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Clinical Study on Female Non-Surgical Sterilization with Quinacrine *

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[Abstract] **Objective:** To study the safety, reliability, and acceptability of large-scale clinical use of non-surgical sterilization (QS) of women with quinacrine. **Methods:** From March 2007 to July 2010, 6,000 women who voluntarily received QS were recruited in Guizhou Province, namely: 7 (252 mg) quinacrine pellets were placed in the modified T-copper IUD placer, and then the quinacrine pellets placed into the uterus at 3 days to 7 days after menstruation ends, or 6 weeks after childbirth, or induced abortion. The second application was completed after at 4 weeks. Follow-up was performed at 3, 6, 12, and 24 months. **Results:** 5,780 follow-up forms and 88 pregnancy forms were recovered with the longest follow-up time of 1,248 days. The main adverse reactions were yellow vaginal discharge, dizziness, fatigue, and irregular menstruation, etc. No serious adverse reactions were found. The effective rate of sterilization was 98.5%, and the drug application status and the number of times of application affect the success rate. **Conclusion:** QS is low cost, easy to be operated, non-invasive, painless, less adverse reactions, and more accepted by women with voluntary sterilization intention and clinicians. Preoperative physical examination excluded contraindications, applied at 6 weeks postpartum or 3 – 7 days after menstruation, 2 doses of medication, patients were instructed to lie down for 2 hours after the QS procedure, and 3 months of postoperative contraception are beneficial to improve the success rate of QS. The promotion of QS has a positive effect on improving the acceptance of female sterilization and reducing the cost of family planning surgery.

[Keywords]: Sterilization, Reproductive Tract; Female (Female) Sex; Quinacrine; and Non-Surgical Sterilization

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Quinacrine, also known as atabrine, mepacrine, used as an antimalarial specific medicine in World War II, which had saved the lives of millions of soldiers, and has also been used for treating cancerous pleural ascites in recent years. Study on its use in female sterilization was began by Chilean doctor Zipper in 1970. The quinacrine pellet method used in this study is the same procedure recommended since 1976. In the early 1990s, nearly 100,000 subjects in 14 countries around the world, including Chile, Vietnam, India, Egypt, Iran, and China, underwent quinacrine non-surgical female sterilization (QS). At the same time, with the increased usage of QS, the failure rate will decrease further ^[1-2]. The purpose of this study is to study the safety, reliability, and acceptability of QS in large-scale clinical use.

1. Subjects and methods

1.1 Subjects: According to the needs of the study and the arrangement of the Family Planning Administration Department of Guizhou Province, experimental sites were established in seven district / county-level family planning stations in Huaxi District, Guiyang City, Nanming District, Zunyi County, Rongjiang County, Fenggang County, Yuqing County and Liping County of Guizhou Province. From March 2007 to July 2010, for those women who voluntarily accepted QS and met the study conditions, it was agreed that women who participated in 4 follow-up visits after operation shall undergo QS operation. General physical examination before operation, such as blood pressure, blood routine, urine pregnancy test, ultrasound, and other examinations, to exclude serious systemic diseases and pregnancy; Meanwhile, general gynecological examinations such as double diagnosis shall be performed to exclude unexplained reproductive system diseases such as vaginal bleeding, pelvic inflammation, salpingitis, cervicitis, genital tract malformation and tumor. Furthermore, women with a history of

ectopic pregnancy and mental illness were excluded. All the selected subjects signed the Informed Consent Form of QS study, a total of 5,917 cases. The age was 19 - 47 years old, with an average of 30.7 years old. Nearly 90% of the subjects were from rural areas, with an average of 2.35 surviving children, and the vast majority of the subjects have more than two children. The youngest child of more than 80% of the objects is under 1 year old.

1.2 Methods: At 3 - 7 days after menstruation ended, or six weeks after delivery, or induced abortion, 7 quinacrine pellets with a total of 252 mg were placed into the modified t-copper IUD placer and then applied into the uterus, and the drug was placed again at an interval after 1 month (4 weeks). After the first dose, the subjects were instructed to use alternative contraceptives (such as condoms) for 3 months. After each application, the doctor shall carefully fill in the Drug Application Form, and conduct follow-up at 3, 6, 12, and 24 months after the first drug placement (including outpatient, home visit, telephone interview and other forms), and fill in the Follow-Up Form at the same time. If the subjects were pregnant, they were considered as failing and the Pregnancy Form shall be filled in.

1.3 Statistical Methods The Recovery Form was reviewed by two persons and entered into the computer. The data were analyzed by SPSS, and the influencing factors of QS failure rate were analyzed by chi-square test in cross tabs.

2. Results

2.1 Follow-up: 5,780 follow-up tables, including 88 pregnancy tables, were recovered in this study. The total recovery rate was 97.7% (5,780 / 5,917). The table recovery conditions, follow-up rate and failure rate of the seven test points are shown in Table 1. The main reason why the follow-up form could not be recovered was that the subjects were less than 90 days after QS. It can be seen from Table 1 that Zunyi County has the most cases, Yuqing County has the least, Fenggang County and Yuqing County have the highest

follow-up rate, while Liping County has the lowest follow-up rate, less than 90%; The failure rate is also just corresponding. Fenggang County and Yuqing County are the most and Liping County is the least. The number of QS cases completed in each county is related to the number of women of childbearing age in the county; The follow-up rate was related to the start time of QS. The QS study was only performed in Liping County in 2010. As of the end of the survey, many QS were still performed. Nearly 10% of the subjects did not arrive at the first follow-up time and did not fill in the Follow-up Form, so the follow-up rate was the lowest. The average menstrual cycle of women was 29.7 days, with an average of 29.1 days. The longest follow-up object in this study was 1,248 days, about 42 female months; The shortest is 91 days, about 3 female months (excluding losers); The average follow-up was 614.2 days, about 20 female months. The total follow-up time was 3,549,816 days, about 118,327 female months. 321 cases (about 5.5%) of the follow-up objects only bought medicine once because of going out to work and being troublesome.

Table 1: Report of "Medication Form, Follow-up Form, Pregnancy Form"

Test Site	N (Proportion)	Number of follow ups (follow-up rate)	Number of pregnant female (failure rate)
Nanming District	975 (16.5%)	970 (99.5%)	10(1.0%)
Huaxi District	976 (16.5%)	969 (99.3%)	17(1.8%)
Zunyi County	1334(22.5%)	1330 (99.7%)	18(1.4%)
Rongjiang County	898(15.2%)	854(95.1%)	17(2.0%)
Fenggang County	799(13.5%)	799(100.0%)	19(2.4%)
Liping County	728(12.3%)	651(89.4%)	2(0.3%)
Yuqing County	207(3.5%)	207(100.0%)	5(2.4%)
Total	5917(100%)	5780(97.7%)	88 (1.5%)

2.2 Adverse reactions: Among the 5,780 follow-up forms received, 1,172 lacked "feelings after QS", and 86.8% of the 4,608 filled in answered

that there was no discomfort. The main adverse reactions were vaginal yellow secretion, dizziness, fatigue, irregular menstruation, abnormal menstruation, etc., as shown in Table 2. These adverse reactions generally do not need special treatment and disappear naturally after 1 day and 2 days (except irregular menstruation).

2.3 Failure: 88 pregnancy tables were received in this study, i.e. 88 cases failed, and the failure rate was 1.50% (88 / 5,780), including 4 cases of ectopic pregnancy. The average age of the failed subjects was 30.1 years old, which was lower than the average age of all subjects. The time between failure (pregnancy) and QS was 39 - 848 days, and the longest was about 28 months; The average is 366.4 days, about 12 female months. There were 5, 14, 29, 25 and 5 cases for the time between failure (pregnancy) and QS <90 days, 90- 180 days, 180-360 days, 360-720 days. The constituent ratios were 5.7%, 15.9%, 32.9%, 39.8% and 5.7%, respectively. Failure (pregnancy) occurs within 0.5 – 2 years at most. Five cases were pregnant within 90 days after QS. There are 5 cases after QS of pregnancy within 90 days.

Table 2: Adverse Reactions after Application

Adverse reactions	Number of cases	Percentage (%)
None	4,001	86.9
Uterine perforation	0	0.0
Dizziness	63	1.4
Severe abdominal pain	1	0.0
Cervical adhesions	2	0.0
Fatigue	40	0.9
Decreased quality of sex life	3	0.1
Increased menstrual flow	21	0.5
Decreased menstrual flow	75	1.6
Intermenstrual bleeding	54	1.2
Irregular menstruation	38	0.8
Lower abdominal pain	74	1.6
Back pain	75	1.6
Yellow discharge	127	2.8
Other	30	0.7
Total	4,608	100.0

2.4 Effective rate: The effective rate expressed as a percentage was 98.5%. Pearl index, which is closer to the concept of natural fertility than percentage, is the most widely used measure of contraceptive effect in the world. Pearl index is an actual risk rate, which is usually expressed as

the number of pregnancies due to contraceptive failure per 100 women using contraceptives for one year. The calculation formula is "the number of all unintended pregnancies during the application of contraceptives divided by the total number of people and months of female using contraception and multiplied by 1200"^[3]. According to this definition, the Pearl index of this study is $88 \times 1,200 / 118,327 = 0.8924$. Life Table is widely used in "Time Decline" analysis. Using life table to judge the effectiveness of contraceptives is also more and more accepted by people. Calculated by SPSS, the cumulative effective rate of 5780 cases of QS life table analysis was 97.54%.

2.5 Analysis of the failure reasons: Analysis of failure causes this study found that the failure rate of rural group (1.57%) was slightly higher than that of urban group (1.45%); The failure rate of the group with lower education level is higher. The failure rate of the group with higher education level is junior middle school and above (1.68%), primary school group (1.55%), illiterate group (1.09%) and missing group (0.99%). "Drug application status" and "drug application times" are the influencing factors (P about 0.05). The results are shown in Table 3. The failure rate of "postpartum", especially "after IUD removal", is significantly higher than that of "after menstruation"; The failure rate of "one application" is significantly higher than that of "two applications".

Table 3: Factors Influencing Failure Rates

Factor	Follow-ups	Number of Pregnant female	Failure rate (%)	χ^2	P
Drug status				40.83	0
Postpartum	3,183	55	1.73		
After menstruation	2,481	24	0.97		
After taking the ring	53	6	11.33		
Missing	63	3	4.76		
Number of doses				5.75	0.016
1 time	321	10	3.12		
2 times	5,459	78	1.43		

3. Discussion: As a new type of non-invasive sterilization, QS has a short history, and there are few clinical follow-up reports of thousands of cases at home and abroad. In 1998, 572 cases of QS clinical studies were reported in Jiangsu Province and Guizhou Province of China ^[4] with the failure rate of 3.13%. 31,871 QS clinical studies around 1995 were reported in Vietnam. Some experts suggested that, the practice of clinical follow-up test was not standardized, and questioned the results (including safety and reliability)^[5]. Furthermore, hundreds or thousands of QS clinical studies have also been reported in India, Pakistan, Costa Rica, Indonesia, and Syria ^[6-10], with a failure rate of 0 - 15% and scattered results. Various family planning operations were affected by the external environment, such as study location, personnel and objects, and the results were different. At present, only 2,592 cases (4 batches) in Chile have been followed up for 25 years, which has attracted the attention of the International Family Planning Study Community ^[2]. The follow-up survey of QS in Chile and some data of IUD birth control and tubal ligation sterilization performed in China before the 1990s ^[11] show that the QS failure rate of this study (1.5%) is lower than that reported by the International (Chile) (4.6%), which is equivalent to IUD (0.3% -3.7%) and tubal ligation (0.18% - 2.01%). Its Pearl Index (0.89) was higher than that of International (0.41), but lower than that of IUD (2.7 - 5.3%). The incidence of abnormal menstruation in this study was 3.3%, which was lower than that of IUD (3.9% - 17.3%) and tubal ligation (10% - 20%). The incidence of ectopic pregnancy (0.07%) was lower than that of IUD (0.6%), which was equivalent to that of tubal ligation (0.06% - 0.3%). It can be seen that as a newly developed sterilization method, the failure rate of QS in this study is not high compared with the failure rate of early clinical use of IUD and tubal ligation (TL). Of course, with the expansion of clinical use, the effective rate of IUD and TL has made great progress compared with the early use. It is

believed that with the continuous accumulation of clinical experience, the effective rate of QS will also be greatly improved. Studies have shown that quinacrine is the most effective drug in blocking the confluence of the oviduct and the oviduct^[12]. For those with thicker stroma, the risk of sterilization failure will increase; during endometrial hyperplasia, drugs are not easy to act on the myometrium to cause inflammation, and the risk of failure increases; Scar formation takes time, generally more than 30d, during which the risk of failure will increase. According to the study and training, lie flat for 2h after operation to melt the medicine and flow into the fallopian tube; It is required to apply the drug twice within one month to increase the depth of drug action. Meanwhile, doctors shall explain to the object that condoms and other alternative contraceptive methods must be used for three months after the first medication. The study and training also stipulates that the medicine shall be applied within 6 months postpartum or 3 – 7 days after menstruation to avoid postpartum and IUD removal, to avoid the failure caused by QS's own defects risk. In this study, one case was found pregnant 39 days after the first administration of medicine and had been pregnant for 6 weeks. This case is very likely to have been pregnant before QS and was not found during preoperative physical examination. Failure occurred within 90 days in 5 cases, accounting for 5.7% of the total failures. These subjects are likely to fail to take alternative contraceptives as required. More than 50% of the patients were treated postpartum, and the failure rate was significantly higher than that after menstruation. It can be seen that standardizing surgical operation is an important link to improve the success rate of QS.

Since the International Conference on population and development was held in Cairo in 1994, while paying attention to family planning and population control continuously, China has strengthened its understanding of population, family planning and health issues, and carried out high-quality family planning services, i.e., people-oriented, all-round human development

as the center and people's needs as the starting point, so as to comprehensively improve the quality of family planning services, Promote the all-round development of population and society, and meet the needs of people of childbearing age for diversified contraceptive methods. In China, with the continuous improvement of people's living standards, most urban people can have a variety of contraceptive methods to choose from. However, about two-thirds of women still live in rural areas and have poor access to effective contraceptives. Sterilization is often the most effective method available to them. Many working women are unwilling to accept "ligation" for reasons such as worrying about their physical strength, and are afraid of the pain of ligation. The improvement of sterilization methods is of great significance to the implementation of China's family planning policy, improving the acceptability of sterilization, and improving the quality of life of women undergoing sterilization. It is found in this study that many voluntary sterilization women prefer to pay for QS rather than enjoy free "ligation". According to their words: "QS women only need to lie in bed for 2 hours and can work in the field when return home; they don't dare to work in the field for 1 week after being ligation, and she has to eat chicken to supplement nutrition". The results of this study show that QS has less adverse reactions than surgical female sterilization. It is a female sterilization method welcomed by women who choose sterilization voluntarily. The study and promotion of QS plays a positive role in improving the acceptance of sterilization, people's satisfaction and reducing the cost of family planning surgery.

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