

Large quinacrine study comes under fire from family planners

A study published in the British medical journal *Lancet* that was supposed to draw attention to the chemical sterilizing agent quinacrine did just that, but not necessarily in the way the authors had hoped.

The large study, carried out among 31,781 Vietnamese women, could have put minds at ease about the chemical that has been used in 13 countries for nonsurgical female sterilization, but instead it provoked lively debate over safety and efficacy issues still to be resolved.

Those issues include high failure rates, ectopic pregnancies, insufficient follow-up, and inadequate recording of findings in the study.

Several months after the Vietnamese study was released, the Association for Voluntary Surgical Contraception (AVSC) in New York City released a technical statement about the use of quinacrine pellets for nonsurgical female sterilization, charging that the safety and efficacy of the drug have yet to be proved and that the study itself was flawed.

The study's authors and other quinacrine supporters have since tried to clarify and defend the method in letters to the editor of the *Lancet*² and in a memorandum to a technical statement issued by an American family planning organization. *Contraceptive Technology Update* has obtained copies of the letters, the technical statement, and the memorandum for this special report.

Overall, the chief problem with quinacrine is that it hasn't gone through an acceptable and thorough regulatory review process, says **Amy E. Pollack**, MD, MPH, AVSC's medical director. That process would include review of existing toxicology studies and recommendations for studies needed to determine long-term safety and efficacy studies, she tells CTU.

'Visionary and exciting potential method

Because quinacrine has a long and safe history for other medical uses, some family planners believe there are no reasons not to introduce the chemical into service-delivery programs as an alternative to surgical sterilization, which can be too expensive and even life-threatening in some locations where adequate health care is not

available. But by taking such a premature step, those providers may be jeopardizing a contraceptive method that women all over the world might eventually want, Pollack says.

"It was [prematurely] introduced into a service-delivery setting because it is inexpensive and easy to administer," she says. "Those are the things that make it a truly visionary and exciting potential method, but they are also the things that have allowed it to be introduced into service delivery without having to go through the normal regulatory and review systems."

In a memorandum to the AVSC document, long-time quinacrine researcher **Elton Kessel**, MD, secretary general of the International Federation for Family Health (IFFH) in Carlton, OR, states that different family planning settings have different needs.

"It is not the role of American organizations to decide whether the quinacrine pellet method of nonsurgical female sterilization is to be studied or used in service programs in other countries," Kessel writes. "This decision needs to be made by local and national political units based on their own risk/benefit assessments."

In Vietnam, where the population is 70 million and growing at 2.2% per year, and where 6.2 million women want no more children, a simple, nonsurgical, inexpensive method was deemed highly desirable.'

The Vietnamese study is actually a cumulative accounting of smaller studies carried out in 24 of the country's provinces from January 1989 until October 1992. The majority of the 31,781 women received two doses of quinacrine a month apart during the proliferative phase of their menstrual cycle. Here are some of the study's findings based on just 11,686 of total women studied:

- There were 818 pregnancies (80 carried to term).
- One-year pregnancy rates were 2.63/100 among 9,461 women receiving two doses and 5.15/100 among 2,225 women receiving only one dose.
- There were no deaths and only eight serious complications.
- There were 19 ectopic pregnancies reported.
- Side effects (mostly abdominal pain, vaginal itching, and headache) were minor and of short duration.
- There was one birth defect (anencephaly), which the study's authors did not believe was

related to the quinacrine.

Failure rates are based only on a subset of 11,686 women, and this has caused significant clamor among scientists. They contend that the authors extrapolate their findings to the group as a whole, which can easily lead to bias in the study. Additionally, ectopic pregnancy rates also were calculated from only one Vietnamese province.

These discrepancies cast a doubt on the entire data-collection process, says **Irvin Sivin, MA**, senior scientist and a statistician at the center for biomedical research of the Population Council in New York City. Sivin expressed his concerns in a letter to the *Lancet*; the study's authors responded by saying that the data "are not meant to represent the total data set but are, rather, illustrative of a great variation in failure rates by study."

Experience and skill not related

The six authors, who are Ministry of Health government officials based in Hanoi and in several of the provinces taking part in the study, contend that the failure rates found in this study could actually be much lower if the skill of the inserting clinician could be improved. Some clinicians had no failures, while some had failures as high as 17.2%. Although the highest failure rate (17.2%) came from clinicians who had performed 10 or fewer quinacrine insertions, and the lowest rates came from those who had performed more than 100 (5.3% failure rate), the authors say that it is skill and not experience that dictates the failure of the quinacrine method. They define skill as "consistent application of proper insertion technique."

"When we looked at that data, much to our amazement, the failures continued no matter how large the series of women," says **Stephen D. Mumford, DrPH**, president of the nonprofit Center for Research on Population and Security in Research Triangle Park, NC. "This suggests that the clinician is not consistently doing the procedure correctly. We don't know exactly why not just yet. The whole thing came as a big surprise to us."

Mumford worked with the Vietnamese researchers during the study and stays abreast of their continued progress on this subject. The assumption that experience leads to skill simply does not pan out in this situation, he says. Experienced providers could be using poor techniques, and because they don't realize that,

they could continue to have method failures, he explains.

Failures among some providers could possibly be related to patient selection, he says. Women with any blood present in the uterus should be asked to come back at another time, because blood interferes with the action of quinacrine, he explains. Likewise, if a clinician causes bleeding in the uterus during the insertion, that could make the method fail, Mumford adds. Another factor related to skill and not experience is the placement of the pellets. All seven pellets of each application need to be placed at the fundus rather than anywhere else in the uterus, he says.

'Failures are failures'

The unfortunate reality is, failures are failures, says **Gary K. Stewart, MD**, who carries out a great deal of international family planning work and is the medical director of the Planned Parenthood Association of Sacramento (CA) Valley.

"You can do everything in the world to reduce failures, which would be training, patient selection, etc., etc., but there are failures and there will be failures; the question is how many," Stewart points out. "We really don't know that."

It's a mistake to blame the provider for a method failure, says **Judy Norsigian** of the Boston Women's Health Book Collective. Rather, blame technology that isn't quite as good as it could be, she says.

"If [a failure] is likely to happen because your training isn't stellar or because you don't listen, it's not a good technique," Norsigian says. "Good technology is one that doesn't leave so much room for error and that doesn't require impeccable training all the time to be used with reasonable efficacy. Let's not blame individuals because they didn't follow directions or because they weren't trained well enough."

Norsigian says high failure rates — with any method of birth control — means that particular approach is probably not as good as needed.

But not all family planners agree. Time and energy should be spent on determining what could make the quinacrine pellet method more acceptable, says Pouri Bhiwandi, MD, MPH, former medical director of Family Health International (FHI) in Research Triangle Park, NC, and now a gynecologist in private practice in Raleigh, NC.

“With all other methods that we have started with initially, like the crude IUDs with high failure rates, as the years go by and you work on those methods, and go back to the drawing board making improvements, you can bring those failure rates down,” Bhiwandi says. “But this method has never been given a chance.”

What about ectopic pregnancies?

Similar to the way the failure rates were presented, Sivin tells CTU he was “flabbergasted” that ectopic pregnancy rates were taken only from one province, and he expressed this in his letter to the *Lancet*. The authors contend that it was the largest province studied — more than 4,500 women were enrolled — and the women were followed long enough to elicit the most meaningful data.

The Vietnamese province in question was the Namha province, where the incidence of ectopic pregnancy was 0.89 per 1,000 woman-years of use. Placing the length of time each study participant used a method end-to-end provides what statisticians call “woman-years” of use.

In comparison, in the United States, researchers at the federal Centers for Disease Control and Prevention in Atlanta have found that the rate of ectopic pregnancy among American women not using contraception is 2.6 per 1,000 woman-years of use, and 0.32 after surgical sterilization.³

The authors replied that they are currently preparing a report that will detail ectopic pregnancies by province. Once the new analysis of ectopic pregnancy rates are published, it will be evident that quinacrine doesn't cause ectopic pregnancies, says Mumford.

With the inconsistencies of the Vietnamese study (for example, there was no standard protocol followed by all providers), the ectopic pregnancy rate calculated from one province still may not be conclusive enough, says Pollack. Also, since the environment is so rural and accurate information is difficult to process, she is not convinced that anyone will know with certainty whether a woman died of an ectopic pregnancy, she says.

Free and informed choice

Although the Vietnamese government seems eager to understand and comply with an international code of ethics, most of the population is

scattered throughout the country's provinces, areas where national standards aren't always followed, says Pollack.

Because Vietnam historically has had an aggressive government population control program, officials at AVSC and other family planners have raised the specter of potential forced participation in the quinacrine method.

Past abuses at the hands of demographically driven family planners make the concern a necessity for all women in the developing world. There is even evidence that a Vietnamese woman was secretly inserted with quinacrine while visiting her doctor for a routine exam, according to a report attributed to the May 1993 issue of a Vietnamese publication, *The Women*.

In the memorandum to the AVSC document, Kessel states that “fear of coercion is not a legitimate reason to reject the quinacrine pellet method. Excellent counseling is needed for all family planning methods and especially for all permanent methods.”

Additionally, he tells CTU, “coercion is related to the program of delivery of the method. I don't buy that coercion is a product of the method and not the program.”

Still, the potential for women's rights abuses is there, Pollack insists. She says that prospective quinacrine studies and service use should be put on hold so that researchers can more clearly determine what studies are needed to show the method is safe and effective.

“I am talking about taking a pause, looking at what we have, not jumping forward so enthusiastically with the method,” she says. “Because if we move too quickly, we could kill the method. We must study this properly or we may lose an invaluable method.”

References

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