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What's New in Contraceptive Patches?

Narrator:

Welcome to CME on ReachMD. This activity, *What's New in Contraceptive Patches*, is provided in partnership with Omnia Education and supported by an independent medical educational grant from Agile Therapeutics.

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Your host is Dr. Lee Shulman.

Dr. Shulman: The negative consequences of an unplanned pregnancy are numerous. For one, they may be maternal or child health issues to consider. Also, an unplanned pregnancy often comes with questions surrounding one's ability to pursue a job with education and economic consequences being tremendous. An unplanned pregnancy can often leave the woman or the couple to have to make difficult decisions about abortion or their relationship status. For all these reasons, contraception is integral to the health and wellbeing of women of childbearing age and their children, families and communities.

This is ReachMD and I am Dr. Lee Shulman. Joining me are two well-known and well-regarded experts in the field of contraception and family planning, Dr. Andrew Kaunitz and Dr. Anita Nelson. Dr. Kaunitz is Professor and Associate Chair of the Department of Obstetrics and Gynecology at the University of Florida College of Medicine where he also serves as director of menopausal and gynecologic ultrasound services at Southside Women's Health. Dr. Anita Nelson is Professor Emeritus of Obstetrics and Gynecology at David Geffen School of Medicine at UCLA in Los Angeles, California.

Our panel today will review historical perspectives with contraceptive patches and clarify common misperceptions that clinicians and patients may hold regarding this option. Doctors, welcome to the program.

Dr. Kaunitz: Nice to be with you Lee.

Dr. Nelson: Thank you Lee.

Dr. Shulman: Dr. Kaunitz, let's start with you. Can you discuss what happened with Ortho Evra, which was an earlier version of a contraceptive patch? I thought it was really popular and then it just seemed to go away. What problems did it have?

Dr. Kaunitz: Lee, when the Evra first generation contraceptive patch first became available in the U.S. in 2002, as you mentioned, it was wildly popular. This patch released substantially more estrogen than associated with the use of a conventional low-dose oral contraceptive. The launch of the patch came at a time when longer-acting contraceptives, specifically the IUD and implant, were not widely used in the U.S. In this context, American women perceived a seven-day patch as an appealing alternative to daily oral contraceptive pills. Between initial availability in 2002 leading up to summer 2004, sales and use of the Evra patch boomed. Specifically, I remember in my office a rep for the patch coming by to pick up samples he had initially provided. This was necessary because, as he mentioned, the manufacturer could not keep up with the intense demand for this new contraceptive. All of this changed in 2005, however, after reports of adverse cardiovascular events began to appear in the media and advertisements from plaintiffs' attorneys followed. What started as a boom then became a bust, and now I see few women using or requesting transdermal or patch contraception. My sense is that clinicians and women would be interested in using a second generation patch which releases

substantially less estrogen than the earlier high-dose Evra patch.

Dr. Shulman: Now there is a newer patch called Twirla. Dr. Nelson, how is this patch different from the earlier Ortho Evra patch as well as the generic version of Ortho Evra, Xulane?

Dr. Nelson: Lee, you are right. There is a patch that is under investigation now and it does have three major differences from the previous patches. Number one, it offers lower ethinylestradiol levels instead of being like a 60 mcg type of product, it is much more like a 30 mcg pill, and it switched from a third generation progestin to a second generation progestin, levonorgestrel. People's concerns again about venous thromboembolism; the third one may sound frivolous, the service is, best described as being fuzzy so that people cannot put decals on it or mess up the absorption at all.

Dr. Shulman: Dr. Nelson, can you explain how the new patch is used, how often it needs to be changed and how well has this been tolerated?

Dr. Nelson: I think that people who are familiar with the older patches will feel very familiar with the counseling that they have to offer patients with this newer patch, because it is very similar – one patch once a week for three consecutive weeks and then the fourth week is a patch-free week, and this new investigational patch can be placed on the lower abdomen, the buttocks or the rest of the torso except around the breast. Different from the previous patches, it is not to be placed in the upper outer arm.

Dr. Shulman: If you are just tuning in, this is CME on Reach MD. I am your host, Dr. Lee Shulman and I am speaking today with Dr. Anita Nelson and Dr. Andrew Kaunitz about the contraceptive patch.

Dr. Nelson, let me have you continue. I understand you just finished a phase three clinical trial with this new patch. What can you tell us about this study and your findings?

Dr. Nelson: Well, the study that Andy and I just finished completing was a single-arm study involving over 2,000 women. This design was an open label, 13-cycle study. It was conducted at 102 U.S. sites. Now, what was really fascinating and very exciting about this, is the subjects who were enrolled in this. Subjects were 18 years old or older, but they had to be at risk for pregnancy, obviously, but there was no upward limit on the age of the women and more importantly, to reflect what is going on in America today, the weight of the women involved in this study included a lot in the upper range. So, we had women who weighed as little as 86 pounds, and there was one woman who weighed 390 pounds, so that meant her BMI in our study went up to 63, which is not seen with a combined hormonal contraceptive trial before. Over 35% of the study population will have BMIs greater than 30%. Also, we had a much more ethnically diverse group that has been studied in other groups. Almost a quarter of the women in the trial were African-American and 20% were Hispanic, so I think that that gives us really something much more to talk about when we are talking about giving realistic Pearl Index estimates to our listeners. Overall, the Pearl Index was 4.8, but it did vary by BMI. I think people would want to know that the mean number of days of spotting or bleeding, range between five and six per cycle, and very interestingly, if you added up all the adverse events that led to discontinuation of the patch, it totaled only 2.2%, very important with a patch is that application site reactions led to discontinuation in only 1.1% of women, so this was very well studied, very well tolerated and gave us a reflection of what we might expect when it comes out onto the market if it gets approved by the FDA.

Dr. Shulman: Dr. Kaunitz, the failure rates seem a bit higher than we typically expect with new contraceptive options. Is it less effective than the pills we are used to?

Dr. Kaunitz: Lee, in the first phase three clinical trial, women seeking contraception were randomized to a currently marketed pill with 20 mcg of ethinylestradiol and 100 mcg of levonorgestrel or the investigational patch known as Twirla. One year failure rates were similar in the pill and patch group and as Dr. Nelson just mentioned, we are between four and five percent, that is between four and five percent annual failure rate. A unique feature of the first clinical trial is that we assessed blood levels of estrogen and progestin in all participants. Specifically, we noted that in approximately 12% of women participating in this first large phase three clinical trial of this lower-dose patch, whether they had been randomized to the pill or patch, had blood levels of contraceptive steroids, which were essentially zero, indicating that more than 10% of clinical trial participants in both groups, both marketed birth control pill group and the investigational patch group, were not taking their study contraceptive. When we repeated the contraceptive efficacy analysis, excluding participants with laboratory verified noncompliance, failure rates were substantially lower in all participants. So, in the more compliant population of study participants, we saw substantially lower failure rates, and these failure rates were similar, once again, in the pill and patch users.

Dr. Shulman: Dr. Nelson, we have just heard some rather interesting results from the contraceptive patch trials with this newer patch. Can you elaborate a bit more about either the study design or the demography of the population that provided these rather unique and interesting outcomes?

Dr. Nelson: Lee, I agree with you entirely, and getting back to what Andy was talking about, the fact that we had people who did not use

the products, either one of them, really tells us a little bit more about what real-world utilization will show, and the other thing about the study that I think you will find interesting is that in advance there was a plan to evaluate the efficacy of this product by the BMI. So, rather than the older patches where they went back afterwards and tried to assess if it works as well or not, this was a planned evaluation and so they looked at the impact of BMI in all of the different study outcomes, but the one I think that interests us the most is in the second trial, we found that of women who had normal weight, the failure rate was less than 2.6% – the PI was, the total index. If you went to the overweight group, it was slightly over 5%, and if you went to women who were in the obese category that starts with a BMI of over 30, it was 5.5%. I think this is very much in line with what we have seen with that generalized Pearl creep that David Grinds described and what Andy pointed out is that in the first study they actually used a pill that had been approved in the 1980s with a Pearl Index of slightly over 1%, but in his trial, they were found to have over a 4% failure rate. So, I think that what we have seen is the way we detect pregnancy, how cycles where there is not risk for pregnancy, if women use other methods, all of those are taken out. The way we design studies today, we should not be surprised to see higher Pearl Indices.

Dr. Shulman: Dr. Kaunitz, with everything that we have just discussed, could this patch be used in an extended cycle regimen?

Dr. Kaunitz: Should Twirla, this lower dose, currently investigational patch become FDA approved and marketed, some women and clinicians will indeed be interested in extended or continuous use. Although in theory, such use would be safe and effective, we do need to keep in mind that no clinical trial data addressing extended or continuous use of this second generation, lower estrogen contraceptive patch is available.

Dr. Shulman: Well, with that I want to thank Dr. Kaunitz and Dr. Nelson for giving us an interesting discussion today by detailing the different contraceptive patches from both a historical perspective as well as newer options that hopefully will be available in the weeks and months ahead.

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