

Long-term follow-up after quinacrine sterilization in Vietnam. Part I: interim efficacy analysis

David Sokal, M. D.,^a Do Trong Hieu, M.D.,^b Debra H. Weiner, M.P.H.,^a
 Dao Quang Vinh, M.D.,^c Trinh Huu Vach, Ph.D.,^d and Robert Hanenberg, Ph. D.^a

Family Health International, Research Triangle Park, North Carolina; Ministry of Health, Hanoi; and Thai Binh Medical College, Thai Binh, Vietnam

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

Design: Observational cohort study.

Setting: Rural provinces in northern Vietnam.

Patient(s): Two thousand seven hundred and nine women who had quinacrine insertions between 1989 and 1993.

Intervention(s): Interviews in 1994, 1995, and 1996 and review of available medical records. Pregnancy rates were corrected for problems in detecting and confirming pregnancies.

Main Outcome Measure(s): Pregnancy rates.

Result(s): Over 90% of women were interviewed at least once. Uncorrected cumulative pregnancy rates were 12.9% at 5 y after two insertions and 27.3% after one insertion. Effectiveness varied by age group: the partially corrected pregnancy rates after two insertions were 6.8% in women 35 or older at the time of insertion and 13.0% in women under 35. A subgroup of women who received oral papaverine at the time of quinacrine insertion had lower pregnancy rates, with a cumulative uncorrected rate of 5.3% at 4 years among women of all ages.

Conclusion(s): Efficacy of quinacrine appears reasonable for two insertions of quinacrine in women 35 and older. It may be possible to improve efficacy by the use of papaverine or the Hieu insertion technique. (*Fertil Steril* 2000;74: 1084-91. © 2000 by American Society for Reproductive Medicine.)

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

Received February 18, 2000; accepted June 15, 2000.

Supported in part by Family Health International (FHI). FHI is an international not-for-profit organization that conducts research and provides technical assistance in health, family planning, STDs, and AIDS. Views expressed in this report do not necessarily reflect those of FHI.

Reprint requests: David Sokal, M.D., Family Health International, P. O. Box 13950, Research Triangle Park, North Carolina 27709 (FAX: 203-785-7134; E-mail: dsokal@fhi.org).

^a Family Health International, Research Triangle Park, North Carolina.

^b Director, MCHFP Department, Ministry of Health, Hanoi, Vietnam, at the time of the study; currently retired.

^c Ministry of Health, Hanoi, Vietnam.

^d Research Center for Rural Population and Health, Thai Binh Medical College, Thai Binh, Vietnam.

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 mo later.

Quinacrine sterilization was first offered by the Vietnamese Ministry of Health (MOH) in 1988 as a pilot study with 200 volunteers selected from two provinces near Hanoi, in the Red River Delta, namely Hai Hung and Ha Nam Ninh. (These two provinces have since

been divided into a total of five smaller provinces, four of which are involved in the current study.)

The results of this pilot study were reported in a joint meeting organized by the Vietnamese MOH and the National Committee for Population and Family Planning in April 1989. In that meeting, the MOH decided that quinacrine sterilization should be introduced more widely in those two provinces, which had a combined population of over five million people. Because of the ease of service delivery and good acceptability, MOH clinics in a number of provinces subsequently decided to use quinacrine sterilization.

By October 1992, 31,781 women in 24 provinces had received quinacrine sterilization (2). The total number of quinacrine steriliza-

0015-0282/00/\$20.00
 PII S0015-0282(00)01596-X

tions in Vietnam is not known, but it has been estimated that a cumulative total of about 50,000 women were sterilized before the program was terminated. The MOH halted the program in December 1993 because of concerns voiced by the World Health Organization (WHO) (3) that quinacrine might be a carcinogen. Subsequently, in July 1994, WHO held a consultative meeting on the development of new technologies for female sterilization (4). The report of that meeting included recommendations for additional toxicologic testing of quinacrine and for additional follow-up of women who had already received quinacrine (5).

After the quinacrine program was halted, the MOH invited Family Health International (FHI) to help evaluate the program because of FHI's experience with quinacrine research (6). In 1994, FHI and Vietnamese researchers conducted a retrospective study to address concerns about whether women had given informed consent before accepting quinacrine insertions and to evaluate other service delivery-related aspects. (Katz K, Waszak C, Hieu D, Vinh D, Sokal D. The lessons of quinacrine introduction in Vietnam. Manuscript submitted for publication.) In 1995, in keeping with WHO recommendations (5), we began a long-term follow-up study, to consist of five annual interviews of the women first interviewed in 1994. One of the study objectives was to estimate long-term pregnancy rates after transcervical quinacrine pellet sterilization. In this paper, we report pregnancy rates from the interim analysis, based on data through the second annual interview in 1996. An accompanying paper presents the interim analysis of the safety data, including rates of ectopic pregnancies (7).

MATERIALS AND METHODS

Study Population and Sampling Methods

This is a long-term, observational cohort study of a sample of women who had quinacrine insertions in Vietnam between 1989 and 1993 (2). 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.

For the 1994 survey, we prepared sampling frames from logbooks of 6,535 quinacrine acceptors. We then selected a random sample of quinacrine acceptors, stratified by province, district, and 5-year age group. The sampling frame included women who had one, two, or more insertions.

In 1995, we added more one-insertion women to the sample to have better statistical power for comparing one vs. two quinacrine insertions. This expansion group included all the remaining one-insertion women in the sampling frame. The data from the 1994 interviews and the current study were pooled to determine participants' pregnancy rates from the date of quinacrine insertion up to the date of last contact.

A participant flow chart is included in the accompanying

paper (7). 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 consists of all women selected for the study, whether or not they were ever interviewed. The *interviewed* population is the subset who were interviewed at least once in 1994 (for our retrospective study), 1995, or 1996. In all, 95% of women were interviewed at least once. We excluded six one-insertion quinacrine women because of invalid insertion dates (e.g., missing year).

Questionnaires and Interview Methods

Questionnaires were initially drafted in English, translated into Vietnamese, and then reviewed, revised, and finalized in Vietnam. The questionnaires asked about pregnancies and the occurrence of any health problems.

In 1994, schoolteachers interviewed 1,679 women for the retrospective survey. In 1995, we used schoolteachers again to interview 2,621 women, including the added sample of one-insertion women. In addition, physicians conducted 536 follow-up interviews to get more information about health problems. In 1996, to improve reporting of medical problems, we used physicians to conduct both the initial and follow-up interviews of 2,520 and 313 women, respectively. If a woman had died, we interviewed relatives and local health workers. For selected cases involving hospitalization, surgery, or death, we sought copies of hospital records.

Other Data Sources

In addition to the annual interviews, we used two additional sources of data:

1. Data regarding the use of drug combinations with quinacrine, collected in July and August 1997, from the original quinacrine insertion logs. We found adjuvant data on 88% of the women from the original insertion logs in the provincial health offices.
2. Passive surveillance data regarding pregnancy tests, menstrual regulations (MR), and abortions. (An MR is an early abortion procedure, often done within a week or two of a missed period and commonly done without a pregnancy test [8].)

To collect the passive surveillance data, we initiated regular distribution of pregnancy tests to hospitals and clinics in the study area and gave each woman in the study a document entitling her to free pregnancy tests. After this distribution, most of the women in our study had access to pregnancy tests. Clinic staff reported the results of pregnancy tests and whether a woman had an abortion or MR. Only pregnancies reported in the annual interviews were included in the analysis, but we used the passive surveillance data to calculate two correction factors: [1] one for unnecessary menstrual regulations and [2] one for unreported MRs or abortions (see Technical Appendix).

Women interviewed in 1996 were asked their current age, either by Vietnamese animal year or (if animal year was not available) by month and year of birth. The Vietnamese calendar has a cycle of 12 animal years. Women reporting an animal birth year were then assigned a specific age by interviewer observation, in other words, either x years of age or $x + 12$ years of age. An improved measure of age at insertion, based on the 1996 data (but using the logbook value if the 1996 data were missing), was created. The 1996 age data were available for 93% of the women. We used the improved estimate of age at insertion to categorize women for pregnancy analysis (<35 vs. ≥ 35). We used the original age strata when accounting for sampling design and in the table of baseline characteristics (see Table I).

Baseline Characteristics

Percentages, means, and standard deviations (see Table I) are weighted for differential sampling probability and non-response. Almost all women were married and literate. The proportions of one- vs. two-insertion quinacrine women are quite different across provinces, and the years since quinacrine insertion at the time of last interview are slightly different. This is probably due to the combined effects of oversampling for women with one insertion and the limited practice of one-insertion trials. Obstetric and contraceptive history and age at insertion were similar in both groups. Most women in both groups had three or four living children. In both groups, 90% of women were 30 years of age or older at the time of insertion, with 40% in the 35to-39-year age group.

Pregnancy Analysis

We estimated the date of conception as the date of the last menstrual period (LMP) plus 14 days. If we had more than one date for the LMP, we chose the earlier date. For the few cases with missing data, we used various algorithms to estimate the date of conception.

Follow-up times ranged from less than 1 year to 8 years. Annual cumulative pregnancy rates through 5 y were calculated using the life-table method (monthly intervals), stratified by the sampling stratification variables (province, district, and 5-year age group). We originally specified that sampling and nonresponse should be taken into account in the pregnancy estimates (i.e., weighted). Later, we considered the possible effects of unnecessary menstrual regulations and underreporting of abortions, and we calculated correction factors for both of these effects (see Technical Appendix).

Pregnancy estimates corrected for unnecessary menstrual regulation and underreporting of abortions are our best estimate of the true contraceptive effectiveness of the method, and we designated these a priori as the gold standard estimates. However, because most studies do not correct for underreporting and have no need to correct for unnecessary MRs (because pregnancy status is typically known), partially

corrected rates, corrected only for unnecessary MRs, are more appropriate for comparison with other studies. Except as noted below, we have calculated pregnancy rates by the reported number of insertions, not by the intended number.

For five women, the only evidence of pregnancy was a positive response to an item in 1996 about whether they had gotten pregnant between insertions. Because related items were not answered and they had reported no pregnancies when interviewed in 1994, we assumed that these were form completion errors.

Statistical Methods

We computed weighted percentages, means, and standard deviations of baseline characteristics using SAS software, version 6.12 (SAS Systems, Cary, NC). We computed weighted, stratified, annual cumulative pregnancy rates and 95% confidence intervals, both corrected and uncorrected, using the method described in the Appendix, programmed via SAS data steps. (Survival analysis estimates are more accurately called *cumulative probabilities* of an event [e.g., pregnancy] rather than *rates*. However, because the latter term is more commonly understood, these terms will be used interchangeably in this report.) For better comparability with the CDC Collaborative Review of Sterilization (CREST) study of sterilization failure (9), we revised the planned method of calculating time to pregnancy so as not to censor on either age or menopause status. Standard errors were computed by Greenwood's method, modified to handle weighted and stratified observations and pregnancy corrections (details available upon request). Results are not given if the number at risk was substantially less than 30 because such estimates may be unstable. We then did Cox proportional hazards regression using SUDAAN version 7.0 (Research Triangle Institute, Research Triangle Park, NC) to account for sampling design, in order to compare one- vs. two-insertion groups for overall uncorrected pregnancy rates ($\alpha = 0.05$, two-tailed).

RESULTS

The gold-standard 5-year cumulative pregnancy rate was 12.6 (95% confidence interval [CI]: 10.6, 14.5) per 100 women receiving two insertions. The 5-year rate for women receiving one insertion was 25.8 per 100 women (95% CI: 23.5, 28.1).

The weighted, uncorrected 5-year cumulative life-table pregnancy rate for women receiving two insertions of quinacrine was 12.9 per 100 women (95% CI: 11.1, 14.7) vs. 27.3 (95% CI: 25.1, 29.5) for women receiving one insertion. The one-insertion group had a 2.47 times higher risk of pregnancy than did the two-insertion group (95% CI: 2.04, 2.98), $P < 0.001$.

TABLE 1

Participant characteristics,^a interviewed population.

Parameter	Quinacrine, two insertions (n = 1,329). wt %	Quinacrine, one insertion (n = 1,380). wt %	Quinacrine, overall (n = 2,709). wt %
Insertion history			
Age at insertion ^b			
20-24	0.0	0.5	0.1
25-29	10.1	9.0	9.8
30-34	36.4	31.7	35.2
35-39	39.6	40.3	39.8
≥40	14.0	18.5	15.1
Mean age (SD)	34.7 (7.71)	35.2 (4.59)	34.9 (6.32)
Median (min/max)	35 (25/48)	35 (20/48)	35 (20/48)
Years since insertion at last interview			
<2	1.0	1.0	1.0
2-3	16.5	13.2	15.6
4-5	71.0	84.7	74.5
≥6	11.5	11	8.8
Mean years (SD)	4.9 (1.94)	4.5 (0.76)	4.8 (1.49)
Median (min/max)	5 (0/8)	4.6 (2/7)	4.6 (0/8)
Sociodemographic			
Marital status ^c			
Married	99.3	93.9	97.9
Not married	0.5	0.6	0.6
Unknown	0.2	5.4	1.5
Education			
illiterate	0.3	0.7	0.4
Primary school (1-5)	14.9	11.7	14.0
Basic school (6-9)	77.3	80.7	78.2
Secondary school (10-12)	5.9	5.8	5.8
Technical/vocational	1.5	1.0	1.4
College/university	0.2	0.2	0.2
Province^d			
1: Nam Ha	58.2	25.9	49.9
2: Hai Hung	28.5	22.9	27.1
3: Thai Binh	13.3	51.2	23.0
Obstetrical history			
Age at first pregnancy			
<20	14.0	16.2	14.6
20-24	68.7	66.6	68.2
25-29	16.1	15.1	15.9
≥30	1.2	2.1	1.4
Number of pregnancies ^e			
1	0.0	0.2	0.0
2	2.1	4.2	2.3
3	14.5	12.8	14.3
4	23.8	20.4	23.5
5	21.8	22.6	21.8
≥6	37.8	39.8	38.0
Number of live births ^f			
None	0.2	0.3	0.2
1	0.2	0.5	0.2
2	7.9	13.1	8.4
3	37.6	39.4	37.7
4	31.8	31.0	31.8
5	14.9	9.7	14.4
≥6	7.4	6.1	7.2
Number of living children ^g			
None	0.0	0.0	0.0
1	0.3	0.5	0.3
2	8.9	14.3	9.5

Continued on following page

TABLE 1—CONTINUED

Participant characteristics,^a interviewed population.

Parameter	Quinacrine. two insertions (n = 1,329). wt %	Quinacrine. one insertion (n = 1,380). wt %	Quinacrine. overall (n = 2,709). wt %
3	42.6	43.4	42.7
4	31.5	28.2	31.2
5	11.6	9.7	11.4
≥6	5.0	3.9	4.9
Contraceptive history: method used immediately before insertion			
None	19.9	19.1	19.8
IUD	57.8	45.1	56.5
oral contraceptives	1.1	2.9	1.3
Condoms	3.5	3.3	3.5
Other	17.7	29.6	18.8

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

^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.

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

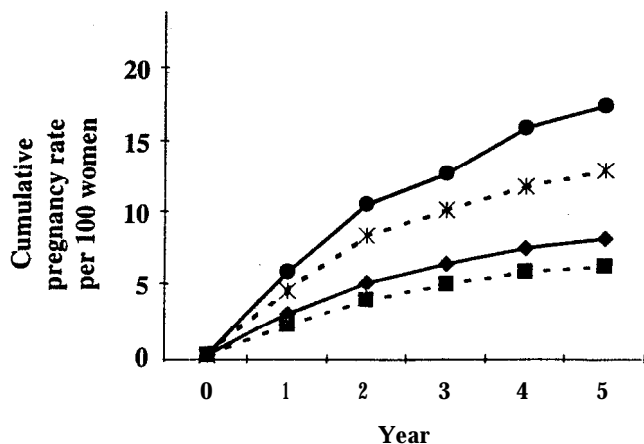
Women Who Received Two Insertions at Age 35 and Above

Quinacrine would probably be most appropriate for women aged 35 years and above (6). For women 35 years

and above who received two insertions, the 5-year gold-standard rate was 9.0% per 100 women (95% CI: 6.5, 11.5). Women aged 35 and above at the time of insertion had substantially lower pregnancy rates than did younger women (see Figure 1); for example, partially corrected rates of 6.8 per 100 women (95% CI: 4.5, 9.0) vs. 13.0 (95% CI: 10.3, 15.7) at 5 y. Figure 1 shows two rates for each age group: the fully corrected, gold-standard rates and the lower, partially corrected rates that are more appropriate for comparison with other studies.

FIGURE 1

Five-year cumulative pregnancy rates per 100 women with two quinacrine insertions, by age, with either full or partial correction* of pregnancy rates. * Full correction corresponds to the gold-standard pregnancy rate, correcting for both unnecessary menstrual regulations and unreported abortions. The partial rates are corrected for unnecessary menstrual regulations but not for unreported abortions. —●—, <35, fully corrected; --*-- , <35, partially corrected; —◆—, ≥35, fully corrected; --■-- ≥35, partially corrected.



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

Intent-to-Treat Analysis

Classifying women by the number of insertions actually received gives a somewhat idealized failure estimate for the two-insertion group, that is, analogous to a perfect-use rate because only those women who came back for their second insertion and who did not get pregnant between insertions are included. Among the 1,279 one-insertion women for whom we have information regarding reasons for only one insertion, 221 (17.3%) reported that they were supposed to receive two insertions but did not return for the second. They gave the following reasons for not returning: 24% were busy; 11% reported side effects from the first insertion; 10% forgot the appointment; 10% were ill, menstruating, or pregnant; 10% did not give a reason; and the remaining 34% gave a variety of miscellaneous other reasons.

We recalculated the gold-standard pregnancy rates, classifying women on the basis of the number of insertions that they were supposed to receive; in other words, an intent-to-treat analysis. The 5-year cumulative pregnancy rate increased somewhat for the 1,530 women in the two-insertion protocol (14.8 per 100 women; 95% CI: 13.0, 16.7) and

TABLE 2

Ad hoc analysis: use of adjuvants by number of quinacrine insertions, interviewed population.

Adjuvant	Quinacrine, two insertions ^a		Quinacrine, one insertion	
	n	(%)	n	(%)
Ampicillin only (intrauterine)	580	(57.5)	207	(22.4)
NET-EN or DMPA	19	(1.9)	466	(50.4)
Oral contraceptives only	42	(4.2)	33	(3.6)
Papaverine only (oral)	237	(23.5)	114	(12.3)
Other	2	(0.2)	1	(0.1)
None	129	(12.8)	103	(11.1)
Total^b	1009		924	

^a Number of insertions at time of pregnancy. Frequencies and percentages are unweighted.

^b Information on 215 two-insertion and 152 one-insertion women is not available; 93 two-insertion and 316 one-insertion women could not be classified into "pure" types.

Sokal. Interim quinacrine efficacy analysis. Fertil Steril 2000.

decreased somewhat for the 1,055 women in the one-insertion protocol (24.3 per 100 women; 95% CI: 21.9, 26.8). For older, two-insertion women, the partially corrected 5-y pregnancy rate shown in Figure 1 would increase from 6.8 to 8.2 per 100 (95% CI: 5.9, 10.5) on the basis of an intent-to-treat analysis.

Drug Combinations and Insertion Techniques

Several drugs were administered in combination with quinacrine, whether orally, unscervically, or by injection. We classified 1,933 quinacrine acceptors into mutually exclusive categories by type of drug combination received (see Table 2). Most women received an additional drug. In the two-insertion group, intrauterine ampicillin (125 mg) was the most commonly added drug. Antibiotics are routinely given in Vietnam at the time of IUD insertion, and some physicians thought ampicillin, either oral or intrauterine, should also be given with quinacrine to reduce the risk of infection. In the one-insertion group, intramuscular injections of 150 mg of depo-medroxyprogesterone acetate, which is manufactured under the brand name Depo-Provera, or 200 mg norethisterone enanthate, manufactured with the brand name Noristerat, were most frequently given to prevent pregnancies immediately after the insertion.

Oral papaverine is routinely used in Vietnam to reduce the painful uterine cramping often associated with IUD insertions and was given to some women at the time of their quinacrine insertions. In most cases, health providers gave each woman four 40-mg pills. Although the exact regimen to be used was not documented in writing, discussions with health providers indicate that women were probably advised to take one pill twice a day to reduce pain from uterine cramping, though some providers recommend two pills twice a day.

We conducted post hoc calculations of unweighted and

uncorrected life-table pregnancy rates and 95% confidence intervals for the most common drug combinations.

Because of the highly exploratory nature of this analysis, generalization beyond the cohort was not advisable; hence the use of unweighted and uncorrected estimates.

The follow-up times in the life-table analyses for these subgroups are shorter and of different lengths, either 2 or 4 years, because of the small number of women in these subgroups. Women with two insertions who got papaverine had a lower pregnancy rate than did women who received ampicillin (see Figure 2). The 129 women who had no added drug had a 2-year pregnancy rate of 11.0 per 100 women (95% CI: 5.6, 16.5), similar to the rate among women who received intrauterine ampicillin.

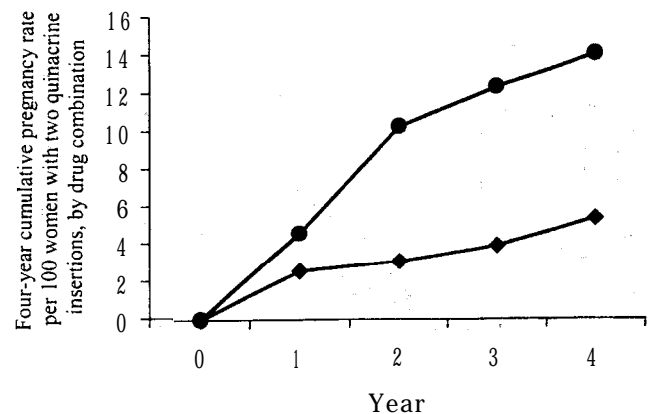
Among women who received one quinacrine insertion, the 2-year cumulative life-table pregnancy rates were 23.5 per 100 women (95% CI: 17.7, 29.3) for ampicillin; 22.6 (95% CI: 18.8, 26.4) for injectable progestogens; 11.5 (95% CI: 5.6, 17.4) for papaverine; and 21.0 (95% CI: 13.0, 29.0) for no added drug.

After both one or two insertions, women receiving papaverine had substantially lower pregnancy rates than the other groups. Looking at the two-insertion papaverine group by age, women 35 years of age or older at the time of quinacrine insertion had a 4-year cumulative pregnancy rate of 2.7 per 100 women (95% CI: 0, 5.7).

The use of papaverine was recommended by Hieu, so it is possible that the Hieu insertion technique, rather than papaverine use, was responsible for the low pregnancy rate in this subgroup. In the original report of the quinacrine pro-

FIGURE 2

Four-year cumulative pregnancy rates per 100 women, with two quinacrine insertions, by drug combination. Papaverine use may have been associated with the Hieu insertion technique. ● ampicillin only; ◆ papaverine only.



Sokal. Interim quinacrine efficacy analysis. Fertil Steril 2000.

gram in Vietnam, Hieu described a new insertion technique: gently advance the inserter to the fundus, withdraw it about 5 mm, and then advance the plunger to deposit the pellets at the fundus (2). This is different from the method previously used by Zipper and other investigators, who used a standard IUD insertion technique, in which the inserter is advanced to the fundus and the outer tube is withdrawn, which would leave the quinacrine pellets dispersed throughout the uterus (6). We have no data as to which insertion technique was used for particular women. To try to disentangle this confounding, we conducted stratified Mantel-Haenszel tests, done separately by insertion group, on the association of pregnancy to papaverine, controlling for health care provider, and vice versa. When controlling for health care provider, the odds ratios for papaverine remained low but were no longer statistically significant. Controlling for papaverine, the health care provider factor was highly significant for the one-insertion group but not for the two-insertion group.

DISCUSSION

A number of small clinical studies of quinacrine pellet sterilization have been conducted in various countries (6) and in the United States (10) during the past 20 years. but many of them have had limitations in study design. Some long-term follow-up data on efficacy have been reported from Chile (6, 11-13). This study is the largest long-term follow-up study of quinacrine pellet sterilization.

Because other studies of pregnancies after sterilization have not corrected for underreporting of abortions, the overall rate that should be used when comparing our data to studies of surgical sterilization is 9.8 per 100 women at 5 years. The CREST study found an overall pregnancy rate of 1.4 per 100 women at 5 y and 1.9 per 100 women at 10 y (9). Participants at the WHO meeting on female sterilization discussed the issue of what would be an acceptable pregnancy rate following a nonsurgical method, but did not come to any conclusions (5).

We found that two quinacrine insertions were clearly better than one. A previous review of clinical data on quinacrine sterilization (6) suggested that quinacrine sterilization was likely to be most appropriate for women ages 35 and above because pregnancy rates are lower and the risk of regret is lower (14). The results of the present study are consistent with that suggestion. The pregnancy rate at 5 y for women 35 y of age and above who had two or three insertions in Chile was only 2.8%; the comparable figure from the current data would be 6.8%. There are at least two possible explanations for this difference:

1. **Relative lack of training in Vietnam: at the time the quinacrine program began in Vietnam, there was a desperate need for new contraceptive method., and it was felt that the quinacrine method was not technically difficult and required little or no formal training for providers already experienced**

in IUD insertions. However, it was later clear that there was considerable variation in pregnancy rates by health provider (2, 15).

2. **Better reporting: the use of carefully designed survey procedures with home visits and an independent system of passive surveillance may have resulted in better reporting of pregnancies than in other long-term studies of quinacrine sterilization.**

The use of drug combinations may have also affected the efficacy rates in unknown ways. The most striking finding was among women who received papaverine, who had substantially lower pregnancy rates than other women. Papaverine is known to inhibit uterine smooth-muscle contractions and was used with the intention of preventing painful uterine contractions after quinacrine insertion. Although the number of women who received papaverine was relatively small, the pregnancy rates in this subgroup were much lower in both the one- and two-insertion groups. Our exploratory analytic attempt to determine whether the lower pregnancy rate was due to the influence of (a) papaverine or (b) better insertion techniques used by certain providers was inconclusive.

The 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. Given the retrospective collection of data about the insertion **procedures, it was difficult** to determine whether women were supposed to receive one or two insertions. Our intent-to-treat estimates may be conservative because our sample over-represents one-insertion women. On the other hand, we may have underestimated the number of one-insertion women who were supposed to receive two insertions.

CONCLUSIONS

Among women of all ages, our best estimate of the 5-year cumulative pregnancy probability is 12.6 per 100 women (95% CI: 10.6, 14.5) for women receiving two quinacrine insertions: and 25.8 per 100 (95% CI: 23.5, 28.1) for women receiving one insertion.

In women with two insertions at age 35 or above, the partially corrected pregnancy rate was 6.8% at 5 years, compared with 2.8% for similarly aged women in Chile. The higher pregnancy rate in Vietnam could be due to several factors, including less uniform insertion techniques by a larger number of providers and better reporting.

In a subgroup of two-insertion women who received oral papaverine to prevent painful uterine cramping, we found that the pregnancy rate was markedly lower, with an uncorrected four-year rate of 5.3% among all women, and 2.7% in women 35 years of age and above. The use of papaverine may have been confounded with insertion technique or inserter skill.

Because these results are from an interim analysis and are from an observational study rather than a clinical trial, they are, by definition, preliminary, and they should be interpreted cautiously.

TECHNICAL APPENDIX

Calculation of Pregnancy Correction Factors

Correction for Unnecessary Menstrual Regulations

When pregnancy tests are not readily available and the woman's pregnancy status is not clinically obvious, it is possible that a menstrual regulation will be performed when, in fact, the woman is not pregnant. Counting all such cases as pregnancies will overestimate rates, whereas counting none of them will underestimate rates. To correct for this, the following steps were taken.

Passive-surveillance data were used to estimate the proportion of menstrual regulations that were likely not to have been true pregnancies. By late 1995, pregnancy tests were more generally available, particularly to study participants. These data showed that 58% of women in the quinacrine sample who sought pregnancy tests had a negative test. Assuming that before the availability of pregnancy tests, these women would have received a menstrual regulation, we estimated that for 58% of "uncertain" menstrual regulations (menstrual regulations not confirmed by a pregnancy test and conducted within 7 wks of last menstrual period, before clinical signs would be apparent), the woman was not really pregnant. We implemented this correction by counting study pregnancies that met this definition as .42 of a pregnancy in the life-table, with the remaining .58 censored at the time of the pregnancy.

Correction for Underreporting of Menstrual Regulations and Abortions

Underreporting of menstrual regulations and abortions was estimated by comparing menstrual regulations and abortions recorded via passive surveillance with events reported by women during the regular yearly interview for the same period (November 1, 1995, through November 1, 1996).

An underreporting ("U") correction factor is defined as: $1/(N_a/N_t)$

where

N_a = number of menstrual regulations or abortions reported during annual interviews and

N_t = number of known number of menstrual regulations or abortions detected by either system.

For the present analysis, $U = 1.46$. Thus, for every 100 menstrual regulations or abortions that were reported, it is estimated that there were another 46 that were not.

Underreporting of menstrual regulations and abortions was incorporated into the life-table analysis by assuming that for each menstrual regulation or abortion in a given interval, another .46 unreported menstrual regulation or abortion occurred.

References

- Zipper J, Cole LP, Goldsmith A, Wheeler R, Riven M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980;18:275-9.
- Hieu DT, Tan TT, Tan DN, Nguyen PT, Than P, Vinh DQ. 3 I, 78 | cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993;342:2 13-7.
- Anonymous. Death of a study: WHO. what and why. *Lancet* 1994;343: 987-8.
- Benagiano G, Sciarra J. Introduction: WHO consultation on the development of new technologies for female sterilization. *Int J Gynaecol Obstet* 1995;51(suppl 1):S1.
- Wilson EW. The development of new technologies for female sterilization: conclusions and recommendations for research. *Int J Gynaecol Obstet* 1995;51(suppl 1):S71-4.
- Sokal D, Zipper J, King T. Transcervical quinacrine sterilization: clinical experience. *Int J Gynaecol Obstet* 1995;51(suppl 1):S57-69.
- Sokal D, Hieu DT, Weiner DH, Vinh DQ, Vach TH, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis. *Fertil Steril*. 2000;74:1092-101.
- Vach T, Bishop A, Hoa V, Hien L, Chien T, Nguyen TI. The potential impact of introducing pregnancy testing into menstrual regulation services in Vietnam. *Int Fam Plann Perspect* 1998;24:165-9.
- Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. *Am J Obstet Gynecol* 1996;174: 1161-70.
- Laufe LE, Sokal DC, Cole LP, Shoupe D, Schenken RS. Phase I pre-hysterectomy studies of the transcervical administration of quinacrine pellets. *Contraception* 1996;54: 181-6.
- Zipper J, Dabancens A, Guerrero A, Trujillo V. Quinacrine revised. *Hum Reprod Update* 1995; 1:324-42.
- Trujillo V, Zipper J, Viel B, Rivera M. Nonsurgical female sterilization using quinacrine: efficacy of two insertions of quinacrine pellets. *Rev Fr Gynecol Obstet* 1993;88: 147-50 (in French).
- Feldblum PJ, Hays M, Zipper J, Guzman-Serani R, Sokal DC. Pregnancy rates among Chilean women who had non-surgical sterilization with quinacrine pellets between 1977 and 1989. *Contracept* 2000;61: 379-84.
- Chi IC, Jones D. Incidence, risk factors, and prevention of poststerilization regret in women: an updated international review from an epidemiological perspective. *Obstet Gynecol Surv* 1994;49:722-32.
- Sokal D, Hanenberg R. Quinacrine family planning method (letter). *Lancet* 1994;343:1426-7.