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

Reducing Estrogen Dosing in CHC: *The Quest to Balance Safety with Tolerability*

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Dr. Shulman:
For our patients who use combination oral contraception, we continue to seek the safest and most effective formulation, one that optimizes the many benefits of estrogen, but also reduces its adverse events, particularly those that are cardiovascular and thromboembolic in nature.

This is CME on ReachMD, and I'm Dr. Lee Shulman. Today, I'm talking with Barbara Dehn, a nurse practitioner with vast contraception counseling and prescribing experience. Barb, welcome to the show.

Ms. Dehn:
Oh, Lee, thank you so much for the invitation. It's a pleasure to be here.

Dr. Shulman:
Barb, let's dive right into our discussion. Can you give our learners some insight into the historical context of the reduction of estrogen in COCs [combined oral contraceptives]?

Ms. Dehn:
Well, of course, right? I mean, you and I have both been practicing a long time, and we've cared for women on pills that contain 50 micrograms or more of estrogen. So reducing the estrogen dose was really important for two main reasons. First, to reduce the bothersome side effects that impact a woman's quality of life, and these are the side effects women should not have to put up with for effective contraception. Those side effects include headaches, enlarged and tender breasts, nausea, fluid retention, and edema. And also, very importantly, and sometimes even more importantly, reducing estrogen in the pill meant reducing the risk of serious, life-threatening events, because as you know, and as you mentioned, higher doses of estrogen are associated with higher risks of cardiovascular events including thromboembolism and myocardial infarction. Those serious risks are more pronounced in women with other predisposing factors like smoking and obesity. And Lee, as you and I both saw in our practice, when we lowered the estrogen doses to less than or equal to 35 micrograms, those serious risks didn't completely disappear, but now they're significantly decreased. And I think we're all looking for a balancing act, right? I mean we – we need adequate estrogen to prevent ovulation and to provide effective contraception, but we don't want too much estrogen because of the serious risks and side effects. But the problem was also compounded because when estrogen doses were reduced further, to 20 micrograms or less, women started to experience a lot more breakthrough bleeding and spotting, which was the main reason they stopped taking the pill, putting them at an increased risk for an unintended pregnancy.

Dr. Shulman:
You know Barb, I can't agree with you more. I think the way to characterize my 30-plus years of contraception practice has been that

balancing act, trying to find the right dose that provided the right side effect profile while lowering the adverse event profile. But again, even at that happy medium, we were frequently still at an increased risk for certain adverse events, and particularly cardiovascular and thromboembolic events.

Barb, that was a great overview. Can you give us some more specific examples of the daily quality of life issues that many women face when they use current combined oral contraceptive formulations? Do you have some examples of issues like breakthrough bleeding, spotting, and breast tenderness from your clinical practice?

Ms. Dehn:
First of all, they are scared. They want to know, what does this bleeding mean? Is this a problem? They think that there's something seriously wrong with them, and they need a lot of reassurance. Many are angry because they've ruined clothes, they don't want to wear pads just in case, and unscheduled bleeding interferes with their work, with sports, their relationships, their sexuality, and their day-to-day life. Now when it comes to breast tenderness and enlargement, women are very understandably distressed. They worry that this could be a risk factor for breast cancer later on down the line. So all of these things really affect women's day-to-day quality of life.

Dr. Shulman:
You know, Barb, it seems for both of us, that while we have sought that happy medium between side effect profile and risk, we actually have never gotten there. And the reason why we've not gotten there is because we've really not eliminated the risk or even profoundly reduced the risk. And for many women, as you so described, the side effect profiles are perceived to be not just nuisance effects, but truly life-threatening effects.

Barbara, you mentioned the need to identify an estrogen for inclusion in combined oral contraceptives that maintains the benefits of estrogen but has less risk for VTE [venous thromboembolism] and pulmonary embolism. Estetrol, or E4, has emerged as an investigative estrogen with some unique pharmacologic qualities related to its potential use in combined oral contraceptives. Could you put some of that background into perspective for our listeners?

Ms. Dehn:
Well, Lee, I think your audience will be very interested in many of the characteristics of estetrol, or E4. It's a naturally occurring estrogen and it's produced in large quantities during pregnancy by the human fetal liver. It was discovered in 1965 and initially it was thought to be an indicator of fetal health. Now, E4 can easily and readily be synthesized from soy, meaning it's plant-based, and that means there's no need for any fetal tissue. Although estetrol, or E4, has a relatively low affinity for both estrogen receptors, alpha and beta, the low affinity is largely compensated by its high oral bioavailability. One of the other characteristics that's most compelling for me is that E4 has mixed agonist and antagonistic estrogenic activity in different tissue. Now, E4 is not a SERM [selective estrogen receptor modulators]. It has what's known as NEST activity, and that's native estrogen with selectivity in tissues. It is unique compared to estrone and estriol, and when compared to ethinyl estradiol [EE], E4 has been shown to have less impact on clotting factors. That's one of the reasons it's been studied as a possible estrogen for contraception.

Dr. Shulman:
You know, I would say, Barb, that we are all looking for this estrogenic molecule, and in some way, it really fills all the check boxes for what we wanted as a part of that combined contraceptive pill.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Barbara Dehn. We're discussing the ongoing efforts to balance the benefits and risks of estrogen in combined oral contraceptives and what the future might look like for the many women using this form of contraception.

Barb, can you provide some of the clinical specifics that demonstrate estetrol is an effective and potentially safer estrogen for contraception? If and when it's approved for inclusion in new formulations of combined oral contraceptives, why should we recommend it to our patients?

Ms. Dehn:
So estetrol, or E4, was studied for years in both the US and Europe and in the phase 2 clinical trials that evaluated the efficacy of different doses of E4 when combined with either drospirenone or levonorgestrel to suppress the pituitary ovarian access and prevent ovulation in healthy, premenopausal women. And what was very reassuring was there was no ovulation in any of the treatment groups, and the endometrial thickness was equally suppressed in all groups. Another phase 2 trial evaluated the acceptability of E4 with drospirenone when compared to E4 with levonorgestrel – and that's acceptability among women. And there, it was demonstrated that women on 15 mg of E4 with 3 mg of drospirenone were more likely to complete the study. They were more satisfied with their regimen, and they had more positive weight control. So women in both North America and Europe were evaluated in the phase 3 trial using a pill pack with 24 active days. That had the 15 mg of E4 and 3 mg of drospirenone, and there were 4 inactive, hormone-free days. In addition

to the contraceptive efficacy, the vaginal bleeding patterns, which of course, indicates cycle control, were evaluated, as well as the general safety and acceptability. Now the results showed Pearl Index of what we all want, which was 2.65. And in the North American trial there were 26 pregnancies, 12 of which were attributed to user failure, all within what's expected. But what I like to see here is what my patients care about. Over 80% of women had acceptable bleeding patterns with only 19.5% experiencing unscheduled bleeding and spotting. And that occurred over 12 cycles.

Dr. Shulman:
You know Barb, I think that summarizes well the clinical experience with the initial trials. And for me, with regard to the safety signal of VTE, that's so critical. And it really shouldn't surprise any of us, based on the information that Mitch Creinin presented at ACOG in 2019. In that presentation Creinin and his colleagues reported the findings of a trial that compared coagulation factor changes in women who were randomized to the E4/drospirenone pill, comparing it with a marketed formulation containing ethinyl estradiol. And what they found was that the E4 formulation had substantially lower impact on coagulation factors compared to the pills that contained EE.

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

Ms. Dehn:
Well, Lee, I have to say that I'm really excited that we may have a new estrogen, estetrol, or E4, in combination with drospirenone, as a contraceptive option. This novel combination has been shown to have an acceptable level of contraceptive efficacy, and a very favorable bleeding profile as well as a favorable safety profile. In addition, I'm encouraged by the minimal impact on coagulation pathways. And because compliance is so critically important for efficacy, the fact that women viewed this combination favorably is a plus. I think the use of this unique estrogen is highly promising for a new contraceptive formulation.

Dr. Shulman:
You know, Barb, I'm going to say, "Ditto." Because I think all these years, we've looked at changing the dose of estrogen. For some pills, we went from estrogen to estradiol. There was talk of even E3 pills – estriol pills. But I think we have finally arrived at an estrogenic molecule that truly does check all of the clinical boxes – the safety boxes, the efficacy boxes, or the adverse outcome boxes. I think there's great promise for this, and if it is, in fact, approved for use, I think it will become a well-accepted part of our contraceptive armamentarium.

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

Ms. Dehn:
Well, thank you very much for inviting me, Lee. I always enjoy our conversations.

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