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The Evolution of Estrogen in Contraception—From E1 to E4

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Dr. Shulman:
When oral contraceptives were first introduced nearly 60 years ago, the active estrogen component was mestranol. When safety concerns led to the dose being reduced to 50 micrograms or less, ethinyl estradiol was by then the estrogen component. Further modifications led to the use of estradiol in some oral contraceptives. There is also a progestin component in oral contraceptives, and there are a plethora of progestins. Whatever the combination, the common goal of the physician and patient is to optimize contraceptive efficacy and cycle control, while minimizing adverse events, which are often a result of the estrogen constituent. New combined oral contraceptives that use new estrogen and/or progestin components have the potential to improve on current options.

This is CME on ReachMD, and I'm Dr. Lee Shulman. I'll be talking with Dr. Anita Nelson about the evolution of estrogen in contraception, and if a game-changing development is on the horizon. Dr. Nelson, welcome to the show.

Dr. Nelson:
Thank you, Dr. Shulman. Over the past 30 years, I've participated in numerous clinical trials of oral contraceptives, assessing, as you said, differing amounts of estrogen, differing active placebo regimens, new progestins, as well as clinical trials of transdermal patches. And if my memory serves me correctly, you were often involved in those same trials, right?

Dr. Shulman:
Quite correct, and I was very pleased to participate in them. So let's dive in. We've seen so many changes in the dosing of estrogen and oral contraceptives, particularly in terms of the reduction of the amount of estrogen. Can you spend a minute or two reviewing the key changes that have occurred and the rationale for these changes?

Dr. Nelson:
I think it's really important, first, to remember why estrogen is included in oral contraceptives. We know that progestin-only methods provide very effective contraception, but they are often associated with unacceptable bleeding patterns. Estrogen is added primarily to stimulate endometrial proliferation, to give good cycle control with predictable bleeding.

Now in the past, the ethinyl group, as you said, was added to estradiol to increase its potency and the duration of its action. It is fairly resistant to hepatic metabolism and can support the endometrium for at least 24 hours. This was needed with early progestins, especially those with short half-lives. Now we know that estrogen is responsible for the cosmetic benefits of the pill, like treatments for hirsutism and acne, but it's also responsible for many of the risks, particularly the venous thromboembolism risks. Each time ethinyl estradiol passes through the liver, it induces the production of prothrombotic proteins and inhibits the production of antithrombotic factors.

Estradiol valerate was introduced when a new progestin, dienogest, which has strong endometrial and anti-angiogenic properties, became available. A phase 4 study demonstrated that this pill had lower VTE [venous thromboembolism] risks than all but the LNG, levonorgestrel pills.

An even weaker estrogen, E4, has now been paired with a fairly familiar progestin, drospirenone, that allows its full expression in a new formulation that we've recently studied.

Dr. Shulman:
You know, our goal has always been to provide a safe and effective contraceptive that would be used consistently and correctly by women who are seeking not to become pregnant. I think you've done a great job in taking us through the travels of pill development over the past several decades.

Now that we've reviewed the rationale for these changes, and before we get into the specifics with respect to ethinyl estradiol and estradiol, can you offer our participants an estrogen primer, detailing the non-contraceptive roles of E1 through E4 in a woman's reproductive life cycle?

Dr. Nelson:
Well, we know that estrogens play pivotal roles in all phases of women's lives. Estrone, E1, is produced throughout a woman's life. During the reproductive years, much of E1 and its metabolites come from metabolism of the ovarian-produced estradiol. In post-menopausal women, it is the pivotal estrogen derived from peripheral conversion, aromatization of androgens, particularly in the adipose tissue. E2, estradiol, is the most potent natural estrogen. It's 10 times more potent than E1. It's produced in the ovary and has important health benefits during the reproductive years. We know that E3 is produced by the placenta and is famous for being a marker of fetal well-being. What most people don't know is that E4 is an even weaker and somewhat unknown estrogen that's produced only by the fetal liver. It is about 1/20 as strong as estradiol.

Dr. Shulman:
Clearly there are many estrogenic compounds that provide an estrogenic milieu, and it's our responsibility to help find the best estrogen molecule and dosing regimen to optimize contraceptive safety as well as efficacy.

So, Dr. Nelson, let's return to ethinyl estradiol and estradiol. Ethinyl estradiol is the estrogen most prevalent in today's combined oral contraceptives. As our learners are probably aware, ethinyl estradiol is the synthetic equivalent of endogenous estradiol, also known as 17 beta-estradiol. Can you discuss the pharmacokinetics of ethinyl estradiol and 17 beta-estradiol and how these translate into their contraceptive activities? And further, what are the clinical benefits and drawbacks of ethinyl estradiol and 17 beta-estradiol?

Dr. Nelson:
As I alluded to earlier, the primary role of estrogen in combined hormonal contraceptives is to support the endometrium and to provide predictable, scheduled bleeding. Once-daily dosing requires that estrogen support endure for a full 24 hours. Now pharmacologic doses of estrogen also provide negative feedback that sort of tempers gonadotropin and release, particularly FSH, and it reduces follicular genesis, that helps with cycle control and contraception. Now when it's taken orally, estradiol unfortunately is rapidly metabolized into a series of weaker estrogens and is often conjugated to inactivate, even before it reaches the bloodstream.

So what was needed was a potent, long-acting estrogen, which is what adding that ethinyl group to estradiol did. So in creating ethinyl estradiol, we wind up with a long-acting, synthetic estrogen that resists metabolism in the liver and conjugation. It generally takes about 5 or 6 passes through the liver to reduce the circulating levels of ethinyl estradiol by 50%. But again, each pass through the liver also increases the prothrombotic proteins. Most women can tolerate the changes in this balance between clotting and anticlotting factors, but we do know that the overall VTE risk is measurably increased.

Dr. Shulman:
You know, while there are many estrogenic molecules, and each of them exert a unique metabolic and physiological effect, I think it's clear that a new estrogenic formulation may actually serve to improve contraceptive effectiveness and safety and, therefore, increase the utilization of contraceptive pills.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Anita Nelson. We're discussing the evolution of estrogen in contraception, and are now ready to focus on estetrol, or E4.

Dr. Nelson, let's transition now to estetrol, or E4, which is currently being evaluated for its contraceptive efficacy and safety. Estetrol has been around for a long time, actually decades, and has never once been an estrogen utilized in a contraceptive. I'm sure our listeners would be very interested in learning about E4. Can you give us some background on its history and what the pharmacologic basis is for its use as a contraceptive?

Dr. Nelson:
Well, you're absolutely right – very few people know about this estrogen. But E4 is the fourth estrogen that was discovered way back – 1965 – at the Karolinska Institute in Stockholm. It's a natural, fetal, estrogenic steroid, synthesized, as I said, by the fetal liver only during pregnancy. And we recognize that because it was so very weak, it did not seem to have a role for contraception. It's a steroid hormone, and it has 4 hydroxyl groups – hence E4 – 2 more than estradiol, which is the estrogen we said that's produced by the granulosa cells of the human ovary during reproductive years.

The two additional OH groups have a critical impact on the oral pharmacokinetics of E4. The half-life of E4 is 20-28 hours. Now this compares with the half-lives of 10 to 20 minutes for E3, 1 to 2 hours for natural estradiol, and the 10 to 12 hours for micronized estradiol.

E4 is minimally, if at all, metabolized, and is not reconverted to either E3 or E2. Studies of the receptors for E4 and its binding and target interactions demonstrated that E4 has high selectivity for the estrogen receptors, indicating the potential for low risk of side effects.

Dr. Shulman:
For decades, we've manipulated dosing of ethinyl estradiol and estradiol, as well as developing novel dosing regimens to provide a safe and reliable contraceptive. The potential availability of a new estrogenic molecule truly may be a game changer, with providing that new and potentially effective and safe regimen that I think all of us have been looking for for decades.

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

Dr. Nelson:
Well, I agree with you entirely, Dr. Shulman. The trend in contraceptive development in recent years has really focused to reduce the dose, then the potency of estrogen, or to completely eliminate it. E4 has important features that you mentioned – low potency, minimal metabolism, and selective binding to the estrogen receptor – that together can offer acceptable cycle control when combined with a progestin that does not reduce its impacts.

Dr. Shulman:
Well, again, the possibility of a new estrogenic molecule, I think, excites those of us in drug delivery as well as those of us who are providing clinical care to a wide array of women who are seeking safe and effective contraception. For me, often the focus in improving the efficacy and safety of oral contraceptives is centered on the progestin. And now we have an estrogen with the potential to positively address the cardiovascular concerns of oral contraceptives, if not other formulations of combined hormonal contraceptives, and do so in a manner that may enhance the patient tolerability profile.

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

Dr. Nelson:
Thank you and goodbye.

Announcer:
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