

Clinical practice

31781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam

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Summary

The quinacrine method of non-surgical female sterilisation involves transcervical intrauterine insertion of 252 mg quinacrine as pellets during the proliferative phase of the menstrual cycle; the drug causes inflammation and fibrosis of the proximal fallopian tube. We have carried out a field trial of 31 781 cases in twenty-four provinces of Vietnam from Jan 2, 1989, until October, 1992. There were 818 pregnancies after the procedure, of which 80 were carried to term. Some women received only one dose of quinacrine; the majority received two doses with an interval of one month. Cumulative life-table pregnancy rates per 100 women at 1 year (for studies of at least 50 cases followed for 12 months) were 2.63 (SE 0.17) among 9461 women who received two doses and 5.15 (0.48) among 2225 who received only one dose. Failure rates (pregnancies) were strongly affected by the skill of the doctor or midwife. There were no deaths and only 8 serious complications were reported (0.03%); by contrast, in a similar series of women undergoing surgical sterilisation, 30 deaths and between 540 and 1812 serious complications would be expected. All reported side-effects were minor and of short duration. There were 19 ectopic pregnancies and the incidence was 0.89 per 1000 woman-years of use. There was one birth defect (anencephaly), in a fetus conceived 2.5 months after quinacrine insertions; however, we believe it is not related to the procedure. An estimated 242 maternal deaths will be averted by these 31 781 sterilisations. This method is safe and acceptably effective for female sterilisation.

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Introduction

Vietnam has a population of 70 million, growing by 2.2% per year, and an income per person of less than US\$200.¹ Surgical female sterilisation has become the most common contraceptive method in use world wide.² However, in Vietnam, only 2.7% of women have been sterilised. Most developing countries, with their large rural populations, lack both the highly-trained physicians and the facilities for safe surgical sterilisation. 6.2 million women in Vietnam want no more children;³ surgical sterilisation cannot possibly satisfy the demand for the foreseeable future. A simpler non-surgical sterilisation method is needed.

A review of current research on non-surgical methods suggests that the quinacrine-pellet method of non-surgical female sterilisation is the only one ready for large-scale use.^{4,5} As developed by Zipper and colleagues,⁶ it involves transcervical intrauterine administration of 252 mg quinacrine hydrochloride as seven pellets through a modified Copper T intrauterine device (IUD) inserter. Two doses a month apart are given to non-pregnant women during the proliferative phase of the menstrual cycle (days 5 to 12);⁷ the drug causes occlusion of the fallopian tubes. Prehysterectomy studies⁸⁻¹⁰ show that the occlusion is due to inflammation and fibrosis, limited primarily to the intramural segment of the tube.

At the first international symposium on this technique in Bandung, Indonesia, in 1991,¹¹ the results of studies on more than 25 000 women in ten countries were presented. No case of life-threatening complications was reported.

In 1989, we undertook a field trial to find out whether this method is applicable in Vietnam. The main aims were to assess safety factors (including side-effects and complications, ectopic pregnancies among women who became pregnant after the procedure, and birth defects), efficacy, method acceptance, and ease of delivery.

Patients and methods

Two preliminary clinical trials of 100 cases each were started in January and February, 1989, in Namha and Haihung Provinces, respectively. Encouraging results led to expanded trials in twenty-four provinces, involving a total of 31 781 subjects (table 1).

All subjects were monitored for serious, life-threatening complications, pregnancy failures (ie, pregnancies after the procedure, including ectopic pregnancy), and birth defects. In the analysis of efficacy, only studies with a minimum of 50 cases at 1 year follow-up (table 2) were included. The earliest study in Namha province (Namha 1) was used for the assessment of side-effects.

The efficacy of an IUD is known to be affected by the skill (consistent application of proper insertion technique) and experience of the person who inserts it.¹² To see if this was true also of the quinacrine method, we examined the incidence of failures with increasing experience of the operator.

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Province	Cases	Inserters	Preg-nancies	Ectopic preg-nancies	Spon-taneous abor-tions	Induced abor-tions	Live-births	Still-births	Preg-nancy conti-nuing	Complica-tions	Malform-ations	Pregnant at laser-tion	Hospital admissions
Namha	8325	164	245	6	2	203	31	1	2	2	1	2	2
Hai hung	4122	252	108	2	0	96	8	0	2	2	0	2	3
Ni hbi nh	2196	131	72	3	0	64	5	0	0	0	0	0	0
Thai binh	2615	102	62	2	3	49	1	0	7	0	0	1	3
Bi nh di nh	972	25	5	0	0	5	0	0	0	1	0	0	1
Hatay	1981	64	31	0	0	31	0	0	0	0	0	0	0
Hoabinh	484	20	17	0	0	15	2	0	0	0	0	0	0
Habac	1982	72	36	1	0	33	0	0	2	2	0	1	2
Hatinh	997	61	91	1	0	53	25	0	12	0	0	0	0
Sonla	216	5	1	0	0	1	0	0	0	0	0	0	0
Vinhphu	2467	60	32	0	0	32	0	0	0	1	0	0	1
Thanhhoa	1316	16	9	2	0	7	0	0	0	0	0	0	0
Nghean	2570	112	97	2	1	85	7	0	2	0	0	0	0
Quangni nh	141	23	4	0	0	3	0	0	1	0	0	1	0
Bachai	149	25	3	0	0	2	0	0	1	0	0	0	0
Baria-Vungtau	59	6	0	0	0	0	0	0	0	0	0	0	0
Bentre	28	5	0	0	0	0	0	0	0	0	0	0	0
Songbe	51	12	0	0	0	0	0	0	0	0	0	0	0
HoChiMinh City	245	59	0	0	0	0	0	0	0	0	0	0	0
Lamdong	169	42	0	0	0	0	0	0	0	0	0	0	1
Quangnam Ganang	152	15	1	0	0	1	0	0	0	0	0	0	0
Tayni nh	153	6	0	0	0	0	0	0	0	0	0	0	0
Anghang	69	8	2	0	0	2	0	0	0	0	0	0	0
Bi nh thuan	302	22	2	0	0	2	0	0	0	0	0	0	0
Total	31761	1307	818	19	6	684	79	1	29	8	1	7	13

Table 1: Study participants and outcomes events

Trials were carried out at rural facilities, including commune health centres. After a physical examination, pellets were inserted by doctors or midwives trained in the Copper T IUD insertion technique. Women undergoing the procedure had to be at least 30 years old and had to have at least two living children, the youngest being at least 3 years old. Women with moderate or severe cervical inflammation were treated before the procedure. All patients were sexually active, not using another contraceptive after first dose of quinacrine, and at least 6 weeks beyond pregnancy termination.

In Vietnam, family planning services are offered on a strictly voluntary basis. The risks and benefits of the method and the procedure were described to interested women. Those who chose it signed a consent form attesting to their understanding of the nature of the procedure and its permanent character, as well as their preference for this method over others available.

Quinacrine pellets were inserted with a cold-sterilised Copper T IUD inserter that had been air dried after a spirit rinse. Aseptic precautions similar to those for IUD insertion were used. A vaginal speculum was introduced to expose the cervix. The uterocervical length was measured with a uterine sound. If the uterine length was more than 8 cm, pregnancy was first excluded. The inserter was gently introduced as far as the uterine fundus. It was then withdrawn about 5 mm and the plunger advanced to release the pellets before removal. Some studies required two insertions a month apart, whereas others required only a single insertion (table 2).

The pellets, which take 30 min to dissolve (Sipharm, Switzerland), were kept clean but not sterilised, since quinacrine is known to be bactericidal.¹⁴

Women were followed up 1, 3, 6, and 12 months after the last insertion and every 6 months thereafter. These studies have complete follow-up since they took place in communes where there is little mobility and coverage by government health services is excellent. For example, in Namha Province, 10 women moved from their communes but continued to be monitored. The cutoff dates for this analysis were in October, 1992 (table 2).

Serious complications were defined according to the Centers for Disease Control and Prevention list,¹⁵ except for transient febrile morbidity, which is seen as a method side-effect.¹⁶

To assess the effect on the efficacy of the method of the operator's experience, we looked at the experience of the 88 healthworkers (61 doctors, 26 assistant doctors, and 1 midwife) who treated the 4010 women in the first two Namha studies. There were 165 procedure failures (pregnancies) among these women. Opera-

tors were ranked according to the number of insertions done and the procedure failure rate for each was calculated. It was possible for two different operators to carry out the two procedures in 1 woman. In these cases, the failure was assigned to the person who administered the first dose. In 1899 cases (47.2%), the name of person who did the second insertion was not recorded. To account for these insertions, we allocated them by weighting according to the total number of recorded insertions (by dividing the number of insertions attributed to each clinician in patient records by 0.7632). This increases total known insertions by inserter to total insertions of 8020. The number of cases for each clinician was then determined by dividing their number of weighted insertions by 2 (table 3).

The risk of ectopic pregnancy among failures was calculated. Infants of women who became pregnant were examined for malformations.

Results

In the Namha 2 study (3502 cases), 473 (13.5%) women were aged 25-30 years, 1236(35.3%) were 31-35 years, 1499 (42.8%) were 36-40 years, and 294(8.4%) over 40 years. 182 (5.2%) had two living children, 1159 (33.1%) had three, and 2161 (61.7%) had four or more.

The pooled data for the two-insertion studies (table 2) gave failure rates of 2.63 (SE 0.17) per 100 women at 1 year and 4.31 (0.31) at 2 years. The 1-year failure rates by study varied from 0.95 (0.95) to 4.54 (0.78).

The two studies of one insertion had a much higher failure rate at 1 year (table 2). However, only one of these studies has followed up at least 50 patients for longer than 1 year. If we compare single one-insertion and two-insertion studies (for example, Nghean 1 and 2 or Haihung 1 and 2), we find substantially higher failure rates for one insertion.

To assess the effect of operator experience, we examined the rates of failure in the first two Namha studies. Among the total 4010 sterilisations, there were 165 pregnancies (crude pregnancy rate 4.1%). However, operators had widely differing crude pregnancy rates. For example, among the 32 who had failures, there were 8 who had carried out more than 100 insertions; their pregnancy rates varied from 2.5% to 9.1%. The failure rate was the highest among operators who had done 10 or fewer insertions (17.2%) and

Two-insertion studies							
Study	Follow-up (months)					First admission	Last admission
	6	12	18	24	30		
Nanha 1 (n = 508)							
n	499	487	467	467	66	Jan 4,	Dec 5,
Failure (SE)	158 (0.55)	376 (0.85)	5.34 (1.00)	6.54 (1.10)	6.54 (1.10)	1989	1992
Nanha 2 (n = 3502)							
n	3445	3005	1442	89		Jan 19,	April 9,
Failure (SE)	174 (0.22)	296 (0.29)	411 (0.37)	446 (0.40)		1990	1992
Nanha 3 (n = 501)							
n	494	490	240			Jan 19,	Jan 17,
Failure (SE)	100 (0.44)	140 (0.53)	164 (0.57)			1991	1992
Haihung 1 (n = 105)							
n	104	104	103	102	100	Jan 2,	April 15,
Failure (SE)	0.95 (0.95)	0.95 (0.95)	1.90 (1.33)	2.86 (1.63)	2.86 (1.63)	1989	1990
Haihung 2 (n = 3083)							
n	2516	1707	816	382	84	Feb 3,	Aug 7,
Failure (SE)	0.84 (0.17)	1.80 (0.27)	2.56 (0.36)	3.36 (0.55)	4.79 (0.89)	1990	1992
Thalbinh (n = 760)							
n	685	625	181	53		April 26,	Oct 31,
Failure (SE)	2.94 (0.63)	4.54 (0.78)	5.08 (0.84)	5.08 (0.84)		1990	1992
Nghean 1 (n = 1002)							
n	878	629	315	51		Jan 4,	June 18,
Failure (SE)	223 (0.47)	248 (0.50)	248 (0.50)	248 (0.50)		1990	1992
Total (n = 9461)							
n	8623	7048	3574	1146	260		
Failure (SE)	154 (0.13)	263 (0.17)	350 (0.21)	431 (0.31)	4.85 (0.39)		
One-insertion studies							
Nghean 2 (n = 1247)							
n	1195	1070	537	103		Jan 15,	Dec 23,
Failure (SE)	417 (0.57)	506 (0.62)	506 (0.62)	506 (0.62)		1990	1991
Haihung 3 (n = 978)							
n	840	129				Oct 4,	May 12,
Failure (SE)	4.75 (0.68)	5.12 (0.73)				1991	1992
Total (n = 2225)							
n	2036	1085	537	103			
Failure (SE)	442 (0.44)	515 (0.48)	515 (0.48)	515 (0.48)			

*22 months follow-up.

Failure = cumulative failure rate per 100 women.

Table 2: Failure rates of quinacrine-pellet method for two insertions versus one insertion

lowest among those who had done more than 100 (5.3%). However, there was little change in failure rate for experience between 11 and 100 insertions.

56 of the 88 operators had no failures at all, including 2 who did more than 100 procedures and 4 who did 75-100. When all 88 were included in the analysis, increasing

experience was not an important factor in lowering the failure rate (table 3). The crude pregnancy rate for the assistant doctors and the midwife was lower than that for senior doctors (3.0 vs 4.5%).

The pattern of side-effects and menstrual changes after quinacrine insertions was similar for the different studies and is reported in detail for 508 cases in Namha Province. The main side-effects after first insertion were lower-abdominal pain (15.3%), vaginal pruritis (23.2%), and headache (20.2%). These symptoms lasted a few hours to a few days. Symptoms were generally milder after the second insertion. No change in menstrual flow was reported by 77.4% of the women; 3.8% reported an increase and 18.8% a decrease. Amenorrhoea that lasted up to 3 months but required no treatment occurred in 0.3% of women.

No uterine perforations occurred, though the rate of perforation with IUD insertions is about 1 in 1000.² Quinacrine insertion is less difficult than IUD insertion. The experience of our clinicians in sounding the uterus may also explain the difference; our family planning workers carried out 1.34 million abortions and 1.05 million IUD insertions in 1992.

8 (0.03%) major complications possibly related to quinacrine sterilisation were reported among the whole cohort (31 781). 2 women had severe bleeding (1 immediately after quinacrine, 1 a year later). 1 woman underwent hysterectomy 6 months after insertions because of severe pain and amenorrhoea; no abnormality was found in the surgical specimen. 1 woman had premenstrual pain and dysmenorrhoea, 1 suspected PID 18 days after quinacrine insertion, and 1 an allergic reaction (severe pruritis). 2 women had synechiae of the cervical canal; 1 was treated with dilation and 1 needed a hysterectomy. 1 other woman with synechiae had a hysterectomy after the analysis cut-off date.

5 other women were admitted to hospital with gynaecological disorders not related to quinacrine administration (1 fibroids, 1 hydatidiform mole [conceived 3 months after quinacrine], 1 infection after a subsequent abortion, 1 for abortion after 12 weeks' gestation, and 1 for surgical sterilisation after failure of quinacrine). These disorders were detected during the intensive follow-up for quinacrine side-effects.

An anencephalic fetus was conceived 2.5 months after insertions of quinacrine. Another case had occurred in the same commune 4 months earlier in a woman who had not had quinacrine insertions. All conceptions within a month of quinacrine pellet insertions were aborted by menstrual regulation.

79 other pregnancies were carried to term. All babies were examined at birth and no major malformations were noted. 1 baby was delivered preterm and died. Another baby was stillborn (conceived 11 months after quinacrine insertions). All other women gave birth to normal infants, who remain well. Of the 32 women whose sterilisations

Number of procedures done per operator	Operators who had failures (n = 32)				Operators without failures		All operators	
	No of operators	No of cases	Failures	Mean failure rate (%) (range)	No of operators	No of cases	No of operators	No of cases
101-406	8	1869	100	1869	2	214	10	2084
76-100	3	267	20	7.5 (5.1-9.1)	4	326	7	593
51-75	7	387	24	6.2 (1.8-9.1)	2	137	9	524
26-60	4	134	8	6.0 (2.2-13.0)	6	227	10	360
11-25	4	70	5	7.1 (4.1-12.2)	10	175	14	246
1-10	6	47	8	17.2 (9.5-43.5)	32	157	38	203
Total	32	2774	165	5.9	56	1236	88	4010

Table 3: Sterilisation failure rates in Namha 1 and 2 studies by operator

failed and who had full-term pregnancies in Namha Province, 17 were breastfeeding at time of conception and the diagnosis of pregnancy was delayed. The other 15 declined pregnancy termination for religious reasons.

There were 2 cases of quinacrine insertion during early pregnancy. 1 was in a case of ectopic pregnancy and the other woman gave birth after the study cut-off date. The infant was normal.

There were 19 ectopic pregnancies in the whole study population and 6 in the three Namha studies ($n = 45\ 11$). 1 of these women had probably been treated in early undetected pregnancy and another had had an ectopic pregnancy 10 years previously. A survey of 18 000 IUD users in the Namha Province showed an ectopic pregnancy rate of 0.14%, similar to the 0.13% for the women who received quinacrine. Of the pregnancies after quinacrine in these three studies, 3.5% were ectopic. The ectopic pregnancy incidence per 1000 woman-years of quinacrine sterilisation use in the Namha studies was 0.89.

Acceptance of the method by operators and women is shown by the rapid increase in the number of cases and dissemination of the method to many provinces in Vietnam (table 1).

Discussion

The quinacrine pellet method is safe. There were no deaths in this series and, to date, none have been reported for this method anywhere in the world. By contrast, studies of surgical sterilisation in developing countries report rates of 19 to 99 deaths per 100 000 cases.^{15,18-22} In a series of 31 781 surgical sterilisations, 6 to 31 deaths would have been expected. Serious complications were also rare. This finding is consistent with the experience of investigators in other countries. The reported rate of serious complications with laparoscopic sterilisation is 1.7%,^{15,23} so in a series of this size, 540 serious complications would be expected. With laparotomy the rate of serious complications is 5.7%,²⁴ which would give 1812 serious complications in our series. All side-effects were minor and of short duration, as found by others.¹⁶

The lack of evidence of mutagenicity supports this finding in toxicology studies in monkeys.²⁵ The single infant with a birth defect diagnosed in our studies (anencephaly) was conceived 2.5 months after quinacrine insertions, when the drug will no longer be present in any tissue.²⁶ Agricultural chemicals in high doses are known to cause this birth defect and may explain this case of anencephaly and another in a woman from the same commune who had not received quinacrine.

All conceptions within a month of quinacrine insertions were aborted by menstrual regulation. We do not know what would happen if this practice were not continued.

We could not study risk of cancer of the uterus by exposure to quinacrine, but long-term follow-up of cases in Santiago, Chile, shows no increased risk (J Zipper, unpublished). Long-term use of this drug for malaria suppression has revealed no increased risk of any malignant disorder.²⁷

The incidence of ectopic pregnancy (0.89 per 1000 woman-years) in the Namha studies is lower than the rate among US women not using contraception (2.60) but higher than the rate after surgical sterilisation (0.32).²⁸ We had a smaller proportion of ectopic pregnancies among all post-sterilisation pregnancies than in that US study (3.5 vs 15.9%²⁸). Our higher incidence rate is primarily due to the higher procedure failure rate.

The quinacrine pellet method with two insertions has a failure rate of about 2% at 1 year of use. However, operator skill (consistent application of proper insertion technique) so dominated the determinants of efficacy in these studies as to mask the true efficacy of the method. The amount of experience the operator had was of little importance compared with his or her skill.

Before this field trial, quinacrine investigators thought that pellets could be placed anywhere in the uterus to achieve occlusion, since they believed that the concentration of quinacrine would be even throughout the uterine cavity. Our results suggest that this may not be the case. The effect of insertion technique on efficacy deserves further study, including a search for other determinants of skill.

There are other possibilities for lowering failure rates. For example, pre-hysterectomy studies show that completion of tubal occlusion takes at least 6 weeks in some women.²⁹ Thus, use of contraception for this period would be advisable. It is possible that the addition of intrauterine antiprostaglandin administration (diclofenac) could reduce the failure rate and the incidence of side-effects (J Zipper, unpublished).

At the end of this trial, 1307 doctors and midwives were providing this sterilisation method in Vietnam. At a rate of 100 procedures per operator per month, 7.8 million procedures could be done during the next 5 years. The estimated unmet need in Vietnam is 6.2 million women. Thus, the ease of delivery of this method is sufficient for us to achieve our goal of fulfilling all unmet demand for sterilisation within 5 years.

The main advantages of this method for a developing country are the possibility of raising contraceptive prevalence among women who want no more children, while providing more effective contraception than temporary methods. We can calculate from the maternal mortality rate in Vietnam of 380 per 100 000 livebirths,²⁹ assuming that each sterilisation procedure prevents 2 pregnancies, that each 1000 sterilisations prevent 7.6 maternal deaths—ie, 242 maternal deaths will be averted by these 31 781 sterilisations. The cost of quinacrine for two insertions is less than US\$1. This procedure represents our most cost-effective way of lowering maternal mortality.

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