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Forward

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Guest Editor

This Supplement provides an update on the extensive quinacrine sterilization (QS) research referenced and reported on in the 25 articles from 15 countries we have included. They reinforce evidence of QS safety, effectiveness and possible innovations to improve efficacy.

Safety, the acid test of initiating trials among rural indigenous practitioners proposed by Zipper and Kessel, is discussed in articles by Pal and Roy revealing the safety of QS in their hands and the advantage of long-term follow-up in rural practices. The ease of dissemination of knowledge of QS in such local communities is also noted. The extended monitoring of Sarin's study among high risk women provides additional evidence of safety of QS while illustrating the need for a nonsurgical method of sterilization.

Hieu offers a rare opportunity to compare safety of three sterilization methods: QS, tubectomy and vasectomy in Vietnam. In an additional report Hieu demonstrates similar rates of ectopic pregnancy for QS and tubectomy. It is clear now that QS is safer than tubectomy and even vasectomy as performed in Vietnam. The question of QS efficacy remains.

The long-term follow-up of Bhatt's trial enables us to be assertive regarding any remaining reproductive risks post-QS concerning safety and efficacy. It appears from this report and others of extended patient monitoring by Sarin, Pal and Roy that late pregnancy failures are less likely for QS than for tubectomy. This brings total lifetime pregnancy risk of QS into a range similar to some accepted tubectomy techniques.

Saroodi-Moghaddam and Alpizar document the fact that hysterosalpingograms (HSG) will increase pregnancy failure of QS and should be avoided.

Hieu explains that the higher than expected pregnancy failure rate of the Vietnam field trial was due to readily available menstrual regulation (MR) procedures, without confirmation of pregnancy. This is important because delayed menses is a common side effect of QS.

It appears from these reports that the involvement of clinicians using QS leads to innovative views for improving efficacy of QS and even challenging discarded techniques. Of considerable interest is the work of Ferreira, visualizing the "lake of dissolved quinacrine" and formation of the intratubal scar by ultrasound. The application of this technique in the FDA-approved phase I trial provided a lead for predicting efficacy by size of the formed scar. The work of Pal in increasing the dose of quinacrine for younger, more fertile women and decreasing dissolution time of pellets are interesting leads for further research toward improved efficacy. The report of Roy suggests deposit of pellets at the cornual areas might improve efficacy.

Lu in China provides comparative data showing improved safety of QS over tubectomy, the similarity in efficacy of the two methods and an innovative approach to reversal of QS for future investigation.

The effect of clinician training in proper insertion technique is dramatically seen in the report of Bashir. This largest single insertion QS experience brings into question whether a second insertion is essential in all circumstances. The use of ultrasound to evaluate the QS scar may eventually determine this decision.

These reports further document the established safety of QS and a better understanding of efficacy issues. But there are many remaining unknowns to be explored. The molecular characteristic of quinacrine that induces inflammation and a scar in only two

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tissues, the pleura and the mucosa of the fallopian tube, is yet to be clarified. The difference in timing of pregnancy failures between QS and tubectomy is poorly understood. Better knowledge of these basic questions might lead to adjuvants to improve the efficacy of both QS and tubectomy. How relevant is the position of patients after quinacrine pellet insertion to the success of the procedure? Does this depend on different positions of the uterus in the pelvis? Evaluation of the QS scar as a predictor of efficacy is a matter of urgency. While *in vitro* fertilization is still an option for reversal of QS, further research should be addressed to opening its occlusive scar. All this critical research should be a high priority for the improved health of women everywhere.

What we know

- Quinacrine sterilization (QS) is safe, effective, easily performed and low in cost.
- Acceptability is high. When QS is offered simultaneously with surgical sterilization, QS is preferred ten to one over surgical techniques. If you want people to use a service it must be made available. Secondly, they must be aware of it.
- QS scars can be seen on ultrasound.
- Hysterosalpingogram (HSG) to determine tubal patency after QS may blow out the scar, thus defeating the purpose of the sterilization procedure.
- We know zinc plays a role in inhibiting some enzymatic reactions and diminishes the effect of the quinacrine's action on the zinc-rich endometrium.

What we do not know

- How does quinacrine work?
- On a molecular biological basis we do not understand how quinacrine produces inflammation and scars.
- Do the anatomical positions of patients make a difference in efficacy?
  - Standing up.
  - Lying down. Will this reduce failures?
  - Trendelenberg position. Would pillows placed under the patient's hips to elevate the pelvis help to assure that quinacrine flows into the lumen of the oviduct?
  - For patients with a retroverted uterus, would lying on the abdomen facilitate the entrance of quinacrine into the tubal ostia?
- What is the value of ultrasound to QS?
  - Is immediate observation through ultrasound of the lake forming when quinacrine pellets dissolve significant in predicting or improving results?
  - Can the size of the scar as measured by ultrasound be a predictor of possible failure? If so, patients must be warned that a small scar might result in failure.
  - If a small scar is seen, would a third insertion of quinacrine produce a large scar?
  - When using sonography, which way do we see scars more efficiently? By transvaginal ultrasound (TVU), or by transabdominal ultrasound (TAU)? Should we do both routinely when ultrasound is available? Should ultrasound be limited for investigational use only? In the end will sonography be of any help, or make no difference in how we manage QS patients?
  - Is there a compound, to be added to quinacrine, that would make it more echogenic so that scars could be more easily seen on ultrasound?
- Drugs for pain relief?
  - How valuable are nonsteroidal anti-inflammatory drugs (NSAID) for relieving pain and cramps associated with QS?
  - Will an NSAID inhibit the inflammation and thereby inhibit scarring? Might this produce a higher pregnancy rate? Should we then rely on a drug other than an NSAID, such as acetomenophen?
- Is there an adjuvant to be added to quinacrine which would facilitate scar formation more rapidly and be more reliable when pellets are inserted? If such an improvement were forthcoming, will we be able to accomplish sterilization with only a single insertion? Are there better drugs than quinacrine?
- Will a muscle relaxant such as papaverine, taken orally, relax the muscles of the tube, and thereby allow more quinacrine to enter the tube and produce a better, more reliable scar?
- When is it advisable to do a third insertion?
  - Heavy bleeding. How much would indicate the necessity for a third insertion? How do we estimate blood loss?
  - Would a canal going through a scar seen on ultrasound, indicate a requirement for a third insertion? Is an alternate contraceptive indicated until we resolve the problem of recanalization seen on US?
- Can we develop a technique to reverse QS? Could

a canula be pushed through the tubal ostia under hysteroscopic guidance and thus reverse the effect of QS?
- Will QS be affected when patients are on concomitant drugs for medical complications such as heart disease, asthma and diabetes?
- Does lactation have an effect on QS results?

The answers to these questions will be found when QS is in the hands of many physicians.