

Could a birth control pill for men be on the horizon?

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Researchers at Columbia University Medical Center are honing in on the development of what may be the first non-steroidal, oral contraceptive for men. Tests of low doses of a compound that interferes with retinoic acid receptors (RARs), whose ligands are metabolites of dietary vitamin A, showed that it caused sterility in male mice.

Earlier results of the experiments using this RAR antagonist were published in the June 1st issue of *Endocrinology*.

The researchers found that low doses of the drug stopped sperm production with no apparent side effects. And crucial for a contraceptive, normal fertility was restored soon after drug administration was terminated.

Earlier research had led the investigators to the discovery that manipulating the retinoid receptor pathway could interfere with the process of spermatogenesis, which is necessary for sperm production.

Scientists have known for almost 100 years that depriving an animal of dietary vitamin A causes male sterility. While investigating targeted loss of function of the gene encoding one of the RARs, RARalpha, which results in [male infertility](#), senior author Debra J. Wolgemuth, Ph.D., ran across a paper by Bristol-Myers Squibb on a compound that was being tested for the treatment of skin and [inflammatory diseases](#). The compound seemed to cause changes in the testis similar to the mutation that she and Dr. Chung were studying in Dr. Wolgemuth's lab.

Dr. Wolgemuth is professor of genetics and development and of obstetrics and gynecology; and Dr. Chung is an associate research scientist, both at Columbia University Medical Center.

Bristol-Myers dropped its interest when it found that the compound also was - in the company's words - "a testicular toxin." The paper did not elaborate on how the drug caused infertility, so Dr. Wolgemuth and her team tested the drug in mice to find out; they noted that the changes it caused were similar to what one sees with vitamin A-deficiency and loss of function of RARalpha.

"We were intrigued," said Dr. Wolgemuth. "One company's toxin may be another person's contraceptive."

To investigate whether the compound prevented conception at even lower levels than those cited in the company's study, Dr. Wolgemuth and her team placed the treated male mice with females and found that reversible male sterility occurred with doses as low as 1.0mg/kg of body weight for a 4-week dosing period.

One advantage of using a non-steroidal approach, the researchers say, is avoiding the side effects commonly associated with steroidal hormone-based methods.

Male steroid-based options have been plagued with adverse effects, including ethnic variability in efficacy, as well as an increased risk of cardiovascular disease and benign prostatic hyperplasia.

Another side effect of hormonal options for men has been diminished libido. That drawback will also likely be avoided if a method involving manipulation of the retinoid receptor pathway proves successful.

"We have seen no side effects, so far, and our mice have been mating

quite happily," said Dr. Wolgemuth.

The researchers say the drug will not affect vision. Although dietary vitamin A is responsible for the production of light-sensitive receptors in the eye, it does not use the RARs in this process.

"An additional benefit of our compound is that it can be taken orally as a pill, avoiding the injection process. It also appears to have a very rapid effect on sperm production and an even more rapid recovery when fertility is desired," said Dr. Chung.

But to make the pill a reality, researchers need to show that the compound is safe, effective – and reversible – when used for years.

Drs. Wolgemuth and Chung are now planning longer-term studies to determine how long fertility can be disrupted and still recover after administration of the drug stops. "We hope that in the not so distant future, we may finally have more choices for people," said Dr. Chung.

Provided by Columbia University Medical Center

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