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Today's Contraceptive Patch: Putting Yesterday Behind – and Offering a Brighter Contraceptive Tomorrow

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This is CME on ReachMD. The following activity, titled “Today’s Contraceptive Patch: Putting Yesterday Behind – and Offering a Brighter Contraceptive Tomorrow” is provided by Omnia Education and supported by an independent medical educational grant from Agile Therapeutics.

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Please be sure to review the faculty disclosure statements, as well as the Learning Objectives, for this activity.

Your faculty is Dr. Anita Nelson, Professor Emeritus of Obstetrics and Gynecology at David Geffen

School of Medicine at UCLA in Los Angeles, CA.

Dr. Nelson
One of the reasons that we are talking about the patch today is that it does give us that blend between that convenience of avoiding daily administration and yet gives her whatever she wants from a combined hormonal, which is oftentimes the wonderful scheduled bleed, right? What happens if I lose my period? I do not want too much; I do not want too little. I want it just right. We try to make it easy for her.

We are going to spend the next 43 minutes talking about contraceptive counseling again, including the ability to screen because this is an estrogen-containing method and we want to make sure that we are selecting the appropriate candidates. We want to talk about the advantages and drawbacks of the patch or patches, and we want to talk about strategies to overcome some of those misperceptions. Just like the IUD that is burdened with a lot of history that is probably no longer relevant, we are going to be talking about some of the newer patches, in particular where we need to work through that other image and then also put that image into context to really understand small, medium and large there.

We are again going to be talking about what it is we want to do when we are counseling women. This has been an interesting journey over the last couple of years. For the first several years, it was all about the efficacy and side effects and maybe the dangers and now we are seeing what is going to work for the woman and what her priorities are; so, clearly we want to find out from her what method she thinks she can use correctly and consistently, right? Where is she going to be a good user? Trying to find out also how important pregnancy prevention is to her and as part of that equation, it is not just all about preventing pregnancy but for many of the methods that we are talking about, it is also about what non-contraceptive benefits is she looking for; what impacts on her health and what other issues, so putting that all together, I think, in our counseling can be important to us.

Taking a worldwide perspective, about 40% of pregnancies worldwide using a generous definition of intended, 40% are unintended, so we still have a large way to go. Contraceptive needs are largely unmet in and among those groups and it brings out an important principle, and I would just like to share this with you because I do a lot of research coming up with new technologies. I think we all hope that at some point we will get that menu that will be just totally irresistible so that any woman who walks in will find something she wants to use. Have you ever met somebody who did not want to use contraception but did not want to be pregnant?

I think there is this whole human element that we have to talk about and that is kind of where some of this other stuff comes into it that maybe she is ambivalent – there is now a difference between ambivalence and indifference about becoming pregnant or maybe I should or should not control my

fertility, but “By golly, I just do not like my periods,” and you know how you can back into contraception from something else. Clearly I think that we will keep charging forward developing new, safer more effective maybe convenient ways of providing contraception but realize that we are going to have marginal effects on it. The biggest single effect that we could have to reduce unintended pregnancies anywhere, including the United States, would be to take the women who say that do not want to be pregnant but are having sex and using no method is to give them any method whatsoever, right, because they contribute a disproportionate amount of intended pregnancies, but first, we really want to get those women out who secretly maybe want to get pregnant – get them out of that number and get us to the women who we really want to provide protection. So, guess what we are doing studies on? A spermicide – forgive me, but if we move people from nothing to a spermicide, we make a huge step forward, and then as we are talking about showing people who maybe are on a pill that maybe an IUD would work better for them, being more effective. You know, we are going to get some improvement from that and that is why we persist in offering things to people that might be more effective, beyond just the lifestyle issues. I think really if we think about where we need to put a lot of our efforts, if we are focusing on that unintended pregnancy, is that 0-1 transition, and I think beyond the technology is really the more profound personal insight into why people would do that, right? They do not see any conflict between their behaviors and their wishes, and it would be interesting to see how they think about things like how they view the world so that we are looking at it from their perspective. We may be able to come up with interventions that could help them meet their goals. So, we are left with the idea that contraceptive needs oftentimes and in many countries are largely unmet and certainly utilization varies from community to community. Did you know in Canada they do not have an implant? They have a lot more IUDs than we do, but they do not have an implant. Is that not strange how this all happens? So, anyway, we are pretty lucky. We have a lot of choices here to get and to just, if you thought today was busy at your office, by 2025 there will be 2.6 billion new couples needing contraception, so maybe you ought to go back to work this afternoon.

So, we do have some good news and we have some bad news. Clearly the introduction of the more effective methods and the new people coming in, we have seen a distinct decrease in unintended pregnancies, right? We have seen contraception working better; we have seen every. . .we shared this last time we got together – in every ethnic group, in every socioeconomic group, in every age group, particularly when we are talking about teens, we have seen a decrease in unintended pregnancies. So, what we are doing is working, but we still have a bit of a challenge, and that is what the bad news is, is that again half of the pregnancies, unintended pregnancies, can occur from incorrect use of a method, so we want to make it easier for them. We know that although adolescent pregnancy rates have gone down that still most of them may be as much as 80% are unintended. That would be such a shame, giving her tools to be able to do it, and again this is a lot older women too – oh, I hate to say that, do

you? – Somebody over 36 is older?

It is all in your perspective I guess, so you can look to see how high the unintended pregnancy rates and the pregnancy terminations are. Clearly, we want to be more effective in educating women; let us talk about what her fears are; let us talk think about what she is learned about what she is thinking, not just assume that we know what are misperceptions are. Talk about making sure that we streamline access to her and that is where we are coming back full circle again to that quick start, right? Identify whether she needs emergency contraception and just get her on a method today. Do not make her wait until the next period, because that may be in 10 months, right?

I know you guys are all strong advocates for women's access, men and women's access to contraception, and since the time we have met, last time we have a whole new profession of people who are helping us with this. You probably know that pharmacists are now able to prescribe and dispense pills, patches, rings and shots, so yep, look at me like that, yes. They had to have – oh, you are going to love this – do you know how much continuing education they had to have to be able to do this? I will tell you. . .

One hour. Our pharmacists are so much smarter than they are in Oregon. In Oregon, they have to take two hours. I think they are going to want to partner with us on this and they are probably going to be using the same tools that we talk about with the USMEC. Alright, so we want to improve contraceptive use and last year we talked about the implants and the IUDs, so I will not rub your nose in it, but we know that not everybody wants to have one of these because of any of these reasons and some of them, if we lose ACA coverage, we may not have them available to women so we want to make sure that we have it. Actually, it is the fear and I would love to talk to some of you about this, but I am working with a colleague who says that since, oh, I do not know, January maybe, she has seen a huge increase in the demand among her privately insured patients for IUDs and she was telling me just the other day that she sees 20 patients a day and she is putting in 5 to 13 IUDs a day. They are terrified out there and if we have not sort of chatted it up. . .now, in California for many of the underserved women, we still have Family PACT, so that is not going to be an issue as much for them, but it is not quite clear whether everybody that is privately insured will have this. We know that pill taking is a bummer and that even if we are really highly disciplined and we set our pill pack by our toothbrush and we set our alarm clock and all that other stuff to remind us to take it, that in real life, women forget to take pills. They do not fill their packs; they fill 8 out of every 10 packs and 54% of women miss at least 3 pills every month, so it is amazing how they do not work. So, there is frequent method interruption as we talked about. So, when we are talking about women and what their choices are, we want to make sure that we are talking about efficacy with them, their need for contraception, we are talking about the safety or the contraindications that they may personally have, I think that is the issue. It is not women that we are

providing contraception to, but each individual patient who comes through, and as much as we can know about her and her desires and what she wants to get out of it, the more effective we will be in making that perfect match. So these are the tools that we mentioned last year when they had just been updated, and I am hoping they are all on your iPhones so you have got the summary of the medical eligibility criteria so when women come in to see you, you will know which ones, maybe off label but are based on evidence which methods they can use. These are the criteria that are being followed by the pharmacists. They are screening women to see whether they have a category 3 or 4 condition for the method that she wants to use and they are only giving methods that are the 1 or 2 categories and they are referring everything back to us. I do not know, have any of you gotten a fax from a pharmacist yet? It is kind of strange, because I have been in my office – yeah, I saw one, okay. They say, "I started Susie Smith on," and they will tell you how many packs they gave her. Now, Susie is your patient, right, and you know that maybe she should not be on the pill, right? So you now have got to go to your chart and make sure that Susie is a candidate for the method that they gave her so that Susie did not get confused in all of this. Are you with me? Now, how are we going to handle that if we find that that is not an appropriate method for her? Do we call Susie, or do we call the pharmacist? I leave that to you.

And then, of course, the quick start, giving her as many packs of pills as we can, and we do have legislation saying that as of January 1st this year that we can dispense a whole year's supply. So, write for it and make sure the patient gets it. Okay, these will be for companies that are licensed in the state of California. So, we very much want them to get the package, and it makes a difference if you are giving her the patch or if you are giving her the pill. Now, the ring still needs to be refrigerated if you are giving more than four rings to her, but if she wants to put it next to the lettuce, that is fine with me, just do not make it too cold. You know, the lettuce wilts but you do not know what happens to the ring.

So, when we are talking about counseling, clearly, we want to know what her contraceptive goals are. This gets back to that theme of things that we were talking about before and is now standard of care that every visit, they say, but at least every year, we want to find out what her reproductive life plan is, and I will confess, I feel kind of foolish talking to a 17 year old about what her reproductive life plan is because I know she sneezes twice and blinks and it is changed, but the whole idea of asking these questions is to introduce the concept that woman and families ought to be planned and that this is one of the most important things we do in our in whole lives and we really want to be prepared for as best we can for the best outcome, so what are her contraceptive goals? Does she have a plan to get pregnant? When does she want to get pregnant? Is she having sex with somebody who can get her pregnant? Has she tried any other methods? Which ones? And then what does she like? What is she looking for? So, when we get down to I want to have, and it is one of those second tier methods that she has identified and you are just talking about how it is you might administer it, is does she want to

have a daily pill? Does she want a patch? Does she want a ring? Is she a good pill taker? I think any of us, if you push that little button, have you ever forgotten a pill? Duh, we do not need to do that do we? What has she heard about? All these questions I think are very, very important in helping narrow it down. I add one more, and that is, do you want to bleed? Yes? I think that is important because certainly we have the ability to use many of these methods to eradicate the scheduled bleeding. There is no medical benefit for it. So, looking at those issues. . .

So, we know the typical use and effectiveness depends upon how well she uses it, right, and how often she has sex, and are there any barriers in her particular situation that might challenge her to be able to take a pill every day, or to remember to put on a patch, or just store the ring? So, we want to make sure that we make access as easily as possible. We want to make sure that she is not afraid of the method, so what does she know about it that she is afraid? Let us dispel any fears or myths. Let us not have a lot of rituals. Does a woman need a Pap smear before you give her a patch? Does she need to have the reflex testing? Do we need to get into her vagina at all? Does she need to get undressed? She needs to roll up her sleeve so we can get a blood pressure, right? So, obviously we get a thorough history and if there is anything there that suggests a contraindication, we would follow up on it, but for most healthy women, we do not need to have a lot of other things. We have separated well-woman care from contraception. We love to merge them whenever we can, but if this is not a good day for her to do this, you do not have time on your schedule to do everything, then it is perfectly alright to move forward with the contraception and to consider the longer-term health altogether. So, then again, talk about administrative barriers, the daily administration and then find the method, as we have said, that she will use consistently and correctly.

So, the transdermal patch – I think that this is something that has been a wonderful option for women, certainly when they do not want to have the daily method, when they want combined hormonal methods and they can use them – they do not have contraindications to them – and as is given today with the doses that we have, this would be for women who want scheduled bleeding. We do not do extended cycle with the current patch. So, we have the patches that we are talking about as a general group that have estrogen and progesterone, though the first one that came out. Does everyone remember Ortho Evra?

Yes. Now, some of you who are younger, I know you may not have heard about this, but it was launched in May of 2002 and by November it was the second best-selling pill. In August, and in the good ole' days (some of you will nod your head), when a product was launched, they came out to our offices and dropped off starter kits. Do you remember those good ole' days? Yes? So you could give her a starter kit if she wanted it and then you could write the prescription for the other. By August, the Ortho reps were out there collecting all those kits, right, because there were not enough in the

pharmacy. They were taking them from our offices over to the pharmacies. That is how popular it was. They could not meet demand. So, today how many of you prescribed a patch in the last week? Look around the room. That is pretty good, pretty good, but you know you are unusual. I get off and ask do they still have a patch? But there are women for whom it has been a boom, but it was not everybody's hand who went up and it would have been around that time. So the question is, what happened and what are we doing now? So, clearly it is very thin, flexible and it is worn on the body. That is good. It is not between the teeth. I like that. And you know it is anywhere on the trunk except the breasts and it can be the upper arm. The one that we had with Ortho Evra was so cute that the teens loved to wear it on their arm and they put decals on it and in Carson it was; you know, which gang? Or you wrote little love notes on it. The problem with that, of course, is it upset the absorption of the drug, so you cannot let them put anything on it, so making it as slick and wonderful – if you are still using what has come out now instead of the Ortho Evra, is Xulane, and you saw their booth over there, so we still have one today and you can still prescribe it, but do admonish women not to put a Band-Aid over it or to reattach it that way.

Certainly, we know that hormone levels from the patch can inhibit ovulation, so the rules is one a week for three weeks and then one week off to have a bleed. So, the side effects were very similar to what we saw with the comparative pill with the exception of two things. In the first two months, the women who were on the patch complained more of breast tenderness and headaches, but by month three, they were back down to exactly what we had in the comparative pill, so I think that that was important to us. Now, what emerged over time was this issue of whether or not the area under the curve for the patch was higher than what we would expect from a lower dose pill, and when we got that combined with a couple of headlines where the coroner said he found a patch on the woman's body and could not rule out that it might have contributed to her demise, then that kind of shook us all up a little bit, and this was at the time when there was a third generation. I think it took us four or five years to get epidemiologic studies that showed that there was a total confusion in the world about this and by then the enthusiasm for the patch had been muted and we had actually discovered the vagina (whisper), right, and we had the once a month. So, we have had a gap for a while over the concerns and it is nice to see that people are still prescribing it to women for whom it would be very important. So, again, discuss what we do not know about it; talk about what you know about the VTE risk and talk about what we can do to make it work well for her if she knows she can do it. So, we did have that meteoric rise and then we had the swift fall, but it did not go away. I was really pleased that Ortho maintained its availability. They did not advertise it. They changed the labeling any time the FDA thought it was appropriate so they kept us informed on that, but they stayed in the market and they kept it for us until we got the generic version and then they have pulled out, and so it still is here and you can still prescribe it for your patients and I think that is very important overall. So, May 2002, okay, and so we

now have Xulane. Can you see it there and that little X for getting rid of unintended pregnancies. I love that that it is on that do you not?

So, the issues and the events that we talked about, the potential for a higher VTE, so we had three things that were with that patch that kind of discouraged use for a while from a liability standpoint and that was area under the curve was closer to a 50 mcg pill. Now, that is not – you cannot walk away from that and say, "See, I proved it is higher risk for VTE" because it is transdermal and so when you put a patch on the arm, everything that goes into her body, everything that her liver sees is reflected in the serum levels. Are you with me on that? When you swallow a pill, it goes through the gut and up to the liver and there is that first pass where a whole bunch of it affects the clotting factors and then it gets conjugated and put back into the gut, so the liver sees more than gets out into the blood stream, and so it was reasonable. You have to wait until the epidemiologic studies come out to show. You cannot compare two different delivery systems and say because one has more estrogen that it is going to cause us higher clot levels, but there we go. That is where we were left and I think we kept it alive because it met a need for quite some time and as you can see, the epidemiologic studies did vary greatly and they are all reported with robust confusion in the labeling and you just pick your patient to make sure that she can use it, but there are two new patches that have been in research and development really looking at the issues that were raised by Ortho Evra and one is one that is from Byer. It has ethinylestradiol and it has a third generation progestin, which we did not see in this country but they did in Europe, called gestodene, and there is a little company called Agile Therapeutics and what it did was it did ethinylestradiol and it abandoned the third generation progestin and went back to a second generation progestin to try to head off the concerns people might have had. But let us talk about what Byer has done with its patch. Certainly you can see that the levels delivered by the ethinylestradiol are much lower area under the curve. Can you see that? So, much lower; the concerns that this will be a high-dose pill are gone and again it is very similar to about a 20 mcg to 30 mcg pill overall. So, we addressed that issue. They had the issue of it being a patch, again, three weeks on and one week off, so it is the same pattern that people are used to and the pharmacokinetics, again the steady state concentration for EE from the other patches compared to – were less than what we saw with the norgestimate-containing pill. Alright, so the hormonal contraceptive pills we are talking about – sorry – the patch from Byer has .55 of ethinylestradiol and 2.1 of gestodene. So what we have got is a phase 3 trial. They have an open label just like you usually do 13-cycle and they have tested it in Europe and in Latin America and you can see it is a very robust study with over 1,600 subjects, that one you saw for the unadjusted Pearl Index was 1.2, which is very low for modern day formulations. We see with modern-day pills today failure rates – the Pearl Indices that are in the fives and sixes because of the Pearl creep. Four of the 5 of the 14 pregnancies were determined to be the results of noncompliance, so if you take them out and you just do the per protocol as they were told to take it, it

has a Pearl Index of < 1. The safety issues that were there, they had 62% of women who reported at least one adverse event during the clinical trial. The most common ones that were reported – now remember, you know this – what goes into the labeling is not necessarily attributable to, right, it is just what happened to the women while they were on it and there was no obvious other cause for it, so we have to report it. Application site reactions are very unique to the transdermal. You have to make sure it is not irritating to the skin that it sticks on, but just to show you, I bet you would not have guessed that that patch causes a cold.

But 7% reported nasopharyngitis and it is there in the labeling and patients do worry about that I am sure, but 15% of women discontinue it because of adverse events, and for a year-long study, that is quite remarkable.

Okay, uterine bleeding: There was a frequency of unscheduled bleeding that declined from 11% in cycle 1 to less than 7% in cycle 12. Compliance: Can you imagine that? About 98% of women said they put it on as we told them to, which is very nice, and complete the detachment of any patch. Remember, she has been using one a week, right, so it is not quite 52, it is more like 40 something because she has that week off, but to have complete detachment in less than 6% is good and then partial detachment or complete detachment at least once is 15% overall. SAEs, serious adverse events, that were related to the drug, that one woman had reactive depression and there were two cases of pulmonary embolism. Darn. So we are giving estrogen these days and we are going to see some of these, but again, this was a low-level, so I think that that is good that they told us about that.

So, the other one, and I will confess, this is the one I have been working with in clinical trials in the United States Anyway, so this is as we talked about, it is ethinylestradiol and it is levonorgestrel, as opposed to being a third generation or fourth generation, so, again, those happen in birth control pills associated with lower rates of VTE. Phase 2 dosing study showed that we suppressed ovulation in both obese and non-obese women and no woman showed ovarian activity or any likely probable ovulation in cycles 2 or 3, so they got the dosing right for the progestin to suppress ovulation and then we looked to the bleeding to see if the estrogen helps us there, and then the release rate, and this is the one you want to take home, right? The area under the curve, what she sees for 24-hour exposure is very similar to a 30 mcg birth control pill. Are we okay with that? So, I think that that will get rid of that little cloud, if there is still any cloud out there.

So, we look to see the estimated daily release rate compared to the old Ortho Evra patch, which is about half of what we saw there. We saw that the levels of the L and G are very similar and maintained very steady overall, so you are not getting the peaks and the troughs as you would with a daily pill. It is a steady-state release, and it can be considered bioequivalent to Ortho-Cyclen with regard to the

release of ethinylestradiol. What else do we know about it? Same thing you would expect – now you are going to all ask me can we do four in a row – and the answer is that is not what we have tested yes, but with the lower levels it may be more possible to do this than we have with the older product, but right now we are talking about three on and one off in the same places that you always know you can put a patch. A little thing that many people did not know – absorption from the abdomen, even slender abdomens was lower than it was when you put it anywhere else, so just as a little pearl, if she is complaining of a side effect, have her put it on the abdomen as opposed to the buttocks or any of the other areas or the arm, or upper torso. And then, as we talked about it, every site was within therapeutic range; it was just lower in the therapeutic when it was on the abdomen.

Okay, so we have had three phase three trials with this drug and putting it all together – in the first one, there was 1,500 patients where they did a patch versus a pill and I want you to look at the women they have enrolled in these studies, because this has been kind of a unique situation where this looks a lot more like America than some of the other trials you and I might have seen. So 30% of the women had a BMI greater than 30; we had 40% with ethnic minorities in it and these were not switchers. These were not all people who were very experienced at using hormones, so they brought in a fair number of newbies to this. Compliance of the patch was 11% noncompliance by cycle 6, but guess what – compared to the pill, very similar, yes? Intent to treat – the failure rates were very similar. There was no statistically significant difference. If you exclude the noncompliant patients, the patients who did not put the patch on, then it looked as if it might be lower, but there was no statistical significance, so again, I think we are doing well on that. Unscheduled uterine bleeding and adverse events were very similar from both methods altogether. So, what do you know about how you would counsel the patients? One would have applied to the outcomes of this.

So, what is the next one that we have? This would be compared to a 20 mcg. Intent to treat – the Pearl Indices – can you see these? Do these numbers disturb you a little bit? Has anybody seen a four for a birth control pill in a clinical trial? – but that is what is happening these days. It is fascinating. There have been studies where a pill was approved in 1988 with a Pearl Index of 1.2; it was used as a control in the late 1990s and the failure rate was close to 3. It is used as a control. I guess it was 2008 or something like that and it was almost 5, and it tells you, it is the same pill, but it tells you how we count pregnancies these days; how we can detect them earlier; how we throw out cycles; if she used anything else or did not have sex that the calculations are different, so that is the basis of what James Trussell and his group has called the Pearl Index Creep that we see creeping higher and higher, and this is a typical use. This came out of clinical trials where women are doing the things we tell them to do, so I just thought I would point that out to you. I do not want you to slide out and think that everything is going to be the way we were used to seeing with pills less than 1%. This is a new day and whether it

is the patients we put into the trials or all of the other things that we are talking about in the way the trial is conducted. It makes a huge difference, so gird yourself when you are looking at some of these new methods, particularly in the second tier; that is where we are seeing this Pearl Creep more than anyplace else.

Okay, what else did we have? Excluding the noncompliant patients, we are down to less than 3% with a failure rate and unscheduled bleeding, again similar for both groups, so I am just marching you through the clinical trials that they have put in, and the latest one – oh, I am sorry – this is #2, the second one where they compared it to a 20 mcg pill; again, 30% were obese and looking at treatment emergent adverse events that occurred to more than 2% of the people – I am just going to let you read that. Do focus on the upper respiratory infection though and counsel your patient. So, again, very similar to what you would expect from a hormonal, and that's what the story said. Again, women reported perfect utilization 90% of the time, and the patch adhesions – this is a different patch. When I show you what it looks like, it does not have that thin – remember Ortho Evra and Xulane have the hormone mixed in with the adhesive? This actually puts a thicker adhesive strip around the perimeter and the hormone sits in the middle. So it is a little thicker, and I will tell you it is not slick, it is furry. It is fuzzy. Are you ready with me on this? Why would you make it less than slick and attractive? What do you want people not to put on it? Anything. So, you try to put a decal on this it will not stick. If you try to write on it, it will bleed. It will make a mess. So, quickly, you will learn, do not mess with this patch. Just put it on and let it do its work. Okay? It is not jewelry. The appearance is a little different, and I just want you to understand why they did it. It was not that they could not make a slick one, but they learned the lesson from Ortho Evra so that you may not have to do that counseling in the future.

Okay, so this is the latest study that we have. It is called The Secure. We evaluated contraceptive user reliability and efficacy and these are the data that we have presented here, but we have not yet published everything, but these are the ones we have put in at different meetings, so it is public information and I can share it with you. What we did was we excluded the cycles where women used another method. This is only at-risk cycles, so you are not going to have any of that burden there. Very stringent early criteria – these women – you could almost say we stopped; okay, they had an electronic diaries; they had to submit all about their bleeding and their sex lives and all this other stuff, whether the patch was on, if they had any skin irritation on a daily basis before midnight and if she got there too late, we locked her out and then they yelled at us and we had to call her and find out what happened, and I had one little patient – honest to gosh, I was so embarrassed to call her. Okay, this lady when we called her, she said she could not get – she had no reception in her home. She was getting in her car and driving to a hilltop so she could input her data before 12 o'clock at night, and it was raining so hard she was afraid to go out, and you know, you really admire people who are willing to share that much

and do that much to get you answers, right? So, I stopped yelling at her, but we thanked her a lot for this. Anyway, let me show you who the women were in this study. We had to have women who were under 35, but look at how many women had a BMI greater than 30, 35%. How many were overweight? 25%. Have you ever seen a study that had that many American women in it? Right? So, what we did was we looked at an efficacy by BMI groups, the probability of pregnancy is related to the BMI, and this was done prospectively. It was not after the fact we planned to do it and just sweep out. The patches do not work quite as well, but look they still work very well. Yes? So this gives you a basis I think to do some counseling. Then we have the upper bound. There is the Pearl Index and the upper bound is something the FDA wants to show you. Adverse events – the most common ones were very low numbers. Can you see? This was very well tolerated. The bleeding for a cycle could be what she came in with, but looking at two to three, we can see on average we are looking at unscheduled bleeding events which are about one and a half days. So, clearly what we have seen is we have had transdermal available to us in this country for over a decade; we had one that was extremely popular and we lost it because of the third generation progestins; there is still one available to us and I am glad they have kept it going for the women – almost a million women – who do want to use this, and then to be able to bring back another one that can make people feel more comfortable in the face of the history here, I think we could, but there is the one that is available in Europe that has ethinylestradiol and gestodene and we have just completed the studies and it is before the FDA now with ethinylestradiol and levonorgestrel. So, again, I think that we can make this mainstream again and put it on the plate as a second tier method that may offer the convenience that women are looking for, for a once-a-week contraceptive.

Thank you all so much for your attention.

ANNOUNCER CLOSING
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