TWO CLINICAL TRIALS DESIGNED TO EVALUATE THE PREVENTION OF PELVIC INFLAMMATORY DISEASE IN IUD USERS

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ABSTRACT: Family Health International (FHI) has sponsored two comparative clinical trials to evaluate the efficacies of the following measures for the reduction of the risk of pelvic inflammatory disease (PID) in IUD users: one by insertion of a stringless IUD, and the other, by oral administration of prophylactic antibiotics (doxycycline) at the time of IUD insertion. Results from the string vs. stringless IUD trial do not indicate a reduced PID risk for women wearing IUDs without strings; however, the removal rate for bleeding and/or pain was lower for stringless IUD users. Preliminary findings of the antibiotic study do not lend support to the efficacy of prophylactic use of antibiotics at the time of IUD insertion. Further research is warranted. (Infect. Med Dis Letters Obstet Gynecol 1990; 12:3-6)

INTRODUCTION

One of the most important questions with the intrauterine devices (IUDs) is whether use is associated with an increased risk of pelvic inflammatory disease (PID). A definitive answer is essential due to the large number of IUD users worldwide as well as the serious medical consequences and public health impact that PID could bring about.

Earlier epidemiologic studies compared IUD users with other contraceptive methods which are now generally recognized to exert a protective effect on the development of PID; thus, the relative risks of the IUD users to acquire PID in these studies were unduly inflated. Also, later findings indicated that the risk of PID can vary significantly among device types. Data pertaining to different types of IUDs should not be pooled for analysis.

Recognizing the weaknesses of previous studies which were mostly observational in nature, Family Health International (FHI) has sponsored two comparative clinical trials in the past few years, one comparing IUDs with and without marker strings and one testing the hypothesis that prophylactic antibiotics would protect against PID developing soon after IUD insertion. This paper summarizes the primary findings from one trial that was recently completed and presents preliminary data derived from another that is ongoing.

MATERIALS AND METHODS

IUD With or Without Marker Strings

This was a randomized, comparative clinical trial of the TCu 200 with and without marker strings to determine the role of marker strings in the development of clinically apparent PID. A total of 1,265 patients were admitted to the trial at five sites located in Yugoslavia, Chile, France, Guatemala and the Dominican Republic.

Insertions were performed on first-time IUD users who were between 20 and 44 years of age and currently menstruating. Contraindications included uterine abnormalities, abnormal uterine bleeding, recent use of antibiotics and clinical evidence of PID. Cultures of the endocervix were taken for Neisseria gonorrhoeae prior to IUD insertion. All subjects were to provide informed consent before officially being enrolled into the study.

Devices with or without strings were assigned by random allocation. The study protocol required that devices that were partially or totally expelled, either before or after the subject left the clinic, were not to be reinserted. In the case of partial expulsion, the device was to be removed and the subject discontinued from the trial.

Subjects were required to return to the clinic for follow-up visits at 1, 3, 6 and 12 months after insertion. Medical examinations, including pelvic examination for PID, were performed at each visit. Any use of antibiotics since the previous visit was noted at these times. Subjects were discontinued from the study in the event of IUD expulsion, removal of IUD for any reason, or if pregnancy occurred. Criteria for diagnosis of PID were those normally used by the clinics participating in the trial. Cultures for Neisseria gonorrhoeae from the cervix and anal crypts at follow-ups were obtained if symptoms of infection were present. Subjects with positive cultures were treated according to standard clinic practice.

Prophylactic Antibiotics

This ongoing study is a double-blind, randomized clinical trial of the efficacy of a single oral dose (200 mg) of doxycycline (Pfizer Limited, Sandwich, England) given at the time of IUD insertion in pre-
venting PID during the first three months postinsertion. A unique potential advantage of doxycycline is that after administration it is found in higher concentrations in the endometrium than elsewhere in the genital tract. In addition, oral administration of doxycycline is as effective as intravenous administration.

All women requesting an IUD at the University College Hospital in Ibadan, Nigeria, who were between 20 and 44 years of age and currently menstruating were candidates for the study. They were not to be admitted if they had one of the following: history of ectopic pregnancy, pregnancy termination within the past 42 days, leomyomata, active PID, a cervical or endometrial malignancy, a known hypersensitivity to tetracyclines, used any antibiotics within the past 14 days or were on long-acting injectable penicillin, an impaired response to infection, lived outside the city of Ibadan, did not have sufficient address for follow-up, or unwilling to return for follow-up. Cultures of the endocervix were taken for both Neisseria gonorrhoeae and Chlamydia trachomatis prior to IUD insertion. All subjects were to provide informed consent before officially being enrolled.

The doxycycline and placebo were in capsule form and identical in appearance. They were prepackaged in bottles containing two 100 mg capsules and consecutively numbered for each patient according to a computer-generated randomization schedule. Subjects were assigned a patient order number on the day of insertion and were administered the capsules from the corresponding prepackaged bottle at least one hour prior to IUD insertion to allow for systemic absorption of the drug. IUDs (primarily the Lippes Loop, with Copper T, Nova T and Multiload) were then inserted by clinic nurses as is the standard practice.

Once a subject was randomized she was not to be withdrawn from the study for any reason. In case of deviations and other intervening factors, her results were to be analyzed with those of the group to which she was originally assigned. Antibiotics or other treatments were not given at the facility unless PID was diagnosed. However subjects were treated customarily for other illnesses that occurred during the follow-up period.

Subjects were scheduled for follow-up at one and three months after IUD insertion. They also were encouraged to report back to the clinic if symptoms associated with PID were observed.

Clinical evaluation for PID was performed by the gynecologists responsible for admitting and evaluating all study subjects. To be diagnosed as having PID, a woman first had to have two of the following: abdominal direct tenderness, tenderness with motion of cervix and uterus, or adnexal tenderness and at least one of the following: positive Gram stain of endocervix for Gram negative intracellular diplococci, oral temperature greater than 38°C, leukocytosis greater than 10,000 al/mm³, purulent material from peritoneal cavity by culdocentesis, or pelvic abscess or inflammatory complex on bimanual examination.

Statistical Analysis

Sample sizes were calculated according to predetermined statistical criteria. In the strings versus no strings trial, it was determined that approximately 1,300 subjects were required to ensure the detection of a difference in PID rates of at least 5% between the two study groups. For the prophylactic antibiotic trial, a sample size of 1,800 subjects was necessary to detect a 1.3% difference in the PID rate (assuming a 4% incidence of PID in the placebo group) between the two study groups.

Chi-square tests were used for the two-tailed comparisons of subject characteristics. For the strings versus no strings study, PID rates and twelve-month gross cumulative life-table event rates were compared using the log-rank method. Preliminary results from the ongoing antibiotic trial were analyzed using chi-square tests.

RESULTS

Strings vs No Strings

The mean age and parity of women who received an IUD with strings (N=636) was similar to that of women who received an IUD with no strings (N=629). Few insertion-related complications and complaints were noted and follow-up of all study patients was attempted through 12 months postinsertion. No differences were found between the two groups of IUD users with respect to the incidence of infection or inflammation. Event rates and overall continuation rates were also similar with the exception of removal rates for bleeding/pain; the 12-month rate per 100 women was significantly higher in the strings group than in the no strings group. (Table I)

Prophylactic Antibiotics

Preliminary results from the ongoing antibiotic trial in Nigeria do not indicate any significant difference between antibiotics and placebo group PID rates. In-depth analysis will be performed when the three-month follow-up of all 1,500 patients is complete. To date, 17 cases of PID have been diagnosed, nine occurring in the doxycycline users and eight occurring in placebo users. (Table II)

DISCUSSION

Results from our strings vs no strings trial do not indicate a reduced PID risk for women wearing IUDs without strings. In an earlier study on a total
### TABLE I

International Randomized Comparative Clinical Trial of IUDs With Strings and IUDs With No Strings

<table>
<thead>
<tr>
<th>Characteristic or Event</th>
<th>Strings (N=636)</th>
<th>No Strings (N=629)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years at insertion: mean (standard deviation)</td>
<td>26.7 (5.7)</td>
<td>27.1 (5.8)</td>
</tr>
<tr>
<td>Total live births before insertion: mean (standard deviation)</td>
<td>1.8 (1.0)</td>
<td>1.9 (1.1)</td>
</tr>
<tr>
<td>Total women with one or more follow-up visits: number (percentage)</td>
<td>621 (97.6)</td>
<td>612 (97.3)</td>
</tr>
<tr>
<td>Total women with one or more diagnoses of PID during follow-up: number (percentage)</td>
<td>22 (3.5)</td>
<td>23 (3.7)</td>
</tr>
<tr>
<td>12-month gross cumulative life-table removal rate for bleeding or pain per 100 women: rate* (standard error)</td>
<td>6.7 (1.1)</td>
<td>3.6 (0.8)</td>
</tr>
</tbody>
</table>

*P<0.05

### TABLE II

Preliminary Date Derived from Randomized Comparative Clinical Trial of IUD Insertion with Antibiotics and IUD Insertion with Placebo

<table>
<thead>
<tr>
<th>Characteristic or Event</th>
<th>Antibiotics (N=644)</th>
<th>Placebo (N=636)</th>
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<tbody>
<tr>
<td>Age in years at insertion: mean (standard deviation)</td>
<td>30.5 (4.8)</td>
<td>30.9 (5.9)</td>
</tr>
<tr>
<td>Total live births before insertion: mean (standard deviation)</td>
<td>4.3 (1.7)</td>
<td>4.5 (1.8)</td>
</tr>
<tr>
<td>Total women with one or more follow-up visits: number (percentage)</td>
<td>642 (99.7)</td>
<td>635 (99.8)</td>
</tr>
<tr>
<td>Total women with one or more diagnoses of PID during follow-up: number (percentage)</td>
<td>9 (1.4)</td>
<td>8 (1.3)</td>
</tr>
</tbody>
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of 23,000 insertions of various kinds of IUDs, Tietze and Lewit also did not find differences in pelvic infections between women wearing devices with strings and those whose devices had no strings. However, we did detect a statistically higher one-year removal rate for bleeding/pain among users of IUDs with strings. This higher rate may be partly due to the relative ease of removal of IUDs with strings.
strings; however, it is also possible that it reflects signs and/or symptoms suggestive of PID. Additional research is warranted.

Prophylactic use of antibiotics at the time of IUD insertion appears theoretically sound, since PID, if it does occur, is most likely to occur soon after insertion. The 1,500-case study in Nigeria is a replica of a jointly sponsored FHI/CDC (Centers for Disease Control) study of 1,800 women in Kenya and is being conducted in order to provide a sample size adequate to detect a difference between the two treatment groups. No statistically demonstrable protection was found in our preliminary findings. When the results of the Nigerian trial are complete and considered in conjunction with those of the original trial in Kenya, sufficient data may be available to confirm or refute the hypothesis that prophylactic antibiotics reduce the probability of PID soon after IUD insertion in which case it will be possible to recommend a standard practice.

If larger studies, as is possible, were to eventually demonstrate the efficacy of any preventive measure, such measures would still need to be evaluated for their overall benefits and risks as well as cost factors. Specifically, possible benefits derived from reducing the risk of PID by using a stringless IUD, would need to be weighed against the potentially increased risk of unwanted pregnancies due to an unnoticed IUD expulsion. In the case of prophylactic use of antibiotics at IUD insertion, the possible savings in medical as well as financial cost in the treatment of PID must be balanced against possible side effects and the logistics involved in providing the antibiotics to a large number of women receiving an IUD.

Trelman and Liskins listed four approaches to be tried for the prevention of PID among IUD users, namely: better screening of clients, better disinfection and insertion techniques, IUD without strings or with strings coated in disinfectant, and prophylactic antibiotics at insertion. Emphasis should be placed on the importance of judicious selection of candidates for IUD use. For instance, the PID risk for IUD users is found to be only minimally increased for women in a stable marital relationship. Meticulous care in disinfection and gentleness in insertion may be equally as important as the above two preventive measures under testing the reduction of IUD-PID risk.

REFERENCES


ACKNOWLEDGMENT

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EDITORIAL COMMENT

Though not a definite, this paper is the first study to look at whether or not the use of pre-insertional antibiotics could alter early onset pattern of disease.

REPRINT REQUEST

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*The PID incidence rate within one month postinsertion for women using IUDs in Kenya was lower (below 2.0% for both the study group and the placebo group) than originally estimated (10%) at the design stage of the study. Thus the study power was not sufficient to detect clinically significant difference as desired. However, the low incidence rate of PID itself is reassuring relative to the safety of IUD use in Kenya. (9)