TRANSCRIPT

IBD & She - Focusing on Living While Managing IBD
Sunanda V. Kane, MD, MSPH & Uma Mahadevan-Velayos, MD

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Kimberly Frederick:

Hello, everyone, on behalf of the Crohn's & Colitis Foundation of America, welcome and thank you all for attending today's program, which was made possible through an unrestricted educational grant by Shire. We would also like to thank all of you who submitted questions in advance of the program. We have worked hard to address many of those in today's program.

We will also have an interactive question and answer session after our two presenters speak. We will take as many questions as time allows from both the telephone and webcast participants. If we are not able to take your question, our Information Resource Center will be open tonight until 10 PM, Eastern Time, following the program. And if you have a pen and paper that number is 1-888-694-8872. And the Information Resource Center also accepts calls Monday through Friday from 9 AM to 5 PM Eastern Time.

I'm excited to share that we have a new section of our website that we designed especially because of this program, to serve as a resource on the topic of Women and IBD, and it features frequently asked questions and some of which we have pulled from tonight's teleconference, and a host of information related to IBD and women. So again, if you have a pen and paper, that URL is www.ccfa.org/living/women_IBD.

And now it is my privilege to introduce to you two of the most prestigious female IBD specialists and researchers, Dr. Sunanda Kane and Dr. Uma Mahadevan-Velayos.

Dr. Sunanda Kane is Professor of Medicine at Mayo Clinic, Rochester, Minnesota. Dr. Kane received her medical training at Rush-Presbyterian-St. Luke's Medical College in Chicago, Illinois, and completed her fellowship training at the University of Chicago Pritzker School of Medicine. Dr. Kane also holds a master's degree in biostatistics and epidemiology. Dr. Kane serves as the Chairman of the Crohn's & Colitis Foundation's National Patient Education Committee. Her work includes caring for patients with inflammatory bowel disease and her areas of interest include gender-specific issues in gastroenterology and medication adherence.

Dr. Uma Mahadevan-Velayos currently serves as the Associate Professor of Medicine at the University of California, San Francisco and Director of Clinical Research at the University of California, San Francisco Center for Colitis and Crohn's disease. Dr. Mahadevan-Velayos completed her medical degree at the State University of New York in Brooklyn and completed a residency in internal medicine at Mt. Sinai Medical Center in New York, a fellowship in gastroenterology at the University of California, San Francisco, and a fellowship in inflammatory bowel disease at the Mayo Clinic in Rochester, Minnesota. Dr. Mahadevan-Velayos has a particular interest in pregnancy and fertility in IBD.

And now I'd like to turn the time over to Dr. Kane to start the presentation.

Dr. Sunanda Kane:

Thank you, Kimberly, it's definitely an honor to be here.

We're going to talk in this first half of our program about a variety of things and specifically talk about the impact of IBD.

It's very interesting that there are some actual gender-based information out there. There is a study that got published a few years ago, looking at the 10-year rate of relapse of ulcerative colitis in men and women separately, and these were patients from eight different countries. And it turns out that the relapse rate for women was 20% higher than in men and that time to first relapse was sooner in women than men. And we don't know why this is yet. It's data that needs to be replicated, but certainly it's hinting that women do not behave the same way as men.

It's certainly true in Crohn's disease that the effect of smoking is much more deleterious to women that it is to men. There are now two studies that have specifically addressed the gender effect of tobacco in women with Crohn's disease. Women smokers undergoing surgery are five times more likely to have a recurrence than nonsmokers and they actually recur more quickly. And women smokers have hastened onset of disease and have an increased need for immunomodulators. So when I'm talking to women I want to make sure that one of their treatment strategies is to get off of cigarettes.

We talk about the gender-related impact of IBD, certainly there are gender-related issues. We're going to hear from my colleague in a few minutes about the reproductive issues, but in terms of the disease-related concerns, women are much more concerned about body stigma and loss of bowel control than men are. And we're going to talk a little bit more in depth about sexuality, but certainly women with IBD have been shown to have decreased sexual activity, probably because of dyspareunia or abdominal pain, other issues like that. It's interesting that men talk about a decreased libido and sexual satisfaction as opposed to decreased sexual activity per se.

The physical complications of IBD on sexuality, I'll just touch on really quickly, and then we'll talk about later also. But there's the impact of the disease itself and certainly women who have Crohn's disease with perianal complications, draining cutaneous fistulas certainly are not sexy, skin lesions that can be very unattractive, the arthritic deformities that make it difficult to engage in physical activity, pain issues, and then fatigue. And then there's the impact of the treatment itself. So any woman who's been through surgery knows that there are surgical scars, there can be a presence of a stoma, and then the medication side effects may lead to fatigue or decreased libido itself.

It's interesting when we talk about inflammatory bowel disease, we talk about different parts of the body, not just the bowels. And in terms of a woman's body, there are certain systemic complications that occur more often in women than in men. And some of those are eye inflammation, lower bone density and sub-fertility. Now women can still, just as a gender, have more gallstones than men, but it's interesting that skin lesions and liver and bile duct inflammation tend to happen more in men than they do in women.

So let's talk a little bit about some very gender-specific things. So menses and preadolescence. It's entirely possible that there's a delayed onset of menses in preadolescent girls who are diagnosed with Crohn's or colitis. They certainly experience delayed growth rates and then subsequent to that have delayed maturation and secondary sex characteristics because they're not menstruating properly.

What do we know about the menstrual cycle and bowel pattern fluctuations? It's very interesting that bowel pattern fluctuation is very common during the menstrual cycle and that's regardless of whether you have inflammatory bowel disease or not. It's interesting that there's an overlay of IBD symptoms that may increase during the menstrual cycle, whether that's during PMS or the actual week of menstrual flow. And it's interesting that menses suppression with birth control medication can actually be very helpful and needed if debilitating symptoms are present.

And this is just a chart from work that I engaged in when I was in Chicago a few years ago, just showing that change in symptoms during menses – and this is a study looking at healthy controls, ulcerative colitis patients, Crohn's patients and patients who have irritable bowel syndrome. And you can see that just in healthy controls, there is already a baseline risk for cyclical symptoms, whether that's diarrhea, abdominal pain or constipation. But certainly in women who have IBD and even more so in IBS, that there is a cyclical symptomatology that is related to the menstrual cycle.

So ladies, if you find that you have these mini-flares once a month, it's worth mentioning to your physician because there are ways potentially to change the medication schedule that you're on or maybe going on to hormonal therapy to help ablate some of these peaks and valleys of your symptoms.

What do we know about oral contraceptives (OCP)? I just said that sometimes we use them to actually treat menstrual-related symptoms. The general guidelines for OCP use is that it can be used for contraception, but probably should have a lower estrogen content overall. They should be avoided in women who have had a history of blood clots, and should be avoided in any woman who has liver disease.

Now these recommendations are for anybody. Blood clots or liver disease are known risk factors for complicating oral contraceptive use. But other than that, oral contraceptives are a very effective way to have contraception.

What to expect with menopause? Now we're at the end of the menstrual cycle history and it's interesting that we have found that menopause potentially changes IBD. And we wonder whether there is more severe or altered symptoms related to menopause. And what should we know about or be aware of to prevent any problems. Particularly those women who may have fistulas.

Well, it turns out that we did a study that we published a few years ago, looking at hormone replacement in women who had gone through menopause. So we studied 65 patients and it turns out that women who were on hormone replacement therapy were significantly less likely to flare within the first three years after menopause. And we think it's because we are just replacing what was naturally there. And it was interesting to note that whether the menopause was natural or surgical, that we still saw this effect.

Okay, let's turn our attention away from the menstrual cycle and talk about Pap smears. It turns out that abnormal Pap smears are associated, as most of us know, with both infection and progression to cancer, which is why we have them. Women with IBD are actually more likely to have an abnormal Pap smear than women who do not have IBD. And it turns out that if you use azathioprine or 6-MP, otherwise known as Imuran®, or 6-mercaptopurine, or purinethol, that your risk increases 3-fold for an abnormal Pap.

Now fortunately we have not seen an increased risk for cervical cancer, but certainly an abnormal Pap smear is the first stage towards that and certainly needs to be intervened. And why

do we think that that's the case? Well, because the drugs like azathioprine or Imuran are actually suppressing the immune system and suppressing the ability to fight off certain viruses.

It's interesting that we did not find this effect with women who were on any of the biologic therapies like Remicade®, Humira® or Cimzia®.

So what do we know about the risks? Actually there was one study published first and then there was a very nice study to follow this up, to show exactly what I just said, that if you look at abnormal Pap smears from women who have inflammatory bowel disease, that the risk is increased by 66% in Crohn's disease patients when they're on oral contraceptives, and it's increased by 40% when you are on steroids and immunosuppressants, meaning the azathioprine/6-MP. Again, not associated with being on any of the biologics.

So the conclusion from these two studies now is that it is immunosuppression and not the IBD necessarily that increases the risk for abnormal Pap smears. But any woman who is taking long-term immunosuppressants should be having Pap smears on an annual basis to make sure that there's nothing abnormal there.

So in order to prevent cancer, we can now get vaccines for HPV, which is human papillomavirus, so there's Gardasil®, which is currently available, and it covers four different strains of the virus and it is FDA approved for women and young girls from 9 to 26. But we do have data now up to age 45. And there is a second vaccine now called Cervarix®, and it covers a couple of other serotypes. And it's actually a different formulation than the Gardasil. We don't know if it's better, it's just a little bit different.

I just want to mention very quickly, because women are very concerned about the significance of the NOD2 gene. When it first came out there was a single study that made a lot of play on the internet, that women, if they had the abnormal NOD2 genes, were the ones that were passing this along to their children and that the chance of having IBD came from the mother. And I just want to dispel that myth. I'm not sure if it's ever gotten off the internet yet, but the significance here is that if you have one copy of the mutated NOD2 gene, you have upwards of a 4-fold risk for developing Crohn's disease. And if you have two copies, it's upwards of 40-fold increased risk. Now that sounds very scary, but you have to remember that only 10% of Crohn's patients out there actually carry two copies of the mutated gene, and 28% of Crohn's patients carry only one copy. So actually the disease presence with one or two gene copies that are mutated is less than 10%. What does that mean in English? It means that the majority of patients, as we know right now, do not have mutated NOD2 gene. If you do have it mutated, then you're at increased risk. But having the disease is not solely based on your genetics.

Alright, so let's talk a few minutes about intimacy and sexuality.

So we understand that all relationships are complex and certainly IBD adds an additional layer. It can be very embarrassing and very personal to talk about these things and sharing this information. However embarrassing, once you get it out on the table and start talking about it, can actually relieve stress and anxiety, related to holding back and dealing with it alone. It can certainly be more difficult if you have IBD to start new relationships rather than just to carry on an established one. And it's certainly difficult to know who to tell, what to tell them and how much to tell. But obviously IBD affects both partners, both the patient and the potential partner.

So IBD has both direct and indirect effects on sexuality. So what are some of the direct effects? Well, we've already mentioned some of them, which are fatigue, diarrhea and abdominal pain. Then you can also have amenorrhea, so your periods can stop and you have a low libido.

And certainly surgery-related complications like scars and stomas add to the effect.

The indirect effects, which most people don't like to talk about, are depression and altered body image and fear of incontinence. How are you supposed to talk to your doctor about that when they're just interested in making sure that your medicine is safe and refilled? These can be very difficult things to bring up, but sometimes, more important than some of your bodily symptoms that you may have.

So I just want to summarize very quickly before I hand over the program, that we've talked about quite a few things, sort of in a very quick sort of way, but at least to give you a flavor that women are different from men. It's important to remember that smoking is bad for women. Women smokers have the worst prognosis of any group of patients with Crohn's disease. We understand that the menstrual cycle can affect disease course, it's not in your head, and that it is worth talking to your doctor about this if it becomes a cyclical phenomenon. Oral contraceptives are not likely to be a high risk for developing Crohn's or ulcerative colitis or for making you flare. IBD does not affect menopause as far as we can tell. And that it is important that you discuss Pap smears and HPV infection with your physician.

With that I'm going to turn it over to my colleague.

Dr. Uma Mahadevan-Velayos:

Thank you, Susie.

My name is Uma Mahadevan, again and I am at UCSF in San Francisco. My part is going to be talking about fertility and pregnancy in women with inflammatory bowel disease. There is a lot of information in these slides that's going to be gone over very quickly. So the key message is that these are points to consider and things that when you are interested in getting pregnant, that you speak to your doctor and your OB about in advance and use these as talking points to make sure that all of your questions are answered.

First you need to be healthy prior to getting pregnant, that is more than just the actual pregnancy itself, but it's also getting your disease under control. So the first thing we wanted to talk about was general health. Healthcare maintenance is something that's important for all patients with inflammatory bowel disease, male and female, pregnant, not pregnant. These are things that go beyond your inflammatory bowel disease and are a part of being healthy and avoiding potential complications of inflammatory bowel disease. You want to prevent infections, you want to be screened for cancers, you want to make sure that your blood tests are where they should be.

And so we actually have a healthcare maintenance check sheet that your physician can get online from the *Inflammatory Bowel Diseases* journal on the CCFA website. And part of those items on the checklist include vaccinations. Make sure that your hepatitis-A and B are up to date. And that's important because if you're on a medication like azathioprine or a biologic like Infliximab (Remicade), or adalimumab, (Humira), your potential of having a bad reaction, if you have hepatitis-B, is quite high and it's important to prevent that. You should get a flu shot every year. You should get a pneumococcal pneumonia vaccination once. Your tetanus should be up to date. And Dr. Kane already talked about cervical dysplasia vaccines. So all of these are preventative and important.

It's very important to remember that if you are on a biologic, such as Remicade, Humira or Cimzia, you cannot get live virus vaccines. This includes MMR and varicella. So if you want

to get pregnant they always check you for rubella prior to pregnancy to make sure you're immune. You want to make sure you get that checked prior to starting your biologic, so that they can vaccinate you if they need to.

The other thing is cancer screening. Once you've had eight years of colitis, either Crohn's colitis or ulcerative colitis, you should start to get colonoscopy every one to two years to look for early evidence of colon cancer. You should get Pap smears every year. If you're on a medication that may suppress your immune system, such as azathioprine or one of the biologics, you should see a dermatologist regularly because there is an increased risk of skin cancer.

Blood tests that should be done at least on an annual level are your B12 and folate levels, your iron, as well as 25-OH Vitamin D. Having a low Vitamin D can be a driver of inflammation, so it can increase the rate of inflammation for many different disease states. Also it is associated with infertility, so this is certainly a vitamin level that you want to make sure is in the normal range. You don't want to overdo it, especially in older patients, taking too much Vitamin D may potentially be associated with forming atherosclerotic plaques, but you want to be in the normal range.

Your liver tests as well as tests for anemia should be checked at least once a year as well, and maybe more frequently, depending on the medication you're on.

Once you have your healthcare maintenance under control, the next issue is talking about getting pregnant. Before you become pregnant, you should make sure that your disease is under good control. Whenever you are going into pregnancy, there is a little bit of an old wives' tale that says you have a one-third chance of getting worse, one-third chance of getting better and one-third chance of staying the same. So if you're in remission going into pregnancy, you have a 66% chance of staying there. Certainly large studies have shown that the chance of flaring during pregnancy is about one-third, the same as in the general population.

If you have active disease you may be at increased risk for spontaneous abortion, you may be at increased risk for other complications, and you may have a harder time getting pregnant as well.

You want to make sure your disease is under good control, you want to make sure that all your healthcare maintenance is up to date, you want to identify a high-risk obstetrician. You can have your regular obstetrician who's going to see you on a regular basis and deliver your baby, but you should be monitored as a high-risk obstetric patient. And this may require a special doctor or you may be able to find an OB that does both. And the reason for this will be in the coming slides.

Also talk to your gastroenterologist before you conceive. Make sure that you're comfortable with the medications that you're on, that they can be continued during pregnancy and breast-feeding. Most IBD medications can, but there are certain ones that cannot.

Common questions that women interested in pregnancy ask include inheritance, will I pass this on to my child? Fertility. Are my chances of getting pregnant the same as other women? Pregnancy outcomes. The safety of medications. And the management of flares.

I did read all of the pre-questions that came in and I will try to address as many of those as possible in the coming slides.

One of the solutions is having good communication with your partner. Trying to get pregnant can be a very stressful time. Getting pregnant can be a very stressful time. You want to make sure that: this is not something you're doing on your own, that you have good

communication both with your partner as well as with your doctors,get your disease under control, share your symptoms with your doctor and don't try to hide your symptoms and hope they'll go away. It's very important to get on top of them as soon as possible and keep your disease quiet. And also don't be afraid to seek counseling for help with coping with disease. This can either be with a specialist or with group therapy. It certainly helps a lot of patients to find out they're not the only ones going through this.

Will you pass on IBD to your child? While Crohn's and ulcerative colitis do have a genetic component, the majority of patients with IBD don't actually have family members that have IBD. If you have Crohn's, the risk of passing it on to your child is estimated to be anywhere from 5 to 10%. If you have ulcerative colitis, it's much lower at anywhere from 2 to 4%. However, if both parents have inflammatory bowel disease, the child's risk can be as high as 35%.

However, inheritance is multifactorial. There are multiple issues that go into somebody developing inflammatory bowel disease. The fact that one parent has IBD should not be the sole determining factor in not having children. That may sound silly now, but as early as ten years ago, patients with IBD were counseled not to get pregnant, mainly for fear of the mother's health, but also for other issues.

What are your chances of getting pregnant? A woman with IBD has the same chance of getting pregnant as another woman her age, unless she's had surgery in the pelvis. With both ulcerative colitis and Crohn's disease, fertility is the same as the general population in that age group. However, if you've had, for ulcerative colitis, a total colectomy with removal of the rectum and creation of a J-pouch, then your fertility can drop by as much as 50 to 80%. This doesn't mean that you cannot get pregnant because many of these patients go on to successfully conceive with in vitro fertilization, but your ability to conceive per menstrual cycle is much lower than a patient with ulcerative colitis who has not had that surgery. So that's something important to keep in mind. With Crohn's disease again, patients who've had surgery may potentially have a slightly lower risk, but it really has to do with surgery in the pelvis with respect to the rectum. And we would assume that patients with Crohn's who have pelvic abbesses and things like that, may also be at increased risk.

How will you do during pregnancy? The majority of patients do great and they have healthy children. However, statistically all women with inflammatory bowel disease have higher rates of abnormal pregnancy outcomes. This was looking at Kaiser Northern California, where the majority of patients were in remission during pregnancy and their rate of miscarriage was higher than patients without IBD, their rates of low birth weight, stillbirth and pre-term birth were higher, their rates of complications of labor and delivery were higher, and the rates of adverse newborn outcomes, which includes NICU stays, were slightly higher, but it was not statistical. And this has been shown in other studies. So even if your disease was in remission, your risk of pre-term birth and other complications may be higher. And this is why we want all pregnant women with IBD, regardless of how active their disease is, to be followed as high-risk patients. This does sound scary, but I'll tell you that we have at least 50 to 60 women per year in our practice who have pregnancies and they all do great. Some of them do deliver early, some of them do have babies that are a little bit small, but they catch up. It's just important that we keep you healthy and that we monitor the progress of your baby.

This is a slide from the Kaiser population looking at disease activity. I'm not sure how well you

can see this, but the light blue line all the way to the left, the top graph is Crohn's and the bottom graph is ulcerative colitis, and it just shows here that at every stage in pregnancy, prior to conception, trimester one, two and three, and after the baby was born, most of these women had inactive disease. Their disease was completely quiet. But despite that, they still had the higher rates of adverse outcomes such as pre-term birth and low birth weight.

People often talk about disease flaring after delivery. With inflammatory bowel disease, while this can happen with some women, the majority of people who do fine during pregnancy and do poorly after delivery, it's often women who stop their medications to breast-feed. And that is something you definitely want to avoid. Most medications are compatible with breast-feeding and you want to try to continue your medications during breast-feeding. We've had a lot of lovely young ladies who stopped their medications to breast-feed and ended up in the hospital with a flare with a brand new baby at home, which is very stressful.

The other issue is, what medications can you take during pregnancy. These are the current FDA categories. This is in the process of being changed, but hasn't happened yet. Category A, no risks. There are no GI drugs that are Category A. Category B, no evidence of risk in humans. C, animal studies show some adverse effects, but without adequate studies in humans, or the benefits may outweigh the risks. D, positive evidence of risks, and X, contraindicated.

Let's start with fish oil. Fish oil is not actually a medication, so it doesn't have a pregnancy category from the FDA. However, a lot of patients with Crohn's and ulcerative colitis take it, and a lot of pregnant women take it. There may be some potential benefit for pregnancy and there does not appear to be a benefit for Crohn's, based on two large studies. However, if you want to take it, this is not something that's harmful to you and it may potentially help. Fish oil is fat, not protein, so there should not be any mercury and that should be clearly stated on the bottle.

This is a list of common medications, so you can see in the far left column, mesalamine or your Asacol®, Lialda®, Pentasa®, Colazal®. All of those are pregnancy Category B as in Boy. They're considered low risk. They're compatible with breast-feeding. Rarely the baby can develop an allergic reaction which is diarrhea. If that happens, you either have to stop the medication or stop breast-feeding.

Sulfasalazine or Azulfidine®, also Category B. Again, low risk and compatible with breast-feeding. However, sulfasalazine does reduce folic acid levels, so women should take at least 2 milligrams of folic acid daily if they're on sulfasalazine during pregnancy.

Steroids are commonly used for flares. And if you're flaring, you need to be treated. Steroids are appropriate, however, don't think that you should stop your medications and use steroids as needed during pregnancy, because steroids are actually Category C. So if you're flaring and you need it, your doctor is going to have to use it, but don't count on that to get you out of trouble in pregnancy and use that as a reason to stop your other medications because it may actually be worse. There is a low risk of cleft palate if used in the first trimester, as well as risk for gestational diabetes and large babies if used later on. It is compatible with breast-feeding.

Budesonide or Entocort®, also low risk and compatible with breast-feeding.

Antibiotics in general should be avoided in pregnancy if you can. But ciprofloxacin should certainly be avoided in pregnancy as well as in breast-feeding. Metronidazole or Flagyl® used short-term after the first trimester may be okay. But it should not be used with breast-feeding. Augmentin® or amoxicillin is a good choice if you need it, for example, if you have pouchitis. It's Category B, low risk in pregnancy and compatible with breast-feeding.

Now these medications are a little bit trickier, actually let me go back here. There was a question about Asacol and phthalates. And Asacol does contain phthalates. Phthalates in animal studies have been associated with urological birth defects, so to the urinary tract. This has not been seen in humans. So even though phthalates are in Asacol, consumption of phthalates by humans in large studies has not been shown to be associated with birth defects. It's really been in animals. If you're on Asacol, all the studies of Asacol really don't show an increased risk of birth defects. Again, further studies are ongoing.

Now these are some of the more complicated medications. Azathioprine and 6-MP are Category D, as in Dog, because animal studies clearly show birth defects. However, in humans it does appear to be low risk. And new studies suggest that it's compatible with breast-feeding. Especially if you take the medication and don't breast-feed for four hours, at that point the amount crossing to the baby is almost negligible.

Methotrexate, on the other hand, is Category X. It is clearly associated with birth defects and associated with abortion.That should not be used in breast-feeding or during pregnancy and you should stop it at least three months, ideally six months, before even trying to get pregnant.

The biologics, infliximab, adalimumab and certolizumab, also known as Remicade, Humira and Cimzia, are all Category B and are considered low risk and compatible with breast-feeding and we'll go over these in greater detail.

Here are other medications to try to avoid. Diphenoxylate and loperamide, Imodium® and Lomotil®, are for the most part, for the majority of patients, optional and if you can avoid it, you should, because there have been some birth defects noted in animals and in humans.

Bisphosphonates, which are used to put calcium back in your bones, are Category C and in animal studies have shown damage to the bones of the fetus. And their half-life can be as long as ten years. So if your doctor wants to put you on Fosamax® or one of those types of medications because you're going on steroids, this is something you need to really discuss with an endocrinologist and make sure they're aware you want to get pregnant. Because if you take it at 25 and want to get pregnant at 30, it may still be in your bones and may potentially have an impact on your child.

Thalidomide is rarely used for Crohn's disease, but it is Category X and should not be used.

Here's just a little bit more data on azathioprine. This is a large study from Israel, 189 women who used azathioprine in the first trimester, and they compared them to women who didn't. There is no increase in birth defects. However, there was a study from Sweden looking at 476 women who used azathioprine and there was no increase in overall birth defects, but a slight increase in the rate of cardiac defects, so ventricular septal defect, atrial septal defect. However, 300 of those 476 were Crohn's and UC patients. The others were lupus and other diseases. And the majority of those cardiac defects were in the other diseases. So the study overall suggested azathioprine is not associated overall with birth defects and the majority of those birth defects were in lupus patients and other patients.

Unfortunately, no clear-cut answer here, but azathioprine still appears to be low risk in patients with Crohn's and ulcerative colitis. And if that's the only thing you're on to keep you in remission during pregnancy, it is something that in our practice we recommend continuing to avoid flares in pregnancy.

This is just some more data on breast-feeding, where again it's very low levels detected in

breast milk and nothing detected if you wait four hours after taking the medication. So now women on azathioprine can breast-feed during pregnancy.

The biologics are infliximab, adalimumab and certolizumab. And they are Category B. And there's really not been an increase in birth defects. A study that we're currently doing is called PIANO. This is Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes. And this is a study funded by the CCFA and 30 IBD centers who are part of the CCFA clinical alliance across the United States are enrolling pregnant women with inflammatory bowel disease and putting them into three groups. The unexposed group and then the group on azathioprine and then the group on biologics and a group both on azathioprine and biologics. And we did a preliminary analysis of 400 of these women and the goal is to enroll 1,000 and we have about 700 now. We looked at complications of 400 women who already delivered,we found that the type of medication used was not associated with any complication, pre-term birth, C-sections or birth defects. So if you were on azathioprine or you were not on azathioprine, there was no increase in birth defects. And we hope when we've enrolled all of the women, up to 1,000, we'll really be able to give a clear answer.

If you're pregnant or planning on getting pregnant and are interested in enrolling in this study, you can join the registry by going to the CCFA website as listed below.

Now one thing with using Remicade or Humira during pregnancy is that they're both IgG-1 antibodies and cross the placenta very efficiently in the second and third trimester. The way you transfer immunity to your baby is the baby grabs IgG-1.There's a receptor on the placenta that grabs IgG and pulls it into the baby's side of the placenta. Now because Remicade and Humira are IgG-1, they get grabbed too, and we've done studies to show that when the baby is born their their levels of Remicade can be higher than their moms.

So what we do in our practice is we give Remicade and Humira on schedule throughout pregnancy and then we give the last dose of Remicade around week 30, the last dose of Humira around week 32 to 34, and then try to hold it until the mother delivers. And this way we hope to reduce the transfer of these medications to the baby.

Certolizumab or Cimzia is not IgG-1 and we've actually shown that it crosses the placenta at very low levels, so if you're on Cimzia you can actually continue it on schedule throughout pregnancy. You can breast-feed on both of these medications. It's very important that you tell your pediatrician that you are on infliximab or Humira during pregnancy because he should not give the baby any live virus vaccine in the first six months of life. In the United States this is for the most part rotavirus vaccine. All other vaccines can be given on schedule.

If you have IBD and are pregnant and want to deliver, almost every patient with IBD can deliver vaginally if the obstetrician feels it's safe. The only time we as gastroenterologists recommend a C-section is if you have active perianal disease at the time of delivery. So it has to be active. Or if you have a J-pouch. Women with a J-pouch can delivery vaginally, however, we worry about sphincter function and incontinence later on in life and so these are the two sets of women that we recommend C-section.

Okay, so what if you flare during pregnancy? Your medication choices are similar as if you're not pregnant. Some of the exceptions are, of course, you would not use methotrexate, and also if you've never been on azathioprine, 6-MP, I would not start it during pregnancy in case you have a bad reaction to it. We want to avoid metronidazole and steroids in the first trimester because the risk of birth defects, but if we need steroids, we use it. Other medications can be

started safely in pregnancy.

If you need an imaging test, an MRI is preferred to a CT scan, to avoid radiation, but if you get an MRI there should be no gadolinium the first trimester. If you need endoscopy, an unsedated flexible sigmoidoscopy can be done. If you need surgery the second trimester is the best time to operate, but that may not be an option.

So to summarize, your chances of getting pregnant are similar to the general population. There's a small risk of passing on IBD to offspring. There's an increased risk of adverse outcomes during pregnancy, though the majority of moms have healthy babies, and most medications are compatible with use in pregnancy and breast-feeding.

So the recommendations are to control disease prior to conception, continue most medications and involve a high-risk obstetrician and make sure your OB, your pediatrician, your gastroenterologist and, if you need one, your surgeon, are all in communication with each other.

One last slide to focus on living while managing IBD. You want to make a life plan. IBD should not impact what you do with the rest of your life. You want your education, you want your family, your friends and your hobbies and you should be able to have all of these things.

Educate yourself on your disease. Maintain communication with your GI and your GYN. Stay up to date on doctor visits. If you're feeling well, that's not the time to stop your medications and stop going to the doctor because being well is what you always want to be at and what you always want to maintain.

Create a support system between family members, friends and the IBD community. There are IBD support groups, including through the CCFA, online and in person. Accept support from others. And offer support when you can.

Thank you.

Kimberly Frederick:

Thank you, Dr. Mahadevan-Velayos and Dr. Kane for that informative presentation. We'll now begin the question and answer session and we know that many of you have questions, so we'll address as many as we can.I'm going to start with a web question while people are submitting for their phone questions.This question is from Janice, "Is there a correlation between hormone levels and flares with Crohn's?" These are open to either Dr. Mahadevan-Velayos or Dr. Kane to answer.

Dr. Sunanda Kane:

I guess I'll take it since I talked about oral contraceptives and menopause and such.

There's been a lot of intriguing work to try to figure out what the relationship is between estrogen, progesterone and flares. There have actually been trials using different estrogen preparations because certain estrogens are anti-inflammatory, but others are pro-inflammatory. So it's actually a lot more complicated than we'd like to think. And I certainly believe that within any individual woman, that hormones can play a role in how she's feeling at any given time.

Kimberly Frederick:

Great. We'll take a phone question.

Operator:

Our first question comes from Laura in Colorado.

Laura:

Yes, I'm having a flare right now and I'm wondering, I'm having a hard time getting in to see my gastroenterologist, and I'm thinking of switching. What is your advice as far as having a gastroenterologist available to you when you've been in the hospital and just gotten out and can't get to see one?

Dr. Uma Mahadevan-Velayos:

I will take one. That is really unfortunate. What I would do is I would call your local CCFA because they have gastroenterologists that they work with who are actually interested in inflammatory bowel disease. I am sad to say that many gastroenterologists are not that interested because IBD patients take a lot of time. And so your CCFA locally should have a list of gastroenterologists with an interest in IBD and who are interested in taking IBD patients. And so I would contact them and get into one of those recommended physicians. In the meanwhile I would contact your primary care physician and I tell all IBD patients you still need to have your primary care and see if they can help you out and if they can also expedite a referral. Because it's very hard to do that on your own.

Kimberly Frederick:

I'll turn to the web, there were a lot of questions on libido and so I'm going to try and make this general in nature. "Can you talk about decreased libido in Crohn's, especially in post-menopause women?" there were other questions about libido and colitis, too.

Dr. Sunanda Kane:

Sure. There are lots of reasons why women have a decreased libido and only one of them is potentially IBD. So if you look at women who have IBD, you have to know whether the disease is in remission or active. Because active inflammation can cause fatigue and malaise and a decreased mood in and of itself. A decreased libido can be from the medications that you are taking, so your colitis or Crohn's may be under control, but it could be a side effect of the medicine.

Certainly we know that from the literature that depression is under-diagnosed in IBD patients. And it doesn't mean that you have to be crying all the time or suicidal, but certainly a prolonged sadness or feeling of helplessness about your condition. Now what do we mean by prolonged? Anything longer than six to eight weeks, that's clinical depression. And it's not a sign of weakness. It's something that can be addressed and helped. And certainly that plays a role.

Menopause itself decreases hormone levels, including testosterone. And testosterone is a very important hormone that women make also, that is involved with sex drive and libido. And I find myself having to check, in my older patients, testosterone levels, and lo and behold they can be low. And when you replace testosterone, then the libido returns.

So it's not a simple one or two kind of checklist thing, but there's multiple factors and all of them have to be taken into account.

Kimberly Frederick:

Okay, great, we'll take a phone question.

Operator:

Our next question comes from Megan in Virginia.

Megan:

I don't know if you addressed this or not, but I have gotten mixed reports from doctors about being on birth control and whether or not that's a good idea for Crohn's or IBD patients. Did you speak to that?

Dr. Sunanda Kane:

I did, but it's worthy of repeating. So the literature, actually the scientific literature is somewhat controversial, and the reason is because the kinds of birth control that are available in different parts of the world are different and there are actually 70 different kinds of oral contraceptives available on the market today in the U.S. The U.S. birth control pills contain less estrogen than those found in Europe. And it turns out that it's mostly the European studies that suggest that there is an increased risk for the development of Crohn's disease or colitis with their use. There are some data to suggest that if you are on oral contraceptives, that you may have more active disease or a flare, but I can tell you that from my practice and practicing predominantly with women in my practice for 13 years now, that I have not found that I cannot find an appropriate oral contraceptive that a woman can tolerate, nor have I had to stop oral contraceptives because of disease activity. I have had to stop it because she's developed a blood clot, but we would stop it anyway for any woman who had a blood clot.

So I recognize that there is some literature out there about this, but it doesn't stop me from using them.

Kimberly Frederick:

Great. I'm going to take a web question from Maggie. "I've heard some people's symptoms get worse during pregnancy and others don't get any symptoms. Is there any way to determine the impact on symptoms during pregnancy?

Dr. Uma Mahadevan-Velayos:

Sure, I'll take that one. For the most part if a woman is in remission, going into pregnancy, the majority of women will stay in remission throughout their pregnancy. There's a one-third rate of flare. It's really not easy to predict because I have some patients who say the best I've ever been is when I'm pregnant and I have other patients who were diagnosed for the first time during pregnancy. So there is really no way to predict it. The best way is to try to prevent it by being on stable medications. And for my patients who've had a bad flare, I ask them to be in remission for six months, off steroids, before attempting conception, so that we know that they have a stable remission going into pregnancy.

Some of it may have to do with having a baby. So in the rheumatology literature, but not so much in the IBD literature, in the rheumatology literature, as well as some work that Dr. Kane has done in IBD patients in the past, the baby is a parasite and because the mother doesn't want to

reject the baby, the body naturally immunosuppresses itself. And so that may be why women with autoimmune diseases may do better during pregnancy. But again, some women do worse. And some of that is medication-related and some of that we really don't understand why.
Kimberly Frederick:

I'm going to take another web question. "Would the Nuva-Ring® birth control have the same issues as OCP oral contraception?"

Dr. Sunanda Kane:

That's actually an excellent question and I want Dr. Mahadevan-Velayos's input on this, too. So I've had just a few patients who have been on the Nuva-Ring and I would say I'm batting about 50% in terms of those who tolerate it and those who don't. So it's not my favorite form of oral contraception. Uma, what do you think?

Dr. Uma Mahadevan-Velayos:

I haven't had a lot of patients on it. I've had a few patients ask about it and I have no issues with them being on Nuva-Ring. And if it doesn't impact their disease, they continue it. But I haven't really had somebody go on Nuva-Ring and do worse. We've had a few try it and be fine.

Kimberly Frederick:

Okay, we'll take a phone question.

Operator:

Our next question comes from Betty in Utah.

Betty:

Hi, glad to talk to you. I'm wondering about rectovaginal fistulas. And if they can be repaired without doing major surgery.

Dr. Sunanda Kane:

It depends on the rectovaginal fistula, the size and the location. Unfortunately, rectovaginal fistulas are one of the hardest things to treat medically. The best data for treating them come from biologics such as the Remicade, Humira, Cimzia type drugs, which can heal it, but sometimes you can heal the inflammation, but leave the scar, and so you still have a track. And if you have loose stool, you may still have leakage of stool through the vagina. The surgical options for treating it can be less invasive, so some surgeons have used the fibrin plug and other ones have tried to place setons through to try to heal it. But in general the success rates of these are less than 50%. And then the more invasive surgeries, such as the muscle flaps and things, also can have poorly healing rates.

So first and foremost you want to heal all the inflammation in the rectum and in the perianal area. And you usually do that with medical therapy. That's the best and least invasive way to do it. There are some new surgical techniques that they are attempting to try to close up fistulas that are noninflammatory, that are scar tissue, such as the fibrin plug. Some people have had good success with that and that is a minimally invasive technique.

Kimberly Frederick:

There was a web question related to fistulas and I just wanted to add it to this, from Jessica. "Does having perianal fistulas give you a higher risk of developing vaginal fistulas?"

Dr. Sunanda Kane:

Uma, wasn't there a paper by Dave Sachar saying that once you had perianal disease that you may have more risk for vaginal? But I don't think that in general that we really necessarily believe that. It's a different entity. A rectovaginal fistula occurs because there's a lot of inflammation in the rectum. Perianal fistulas are away from the rectum and into the gluteal region and the anal canal.

Dr. Uma Mahadevan-Velayos:

I would agree with that.

Kimberly Frederick:

There are several questions that also came in over the web, asking if there's a way to locate an OB/GYN who is familiar with IBD issues.

Dr. Sunanda Kane:

Excellent question.

Dr. Uma Mahadevan-Velayos:

So that is hard because we've actually had OBs who refused to take care of patients on azathioprine, which I think is insane. And we've actually had to find a new OB. Often a high-risk OB will be more familiar with complications. So having a chronic disease or having other issues. So if you find a high-risk OB practice, they are more likely to be willing to take care of someone with inflammatory bowel disease.

Now for our practice, because I do see a lot of pregnant women, we have a particular practice we work with and so asking your gastroenterologist is the first step and see if they have an OB that they work with and who they refer their patients to. And if they do not have somebody they work with who's familiar with IBD, the next step would be to go to high-risk OB that's comfortable working with patients with chronic illness.

Kimberly Frederick:

Okay, great. We'll take a phone question.

Operator:

Our next question comes from Christine in Washington.

Christine:

Hi, thank you for taking my call. I heard through the presentation that you have recently found data on the HPV vaccine for women who are upwards of 45. And I was in my late 20s, early 30s, when the vaccine came out and they were still refusing to use it on women who were over 26. So I just wondered what your thoughts were for women who are in their 30s and 40s that

wanted to use the HPV vaccine.

Dr. Sunanda Kane:

Right. So I guess to clarify, the data exist, they are in the hands of the FDA right now, not common knowledge. We believe that it's efficacious and safe, but there is no formal FDA approval yet. But we know the data are available and so it should just be a matter of time before we're able to give the vaccine to those over 26 and upwards to the age of 45.

Dr. Uma Mahadevan-Velayos:

And I will say that as far as we know there's no harm in a woman over 26 getting it. It's really a question of insurance paying for it. And so if you wanted to pay for it out of pocket, I'm sure your GYN would give it to you, though it is expensive.

Kimberly Frederick:

Okay, we'll take another phone question.

Operator:

Our next question comes from Darlene in Illinois.

Darlene:

Question about a new study that I will be entering in Chicago at Rush-Presbyterian, on a medication called – oh, boy, I hope I'm saying this right, vedolizumab?

Dr. Sunanda Kane:

Vedolizumab.

Darlene:

Thank you so much. My doctor has suggested that since I have reacted to other medication, Remicade, I have allergic reaction. I've taken Cimzia. They've all made me quite sick. What do you know about this medication? It's been approved in England and in Canada. Since I am inflamed now and only on steroids, do you recommend it, do you know anything about this medication?

Dr. Uma Mahadevan-Velayos:

Vedolizumab, as far as I know, is not approved anywhere. Vedolizumab is similar to a drug that's on the market called Tysabri® or natalizumab. But natalizumab has two components, alpha-4 beta-7, alpha-4 beta-1. Beta-7 works on the gut. Beta-1 crosses into the brain and they think that that may be why some patients on natalizumab get a brain infection called PML. The goal of vedolizumab is to avoid the brain issues, but still have the GI benefits, so it's just the beta-7 part. It is experimental, so we don't know what the safety is. But the preliminary data suggests that there may be some benefit in patients with Crohn's. So if you've failed or if you weren't tolerant of those other medications, and your doctor feels that this would be a good option for you, it's certainly worth considering.

Darlene:
Thank you so much, I will.

Kimberly Frederick:
The next question is from the web from Virginia. There were several questions related to this. "Could you speak more about treatment of perianal disease?"

Dr. Sunanda Kane:
I actually think that that's too broad of a question to sort of answer here.

Kimberly Frederick:
Another person is asking, "I'm a patient with Crohn's. Do you think Remicade treatment is better than prednisone?"

Dr. Uma Mahadevan-Velayos:
Absolutely.

Dr. Sunanda Kane:
Absolutely. That's a no-brainer.

Dr. Uma Mahadevan-Velayos:
If prednisone was going through the FDA now and you looked at its long list of side effects, it's unclear it would actually get approved because it has more side effects than anything else we use.

Kimberly Frederick:
Great. Next question. "If a patient is on Remicade, are there certain kinds of oral contraception that increase the chances of blood clots than other birth control?"

Dr. Sunanda Kane:
The ones that have the higher estrogen components are the ones that will predispose to blood clot risks, but all of them do have some slight risk.

Kimberly Frederick:
"I've got IBD. I'm 55 years old. I'm on infusions and pills. It seems to make me tired. Is this normal?"

Dr. Uma Mahadevan-Velayos:
Fatigue can be from many different things and so I think I would start with your primary care doctor and make sure that your B-12 and your folate are normal, that your iron and your hematocrit are normal, that your Vitamin D is normal. And then infusions, if you are referring to Remicade, should not be associated with fatigue unless you're having a reaction to these medications. So if you're tolerating the Remicade, if that's your infusion, then it shouldn't be giving you fatigue. I'm not sure what the pills are, but certain medications can be associated with

fatigue, including azathioprine, 6-MP, methotrexate, etc. But fatigue is on multiple levels. If you're very inflamed, your body is spending all of its energy fighting itself. And there's very little resource left for anything else. That gives you fatigue. If you've been on steroids for a long time and you're trying to come off steroids, that can give you severe fatigue, which can last several months after coming off prednisone. So inflammation, certain medications like prednisone withdrawal, azathioprine, 6-MP, methotrexate can be associated with fatigue. Make sure your vitamin levels, your hematocrit are all normal. Those can be contributing. So you just need a more general evaluation to answer that question.

Kimberly Frederick:

Great. We'll take a phone question.

Operator:

Our next question comes from Sharon in West Virginia.

Sharon:

You mentioned the rotavirus vaccine and that sometimes that wasn't advised for babies that were being breast-fed. Could you repeat that information again?

Dr. Sunanda Kane:

Sure. This is actually very important, so I think you for asking. So anyone on a biologic therapy should not get live virus vaccine, so if you are on Remicade, Humira or Cimzia, you should not get varicella, you should not get zoster, you should not get MMR. Inactive vaccines are no problem. So hepatitis-A and B, flu shot, but not the mist, because the mist is live. If you're in the military you cannot get smallpox. Your doctor will know what is a live vaccine and what is an inactive vaccine. You can get any inactive vaccine, but no live virus if you're on a biologic. If you are a mom and you are on Remicade or Humira during pregnancy, that crosses into the baby's blood and the baby will have levels of Remicade and Humira for up to six months from birth. So if you were on those during pregnancy, your baby should not get rotavirus or any other live virus in the first six months. In the first six months of life in the United States the only live virus vaccine is rotavirus.

Now if they want to give your baby a flu vaccine, it should be the shot and not the mist. Because the nasal one, the one that goes in the nose, is live.

Oral polio virus is no longer used in the United States, as far as I know, but that is live. The polio shot is fine.

If you're in Europe or from another country, they give BCG vaccine, which is live, and that should not be given as well. And there's actually a report of a baby who was given BCG at 3 months and died from that vaccine.

Does that answer your question?

Sharon:

Yes, it does. I'm a public health nurse and we give immunizations and I really didn't know that knowledge, so this has been wonderful, thank you.

Dr. Sunanda Kane:

Thank you. And again, it has nothing to do with breast-feeding. Breast-feeding is fine. So if your mom is breast-feeding at one year and they need to give MMR, no problem.

Sharon:

Okay. That's what I wanted to make sure I understood the information. Thank you very much.

Kimberly Frederick:

We've had a couple of questions asking how long is a person normally on Remicade or any type of biologic.

Dr. Sunanda Kane:

If you're on a medication for your inflammatory bowel disease and it's working for you, you can be on it indefinitely. So you should be on it for as long as it works for you. So that's the same as whether you're on azathioprine, 6-MP and you're in remission, you should continue it. If you stop it you have about an 80% chance of flaring with the year. If you're on a biologic such as Remicade, Humira or Cimzia and it's working for you, you should continue it on schedule until it stops working for you. And you have to think of it like diabetes or high blood pressure, you would never stop your diabetes or high blood pressure medication if you're feeling well. Same thing, you really shouldn't stop your Crohn's and colitis medication if you're feeling well because the disease will come back.

Kimberly Frederick:

Next question is what vitamins do you recommend for females and should we get liquid vitamins for better absorption?

Dr. Uma Mahadevan-Velayos:

A patient with inflammatory bowel disease who has the majority of their small bowel intact, if you've had a few small bowel surgeries, that's okay, can tolerate oral vaccines that are pill form. So I generally tell my female patients to take a prenatal vitamin once a day. The benefit of the prenatal, it has iron, it has folate, and can come in multiple different forms that your insurance covers. Some of these very fancy vitamins that may be more specific and more expensive really don't make a difference. So for a woman a prenatal vitamin is actually perfect. Other ones that you may want to consider are calcium, particularly if you're over 50 or if you're on steroids. Vitamin D if your level is low. You may need B-12 shots if your B-12 is low and again, at least once a year your B-12, folate, and Vitamin D should be checked.

Kimberly Frederick:

And Tiffany asked from the web, "Does breast-feeding my child decrease his risk of getting UC even more?"

Dr. Uma Mahadevan-Velayos:

That is actually a great question and we don't know the answer to that. What we do know

is that women who don't have inflammatory bowel disease, who breast-feed their child, that child has a lower risk of IBD. But they haven't done the same study in women with IBD who breast-feed. We definitely know, though, that breast-feeding reduces the risk of developing Crohn's and ulcerative colitis, if the mom doesn't have IBD. We assume that it would be the same if the mom has IBD, that breast-feeding is protective. So you would need a much larger study because, of course, there are more complex risks here. So I do recommend to my moms to breast-feed if they can because it is beneficial to the baby in multiple ways and we would suspect that it would reduce the risks, as it does in the non-IBD moms.

Kimberly Frederick:
We'll take a phone question.

Operator:
Our next question comes from the location of John in Ohio.

John:
Thank you for taking my call. I'm glad I had a second question for you because the lady already talked about the anal fistulas. My mother just – in fact, I'm calling for her – she just started to leak here about a week or so ago from the rectal area and the family doctor said that there was probably an anal fistula there and the only thing that they could do would be surgery for her. But the other question I have, very quickly, is she's had a lot of skin eruptions as of late. She has them on her right arm. It looks like a case of roseola. And she got it in March, they gave her an antibiotic for it, went away, the thing came back here a week ago and they gave her an antibiotic injection again and I'm wondering if it's related to her Crohn's at all or if it's something else. He thought it was perhaps staph that she picked up somewhere.

Dr. Uma Mahadevan-Velayos:
So we can't specifically answer a question about a patient. In general I could say there are two different things. There are multiple skin lesions that are associated with inflammatory bowel disease. So one of those include erythema nodosum, which are big red welts that can form on the skin. And those are associated with having a flare of Crohn's or ulcerative colitis. There's also pyoderma gangrenosum, big black ulcers that are associated with having IBD. Now there's also reactions to medications such as if you're on Remicade, Humira, Cimzia, you can develop a rash that looks like psoriasis. It's called a psoriasiform rash and that can be a reaction to the medication. So skin lesions in inflammatory bowel disease can be part of the IBD itself. Sometimes they can be independent of disease. Sometimes they can be due to active disease. And they respond to the same medications that you would use to treat the underlying IBD. Also they can be a reaction to the medications. And if you have a skin reaction to one of the biologics, often you can treat it with a topical and not stop the biologic. And then finally you can also have infections because you're on these medications. You can have fungal infections, you can have staph infections. So I would definitely recommend if you're having skin issues, show it to your gastroenterologist. If it's not a classic lesion associated with IBD, then a dermatologist should be called in to evaluate it.

Kimberly Frederick:

Thank you to everyone for your great questions. Like I said, the Information Resource Center is open until 10 tonight. You can also download the slides off the website and also through the link in the reminder email we sent you.

I'd like to thank Dr. Kane and Dr. Mahadevan-Velayos for your time and your expertise. And a special thank you again to Shire for making today's program possible.

We truly you being here with us today and we, most importantly, hope that you enjoyed today's program. Thanks everyone and have a good night.

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