SUNANDA KANE, M.D.: All right. It's 12:15, so I think I'd better get started. I know there are some people still waiting to get food, but we'll start. So Happy New Year. This is GI Grand Rounds, and its IBD's turn to present. And so I thought that what I could do is present for about 30 minutes, and give everybody just sort of an update of where we are with the management of IBD and pregnancy. This is a talk that I give nationally and internationally, and never seem to give it to my own home crowd. So I think this might be a very good learning opportunity for the Fellows, as we take care of some of these patients in the outpatient clinic.

And I will put in a plug right now for the CCFA PIANO Registry, which is these funded pregnancy registry that we are a site for. And now there are over 1,000 women registered. And this is a prospective pregnancy registry, from which we are gathering a lot of data. Plus, we have follow-up on the children born to mothers on these various different medications, with either ulcerative colitis or Crohn's disease, to look at long term outcomes-- not just maternal outcomes.

So anybody who is seeing a patient in their clinic who has IBD, and who gets pregnant, we would love to get them into the registry. And you can just page me, or talk to Brenda Becker, who is my research coordinator, and we will take care of everything else. The patient does not need to do any additional blood work or have any extra visits. This is all done by telephone and by survey.

So I'll just shamelessly plug our study. And, just to let you know, we're the second highest recruiting center of all the 38 centers in the US. We follow only the University of California at San Francisco, which is where the PI is at. But we're number two in recruitment.

All right, so we're going to talk about fertility, we're going to talk about the effect of pregnancy on IBD, and we're going to talk about the management of IBD during pregnancy. And I hope what I do is update you with references that are not from 1996, but are from 2011. And then, I even have one from 2012, so there you go.

So we're right on the cutting edge here, so I think it's important that we all sort of are on the same page about fertility definitions. And so fecundity, which is a term that not a lot of us typically use, is the ability to have children. All right, just across the board, are you able to carry a child? And so fecundation is the ability to become fertilized and carry that child, whether it's through natural means or in vitro fertilization.

So then, what's fertility? Fertility is the ability to conceive and become pregnant through normal sexual activity. So somebody who's infertile means that they have been unable to, on their own, conceive and get pregnant. But it's fecundity that is really impaired, meaning that you can't even carry a child. And so what's infertility? It is the failure to conceive status post one year of intercourse. And the background rate of infertility in northern America is 14% percent.

And why is this important? Well, because if you're taking care of a Crohn's patient, or a UC patient, and they're concerned about their fertility, or their inability to get pregnant, then it doesn't necessarily have anything to do with their underlying IBD, that one in every seven couples turns out to be infertile. Does that mean that they can't have children? No. It just means that they may need modern science to help them. So that's the main difference.

So when you're reading papers about the effect of J-pouches, that is the effect on fecundity, because women have lots of issues with delivering eggs to their uterus. And if they aren't having periods or normal ovulation, they can't get pregnant any which way. But it may be that they're just infertile because of that pouch, because they can't deliver eggs from their ovary to their uterus. But with the help of in vitro fertilization, they're able to.

So it's very important that, when you're reading a paper about pouches and impaired fertility, are they talking about impaired fertility, or are they talking truly about fecundity? And the patient doesn't know the difference between the two, but wants to know, can I get pregnant? And the bottom line is yes, basically, that with a lot of modern science, most women with pouches can get pregnant.

And so here are some of the data that we have. It turns out that the landmark paper is from 2006, but once you have a landmark article, then you have six more articles after that. And then of course, article number seven is a meta-analysis looking at all the previous literature.

And so Peter Higgins at Michigan did a very nice meta-analysis looking at the risk of infertility. So he wanted to put all of the literature together and try to make sure that people understood the differences between all of the papers. There were eight studies included in the analysis. The relative risk for infertility for medically treated ulcerative colitis was 15%. What did I just tell you that the background rate was in North America? 14%. So the medically-treated ulcerative colitis has no greater risk for infertility. That's point number one.

It turns out that, if you've had a J-pouch procedure, your risk for infertility increases to 48%. So that's where the rubber hits the road, in terms of talking about the chances of getting pregnant.

Now, it's interesting that there were no procedural factors identified that consistently affects this risk of infertility, probably because it's adhesions that are causing the tubal blockages, and that women have intact uterus, they have functioning ovaries. They just can't get those eggs from that functioning ovary to a functioning uterus.

Now, our surgeons here tell us, well, now that we're doing a lot less invasive type of procedures, that there's a lot less risk for adhesion development, and that they're putting in all sorts of things like Seprafilm, and these fancy voodoo powders to keep adhesions from forming, and that they believe that the statistic, over time, is going to go down. So keep your antenna up, because we are going to be looking at this issue again in about five years, after we've had a chance to understand enough hand-assisted, laparoscopic J-pouch procedures.

Now, you can always offer a patient an ileorectostomy for ulcerative colitis if she wants to preserve her fertility, for sure. But you have to remember that they still have disease. They're still going to need surveillance and they're going to have a lot of diarrhea. And if they have active proctitis, this is not necessarily a good option, just to save fertility.

All right. So this is actually a really interesting study, and it is from 2006, but I bring it up because, for Fellows out there, this is potentially low-hanging fruit, because we really need to try to replicate this study here in the US. And this would be a fabulous research project. But this is a paper that looked at a European cohort of women followed over 10 years. And this was prospective, 580 pregnancies. And 403 were prior to the diagnosis of IBD, and 177 afterwards.

Now, there were some conclusions from the paper that were not new, which was the rate of spontaneous abortion in those women who had a diagnosis of IBD was higher than prior to diagnosis. We already knew that, so not new. The c-section rate was higher after an IBD diagnosis. Again, not new.

But, however, something new that did come out was it the rate of relapse for women with IBD decreased in the years following pregnancy, for both ulcerative colitis and Crohn's disease. And the thought here is that changing the hormonal milieu and the immune environment-- because a woman has to not reject this foreign entity growing within her-- resets her immune system. And somehow, that cross-talk of her new, if you will, immune system, somehow down-regulates disease activity.

So there are a lot of questions here that we don't yet understand, and I'm not bright enough to ask the question correctly to study this. But I think that these are data that need to be replicated. And it's fascinating, because if you read about what the placenta does as an organ, you'll find that, absolutely, there's cross-talk and a change in the immune environment in a woman after she's been pregnant.

So this is the study that I'm going to quote from 1986. It's the classic Miller paper that shows us the rule of thirds. So when a patient comes, and they say, "You know, I'm worried about flaring if I get pregnant. What's my chance of having a flare?" you have to decide whether the patient is in remission at the time of conception. And that's what leads that discussion. So if a woman is in remission at the time that she conceives, then her risk of disease activity is no greater than the non-pregnant state.

Now, that risk is not zero. She has to be reminded she still has about a 25 to 26% chance of having a flare in that nine month period. But it's no greater than the non-pregnant woman. However, if she is active disease at the time of conception, that's when we talk about the rule of thirds. And for the Fellows out there, and for those who have to re-certify, this is a Prime Boards question that they're going to ask you, about the prognosis of a woman who has disease when she conceives.

So a third will get worse, a third will get better, and a third will stay the same. Can we predict which third a woman is going to fall into? No. What we do understand, though, is that, again, it's potentially cross-talk, and a maternal-fetal antigen mismatching that may play a role here. And that the more foreign the baby, the more the mom has to down-regulate her own immune system to not reject this foreign entity, and the less disease activity she will have.

All right, so here's where I'm starting to put in some of the newer literature. I'm excited that I'm finally getting to talk about some newer things. So we keep talking about it. We keep emphasizing how important it is that a woman is in remission when she gets pregnant. So clinically, from the epidemiology, we understand that we see the decreased risk. But what's happening at the scientific level, and the basic level?

So what I'm going to show you are three slides that are not specific to the IBD population, but are in relation to active inflammation during pregnancy, and how bad this is on outcomes. So this first study is 8,000 women as part of the Generation R study. So this is done in Rotterdam. And 6,000 women had CRPs that were measured early in their pregnancy, and then fetal growth in each trimester, and the neonatal outcomes were studied.

And it turns out that women who had an CRP greater than 25-- remember that CRP goes up during a normal pregnancy. So that's why they used the cutoff of 25, because they said that, greater than 25, there's no way that's a normal pregnancy, or that you have a non-inflamed state. So a persistently elevated CRP of greater than 25 was associated with lower fetal weights in the third trimester, and with lower birth weights, and small for gestational age.

So again, this is not IBD-specific, but it just shows you that, in general, the physiology of having active inflammation is bad for baby. So this was in the American Journal of OB/GYN, as was this article. So I actually subscribe to this journal, because there's some very nice basic science that I do use for translation into the IDB world.

So this is, again, another paper looking at the effect of cytokines on pregnancy outcomes. So CRP is very nonspecific, as we all know. So what happens with some of these other cytokines that we do know are pro-inflammatory, versus anti-inflammatory? So this is not Generation R study, but this is a different study looking at women who had threatened miscarriage. So what they did was, any woman who presented with signs and symptoms of a threatened miscarriage had circulating levels of TNF alpha interferon, gamma IL-6 and IL-10 measured. And it turns out that those women who actually did go on to miscarry had significantly higher levels of the bad players, the TNF alpha and the ratio of TNF alpha to interleukin-6 was much higher than those women who were able to carry to term. So the more pro-inflammatory her cytokine profile, the worst that she did.

And then, thirdly-- and yet another study-- again, looking not at the IBD population, but an effect of cytokines on pregnancy. Women who presented at gestation weeks seven to 10-- so in their first trimester, had interferon IL-2-7, 10 and 12 measured, and the outcomes of pregnancies were documented. And it turns out that those, again, with interferon gamma IL-2-7 and -12, which are pro-inflammatory cytokines, and if they had higher of those, and a lower IL-10, which is an anti-inflammatory cytokine, had babies that were small for gestational age.

So some of this is circumstantial, and we have yet to look at more of this. But I've just shown you three studies now-- three different institutions-- where having a pro-inflammatory cytokine profile during pregnancy is a bad thing. So if we want to try to translate that into the clinic-- that, hey, if you have active inflammatory bowel disease, you're going to have an elevated CRP. You're going to have some of these evil humors circulating, and it's probably bad for baby. Which is how we could potentially explain why, if you have IBD, you do have a higher risk for small for gestational age, lower birth weight, and spontaneous abortion.

So this is very nice paper-- again it's a meta-analysis. Because again, you have all of these papers out there. It would be nice to have a thoughtful meta-analysis. And actually, Dr. Cornish is very good at doing these kinds of studies for us. So this was actually 12 studies put together, 1986 through 2005, so it did include the era of biologics-- 3,900 patients versus 320,000 population controls. And so she was very mindful to only look at those studies that actually were population-based, and was actually able to show, again, what we believe and talk about in the clinic-- consistently, that if you have Crohn's disease, you have an increased risk for a low birth weight baby, that your baby has a chance of being premature, and that, certainly, you have a higher risk for having a c-section.

And the thing about the c-sections isn't necessarily a scientific one. It's just the fear and the nervousness of the OB/GYN, rather than necessarily mandating it for any particular medical reason. So this is actually a fairly new paper as well, and it's a very nice population-based prevalent study from the home of our esteemed guest here, who we'll be hearing from in a little bit. Again, 2,300 women, 869,000 controls from the population, and they were very nicely able to show that there was no increased risk for congenital abnormalities, but that the risk for birth outcomes was higher if you had a history of maternal surgery, which is a marker for more active disease.

So what is the mom asking about? She is really worried that her baby's going to, one, have IBD, and two, is going to have a birth defect. So basically, what you're going to tell mom is that all of the literature does not suggest congenital abnormality or birth defect increased risk. And once she's heard that, she doesn't care about the low birth weight or small for gestational age, because once those kids are born, they eat voraciously and they catch up very quickly with their cohorts, and their milestones are normal. So the reassuring data here is that there isn't an increased risk for congenital abnormalities just because you have the disease.

Now you have to tease out the effect of medications, right? Because that's what Mom's really worried about-- is that you're giving me that medication that's going to cause a problem with my baby. I'll just throw in here, very quickly, that this was EPUB at the end of 2011, so it's going to be published in full in 2012. And again, this is low-hanging fruit for any Fellow out there, because this is the world's literature, folks, on pregnancy and PSC. Why is it the world's literature? Because usually, PSC is not really something that you have a critical N that you can study.

But this is a German case series, N of 17. So at the Mayo, probably in a week of Dr. Talwalkar's clinic, we could probably get more than 17 patients. But these were compared to healthy controls, and basically, they were looking at fertility. So they weren't even looking at outcomes, necessarily, so again, that there's a lot of room here for information and good papers.

There was no difference in the number of children between those women who had PSC and healthy controls. During pregnancy, there was an increase in liver enzymes. In five of those patients, there were two that had preterm children, and there were four fetal losses. And so, because this was a case series, you can't really say a lot. There was no statistical significance here because of the N. And so we have a lot of room to understand what's happening in this population.

All right, I present this again, because we just talked about Crohn's disease, but this is a very recent paper looking at ulcerative colitis, specifically. And again, what I highlight in yellow is that the congenital abnormality rate is not statistically significant. So whether you're talking about Crohn's or ulcerative colitis, we have very nice population-based studies to show that, really, the outcomes that moms care about are not increased, but that adverse birth outcomes are associated with maternal disease activity. OK. So we're seeing that epidemiologically. And then as well, I showed you some of the basic science work. So you want mom to be well before she conceives.

OK. So this is data that we've collected out of the CCFAP PIANO Registry. This will be presented at DDW, and I'm sharing it with you now. If it leaves this room, I'll have to shoot you. I'm teasing you with some of this. This is, obviously, not all of what we have to present. But basically, like I said, it's a prospective pregnancy registry. There are 30 sites across the US that we collect data per trimester, and then again at four, nine, and 12 months postpartum on the children.

And we have three groups that we are comparing. So there's what we call the unexposed group, which are women who are just on steroids, or 5-ASAs, or antibiotics. Group two are those patients who are on a thiopurine or a biologic. And then the third group are on both. So they're on combination therapy. we've enrolled 1,052 women to date, and we have 797 complete pregnancies. We've found the spontaneous abortion rate to be 4%, which mirrors the population, and a congenital abnormality rate-- which is birth defects-- of 4.6%. What's the baseline birth defect rate in North America? It's 4%. So this is not higher. So we're very encouraged by this.

Now, what is interesting is that we have seen an infant infection rate of 50% higher-- and that is statistically significant-- at 12 months in mothers on combined therapy. So we have to understand a little bit more what these infections are, how clinically relevant they are. Are these patients who are in ICUs because of RSV? are these self-limited sinus infections, for which they get antibiotics? So we have a little bit more teasing out to do. But this is a signal that bears more of our attention. So here, what we're looking at are early pregnancy outcomes that look very reassuring. Maternal health looks good. But maybe we have to start thinking about what's happening down the road a little bit.

So there's actually an extension of PIANO where we're following kids out to four years. So again, any patients that you have that are pregnant, we would love to get them into PIANO, and then into the extended PIANO, so that we follow these kids out to four years. So there might be a signal here. It's a little early to tell, but those moms who are on combined therapy, compared with those who are on monotherapy-- or just on steroids or 5-ASAs-- seem to have an increased risk for infection at 12 months.

So I'll just remind everybody what you can and cannot do to a pregnant woman. Again, as I've said, the CRP goes up during pregnancy. So you just have to remember that and not get fooled when you see an elevated CRP. Hemoglobins change based on the trimester because of circulating volume. Ultrasounds are safe, but in the US are impractical. But when I give this talk to anybody in North America, where there are Canadians in the audience, the Canadians have access to ultrasonographers who can assess terminal iliums with ultrasound. And so they have a distinct advantage over us.

Low dose x-rays pose a minimal fetal risk. Usually, you don't need an X-ray to tell if somebody's obstructed. Get a good history. MR, you can do if you're worried about an abscess or obstruction, but you cannot give gadolinium in the first trimester. So just call the radiologist, let them know that you have a pregnant patient. They're willing to do the MR. And-- at least, here at Mayo-- at most a tertiary care centers, they will do it. There's actually good literature in the radiology world that says that MR is safe in pregnancy. So if you end up someplace where the radiologist is balking, I can actually send you the reference for the radiologists to show that it's standard and acceptable to do.

Endoscopy we do, if it's for the appropriate indication. Do you need to do one for someone who's having dysphagia or heartburn? No. But if they're having haematemesis, or unable to swallow their secretions, then obviously, you need to do an upper Endoscopy.

Do you need colonoscopy? Very rarely, but the oncologists now tell us that, for a patient who has anemia and hematochezia, that they want to know if that patient has colon cancer, because they can treat colon cancer during pregnancy now. So you may be asked to do a colonoscopy, not for IBD reasons, but to make sure they don't have a malignancy.

This is an interesting paper that came out at the end of 2010. It's not rocket science, and it's not going to change anybody's world, but I thought it was interesting, because this was just a small Danish study that questioned women who had been pregnant. And they were asked, "How adherent were you to your medications while you were pregnant?" And they were actually able to go back and look at, and link up, answers with the Danish prescription database. And it turns out that those who were non-adherent were because of fear of effects on the fetus, and that smokers were more non-adherent with their therapy than non-smokers. So women who are smoking during pregnancy are obviously going to be a lot less adherent to medication, as well.

And it turns out that adherence was about 72%, which is a little lower than would be considered acceptable. But really, the reasons why women were not taking their medication was because of fear. And so this is an opportunity for physicians to do education. Because if it's only fear, then it's just a matter of explaining why you don't want to have active disease at the time that you're pregnant.

So here's another study that, again, made it into our IBD journal, again, late in 2011. And again, these Danish folks are very active in looking at pregnancy for us. And these were women with ulcerative colitis who were surveyed about medication use. And the bottom line was that women were more likely to be adherent if they had received counseling from their physician. So if you take the results from the last paper, and you look at the results from this paper, that basically, if a woman hears from her trusted doctor that, yes, you need medicine, and here's the risk-benefit of that, they'll more likely take their medicine. So I think the combination of these two papers together makes a nice little story.

So just to remind everybody where we're at with state-of-the-art for therapies. Sulfasalazine-- we have some patients on it. But the key thing to remember, particularly for boards, is that you need to supplement folic acid if you're on sulfasalazine, because of the neural tube defect issue. And that sulfasalazine does cause reversible sperm abnormalities, and it's not dose-dependent. So if the board's question is, "What do you do with a male who wants to father a child, and he's having problems," the answer isn't to decrease his sulfasalazine amount, it's to stop it and switch over to another 5-ASA.

Again, I'll show you a nice meta-analysis. Is a little old, but it's from the Journal of Reproductive Toxicology. I don't think very many people here read that, but it's actually a really nice journal for the kinds of interests that I have. And they actually did publish a very nice meta-analysis of mesalamine. So we think that it's a very low-risk therapy. Whether it works in Crohn's disease is controversial, and is for another topic and another day. But basically, this shows that you have a very nice N here, and that the risk of bad outcomes is not associated with mesalamine use. So they were able to tease out the effect of mesalomine. So preterm, spontaneous abortion, stillbirth, or congenital abnormalities were not higher with mesalomine use in IBD.

I will tell you, OK, that your patient who is savvy, who has been on the internet, will come and say, "You have me on Asacol, and I know it's been changed to a category C medicine." And I'm using the brand name here, because it's only a Asacol that this pertains to. So phthalate is used as a coating for several different oral medications, and it happens to be the oral coding that's on Asacol. It's also on Videx, Prilosec, as well as generics omeprazole and Theo-Dur.

So what's so about phthalate? Well, it's linked to adverse events in animals, and it turns out that it causes genital urinary problems in the male offspring of rats. And the FDA, in its infinite wisdom, got really hyped up about this because of the rat studies, and found that, if you do urinary sampling on women who take any of these medications with phthalate coding, that you will get urinary levels that are 50 times that of a normal population. But having said that, OK, so that sounds scary, right? But if you actually do the dose conversion, how much phthalate exposure you have to have, compared to what those pour rats got, to show those congenital abnormalities, you'd have to take 234 Asacol pills a day to get enough phthalate to reach what was exposed in those rats, to show you the adverse events.

So, even though you can measure phthalate in the urine of humans on these medications, it does not appear to be of any clinical consequence. And so that's why the Asacol rating went from B to C, not to D. Because even though there's lab data, it does not appear to be held up in human data. But your patient will ask because it's all over the Internet, and I'm sure it'll soon be on the 2:00 a.m. lawyer commercials on cable TV: "Have you been on Asacol? Do you have a baby with spina bifida? Give us a call."

Steroids. So steroids are the mainstay for treating active disease in pregnancy, at least in my clinic, because they're going to work, and it doesn't take long for them to work. There are increased spontaneous abortion rates and stillbirth in mice. I don't treat mice, I treat women, so I'm not so worried about that. I am worried about spontaneous abortion and stillbirth and women who have really active disease that is uncontrolled.

Cleft palate is seen predominantly in the asthmatic women who get prednisone. It's not as much of a signal in the IBD population. There hasn't been any good literature to say that, if you give women steroids during pregnancy, that their babies have any adrenal-cortical insufficiency when they're born, and there's very good data for neonatal T cell function is intact after steroid exposure in utero.

The clinical pearl here, for those who haven't heard this yet, is that prednisolone is much more effectively and efficiently metabolized by the placenta than any other steroid preparation. So the board's question is going to be, "You want to put your patient on steroids because she's flaring," and you're given the option of putting her in the hospital on prednisolone or budesonide. Don't give her budesonide, thinking that you're saving her from steroid exposure. The pregnant state and the placenta are different organs, and pharma code kinetics are completely different. And so, you are not saving her steroid exposure if you give her budesonide. Give her prednisolone.

All right. So this is a little bit of a busy slide, and breaks some of the PowerPoint rules, but I wanted to make sure it all got onto one slide. So these are data from the CESAME cohort. These are the French that got together, and they are following every patient who's newly diagnosed with Crohn's disease-- something that we could never do here in the US. And what they were able to do, is they were able to publish a heck of a lot of studies out of this cohort. So it's brilliant from that standpoint.

Just last year, they published their data looking at pregnancy-- 215 pregnancies in 204 women. And again, they had three exposure groups, as well as PIANO. So they had a thiopurine group, a drug other than thiopurine, and then those who are were on no meds whatsoever. And they were able to show that thiopurine use was not associated with an increased risk for congenital abnormalities, which, again, is what your mom is really concerned about. So I showed mesalomine, and now I'm showing you the thiopurines, which are the category D therapy. There is an increased incidence of low birth weight and prematurity in women who were exposed to thiopurines, but some of these odds ratios were not significant. And they actually believe that thioprine use is a marker for underlying disease activity. So again, the bad player is active disease.

So again, another nice little paper. And this was published by Laurent Peyrin Biroulet, who actually spent a year here with us. And he just basically showed that doctors are no longer afraid of giving thiopurines, and recommending them to their pregnant patients. So I think that we've made a lot of headway in this way.

Dads-- we get a lot of questions about the dads. Let me just tell you that we have good science now, to show that 6MP use in men is not associated with any adverse events.

And biologics-- so biologics cross the placenta. They do so because they are IgG antibodies, and they start to cross at week 20, and then logarithmically increase until birth. So if we believe that, then when do we start or stop our biologic? So this is infliximab in the newborn-- 10 patients that it's been documented now that kids are born with infliximab because it crosses the placenta. So we usually make the recommendation that, if the mom can tolerate not being on infliximab, we'll stop it around week 30 or week 32, and wait until she's delivered, and then give her next dose of Remicade.

However, this is the newest paper that came out. This was in '04, and the infliximab was stopped at week 20 or week 21, and there was none in the cord blood, or in the mom at delivery. But as early as week 26-- when the baby was born-- it was in cord blood. Huh. Maybe we've got to be thinking about this week 30.

So again, these are data that just make us take pause and think about, why are we treating mom? Does she really need the infliximab? If she does, you give it, because again, it's disease activity that's going to drive a poor outcome.

Certolizumab is a pegylated Fab' fragment, not a full antibody. And it turns out that it does not appear to cross the placenta. So we don't switch patients during pregnancy. If they're on infliximab or adalimumab, we don't switch them. But if you have a patient who needs a biologic, and is female, and is thinking of getting pregnant in the very near future, you may want to consider giving her certolizumab.

And I think I'm going to actually stop there, because I didn't realize I was going to go this far. But basically, a healthy mom is the best prognostic indicator, most IBD meds are low-risk during pregnancy, the number one teratogen still remains alcohol-- which you can go and buy at the corner store. So, for anything that we prescribe, there's still stuff out there that mom can get freely, without our knowledge or consent. Induce and then maintain remission, c-sections are not mandated, and the majority of pregnancies are harder on you than they are on your patient. And with that, I'll stop. Thank you so much.