatory complex on bimanual examination.

Sample size and statistical analysis

We calculated a requisite study sample size of at least 1800 women (900 in each group) by assuming an estimated incidence rate of PID in the placebo group of 4% and our desire to detect a true 50% decrease in the prophylactic doxycycline group. We used a one-sided alpha-error of 0·05, and a power of 0·80. We decided upon one-sided tests because we were only interested in whether doxycycline was more effective than placebo (Pocock 1983). Having calculated our sample size based on the probable occurrence of PID, we knew our analyses of unplanned IUCD-related visits would have more than sufficient power.

Mantel-Haenszel chi-tests were used for the one-tailed comparisons of prophylactic doxycycline patients with placebo patients on dichotomous outcome variables (Rothman & Boice 1979; Rothman 1986). χ^2-tests were used for the two-tailed comparisons of patient characteristics. One-way analyses of variance were used for comparisons on interval-scaled variables. In analysing dichotomous outcome variables, the effects of potential confounding variables, even though very unlikely because of the randomized design, were controlled for by the Mantel-Haenszel procedure (Rothman & Boice 1979). The relative risk of dichotomous outcome variables for the prophylactic antibiotic group compared with the placebo group were calculated with corresponding 95% confidence intervals (CI) by the test-based method (Rothman & Boice 1979). In situations with small expected values in the numerator, we used an exact procedure (Thomas 1975).

Results

Women studied

We enrolled 1813 women: 904 were allocated to

Table 1. Characteristics of the women in the study

Characteristic	Prophylactic doxycycline (n = 827) Mean	Placebo (n = 828) Mean	Lost to follow-up (n = 158) Mean	P*
Age (years)	25·5	25·3	25·6	0·51
Years of education	9·5	9·7	9·2	0·02
No. of live births	2·5	2·3	2·4	0·03
No. of miscarriages	0·2	0·2	0·2	0·78
Coital frequency/week	2·4	2·4	2·5	0·48

* One-way analysis of variance on the three groups.

the prophylactic doxycycline group and 909 to the placebo group. Follow-up information was obtained from 91% in both groups. Our 1-month comparative analyses included those women for whom we had follow-up information: 827 in the prophylactic doxycycline group and 828 in the placebo group.

The treatment groups and those lost to follow-up were similar in terms of age, years of education, live births, miscarriages and coital frequency per week (Table 1). There were statistically significant but practically unimportant differences in years of education and live births. Marital status, type of IUCD inserted, and bacterial status before IUCD insertion were similar in the treatment groups (Table 2). No known perforations of the uterus occurred during the study, and an equal number of failed insertions occurred in each group. The only statistically significant difference in side-effects between the two groups was for vomiting which occurred in 4·8% of the doxycycline group, and in 1·9% of the placebo group (P<0·001).

PID

Prophylactic antibiotics reduced the risk of PID. Overall, the PID rates were low, 1·3% in the doxycycline group and 1·9% in the placebo group (Table 3). The rate in the doxycycline group was 31% lower than in the placebo group (P = 0·17), and the results changed negligibly when we adjusted for potential confounding factors such as education, parity, coital frequency, age, and previous type of contraceptive used. This reduction in PID in the group receiving doxycycline prophylaxis occurred primarily in the women without endocervical chlamydial infection. Those women in whom cultures for endocervical gonorrhoea and chlamydia were negative at insertion showed a 33% reduction in PID (Table 4). In women positive for gonorrhoea but negative for chlamydia, doxycycline produced a substantial protective effect, but small numbers led to some imprecision. However, in women positive for chlamydia only, doxycycline did not produce a substantial protective effect.

Doxycycline had a greater protective effect with the active IUCDs. We combined the results from the Copper T, Nova T and Multiload into an active IUCD category; in this category doxycycline produced a 78% reduction in PID [RR 0·22; 95% CI 0·03 to 1·5; P = 0·06). With the Lippes loop, doxycycline produced only an 11% reduction (RR 0·89; 95% CI 0·38 to 2·1; P = 0·39).

Unscheduled IUCD-related visits

Prophylactic antibiotics reduced the risk of problems leading to unplanned IUCD-related visits. The rate of return to the clinic for a problem related to the IUCD in the doxycycline

Table 2. Bacteriological status and types of IUCD in the two treatment groups

Characteristic	Prophylactic doxycycline (n = 827) (%)	Placebo (n = 828) (%)	Two-tailed P
Currently married	68·0	67·0	0·81
Lippes loop	82·2	80·2	0·35
Copper T	5·3	5·8	
Nova T	8·8	8·6	
Multiload	3·3	5·0	
Failed insertion	0·4	0·4	
Gonorrhoea positive	3·2	4·0	0·35
Chlamydia positive	12·9	12·0	0·59

Table 3. Rates and relative risks (RR) of the major outcomes for the first month after IUCD insertion by treatment group

Outcome	Prophylactic doxycycline (n = 827)	Placebo (n = 828)	RR	95% CI	One-tailed P
PID	1·3%	1·9%	0·69	(0·32 to 1·5)	0·17
Unplanned IUCD-related visit	8·9%	13·0%	0·69	(0·52 to 0·91)	0·004

PID, pelvic inflammatory disease; IUCD, intrauterine contraceptive device.

group was 31% lower (P = 0·004) than in the placebo group, with a narrow confidence interval (Table 3). The results changed negligibly when we adjusted for potential confounding factors such as education, parity, coital frequency, age, and previous type of contraceptive used.

We reviewed the women's complaints for their unplanned IUCD-related visits: 66% were for lower abdominal pain, back pain, bleeding and/or vaginal discharge, with most women reporting at least two of those complaints, and 27% were related solely to expulsion or to the woman's concern about the position of the IUCD. Prophylactic doxycycline reduced the risk of an unscheduled visit for lower abdominal pain or bleeding by 41% (RR 0·59; 95% CI 0·39 to 0·89; P = 0·006). The effect of doxycycline on unscheduled visits for the other complaints was less pronounced, a 21% reduction (RR 0·79; 95% CI 0·53 to 1·2; P = 0·12).

When the unscheduled-visit rates were stratified by bacteriological findings at insertion, a similar picture to the PID results emerged. In women with cervical chlamydial infection there was no protective effect of doxycycline on unplanned visits. In women without any endocervical infection at insertion and in those positive for gonorrhoea but negative for chlamydia, doxycycline effected a 38% and 59% reduction, respectively, in the rates of unplanned IUCD-related visits (Table 5). In women with chlamydial infection the protective effect of doxycycline was negligible.

Discussion

In the present study the frequency of PID in women using IUCDs was much lower than expected from previous estimates in Kenya. The general belief was that the PID rate in IUCD users was about 10%. In retrospect, these high estimates of PID were presumably a reflection of experience with unscheduled IUCD-related visits, and not PID as defined in the present study. We planned conservatively for an incidence rate of 4% in the placebo group; the resultant rate was <2% thus lessening the power of the trial to demonstrate a difference. The magnitude of our error is perhaps not surprising since that has been no other completed study of PID incidence in Africa. The fact that we found much lower incidence rates of PID is detrimental to study power, but is reassuring in terms of the safety of IUCD use in Kenya.

Table 4. Rates and relative risks (RR) of pelvic inflammatory disease (PID) for the first month by bacteriological status at the time of IUCD insertion and by treatment group

Bacteriological status	PID rate: Prophylactic doxycycline	PID rate: Placebo	RR	95% CI	One-tailed P
Neither gonorrhoea nor chlamydia	0·90% (n = 669)	1·3% (n = 670)	0·67	0·24 to 1·9	0·22
Gonorrhoea only	0·0% (n = 19)	11·1% (n = 27)	0·00	0·00 to 2·3	0·19
Chlamydia only	2·1% (n = 96)	2·2% (n = 90)	0·94	0·07 to 12·7	0·67

* This table does not include the results of 73 women who were not tested for gonorrhoea and chlamydia and 11 women who were positive for both chlamydia and gonorrhoea.

Table 5. Rates and relative risks (RR) of unplanned IUCD-related visits for the first month by bacteriological status at the time of IUCD insertion and by treatment group

Bacteriological status	Unplanned visit rate: Prophylactic doxycycline	Unplanned visit rate: Placebo	RR	95% CI	One-tailed *P*
Neither gonorrhoea nor chlamydia	8·1% (n = 669)	13·0% (n = 670)	0·62	0·45 to 0·86	0·002
Gonorrhoea only	10·5% (n = 19)	25·9% (n = 27)	0·41	0·10 to 1·7	0·10
Chlamydia only	10·4% (n = 96)	11·1% (n = 90)	0·94	0·41 to 2·1	0·44

* This table does not include the results of 73 women who were not tested for gonorrhoea or chlamydia and 11 women who were positive for both gonorrhoea and chlamydia.

Clinical criteria for diagnosing PID are not well established or uniform. Even in experienced hands, the predictive value of a positive diagnosis may be as low as 0·65 (Jacobson & Westrom 1969), which means that one in three patients admitted with a diagnosis of PID does not have this disease as judged by laparoscopy. Hence, we chose to use a rigorous case definition of PID (Hager *et al.* 1983). PID was sought using these criteria at each follow-up visit, both scheduled and unscheduled. By using a strict case definition, we believe we minimized the possibility of cramping related to the IUCD being misdiagnosed as PID. Using a less strict case definition, however, such as unplanned IUCD-related visits, leads to similar but statistically stronger conclusions.

Our results showed that a single oral dose of doxycycline at the time of insertion reduces the likelihood of PID by 31%. Whilst the alpha error of 0·17 does not meet the conventional standard of 0·05, the observed reduction in PID is consistent with current knowledge and our results for unplanned IUCD-related visits. That prophylactic doxycycline would reduce the likelihood of PID is biologically plausible. Moreover, in this study, the similar reduction found for unplanned IUCD-related visits was strongly statistically significant and corroborates the reduction found for PID. Of these visits, prophylactic doxycycline reduced those for lower abdominal pain or bleeding by 41%, and both have been associated with histological evidence of acute and chronic endometritis (Ober *et al.* 1968, 1970). Hence, the statistically significant reduction in the frequency of clinic visits is probably due largely to a reduction in the occurrence of endometritis in the group receiving prophylaxis. These findings are consistent with the effect of prophylactic antibiotic administration for induced abortion (Grimes *et al.* 1984; Park *et al.* 1985). In the largest study of prophylactic antibiotics for induced abortion, minor side-effects such as cramping and bleeding were consistently reduced in the group receiving tetracycline (Hodgson *et al.* 1975). Thus, this study suggests that antibiotic prophylaxis protects against both endometritis and salpingitis.

The stratified analyses by cervical culture results were pre-specified but, nonetheless, are intended primarily for hypothesis generation. The benefit of prophylaxis appears evident for women whose cervical cultures were negative for both *N. gonorrhoea* and chlamydia at the time of insertion, but the benefit appeared to be greatest for women with cervical gonorrhoea whereas doxycycline had little benefit for women with cervical infection with *C. trachomatis*. These findings might seem paradoxical, since doxycycline is a drug of choice for treating *C. trachomatis* infection but not for treating gonorrhoea (Centers for Disease Control 1985). These differential effects of prophylaxis probably stem from the different rates of growth of these pathogens. The gonococcus replicates in a matter of hours, compared with several days for *C. trachomatis* (Thompson & Washington 1983). Therapeutic levels of a single 200 mg dose of doxycycline would be present in the endometrium during several life-cycles of the gonococcus as compared with a fraction of that for *C. trachomatis*. Thus, the lack of benefit seen among women infected with *C. trachomatis* probably represents inadequate duration of therapeutic levels of doxycycline.

Ideally, an IUCD should not be inserted in

women with gonorrhoea or cervical infection with *C. trachomatis*. To accomplish this, however, all women would have to be screened for these infections at an earlier visit, and those with infections adequately treated. Unfortunately, in countries where health care resources are overextended, resources that can reasonably be put into identifying women at risk of PID are limited. The additional clinic visit would impose extra costs and inconvenience that in most cases neither the woman nor the clinic would be willing to accept. Furthermore, even if screening were implemented, if a woman had negative tests for these pathogens, she might be infected at the time of IUCD insertion because of false-negative tests or acquisition of infection in the interval between screening and insertion. Moreover, women without either of these cervical infections appear to benefit from prophylactic doxycycline. Hence, the routine use of prophylaxis for all women receiving IUCDs needs to be considered as a practical alternative.

The use of prophylactic doxycycline may not only reduce human suffering and free encumbered health care resources, but may provide cost-savings as well. The cost of prophylaxis is low. When purchased in large quantities, the wholesale price of doxycycline is about $0·05 for a 100 mg tablet or capsule (*Drug Topics Red Book* 1988). Assuming that a 200 mg dose costs $0·10, then prophylactic treatment of 1000 women receiving an IUCD would cost $100 and might avert six cases of PID and 41 problems requiring an unscheduled IUCD-related visit to the clinic. Nearly all patients in the study with PID were admitted to hospital, but the proportion of patients with PID who were admitted may not be capable of extrapolation to other Kenyan women. However, when one considers the direct medical cost of six ambulatory or admitted women with PID and 41 problems requiring unplanned clinic visits, the figure would greatly exceed $100. The averted costs of ectopic pregnancy, infertility, and lost productivity would make prophylaxis even more cost-effective (Washington *et al.* 1986). In lower risk populations, such as the UK, the number of averted cases and visits per 1000 women would be fewer. Treatment costs, however, are much higher, and the savings would be greater. As has been shown for prophylaxis for suction curettage abortion, use of antibiotics is cost-effective even when the risk of infectious morbidity is lower than 1% (Grimes *et al.* 1984).

In summary, the prophylactic use of doxycycline at the time of IUCD insertion appears effective, well tolerated, and cost-effective. Because of the potential importance of this observation, corroboration by other studies is needed. One such trial is currently in progress in Nigeria using the identical protocol to this study (P. Lamptey, personal communication). Also, the advisability of giving more than one dose of doxycycline to prevent chlamydial PID should be investigated. Prophylactic antibiotic administration may make intrauterine contraception an even safer option in the years ahead.

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