

**QUINACRINE NON-SURGICAL FEMALE STERILIZATION (QS)  
IN A PRIVATE AMERICAN OFFICE PRACTICE**

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**INTRODUCTION**

• **HISTORY OF QUINACRINE HYDROCHLORIDE**

Quinacrine hydrochloride is a synthetic yellow dye and antibiotic manufactured in powder form for medical usage. It has been available since the 1920's and was used extensively in oral tablet form as an anti-malarial prophylactic & treatment in U.S. service men and women during World War 2 (as much as 36,500 to 52,000 mg. per year per person). A great deal of research on its oral usage has shown it to be very safe in doses under 3000 mg per month; millions of American and foreign children have taken the drug for the intestinal parasite, Giardia, and it remains the only FDA approved drug for this purpose. Doctors around the world continue to use it for these and other medical conditions such as lupus and tapeworm. Unfortunately, the drug's manufacture in the U.S. was discontinued in the mid 90's, and our FDA has refused to allow the importation from a Swiss manufacturer of inexpensive, previously made Q pellets for the sterilization procedure. Thus, at present, the powder must be imported and "compounding" pharmacies are then able to laboriously make much more expensive pellets for the IUD-like insertion process. Dr. Stephen Mumford, Dr.P.H., president and director of the Center for Research on Population and Security, one of the three noted American scientists advocating QS, is the supplier of the pellets for international trials.

• **INTERNATIONAL EXPERIENCE**

In the past 25 years, more than 140,000 women in 34 countries have undergone the quinacrine pellet intrauterine sterilization procedure. This technique, with its unquestionable safety, simplicity, good efficacy, and low cost, has primarily been offered in third world countries. Both the IFFH (International Federation for Family Health) and FHI (Family Health International) have endorsed research into this method.

• **QS DEVELOPMENT & TECHNIQUE...DR. JAIME ZIPPER**

The QS method was developed in Chile in the late 70's by Dr. Jaime Zipper, the inventor of the Copper--T IUD, and after some trial and error, the optimal dose for trans-cervical insertion of the pellets was found to be 252 mg. in 7 pellets ejected from the modified copper IUD inserter high in the uterus about .5 to 1 cm from the fundus with the sheath held steady at that depth (slide 1). This must be done twice: in consecutive months, and in the week following a menses (slide 2). If the woman is using the depo-mpa method of

contraception, which may enhance the success of the technique, there may be no menses to guide one. It is important to the success or efficacy that there be no blood in the uterus, as this interferes with the action of the quinacrine. Concentrations of quinacrine in the uterus after insertion are higher than for oral administration for only a matter of a few hours, but they are adequate to cause a significant chemical endometritis from which the thick endometrium always recovers. However, with proper flow into the proximal tubes where the mucosal lining is only a single cell thick (slide 3), recovery is unlikely and scar tissue “plugs” develop to obstruct any future access of sperm to ovum (slide 4).

## • AMERICAN HISTORY

It is only within the last five years that three American advocates, all internationally respected scientists, began to focus efforts to bring the method into the mainstream of reproductive control choices in the United States.

- FDA Modernization Act of 1997 Pharmacy Compounding Provisions: became effective November 1998, thus enabling American physicians to offer QS to their private patients with individual prescriptions filled by “compounding” pharmacists
- 2000: FDA approval of an investigational new drug trial application for the intra-uterine QS technique: clinical evaluation in U.S women.
- Jack Lippes, m.d. : Dr. Lippes, inventor of the famed Lippes loop intra-uterine device, and now principal investigator with the FDA, has recently completed a phase one trial with ten women. A national trial is expected soon.

## risks and the opposition

## • DETRACTORS' UNPROVEN SUPPOSITIONS

Many of the method's detractors express concern about possible increased likelihood for cancer, ectopic pregnancy, and birth defects in any subsequent pregnancies. We know there are none of these risks with oral consumption of the drug-- at much higher doses than used in the sterilization process-- and pathology studies suggest that if the quinacrine reaches the fallopian tubes, it closes them completely (7). The risk of ectopic pregnancy following failure of surgical sterilization in the U.S. is higher than for QS, using newer insertion technique. Every year in my country there are about a dozen deaths and about a thousand hospitalizations from complications of surgical sterilization. There has never been a death recorded with the QS pellet method---a remarkable safety record! ! This includes the rare case of uterine perforation with the inserter and depositing the pellets in the peritoneal cavity. Although painful, once the quinacrine is absorbed, pain diminishes and there are no other sequellae (8).

Antagonists make much of the fact that quinacrine is a mutagen (so is tetracycline) and would have others believe such drugs can cause cancer because of this factor. Direct

evidence of quinacrine carcinogenicity in humans or animals has never been established. Finally, the drug does not appear to be teratogenic. In a 31,781 case Vietnamese trial, “there were two cases of quinacrine insertion during early pregnancy. One was a case of ectopic pregnancy, and the other woman gave birth after the study cut-off date. The infant was normal (9). There are some animal data for both monkeys and rats showing that exposure of the fetus at the time of embryogenesis leads to resorption or abortion, especially in early gestation, but there was no evidence for treatment-related malformations (7). Nevertheless, fierce opposition from certain quarters has led several countries to suspend their programs.

- **DR. MALCOLM POTTS, GIUSEPPE BENAGIANO, & W.H.O.**

Some detractors still insist on expensive and time-consuming animal research before using women as subjects. Other investigators, among them Malcolm Potts and Giuseppe Benagiano, have stated these “cannot prove human safety”. They also observed that such animal tests can produce results “qualitatively different from those subsequently found in humans, as occurred with Depo-Provera”(1). It is interesting to note that for many years, the World Health Organization (WHO), under the direction of Dr. Benagiano, opposed QS. In the above commentary, the authors note a cumulative low risk of serious, immediate side effects, but insufficient data to answer questions about potentially important, long term side effects. They are glad FDA trials are underway, but, while admitting the safety answer lies in “a very large scale of controlled use”, they cautiously advise offering QS only to women who ask for sterilization and “for whom existing methods are not available” or who “present unacceptable risks”. A very conservative and limiting “middle road” indeed!

### **AUTHOR'S AMERICAN EXPERIENCE**

- **ELEVEN QS PROCEDURES (2000 TO PRESENT)**

The 11 women, ranging in ages from their late 20s to their early 40s, have tolerated the two insertions very well, with minimal side effects: mainly low back and/or abdominal ache. None have required pain medications, had fever or headache, or missed any daily activities, such as work, afterwards. Nine are Caucasian, one is Hispanic, and one is East Indian --- all without insurance coverage. They have been extremely pleased with the method. I will continue to follow them at 6-month intervals. Questions asked of them recently have produced negative responses about: 1) adverse menstrual changes, such as a missed period followed by a heavy/crampy one (which could be an early miscarriage); 2) sexual discomfort; 3) any changes or abnormal feelings in the abdomen.

I use the IFFH sterilization register and follow-up to record my cases, and have developed my own office protocol for information calls, workup, and history and physical exam forms. My consent form is extensive and only slightly modified from that developed by Dr. Mumford and others. I have Spanish translations of everything, including a training manual for providers.

## • **A FEW PRACTICE POINTS...**

- Sedation before insertion is unnecessary, but one might wish to do an anterior cervical lip anesthetic injection for the tenaculum (I use a sharp toothed one), or an atraumatic instrument.
- Be certain of the position of the uterus in the body in the initial bimanual pelvic exam. When sounding to the fundus, try a gentle rotation or side-to-side motion of the sound to see if there might be a septum.
- Immediately after insertion, the woman should lie down on a couch or bed so as to maximize the uterine fundal position downward. We are experimenting with a long foam wedge to facilitate this (slide 5), and hopefully make more of the quinacrine available to the cornuae.
- After 30 minutes, one can see thru a reasonably full bladder with ultrasound whether there is quinacrine flowing to the cornuae.
- With the second insertion, one may encounter some immediate cervical bleeding on sounding, probably a residual of the quinacrine inflammatory effect of the previous insertion. I do not consider this a contra-indication to continuing with the insertion.

## • **FEMINIST CHALLENGE TO MY LICENSE**

In early 2002, 4 women ( mostly radical feminists and sociologists from a New England college ) brought a complaint against my medical license re my advertising and practicing QS. There was absolutely no scientific merit whatsoever, and the complaint was investigated by the Agency for Health Care Administration and the Florida Department of Health. On 17 October 02, a letter was written to my attorney stating: "Please be advised that the complaint in the matter referenced above has been investigated and reviewed by the Probable Cause Panel of the Board of Medicine. Pursuant to section 456.073(9)(c), Florida statutes, the panel found that there was insufficient evidence to support prosecution and directed the case be dismissed." These same women also oppose our FDA even investigating the validity and safety of QS with Dr. Lippes !!

## **DISCUSSION: UTERINE ANOMALIES AND FAILURE RATE**

I suspect that some of our +/- 5% failure rate may be due to uterine anomalies, the most likely of which is some degree of intrauterine septum (slide 6). Various authors have estimated the incidence of anomalies as high as 10% (2) (3) , but in my 35 years' gyn experience with IUDs and abortion, I believe some septum to be about 5%. Now we have 3-D vaginal ultrasound to more accurately differentiate between a significant septum and a bicornuate or arcuate uterus (slide 7), and also to better define the QS cornual scar tissue (4)(5). Patients who have had significant pregnancy wastage or

premature labor and delivery may be good candidates for both pelvic and abdominal 3-D sonography, for many studies have often shown ipsi-lateral agenesis of a kidney with uterine body malformations (6). Any QS failure should have an ultrasound study, and it would be very beneficial if all first insertions had access to at least a reasonably good resolution machine to check for symmetry of flow of “Q” toward the cornuae. I also suspect there is a majority of fundal septae which are insignificantly shallow, or less than 2 cm deep and would not likely cause pregnancy wastage. They might, however, deflect the “Q” pellets to one side with high insertion. Therefore, I have modified my insertion depth to 1 – 2 cm back from the fundus for a more central ejection.

## **CONCLUSION**

The level of need for contraception in the world is rising rapidly. To satisfy the U.N. median variant population projection of 12 billion people at the end of the 21<sup>st</sup> century, we must achieve by 2035 a replacement fertility rate of 2.1 children per woman. The UNFPA estimates that this will require 200 million sterilizations in the 10 years ending in 2005, or two years from now. About 85% of these were projected to be female, the rest vasectomies. Given this situation, it is obvious that there is urgent need for a safe, effective, inexpensive method of sterilization that can be delivered by paramedical personnel in rural areas (10). QS may be the answer, and a wide, controlled clinical study with good patient information and consent, combined with a parallel, retro-study of previous patients mentioned above, should be implemented immediately. In the U.S.A., our society’s litigious nature will be a severe restraint unless or until the FDA gives its seal of approval to this remarkable method. Meanwhile, Dr. Mumford and others have been informing clinicians about QS at their professional meetings. The response has been gratifying, but we need more American physicians actively involved with office patients.

**IT IS TIME FOR QS TO BE MADE AVAILABLE TO WOMEN EVERYWHERE! I HOPE YOU WILL JOIN US IN OFFERING IT TO THEM. THANK YOU!**

**YA ES HORA PARA QUE LA QUINACRINA SEA DISPONIBLE PARA LAS MUJERES EN TODAS PARTES DEL MUNDO! ESPERO QUE USTEDES NOS ACOMPAÑEN A OFRECER ÉSTO A ELLAS--- GRACIAS!!**

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