



## 25 years of quinacrine sterilization experience in Chile: review of 2,592 cases

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### Abstract

**Objectives:** To assess short-term side effects, long-term risks and efficacy of quinacrine sterilization (QS) in Chile. **Methods:** Review experience of 2,592 cases sterilized with 2 or 3 transcervical insertions of 252 mg quinacrine as pellets since 1977; review the Chilean pre-clinical experience and epidemiological studies on cervical, endometrial and other cancers. **Results:** Among 2,592 women who underwent QS, the total number of pregnancies was 119 (4.6%); 59 (49.5%) were carried to term with no birth defects related to QS. Nine cases were ectopic pregnancies. The ectopic pregnancy risk per 1,000 woman-years was 0.41, similar to that for surgical sterilization. The cumulative life-table pregnancy rates per 100 women at 10 years varied from 5.2 to 6.9. Mild and transient side effects were reported in 13.5% of quinacrine intrauterine insertions and pelvic inflammatory disease was diagnosed in 4 cases (0.15%). Long-term follow-up of quinacrine-sterilized patients shows no increased risk of cervical, endometrial or other cancer. **Conclusions:** QS efficacy at 10 years is comparable to widely accepted tubal clip and single point bipolar electrocoagulation laparoscopic procedures. QS has a low risk of serious, immediate side effects. No long-term risks have been identified after 25 years of use.

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**Keywords:** quinacrine sterilization, non-surgical female sterilization

### 1. Introduction

In the 1960s Dr. Jaime Zipper initiated a study of reproductive physiology in Chile. Using rabbits, he demonstrated that, by placing a copper wire in the lower portion of the uterus, he was able to totally prevent pregnancy implantations. Rabbits have a double uterus and on the side with no copper, implantations were normal. This discovery led to the development of the copper IUD that once generated controversy but is now recognized as one of the safest and most effective reversible methods of birth control. At that time, IUDs were mistakenly associated with a carcinogenic

potential, especially cervical cancer, but long-term controlled studies finally disproved this theory [1,2]. Similar controversy engages our attention today with Quinacrine Sterilization (QS).

QS began in Chile in the mid-1960s. Zipper and his colleagues were searching for a contraceptive method that could curtail the alarming increase in septic abortion cases and their related deaths. They tested various agents. Using the rat as an experimental animal, they evaluated the effect of intrauterine administration of such compounds on fertility [3]. Quinacrine had been extensively used in humans orally as an efficient anti-malarial therapy and prophylactic. It is still used in the treatment of lupus erythematosus and giardiasis [4–7]. Previous knowledge of quinacrine action in pleural and peritoneal cavities, where it produces adhesions, led the

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group to choose it for the first clinical trial for transcervical sterilization in 1970 [8]. Because a quinacrine slurry was the form used for treatment of neoplastic effusions, a slurry was used in this trial. The instillations consisted of 1.5 gm quinacrine in 5 ml of xylocaine. After the first instillation, this was repeated one and 6 months later. Instillation was done under syringe pressure, unexpectedly resulting in entry of quinacrine through endometrial capillaries directly and rapidly into the bloodstream. The high pregnancy rate and a 2% incidence of cortical excitation led to a halt in the trial.

In 1975, Dr. Zipper and Robert Wheeler of the International Fertility Research Program in North Carolina, devised a quinacrine pellet to eliminate the problems associated with the liquid preparation. Five years later, a preliminary report on quinacrine pellets was published [9]. Pellet use resulted in the total elimination of cortical excitation and a significant reduction of pregnancy rates.

Since Chilean women sterilized with quinacrine pellets have the longest experience of any patients worldwide, pathologic conditions or abnormalities attributable to quinacrine would be detected first in this primary group. One could ostensibly consider QS experience a completed phase III study because more than 100,000 cases have been documented with no deaths and no complications requiring surgery [10].

Recent studies of Chilean subjects show no increased risk of reproductive tract cancers for this method [11–13]. Review of these cases provides considerable evidence that the frequency of ectopic pregnancies is no higher in QS cases than in surgical sterilization. Also, amenorrhea, uterine lesions and fetal exposure are acceptable risks [14–19]. Sokal and his colleagues, in a recent long-term follow-up study of quinacrine acceptors in Vietnam, demonstrated another advantage to QS, i.e., that the number of hysterectomies in a period of 5 years is much higher (8%) in patients surgically sterilized than in women with QS (0.5%) [20].

The present study reviews the Chilean experience with QS as it relates to gynecologic cancer in Chilean women.

## 2. Materials and methods

Three hospitals in Chile were recruited for QS: Sótero del Río Hospital and San José Hospital in Santiago, and

Valdivia Hospital. They initiated their quinacrine programs on different dates: 1977, 1989 and 1979, respectively. At first, the sterilization technique was the same in all centers: transcervical application of 7 quinacrine pellets (36 mg each, 252 mg total dose) in the proliferative phase of the menstrual cycle, using an inserter similar to a copper-T IUD inserter. The procedure was carried out under aseptic conditions two to three times, with a monthly interval between each quinacrine placement. After performing hysterometry, the inserter was introduced as far as the uterine fundus. However, at San José Hospital, Dr. Trujillo noted that the technique was difficult since the pellets formed a row and sometimes one of them could be placed next to the cervix. After discussion with Dr. Zipper, a new approach was initiated. The inserter was withdrawn 0.5 cm and the pellets were pushed into the uterine cavity. This technique was not described as a standard in all hospitals. It was not until 1993, after publication of Hieu's paper, that the other hospitals adopted his recommended technique. The dissolution time of pellets was 30 minutes (Sipharm, Sisseln, Switzerland). In two series an anti-inflammatory drug (diclofenac 25 mg–50 mg) was administered with quinacrine into the uterine cavity.

Women had revisits at 3, 6 and 12 months after the last insertion and every 6 months thereafter. At Sótero del Río Hospital, insertions were performed by two midwives; at San José and Valdivia Hospitals two gynecologists were the operators.

Only women who requested sterilization for family planning reasons, with a previous informed consent and completed follow-up, were included in this study. In each hospital a committee reviews all applications for sterilization. National regulations at the time of the study required that, for approval of tubal sterilization, a woman must be 30 years old and have 4 living children, or 35 years old with 3 living children. Women suffering from a serious illness would qualify for approval.

One group of 1,061 women from Santiago, Chile, who had requested quinacrine sterilization since 1977, were evaluated for possible cytologic changes in their Pap smears. Papanicolaou tests were carried out before and after QS.

Table 1 shows the experience in Chile with QS. A total of 2,592 patients were sterilized from 1977 to 1998. Two groups of women received 3 insertions of quinacrine pellets, containing 252 mg and no intrauterine diclofenac. Three other groups received

Table 1  
2,592 patients sterilized with quinacrine pellets: 252 mg at hospitals in Chile, between 1977 and 1998

Hospitals	Patients (N)	Period	Insertions (N)	Use of NSAIDs
Sótero del Río	733	1977–1989	3	no
Sótero del Río	508	1977–1989	2	no
Valdivia	151	1979	3	no
San José	445	1989–1994	2	50 mg IU diclofenac
Sótero del Río	755	1995–1998	2	25 mg IU diclofenac
<b>Total</b>	<b>2,592</b>			

Table 2  
Efficacy and ectopic pregnancy risk among 2,592 quinacrine sterilization acceptors, Chile 1977–1998

	(I) Sótero del Río 1977–1989	(II) Valdivia 1979	(III) San Jose 1989–1994	Sótero del Río 1995–1998	Total (N)
Patients: all	1,241	151	445	755	2,592
Pregnancies N (%)	68 (5.5)	9 (6.0)	19 (4.3)	23 (3.0)	119 (4.6)
EP <sup>a</sup> N (%)	4 (0.32)	3 (1.98)	2 (0.44)	0	9 (0.34)
WY <sup>b</sup> follow-up	15,756	2,416	2,330	1,284	21,786
EP risk per 1000 WY	0.25	1.24	0.85	0	0.41
Pearl-Index	0.43	0.37	0.81	1.79	0.54
Cumulative life-table pregnancy rates per 100 women and (SE)	5.2 <sup>d</sup> (0.87) <sup>c</sup> N = 733 6.9 <sup>e</sup> (1.24) <sup>c</sup> N = 508 at 10 years	5.9 (1.7) <sup>c</sup> at 10 years	5.5 (1.41) <sup>c</sup> at 5 years NSAID	4.9 (1.22) <sup>c</sup> at 2 years NSAID	

<sup>a</sup> EP, ectopic pregnancies.

<sup>b</sup> WY, woman-years.

<sup>c</sup> SE, standard error.

<sup>d</sup> 3 insertion data set.

<sup>e</sup> 2 insertion data set.

2 insertions, and two of these groups were also given 50 mg or 25 mg of IU diclofenac. Although the groups presented in Table 1 are not strictly comparable, they summarize the global Chilean experience with QS, representing the group with the longest follow-up.

**The inclusion criteria were:** The subject is between 21 and 45 years of age; has three or more living children, the youngest of whom is at least 3 years old; is generally healthy; is sexually active; is not using another contraceptive method; has had a recent and normal Pap smear; is not known to be infertile or sterile. The patient must carefully read and sign an informed consent, freely agreeing to participate in the study. She must find it convenient to return for follow-up visits. The hospital sterilization committee grants authorization for the procedure.

**The exclusion criteria were:** The subject suspects

she may be pregnant; has abnormal uterine bleeding; has gynecologic anatomical abnormalities such as myomas or cervical synechia; has any serious illness; has pelvic inflammatory disease (PID), acute or chronic; is allergic to quinacrine; is taking any drug that alters fertility, i.e., anticoagulants, furosemide, methotrexate, etc.; has had previous pelvic surgery; has a seizure disorder; is amenorrheic; and/or has gynecologic cancer.

### 3. Results

Table 2 shows that a total of 2,592 women were sterilized at three hospitals in the following groupings: 1,241 (from 1977–1989) and 755 (from 1995–1998) at Sótero del Río Hospital; 151 at Valdivia Hospital (1979); and 445 (from 1989–1994) at San José Hospital.

Table 3  
Patients' complaints and complications<sup>a</sup> by insertions, hospitals and period of years, Chile 1977–1994 (N = 1837)

	(I) Sótero del Río 1977–1989	(II) Valdivia 1979	(III) San José 1989–1994	Total
Patients	1241	151	445	1837
Insertions	3215	450	890	4555
<b>Complaints/Complications N (%)</b>				
Vaginal bleeding	6 (0.2)	5 (1.1)	19 (2.1)	30 (0.7)
Feverishness	57 (1.8)	–	15 (1.7)	72 (1.6)
Headache	107 (3.3)	3 (0.6)	20 (2.2)	130 (2.9)
General discomfort	74 (2.3)	–	10 (1.1)	84 (1.8)
Vomiting	3 (0.1)	1 (0.2)	10 (1.1)	14 (0.3)
Lower abdominal pain	175 (5.4)	45 (9.9)	23 (2.6)	243 (5.3)
Vulvovaginitis	6 (0.2)	2 (0.4)	8 (0.9)	16 (0.4)
Myalgia	–	1 (0.2)	–	1
Emotional reaction	–	1 (0.2)	–	1
Fever	–	1 (0.2)	8 (0.9)	9 (0.2)
Cervical synechia	2 (0.1)	–	2 (0.2)	4 (0.1)
Amenorrhea	–	–	4 (0.4)	4
Back pain	–	–	1 (0.1)	1
Allergic reaction	–	–	1 (0.1)	1
PID <sup>b</sup>	3 (0.1)	1 (0.2)	–	4 (0.1)
Hepatitis <sup>c</sup>	–	1 (0.2)	–	1
Total	433 (13.4)	61 (13.2)	121 (13.5)	615 (13.5)

<sup>a</sup> One or more events can be reported by each patient. There was one uterine perforation.

<sup>b</sup> Pelvic inflammatory disease.

<sup>c</sup> Probably in incubation at insertion.

Table 2 also shows the efficacy and ectopic pregnancy risk among the 2,592 acceptors from 1977–1998. The groups with longer follow-up (I, II, III) have a pregnancy rate that varies from 5.2% following 3 insertions to 6.9% following 2 insertions at 10 years. Intrauterine diclofenac had no apparent effect on efficacy. In all groups, two-thirds of all pregnancies occurred during the first 2 years after QS. There was a total of 3 pregnancies between insertions; 2 resulted in induced abortions and one in a spontaneous abortion.

The ectopic pregnancy risk per 1000 woman-years (0.41) is similar to that for IUD users (0.3) [21], lower than for surgical sterilization (0.7–0.8) [22] and much lower than for non-contraceptive users (2.6) [23]. All such cases were surgically resolved with no serious post-operative complications or deaths. The 9 ectopics correspond to 7.5% of the 119 pregnancies.

Table 3 shows complaints and complications reported by QS patients. Headache and lower abdominal

pain are most frequent. All complaints, except amenorrhea, PID and hepatitis, were mild and transitory, did not require hospitalization and disappeared in the first 3 days. The patient in distress presented with an emotional reaction with sadness and weeping. The problems for four patients with cervical synechia were resolved by hysteroscopy with no further complications. One case with hematometra was easily treated with a uterine sound. Patients with amenorrhea started their menstrual cycle before the third month after their last insertion. The allergic reaction was reported as a mild sun-burn sensation that remained for less than 8 hours. One woman with PID had a previous undiagnosed chronic adnexial disease and should have been excluded from the study. All of these patients were treated successfully without surgery. The case of hepatitis A, an endemic disease in Chile, probably was in its incubation period before the woman was sterilized. The uterus of one patient was perforated by the inserter, but pellets

Table 4

Comparison of the number of *in situ* carcinomas and woman-years of exposure by age<sup>a</sup> among 1,061 quinacrine sterilized women between March 1977 and October 1990 and the general female population in Santiago, Chile

Age group	Quinacrine <i>in situ</i> cancer	Woman-years	Comparison <i>in situ</i> cancer	Woman-years	Chile 1970 female population <sup>b</sup>
30 to 34	3	729	13	4,951	299,200
35 to 39	3	975	5	3,374	259,400
40 to 44	1	1,046	1	2,309	248,100
45 to 49	1	535	3	1,721	200,200
Total	8	3,285	22	12,355	1,006,900

<sup>a</sup> Age-standardized rates: quinacrine, 2.62 per 1000 woman-years; control, 1.56 per 1000 woman-years (RR: 1.62, CI: 0.73–3.61).

<sup>b</sup> Population used for age adjustments.

Table 5

Incidence of cancer in women sterilized with quinacrine pellets (QS) and controls, Chile, 1977–1996 ( $N = 1514$ )

Type of cancer	Number of cases		Rate per 100,000		Relative risk
	QS	Control	QS	Control	
All cancers	17 <sup>a</sup>	217.2 <sup>b</sup>	134.5	124.2	1.1
Endometrial	0	9.1	–	2.2	–

<sup>a</sup> 1514 women (17,450 woman-years).

<sup>b</sup> 215,171 woman-years among patients over 30 years of age.

were not introduced into the abdominal cavity. No hospitalization or specific therapy was needed. A rate of 13.5% of adverse events was reported.

One group of 1,061 women from Santiago, who had requested sterilization since 1977, were evaluated for possible cytological changes in their Pap smears [24]. Some grade of a cervical lesion was observed in 75 women (7.1%). The prevalence was 3.4% (36 women) and the incidence was 1.1% (34 women) in a total of 3,654 woman-years between the first and the last Pap smear. From this group, 30 patients were found with low grade intraepithelial cervical lesions, and 8 with high grade cancer *in situ* (CIS). One patient with squamous cell carcinoma was surgically treated in 1986 (Table 4). After standardizing the incidence rates, the results were compared with a control group of women in Santiago. The incidence of CIS, precursors of cervical carcinoma, in patients treated with quinacrine (2.62%) was not higher than that found in other areas of Santiago (1.56%,  $P > 0.05$ ).

A retrospective cohort study of 1,514 women sterilized with quinacrine was carried out between 1977 and 1996. Seventeen cancer cases of any location

were diagnosed after quinacrine insertion. Prior to sterilization, 12 cases of CIS were diagnosed. No endometrial cancer was found in QS patients. The latest up-date in 1996 found no endometrial cancer in the QS group, with a follow-up of 12,468 woman-years [25]. The cohort members provided 17,450 woman-years of follow-up. No evidence of increased cancer risk was found to be associated with QS (Table 5) [26].

Fifty percent of 119 pregnancies were carried to term. Most of them were vaginal deliveries (42 of 59). All ended in normal births. No birth defects related to quinacrine and no macroscopic uterine pathology were detected at the time of delivery. Premature deliveries were not considered abnormal pregnancies. Forty-one pregnancies (34%) ended in abortions; 16 of them (13%) were spontaneous. One case of hydatidiform mole was reported (Table 6).

Patients with QS failures were scheduled for surgical sterilization or other contraceptive methods because we assume that for some anatomical reason quinacrine did not reach the tubal ostium. Also most patients reject a second quinacrine sterilization after a failure.

Table 6  
Outcome of pregnancies in women sterilized with quinacrine pellets (QS) in Chile, 1977–1996 ( $N = 119$ )

Outcome	$N$
Normal pregnancies	59
42 vaginal deliveries	
17 cesarean deliveries	
Ectopic pregnancies	9
Spontaneous abortion	16
Induced abortion	25
Hydatidiform mole	1
No information	9
Total	119

Hysterosalpingograms (HSG) were routinely performed only in the group from Valdivia Hospital, where 80% of patients underwent this examination 3 months after the first quinacrine insertion in order to confirm occlusion. Hysteroscopies were performed in 5 patients from San José Hospital who wanted to reverse the sterilization. Fibrotic tissue blocking the tubal ostium was noted. Attempts to unblock the tubes through pressure of HSG were not successful.

#### 4. Discussion

The Chilean experience with QS encompasses more than 30 years of basic and clinical research and numerous scientific publications. This group of Chilean women who have had QS have been closely monitored and constitute the first cases with this non-surgical method. Data presented in this study amply support the initial concept of QS, i.e., it is a simple, safe and highly acceptable ambulatory method of non-surgical sterilization. Is there another reasonable option that could help to meet the increasing demand for sterilization, especially in developing countries?

The anti-inflammatory drugs were used in an attempt to diminish the mild side effects associated with intrauterine insertion and theoretically to potentiate quinacrine tubal occlusive action. No additional contraceptive method was used in any group. Intrauterine quinacrine produces a fibrotic and granulomatous tissue in the tubal ostium that obstructs the oviductal lumen. Failure rates of QS can be compared to those for

IUD users. QS efficacy at 10 years is comparable to widely used surgical procedures such as laparoscopic tubal sterilization by clip or by bipolar single point electrocoagulation [22]. In surgical sterilization, one-third of the failures are an ectopic pregnancy [27]. In this series, only group II follows this trend. With the Progestasert® IUD, one half of failures are ectopic pregnancies [28].

Since the contraceptive potential of quinacrine has become known, controversies have arisen, based mainly on its mutagenic activity in Ames test (*in vitro*) and its theoretical carcinogenic effect in humans. *In vitro* tests cannot be extrapolated to humans. They have low specificity, 67% false positives [19] when nitrogen organic compounds (i.e., quinacrine) are tested and only 60% valid extrapolation to rodents [29]. Also frame-shift mutations induced by amino acridines are inhibited when glucose, cAMP or adenosine derivatives are present in the cell medium [30–31]. There is no evidence that quinacrine can be carcinogenic in humans or rodents. Data on the *in vivo* genotoxicity of quinacrine (micronucleus cytogenetic assay in mice) represent evidence that quinacrine lacks *in vivo* genotoxic activity [32].

Although the efficacy of QS is lower than surgical sterilization, the absence of deaths and serious complications is a great advantage of QS, especially for high risk patients [33]. One examines the results with QS and notes that abnormal uterine lesions or damage have not been detected. In the pregnancies carried to term after QS, we have seen no fetal abnormalities. The rate of ectopic pregnancies with QS is similar to those with IUD use and surgical sterilization, but far lower than for non-contracepting women. Long-term follow-up of QS cases in Chile shows no increased risk of gynecologic or any other type of cancer associated with QS in this population [24].

#### 5. Conclusion

After 30 years of research, we firmly believe that there is no scientific reason to consider QS an experimental or dangerous procedure. There is no evidence to believe that QS may increase the incidence of cancer. Acceptance of QS could help to reduce the maternal mortality in developing countries. It may be the safest option for women at high risk for surgery who desire to limit family size by sterilization.

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