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THE QUINACRINE METHOD OF NONSURGICAL STERILIZATION: REPORT OF AN EXPERTS MEETING

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SUMMARY

In July 1993, Lancet *published a report by Hieu et al. (1) of 31,781* **cases** *in Vietnam in which quinacrine hydrochloride pellets were used for nonsurgical female sterilization. The report raised a number of substantial issues for professionals in the fields of family planning, women's health, and contraceptive research. The report focused attention on quinacrine, rekindling hopes for the development of a safe, effective, and simple nonsurgical method of female sterilization. However, the report also prompted questions about the safety and effectiveness of quinacrine, suggesting that systems for drug approval and regulation have not been well suited for dealing with this method. The report also raised other questions about use of the drug for sterilization, including possible problems in ensuring free and informed* **choice.**

On *December* **2,** *1993, the Association for Voluntary Surgical Contraception (AVSC) held a meeting of experts in New York to air these issues and to assemble the latest information and thinking about this method of sterilization. AVSC invited representatives of institutions working with quinacrine and organizations concerned about the issues raised about the drug to participate in the meeting. Many participants made presentations on issues related to the quinacrine method of sterilization (see page 5). In this paper, the authors summarize the opinions and recommendations made at the meeting.*

The authors assembled the information for this paper after conducting an extensive review of presentations made at the meeting and gathering additional input from meeting participants. This paper does not represent a consensus of the group; it is a representation of many points of view on a complex subject.

This paper includes only information directly related to discussions at the meeting and additional information for the purposes of clarification. An extensive bibliography on the quinacrine method of sterilization appears on page 11.

BACKGROUND

For many years, researchers have sought a nonsurgical method of female sterilization-an approach that would be safer, provide better access to sterilization, and require less expertise and less of a technological investment than surgical sterilization. Investigators have explored various chemical methods, including intrauterine insertion of quinacrine hydrochloride. While much has been published about chemical methods of sterilization, some questions about efficacy and long-term safety remain unanswered.

In a study of oral quinacrine administered for malaria prophylaxis to soldiers stationed in Asia during World War II (2), researchers noted that the drug was toxic when given in large doses or when a large cumulative dose was given over time. The

The report rekindled hopes for a safe, effective, and simple nonsurgical method of sterilization

side effects associated with oral administration (including central nervous system excitation, skin rashes, headaches, dizziness, gastrointestinal disturbances, and, rarely, aplastic anemia) were magnified when the drug was given intravenously to a few of the soldiers. When chloroquine became available, the use of quinacrine for malaria prophylaxis sharply declined.

Quinacrine is an effective sclerosing agent that causes inflammation that eventually leads to scar formation. It is this property that first attracted Dr. Jaime Zipper, working in Chile in the late 1960s, to consider intrauterine instillation of quinacrine for tubal sterilization.

In initial studies by Zipper et al. (3,4), quinacrine was dissolved in a solution, and this "slurry" was instilled into the uterus of the subject through the cervix. Central nervous system excitation occurred in 2% of the women who received the slurry. Three deaths were anecdotally reported in other study sites in which lidocaine may have been combined with the slurry or used as a paracervical block. It is unclear whether the deaths were related to quinacrine or to lidocaine sensitivity. Nonetheless, out of concern for toxicity and possible intravasation of quinacrine into the small capillaries of the uterus during instillation, researchers sought a different form of the drug. Family Health International (FHI; formerly the International Fertility Research Program) formulated quinacrine into pellets to alleviate the problems of the slurry, and Zipper et al. first used this form of the drug in the late 1970s (5). Since then, quinacrine pellets have been used in clinical trials conducted by several investigators. To date, over 50,000 women have received intrauterine quinacrine pellets for sterilization.

The *Lancet* report from Vietnam (1) as well as other published and unpublished reports of use in Bangladesh (Pollack A, unpublished report), Chile, India, Indonesia, and Pakistan 6-9), raise many questions. The first of these are about the safety and efficacy of quinacrine--specifically, the local toxicity of the drug and the complications that arise during or after insertion, including the risk of ectopic pregnancy. To address these questions, researchers need to conduct a critical review of the current scientific literature to identify the gaps in our knowledge about the drugs safety and efficacy and to encourage the design of studies to fill those gaps. Retrospective analyses of field-based data can rarely answer the critical questions that can be addressed by well-designed prospective studies.

The next questions raised by these reports are less scientific and more sociopolitical; they relate to women's right to informed consent and to the choice of safe, proven contraceptive methods. If a new contraceptive method is introduced before

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The purpose of *AVSC Working Papers* is to capture on paper AVSC's experience and to disseminate the results of AVSC-supported research. We welcome your comments and suggestions.

ACKNOWLEDGMENTS

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remaining questions about long-term safety and efficacy have been answered, it is difficult to develop an adequate process for obtaining informed consent in the service-delivery setting. The information available about intrauterine quinacrine may not be adequate to support a presumption of the methods long-term safety and effectiveness or to determine the degree of risk of ectopic pregnancy, a condition that can be fatal if not diagnosed and treated promptly.

As with any contraceptive method considered to be permanent, concerns about the use of quinacrine sterilization in settings where circumstances or policies may not be conducive to free and informed choice must be raised automatically. Intrauterine insertion of quinacrine for sterilization is inexpensive and easily performed. While these are clearly positive attributes, they must be considered as potential liabilities from the vantage point of ensuring free and informed choice in family planning programs.

SAFETY

Pharmacokinetics

Pharmacokinetic data on quinacrine are available from studies on oral and intravenous administration in humans (2). Data are also available on intravenous and intrauterine administration in animals (10). No pharmacokinetic data for human intrauterine administration have been published, and no studies have examined how long after administration quinacrine is detectable in human tissues.' Some experts are concerned about the possible toxic effects of dissolved quinacrine leaking into the peritoneal cavity (although this risk is much lower with quinacrine pellets than with the slurry) and of possible perforation of the uterus during insertion, with subsequent intraperitoneal deposit of the pellets.

Animal studies by Dubin et al. (11) have shown a significant difference between peak serum levels in cases in which quinacrine is given intraperitoneally or inserted into the uterus of a pregnant animal and those in cases in which quinacrine is administered intravascularly or inserted into the uterus of an animal that is not pregnant. In the Rochlin et al. studies (12) of patients who received quinacrine for sclerosis in the peritoneal cavity, side effects were dose related at much higher doses than those used for sterilization. However because ascitic fluid would dilute quinacrine and because the presence of gross tumor would affect absorption in the peritoneal cavity, the studies may not accurately reflect the effect of quinacrine given intraperitoneally to healthy subjects. Panel members at the AVSC experts meeting recommended further pharmacokinetic studies.

*Questions **about efficacy and long-term safety remain unanswered***

Toxicology

Quinacrine has been shown to be embryolethal, and it may have other effects when used in combination with other drugs, such as ibuprofen. The Dubin et al. studies (11) suggest that systemic quinacrine has at least a transient effect on the liver and cardiovascular system in primates. Toxicology experts at the AVSC meeting indicated that data from animal studies have been inconclusive: one study **(13)** used two strains of rats, making it difficult to compare data, and another study (11) used too few monkeys as subjects.

Mutagenicity

In the past, mutagenicity of a drug or chemical was initially determined through use of the Ames test, which identifies whether a drug or chemical causes changes in the structure of bacterial DNA. The Ames test is now only one of a series of four tests for mutagenicity commonly used. In 1983, Blake et al. **(13) performed the Ames test on quinacrine** and reported a positive result (that is, quinacrine did cause changes). Although one panel member at the experts meeting reported that there was evidence that quinacrine causes changes in the DNA of mammalian cells, a literature review by Blake et al. **(13)** shows no clear-cut evidence of this.

Although a positive result from the Ames test does not necessarily indicate that a drug or chemical presents a definite risk of cancer, mutagenicity and carcinogenicity are correlated. The U.S. Food and Drug Administration (FDA) has approved drugs that are known to be mutagenic, but such drugs are usually approved for use as treat-

*In **1984,** Laufe (unpublished **abstract on file at FHI) studied quinacrine pharmacokinetics following transcervical administration of 250 mg of quinacrine in pellet form in 10 patients about to undergo hysterectomy. These data show residual low levels of quinacrine in serum in two of the 10 women at 4-6 weeks following administration (Connell C, personal communication).**

ment for cancer or life-threatening illnesses. Some drugs known to be mutagenic are specifically approved only for uses that do not entail chronic administration. In the case of quinacrine, the FDA has approved the drug for oral administration for the treatment of intestinal cestodes, Giardia, and malaria but would have to reevaluate the drug for local and systemic effects before approving it for intrauterine use.

Carcinogenicity

Concerns about ***free and informed choice must be raised automatically***

No animal or prospective human studies have examined the carcinogenicity of intrauterine quinacrine. While some experts at the meeting pointed to the apparently safe use of oral quinacrine by a large number of soldiers during World War II, others pointed out that no long-term follow-up was done to determine the incidence of cancer in these recipients. Assembling a sample of the group would be difficult now since many of the soldiers might not know that they received the drug. Because the drug may have local effects in addition to systemic effects, a comparison of oral and intrauterine administration is difficult. Some panelists expressed concern that quinacrine may enhance carcinogenicity by causing local inflamrnation that leads to cell division and repair

Tracing cancers in a population is difficult: carcinogenicity is related to the dose and frequency of exposure to a substance, and the effects of a substance cannot be noted until at least 10 years after its use. Because quinacrine is administered in small doses and on only two or three occasions and because the drug is likely to be a weak carcinogen, studying quinacrine's effects without a reliable, long-term follow-up study in a large population would be nearly impossible.

During a long-term follow-up study of 572 Chilean women who underwent quinacrine sterilization, Sokal et al. (unpublished abstract on file at FHI) noted a cluster of cancers. Most worrisome was the occurrence in one quinacrine recipient of a leiomyosarcoma, a rare cancer of the uterus. These results prompted Sokal et al. to conduct a retrospective study of cancers in a larger cohort of quinacrine recipients. Investigators collected data on 1,492 women during 1991-1993. Using data from the Cali, Colombia cancer registry for comparison, investigators found no increase in the expected number of cervical or other genital tract cancers and concluded that the one leiomyosarcoma could be attributed to chance. FHI plans to follow the group for five more years. At the AVSC meeting, one panelist pointed out that Cali, Colombia is known to have an above-average rate of cervical cancer and that use of the Cali cancer registry was therefore inappropriate. The same panel member pointed out that, since virtually all cervical cancers are attributable to infection with the human papilloma virus, quinacrine is unlikely to increase the risk of cervical cancer

No animal models have been used to study the potential carcinogenicity of quinacrine. Meeting participants recommended that researchers conduct a long-term carcinogenicity study in a rodent model that would use the same insertion and dosing schedule as is used for human sterilization and an equivalent mg/kg dosage. They further suggested that researchers follow the animals for the course of one lifetime and investigate sacrificed animals for cancers.

Teratogenicity

In the early 1980s, Blake et al. (13) carried out teratogenicity studies in rats. These studies were small, but indicated that quinacrine was embryolethal in rats. In rats that delivered live, full-term offspring, no increase in malformations was noted in the quinacrine group as comparedwith the control group. Some panelists felt that these studies were invalid because the use of two strains of rats made it difficult to compare data. In a phannacokinetic study using monkeys (10), teratogenicity could not be assessed because too few animals were used, none of the monkeys delivered live offspring, one of the animals died following quinacrine slurry instillation, and one animal had a grossly malformed fetus that was most likely unrelated to the use of quinacrine.

In the Hieu et al. field trial (1), the only abnormal birth noted was an anencephalic offspring conceived 2.5 months after the insertion of quinacrine. Investigators believe this anomaly occurred too long

QUINACRINE MEETING PRESENTATIONS

Moderator

Dr. Allan G. Rosenfield
School ***of Public Health, Columbia University***

Presenters	Subject
Dr. Elton Kessel ***International Federation for Family Health***	Historical background of the quinacrine method of sterilization
Dr. Theodore M. King ***Family Health International***	Human toxicity of quinacrine
Dr. David C. Sokal Family ***Health International***	Quinacrine: long-term safety and efficacy in Chile
Dr. Lisa Rarick, Dr. Alex Jordan U.S. ***Food and Drug Administration***	FDA historical involvement
Dr. Patrick Rowe ***World Health Organization***	WHO historical involvement
Dr. James Shelton U.S. Agency ***for International Development***	International donor perspective on quinacrine
Dr. Cynthia Waszak ***Family Health International***	Retrospective study of quinacrine in Vietnam
Ms. Carol Connell ***Family Health International***	Proposed prospective clinical trial of quinacrine
Dr. Patrick Rowe ***World Health Organization***	International contraceptive technology: how governments make decisions if they do not have regulatory boards
Mr. Hugo Hoogenboom AVSC	Introduction to voluntarism issues
Ms. Deborah Rogow ***Women's health advocate***	International experience with the introduction of new contraceptive technology: the feminist perspective
Ms. Judy Norsigian ***Boston Women's Health Book Collective***	How to develop a dialogue
Dr. Allan G. Rosenfield School ***of Public Health, Columbia University***	Next steps

after exposure to be related to the drug, and, because one other case of anencephaly had occurred in the community, suggested a possible environmental effect.

Recommended Research

Some panelists at the AVSC meeting suggested that additional research must be performed before quinacrine can be considered adequately studied for intrauterine use. Recommendations included:

- A study of the effects of a single per-kilogram human-dose equivalent, administered inttaperitoneally, in rodents and in nonrodent species
- An intraperitoneal repeatdose study in animals
- Formal animal-model pharmacokinetics
- Mutagenicity studies in bacteria and mammalian cells and in vitro and in vivo cytogenic tests

The *FDA* would have to reevaluate the drug for *intrauterine use*

Some panelists suggested additional research More qulnacrine is considered adequate@ studied for intrautetine use

EFFICACY

It is difficult to make a precise determination of the efficacy of quinacrine sterilization based on the available data. Various clinical trials have used one, two, or three insertions and doses of 100 mg, 252 mg, and 324 mg per insertion. In one prehysterectomy study (14), researchers found that a single insertion of 324 mg of quinacrine resulted in more consistent tubal occlusion than did a single insertion of a lower dose. The higher dose also caused more damage to the isthmic portion of the tube than did the lower dose. The presence of intrauterine blood at the time of insertion may decrease efficacy, whereas waiting a longer interval between insertions may increase efficacy One panelist suggested that efficacy may be affected by insertion in the follicular, rather than the luteal, phase. No controlled studies have confirmed these anecdotal reports.

For women who received two doses of quinacrine, Hieu et al. (1) reported failure rates at different study sites of between 0.95 and 4.54 per 100 women after one year Investigators attributed the variations to the different levels of skill of the providers. Long-term efficacy is uncertain because there have been few long-term follow-up studies using the same insertion protocol. In the follow-up study of Chilean women who received three insertions of quinacrine nearly 10 years ago, researchers found that the women had a cumulative pregnancy rate of approximately 8%. For those who received two insertions, the slope of the curve follows that of the three-insertion group after only a five-year follow-up (Sokal D, personal communication).

For quinacrine sterilization, the need for multiple insertion of the drug and the greater possibility of incomplete occlusion of the tubes are cause for greater concern about ectopic pregnancy with this method than with surgical sterilization. Based on the findings of one ectopic pregnancy in 125 pregnancy failures in a study of 1,723 women followed for one year, Kessel et al. (15) estimated the ectopic pregnancy rate for quinacrine to be 0.14 per 1,000 woman years. The ectopic pregnancy rate reported from the Hieu et al. trial (1) was 0.89 per 1,000 woman-years, though this rate is based on a two-insertion protocol with data from only one province. Ectopic rates were found to vary between provinces, and Hieu et al. are conducting further analysis of the data. The ectopic pregnancy rate often quoted for surgical sterilization, based on a mathematical model (16), is estimated to be 0.32 per 1,000 woman-years.

Several panelists commented on the difficulty of assessing ectopic pregnancy rates in rural areas of developing countries. In these areas, the cause of death for women who die as a result of ectopic pregnancy may not be identified or recorded. Conducting follow-ups is especially difficult in long-term studies. One panelist cited a 40% loss to follow-up of IUD users in urban Vietnam. However, Hieu et al. (1) reported that follow-up of women in their study was facilitated by the minimal migration and communal nature of the rural population.

SIDE EFFECTS AND COMPLICATIONS

The side effects noted in several clinical trials (1,6-8) include pelvic pain, vaginal pruritus, headache, dizziness, and amenorrhea. Major complications reported in these studies include bleeding, chronic pelvic pain, perforation, and cervical stenosis. Hieu et al. (1) reported no cases of perforations in 3 1,78 1 quinacrine sterilizations. No study has reported central nervous system toxicity or death related to quinacrine intrauterine pellets.

The number of reported side effects and complications per number of cases was substantially higher in the Chilean studies (6) than in the Vietnamese study (1). Because of this, participants at the AVSC meeting raised the question of whether the protocol for follow-up of cases in Vietnam was different than that used in the prospective trials in Chile. In fact, while the Vietnam study did not have complete reporting for the whole group, the Zipper et al. (6) study had a high rate of follow-up at a single clinic, and all untoward events were noted within a 12-month period from the time of sterilization.

ONGOING RESEARCH

FHI is currently conducting a retrospective study of client perspectives from a sample

QUINACRINE MEETING PARTICIPANTS

Panelists

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AVSC Medical Committee

Ms. Carol Connell
***Family Health** International*

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Dr. Lisa Rarick
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Ms. Deborah Rogow
Women's health advocate

Dr. Allan G. Rosenfield
School *of Public* ***Health, Columbia University***

Dr. Patrick Rowe
World Health Organization

Dr. James Shelton
U.S. Agency ***for International Development***

Dr. Beverly Winikoff
Population council

Invited guests

Dr. Susan Allen
Contraceptive Research and Development Program, Eastern Virginia Medical School

Ms. Claudia Ford
Pathfinder International

Dr. Fernando Hurtado
United Nations Population Fund

Dr. Alex Jordan
U.S. Food and Drug Administration

Mr. Michael Klitsch
Alan Guttmacher Institute

Dr. Jack Lippes
Department ***of Obstetrics and Gynecology, State University of New York-Buffalo***

Ms. Carolyn Makinson
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Ms. April Taylor
Boston Women's Health Book Collective

Dr. Cynthia Waszak
Family Health International

FHI is currently conducting a retrospective study of client perspectives

of 1,800 women in Vietnam who had quinacrine insertion between 1989 and 1993. Local school teachers will conduct face-to-face interviews to collect information on how women decided to accept quinacrine, the quality of care they received, and their views on the acceptability of the method. FHI will also analyze clinical data collected for the Hieu et al. study (1) more extensively and will follow up women from the Sokal et al. Chilean cohort study for another five years. In addition, FHI is planning a prospective clinical trial using two insertions of 252 mg of quinacrine. In this study, tubal occlusion following quinacrine insertion will be verified through use of hysterosalpingography (HSG). Some panelists at the AVSC meet-

ing raised concerns about using HSG because of the potential for reopening previously occluded tubes. The FHI investigators noted this concern for consideration during finalization of the **protocol.**†

†*Authors* Note: AVSC received the following written communication from D. Sokal of FHI in February 1994:

After the December 1993 experts meeting, FHI began its retrospective study in Vietnam. FHI's prospective study of quinacrine in Vietnam has been postponed because the govemment of Vietnam decided to suspend the use of quinacrine. FHI plans to host a panel of toxicology experts in early or mid-1994 inordertoassessquinacrine from toxicologic and regulatory perspectives.

FREE AND INFORMED CHOICE

While there has been increased attention to the problem of ensuring free and informed choice for clients of family planning services, most experts would agree that much remains to be done in this regard. The use of quinacrine pellets for female sterilization raises a number of questions about informed choice. First, to meet the standards of informed choice, women who choose quinacrine sterilization must make the choice from among a reasonable array of other methods, including temporary methods. The choice of quinacrine must be based on a full understanding of the method, including its characteristics, actions, and possible risks. This raises a particular issue for quinacrine, since many experts believe it is an investigational method. Because of this, providers and counselors would first have to tell women that the method is investigational and then discuss the drug's risks and benefits. Participants at the AVSC meeting suggested that it is important to inform women about the risk of ectopic pregnancy and the lack of conclusive information about other possible risks, such as toxicity and carcinogenicity.

Some meeting participants seriously questioned whether it is appropriate to offer a method like quinacrine in large clinical trials when the World Health Organization and the FDA have both stated that additional studies of the drug need to be done. Given the lack of answers to certain research questions, panelists expressed concern about the routine, widespread use of quinacrine in some service-delivery settings. Other participants emphasized that authorities in each locality must make their own risk-benefit assessment and noted that, while international agencies can advise, they should not impose their opinions on local authorities.

Participants noted that the following practices and situations tend to compromise informed choice:

- Incentives for providers, recruiters, or clients
- Quantitative targets for family planning Programs
- The absence of reasonable choice among contraceptive methods (the combination of one hormonal, one barrier, and one permanent method were suggested as a minimumstandard)
- Provider bias for or against methods, based on the providers personal beliefs, government-established targets, or reimbursements to providers for particular procedures

When any of these conditions prevail, clients may not receive full and accurate information about each contraceptive method and may be less likely to know about the investigational nature of a method.

Assuring free and informed choice is especially important when offering methods that are either permanent or investigational, and many consider quinacrine sterilization to be both. Several meeting participants were apprehensive that enthusiasm for quinacxine has been high in countries that have a history of problems regarding free and informed choice. The underlying concern with a relatively simple and inexpensive procedure such as intrauterine quinacrine is that women might be sterilized without having given informed consent.

Participants cited specific examples of cases in which free and informed choice has been compromised in countries in which quinacrine has been introduced. For example, at each visit, quinacrine users in Vietnam are paid US **$3.00—the** equivalent of a weeks salary for a doctor. The govemment program considers this payment to be "travel and time compensation."‡ **A** meeting participant also noted that the informed consent forms in Indonesia and India do not indicate the investigational nature of the drug or the possibility of **failure.**§

‡It was reported after the meeting that surgical sterilization clients in Vietnam also receive payment for undergoing the procedure.

§A copy of an Indonesian consent form was reviewed after the meeting; in contrasttothecommentmade at the meeting, the form discusses the risk of failure, and the investigational nature of the drug is disclosed to the client In India, over 10,000 women have received quinacrine through a program supported and funded by an individual provider and not approved by the Indian Council on Medical Research.

Although a major goal underlying the development of new contraceptive methods is to increase choice, in practice the introduction of a new method does not necessarily lead to greater choice. Overstretched programs often simply substitute new methods for current ones, and there is a

trend in some countries to favor provider-dependent, long-acting methods. A woman may not be given the choice of chemical or surgical sterilization, but might be offered only quinacrine.

Several meeting participants emphasized that a number of conditions must be met in order for increased choice to be realized when a new method is introduced:

- The new technology must have passed standard safety and toxicology testing in animal and human trials.
- The new technology must complement the existing method mix and fill a real need in the particular country
- Mechanisms to protect free and informed choice must be in place, with special safeguards for provider-controlled and permanent methods.
- Quality of care in the country must be adequate for safe and appropriate delivery of the method.
- Method introduction must include a careful and open evaluation phase that precedes widespread provision of the method.

The responsibility for assessing whether these conditions have been met must rest with national regulatory committees or the equivalent? These bodies should seek input from a wide range of disciplines and constituencies involved in family planning. Researchers should conduct acceptability studies that assess the methods women choose, why they choose them, and their satisfaction with chosen methods.

In light of the conditions described above, several panelists were concerned about the use of quinacrine in prospective clinical trials and in service-delivery sites. Because of limited data on the drug's efficacy, many were concerned that quinacrine may, in fact, be no more effective than some long-acting temporary methods. If this proves to be true, these panelists believe that intrauterine quinacrine should not be considered an effective permanent method.

In addition, because of the drug's action as a sclerosing agent and because it is applied to the tubal ostia at the cornua, reversal of the damage caused by quinacrine appears to be very difficult. The risk of regret following sterilization in many low-resource settings where infant and childhood mortality rates are high has caused concern in recent years. After aggressive introduction of sterilization, some countries in Asia established nationally supported microsurgical reversal programs. These programs encouraged young women of lower than typical parity to limit family size without regard to the potential risk of child loss due to high child mortality.

MATERNAL MORTALITY

One panelist pointed out that because of high maternal mortality, the use of methods without regulatory approval in a developing country is warranted in order to save lives.

Other experts presented two arguments against this position. First, maternal mortality is not necessarily lowered by sterilization: many pregnancies that lead to maternal death are intentional pregnancies. Second, other contraceptive methods that have better safety data and are known to be at least as effective as quinacrine sterilization are available and could be made mom readily available.

UNMET NEED

There is certainly a need for increased access to sterilization in many countries. The availability of an inexpensive and nonsurgical method like quinacrine could dramatically increase programs capacity to meet this need. However, one panelist pointed out that not all women who state that they have completed their families (called "limiters") desire sterilization; therefore estimates of unmet need for sterilization drawn directly from data about limiters may overstate the demand.

SERVICE DELIVERY

Quinacrine appears to require less technical expertise than surgical sterilization, which still presents clinical challenges in many settings. However, the insertion of intrauterine quinacrine also requires technical competence. In the Hieu et al. study (1), method effectiveness varied widely

Women who choose quinacrine *sterilization must make the choice from among a reasonable array of other methods*

There are no written international guidelines that describe a standard regulatory process for the introduction of a new drug or for the use of a new drug. For the most part, new contraceptive methods are thoroughly investigated before they are used in national programs. These investigations are supported and conducted by academic institutions, foundations, or committed individuals. In general, the results of investigational studies of a new drug are submitted to regulatory review boards before human trials are conducted and then again before introduction into national service-delivery programs. Most governments establish a national scientific committee and, by controlling commodity provision in the public sector, regulate introduction of new drugs and technology.

Researchers should conduct acceptability studies that assess the methods women choose, why they choose them, and their satisfaction with chosen methods

among individual providers according to skill. Morbidity may also vary depending upon the skills of individual providers (for instance, the ability to maintain a clean field or to sound the uterus).

Criteria for site selection for the intro duction of quinacrine must be established. Only limited conclusions may be drawn fi-om introductory trials in "best-case settings." New methods should not be introduced on a broad scale without first reflecting on the information gleaned from careful study.

In addition to ensuring technical competence, programs must provide follow-up since quinacrine provision requires repeat insertions. Other servicedelivery components of quality, such as choice, information, and client-provider relations, have been discussed above.

A "PAUSE" IN THE INTRODUCTORY PROCESS

Several panelists recommended that practitioners in the field at large consider a pause in the introductory process--a chance to stop, stand back, and reflect on quinacrine, its use, and introduction. This period of reflection would allow time to conduct additional research and to involve diverse constituencies, including consumers, in the dialogue. Such openness would help to build trust among family planning programs, women's organizations, and clients that could lead to improved services.

National recommendations regarding the use of intrauterine quinacrine should take into account the current ongoing use and, in that context, the implications for programs already dependent upon this method. For example, the Indian Council of Medical Research has approved toxicology testing that would run parallel to small dose-finding studies in human trials.

CONCLUSION

To withdraw or to rush forward would be a mistake

Quinacrine has been under investigation for use as a method of female sterilization since the 1960s. During the past 25 years, investigators funded primarily by private individuals and foundations have produced limited scientific data to support the drug's efficacy or safety for tubal sterilization. Quinacrine's widespread use in some countries and the *Lancet's* publication of the Hieu et al. study (1) have led the scientific community to focus more closely on this drug.

A Dilemma for the Family Planning and Women's Rights Communities

The family planning and women's rights communities are left with a dilemma. If quinacrine is, in fact, as safe and effective as other accepted methods of family planning (that is, if it does not result in troubling rates of failure and ectopic pregnancy, and if it does not have serious short- or long-term effects), then it is a truly remarkable method that could break down technical barriers to the provision of sterilization services. If quinacrine is unsafe or not adequately effective, it should not be introduced for use.

Many participants at the meeting felt that the cart has come before the horse in the case of quinacrine. Despite previously voiced concerns over insufficient data, intrauterine quinacrine is already being used in some countries. Furthermore, the drug is inexpensive and easy to use. These facts make it unlikely that quinacrine will be withdrawn completely, despite the lack of scientific evidence to support its long-term safety and efficacy. If the scientific community fails to conduct the needed studies, it may take another 20 years to confirm safety or identify real problems resulting from the drugs widespread use. It is crucial that adequate funding be made available for this effort in order to rapidly obtain a better assessment of quinacrine's long-term safety We run the risk of a major setback if we do not carry out research to assess the safety and efficacy of quinacrine. If the method is introduced without the standards and guidelines customarily developed for contraceptives now in use, the potential for misuse is considerable. When introduction of a method is poorly orchestrated, there is a risk of losing the use of the method altogether.

To withdraw or to rush forward would be a mistake. Social and biomedical scientists must work together to design comprehensive and ethical studies that progressively fill the gaps in our knowledge of

quinacrine. In this way, quinacrine can be fairly evaluated and will have the best prospects for a successful introduction.

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