

**The Future of Contraception: What’s in the Pipeline?**

**Transcript**

**NCTCFP:**

Hello everyone. Good morning, good afternoon, good middle day, wherever you are in the country. My name is Shelby Webb and I'm from the National Clinical Training Center for Family Planning. And I just want to say thank you and welcome to this live webinar, The Future of Contraception: What's In The Pipeline? First, I'm just going to go ahead and go over some technical information, some housekeeping. This webinar is being recorded and archived and will be available to all webinar participants. Audio will be streaming through your computer or device, but if you do prefer to call in, the phone numbers are included in your registration confirmation email. You may type questions for our presenters at any time during the presentation in the Q&A feature, and we will be hosting a Q&A session after the slide presentations. You may also use the chat feature for comments and questions.

**NCTCFP:**

And about the chat feature, you'll want to make sure that it goes to all panelists and attendees, if that's your audience, and you can do that by selecting the "to" select the down arrow and select "all panelists and attendees." And that's how you can make sure that your chat is seen by all attendees. So first, I'll go over some CNE disclosures and accreditation information. This webinar offers 1.0 contact hours for nurses. To receive contact hours, participants must complete the evaluation and request for credit form CNE and CME certificates, as well as certificates of attendance will be emailed within three to four weeks.

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Dr. Alison Edelman is an author of Up to Date Inc and has grant funding from NIH, Merck and HRA Pharma. She is also a consultant for CDC, WHO, and MedinCELL. Dr. Michael Policar and Dr. Daniel Johnston have no disclosures. Shelby Webb, Angela Bolen, and Sharon Colbert have nothing to disclose. Jacki Witt serves on the advisory panel for Afaxys, which has been resolved. Kristin Metcalf-Wilson also serves on the Afaxys Pharmaceuticals advisory board, which has also been resolved.

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The AAFP has reviewed Future of Contraception: What's In The Pipeline? and deemed acceptable for up to one online only live AAFP elective credit. Term of approval is from September 1st, 2020 to September 1st, 2021. Physicians should claim only the credit commensurate with the extent of their participation in the activity. The University of Missouri, Kansas City School of Nursing and Health Studies, is accredited as a provider of continuing nursing professional development by the American Nurses Credentialing Center's Commission on Accreditation. This activity offers up to one contact hour for nurses.

**NCTCFP:**

So now it's my great pleasure to welcome our first speaker, Dr. Policar. Dr. Michael Policar, is professor emeritus of obstetrics and gynecology and reproductive sciences at the University of California, San Francisco, School of Medicine. Since 2015, he has been a clinical fellow for the National Family Planning and Reproductive Health Association, providing advice on clinical issues and reproductive health policy. He also is a senior medical advisor to the California State Office of Family Planning on clinical issues related to the Family PACT Program, the state's family planning program.

**NCTCFP:**

He is retired from clinical practice after a 34 year career, as a clinician educator of OB-GYN and primary care residents at the San Francisco General Hospital. Since March 2020, he has produced a number of guidelines on COVID-19 and family planning services that are posted on the Family Planning National Training Center website. He is a senior author of the textbook Contraceptive Technology, 16th through 21st editions. He has served on expert advisory panels of the Centers for Disease Control that resulted in the publication of the CDC Medical Eligibility Criteria For Contraceptive Use, the CDC selected practice recommendations for contraceptive use and providing quality family planning services, recommendations of CDC and the US Office of Population Affairs. Welcome Dr. Policar.

**Michael Policar:**

Thank you, Shelby, for such a nice introduction. I was just smiling about the fact that the introduction you just gave actually took longer than the time I'm going to be speaking with the introductions, but that's perfectly fine. So thank you all for joining us. I was noticing in the chat box that we have almost 400 participants from all over the country. And so it's terrific that you are able to be with us today. Just a little bit about this topic and how we came to it.

**Michael Policar:**

As you know, a few weeks ago we had the virtual National Reproductive Health Conference that was originally supposed to be in San Francisco for clinicians who work in Title X supported clinics. Of course, that had to go virtual. And this particular topic was going to be a keynote at the National Reproductive Health Conference. But it was deemed to be so important that it was actually split off. And now we're doing it as the webinar that you were participating in this morning. I'm glad that you were able to join us for that.

**Michael Policar:**

We're going to hear from two absolutely terrific speakers about contraceptive methods that are in the pipeline. First from Dr. Edelman, and from the point of view of clinical research, and then from Dr. Johnston about more basic science bench research. And lastly, I know that you may have some questions about some of the newer contraceptive products which have come on the market, let's say in the last year or so, or there are even a few that have been recently FDA approved, which are not actually on the market yet. Probably will be later this year. We're going to save any questions you have about that until the Q&A session that we're going to do at the end. And we should have some ample time to be able to talk about any of those questions that you have.

**Michael Policar:**

So with that, I am going to introduce our first speaker. Dr. Alison Edelman is a professor of obstetrics and gynecology and the director of the Oregon Family Planning Fellowship and director of the Section of Family Planning at Oregon Health and Sciences University. She is an active clinician scientist. Really pay attention to that folks, because she's still a doctor that that sees patients, spends time in the operating room in labor and delivery, in addition to the prolific writing that she does and all of her international work as well.

**Michael Policar:**

For close to 20 years, she has been a global technical consultant in reproductive health with extensive in-country experience in Latin America, the Caribbean, Asia, and Africa. Her role has included developing and implementing curricula, providing technical support and training medical personnel, designing standard operating procedures and performing quality assurance audits. She also has a number of other activities, the list goes on and on. But she is the Lead Editor of the Cochran's Fertility Regulation Review Group. And hopefully all of you are familiar with Cochran reviews. An Associate Editor of the journal Contraception, a member of the Medical Eligibility Criteria and SPR Expert Panels for the Center for Disease Control.

**Michael Policar:**

And she's currently on the World Health Organization, steering committee for the MEC, which of course is developed globally in addition to what we have a from the CDC in the United States. And was also chair of ACOG's Committee on Clinical Practice Bulletin. And the last point is to say, I'm delighted to say that she is also one of the coauthors on our book, Contraceptive Technology. So with that, Alison you're on.

**Alison Edelman:**

Thanks, Mike. Thanks for the introduction and thanks to the host for having both me and Dan today to speak to you. I'm going to see if I can get my slide presentation up to share. It worked in practice. This is almost like me walking up to the podium, so you can just pretend that I guess I'm walking up. I'm going to see if we can get that to work and hopefully you guys can all see my slides now. Mike, is that true?

**NCTCFP:**

Looks great.

**Alison Edelman:**

Okay, great. So we'll get started here and again, it's a pleasure to join you. It's actually nice to talk about something in the future since the present feels a little overwhelming. Particularly, I'm also located in Portland, so we've been in the news quite a bit. And so it's nice to get to look into the future. And oftentimes when I give this talk and the last time I gave it, I actually said that, "How will contraception look in 2020?" And then I said, 2030, and now I'm saying 2050. Because it just seems like things are kind of coming onto us fast. It's also hard to remember if it's Monday or Tuesday.

**Alison Edelman:**

But going with that, you already heard my disclosures. What I'm here to talk to you about is kind of why we need new methods. I think I'm kind of speaking to the audience that probably knows why we need new methods, but we'll just review some of the evidence around that. And then also we'll describe kind of some out of the box methods that people are thinking about and then getting closer to approval methods. And then an example of one method that actually has come to market recently, that's been part of the work that we've been working on and then a little bit about male methods. Because I feel like that's something that's really coming down the pike pretty quickly, and folks are particularly interested in that.

**Alison Edelman:**

I'm going to do kind of like the macro a little bit more clinical view of things. And then Dan Johnston is going to talk more, a little bit of the micro pre-clinical trials, kind of what people are focusing on there to hopefully give you kind of a grounding to move that way. We thought maybe it would be the opposite way, but we felt like people needed kind of an overview first and then come back to kind of what's happening pre-clinical.

**Alison Edelman:**

What's really interesting, is a lot of times we talk about kind of women who don't use their methods well, which is a reason for trying out new methods. But what's really driving, or it looks like is driving excess fertility is the non-use of contraceptives. And you can see here that on the X axis, the different types of methods, or not methods. You can see the long acting methods, pills, which are always popular and continue to be popular. And then non-use of methods.

**Alison Edelman:**

Then the percentage of reproductive age women that are sexually acting that are using those methods and the bars are representing over time. And the last time bucket that we have for this is 2015 to '17, and you can see here this big increase in long acting methods and kind of a decrease in pill use. And then you see that non-use is really continuing to be consistent over time. We really haven't impacted that group of women very well. And what this groups represents is about 900,000 unintended births per year. So close to a million. And we really haven't had an impact.

**Alison Edelman:**

Why is this group happening? What drives this? I think for a lot of time, we blame women, women blame themselves. I think we all see this in clinical practice. In particular, we say, "Well that person's tried everything and she's not willing to try it again." Or even just people who say they're bad pill users. Well guess what? Everybody's a bad everyday pill user. So this blame approach of like why that contraceptive method doesn't work for people, it may just be that we don't have enough methods.

**Alison Edelman:**

And so what women really are interested in is effectiveness, safety and affordability. And when studies have been done of women across the world, what's interesting is not only what they're interested or what's important to them in a contraceptive method, but what influences their choice. And there was this very interesting study of several thousand women looking at kind of different domains of what influences choice of contraception. And that includes mechanistic, not necessarily how the contraceptive method works, but actually how you use it. Like how easy is it to use? Do you need a foreign body? Do you need an injection? How fast does it return to fertility?

**Alison Edelman:**

Method effects, which we see all the time. What are the side effects? Does it also prevent STIs? What does it do for your menstrual period? And then social or normative factors. What's their prior experience? Does their partner support it? What's its reputation? And then practical. Financial, access, how it impacts sexual pleasure, ability, availability, all of those things. So those things go into influence or choice. And what we've found is that we don't really have the method mix. We have more method mix than we ever had before, but we still aren't hitting everybody's choices or everybody's need. And that's the importance around contraceptive development and continuing to have methods that really change over time with how people change over time and also increase the number of different things that we can have.

**Alison Edelman:**

Where is this going? What are people thinking? Are they just thinking, "Okay, let's get another pill?" Or are they really going big? And what's really interesting is people are going big. Now the amount of resources behind this, is a little bit smaller than it used to be because a lot of people are focused on a lot of other things, but people are actually going big. And some of the pie in the sky research that is happening right now, is being influenced by a lot of drug delivery systems.

**Alison Edelman:**

And one of them is, could you imagine having a contraceptive method that you could turn on and off remotely in your body? So this is a microchip technology that you put underneath the skin. It has reservoir of drugs and you could turn it on and off how you need it. Pretty cool. So it's not go live yet. And actually it's been looked at for kind of malaria prophylaxis and other long-term drugs, but it is something that is also being applied to contraception. So just a really cool kind of long acting method that you could actually turn on and off yourself.

**Alison Edelman:**

What are the other kind of pie in the sky things that are happening right now? Well, there's also high interest in a biodegradable implant. And I think for those of us that provide contraceptive care, we know that removal is a very big access issue and social justice issue. And if you had an implant that just over time, went away on its own, then the removal need wouldn't be there.

**Alison Edelman:**

Now, all of us that also do contraception know that, if it degrades over time, there might be a problem if somebody wanted to stop it early. So that's something that they're going to have to work into it. Again, this is kind of pie in the sky, really big innovations that are happening right now that people are just trying to figure out something that works and might be applied to contraception. And we don't have actual a model that's kind of going into human trials yet. But just some really exciting technologies that people are thinking about.

**Alison Edelman:**

What's at the human stage? What are we looking at right now? There's a lot of talk and studies around different types of IUD technologies. And we know that we have some great IUD technologies, but there may be some advantages that we can improve upon. And we all know that copper IUDs, great, fantastic non-hormonal contraceptive method, but it has some downsides. One of them is kind of increasing menstrual bleeding, increasing cramping. And if we could make that more comfortable for women, that would be fantastic without suffering decreases in efficacy.

**Alison Edelman:**

One of the things that people are really excited about is this flexible nitinol wire frame. And if you want to look into, I don't know if it'll show up very well, because it's so tiny. This is a prototype of it that I'm showing in my camera. And you can see it's like really, really tiny. It's super flexible. You can actually just totally cram it in your pocket all the way around and it just completely bounces back. So a lot of technologies are kind of hopping on this. Can you add hormone to it like a little reservoir on the shaft or add the copper, like we do for copper IUDs?

**Alison Edelman:**

We don't know yet. This is yet unproven because the studies are ongoing. They are in humans right now. And it may be more comfortable just because it's nice, flexible frame that may decrease expulsions, it may decrease bleeding. Right now, they're still studying that. And so those studies are ongoing, and we're doing that as part of a bunch of different clinical trials. But really cool technology that they're looking at for hormonal and also copper IUDs.

**Alison Edelman:**

The other thing that they're doing, and you'll see a lot of this is how can we improve upon the current methods that we have? It does feel kind of like just another pill, but there's also some cool things about improving the technologies that women love and use now. And one of them is actually an injectable that perhaps lasts longer than Depo-Provera or medroxyprogesterone acetate. This one in particular, again, is in early stages of studies in humans. It's using Levonorgestrel, which is a very safe progestin. One of our oldest progestins that we've had available. And right now, we're looking to see if this injectable will last longer. So six to nine months maybe be able to use sub-Q, which means that possibly we might have women be able to do this themselves.

**Alison Edelman:**

And we want to make sure that women have, hopefully less side effects from it, because it is such a kind of well tolerated progestin. And maybe we would have less outcome impact on bones and things like that, depending on how well it works or what it does with the whole kind of human systems. So can we improve upon the injectable that we have now? Again, this is in current studies right now in humans.

**Alison Edelman:**

The other thing that was pretty cool, that was coming down the pike, but unfortunately is on hold, is ulipristal acetate pill. This would have been a non estrogen pill, an anti progestin. And we know that ulipristal acetate blocks ovulation. And the reason why it's on hold as I'm sure some of you have heard about, the hold on the ulipristal acetate medication for fibroids, it's not on hold for emergency contraception, it's more on hold for a situation that you have to take it daily because of concerns about severe liver toxicity.

**Alison Edelman:**

Again, right now, we don't know if that's due to the drug or due to the patient outcome. So right now this is on hold until they can further discover kind of why that serious outcome might be happening. But pretty cool to have kind of a different type of non estrogen based pill, that might have a great bleeding pattern and blocks ovulation. So works really well for preventing pregnancy.

**Alison Edelman:**

The other thing that's been going on for a really long time is different technologies with the contraceptive vaginal ring. And the why and why rings are really exciting is that they're also using this for dual technology, so for HIV prevention. And so the Population Council in conjunction with the NIH Contraceptive Clinical Trials Network, which is a network in the United States that basically helps bring many of these studies through all the trials that need to get to the FDA for a new method, has been very excited about contraceptive vaginal rings for a number of reasons.

**Alison Edelman:**

One of the rings, which you all probably are familiar with because it's now on the market, is the year long ring. And that was studied for the last 20 years. It was developed by the Population Council which is an independent research group and then brought to the NIH to do these studies, to kind of bring it to market and then have kind of an industry move forward with it.

**Alison Edelman:**

And that bring is very similar to the ring that we have now. So the ring that we have now, since about 2002 on the market is the NuvaRing or the contraceptive vaginal ring. And this ring is similar in that it is a combination ring, so it contains ethinyl estradiol and progestin. So really the contraindications in use are going to be very similar. What's super exciting about this ring is the one ring lasts all year. All year. So you don't have to use one ring per month. It lasts all year. And then at the end of that year, you need to get a new ring.

**Alison Edelman:**

This ring was studied in a cyclical fashion. It was placed for 21 days and then removed for seven days. And there's still yet to be studies of it being used in a continuous fashion. You'll see here, and you've probably seen on the market in the pictures, it is slightly bulkier, but participants who were in the studies really loved it. They felt like it was very comfortable. So just because it's a little bulkier, don't let that scare you away from encouraging use of it, i you have a patient that wants to use it. It isn't less comfortable or anything like that. It's actually kind of, it's almost like a little squishier than the contraceptive vaginal ring that we have the NuvaRing. But it's just a little bit bulkier in its girth, so to speak.

**Alison Edelman:**

I think what many people are interested in is bleeding profiles of different new agents that we have. Women are interested in this too. And this is just kind of a depiction on some of the landmark studies of this new ring and what they did for the bleeding profile. And so just walking you through this, when they studied it for over a year, you'll see here in the dark blue, that bar means that people had a scheduled bleed. Because this was used in a 21, seven day fashion, those people had a schedule bleed just like you have many other products like pills that do a 21, seven fashion.

**Alison Edelman:**

You'll see here that there's also the middle bar the lighter blue bar, shows unscheduled bleeding or spotting. And then I just pulled out the unscheduled bleeding. So you could see that the majority of that unscheduled-ness is spotting, not bleeding. But you still do have some unscheduled bleeding and spotting even up to a year. We also see that with other cyclic methods that we use, this is not all the same women that are experiencing this. But you'll see in particular, I think the main point is that it doesn't necessarily over time change, but it may change with the different person that's using it. So it may not be the same person that's experiencing this all the way across.

**Alison Edelman:**

Just know that as we get better at developing contraceptives, we also get better at knowing kind of what to look at. So we don't have profiles like this for every single method that we have, but as we move forward, we're able to depict the method a little bit better.

**Alison Edelman:**

What about male contraception? What's going on with that? And I know a lot of people are like, "Why even go there? Why even have male contraception?" The fact is we already do male contraception. People just don't think of it that way. 30% of couples actually rely on male methods, either condoms or vasectomy or family planning withdrawal methods. And so this is all already a significant part of our armamentarium for contraceptive use.

**Alison Edelman:**

Actually, there's a lot of women who don't want to use a method and would rather have their partner use a method. So this is just monopolizing on that large percentage of women and couples that already want to be using a male method. And what's interesting about male methods is, it's very similar in contraceptive development in some ways to female methods. And you'll see here that we either are trying to hit the brain, talking to the testes, just like we would hit the brain talking to the ovaries and the uterus.

**Alison Edelman:**

How do we do that? We do that through hormones. And for men it's testosterone with progestin. So kind of very similar to women. There's also the possibility of GnRH agonists or antagonists. And then there's also the idea of non-hormonal methods. Now with men, the interesting part is there's a lot of sperm to deal with. And so it's not just one egg that we're having to deal with. It's actually a lot of sperm to deal with. But it's not getting sperm or the semen count to zero. It's actually getting it to less than one million. Because that's the contraceptive level for sperm count.

**Alison Edelman:**

The studies that we're looking at are trying to get this level to less than a million, which when we do get something on the market is going to be a little bit harder to explain to people because it's not zero, it's less than a million. Which is essentially zero for contraceptive effectiveness.

**Alison Edelman:**

This made a lot of the news about how a male contraceptive study was stopped because of side effects. Poor men, right? But in actuality, this was actually pretty significant. It wasn't just that they had some side effects that were kind of bothersome. Again, as we get better and better at following contraceptives and what we should look for, we're tracking these so closely and we are using a method in an individual that's not experiencing the health outcome.

**Alison Edelman:**

Now pregnancy affects couples, I'm not saying it doesn't, but then male is not experiencing the health issue in his person. So there's also a higher bar for side effects and adverse events. In particular, this was studying an injectable and actually the side effects were quite high. Even though the participants actually really liked it and the women couples. So the other part of the partner, really liked the method too, as well. Nice there for the couple to have that.

**Alison Edelman:**

But they actually had a significant amount of the study participants actually experienced emotional or mood disorders. And in fact, one of the participants committed suicide. And so actually an independent external review committee stopped this study. And so this in particular, as we're studying male methods is of particular concern, especially with using hormonal methods that are suppressing kind of the hypothalamic pituitary testes access. And just ensuring that we have side effects that are reasonable for the people that are using it. This is also reflective of kind of what we're doing with female methods too, as well, and ensuring that we have a greater understanding of how it impacts the whole body and not just the contraceptive effect.

**Alison Edelman:**

Right now the method that we're studying is pretty cool. It's also in conjunction with the Population Council and the Contraceptive Clinical Trials Network supported by the NIH. We are enrolling couples now. So this is interesting about male research too. We enrolled the couple, not just the man or the woman. And it's a gel. So it's a skin gel that you put on your body and it absorbs through the skin and it has testosterone, Nesterone or segesterone, which is very similar to the new ring that came out for women. So it's a gel that you put on and it decreases the sperm count to less than a million and it's reversible.

**Alison Edelman:**

We're studying that right now. And we're actually doing efficacy trials. So if you're interested or you have somebody that might be interested to enroll, I'd be happy to help hook you into where the sites are that are enrolling for this.

**Alison Edelman:**

And then I just kinda want to end up with, contraceptive clinical trials and development is all of us working together to identify things that might be useful to help support people doing clinical trials. And then to also, when we get these new methods out here, to see how they're working for people and to report on them. Those are part of the phase four trials that we do. Once it's on the market and it's out into the world, we continue to track it to see if rare outcomes come to light.

**Alison Edelman:**

All of us together are actually important in parts of contraceptive development. The whole field is. And so if you see the option and having this available for folks in your area, encourage your more interested clients to possibly seek out a clinical trials. I swear they won't feel like Guinea pigs. We really track people very closely and by the time it gets into humans, it really is something that we are trying to ensure safety with our study participants.

**Alison Edelman:**

I encourage you to do that, and I'm happy to to continue to respond to questions after Dan speaks. But I'm going to turn it over to him. And if you continue to be interested in contraceptive pipeline stuff, there's a really cool website run by Family Health International, that's Calliope and so that's the website for that. Thanks so much. Now I'm going to see how I can like stop sharing my screen. Because this was-

**Michael Policar:**

While you're doing that, I will introduce Dr. Daniel Johnston. And thanks so much. Very quick thing before I introduce Dr. Johnston is to remind you to submit your questions in the Q&A box. We have a few so far but I'm sure you have lots and lots of questions for our two speakers today, as soon as Dr. Johnston has finished. So be sure to descend to send them up. We can also accept them in the chat box, but it's a little bit easier to access them through the Q&A box.

**Michael Policar:**

Dr. Daniel Johnston is the chief of the Contraceptive Research branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Dr. Johnston, completed his PhD Reproductive Biology at the Johns Hopkins University, Bloomberg School of Public Health. He subsequently completed the doctoral fellowship at Washington State University.

**Michael Policar:**

He has extensive experience in private sector, pharmaceutical research and development, including as a team leader at the Women's Health Research Institute at Wyeth Pharmaceuticals, where he worked on small molecule programs to identify, validate, and develop inhibitors against targets for male and female contraception. His research interest has included [inaudible 00:32:58] maturation, fertilization, andrology, biomarker development, contraceptive development. And he's going to be discussing many of those topics in his talk.

**Michael Policar:**

He has a long track record of research, research oversight, and management, executive service and effective relationships with a combination of industry, academic institutions and investigators and governmental agencies. And so with that, Dan, take it away.

**Daniel Johnston:**

Thank you very much. Can everybody hear me? Can you hear me, Michael? Okay. It's a pleasure to be here today. I am going to turn my camera off. I'm having a little bit of connectivity issue here in my home in West Virginia. So to ease up on my ease up on my computer stress, I'm going to probably come off video here and continue to talk. But anyway, it's a pleasure to be here to represent the NICHD and to talk to you a little bit about preclinical contraceptive development, some of the techniques that we use, the things that we think about, and I will also demonstrate a couple of programs.

**Daniel Johnston:**

I have no disclosures to report. By the end of this webinar, we hope that you can summarize that the male reproductive system has many more non hormonal contraceptive targets than the female reproductive system that you can defend target validation, you can describe the potential on demand, male contraceptive, under development. You can explain how male targets can be used for the development of female contraceptives. You can discuss a novel vaginal ring technology under development, and you can define multipurpose prevention technologies.

**Daniel Johnston:**

So with that, we'll get started. A lot of what I'm going to talk to you about today was covered in a review that was published a couple of months ago. In many cases, the review covers the topics in greater depth than I'll speak about today. So this is part of a special edition put out by the Biology Of Reproduction, just on contraception. And this is a review which starts that second issue.

**Daniel Johnston:**

So let's talk about contraceptive paradigms and let's think about them over time. Obviously, nearly 60 years ago, the combined steroid formulations entered the market. And over time there was a great movement in reduction of the number of steroids, which was outstanding for safety. There was also a move towards steroid receptor modulators. So moving away from estrogen and progesterone into other types of molecules.

**Daniel Johnston:**

And then around 2000, a lot of pharmaceuticals and shortly thereafter, even the NIH, started working on the development of novel and specific non-hormonal modalities. And this is right at the time they came out of my postdoc and I did, I went straight into YF into what was a contraceptive development group, there to begin developing non hormonal contraceptives. What this really means is a shift away from the administration of exogenous hormones that affect the expression of hundreds, if not thousands of genes towards the development of a product, which acts on a single gene product or protein. So there's an inherent shift towards greater selectivity and specificity.

**Daniel Johnston:**

Now I made this slide 15 years ago, believe it or not. And I could use it almost unchanged except for, I think I need to put in another thing that's really occurred. And that is in the area of non-hormonal would be pH modulation and the development of contraceptives that work by maintaining an acidic environment within the female reproductive tract, leading to the death of sperm and contraception. And there was a contraceptive that was just recently approved by the FDA that acts by this mechanism.

**Daniel Johnston:**

Let's think a little bit about drug development. Alison actually talked about some really nice parts of drug development. Let's just walk through it quickly, because we're going to spend a lot of time talking about this kind of early phase. When you want to inhibit a specific molecule, that's called your target. And then you develop an inhibitor, be it a small molecule, be it an antibody, to inhibit that target and to modulate it. Maybe not to inhibit it, but definitely to modulate it, to achieve a contraceptive effect. And then showing or demonstrating before you start investing all this money, that if you can modulate your target, you should achieve a contraceptive effect, that's called target validation. And I will talk about that more later in the talk.

**Daniel Johnston:**

Then the next phase is lead discovery and optimization. Here's where you basically make your molecule, you optimize it, you make your antibody or whatever you're going to make. And then you start doing IND enabling studies, which of course are studies that allow you to ultimately put together a package IND stands for investigational new drug. So you do the studies, demonstrating safety and demonstrating efficacy. And then you basically put together an investigational new drug application, make your clinical formulation. And then you do your clinical trials, which Alison referred to, phase one, phase two and phase three.

**Daniel Johnston:**

Now the portfolio that the branch at the NICHD that I manage our portfolio looks something like this at the moment. So we have a few you in this early phase, a lot in this kind of lead discovering optimization phase. And then we have a number that are heading for the clinic. Ideally, you want to have this phase of your pipeline over here very much overloaded. But for reasons I won't get into, we basically get fed into the pipeline here by another branch at the NICHD.

**Daniel Johnston:**

What I'm going to do today is to talk a little, a bit about some principles of preclinical, contraceptive development. And then I'm going to discuss two of these. If I sat here for a half an hour and just blew through all 20 of these or 15 of these, I don't think it would be fun for you. And I know it wouldn't be fun for me. So let's talk a little bit about male contraception, first, a subject near and dear to my heart.

**Daniel Johnston:**

First of all, we have the biology here. It would be the testis. This is the site where sperm are formed. They're formed within these tubules within the testis known as the seminiferous epithelium or seminiferous tubules.

**Alison Edelman:**

Hey, Dan, I'm not seeing the slides advance at all. Are you-

**Daniel Johnston:**

I'm sorry.

**Alison Edelman:**

I don't know if it's your technology or it's still on the-

**Daniel Johnston:**

[inaudible 00:39:06].

**Alison Edelman:**

Contraceptive paradigms. One still. I thought I was frozen, but I think you're frozen, maybe.

**Daniel Johnston:**

Let's see. All right, okay. I didn't see. Shelby, do you want to throw them up? Do you throw up the slides? Do you have them? And I can work off yours if we're having an issue.

**NCTCFP:**

Yeah. Let me pull those up real quick. One moment.

**Alison Edelman:**

Shelby. Is it frozen for you too?

**NCTCFP:**

Yes it is. Just one second.

**Alison Edelman:**

Okay.

**Daniel Johnston:**

Okay. Sorry about that.

**Alison Edelman:**

Sorry to interrupt you, Dan.

**Daniel Johnston:**

No, it's good that you caught it. I apologize. I know I'm having some connectivity issues, but I was able to follow your presentation just fine.

**Alison Edelman:**

Yeah. Well maybe while Shelby stirring them up. I'll answer one of the questions in the chat box. Thank you so much for pointing out the inclusive language. And I completely agree with you, especially as we're treating patients and we're offering methods to patients, it's really important to use inclusive language. I'm going to give you the excuse and then you guys can help me know how to overcome the excuses. In contraceptive research, we very much have to, and this doesn't mean how people identify in the studies, but we need reproductively intact along the lines of kind of that dichotomy of male, female, because we can't have external hormones kind of impacting the contraceptive method. I'll put that out there and then maybe you guys can put in the chat, like what I should be using instead. Because I'd love to see it.

**Daniel Johnston:**

Okay. I can see the slides now. Can everybody else see them?

**Alison Edelman:**

I can see them. Yeah. You're on the contraceptive research branch program status.

**Daniel Johnston:**

Yeah. So we just went through the pipeline and I'm sorry if that was difficult to understand without the help of this image, but I kind of just walked us from left to right, a process. If we can hit next action, Shelby, you're going to have to need to advance for me. I got quite a bit. So this shows what our pipeline looks like in the contraceptive research branch over on the left hand... Hold on. Shelby, can you go back?

**NCTCFP:**

Yeah. Sorry. I think there's a slight delay.

**Daniel Johnston:**

Okay. Actually go to the next slide, because that's where I was when I got cut off and I'll pick up from here. Okay. On the right hand side, we have an image of a testis and that tubule, which comes out, is known as the seminiferous tubule. This is where sperm are produced. They're released to the inner part of this tubule and they actually are carried down to a central location known as the rete testes. And then they move across those tiny little threads you see up near the top, which are called the efferent ductules into the top of an organ, which is probably my favorite organ which it's just called the epididymis.

**Daniel Johnston:**

And all of those little tubes, eventually a form one single tubule that in a human is about 35 to 40 feet long. And the sperm traveled down that tubule and continually are exposed to it and ever changing microtubule or micro luminal environment. And during this transit down the tubule, they acquire the ability to both be modal and to complete the process of fertilization. And this connects to the vas deferens, which is shown there near the end, kind of the single wide diameter tubule.

**Daniel Johnston:**

Can we have our next action? I just covered that, so let's do the next action. Site of action. Okay. That's great, stay right there. Site of action is something we talk about in the review quite a bit, and somebody may ask, "What's a better place to have your target be?" And everybody who works in this field seems to think that their target is in the best possible location. And I'm not sure that's true. But let's take the two extremes and I'll point out one potential concern about each end.

**Daniel Johnston:**

If you look at the left side of this area and we think we're going to stops spermatogenesis, right at the beginning. Which is just about where the hormonal contraceptives that Alison talked about start. One of the things that can cause some people some concern about that, is that the process of spermatogenesis in the human takes about 64 days. And epididymal transit and it's usually considered to be about two to 11. So what that means is, from the time you start treating the male, it's going to be about 75 days before you begin to see the levels fall below, what Alison said was one million sperm per mil. That's the target. So it can take 75.

**Daniel Johnston:**

That may not be a problem, but it's a long time for onset. And the time to recover from the treatment is about the same. It's about 75 days, probably more like 90 days before you start seeing significant levels of sperm in the epididymis for fertility.

**Daniel Johnston:**

One of the good things about this method though, as Alison mentioned is if you have very few sperm, it's very easy to monitor how well the contraceptive is working. You simply get a sample from the patient. And you can count this from, and you know if you have an effect. Another benefit is that the FDA is very comfortable with using total sperm count as a measure of a contraceptive effect. Now, if you go to the other end of this, and we think now let's think about working at the bottom of the epididymis, that area, where you're budding up against the vas deferens these sperm are just about ready to ejaculate and they're ready to go.

**Daniel Johnston:**

I like to think of these as being almost like a horse in a gate at a horse race. They're completely ready to go. They're just waiting for that last signal with which to go and be active. And the potential good thing about affecting sperm in this area is that you may have a very rapid onset. You potentially could even have something like an on demand male contraceptive. Take a pill, within three or four hours, those sperm may be inactivated and your covered. Which would be great.

**Daniel Johnston:**

One of the problems is that, and Alison said, if there's about 150 to 200 million sperm per ejaculate, and a normal ejaculate is two, two and a half, three millimeters. You're now trying to stop 500 million sperm in the course of a couple hours. And that can be a large ask. Similarly, the FDA is not going to have likely a high comfort level as they move into these new methods of assessing for potential fertility before they allow it into a human. That's just a point about side of action. Next slide.

**Daniel Johnston:**

When we think about contraception, there are three things we tend to think about contraception targets. One is the target reproductive track specific. So stop and think about this for a second. You're going to give these to healthy people for a long period of time. Ideally, your method of inhibiting will affect only the molecule that you want it to affect. And if that molecule is found in the heart or the liver or the brain or somewhere else, theoretically, you will be affecting it there too.

**Daniel Johnston:**

So reproductive track specificity is something that is highly desirable, not always mandatory. And we can talk about that in the Q&A period of people are interested. Next action. Druggable. Some targets are inherently druggable, these include enzymes, ion channels transporters, and some are much harder such as protein-protein interactions, protein-DNA interactions, things like trying to inhibit cytoskeletal components. They're generally not thought to be druggable. Next move, Shelby.

**Daniel Johnston:**

This one may seem funny when I put it on here, but I've already spoke about this. It's very important before you started investing in millions of dollars that you know, that if you achieve the modulation, you're trying to effect, it will result in a contraceptive effect. That's all validation. So next hit, Shelby.

**Daniel Johnston:**

Validation for a defined target is data demonstrating that if the proposed modulation of the target is successful, the therapeutic will be effective. That is incredibly important, and it's overlooked by a surprising number of people who submit applications. Next slide.

**Daniel Johnston:**

Take a minute and we'll go through the statement. So this is from our paper titled, the multitude of genes expressed solely in meiotic or postmeiotic spermatogenic cells offers a myriad of contraceptive targets. From a paper in PNAS in 2003. It contained the statement that upon further analysis, their data indicates that 4% of the mouse genome is dedicated to the expression of post-meiotic germ cells. At the time they thought there was about 30,000 genes in the human and the mouse. So that means it would be about 1200 genes dedicated to the production of sperm. And incredibly high proportion of your genome to contribute to this process.

**Daniel Johnston:**

At this point I was pretty new at Wyeth, and I began a process of three or four years of trying to identify what all of these genes and proteins were. I think what we found, because we use slightly technology with more sensitivity, is that that number is not high, but there are a tremendous number of genes that are expressed, if not uniquely, then selectively at a very high level in the testis. And briefly the next slide, Shelby, shows this.

**Daniel Johnston:**

I want to work on the slide comes up. Next slide. Okay. Look at on the right hand side of this, where I have these little branches, we actually found six that using very sensitive techniques were absolutely testis specific. We found seven that were not detected in other reproductive tissues. But then what you see is, you start to see these other ones are, this one's about 12,000 fold higher than any other tissue, 9,000 fold higher than any of the tissue, 8,000, 8,0000, 8,000, 7,000. And this list when all the way down to 1,000.

**Daniel Johnston:**

The point is there are a tremendous number of potential targets in the testis. And I will tell you right now, in case I forget to tell you later, this does not occur in the ovary. This is very much unique for the male reproductive system. Next slide.

**Daniel Johnston:**

How do we validate these? Normally, the current way to do it is to make a knockout mouse. A mouse that lacks the gene of interest and if that animal is infertile, then it's perceived to be a validated target. But when we can also do is we can use this. This is the International Mouse Phenotyping Consortium. And what they are doing is they are systematically knocking out every gene in the mouse, one by one. And with this, you can play this both in a push and then a pull. You can identify a target and then go here and see if they've knocked it out yet. And the other way, you can actually look at this database and go in identify genes that were required for fertility and the animals were otherwise normal. So this is an extremely important resource for helping us with validation. I have an example of a one that's under development starting in the next slide.

**Daniel Johnston:**

This is Eppin, it's a small molecule program. Hit the advanced, Shelby. Eppin is on the right hand side of this time on the bottom. It is epididymal protein. It is very much involved with basically, if you go back to the analogy of the horse at the beginning of the race, it is crucial for keeping that horse from moving. So this is important with keeping sperm, basically from not moving and expending energy and so forth up until the time of ejaculation. That basically is part of locking the sperm and keeping them not modal until ejaculation.

**Daniel Johnston:**

I'm going to show you a piece of data. It looks a little confusing at the start, but I guarantee you it's easy. This is from an investigator named Michael Loran, next slide, Shelby. And he basically, towards the end of his funding period, be swung for the fences, swung from his heels and he injected monkeys with a very high dose of his compound, which is called EPO55, He dosed at 125 to 130 milligrams per kilogram, intravenously. And what he saw here on the graph is there are two Y axes shown. The left hand is simply the level of the drug that he found in the ejaculate. And as you see, it goes down over time after he administered.

**Daniel Johnston:**

The more interesting one for our point though, is to look at the percent of normal sperm motility. And what you see is at six to eight hours, the average fertility of these primates was actually down to about 20% of normal. At 28 hours, it was at zero implying that the sperm motility was highly consistent with some fertility or infertility. And then at about 78 hours, it had started to come back up. And by the time you get out to about 20 days the motility of those sperm has returned.

**Daniel Johnston:**

The reason I show you this is, it comes back to that idea of not only developing male contraception, but this is the potential not with this compound, of course, but the potential for achieving something like on demand, male contraceptive. And I'll tell you having another program in the portfolio that actually has a similar effect that they can dose, and they can see a dramatic decrease in sperm function within hours that last a matter of days and then returns.

**Daniel Johnston:**

I'm trying to show you things that are still very, very early. As I said, requiring this kind of dose, I don't think this compound may not be the one that does on demand contraception, but it just shows the potential for on-demand contraception.

**Daniel Johnston:**

Now we'll move to the female side and do a couple of points here and then close it up. The biology, I'm sure everybody here is very familiar with this. The ovaries, the fallopian tubes, uterus, cervix, and vagina. Obviously the gametes are made within the ovaries. And the fertilization occurs in the area in the fallopian tubes that's approximal to the ovary. That's the area, at least pre fertilization, that we're interested in working in. And therefore a lot of the targets for female contraception would be in the ovary.

**Daniel Johnston:**

Next slide. Next move. We already covered the site of action, next one. Here, I want to reiterate the point that all of the work that I had done in the male to identify contraceptive targets, I did the same thing in the female. I dissected hundreds, hundreds of ovaries were dissected to look at oocytes, eggs, cumulus cells both neural and cumulus. We looked for everything. And I found about 15 genes that were specific to the female or male reproductive track. These would include things should expect like the zona pellucida effector protein, there were a couple of transcription factors, putting FIGalpha, which drives zona pellucida expression. But we really didn't find very much that was unique. So this is a large hurdle in trying to develop non-hormonal female contraceptives to act in the ovary.

**Daniel Johnston:**

Next slide. This is a schematic that I made, and I apologize to anybody who's highly familiar with ovarian follicular Genesis. The point I want to make here is, this shows the different stages of folliculogenesis excluding the corpus luteum. And you can imagine you never want to hit the primordial follicle, because if you do that, you'll render the woman sterile. So that's not desirable. Nor do you want to freeze things potentially in the primordial follicle, the primary follicle or the secondary follicle phase.

**Daniel Johnston:**

Theoretically, if you do that, a woman is not likely to get the amount of estrogen that she needs, and therefore you'd have to administer back estrogen and moving away from the idea of administering endogenous hormones is part of the plan. I will say, I've had some very interesting conversations in the last six months with some people that are starting to generate data that they say suggests that if you do get to the secondary follicle phase, you will generate sufficient estrogen to not affect things such as bone.

**Daniel Johnston:**

But anyways, the point is this lives to say a lot of your targets then are going to be directed at the late stage antral follicle. Again, having very few targets that are unique, what this means is you're really trying to block ovulation. I know the Bill and Melinda Gates Foundation funds several programs focused on inhibiting ovulation. And we actually fund one program ourselves aimed at inhibiting ovulation. So with that, next slide.

**Daniel Johnston:**

Another way to think about it is, next slide, we use our male targets in the female reproductive tract. There obviously a lot of targets in the male, and then you can toggle through the next three or four, Shelby to get through this list. These are things you could potentially target. Energy production, motility, sperm maturation, I think there's one more, you can show them one more Shelby. And egg binding. I cannot say I'm a big fan of trying to inhibit sperm zona or a sperm egg plasma membrane. I think you're letting them get a little too close to each other at that point. But these are all areas that you could imagine working into the female reproductive tract to try to stop sperm after they enter. Next slide.

**Daniel Johnston:**

These of course would be delivered are the two most obvious candidates are vaginal films and vaginal rings and technology in these areas has been just incredible over the last 10 to 15 years. They now have vaginal films that can last for a couple of weeks, potentially even closer to a month and keep releasing active compounds. Vaginal rings technologies have come a long way. And I want to talk about one that I find very exciting.

**Daniel Johnston:**

One of the big issues with either vaginal films or vaginal rings are issues around compliance. Obviously not taking the vaginal film, but in the case of vaginal range removing them, taking them in and out during the month. There's a group that started develop the following. Next action, Shelby. This is a vaginal ring is a vaginal ring, perfect, that contains a temperature sensor, and they have used this on a really interesting paper where they use sheep, and they developed it. And over the course of about 30 days, they took it in and out at defined times. And this basically reads the temperature of the vaginal ring for an instant about every 15 minutes.

**Daniel Johnston:**

And what it does is, it allows you to go back and then evaluate your compliance during the clinical trial period to see if in fact it was used for the entire trial as expected. I find this really interesting because I think we need to find ways to better monitor compliance, because I think a lot of really interesting products over the last 30 years have gone down the drain maybe not do more to patient compliance than the quality of the device.

**Daniel Johnston:**

I thought that was interesting point to make. So I'll give you an example of a male targets that is being used in the female reproductive tract. This is called human contraceptive antibody. It works against a target known as CD52g. And Shelby, you can toggle a few for me and I'll go through this. CD52g is found in the [inaudible 00:58:34] or the top region of the epididymis. It is a glycoprotein which means it's a protein that has sugars on it. It's this like a protein in its form is only found in the male reproductive tract. The fascinating thing about this, is the protein is not unique to the male reproductive tract. In this case, it's the carbohydrate that's attached to the protein that expressed only in the male reproductive tract and nowhere else.

**Daniel Johnston:**

So this molecule is released into the epididymal lumen. It goes and attaches to the sperm via what's called the GPI anchor. And interestingly, one more quick, Shelby. It is a very common antigen for people who have anti sperm antibodies. In fact, anybody I'm going to talk to you about was isolated from a woman who was infertile due to anti-spam antibodies and the sequence which created this antibody was modified and engineered into new antibodies. So we have like three or four slides left, we'll get pretty quick. Next slide, Shelby.

**Daniel Johnston:**

It was initially an IgM type antibody. It was converted to an IgG that's called human centered antibody. A point of interest is that they're actually producing this antibody in large quantities in tobacco plants, which are shown on the right. The principal investigator is Dr. Debra Anderson. Now let's take a look at a couple of pieces of data. Next slide.

**Daniel Johnston:**

If you take a hundred micrograms per milliliter of antibody and you treat a hundred million washed sperm per mil, next click, you get the following. What you see is ACA again, is our molecule under development. You can see it takes about 15 seconds to get massive agglutination of sperm. And that continues, whereas the control antibody, which is an anti HIV antibody, the sperm just keep on swimming and they don't have gluten at all. So very potent. So the next slide shows a very similar study, but it puts it into different form. Same two antibodies. This was 30 million sperm per milliliter. So suddenly lower concentration of sperm, which should make agglutination a little more difficult. And what you can see is the VRC01 never agglutinated. Study only went 120 seconds. But you can see even down to the lowest 12 micrograms per mil, you were still getting agglutination very rapidly. You're agglutination of the sperm within 20 seconds.

**Daniel Johnston:**

What can you do with this? One more click. Perfect, right there. You can stop right there. They've made the IgG and what else can they do with it? Well, they can now genetically engineer things that are still IgG, but now they have 10 of these units with which to grab CD52g. And this one, one they've made and tested, is 16 times more potent than the IgG. And interestingly, there's a way that they can make an IgG based antibody on the right, which mimics the design of an IgM molecule, which would be highly analogous to the type of antibody that was in the woman that had the anti sperm antibodies that wasn't fertile. So the engineering, is just fascinating that they're doing. The reason why they didn't stay with the initial IgM, in case anybody's wondering is twofold.

**Daniel Johnston:**

One it's much easier to purify IgG, and second is regulatory agencies, once again, will be far more comfortable with an IgG type molecules than they would be potentially with an exogenously administered IgM. Because a lot of the antibodies, all of the ones that I know of antibodies that are prescription drugs are IgG.

**Daniel Johnston:**

Last point, and then we're done. One more click and we'll stay on this slide. These have the potential to be used as multipurpose prevention technologies. A multipurpose prevention technology has not only a contraceptive effect, but also an anti-infective effect. And so what happens is that loose CD52g, in our reproductive track can also GPI anchor into things like HIV and envelope coded viruses and things of that nature. So what you have the potential for, next slide, is that not only will you trap and agglutinate sperm, but you can also trap and agglutinate these other factors, including HIV infected cells tripping on [inaudible 01:02:59] envelope viruses. And this PI had a grant actually this [inaudible 01:03:03]doesn't fact trap. I'm not sure it as itself could stand alone as an anti-infective, but it certainly will be a potential benefit. And you compare this antibody with other antibodies that are anti HIV, anti HSB, and so forth.

**Daniel Johnston:**

Last slide. Hopefully, during the course of this presentation you've understood that there are many reproductive specific or selective contraceptive targets in the male reproductive tract as compared to the female. Modulation of male contraceptive targets maybe ineffective as a female on demand contraceptive. That preclinical pharmacologic on-demand sperm inhibition consistent with male contraception has been demonstrated. And lastly, that the NICHD supports the development of multipurpose prevention technologies which not only provide contraception, but also inhibit STI transmission. So thank you.

**Daniel Johnston:**

Michael, you're on mute.

**Michael Policar:**

Alright, there we go. Thanks Dan. That was terrific. As you know, we are a little over time, but we do have permission to take some time to answer questions. Given the fact that we were just talking about multipurpose of technology. One of the questions to Dr. Edelman is that she mentioned that the new Annovera ring was also being studied for HIV prevention with treatment. Is there more information on this. And Alison, while you're mentioning that, and of course Dan can help out as well. You might mention the work that's being done with Phexxi on its effect on gonorrhea and chlamydia.

**Alison Edelman:**

Just to clarify, it's not necessarily the Annovera ring that's been approved that they're using for HIV prevention. It's the ring technology that the Annovera is using that is being used for multipurpose technology. So they're doing all sorts of stuff with the different types of ring technologies. Some of them have like an inner ring that releases the different medication, so a different reservoir to release a different medication at different times. Because you know, different medication has different release rates.

**Alison Edelman:**

They're also under development of an estradiol progesterone ring which is super fascinating because it may be that estradiol and contraceptive levels might be safer than ethinyl estradiol, which is what we traditionally use as the estrogen in contraceptives. So maybe less clot risk, but we don't know that for sure. So just a lot of interesting things with ring technology. And as Dan mentioned it's for the local delivery system to prevent HIV transmission is really important. I'm going to let you address that Phexxi and the gonorrhea, chlamydia. I haven't seen that data. So Mike, if you want to talk about that for a second, that'd be great.

**Michael Policar:**

I don't have a lot of data on it. I just know that the study is being done. That Phexxi has been FDA approved. It's going to be marketed as a barrier contraceptives soon. Certainly it's not going to be immediately FDA approved for the purpose of preventing gonorrhea and chlamydia because their studies are ongoing.

**Alison Edelman:**

Dan, maybe you could speak to that. Phexxi is the lactic acid, new kind of gel that's on the market. What do you think about that for kind of gonorrhea chlamydia? Do you have-

**Daniel Johnston:**

Sorry [inaudible 01:06:51]. I think it has the potential. I know there are other people at Buffer Gel years ago, was worked on by the [inaudible 01:06:59] and Wally was effectively thought to also have potentially those properties. And Buffer Gel didn't make it, and one of the things I think about when I wonder about compliance. I think the data has to speak for themselves, but I think doing the study to see if Phexxi and I still call it Amphora effectively because that's what was called until recently. I think it's a study we're doing, and I'm excited to see the outcome, but I don't want to make a prediction as to what the outcome will be.

**Michael Policar:**

Okay, great. Here's a question from Mark Hathaway. I've heard talk of the newer female sterilization method that will block the hysteroscope. Alison or Dan, have you heard anything about sort of the next generation of that?

**Alison Edelman:**

We have a site here at Oregon that's funded by the Gates Foundation for kind of noninvasive sterilization processes, including being able to do that without a hysteroscope. It's still fairly early in its development. It's in preclinical trials looking at kind of a sclerosing agent that only scleroses, small, tiny spaces. So then once we get to the abdomen, it would be completely inert. So that's what they're studying right now. I don't know of anything that's kind of in clinical trials, unless Mark, you want to write that in and I'll see if I can. I'm not recalling anything. Maybe I haven't had enough caffeine yet today.

**Michael Policar:**

Okay. A question came in early about, can you explain why ulipristal is on hold again. I guess that had to do with a fibroid trial?

**Alison Edelman:**

The fibroid ulipristal acetate is a five milligram tablet that's taken daily and it's just impressive, the impact on fibroids and fibroid related bleeding. In fact, people stopped within about six days of taking the drug. It's been used on the market and about a million women or people with uteruses and fibroids. What they found in post-marketing studies, those are those phase four studies once it's on the market, people are still tracking new medications. And what they found is a small group, I think four or five patients reporting significant liver toxicity, to the fact that even a couple of the patients needed a liver transplant. This is not just a like a hepatitis type thing.

**Alison Edelman:**

They don't know for sure if it's because we're using the medication in people that may not be a great surgical candidates, so it might also have other medical problems or comorbidities. And so that may be the issue, versus his admitted location itself. However, since it was so concerning and such a severe event, any kind of further development of UPA as any sort of other medication or contraceptive pill is on hold. However, that is not a concern for the kind of very limited use that we use it for emergency contraception.

**Michael Policar:**

Okay. Another question is, can you speak to Slynd? And for those of you who don't know, that's a new progestin only pill that has [inaudible 01:10:16] in it. Is it being used? What about private and public insurance coverage, is it being considered for over the counter status?

**Alison Edelman:**

Yeah. And Mike and Dan feel free to jump in. So Slynd is a new drospirenone only pill, so it's a progestin only pill with drospirenone. Many people are familiar with drospirenone because of Yaz and Yazmin which is a combined pill. Basically this progestin only pills is a little bit different than the pill that we're used to, or the mini pill. And it's actually a slightly higher dose of drospirenone than what's in a combined pill. And what's nice about this pill is it does provide suppression of ovulation. So you don't get that kind of concern if you have somebody that's not adherent to the regimen of possibly having a breakthrough ovulation or maybe favorable cervical mucus.

**Alison Edelman:**

It much more probably will have real, or at least in the United States. Actually our studies have much more impact around compliance and adherence with methods than outside the United States where we study them. And so that's why Dan was talking about the importance of trying to determine compliance and adherence with methods in clinical trials, because that greatly affects the efficacy rate. And so it's a little different than the mini pill too, as well, because you take it in a 24/4 regimen, instead of a continuous regimen, like our regular mini pill that doesn't have a break.

**Alison Edelman:**

It hasn't been studied yet in a continuous fashion, but one would think that it should work the same in a continuous fashion. And then Mike, have you heard of about insurers and how they cover that? I know we've had some patients here that we've had some good success in getting on Slynd because of medical comorbidities and needing something for ovulation suppression. But I don't know if just kind of somebody every day walking in can easily get it yet or not.

**Michael Policar:**

I know that they can in commercial pharmacies. I just checked a few days ago on a goodrx.com to see if that was something that would be available through commercial pharmacies, and it is. But I really haven't heard very much about is whether or not there's a 340B price or some way of improving access to public Family Planning Clinics. If any of you in the audience have had experience with that, type it in, and if we have enough time we'll go ahead and mention it.

**Michael Policar:**

As far as the question of, is that one of the products that might be considered for over the counter status, I think there's widespread agreement that progestin-only pills is the most likely candidate for an all contraceptive to go over the counter. Whether it's going to be this progestin only pill or a different progestin only pill is a little too early to tell.

**Alison Edelman:**

Yeah. We're part of trials here that just completed as also a California site for a progestin only pill, that's trying to move over the counter. So we're really excited about that. And that's the fun part of being part of clinical trials, kind of seeing things come down the pike and being really thrilled about kind of the options that they'll hopefully be available to us.

**Michael Policar:**

Yeah. What do you guys think about the timeline on this? Do you think that an over the counter pill is something we might change in the next year or two or?

**Alison Edelman:**

I dot know. Hopefully the industry representative isn't online. I think they're hoping to have this kind of in the next year or so maybe go to the FDA, but I don't know anything specific besides that. We're all pretty excited about it.

**Michael Policar:**

Okay. So let me ask you a question, and this is for both of you given the fact that you were so involved in contraceptive research. What do you think is the environment now, particularly with big pharma, regarding their willingness to engage in contraceptive research that ultimately would lead to a new product. Because it seems like at least in the last five years, if not longer, most of the new methods that we've seen are actually coming from small companies. You mentioned a number of them. For example, Annovera coming from Therapeutics MD, [inaudible 01:14:40] coming from [inaudible 01:14:41] Med, Twirla coming from Agile, Phexxi effective coming from Evofem. Those are our newer methods that are on the market. Now, what would your sort of being shepherded through clinical trials and ultimately marketing through these smaller companies, do you think that's the wave of the future?

**Daniel Johnston:**

Alison, do you want to take that first, or do you want me to take it?

**Alison Edelman:**

I'm interested to hear Dan's perspective. From my perspective, and some of this is just obviously opinion. Doing contraceptive work is high risk for people because there's a lot on the line and there've been products in the past that the industry has really gotten burned on. Industry at some point has to get reimbursement for all of the development that they've done at some point. I'm not going to go into the politics of drug pricing because that's really complicated too.

**Alison Edelman:**

And I know we all want to make sure that everything's available for everybody. But sometimes that doesn't help with the cost of development and the risks to it. It makes it hard and a lot of the big companies are no longer focusing on women's health care and contraceptives in particular. And that makes it difficult for having new products available.

**Alison Edelman:**

The Contraceptive Clinical Trials Network is one of the most active networks and trying to bring products to market. And that was originally under Dan's auspices with Diana Blithe. Because of some stuff is kind of moved a little bit out from his office, but I know he's been incredibly supportive of the work that we've done there. And it's nice to have the NIH behind us for that.

**Alison Edelman:**

Because of the partnership, we're able to help either companies go through the trials to bring it to fruition, to the FDA. So we partnered with kind of nonprofits like the Population Council research units or smaller companies to be able to kind of execute these studies at the level that the FDA needs to see to bring something to market. But I'm sure Dan has stuff to add too as well. Because I'm not even sure I answered the question.

**Daniel Johnston:**

Yeah. I can actually talk on that one for a while if I need to. I would say the withdrawal actually came, it was really 2006 to 2007. As I said, I used to work in this field at Wyeth Pharma and they shut down all of preclinical contraception development in 2006. J&J soon followed sharing [inaudible 01:17:16] had a large unit. And then shortly after that, actually the Woman's Health Departments closed. Including Wyeth again. As Pfizer was buying them, they were shutting down Women's Health.

**Daniel Johnston:**

To me it's been dead for about 50 years. But I actually see signs of coming back to life. I think the fact that Bayer signed the licensing agreement with Evofem for Phexxi, if I'm pronouncing that right a while ago. It was a milestone driven agreement. I think it was in the range of $300 million. That is a fantastic sign. I think Merck is still has some level of activity going. I think that's good. But I think you'll consider to see a small mid range pharma develop portfolios of contraceptives if they can.

**Daniel Johnston:**

And then I think the only way you'll probably see new big pharma come in, is if they can find an entire company and give themselves an immediate, automatic pipeline. Basically they'll buy a pipeline, because they're not going to make one now. So somebody else wants to make it, they'll buy the company. A big issue for these companies is the idea of who's going to sell it. The idea of selling now within pharmaceutical companies and putting out people to go sell is pretty much specialty pharma, which is oncology and gastroenterology and things like that. You don't have a lot of farmer reps visiting places.

**Daniel Johnston:**

I don't think where they're necessarily going to be... Even if you get a male contraceptive, who is going to sell it? Where's your sales force to go sell a male contraceptive? Is it going to be the general practitioner or do you go to urologist? And then you have to start working deals to get your product in front of them. So there are some issues, and so I think they'll let small and midsize pharma handle them. And then if it ever happens to get large pharma back, it'll probably be a purchase to give themselves an automatic pipeline.

**Michael Policar:**

We're 20 minutes over. Had a lot of time. It's time to wrap it up. Any last comments?

**Alison Edelman:**

This has just been so fun. It's nice to be able to, to talk to the community and get your feedback. And it's just a fun topic and thanks for having me.

**Daniel Johnston:**

I'll echo that. Thank you for having me. This was very enjoyable. I apologize for my IT issues, but this was a lot of fun. I'm grateful for the opportunity. Thank you.

**Michael Policar:**

You got it. Shelby, any last words from you?

**NCTCFP:**

No last words, thank you, Dr. Policar, Dr. Edelman and Dr. Johnston so much. It's been wonderful. Thanks everyone for tuning in. And as you've seen, you will get slides, the recording of the webinar and an evaluation. Please fill that out, we'd love to hear feedback. Thanks everyone, have a great day.