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

New CHCs: Native Estrogen with Specific Actions in Tissues (NEST)

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You're listening to CME on ReachMD. This activity, titled "New CHCs: Native Estrogen with Specific Actions in Tissues (NEST)", is provided by Omnia Education and is supported by an independent grant from Mayne Pharma.

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Dr. Shulman:
The estrogen component of combined oral contraceptives, in part, helps to suppress FSH [follicle-stimulating hormone] and folliculogenesis. It also stabilizes the endometrium, helps minimize unscheduled bleeding, and supports progestin activity. Nonetheless, there are downsides to the estrogen in oral contraceptives, including an increased risk for cardiovascular and thromboembolic adverse events, such as pulmonary embolism and deep vein thrombosis. Thus, there's an unmet need for a form of estrogen that can be used in combined oral contraceptives that maintain these benefits while offering a lower risk of thromboembolic events.

This is CME on ReachMD, and I'm Dr. Lee Shulman. Today, I'm speaking with Dr. Andrew Kaunitz about combined hormonal contraceptives, or CHCs, and the evolution of a native estrogen that demonstrates specific actions in tissues, also known as NEST. And further, we'll discuss why a high NEST activity is important when developing an oral contraceptive with an improved safety profile.

Dr. Kaunitz, welcome to the show.

Dr. Kaunitz:
Thank you, Lee, it's a pleasure to be working with you again.

Dr. Shulman:
Andy, let's dive in. Ethinyl estradiol – the potent estrogen used in almost all oral contraceptives – helps to suppress ovulation and stabilize the endometrium but also has downsides. Can you explain for our learners what some of the downsides of ethinyl estradiol are, especially as related to an increased risk for venous thromboembolism?

Dr. Kaunitz:
Lee, the original oral contraceptive formulations, and I'm talking now all the way back to the late 50s or early 1960s, included between 80 and 150 micrograms of ethinyl estradiol. Although those high doses were associated with a low incidence of breakthrough bleeding, these formulations also rather dramatically increased risk of venous thromboembolism, or VTE, including pulmonary embolism [PE]. Today's combined oral contraceptive formulations use between 10 and 35 mcg of ethinyl estradiol, resulting in substantially less VTE than the older, high-estrogen-dose pills. However, pills with lower doses of ethinyl estradiol have higher rates of unscheduled or breakthrough bleeding. As we envision a better oral contraceptive, formulating it with an estrogen that has less potential to increase risk of VTE while maintaining good cycle control would be an appealing option.

Dr. Shulman:
You know, Andy, we've really tried to strike the right balance with ethinyl estradiol dosing with regard to the risk of VTE and pill-related side effects. But that task has actually proven to be unsuccessful for some women, and in fact for many women who are using an oral

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contraceptive.

Andy, you mentioned the importance of identifying an estrogen for inclusion in combined oral contraceptives that maintains the many benefits of estrogen but offers less risk for VTE. One candidate is estetrol , or E4, which is produced by the fetal liver and is an estrogen with a high NEST activity. That term, NEST, or native estrogen with selective actions in tissues, may actually be a new term for many of our listeners. What is NEST activity, and how is it important when developing a combined oral contraceptive with a more favorable safety profile?

Dr. Kaunitz:
Lee, estrogens function by binding to estrogen receptor, or ER, alpha (α), thereby either suppressing or enhancing transcription of various target genes and causing rapid steroid signaling. ERα are present in the nucleus as well as the cell membrane. Estradiol, or E2, is the estrogen produced by ovaries and binds and activates ERα in both the nucleus and the cell membrane. In contrast, estetrol , or E4, binds and activates nuclear estrogen receptor alpha, but antagonizes the activity of membrane ERα by blocking steroid signaling.

E4 activity differs from that of selective estrogen receptor modulators, or SERMs, which alter alpha estrogen receptors such that these receptors recruit other cellular cofactors that act as agonists or antagonists. In contrast, E4 itself has mixed agonist and antagonist estrogenic activity in different tissues. Accordingly, E4 is a native estrogen with selectivity in tissues, that is, it has NEST activity. An observation worth noting is that compared with ethinyl estradiol, E4 has substantially less impact on clotting factors.

Dr. Shulman:
We are clearly in need of an estrogenic molecule that will maintain the benefits of the older or conventional estrogen methods and yet reduce the adverse event profile that had been historically associated with them. This is very exciting stuff.

Well, that being said, we haven't heard much about E4 over the years. What has been its developmental history, and what pharmacologic properties suggest that it may be suitable as the estrogen component of a combined oral contraceptive?

Dr. Kaunitz:
Estetrol , or E4, as you've mentioned, is a naturally occurring estrogen discovered in 1965 – decades ago. This steroid is produced exclusively and in large quantities by the human fetal liver. Although E4 has a relatively low affinity for the estrogen receptor, this is largely compensated for by its high oral bioavailability. After its initial discovery, research on E4 was performed for approximately 2 decades in unsuccessful attempts to discover its function or to correlate its maternal plasma levels with fetal well-being. Subsequently, scientific interest in the hormone declined. In recent years, however, preclinical and clinical studies have suggested that E4 might be effective for several indications, including contraception. And it's important to note that E4, or estetrol , is plant-based – in fact, specifically, it's soy-based, and this obviates the need for fetal tissue.

Dr. Shulman:
Well, Andy, a plant- or soy-based product is clearly a strongly desired characteristic, and I believe further adds to the potential of E4 in contraceptives, as well as for other clinical uses.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Andrew Kaunitz. We're discussing the evolution of estrogen in contraception and are ready for a deeper discussion on estetrol , or E4, which is currently being evaluated in clinical trials for its contraceptive efficacy and safety.

Andy, you mentioned that estetrol has been around for a long time – decades – and never once has this estrogen been used in a contraceptive. I'm sure our listeners would be very interested in learning about the range of data supporting the use of E4 as a component of a combined oral contraceptive. Can you give us a brief synopsis of why E4 might be appropriate for use in a contraceptive?

Dr. Kaunitz:
Lee, in a dose-ranging pilot study published in 2015 in *The European Journal of Contraception and Reproductive Health Care*, investigators found that when combined with a progestin, doses of E4 greater than 10 mg consistently suppress ovulation. Investigators then performed a study comparing oral contraceptive with different doses of E4 combined with the progestin drospirenone or levonorgestrel. This report was published in 2016 in the journal *Contraception*. The conclusion was that a formulation which combined 15 mg of E4 with the progestin drospirenone had the most favorable bleeding patterns, minimizing unscheduled or breakthrough bleeding, as well as the absence of withdrawal bleeding. In a presentation made at the 2019 ACOG annual meeting, investigators reported findings of a trial which compared coagulation factor changes in women randomized to 15 mg of E4 combined with 3 mg of drospirenone compared with the marketed formulation of ethinyl estradiol combined with the same dose of drospirenone. The investigators concluded that the E4 formulation had substantially less impact on coagulation factors compared to the ethinyl estradiol

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formulation. Finally, two large, phase 3 studies of the investigational oral contraceptive, combining 15 mg of E4 with 3 mg of drospirenone, found that this formulation is highly effective and associated with excellent cycle control.

Dr. Shulman:
Andy, this is incredibly exciting news for clinicians and women alike. We have seen over the last decade the development and the use of long-term contraceptive methods – the LARC methods. And this, to me, has the potential of completely changing the oral contraceptive marketplace, which as you have said, has mostly been using ethinyl estradiol as its estrogen component.

Well, this has certainly been a fascinating conversation, but before we wrap up, Andy, can you share your one take-home message with our audience?

Dr. Kaunitz:
Certainly, Lee. An effective oral contraceptive that's associated with a lower risk of VTE than conventional pills formulated with ethinyl estradiol certainly would represent an attractive option for clinicians and our patients. I'm hopeful the investigational E4/drospirenone oral contraceptive represents such a contraceptive.

Dr. Shulman:
You know, for me, Andy, the potential to combine E4 with a progestin, in a sense, almost provides the kind of method that all of us have been looking for, for so long. A method that provides the contraceptive effectiveness, as well as the side effect profile that we saw with higher-dosed contraceptives, but at this point now, to combine that with a safety profile with a profoundly reduced increased risk for VTE. I think such a pill would be an exciting addition to our contraceptive armamentarium and would further empower women to choose a method of contraception that they would use consistently and correctly for as long as they choose 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, Andy Kaunitz, for joining me and for sharing all of your valuable insights today. It was great speaking with you.

Dr. Kaunitz:
Lee, it's always a pleasure, and for that matter, an honor to work with you. Thanks very much.

Announcer:
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