

Clinical evaluation of quinacrine pellets for chemical female sterilization

T. AGOESTINA and I. KUSUMA

Department of Obstetrics and Gynecology, Hasan Sadikin Hospital, 38 Jalan Pasteur, Bandung 40161, Indonesia

Abstract

Under the auspices of the Coordinating Board of Indonesian Fertility Research (BKS PENFIN), a clinical trial was undertaken to examine the safety and effectiveness of the quinacrine pellet method for nonsurgical female sterilization. One hundred women were selected to receive 3 monthly insertions of 250 mg of quinacrine and were followed up at 1, **3, 6** and **12** months after the third insertion. Socioeconomic data and complaints and menstrual patterns at each insertion and every follow-up visit were recorded, as were all failures. The life-table failure rate was determined to be **3.1**. The continuation rate in this study was % % at 1 year. Just over one-fifth of the women had amenorrhea by the third insertion, but most returned to normal by 1 year, and it appears that this amenorrhea was transient in nature. The method proved to be safe and effective, suggesting that larger clinical trials are in order.

Introduction

With the increasing demand for effective contraception, surgical female sterilization has become the most reliable method used throughout the world. However, most developing countries, with their essentially rural populations, lack both the highly trained physicians and the facilities such procedures require. Could a simplified nonsurgical method be devised that could be performed by paramedical personnel?

The work of Dr Jaime Zipper seems to provide such a solution. It involves the use of quinacrine hydrochloride pellets and a delivery system designed to bring the chemical into prolonged contact with the tubal ostia through uterine retention [1]. Insertion of quinacrine pellets into the uterine fundus is the same as the procedure for inserting an IUD, and, hence, appropriate for use in remote rural areas. Since the majority of IUD services in the Indonesian Family Planning Program have been carried out by trained paramedics, with considerable success, these same technicians could readily learn the protocol for administering quinacrine pellets.

Quinacrine is a drug of proven efficacy and safety, as has been learned from its long and extensive use, since the onset of World War II, as an anti-malarial. Millions

of people in the armed forces of many countries have taken this substance for long periods with no apparent ill effects. Results of early clinical trials of the quinacrine pellet method for nonsurgical female sterilization have been encouraging. The cumulative gross life table pregnancy rate has been found to be 3.1 per 100 women at one year [1] and 4.3 per 100 women at 3 years [2]. This method appears to be associated with very few complaints [3,4]. Our clinical trial was undertaken to evaluate the efficacy and safety of the quinacrine pellets as a method of nonsurgical sterilization.

Materials and methods

The study, conducted in Bandung, at Hasan Sadikin Hospital and the Health Center Astana Anyar, was initiated in July 1985. One hundred healthy women, who did not want any additional children and requested permanent contraception of a nonsurgical nature, consented to participate in the study. Each subject had a normal Papanicolaou smear prior to admission. Out of 100 women, 71 had normal menses, 25 were postpartum and had breastfeeding amenorrhea, 3 were on Depo Provera and 1 had post-pill amenorrhea. No additional contraceptives were used. Quinacrine pellet insertions were performed in women who had not recently been pregnant and in postpartum women after complete uterus involution, or at least 8 weeks after delivery. For those who were menstruating, insertions were performed during the proliferative phase. Amenorrhea was defined in this study as menses not having occurred on the expected date at follow-up visit.

Each quinacrine hydrochloride pellet is cylindrical with a diameter of 0.32 cm. The pellets are compacted, each containing 36 mg of quinacrine hydrochloride. Seven pellets containing a total of **250** mg quinacrine hydrochloride were inserted at admission and again at one month and two months after admission.

Aseptic insertion was accomplished by placing the pellets in a plastic tube with a push rod positioned behind them. This procedure is essentially the same as the one for inserting an IUD, so that 250 mg quinacrine hydrochloride is deposited in the uterus. No difficulty was encountered during insertions in all study cases. The patient was placed in the recovery room and asked to lie down for about 10 minutes after each insertion.

Clinical follow-up examinations were scheduled at 1, **3, 6** and 12 months after the last insertion of the quinacrine pellets and any time when complications and complaints occurred. If the patient did not appear for the expected follow-up visit, a trained field worker went to her home to urge her to return for her examination. At the same time, she discussed with the acceptor complaints that might occur eventually. Data were recorded on reporting forms for all study cases at each visit, after which quinacrine pellets were inserted. After the last insertion, follow-up records were kept to document whether the woman kept each scheduled 1,3,6 and 12 month appointment as well as any unscheduled visit due to complications or complaints.

Data analysis was done by using a computer program, Statistical Package for the Social Sciences (SPSS). For effectiveness, the gross cumulative life table rate was calculated.

Results

Quinacrine hydrochloride pellets for nonsurgical female sterilization in this series of 100 women was accepted by older women with high parity, with a mean age of 32.2 years and a mean of 5.2 live births. Most have attended primary school (66%), and the mean duration of education was 7.1 years (Table 1). Most of their husbands reached higher levels of education, with a mean duration of 9.0 years (Table 2).

Table 1. Age of patient (n = 100) by total live births

Age (y)	Total live birth					Total n	Total %
	2-3	4-5	6-7	8+	n		
<26	5	33.3	1	2.2	-	6	6.0
26-30	6	40.0	13	27.7	6	25	25.0
31-35	3	20.0	26	55.3	17	49	49.0
36-40	1	6.7	7	14.8	6	20	20.0
Total	15	100.0 (15.0)	47	100.0 (47.0)	29	100.0 (20.0)	100 (100.0)

Age (y): Mean = 32.2 ± 3.8; Minimum = 24; Maximum = 40
Live births: Mean = 5.2 ± 1.7; Minimum = 2; Maximum = 10

Table 2. Education of candidates for quinacrine sterilization and their husbands (in years)

Years of education	Patients (n = 100)		Husbands (n = 100)	
	Total	%	Total	%
<1				
1-6	66	66.0	1	1.0
7-9	21	21.0	42	42.0
10-11	1	1.0	21	21.0
>12	12	12.0	36	36.0
Mean:	7.1 ± 2.5		9.0 ± 3.4	
Minimum	1		0	
Maximum	15		18	

Table 3 shows that quinacrine pellet method is definitely effective. The gross life-table pregnancy rate is 3.07 ± 1.70 per 100 women at 6 and 12 months.

After completing 3 quinacrine pellet insertions, three women whose last pregnancy outcome had been a live birth were reported to be pregnant at 3 months' follow-up, in 1 case, and at 6 months' follow-up in 2 cases. These patients were 34,35 and 37 years old, with a parity of 5, 4 and 4 and duration of education of 9, 6 and 15 years, respectively. Confirmations of pregnancies were established by delayed menses, pelvic examinations and urine pregnancy tests (pregnosticon plano tests). Vacuum aspiration was done for each woman with delayed menses of 40,44 and 37 days. In one case, the third quinacrine hydrochloride pellet insertion could not be performed because of personal objections. One subject did not return for follow-up 1 and 6 months after 3 consecutive insertions. Out of all 100 women, 98 returned to the clinic for follow-up at 1 month, 97 at 3 months, % at 6 months and 86 at 1 year. For the remaining 10 cases, home visits were made where we were informed that no pregnancy had occurred among them.

As can be seen from Table 4, among 71 women who had regular cycles in the beginning, amenorrhea occurred immediately after the second insertion in almost 27%, decreasing until around 22% after the third until the 3 months' follow-up visit. Then, the percentage was reduced significantly to 8.4% after one year.

Table 5 shows the return of menses among the 29 women with initial amenorrhea. Of these women, 25 had postpartum lactation, 3 were post-Depo Provera and 1 was post-pill amenorrhea. Among the 25 postpartum subjects, menses were reported at second (1 case) and third insertion (6 cases). Among the 3 post-Depo Provera women, menses returned at 1 month follow-up in one and 6 months' follow-up in two. In the single post-pill amenorrhea, menses returned after 1 month follow-up.

When analysis was done for all 100 cases, including those with initial amenorrhea, it appeared that amenorrhea was transient in nature in relation to quinacrine pellet insertions (Table 6).

Although the mean length of a cycle became longer (30 days) after the 3rd insertion when compared to the initial 29 days, during the follow-ups it gradually shortened to 28 days at 12 months, although this was statistically not significant. As seen in Table 7, among the subjects with initially regular cycles at the first insertion, the mean duration of menstrual flow was around 5 days. Afterwards, during the successive insertions and follow-up it became constant at around 4 days.

On considering the overall 100 recruited cases, irrespective of whether they had normal menses or amenorrhea at first, it was revealed that indeed during the insertion period the mean duration of menstrual flow had decreased from approximately 5 to 4 days, which thereafter remained constant (4 days) during successive follow-ups (Table 8).

Table 3. Gross life-table pregnancy, continuation and follow-up rates for 100 women having three complete insertions of quinacrine hydrochloride pellets (n = 98)*

Period (months)	Rate		
	Pregnancy	Continuation	Follow-up
3 (n=97)	1.01 ± 1.02	99.0	99.0
6 (n=96)	3.07 ± 1.07	96.9	98.0
12 (n=86)	3.07 ± 3.07	96.9	87.8

*Of 100 women admitted to the study, one became pregnant after the first quinacrine pellet was inserted and one did not return after the second

Table 4. Amenorrhea associated with insertion of quinacrine pellets among 71 women with initial regular cycles

Occasion	n	Amenorrhea %
Insertion		
1st	19	26.7
2nd	15	21.1
3rd	15	21.1
Follow-up at		
1 month	15	21.1
3 months	16	22.5
6 months	8	11.5
12 months	6	0.4

Table 5. Return of menses after insertion of quinacrine pellets among 29 women with initial amenorrhea

Occasion	n	Return of menses %
Insertion		
1st	0	0
2nd	1	3.4
3rd	6	20.7
Follow-up at		
1 month	8	28.6
3 months	15	53.6
6 months	17	60.7
12 months	25	92.6

Table 6. Amenorrhea associated with insertion of quinacrine pellets in 100 women admitted to the study (71 had normal menses and 29 had amenorrhea at first)

Occasion	n	Amenorrhea %
<i>Insertion</i>		
1st	29	29.0
2nd	48	48.0
3rd	39	39.0
<i>Follow-up at</i>		
1 month	36	36.0
3 months	30	30.0
6 months	20	20.0
12 months	10	10.0

Table 7. Mean length of menstrual cycle and mean duration of menstrual flow in 71 women with initial regular cycles

Occasion	Mean length	
	We (days)	Flow (days)
<i>Insertion</i>		
1st	29.5 ± 3.0	4.9 ± 1.8
2nd	29.5 ± 4.2	4.4 ± 1.7
3rd	30.3 ± 3.4	3.7 ± 1.6
<i>Follow-up at</i>		
1 month	29.4 ± 2.7	3.9 ± 1.6
3 months	28.5 ± 3.0	4.2 ± 1.4
6 months	28.5 ± 3.0	3.8 ± 1.3
12 months	28.1 ± 2.2	4.0 ± 1.3

Table 8. Mean duration of menstrual flow in 100 women after quinacrine pellet insertions (71 had normal menses and 29 initial amenorrhea)

Occasion	Mean duration of flow (days)
<i>Insertion</i>	
1st	4.9 ± 1.7
2nd	4.5 ± 1.7
3rd	3.7 ± 1.5
<i>Follow-up at</i>	
1 month	4.0 ± 1.6
3 months	4.2 ± 1.5
6 months	4.0 ± 1.3
12 months	4.1 ± 1.3

Intermenstrual bleeding, either spotting or moderate, occurring after **quinacrine** hydrochloride pellet insertions, seemed to be very rare and transient (Table 9).

Dysmenorrhea decreased significantly after the second quinacrine pellet insertion, from 24.0% initially, to 2.0% at further insertions and follow-up, to complete disappearance at 6 and 12 months' follow-up. Dyspareunia, found only in 4 cases initially, was no longer seen after the 3-month follow-up. Allergic reaction in the form of itching was observed only in 1 or 2 cases at the time of insertions, and not given special treatment (Table 10).

Table 11 shows that more than half of the study cases had no complaints during and after successive insertions. Around 10% or fewer had the same general complaints found in other intrauterine insertion manipulations which gradually decreased after the third insertion. This also occurred with leucorrhoea and the presence of a yellowish vaginal discharge, though in the beginning they showed higher percentages of 16% and 11%, respectively. The discharge occurred at home several hours after quinacrine insertion and disappeared within a few hours. No additional treatment was given.

As can be seen in Table 12, there were very few complaints at follow-up after completing 3 insertions and no additional treatment was given. At the year-end follow-up, more than 87% of women had no complaints.

Pelvic examination findings

Clinical findings on pelvic examination at 12 months follow-up showed cervical erosion in one case and topical treatment was given. A fibroid, which was slightly larger than a normal uterus, was also found in one woman.

Table 9. Intermenstrual bleeding prior to and after quinacrine pellet insertion in 100 women

Occasion	Intermenstrual bleeding	
	Spotting % n	Moderate % n
<i>Insertion</i>		
1st	6	1
2nd	5.9	1.0
3rd	5	5.0
<i>Follow-up at</i>		
1 month	1	2
3 months	1.0	2.0
6 months	1	1.0
12 months		

Table 10. Dysmenorrhea, dyspareunia and allergic reaction at and after quinacrine pellet insertions in 100 women

Occasion	Dysmenorrhea		Dyspareunia		Allergic reaction	
	n	%	n	%	n	%
Insertion	1st	24	4	4.0	1	1.0
	2nd	2	4	4.0	2	2.0
	3rd	2	2.0	1	1.0	1
Follow-up at	1 month	2	2.1	2	2.1	
	3 months	3	3.1			
	6 months					
	12 months					

Table 11. Events (complaints) after successive quinacrine pellet insertions in 100 women

Events (complaints)	Quinacrine insertion					
	n	1st %	n	2nd %	n	3rd %
Fever	10	10.0	5	5.0	2	2.0
Headache	9	9.0	11	11.0	10	10.2
Lower abdominal pain	6	6.0	2	2.0	2	2.0
Dysuria	5	5.0	6	6.0	3	3.1
Leucorrhoea	16	16.0	12	12.0	9	9.2
Yellowish vaginal discharge	11	11.0	9	9.0	5	5.1
Women without complaints	54	54.0	65	65.0	69	70.4

Table 12. Events (complaints) reported at each follow-up (after 3 completed insertions)

Events (complaints)	3 months		6 months		12 months	
	n	%	n	%	n	%
Rever	1	1.0				
Dizziness + nausea	1	1.0				
Headache	4	4.1	6	6.2	6	7.0
Lower abdominal pain	1	1.0	1	1.0	1	1.2
Backpain	1	1.0				
Leucorrhoea	4	4.1	5	5.2	2	2.3
Women without complaints	87	89.7	85	88.5	75	87.2
	(n = 97)		(n = 96)		(n = 86)	

Discussion

The mean age and mean number of live births of women entering this study were 32.2 years and 5.2, respectively (Table 1). The mean age in other studies was around the same, ranging from 31.4 to 33.5 years, but the mean number of live births was obviously lower, around 3.3 to 4.1 [3-5]. Findings from this study have shown that among 71 women with initial regular cycles, amenorrhea significantly increased at the third insertion (21.1%), continuing until the 3-months' follow-up (22.5%), diminishing with longer use and becoming only 8.4% at the 12 months' follow-up (Table 4). It appeared that amenorrhea was transient in nature. Analysis of all 100 study cases, irrespective of whether the subjects had amenorrhea or regular cycles in the beginning, revealed that in the majority of cases their menses had returned at further follow-up (Tables 5 and 6). Guzman, however, reported that among 98 women who had initially regular cycle length, amenorrhea was found in 35.7% at one or more visits during quinacrine pellet insertions. But in all cases, menses returned by the 6 months' follow-up visit [4].

The apparent efficacy of the quinacrine pellet method in this study may be due to amenorrhea initially experienced among 29 of the women, which continued for 6 months in 12 of these women (39.3%) but in only 4 women (7.4%) by 12 months after the third insertion. Of the 3 pregnancy failures, none were among these 29 women.

The use of quinacrine pellets appeared to cause a very low incidence of minor complications and complaints, which in most cases were of a temporary nature, disappearing within several hours or a few days after insertion [2-4]. In this series, there were several types of complaints at and after quinacrine insertions such as dysmenorrhea, leucorrhoea, fever, headache and others (Tables 10, 11, 12). At follow-up after completion of 3 insertions, the decrease of complaints was evident in type and incidence.

It has been stated that by using quinacrine slurry instillations of 1.5 g quinacrine powder suspended in 5 ml of 2% xylocaine and agitated for one minute, complications were infrequent, i.e. only in 2.0% at the time of the first instillation (cortical excitation). No complications occurred during the second or third instillations. After treatment with central nervous system depressants, e.g. diazepam, the symptoms usually disappeared within 4 hours [5]. By using quinacrine pellets, as was done in this study, no complications involving the nervous system were found.

In this series of 100 women admitted to the study, 97 returned for the 3 months' follow-up, 96 for the 6 months' and 86 for the 12 months', with continuation rates of 99.0, 96.9 and 96.9 and follow-up rates of 99.0, 98.0 and 87.8, respectively (Table 3). Comparison of results from studies conducted by Zipper has revealed that the pellet method is an improvement over the solution method: the life-table pregnancy rates per 100 women completing 3 administrations of quinacrine solution and quinacrine pellets were 5.7 (SE 2.1) vs 0.8 (SE 0.8) at 6 months and 9.1 (SE 2.6) vs 2.5 (SE 1.4) at 12 months [6]. In our study after completion of 3 quinacrine pellet insertions, 3 pregnancies have been reported, occurring at 3 months' in one case and 6 months' follow-up in two cases, with gross life-table pregnancy rates of 3.07 ± 1.07 per 100 women at 6 and 12 months' follow-up (Table 3). Our findings are similar to those of

other study series which have shown gross life-table pregnancy rates for women who completed 3 quinacrine hydrochloride pellet insertions at 12 months to be $0.7 + 0.7$ [2] and 3.1 ± 2.2 [3]. An additional report on 4 pregnancies out of 80 study cases is also available, consisting of one case after the first, one after the second, and two after completion of 3 insertions [5].

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Resumé

Sous l'égide du Conseil de coordination indonésien pour la recherche en matière de fécondité (BKS PENFTN), un essai clinique a été entrepris en vue d'examiner la sécurité et l'efficacité de la méthode non chirurgicale de stérilisation féminine à l'aide de pellets de quinacrine. Une dose de 250 mg de quinacrine a été administrée par insertion tous les 3 mois à cent femmes sélectionnées qui ont été suivies 1 mois, 3 mois, 6 mois et 12 mois après la troisième implantation. Les données socio-économiques, les plaintes et l'évolution du cycle menstruel ont été enregistrées au moment de chaque insertion et à chaque visite de suivi, comme l'ont été également tous les échecs de la méthode. Le pourcentage d'échecs dans la table de survie a été 3.1 et le taux de continuation pour cette étude était de 96% après un an. Légèrement plus d'un cinquième des femmes s'étaient plaintes d'aménorrhée à la troisième insertion mais, pour la plupart, le cycle s'est normalisé au bout d'un an. Il semble donc que l'aménorrhée soit de nature passagère. Cette méthode s'est révélée sûre et efficace, laissant penser qu'il serait bon de procéder à des essais cliniques de plus grande envergure.

Resumen

Bajo los auspicios del Consejo de Coordinación de Indonesia para la investigación de la fecundidad (BKS PENFTN) se realizó un ensayo clínico a fin de examinar la seguridad y eficacia del método no quirúrgico de esterilización femenina mediante bolitas de quinacrina. Una dosis de 250 mg de quinacrina fue administrada por inserción cada 3 meses a cien mujeres seleccionadas que fueron seguidas 1 mes, 3 meses, 6 meses y 12 meses después de la tercera inserción. Los datos socioeconómicos, las quejas y la evolución del ciclo menstrual fueron registrados en el momento de cada inserción y en cada visita de seguimiento, así como todos los fracasos del método. El porcentaje de fracasos en la tabla de supervivencia fue de 3.1 y el porcentaje de continuación en este estudio fue del 96% después de un año. Algo más de la quinta parte de las mujeres tuvieron amenorrea a la tercera inserción pero en la mayoría de los casos el ciclo se normalizó al cabo de un año. Por consiguiente, parece que la amenorrea es de índole pasajera. Este método demuestra ser seguro y eficaz, haciendo pensar que sería conveniente pasar a ensayos clínicos más amplios.