

Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis

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Objective: To determine the long-term safety of nonsurgical sterilization with quinacrine.

Design: Observational cohort study.

Setting: Rural provinces in northern Vietnam.

Patient(s): Two thousand eight hundred forty women who had had quinacrine insertions and an age-matched comparison group of 1,658 women who had an intrauterine device (IUD) insertion between 1989 and 1993.

Method(s): Interviews in 1994, 1995, and 1996 and review of available medical records. This is a planned interim analysis.

Main Outcome Measure(s): Ectopic pregnancies and the occurrence of other adverse health events.

Result(s): Over 90% of women were interviewed at least once. Despite matching on age, the groups differed on baseline parity. The ectopic pregnancy rates were similar after either one or two insertions and were similar to the rate of ectopic pregnancies after surgical sterilization in the United States. The quinacrine group reported more gynecologic health problems than the IUD group. However, after correcting for information bias, there was no dose-response effect between the one- and two-insertion quinacrine groups, suggesting the possibility of recall bias or differing baseline health status.

Conclusion(s): Ectopic pregnancies do not appear to be increased compared with U.S. surgical sterilization rates. The data on other adverse events are more difficult to interpret. (Fertil Steril® 2000;74:1092-101. ©2000 by American Society for Reproductive Medicine.)

Key Words: Quinacrine, tubal sterilization, nonsurgical, pregnancy, follow-up studies, safety, intrauterine devices

Nonsurgical sterilization has the potential to be an inexpensive, safe, and well-accepted procedure that would be of benefit to women in both developed and developing countries. One nonsurgical approach, first described in 1980 (1), involves the use of quinacrine pellets to produce occlusion of the fallopian tubes. In the most commonly studied regimen, seven pellets, each containing 36 mg of quinacrine dihydrochloride dihydrate, are inserted into the uterus with a modified intrauterine device (IUD) inserter. A second insertion is done 1 month later. It has been estimated that 100,000 women have undergone a quinacrine pellet sterilization procedure (2).

The short- and medium-term side effects of quinacrine pellet insertions have been reviewed

(3), and a risk assessment has estimated the potential risks of ectopic pregnancy, birth defects, and cancer from quinacrine use (4). A long-term follow-up study of women in Chile examined the risk of gynecologic cancers after quinacrine pellet sterilization (5, 6). Close examination of a cancer cluster in Chile showed no plausible relationship between the cancer cluster and quinacrine. The sole remaining finding at the end of that analysis was a single case of uterine leiomyosarcoma, the same case that had led to the investigation.

In this study, our goal was to compare the rates of ectopic pregnancy and other adverse events between women who received quinacrine and a comparison group, as well as between women who received one vs. two quin-

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acrine insertions. We chose IUD acceptors as the comparison group. We considered the use of a surgical sterilization comparison group, but surgical sterilizations were rarely done when the quinacrine program began in Vietnam, so there were few women who had had surgical sterilization in the same time frame. In this report, we present the scheduled interim analysis of long-term safety data, including data on ectopic pregnancies. The interim analysis of overall pregnancy rates and additional background information are in an accompanying article (7). As noted in that article, Family Health International (FHI) had not been involved in the quinacrine insertion program in Vietnam.

METHODS

This is an observational cohort study of a sample of women who had quinacrine insertions in Vietnam between 1989 and 1993. The study also includes a comparison group of women who had IUD insertions in the same provinces during the same time period. We obtained approval from Family Health International's (FHI's) institutional review board to conduct this study on August 26, 1994. Enrollment and observations began several years after the quinacrine and IUD insertions had taken place. Most of the women in this cohort were initially recruited during a 1994 retrospective survey.

Sampling Methods

The methods for the 1994 survey are described in more detail in another report (Katz K. Waszak C, Hieu D, Vinh D, Sokal D. The lessons of quinacrine introduction in Vietnam. Manuscript submitted for publication.). We will summarize them briefly here. We chose three provinces near Hanoi and the four districts within each province with the greatest number of quinacrine acceptors. Since the study began, two of the provinces have been split, but for this analysis, we are using the original grouping.

Sampling frames were developed from logbooks of 6,535 quinacrine acceptors and 6,446 IUD acceptors. A random sample of quinacrine acceptors was selected, stratified by province, district, and 5-year age group. The sampling frame included women who had one or two quinacrine insertions. We selected a frequency-matched IUD sample using the same three variables.

When we began this study, we recruited an expansion group composed of women who had had only a single quinacrine insertion, in order to have better statistical power for comparing long-term effects of one versus two quinacrine insertions, especially with respect to ectopic pregnancies. This expansion group included all the remaining one-insertion women in the sampling frame.

Questionnaires and Interview Methods

Although the 1994 survey focused on issues of regret and informed consent, it did include limited items regarding

health problems, which were used in the present analysis. Questionnaires for the current study were initially drafted in English, translated into Vietnamese, and then reviewed, revised, and finalized in Vietnam. We reviewed data quality after each annual round of interviews and made minor revisions to the questionnaires as needed. We found that the best way to gather accurate age data was to ask women for their animal year of birth, using the Vietnamese 12-year cycle of animal years.

We conducted interviews in June 1995 and in November 1996. Annual interviews continued through 1999. During the interviews, women were asked to describe any health problems. The definition of a health problem was any problem that led a woman to see a health worker or kept her from her usual activities for 2 days or more. Thus, the reported health problems include many minor health problems. If a woman had died, we interviewed relatives and local health workers.

For serious health problems or health problems related to the reproductive system in which the diagnosis was unclear, a physician conducted a follow-up interview. The decision on whether or not to conduct a follow-up interview was made by FHI staff masked to study group. For selected cases involving hospitalization, surgery, or death, we sought copies of hospital records.

In 1995, schoolteachers conducted the initial interviews, as had been done during the retrospective study. For the second year, in order to improve reporting of medical problems, physicians conducted both the initial and follow-up interviews. We conducted 536 medical follow-up interviews in 1995 and 313 in 1996.

We coded the questionnaire data after translation by an independent translator. We used the Co-Start coding system (8). We conducted an audit of the medical codes as part of the interim analysis.

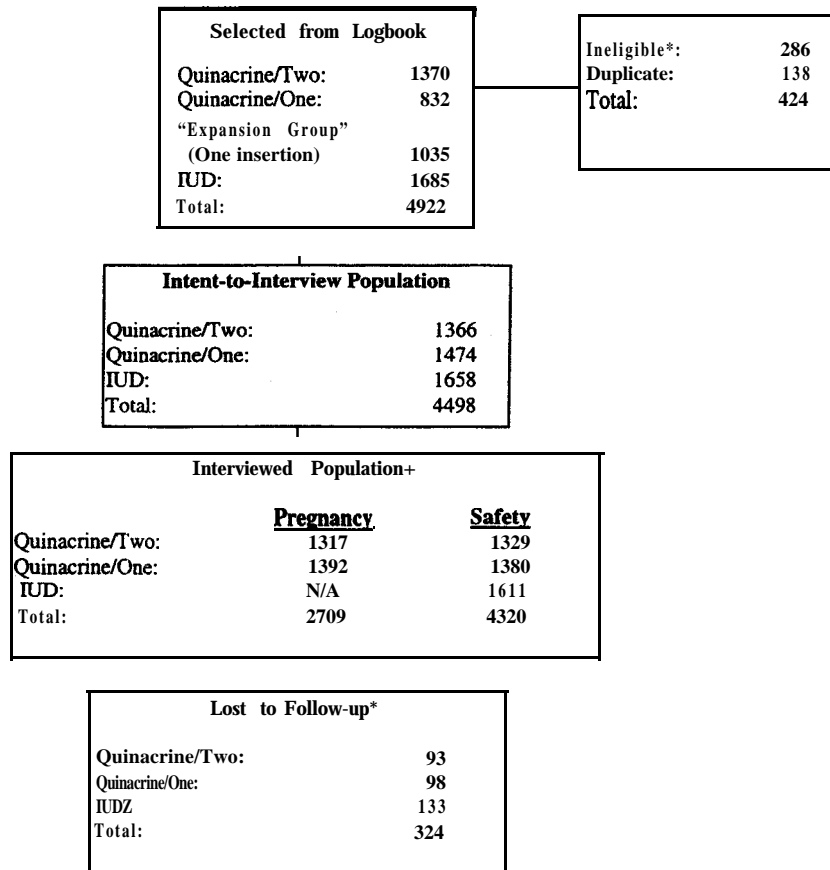
Other Data Sources

The data from the retrospective study and the current study were pooled to determine participants' health experiences from the date of insertion of either an IUD or quinacrine pellets to the date of last contact. The 1994 data set included specific information on ectopic pregnancies and hysterectomies but did not include detailed descriptions of other gynecologic health problems. Thus, we could not categorize those health problems, other than to say they were gynecologic in nature.

In addition to the annual and follow-up interviews, we used an independent passive-surveillance system to identify ectopic pregnancies and other serious health events. We describe the passive-surveillance system in more detail in the accompanying article (7). We also reinterviewed women who were reported to have received hospital care, for suspected pelvic inflammatory disease (PID).

FIGURE 1

Flow chart diagram of patient follow-up. *Ineligibles; women selected for the one-insertion expansion sample who reported having received two insertions. †Interviewed population; persons who were interviewed in 1994, 1995, or 1996. For the various pregnancy analyses, women with invalid insertion dates are excluded, whereas they are kept in the safety analysis. Quinacrine acceptors who got pregnant after one insertion and then had additional insertions are counted in the one-insertion group for pregnancy analysis and in the two-insertion group for safety analysis. This will create some differences in group sizes between this paper and the pregnancy analysis paper (7). ‡Lost to follow-up; these women were not interviewed in 1996.



Sokal. Interim quinacrine safety analysis. *Fertil Steril* 2000.

Study Populations

As shown in the participant flow chart (see Figure 1), women found to be ineligible or duplicates (e.g., more than one entry in the sampling frame) were removed before analysis. The intent-to-interview population consisted of all women selected for the study, whether or not they were ever interviewed. The interviewed population is the subset who had been interviewed at least once in 1994 (for the retrospective study), 1995, or 1996. Of the eligible women, 96% were interviewed at least once. Only 7.5% of women interviewed in 1994 or 1995 were not interviewed in 1996; the percentages were similar in the three study groups.

Baseline Characteristics

Percentages, means, and standard deviations (see Table 1) are weighted for differential sampling probability and non-

response. Almost all women were married and literate. The age distributions in the quinacrine and IUD groups were similar, but quinacrine users had higher parity. Among IUD women, only 12.4% of women reported five or more live births compared with 21.6% of quinacrine women. Quinacrine users were more likely to have used IUDs than other birth control methods immediately before undergoing their nonsurgical sterilization.

Safety Analysis

Protocol Endpoints

We initially specified four categories of serious adverse events to be evaluated in the interim analysis: ectopic pregnancy, hysterectomy, hospitalizations, and deaths. During the interim analysis, we found that participants sometimes

TABLE 1

Participant characteristics^a, interviewed population.

Parameter	Quinacrine, overall (n = 2,709), wt %	IUD (n = 1,611), wt %
Insertion history		
Age at insertion ^b		
20-24	0.1	0.0
25-29	9.8	10.1
30-34	35.2	35.2
35-39	39.8	39.2
≥40	15.1	15.4
Mean (SD)	34.9 (6.32)	34.3 (4.42)
Median age (min/max)	35 (20/48)	35 (25/40)
Years since insertion at last interview		
<2	1.0	1.8
2-3	15.6	26.5
4-5	74.5	45.3
≥6	8.8	26.5
Mean years (SD)	4.8 (1.49)	4.9 (1.46)
Median years (min/max)	4.6 (0/8)	4.8 (1/8)
Sociodemographic		
Marital status ^c		
Married	97.9	97.7
Not married	0.6	1.4
Unknown	1.5	0.9
Education		
Illiterate	0.4	0.3
Primary school (grades 1-5)	14.0	10.2
Basic school (grades 6-9)	78.2	75.1
Secondary school (grades 10-12)	5.8	9.4
Technical/vocational	1.4	3.7
College/university	0.2	1.2
Province^d		
1: Nam Ha	49.9	50.9
2: Hai Hung	27.1	26.2
3: Thai Binh	23.0	23.0
Obstetrical history		
Age at first pregnancy		
<20	14.6	9.7
20-24	68.2	62.3
25-29	15.9	24.9
30+	1.4	3.1
Number of pregnancies ^e		
1	0.0	4.3
2	2.3	17.4
3	14.3	25.2
4	23.5	22.1
5	21.8	15.5
6+	38.0	15.5
Number of live births ^e		
None	0.2	0.0
1	0.2	6.3
2	8.4	29.7
3	37.7	33.4
4	31.8	18.3
5	14.4	8.3
≥6	7.2	4.1

Continued

cited outpatient hospital visits as hospitalizations because of ambiguous wording in the questionnaire, thereby blurring the distinction between inpatient stays (for presumably more serious events) and outpatient visits. This endpoint was

TABLE 1

Continued.

Parameter	Quinacrine, overall (n = 2,709), wt %	IUD (n = 1,611), wt %
Number of living children ^e		
None	0.0	0.1
1	0.3	6.6
2	9.5	32.4
3	42.7	35.2
4	31.2	16.4
5	11.4	6.7
≥6	4.9	2.7
Contraceptive history: method used immediately before insertion		
None	19.8	38.6
IUD	56.5	36.7
Oral contraceptives	1.3	2.1
Condoms	3.5	5.7
Other	18.8	16.9

^a Percentages, means, medians, and standard deviations are weighted for differential probabilities of selection and nonresponse. Frequencies are unweighted.

^b Based on logbook/sampling frame.

^c At the 1994 interview. If not available, then at the 1996 interview.

^d Provinces as they existed at the time sample selection was conducted.

^e As of the 1994 retrospective study interview.

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therefore changed to any hospitalized or nonhospitalized health problem. The questionnaire was modified to avoid this problem with data collection in later years.

The diagnoses of ectopic pregnancies, deaths, hysterectomies, pelvic and abdominal surgeries, and cancer hospitalizations were confirmed by data reviews conducted independently by Thai Binh Medical College and FHI clinicians. Diagnoses for minor, nonhospitalized events were added later, with diagnoses agreed upon by the Thai Binh and FHI clinicians. One of the authors (D.S.) and other FHI clinicians not involved in this study reviewed medical codes for accuracy and consistency across cases. Clinicians were generally masked to method group, but sometimes the descriptions of the health problems referred to either quinacrine or IUD use.

Other Clinical Endpoints: Pelvic and Abdominal Surgeries as Well as Gynecologic Health Problems

During the course of clinical review, we decided to tabulate, but not compare statistically, pelvic and abdominal surgeries as a separate category. These are defined as surgeries reported in the 1995 or 1996 interviews. We also added another new endpoint, gynecologic health problems, in the multivariable analysis described below. For events reported during the retrospective study, this was defined as any gynecological illness because precise diagnoses were not available. For events reported during the current study, in which detailed medical coding was used, this was defined as

[1] any genital health problem (excluding breast and pregnancy disorders) or [2] pelvic pain or endocrine ovarian problems. Health problems in this category include diagnoses such as menstrual disorders, vaginitis, cervicitis, pelvic inflammatory disease, ovarian cysts, and uterine fibroids.

Statistical Methods

We computed weighted percentages, means, and standard deviations using SAS, version 6.12 (SAS Systems, Cary, NC). We computed weighted, stratified annual cumulative ectopic pregnancy rates and 95% confidence intervals using the life-table method (with monthly intervals) using customized SAS programs. For better comparability to the CDC Collaborative Review of Sterilization (CREST) study of pregnancies after sterilization (9), the planned method of calculating time in pregnancy analysis was revised so as not to censor on either age or menopause status. We computed standard errors using modifications of Greenwood's method to allow for weighted observations and stratification. We do not present results if the number at risk was substantially less than 30 because such estimates may be unstable. We used Cox proportional hazards regression using SUDAAN (release 7.0, Research Triangle Institute, Research Triangle Park, NC) to account for sampling design and to compare one- versus two-insertion groups for ectopic pregnancy (a = 0.05, two-tailed).

Our interim analysis plan was to test safety events by comparing proportions of groups experiencing the end points, whereas our final analysis will conduct a time-to-event analysis. This decision is supported by the fact that follow-up time did not differ significantly across groups.

We calculated odds ratios (OR), 95% confidence intervals, and tests of significance for comparison of the study groups using logistic regression analyses, using SUDAAN to account for the sampling design. The analysis assumed stratified random sampling, with replacement, with stratification on province, district, method group (quinacrine/IUD), and logbook age category. The comparison between groups was tested by the Wald χ^2 statistic. Because of the rarity of ectopic pregnancies, hysterectomies, and deaths, these ORs approximate relative risks.

Small numbers of events are a concern for logistic regression because the overall type I error rate can be inflated. Poisson regression is preferable, but methods for dealing simultaneously with unequal sampling weights and Poisson regression are not readily available. We therefore decided to analyze the data by logistic regression but to use a more stringent alpha criterion (0.01) to avoid inappropriate inference. We made this decision before the analysis was conducted.

Covariate Adjustment

Although we originally did not plan to include a covariate adjustment of safety events in the interim analysis, we later

decided to add some basic potential confounders to the logistic model, mainly because of the unanticipated difference in parity between the two groups. The study clinician (D.S.) selected three potential confounders: age at insertion (using an improved age measure based on animal year of birth), parity at insertion (defined as number of live births at time of insertion), and education. These covariates were specified before knowing their impact on the comparison.

Subgroup Analysis to Handle Information Bias

The expansion group of one-insertion women had only two chances to be interviewed (1995 and 1996), as compared with other one-insertion women and all of the two-insertion women, who had three chances to be interviewed (1994, 1995, and 1996). This created an information bias: women in the expansion group reported far fewer health problems than did other one-insertion women: 28% vs. 64% ($\chi^2 = 160.10$, $P \ll .001$). Presumably, because of the longer recall period at the first interview, minor illnesses may have been forgotten. This information bias will artificially decrease the difference in health problems between the quinacrine and IUD groups and artificially increase the difference in health problems between the one-insertion and two-insertion groups. To eliminate this bias, we conducted subgroup analyses including only women interviewed in 1994 but using all available data for this subset of women.

RESULTS

Primary Analysis

The primary safety analysis (see Table 2) was conducted on the intent-to-interview population, including women who were never interviewed because they had died before contact. A woman was counted only once in each category but could contribute to more than one category. For example, the tabulation of *any health problems* includes women who had ectopic pregnancies or hysterectomies. Percents are weighted for differential probability of selection **and** for nonresponse.

Quinacrine-treated women had more ectopic pregnancies and hysterectomies than did IUD-treated women, with ORs of 2.33 (95% CI: 0.84, 6.51) and 2.62 (95% CI: 0.85, 8.09), respectively. But these differences were not significant, perhaps because of the small numbers of events. The numbers of deaths were similar in both groups, with an OR of 1.33 (95% CI: 0.49, 3.59), and none of the deaths were attributed to either quinacrine or IUD use. A fatality due to a choriocarcinoma occurred in a woman who had received quinacrine about a year after having a molar pregnancy. A fatality due to a uterine cancer occurred in an IUD user, but we were unable to locate her hospital records to determine the type of uterine cancer.

We repeated these analyses, excluding the 62 women in the IUD sample who later received quinacrine and the 181

TABLE 2

Comparison of study groups reporting selected adverse events: intent-to-interview population, all participants.

Event	Quinacrine, two insertions (n = 1,366)		Quinacrine, one insertion (n = 1,474)		Quinacrine, overall (n = 2,840)		IUD (n = 1,658)		Overall quinacrine vs. IUD		
	n	(wt %)	n	(wt %)	n	(wt %)	n	(wt %)	Odds ratio (95% CI)	Chi square ^a	P value
Ectopic pregnancy	9	(0.7)	9	(0.6)	18	(0.6)	5	(0.3)	2.33 (0.84, 6.5)	2.66	0.1031
Hysterectomy	7	(0.5)	11	(0.7)	18	(0.6)	4	(0.2)	2.62 (0.85, 8.09)	2.83	0.0924
Any health problems	865	(63.2)	547	(37.0)	1412	(56.3)	789	(47.1)	1.45 (1.27, 1.65)	31.68	<<.0001
Death	5	(0.4)	13	(0.9)	18	(0.5)	6	(0.4)	1.33 (0.49, 3.59)	0.32	0.5738
Post hoc: my abdominal or pelvic surgery	14	(1.0)	17	(1.2)	31	(1.1)	7	(0.4)	—	—	—

Note: Ectopic pregnancy, hysterectomy, hospitalization, and death were specified in protocol as key safety events for interim analysis. Frequencies are unweighted; percentages are weighted for sampling and nonresponse. Because of concerns regarding misinterpretation of the question, the hospitalization endpoint was revised to include all health problems. See text.

^a Wald χ^2 for study group (quinacrine vs. IUD) from logistic regression model. Takes sampling design and nonresponse into account.

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women in the quinacrine sample who later used an IUD (data not shown). Such cross-overs might blur the distinction between groups and underestimate the effect of the method. However, because cross-over could be related to method problems, the exclusion itself can introduce bias. Results were similar, except that the risk of ectopic pregnancy in quinacrine users appeared to increase because of the elimination of two ectopic pregnancies from the IUD group. In fact, one of those two women had had her ectopic pregnancy before her quinacrine insertion. The other woman's quinacrine insertion status is uncertain, but she was eliminated because we used a very liberal definition of cross-over.

In case a woman's decision not to come back for a second insertion stemmed from health problems after the first insertion, we also conducted a post hoc analysis to compare IUD women with quinacrine women who were intended to receive two insertions. Results were similar to those of the main analysis (data not shown).

The most common reasons for "any abdominal or pelvic surgery" were enlarged uterine fibroids, ectopic pregnancies, appendicitis, and ovarian cysts. This post hoc tabulation includes women who had hysterectomies and ectopic pregnancies, but the numbers are less than the totals of hysterectomies and ectopic pregnancies given in the upper rows of the same table. That is because the post hoc tabulation includes only surgeries reported in the 1995 and 1996 interviews, for which more detailed clinical data were available. A higher percentage of quinacrine than IUD acceptors had surgery: 1.1% compared with 0.4%. Comparing women who had two vs. one quinacrine insertions, the percentages are similar: 1.0% vs. 1.2%, respectively.

Quinacrine acceptors were more likely than IUD acceptors to report "any health problem," and women who had two quinacrine insertions reported more health problems than women who had one insertion. However, further analysis controlling for information bias (see below) showed that the difference between the one- and two-insertion quinacrine groups was most likely due to information bias.

Ectopic Pregnancies: Two vs. One Quinacrine Insertions

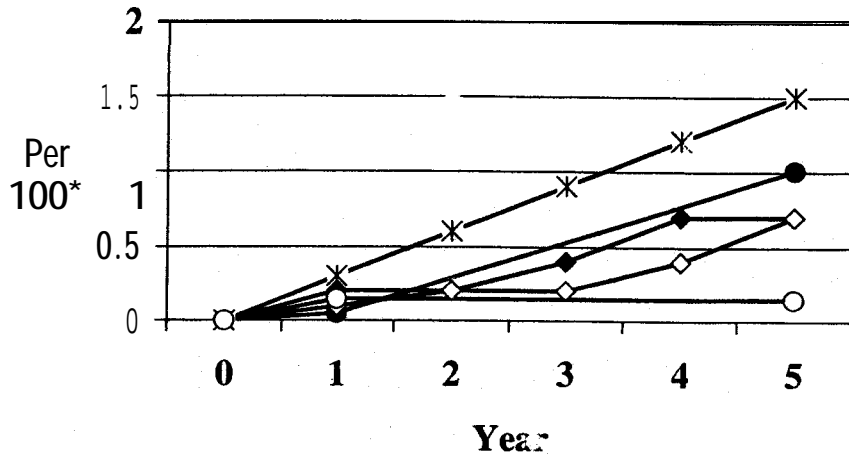
We identified nine ectopic pregnancies in each quinacrine insertion group. All the ectopic pregnancies were identified by both the annual interviews and the passive-surveillance system. We identified only one ectopic pregnancy among women who received two insertions at age 35 or older (data not shown). The cumulative life-table ectopic pregnancy rate at 5 years was 0.7 per 100 women after both the one- and two-insertion groups (see Figure 2). Though the rate at 5 years was identical, one-insertion women tended to have their ectopic pregnancies sooner than two-insertion women, giving a hazard ratio of 0.77 (95% CI: 0.25, 2.41).

Multivariate Logistic Analysis of Health Problems

Adjusting for age, education, and parity, we compared quinacrine versus IUD and one- vs. two-insertion groups for odds of experiencing [1] any health problems, [2] nongynecologic health problems, and [3] gynecologic health problems (see Table 3). These adjusted analyses were conducted with all participants and then repeated for those who were interviewed in the retrospective study, as a way to control for information bias among the one-insertion group. A tabula-

FIGURE 2

Five-year cumulative ectopic rates per 100 women for one- and two-insertion quinacrine groups, compared with a US estimate for noncontraceptors and with US CREST data for surgical sterilization by bipolar cautery and postpartum partial salpingectomy. CREST = Collaborative Review of Sterilization. CREST data are from Peterson (10); the "no method" estimate is from DeStefano (11). Postpartum partial salpingectomies include the Pomeroy method and similar methods. *, No method (11); —●—, CREST, bipolar cautery; —○—, CREST, postpartum partial salpingectomy; —◆—, one-insertion quinacrine; and —◇—, two-insertion quinacrine.



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tion of the gynecologic events included in this latter analysis is given in Table 4.

Controlling for covariates and including data from all participants, we found that quinacrine-treated women reported more gynecologic health problems than did IUD women, OR 1.45 (95% CI: 1.13, 1.86) and reported more

nongynecologic health problems, OR 1.64 (95% CI: 1.42, 1.90). When the analysis was restricted to those interviewed in 1994, this pattern did not change.

Comparing women who received two insertions **versus** those who received one insertion and including data from all participants, we found that two-insertion women reported

TABLE 3

Post hoc analysis: comparisons between quinacrine and IUD groups and between two- and one-insertion quinacrine groups on overall health problems and gynecologic health problems.

Analysis group	Quinacrine vs. IUD ³				Two insertions vs. one insertion ^b			
	Odds ratio	95% CI	Chi-square ^c	P value	Odds ratio	95% CI	Chi-square	P value
All participants								
Overall health problems	1.39	(1.21, 1.61)	20.26	<0.0001	2.13	(2.32, 3.22)	143.55	<<0.0001
Nongynecologic problems	1.64	(1.42, 1.90)	45.06	<<0.0001	2.77	(2.35, 3.26)	146.61	<<0.0001
Gynecologic health problems	1.45	(1.13, 1.86)	8.54	0.0035	1.49	(1.15, 1.94)	8.81	0.003
Participants in retrospective study ^d								
Overall health problems	1.84	(1.56, 2.16)	52.01	<0.0001	1.10	(0.86, 1.40)	0.56	0.4540
Nongynecologic problems	2.15	(1.83, 2.53)	84.49	<<0.0001	1.17	(0.92, 1.48)	1.61	0.2044
Gynecologic health problems	1.60	(1.23, 2.09)	12.04	0.0005	0.90	(0.64, 1.26)	0.40	0.5263

Note: Adjusted for age at insertion, number of live births at insertion, and education of interviewed population.

^a 2.5 13 quinacrine women and 1.477 IUD women had nonmissing data and are included in the analysis.

^b 1.234 two-insertion women and 1.279 one-insertion women had nonmissing data and are included in the analysis.

^c Wald χ^2 from logistic regression analysis. 1 df. Takes sampling design and nonresponse into account.

^d The retrospective study participants include women who were interviewed in the 1994 retrospective study and exclude an expansion group of one-insertion women who were first interviewed in 1995.

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TABLE 4

Gynecologic health problems^a reported 1994-1996 by women interviewed in the retrospective study.

Gynecologic problem	Quinacrine, two insertions (n = 1,271): wt %, (n)	Quinacrine, one insertion (n = 405): wt %, (n)	Quinacrine, overall (n = 1,676): wt %, (n)	IUD (n = 1,499): wt %, (n)
From the 1994 survey	8.25 (105)	10.34 (42)	8.45 (147)	4.94 (75)
Reported in 1995 or 1996	5.70 (72)	3.80 (15)	5.52 (87)	3.02 (47)
Amenorrhea	0.00	0.24	0.02	0.00
Cervicitis	0.23	0.27	0.24	0.30
Cervix disorder	0.08	0.00	0.07	0.00
Dysmenorrhea	0.79	0.24	0.74	0.56
Endometriosis	0.00	0.00	0.00	0.06
Endometritis	0.56	0.00	0.50	0.26
Hypomenorrhea	0.08	0.25	0.09	0.06
Leukorrhea	0.55	0.76	0.57	0.37
Menopause	0.24	0.00	0.22	0.06
Menorrhagia	0.16	0.00	0.15	0.37
Menstrual disorder	1.01	0.27	0.94	0.31
Ovarian cyst	0.40	0.24	0.38	0.06
Pelvic pain	0.32	0.54	0.34	0.12
Premenstrual syndrome	0.16	0.00	0.15	0.00
Salpingitis	1.34	1.55	1.36	0.48
Uterine disorder	0.16	0.00	0.14	0.00
Uterine fibroids enlarged	0.24	0.49	0.27	0.13
Vaginal moniliasis	0.08	0.00	0.07	0.00
Vaginitis	0.16	0.51	0.19	0.24
Vulvovaginitis	0.08	0.00	0.07	0.00

^a Based on definition of gynecologic end point used for multivariable analysis.

Sokal. *Interim quinacrine safety analysis. Fertil Steril* 2000.

more gynecologic health problems than did one-insertion women, OR 1.49 (95% CI: 1.15, 1.94), and more nongynecologic health problems, OR 2.77 (95% CI: 0.92, 1.42). When the analysis was **restricted** to those interviewed in 1994, the findings changed substantially. Two-insertion women did not report more gynecologic health problems than did one-insertion women, OR 0.90 (95% CI: 0.64, 1.26), nor nongynecologic health problems, OR 1.17 (95% CI: 0.92, 1.48).

Although the two-insertion group initially appeared more likely than the one-insertion group to report gynecologic or nongynecologic health problems, this difference disappeared when we controlled for information bias.

Pelvic Inflammatory Disease

Table 4 shows a list of the problems and the percentages of women who reported gynecologic problems among the women in the restricted analysis. About 8% of women who received quinacrine reported gynecologic problems in the retrospective survey, but we **did** not have the clinical details needed to permit detailed categorization.

Based on the interviews in 1995 and 1996, women who received a diagnosis of either salpingitis or endometritis (see Table 4) were considered to have had pelvic inflammatory disease (PID). PID was the most commonly reported gynecologic health problem; it was found in 1.86% ($n = 30$) of

quinacrine acceptors and 0.74% ($n = 12$) of IUD acceptors. However, the clinical diagnosis of PID is difficult and often inaccurate. Without careful confirmation, a clinical diagnosis of PID may actually reflect lower-genital tract infection such as cervicitis, vaginitis or other gynecologic or even gastrointestinal disease.

To try to clarify the data, FHI and Thai Binh clinicians reviewed the questionnaires of women that reported receiving hospital care for gynecologic or abdominal illness, blinded to study group. We identified 39 women with symptoms suggestive of PID reported in a 1994, 1995, or 1996 interview. Of 17 women identified from the 1994 survey, 11 were IUD users, and six were quinacrine users. Of 22 women identified from the 1995 and 1996 surveys, three were IUD users, and 19 were quinacrine users.

The women who reported events during 1995 or 1996 were then interviewed again to gather additional details concerning their illnesses. We did not reinterview women who were identified from the 1994 interviews because of concerns about recall because those events could have occurred anytime between 1989 and 1994. Among the 22 events reported in 1995 or 1996, we found that eight of the 22 women who reported hospital care for PID had been hospitalized. Thirteen women had visited a hospital but had been treated as outpatients, and information was unavailable

for one woman who had moved to Hanoi. In reviewing the description of the illnesses, two of three reviewing physicians doubted the diagnosis of PID in four of the nonhospitalized women. We did not identify the occurrence of any abortions before the suspected PID events. Two of the hospitalized women had had surgical sterilizations after entry into this study and within a year or two before being diagnosed with PID.

We did a post hoc breakdown of the 39 PID cases by time of report (either before or after increased publicity about quinacrine in 1994; cases are divided by diagnosis or onset dates before vs. on or after January 1, 1994) to see whether the data were compatible with a reporting bias. We found that in the earlier period, there were eight cases (0.3%) among quinacrine users and IO cases (0.6%) among IUD users. In the later period, IO cases (0.4%) occurred among quinacrine users, and only one case (0.1%) occurred among IUD users. The proportion of quinacrine women with PID was comparable before and after 1994, whereas the proportion of IUD women with PID was higher during the earlier versus the later period. To see whether the episodes of PID among IUD acceptors might have been attributed to IUD insertions, we reviewed the intervals between IUD insertion and diagnosis of PID and found exact dates of both events for six women. For these women, the intervals ranged from 2 to 22 months. All but one of the intervals were greater than 6 months, suggesting that the cases were not related to the IUD insertion procedures.

DISCUSSION

Ectopic Pregnancy Rates

Despite the relatively high pregnancy rate after one insertion (7), the ectopic pregnancy rate after one insertion was similar to the ectopic pregnancy rate after two insertions. Although the risk of ectopic pregnancy in the quinacrine group was higher than that of the IUD group, it was similar to ectopic rates reported in the CREST study (IO) and lower than an estimate for the rate among nonconceiving women in the United States (11). For women in the CREST study who had bipolar coagulation, the most common form of surgical sterilization in the United States, the rate at 5 years was IO per 1,000 women, slightly higher than the rate of 7 per 1,000 women for women receiving quinacrine. For women in the CREST study who had postpartum partial salpingectomy, the rate at 5 years was 1.5 per 1,000 women, lower than the quinacrine rate. A recent more detailed analysis of the CREST data (12) suggests that the original CREST report (10) may have overestimated the risk of ectopic pregnancy after bipolar cautery when improved surgical techniques are used. Based on more detailed analysis by year of the procedure, the pregnancy rate after bipolar cautery sterilizations that were performed more recently with at least three burn points per tube is estimated to be 3.2 per 1,000 women at five years. This would necessarily mean

lower rates of ectopic pregnancy than the curve shown in Figure 2, which is based on the earlier CREST report.

Another way to look at ectopic pregnancies is as a proportion of all pregnancies. As would be expected given the higher pregnancy rate after quinacrine, the proportion of ectopic pregnancies among all pregnancies after quinacrine was lower than after surgical sterilizations in the CREST study, 5.8% vs. 32.9%, respectively.

The CREST study gathered data by telephone rather than by home visits and did not evaluate possible underreporting of pregnancies, as we did with our passive-surveillance system (7). We are confident of the accuracy of the number of ectopic pregnancies identified since 1995 because we identified all the ectopic pregnancies in both the annual interviews and the passive-surveillance system. In addition, the ectopic rates reported here appear similar to rates reported from Chile. 2 per 1,000 women at 5 y and 9 per 1,000 at 10 y (13).

Hysterectomies

We found an increase in the risk of hysterectomy in the quinacrine group compared with the IUD group (OR 2.6) that was not statistically significant. A recent CREST report showed a statistically significant 4-fold higher rate of hysterectomy among women who underwent surgical sterilization compared with women whose husbands had had a vasectomy (14). However, the authors note that "biologic factors are unlikely to be responsible for this association." The increase in the rate of hysterectomies in the CREST study probably involves patient and physician behavior rather than adverse biologic effects of the sterilization procedure. It is possible that an analogous effect could be operating in Vietnam with respect to quinacrine sterilization; however, biologic factors cannot be ruled out.

Limitations

Major limitations of this study with respect to safety issues are its observational nature and the use of an IUD comparison group rather than a group of women who had had surgical sterilizations. Although matching and multivariate analysis can adjust for certain differences between groups, women who choose permanent vs. temporary methods may have intrinsic differences that defy statistical adjustment. For example, physicians often advise women with serious systemic diseases to be sterilized. In addition, the abrupt halt of the quinacrine program and associated adverse publicity about quinacrine may have produced a reporting bias.

Media publicity about contraceptives has been clearly shown to have substantial effects on women's health concerns, perceptions, physician visits and contraceptive preferences. Adverse publicity can lead to abrupt and sometimes disproportionate changes in contraceptive practice when the media report medical problems. For example, publicity about oral contraceptives and the risk of breast cancer has periodically caused fluctuations in the use of oral contraceptives,

and problems with the Dalkon Shield caused the virtual disappearance of all IUDs from clinical use in the United States. Media reports of a potential increase in prostate cancer risk following vasectomy may have caused a leveling off of the demand for vasectomy, but the evidence is inconclusive (15). In this study, we did not attempt to control for possible reporting bias due to adverse publicity **about** quinacrine.

Other limitations of this interim analysis include limited statistical power and the conduct of exploratory analyses, designated in the tables as ad hoc if requested generally before other results were known or as post hoc if clearly following up observed findings.

CONCLUSIONS

First, the proportion of quinacrine acceptors with ectopic pregnancies was higher than among IUD acceptors. However, the ectopic pregnancy rate in quinacrine acceptors was similar to the rate among women who had surgical sterilizations in the United States. Within the quinacrine group, women who had received either one or two insertions were at similar risk for ectopic pregnancy.

Second, a higher proportion of quinacrine acceptors reported gynecologic and nongynecologic health problems, compared with the IUD group. Because this was observed for nongynecologic events unlikely to be associated with quinacrine use, this may be due to intrinsic differences between the two groups or to reporting bias associated with the adverse publicity about quinacrine. Within the quinacrine group, a similar proportion of women who had received either one or two insertions had gynecologic problems once we controlled for information bias. We emphasize the preliminary nature of the results at this stage of the study.

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