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## Expanding Choices in Combined Hormonal Contraceptives—The Contraceptive Patch

Announcer:

Welcome to CME on ReachMD. This activity, entitled “Expanding Choices in Combined Hormonal Contraceptives—The Contraceptive Patch” is provided by Omnia Education and is supported by an independent educational grant from Agile Therapeutics.

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Dr. Shulman:

Nearly all women will use contraception at some point in their lifetime. Women not only weigh various factors such as effectiveness, but also other factors, such as dose, hormonal versus nonhormonal, and also non-contraceptive benefits. What are some of the advantages to utilizing a contraceptive patch?

This is CME on ReachMD, and I'm Dr. Lee Shulman.

Dr. Portman:

And I'm Dr. David Portman.

Dr. Shulman:

So, let's dive right in. Dr. Portman, can you please give us some background information on the newer contraceptive patches? How do these newer contraceptive patches differ from the older patches?

Dr. Portman:

Well, the contraceptive patch was introduced in 2002. Right now, the patch that we have that was recently approved is a lower-dose patch using some newer patch delivery technology. As you can imagine, over the last decade and a half, that kind of technology has improved. The new patch doesn't deliver close to 50 mcg of ethinyl estradiol per day, but closer to 30 mcg, which is more in line with a low-dose contraceptive pill. As we know, transdermal delivery offers several advantages. Its controlled-release dosage form could potentially reduce incidence and severity of side effects. It avoids reduced bioavailability with oral administration, and it certainly could be more desirable to women who have difficulty or avoid taking oral medications. Taking a daily oral contraceptive pill has been found to be burdensome in up to 50% of women surveyed. So, clearly, a non-daily, non-oral contraceptive method is needed. And not being invasive like a vaginal ring or other procedure-related long-acting reversible contraception is an advantage.

The Ortho Evra patch, which was introduced, as I mentioned, in 2002, was quite popular, so we know that patients would likely seek this kind of option. However, with the higher dose exposure discovered several years later, as well as possible links with higher rates of thrombosis, it saw its utilization plummet from 1 in 10 women using it to very small fractions. So now with the new lower-dose patch that has a soft cloth backing that delivers the active steroids within the middle of the patch, rather than all the way out to the edge, it is quite a nice innovation and offers patients an alternative to that higher-dose patch. The Twirla patch, which was approved in the lower dose, which I mentioned, has levonorgestrel as its active progestin, which is a very well established and well characterized progestin.

Dr. Shulman:

I would say that given the extreme popularity of the older patch, that new patches that feature comparable effectiveness along with lower doses would likely lead to a popular choice for women who are seeking effective contraception but not wishing to use a pill on a daily basis.

So let's follow up on the contraceptive patches. How do these non-long-acting reversible contraceptives, or non-LARC options, compare to other choices? How do you counsel patients when they are interested in the contraceptive patch?

Dr. Portman:

Well, this is clearly a patient-driven choice, and we're really not there to tell patients what they should or shouldn't utilize in their contraception. They're going to help identify the methods that's right for them. As I mentioned, taking a daily pill could certainly be burdensome, especially for women who have non-24-hour types of schedules, and in this gig economy, we know that there's lots of women who don't stick to that clear 8 to 5, 9 to 5 type of schedule. So something that's not dependent on that is clearly attractive.

The patch also provides autonomy as opposed to some of the LARCs, which, Dr. Shulman, you're very aware of through your extensive research. We do know that they clearly are the most effective, but they also require procedures to place and remove, and certainly there's women who would like to avoid those types of invasive procedures in addition to even the invasiveness of inserting a monthly vaginal ring.

So, when I counsel patients, if they have decided that a non-daily, non-oral hormonal contraceptive is right for them, a patch could certainly fit in with their lifestyle. They need to apply it once weekly to clean, dry, non-oily skin. There is a little bit of a learning curve, so they'll learn which location is best for them, whether the abdomen, the upper torso, or the buttocks area. And they'll really do what is most convenient, and I think that the patients do like this visual reminder that their contraceptive is there, it's working, they know that that they can rely on that, and that gives them a great sense of autonomy and security. Skin irritation clearly would be a challenge with any skin delivery system. Fortunately, the new products have low rates of irritation and high rates of adhesion. So it really has optimized those advantages. And as we mentioned, with lower amounts of estrogen, we're hoping that this may mirror the other risks and tolerability issues that we do see with low-dose pills.

Dr. Shulman:

You know I think you bring up an incredibly important point. We have witnessed the increasing use and excitement about long-acting reversible contraceptives, but the reality is, is that a sizeable number of women, in fact, maybe a majority of women, don't necessarily want a long-acting reversible method. They'd like contraception for a year or two. And having new patches that are potentially going to be better accepted by women, is going to add more choice, going to make our jobs as clinicians easier because we'll be able to provide them with more options that they can choose from and hopefully help them find a method that they'll use consistently and correctly.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. David Portman. We're about to discuss the creeping Pearl Index, and the efficacy of the contraceptive patch.

As you've mentioned previously, Dr. Portman, we've seen the introduction of several new contraceptive methods, like the patch. These options have pregnancy rates that are higher than older contraceptives. These higher rates are interesting because they're coming out of clinical trials that used updated FDA guidance on factors like patient populations and the inclusion or exclusion of certain data. The late James Trussell coined this the creeping Pearl Index. How does the creeping Pearl Index come into play with the contraceptive patch?

Dr. Portman:

Well, thank you for mentioning Dr. Trussell, a real pioneer in contraceptive research and epidemiology, and I was privileged to coauthor the paper, *The Creeping Pearl*, back in 2013 in the journal of *Contraception*. The Pearl index is an easy but a flawed calculation. It's the one that clinicians are most familiar with because it does end up on most contraceptive prescribing information. It's essentially the number of pregnancies per 100 women-years of contraception, and it's highly dependent on both the numerator, number of pregnancies, and the denominator, the number of cycles or months.

And because of that, modern trials, which are capturing far more pregnancies and increasing that numerator and excluding more cycles such as those that use backup methods or don't include active vaginal sexual intercourse during the month, tend to decrease the denominator. So that's a perfect storm to have this Pearl start creeping up. We're identifying more pregnancies; we're excluding more cycles. So earlier trials that were done several decades ago where there weren't routine pregnancy tests done, where there weren't high-sensitivity ultrasounds to confirm early pregnancies, where they didn't keep diaries about sexual activity or eliminate cycles that use backup methods, had these very artificially low Pearls, less than 1. In fact, some studies that use the same exact contraceptive methods, oral contraception, as a control group in later studies, found that the identical pill may have gone from a Pearl Index of 0.5 to 4. So we know that these pills are no longer 10 times less effective, but the trial design has greatly impacted or caused the Pearl Index

to creep. And it's with these modern trial designs that are capturing all of this data, as well as including very diverse populations and women of a variety of BMIs that are far more representative of our population. I think the good news is that while we are seeing Pearl Indices creep up and they're no longer below 1, we can certainly rest assured that these methods are effective and yet that the trials are far more generalizable, and we just have to acknowledge that.

Dr. Shulman:

You know, with all due respect to you and James, perhaps the term "creeping Pearl Index" is – I don't want to say part of the problem. The issue isn't that the pills are less effective; the issue is that the trials are different. They're being evaluated in a different fashion. And we, as you said, we're seeing Pearl Indices that were less than 1 coming back at 4 and even higher because we're adjudicating their use in a far more real-world fashion than we did before.

Now that we have the background knowledge of the creeping Pearl Index, can you please go into greater detail of the SECURE trial? What was the significance of this study?

Dr. Portman:

The SECURE trial was the pivotal study – phase 3 study – that led to the approval of the new contraceptive Twirla patch. And just as we had discussed, Pearl Indices have gone from sub 1 to the 2, 3, and even 4 range in the most recent decade. So it's no surprise that the cumulative Pearl Index in the entire population was 5.8 in the SECURE trial. What's important to remember is the SECURE trial essentially enrolled all comers. They did not screen out for weight. Many trials conducted earlier in the last few decades didn't allow women who had a BMI of greater than 30 in. European studies are largely limited to Caucasian populations. The SECURE trial enrolled over a third of the patients with BMIs over 30 kg/m<sup>2</sup>. It had 24% of the population were African American and close to 20% Hispanic. So when patients look at these results, they can rest assured that this study was conducted in women that look just like them. And it's not artificially representative of a population that may have higher efficacy in a clinical trial, but in the real world, this should translate into very reasonable results.

And we shouldn't disregard the significant impact of BMI. In fact, the FDA's recent meta-analysis of oral contraception – combined hormone contraception, showed that women with a BMI over 30 had a 44% greater risk of pregnancy. And when they looked at the Ortho Evra patch, although there were very few obese women enrolled in that trial, it was about an 8-fold greater risk for those women who had high body mass. So it is no surprise that obesity impacted the overall efficacy rates, and in women over a BMI of 30 Twirla is contraindicated. However, it had an effectiveness rate of 93% even in that cohort and a 97% efficacy rate in those with normal weight and even those who are slightly overweight, 95% efficacy. So we're still talking about highly effective contraceptive methods, but conducted in a setting that is much more real-world than we would have found in trials conducted in years past.

Dr. Shulman:

You know, anytime we're able to access a more realistic and more accurate assessment of a contraceptive, for me, invariably leads to empowering not only us as clinicians, but patients as well, allowing them to truly choose a method that is going to work best for them for their contraceptive needs in addition to non-contraceptive issues. And I think we're all hoping that as we go forward, these new approaches to contraceptive assessment will, in fact, continue with other methods of contraception.

Well, this has been a fascinating and educational conversation, Dr. Portman. And to conclude this valuable discussion, can you share your one take-home message with our audience?

Dr. Portman:

Well, I think understanding the design of modern, inclusive clinical trials with generalizable results for our diverse US population is critical. And now with a new low-dose contraceptive patch recently approved, based on a study consistent with updated FDA guidance, broadens our armamentarium, and it's a welcome option we now have to offer to our patients.

Dr. Shulman:

I'll finish with this. Anytime we're able to bring new options to the table, we're able to be more effective clinicians. We're able to provide more choices and allow women to make decisions not based on hearsay or based on what they've been told to use, but rather what's available to them and what works best for them. And that will only go on to allow that unintended pregnancy rate to drop further.

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

Dr. Portman:

It was great speaking with you, Dr. Shulman, as well.

Announcer:

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