Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/applying-clinical-trial-data-on-newer-cOcs-into-real-world-patient-care/12689/

Released: 06/29/2021
Valid until: 08/31/2022
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Applying Clinical Trial Data on Newer COCs into Real-World Patient Care

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Applying Clinical Trial Data on Newer CHCs into Real-World Patient Care” is provided by Omnia Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Shulman:
Our patients continue to report side effects related to their combination oral contraceptives, or COCs. A major concern for them is breakthrough bleeding. They also worry that their particular COC formulation is putting them at an increased risk for a cardiovascular or thrombotic event. Today, we will be discussing the recent FDA approval of an estetrol/drospirenone combination. Will this oral contraceptive formulation allow us to better address these issues?

This is CME on ReachMD, and I'm Dr. Lee Shulman. Today, I'm speaking with Dr. Jeffrey Jensen. Dr. Jensen, welcome to the show.

Dr. Jensen:
Thanks, Lee. It's great to be here.

Dr. Shulman:
On the clinician side, Jeff, we're always looking for ways to reduce the estrogen concentration in COCs to strike the right balance between efficacy and safety. Now, before we get into a discussion about the recently FDA-approved estetrol drospirenone COC formulation, can you explain why finding the right estrogen and/or estrogen formulation for COCs is so important for our patients?

Dr. Jensen:
Yeah, Lee, as you look back upon the history of oral contraceptives, one of the first major health risks that were discovered very rapidly upon introduction in the 1960s was, the risk of venous thrombosis. And this is a devastating event occurring in a young and healthy woman. By the time that most of these epidemiologic studies were published, doses were actually already beginning to reduce, and we understand that there's a clear dose-related effect of estrogens with thrombosis.

Now, it's important to remember that all of the current preparations or traditional preparations of oral contraceptives, combined pills, and combined hormonal methods contain a synthetic, highly potent estrogen ethinyl estradiol. And this is the compound that is associated with the majority of this risk, regardless of the route of administration. So there's been attempts over the years to lower doses of estrogens. And with this comes in a related problem that actually affects many more women, and that is the risk of breakthrough bleeding.

The clinicians and pharmaceutical companies have needed to strike a balance between dose and actually getting the right effects and combinations to reduce a whole range of side effects. Higher estrogen doses are related to a number of common side effects, breast tenderness, nausea. Again, most of these are less important from a health standpoint to health risk, but they are certainly annoyances for women. So these relationships between dose, between risk, and the benefits of cycle control are what we've needed to balance over

the last almost 60 years of oral contraceptive pill development.

Dr. Shulman:
You know, Jeff, I think that you and I truly can be the bridge from the older much higher-dose pills to the more modern lower-dose pills. We've been able to watch how they have worked with our patients, how safety has improved with regard to thrombotic events, but breakthrough bleeding has also been exacerbated by the lower doses.

You gave us a great overview of some of the safety and quality of life issues we confront when prescribing COCs for our patients. With that as a background, this would be a good time to discuss estetrol, or E4, a new estrogen with some unique properties that led to the recently approved estetrol/drospirenone COC formulation. Jeff, what can you tell us?

Dr. Jensen:
As I mentioned earlier, one of the reasons that a synthetic estrogen, ethinyl estradiol, is used in combined hormonal preparations is its high potency. And that's important because it allows for prolonged bioavailability, and it enables the doses to be very small. Along with this, you get reliable suppression of follicle development and assistance in the suppression of ovulation, which is a progestogen-mediated event. So finding a combination of a natural estrogen that would result in an acceptable bleeding pattern has been extremely challenging for the pharmaceutical industry.

There have been some attempts using natural estradiol, the natural ovarian estrogen. One product is currently FDA-approved for use as a birth control pill, but it has a quite complicated regimen. So finding this balance that would be a simple regimen, that would be acceptable and safe has been challenging.

Estetrol is a game changer in my opinion. Now, estetrol is a natural estrogen. It's present only in humans during fetal life, and it's felt to serve as a mechanism to reduce the effects of estrogen that are circulating on estrogen receptors. So what this new formulation has done is combine an estetrol with drospirenone, a very well-known progestogen with a great safety profile, that is relatively benign metabolically as far as having no androgenicity associated with this. And this combination has now been studied. It's been well documented to have very, very minimal impact on hepatic globulins, and it is something that in combination with drospirenone has been shown in clinical trials to be safe and effective as a contraceptive method in women.

So there's a lot going on with estetrol that is unique, and we could spend many hours speaking about this, but very, very briefly, we think mainly of steroid hormone actions acting through a classical steroid hormone receptor interaction that involves DNA transcription and then translations into proteins. Steroid hormones can also act through membrane receptors that do both rapid and nuclear signaling, and these are different pathways. And different select pathways in the body are influenced by relative effects that are both classical and membrane binding. You can consider estetrol as a selective agent that has mixed agonist, antagonist, estrogenic activities in different tissues. Now, some people have gone to term this a natural estrogen with selectivity in tissues, or NEST. It has to do with the unique differences between the classical steroid hormone DNA transcription/translation response and the membrane response that I spoke about earlier. And the net effect of this is a product that maintains the femininity aspects of a good estrogen effect, stimulates the endometrium, results in good bleeding profiles without the strong hepatic effects and breast effects that may be deleterious.

Dr. Shulman:
You know, you bring up, Jeff, an excellent point that this truly is a unique molecule that really we have not dealt with in the decades since the introduction of the combination pill. I think it's also important to sort of reaffirm that while in nature this particular estrogen is found in the fetus mostly, it is readily synthesized from soy, and therefore the product that is used is a plant-based product. It is an easily synthesized product, and that is the source of the estetrol that is found in the contraceptive pills and in the other regimens that will follow that will utilize this particular molecule.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Jeffrey Jensen. We're discussing the ongoing efforts to balance the benefits and risks of estrogen in combined oral contraceptives, and how that effort may have just become a bit easier to accomplish.

You mentioned clinical data supporting the use of estetrol as part of the formulation for a combined oral contraceptive. Perhaps you can discuss some of the early clinical data for estetrol and then focus on key data presented at ACOG 2021.

Dr. Jensen:
So estetrol has been studied as an oral contraceptive in a variety of ways. In early-phase studies, it has been combined in different dosage with 2 different progestins, drospirenone and levonorgestrel. These studies were used to evaluate ovulation inhibition and endometrial effects. The summary results of these studies have also been used to evaluate satisfaction, body weight, and general well-being. Taken together, the results pointed to a combination of 15 mg estetrol and 3 mg drospirenone as having the higher user acceptability and satisfaction and a positive benefit on weight control.

And they showed very strong and potent suppression of the pituitary-ovarian axis and inhibition of ovulation in otherwise young healthy women. A lot of background studies were looking in combining this effect, evaluating hepatic globulins, looking at markers that are associated with perhaps coagulation risk. All these showing a very, very favorable profile. And comparison studies were done looking at this combination of estetrol and drospirenone with the existing EE-drospirenone type of pills. And these showed very satisfactory cycle control and the effects on liver enzymes.

So in order to register a product as a contraceptive, pivotal phase 3 studies must be performed. Two studies with the same study design were organized; one in Europe and Russia, and one in the United States and in Canada. And these were studies that evaluated the 15-mg estetrol, 3-mg drospirenone combination in a 24-day active pill a 4-day hormone-free interval regimen. So this is the same sort of monophasic regimen that most clinicians favor and most women are used to.

These studies evaluated over 3,600 women and the results were very impressive. The primary outcome was the Pearl Index, the standard measure of pregnancy risk. What we saw in the US and Canada trial was a Pearl index of 2.65 which compares extremely favorably with recently approved combined hormonal preparations. The pregnancy rates in the Europe and Russia study were closer to 0.4. These are effectiveness studies, they reflect real-world use of the product, so it's not surprising that the rates are higher in our population in the US.

The secondary outcomes included bleeding patterns and safety in the US trial. We saw the unscheduled bleeding/spotting occurred over 12 cycles in 19.5% of women. When you look at these results overall, there were no major differences in subgroup analyses. So when we looked at age, BMI, or prior contraceptive use, that is whether women had switched from another method in the past 3 months or never used an oral contraceptive. Notably the average age of the participants in this study was 26. About 20% were Black and about a quarter had a BMI over 30. And this is really remarkable in a contraceptive phase 3 study. So with that, I think there is substantial evidence supporting the safety and the efficacy in a broad use of women from 2 global studies.

So when I look and compare it with some other recently approved products, only one case of VTE was reported in these 3,600 women. And if you look at a baseline incidence of VTE that we consider now, the population estimates are somewhere probably between 2 to 4 per 10,000 because recent diagnostics have increased the baseline incidence of DVT. So if you're looking at almost 4,000 women to see a single case of VTE, it really could almost be considered baseline risk.

Now, I do want to stress that there's insufficient power in a phase 3 study to really give us any confidence about occurrence of VTE. These are uncommon events and may be reported higher or lower in a clinical trial. But taken together, I think that this study really demonstrates a very high efficacy and excellent cycle control of the estetrol/drospirenone combination and gives us some preliminary indication that is highly supportive of the observation of reduced hepatic impact of the product.

Dr. Shulman:
Jeff, that's a wonderful overview. The only thing I would add is that for me, in addition to the only single case of documented VTE, was that the unscheduled bleeding and spotting profile was really not impacted by age, BMI, or prior contraceptive use. And that's something we've really not seen with the older conventional pills.

Jeff, some of the information on patient characteristics that you shared from the ACOG 2021 presentation really takes me to my next question. Based on the breadth of clinical data for estetrol/drospirenone, how would you go about deciding which patients should be offered this formulation in the real world of our clinics?

Dr. Jensen:
First, as I did not state earlier, 24-day regimens have been shown to be more effective, so having a 24-day regimen is an excellent option. As I mentioned earlier, this is great clinical data, very broad clinical data from the two pivotal studies really showed that effectiveness was not influenced by BMI or other baseline patient characteristics. So this is a safe product and it was well studied in women of higher BMI. Specifically, about estetrol, it's a unique formulation, and its chemistry is really highly suggestive of reduced hepatic impact. Clearly, in relationship to ethinyl estradiol, EE, but also with respect to estradiol, that it may have favorable properties that make it uniquely suitable as an oral contraceptive.

And finally, I think that this is a pill that can really benefit all women. It's a product that's applicable to younger women, older women, really all women who might be in clinical practice. So I think that this will be a regimen that's well accepted and well tolerated by patients and recommended by clinicians.

Dr. Shulman:
I absolutely agree with you. For me, this is a first-line mainstream option for a woman who chooses to use a pill and who has no contraindications to estrogen and progestin use.

Jeff, this has been a fascinating conversation. But before we wrap up, do you have a take-home message that you want to be sure our audience really heard?

Dr. Jensen:
Yeah, I think the take-home message, Lee, is that combined hormonal contraception is extraordinarily well studied and safe, and there has been a lot of efforts over the years to better understand these formulations. There has been tremendous progress made as far as improving safety. Estetrol represents a potentially groundbreaking step in the direction of reducing potential risks associated with hepatic globulin changes in coagulation. We won't get the final answer about this until phase 4, after the product has been in widespread clinical use, but I'm optimistic that this may represent a major breakthrough in improving the safety of oral contraception.

Dr. Shulman:
You know, Jeff, the only thing I'm going to add to that is that as opposed to over the course of the last several decades, new pills came out, they changed dose, they changed regimens, perhaps a new progestin. This particular regimen truly heralds the introduction of a completely new estrogenic molecule. And I think as you well summarized throughout this presentation, this really has the opportunity to minimize many of the adverse issues associated with conventional estrogens and potentially maximize our ability to find a method that woman is going to use consistently and correctly for as long as she chooses not to be pregnant.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in, and thank you, Jeff, for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Jensen:
Lee, it’s always a pleasure. I look forward to getting together again soon.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Omnia Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Omnia. Thank you for listening.