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Jill E. Long, Min S. Lee, and Diana L. Blithe.

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Guest: Dr. Diana Blithe is Chief of the Contraceptive Development Program at the National Institute of Child's Health and Human Development and Director of the Contraceptive Clinical Trial's network at the U.S. National Institute of Health.

Bob Barrett:

This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

The unintended pregnancy rate in the United States is approximately 45% despite of variety of contraceptive options available to women. Today, male condoms and withdrawal are the only reversible contraceptive methods available to men with typical failure rates between 10% and 20%. But what about a male contraceptive pill? Studies indicate that more than half of men would be interested in using a reversible method if it was available. And many women would be willing to rely on their partner to use such a contraceptive. Unplanned pregnancy rates could improve if both partners use a contraceptive method or if men had more options to control their own fertility.

The January 2019 issue of *Clinical Chemistry* is devoted to topics of men's health. And in that issue, an article examined developments in male contraceptives with an update on both novel hormonal and non-hormonal methods. One of the authors is Dr. Diana Blithe. She is Chief of the Contraceptive Development Program at the National Institute of Child's Health and Human Development and director of the Contraceptive Clinical Trials Network at the U.S. National Institutes of Health, and she is our guest in this podcast.

Dr. Blithe, do you think that men will use a systemic form of contraception and will women buy into that?

Dr. Diana Blithe:

Well, we are currently conducting a study in couples of a gel preparation that we know based on a prior study that we did in men only, in which the men were willing to use the product for six months and during that time, we were able to show that their sperm counts dropped down to very low levels to zero. And that stayed, as long as they continued to use the product, that stayed at the level. Now, we're taking that same product and testing it in couples where the male uses the product and will assess his sperm counts on a monthly basis and when he gets down to a low enough

sperm count that we know its contraceptive level, then the couple will agree to use this as their method of birth control for a year. So, in that case, the couples are enrolling. So, the man is expressing his willingness to use it and the partner is expressing her willingness to believe he will use it.

Bob Barrett: What is the biggest barrier to developing a so-called, "male pill?"

Dr. Diana Blithe: Well, the biggest barrier for a male pill, which means it has to be taken orally as compared to the gel which one would put on the skin, is that the way we are able to make this method work is there are two hormones. One of the hormones suppresses the testes' ability to make testosterone. And the amount of testosterone in the testes has to be high enough that it can support sperm production and the amount of testosterone it takes to do that is very high, much higher than the amount that circulates in the blood to maintain all of the other functions that are dependent on testosterone.

So, if we could shut down the local testosterone production in the testes with this one hormone, then we reduce the testosterone very low and we if didn't replace the blood levels, the man would not only not make sperm but he wouldn't be able to have ejaculations and he would have mood issues and a lot of things wouldn't be going right and it wouldn't be acceptable. So, we need to replace the testosterone.

So, that first hormone, we could deliver orally as a pill, that will shut off the testosterone in the testes, but to deliver testosterone orally has been an incredible challenge. Currently, even though companies have struggled for years to make an oral preparation of it, the best preparations, it's cleared so quickly that it requires multiple pills per day and that wouldn't be practical for a male contraceptive pill.

So, we're looking to try to find new compounds that would have the same androgenic properties of testosterone, but would be active orally, and we have some products that are in very early clinical trials that we hope will have that function but that's been the challenge. The challenge has been, "Can you develop an oral androgen that will work with the first hormone which is called a progestin to shut everything down but keep everything working."

Bob Barrett: What are the most promising methods of male contraception being developed today? Obviously, you have a gel now?

Dr. Diana Blithe: Right. So, the gel is probably the most promising. At least, it's the most advanced, I should say, because it's in what we

call Phase 2B. It's the first time that we're actually measuring contraceptive effectiveness.

So, the first part, Phase 2A, we're measuring the ability to suppress sperm production, which is a surrogate marker for contraceptive effectiveness, but now, we're actually subjecting couples to risk of pregnancy but using this method to prevent sperm production and in prior studies, some that were done in Europe through injectable methods, it's been very effective.

If you can suppress sperm below a certain level, one million per milliliter, which that still sounds like a lot of sperm but it turns out it's not enough to produce pregnancy. If you can keep sperm below that level, then the expectation is that it will work as a method. So, that's the one that's furthest along.

We know that at least in the U.S., gel is fairly acceptable because of the products that are available for low testosterone. We think it's an acceptable method, but as with any other user-dependent method like a birth control pill, it requires the user to use it regularly and not miss applications or pills because that will cause failures.

Bob Barrett: Will there be a role for a clinical laboratories in monitoring use of some of these contraceptive compounds?

Dr. Diana Blithe: I'm not sure what you mean by clinical laboratories but if what you're suggesting is could clinical laboratories do sperm counts? There's actually a product on the market right now that was developed through some research that my institute supported years ago that actually can measure sperm count in two different ways.

It can measure to see how low sperm counts are because if someone has a vasectomy, it takes a few months for all the sperm to clear out and you want to be able to determine that you're okay and safe now to not have to use another method. But, for men who are concerned about low sperm counts and they're trying to achieve pregnancy, there's another kit of similar design that can determine if your sperm counts are in the normal range. So, those are both available commercially. I think one's called Sperm Check Fertility and the other is Sperm Check Vasectomy or something like that, but anyway.

So, those are methods that are out there. I'm not sure what other clinical laboratory assessments one would want to do other than just to make sure everything is functioning normally, you have normal blood count, some things like that.

Bob Barrett: Okay. Well, finally, let's look ahead. How long would it be before a male contraceptive method could be on the market in the U.S. and is there more rapid progress on this overseas?

Dr. Diana Blithe: Okay. So, this is where I get everybody very depressed because the reality is when you're developing a method for healthy people that they're going to take for a very long period of time, the bar for safety is extremely high. So, if this were a new product for women, it would require 20,000 cycles of safety which is about 2,000 women using a product for year or maybe a little bit more, which is a fairly long time. If it is for men and they are not the ones who are going to have the risk of pregnancy, in other words, they won't have some of the risk of mortality or morbidity that comes with pregnancy, it's harder to assess what their risk benefit ratio is in taking this product.

So, again, the bar of safety is very, very high and that means treating large numbers of men for fairly long periods of time to make sure that there isn't some safety concern that would emerge with larger user numbers rather than in a small study.

So, that current trial that we're working on with the gel is beginning in 2018, I hope that it will be finished by 2022 and if that goes really well, then we would have to do a Phase 3 study that might be a larger and a little bit longer. And so, now you're talking about another five years and then it would take a couple of years to get it all together and submit to the FDA and have them review it and approve it. So, at least 10 years minimum, I would say probably closer to 12 to 13 is realistic, and could it be done faster? Possibly, if a pharmaceutical company had a lot more resources to do it. It's possible they could do it a little bit faster but you still need large numbers of individuals who are taking it for fairly long period of time to assure that the safety profile is acceptable.

And in Europe, as I said, they had done some preliminary work in a study that was using the two hormones, but both them deliver by injection rather than by gel. And they had some mood swing issues that caused them enough concern that they stopped the trial. Although, the subjects who were using it really liked it and wanted to continue, but the regulatory agencies were unsure whether it was, again, with the risk benefit ratio being hard to calculate whether it was worthwhile. So, I don't think there is anything out there that is further along in the published literature. There are some unpublished studies that I hear rumors about, so in Indonesia or India and so forth. But because they're not published, it's really hard to evaluate how far along they are, what they still have to do to get on the market.

- Bob Barrett: So, bottom line, sorry guys, you're still going to have to deal with condoms for the foreseeable future.
- Dr. Diana Blithe: Or enrolling in our studies.
- Bob Barrett: There you go.
- Dr. Diana Blithe: I wish I had a more optimistic and faster timeline to report, but having done this work now for a while, I know it's not something that happens fast and I know people get very excited when they have results in mice where the sperm are not working, and they say, "Oh five years to a method." Well, no, not really. Maybe five years until you actually can qualify a compound to be tested in a clinic. But then after that it's another 15 or so years.
- Bob Barrett: That was Dr. Diana Blithe, Chief of the Contraceptive Development Program at the National Institute of Child's Health and Human Development and Director of the Contraceptive Clinical Trial's network at the U.S. National Institute of Health. She's been our guest in this podcast covering developments in male contraceptives. Her article on that topic appears in the January 2019 issue of *Clinical Chemistry* that's devoted to the area of men's health. I'm Bob Barrett. Thanks for listening.