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Ultrasound male contraceptive, overlooked for decades, confirmed to work

Peer-Reviewed Publication

MALE CONTRACEPTION INFORMATION PROJECT

Imagine a contraceptive that could, with one or two painless 15-minute non-surgical treatments, provide months of protection from pregnancy. And imagine that the equipment needed were already in physical therapists' offices around the world.

Sound too good to be true? For years, scientists thought so too. But new research headed by Dr. James Tsuruta in the Department of Pediatrics at the University of North Carolina-Chapel Hill, published Monday in the journal *Reproductive Biology and Endocrinology*, is gaining the contraceptive method increased respect. The kicker: This treatment would be for men—giving them the first new option since condoms and vasectomy were introduced more than a century ago.

HOW IT WORKS

The testes need to be slightly cooler than the rest of the body to properly produce sperm—the subject of countless jokes and warnings about hot tubs, laptops, and tight pants. But although hot tub or laptop use can push a man's sperm count over the edge if he's already low, it's not reliable enough for contraception. What if this heat effect could be enhanced?

That's where ultrasound comes in. Relatively inexpensive and already in use in physical therapists' offices around the world, therapeutic ultrasound (as opposed to diagnostic ultrasound) heats deeply and increases circulation to injured joints. The physical therapist applies lubricating gel to the joint, turns on the machine, and runs the wand back and forth over the joint for 5 or 10 minutes, creating a pleasant warming sensation.

It turns out, though, that ultrasound can be used on other body parts as well. That includes the testes, and it would be for contraception rather than healing. In the current study, researchers got more than 2 1/2 months—and possibly long-lasting—contraception in rats with two 15-minute sessions of ultrasound, two days apart. And their study is the first to provide detailed insight into how ultrasound might be working, using modern equipment. But the published evidence that it works has been in plain sight for more than 35 years—not taken seriously until recently.

OVERLOOKED FOR DECADES

Dr. Mostafa Fahim of the University of Missouri, Columbia was the first to try therapeutic ultrasound for contraception. He and his team showed effect in rats, cats, dogs, monkeys, and even 8 men, publishing journal reports and book chapters in 1975-1982 and patents in 1977 and 1978. But it seemed too strange to be true. Were those effects really reproducible? Other researchers were suspicious enough that a site visit team was even sent to his lab.



IMAGE: THIS IS THE METTLER SONICATOR, THE ULTRASOUND UNIT CURRENTLY USED IN RAT STUDIES. TWO APPLICATIONS TO THE TESTES 48 HOURS APART PRODUCED LONG-LASTING CONTRACEPTION. [view more >](#)

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Then in 1988 a more respected researcher, Ronald L. Urry of the University of Rochester, dealt what seemed like the death blow for ultrasound as contraception. In trying to repeat Dr. Fahim's experiments, he showed no significant effect on sperm production. Even when he turned it up so high that he saw burns, he still saw little to no effect.

Ultrasound was down, but not out. In the meantime, heat's impact on fertility was becoming more accepted. A landmark review article on the subject was co-authored by noted University of California, Los Angeles researcher Dr. Ronald Swerdloff, and a growing literature on occupational heat's impact on workers (such as welders) was emerging.

And one nonprofit organization continued to be intrigued. The Male Contraception Information Project pointed out that upon careful reading, several of Dr. Urry's techniques clearly differed from Dr. Fahim's earlier work. For example, Dr. Urry exposed the animal's whole tail end, not just the testes, to ultrasound. Not surprisingly, he could not find a power level that was effective without burning the bony, delicate tail structure!

"Nobody really took Dr. Fahim seriously. But it just seemed like too much data to be made up," explains Elaine Lissner, director of the Male Contraception Information Project (MCIP). "By the time I met him, he was pretty bitter about the whole thing, which didn't help."

The information on ultrasound languished for decades, available on MCIP's website but not pursued scientifically. During those decades, it became clear that many men were desperate for new options, with two advocacy sites springing up and thousands of men signing petitions for new methods at MaleContraceptives.org. Men in couples saw their partners suffering with female contraceptives and wanted to relieve them of burden; single men wanted a backup to condoms in a world of paternity tests and child support.

A NEW LOOK

Ultrasound's fortunes finally started to change in 2006, when the Parsemus Foundation, a small funder with roots in the male contraceptive advocacy movement, decided it was time to give ultrasound one more chance to prove itself. The newly formed foundation approached Dr. David Sokal of Family Health International (now called FHI360), known for his open mind and his knowledge of male methods. Dr. Sokal recruited James Tsuruta (UNC-Chapel Hill) and team, experts in evaluating sperm, to join the effort. Since Dr. Fahim had passed away in 1995, they even consulted with Dr. Fahim's only living colleague, Dr. Min Wang of the University of Missouri, to make sure nothing was missed. "There wasn't any more money where this came from," explains Lissner. "If this team of top-notch researchers couldn't pull it off, it would be ultrasound's last chance."

Things looked dicey at first. As Dr. Tsuruta explains, "The original ultrasound conditions from Dr. Fahim (1 MHz, 1 W/cm², 10 minutes) that were reported to eliminate essentially all germ cells did not come close to achieving his reported result" in the first attempts. "The process of treating rat testes with ultrasound involves more variables than I imagined at the start of these studies."

Yet with persistence, the team finally found a combination that worked. The best results came from undergoing two sessions, each consisting of 15 minutes of ultrasound, two days apart. During the sessions, the testes were placed in a cup of saline to provide conduction between the ultrasound transducer and skin.

The researchers were not able to continue their study for long enough to see when, or whether, fertility would return. But they knew it was effective: microscopic examination showed dramatic changes after just two weeks. Normally, testes are full of many layers of cells developing into sperm, but now the tubes of the testis were almost empty. "Sperm production is very robust; this ensures the survival of a species. It's really difficult to find a way to turn off the production of sperm, but ultrasound seems to do the trick," Dr. Tsuruta continues. "There is something special about heating with ultrasound—it caused 10-times lower sperm counts than just applying heat."

CONFIRMED IN OTHER SPECIES

Encouraged by the preliminary results in rats, the foundation commissioned a small study in monkeys: the closest species to human. These researchers, working at the University of California-Davis, also had a tough time getting the ultrasound treatment to work. They tried many variations and did eventually get a shorter period of effect (six weeks) with a longer treatment (three 30-minute sessions two days apart). "We were pretty discouraged at first," says Dr. Catherine VandeVoort, lead researcher. "The monkeys didn't seem to mind the treatment a bit, but we were having a rough time of it. Thirty minutes of treatment three times a week is a lot of monkey testicular massage. We felt pretty silly, and it didn't help when the techs would come around and wonder what kind of research we were doing! We were relieved when we finally saw an effect."

Unbeknownst to either team, another researcher halfway around the world had also gotten intrigued. "A friend of mine works at an ultrasound company in Germany and had asked me whether I could think of any additional applications for ultrasound," says Dr. Raffaella Leoci, a veterinary researcher at the University of Bari in Italy. "I started poking around and found Dr. Fahim's publications. I was particularly intrigued by his mention that with two or more applications two days apart, permanent sterilization could be done. We have a big problem with stray dogs here; if it really worked, that might be a more humane and affordable way to sterilize them than surgery." She found the permanent effect she was hoping for, with Monday-Wednesday-Friday treatments of five minutes each, and published "Ultrasound as a Mechanical Method for Male Dog Contraception" in 2009.

Dr. Ted Tollner, a member of the UC-Davis team, points out that their struggles to show effect turn out to have a silver lining. "As luck has it, we're the only ones who can show that ultrasound can be reversible. The UNC team's rat study has the numbers, and they have beautiful histology data showing what's going on inside the testes. The Italian team was first to publish and showed ultrasound could be very effective in a large animal, not just rats. Together with our results showing the possibility of reversibility along with effectiveness in the closest animal to humans, it makes a pretty compelling package."

ALTERNATIVE TO VASECTOMY?

With permanent effect from three treatments in dogs and researchers not sure whether their rats would have gained fertility, ultrasound is beginning to look like a better permanent contraceptive than temporary one. But permanent contraception might not be such a bad thing. "I think one of the highest priorities in the area of new contraceptive development is nonsurgical sterilization, for men and for women," explains Jeff Spieler, Senior Technical Advisor for Science and Technology Office of Population and Reproductive Health Bureau for Global Health at the U.S. Agency for International Development. The agency works, among other priorities, to develop safe, effective and acceptable family planning methods to prevent unintended pregnancies, reduce maternal mortality and prevent the resort to abortion. "About 25% of couples worldwide rely on sterilization as their method, and I believe many more would choose permanent methods of contraception if they were nonsurgical. Of course, such methods would have to be easy to perform, including by non-physicians, highly acceptable and safe."

LIMITATIONS AND OPTIONS

He sees a limitation for ultrasound as a nonsurgical alternative to vasectomy, though, if it requires two visits. "Two visits is a concern. Ideally a method should be highly effective after one visit, because many people may not come back for the second treatment."

Two competing areas of research could get around the problem. They include RISUG(TM) long-acting vas deferens gel, which has been effective for more than a decade in studies in India ((now being modified and developed as Vasalgel(TM) for use outside India)), and a high-tech laser vasectomy—using light to seal off the vas deferens sperm

tube without cutting the skin—showing promise in early studies at the University of North Carolina at Charlotte.

All three alternative methods are worth pursuing, says Lissner of the Male Contraception Information Project. "RISUG is far more advanced, but ultrasound and the laser vasectomy are the only ones that are completely nonsurgical. We try to keep in mind the concept of a 'contraceptive supermarket'—the more options there are, the more likely there is to be something that's right for everybody."

COMPLIMENTS AND CAUTION

"This is an interesting development in a challenging indication," says regulatory consultant Gary Gamerman of Seraphim Life Sciences. Though much remains to be done, there's nothing inherent to the method that would make ultrasound dead in the water from a regulatory standpoint. "The only concern is proof of safety and durability of response. As long as it prevents fertile sperm, is overall safe and doesn't cause secondary safety or adverse sexual effects, there wouldn't necessarily be anything that would hold it back. You just have to do the studies."

But he seconds the concern over ultrasound use as a temporary contraceptive, rather than permanent sterilization. Unless they had sperm tests performed, couples would have no way of knowing when they became fertile as the method wore off. The method would have to be long-acting, or highly consistent from man to man, to get around this.

"Permanent is good, or it could be semi-permanent, or 12 months or longer. But two or three months is a bit short to ask people to come back for treatment, especially in the developing world," explains Gamerman.

And there's one more concern about a method that wears off over time: the quality of the first sperm that return. "I am convinced that any procedure which leads to subfertility in males is likely to have effects on embryo development," explains Dr. Brian Setchell of the University of Adelaide, a pioneer in examining heat and environmental effects on sperm. "The effects are not only after heat. Sperm from obese males produce embryos that develop more slowly, and there is evidence for diabetes, various toxins and therapeutic agents having the same effects in males." These are all reasons for caution about short-term, rather than permanent, use. Dr. Tsuruta agrees: "Safety and efficacy are paramount. Studies in the rat are an excellent way to validate these methods without risk to humans."

EARLY ADOPTERS

But some men aren't waiting for the results of years of studies. They have a scientific background—they know enough scientific jargon to read the papers and understand exactly what the risks are—and are willing to take a chance.

In a long-term relationship and looking for an option other than condoms or vasectomy, Dr. Chris Jenks decided to give heat methods a try. Other men have tried heat methods and even posted their results to the online discussion group at the MaleContraceptives.org advocacy website. But with his chemistry background and skills with a microscope, Dr. Jenks decided to go one step further: he documented every sperm count and posted it on his website PuzzlePiece.org.

With a simple modification to his underwear (known as artificial cryptorchidism or the "suspensory method"), Dr. Jenks was able to keep his testes closer to his body, too warm to properly produce sperm. Reassuringly, in one- to two-year tests in France in the 1980's and 1990's the method had been both effective and reversible. Sure enough, within a month his sperm count dropped below the fertility cutoff. The method worked well—so well that he continued using it for nearly 12 years, giving his partner a 12-year break from pills and producing the first long-term data on the effect of heat.

But Dr. Jenks knew that being a pioneer, there might be surprises. In 2010 he discontinued the heating, wondering how his system was doing. By two months later the sperm numbers seemed to be climbing back up, and he thought he was regaining fertility as in the 2-year studies. But there was a catch: even a year later, most of the sperm were not

swimming.

"Of course, my lack of return to fertility could have something to do with using the method for over 10 years," says Jenks. "And it isn't a problem for me, since we aren't trying to have a child. But it's something to know about. It's best to be really clear about the possible outcomes, and that you're okay with them, before trying something like this."

One man has even tried ultrasound; but without publications that list the best settings, he was not able to get it to work on the first try. Ryan, 34, of New Jersey, bought an ultrasound machine on eBay and posted his results to the online discussion group. "Honestly, I'd rather be able to have the ability to control my own fertility rather than permanently shut it off," he explains. "But I had no way to test that the machine was working right. Due to bills at the time, I couldn't afford to throw more money into testing ultrasound... whereas I found out my insurance covers vasectomies. I feel I've waited long enough."

A NEW LEAD TO FOLLOW?

Ultrasound's future is uncertain. The 2010 Bill & Melinda Gates Foundation Grand Challenges Explorations grant that the UNC team won to complete their current study has run out, and Parsemus Foundation (the small funder that supported the preliminary tests) had only enough funds to support the proof of principle work. "We're very grateful to have received the Grand Challenges grant and be able to show that it actually works," says Tsuruta. "The quickest path to eliminating unwanted or mistimed pregnancies has men and women sharing responsibility together for family planning... and it might take new male methods for this to happen regularly."

With men looking for options, ultrasound's new credibility may have arrived at the right moment. "There are a lot of 'me too' contraceptives being introduced—pills with iron, pills with a few more days of estrogen, pill hormones in ring or patch form—but not a lot that is truly new," concludes Lissner. "This isn't as far along as RISUG; but it would be the first truly new male contraceptive in over a century, and would be one of the only contraceptive leads out there that has so few access issues, being based on equipment already in medical offices all over the world. We think it's worth giving it a chance."

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Press resources and help for journalists writing about male contraceptive development are available from the nonprofit Male Contraception Information Project: <http://www.NewMaleContraception.org> .

Read the release from BioMed Central, *Reproductive Biology and Endocrinology*: http://www.eurekalert.org/pub_releases/2012-01/bc-ss012712.php

To read more about ultrasound, see <http://www.newmalecontraception.org/usound.htm> .

ABOUT THE UNIVERSITY OF NORTH CAROLINA TEAM AND GRAND CHALLENGES EXPLORATIONS

Read the full UNC press release of grant award here: UNC researchers receive \$100,000 Grand Challenges Explorations Grant to develop male contraceptive http://www.eurekalert.org/pub_releases/2010-05/uonc-urr051010.php

ABOUT THE MALE CONTRACEPTION INFORMATION PROJECT

The Male Contraception Information Project is entirely nonprofit and works in three areas:

- raising public awareness of promising nonhormonal male contraceptives
- advocating increased and expedited government research
- serving as a resource for journalists who wish to write about the subject

Website: <http://www.NewMaleContraception.org> (or <http://www.mcip.info>) San Francisco, California

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