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## Bleeding Disorders & Female Patients: Emerging Options in Hemostasis

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Bleeding Disorders and Female Patients:

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Dr. Singer:

Women with bleeding disorders are disproportionately affected compared with men. Could you describe the types of issues seen in the OB/GYN setting that result from bleeding disorders and why they should be important to all of us as practitioners?

Dr. Ahuja:

Sure. So, yes, that is true that women are at a disadvantage when they have a bleeding disorder, only because they have more chances of having bleeding issues throughout the spectrum of the age group. So, going from adolescents till they enter menopause. And we see this throughout the spectrum – patients coming in at different stages. So, we depend on family practice physicians and pediatricians and gynecologists to send us patients that will be deserving to look further. And what I am trying to explain in this slide is how you figure that out. Which are the patients that are at most risk of having a bleeding disorder or a diagnosis? So, if you look at this question, it's a very simple – and it was Claire Philipp who published this way back in 2011. And, you know, you cannot administer questionnaires or tools or screening in your office, but this is very easy to do and even your medical assistant can ask this and let you know. So, how many days does your period last. So, nobody should be having periods 10 days or 14 days. That's not normal at all. How – do you experience any flooding or gushing during your period? For adolescent girls, I ask them, do you have to get up within, you know, in your school, do you have to leave in your class to go and change your pads or tampons? That's not normal. And, do you have to change your pads or tampons more than every two hours? So, that is also not normal. But then we go

on to ask them, have you ever been diagnosed with anemia? So, you know, that is directly in relationship to how much bleeding you have. And then from then on, it's about other things that are happening in your life – do you get easy bruising? Did you have dental extraction and that bleeding lasted for days, and days, and days, which is not normal? And how about other family members? Does your mom have heavy cycles? Does your aunt have heavy cycles? Have you had any surgery? Did you have bleeding problems after surgery? So, these go through the variety of life situations which can point towards. And then we go on to pregnancy and so on and beyond that. So, postpartum hemorrhage is what we focus on. You may be surprised to know that women with bleeding disorders tend to have more ovarian cysts. So, we want to, at the onset, figure out which women now need more help from a hematologist and more workup.

Dr. Singer:

So, you mentioned how common this is any how many patients we may actually encounter that have a bleeding disorder. In the women's health setting, how good are we at identifying women with bleeding disorders? And, perhaps, what could we do better? So, I guess I led that question, because if we need to do something better, then maybe we're not so good, but maybe you could talk about that.

Dr. Ahuja:

Yeah, so, statistics show that the first diagnosis of a bleeding disorder in a woman – so as you know, all of these are congenital bleeding disorders, so you're born with them. Most of them. There are very few acquired. So, you would assume that the diagnosis is done way before a woman reaches the reproductive age group, but that is not true. In fact, we diagnose more women in – around their pregnancies or childbirth, with bleeding disorders than we do earlier on. So, this was realized a few years back. So, the American College of Obstetrics and Gynecology then put out a statement that any adolescent female who has heavy menstrual bleeding that causes her to have anemia or puts her in the hospital because of severe anemia, should be screened for a bleeding disorder, and that included von Willebrand's disease because that was the most common bleeding disorder.

Dr. Singer:

You started to sort of elaborate already about this collaborative approach, but let's turn to the collaborative care for women with bleeding disorders. What are some of the best practices and how should be consider implementing them when we're managing such patients, hopefully, not at the extreme that you've just described. We can do this and be collaborative before somebody ends up in the ICU.

Dr. Ahuja:

So, a lot of HTC's throughout the country, and Chicago has several as well, will partner with a gynecologist or an adolescent medicine specialist who are seeing these women who come in with heavy menstrual bleeding, and they partner with a hematologist, and we depend on our GYN colleagues for that as well. In fact, I also have – I have a clinic that is once a month, that is – I do it in the same office as a gynecologist, so I said I will come to your office and I will see any primary referral with heavy menstrual bleeding. And the idea here is that we see these patients together because once I see them and they're sent to the gynecologist, or the gynecologist sees them and sends them to me, we lose patients in the process because people don't keep up appointments or they think their problems are resolved now, so they don't need to go to a second doctor. So, we have circumvented that by seeing these patients together and we call it the Hem-Gyn Clinic, and the patient sees both the physicians and we talk right away face to face, and collaboratively care for that patient, and this has made a huge difference.

Yeah, so, you know, not everybody's going to have the combined clinic that I was talking about, right? So, we tell – we obviously collaborate with the GYNs who are far away from us as well, and there are tools to identify who should be getting more of a workup. So, one of such tools is right up on the screen, called a PBAC score, a Pictorial Bleeding Assessment Calendar, and this can be easily administered in the waiting room of a family practice physician or a gynecologist, and this actually pictorially goes through what you're product looks like, what your tampon looks like or pad looks like, and there is a score assigned to each day of your menstrual cycle. So, as you can see, this goes up to eight days because obviously this is looking at heavy cycles. And a score of more than 100 on this scale is – has an 80% sensitivity and specificity of identifying women who may have a bleeding disorder. And if you add anemia to this, and if you add ferritin to this, so ferritin being low, and that increases the sensitivity to more than 90%. So,

this is a very easy tool. Besides this, we empower the women themselves. So, now it is the age of, you know, social media. So, there are a lot of apps that will track your period. So, one of them is called iPeriod. There is an app called Flow.

And, finally, they can go to a website. So, the National Hemophilia Foundation has a website that is called "It's Better You Know." So, [itsbetteryouknow.org](http://itsbetteryouknow.org), and women can go themselves and self-administer a questionnaire. So, there's a category of men at risk or women at risk. If you're a woman at risk, you can click on that and that will take you through all of these questions and other – and resources. They will actually point out the hematologists in your area, depending on your zip code, that you can go to to find help, and a gynecologist that may be available as well. So, there are a lot of resources that we –

Dr. Singer:

That's great. So, let's turn our attention for a moment in the brief time that we have left and focus a little bit on how we treat women with bleeding disorders, and that probably starts with a little bit of a discussion on hemostasis. What we need to know – perhaps a little bit of a refresher course for people – but we'll keep that brief, and then perhaps move into some of the current treatments, or new and emerging treatments, that are available.

Dr. Ahuja:

So, I won't go into the specifics of the whole cascade, of course, but, you know, suffice to say that when you have menstruation, you have disruption in the blood vessels integrity, and you need the whole hemostatic system to get back to repair it, to resolve it. So, you need enough coagulation factors. You need the platelets to be functioning well, and then, finally, you also need the lytic system – the fibrinolytic system that we have. So, if anything is missing, as you can imagine, that blood vessel integrity is not repaired properly. So, because of that, there can be excessive bleeding, and it is our job as hematologists to figure out where in that hemostatic system, where the defect lays.

So, this is exciting times in hematology and hemostasis because we have a plethora of new treatments that have – that are under trials and some of them are approved. So, one example is this on the screen. It's called emicizumab have entered the hematology world as well. This is actually a humanized antibody. So, it's a bispecific antibody that identifies factor IX and factor X. That's how factor VIII works in the body. So, this is not factor VIII, but it is an antibody that does the function of factor VIII. So, that's why it's called a mimetic, and it can be given to anybody who has low factor VIII levels. Anybody – women with, who are mild hemophilia or carriers of factor VIII can also get this, and this has a very long half-life, so four to five weeks, and it's subcutaneous. It can be self-administered at home. So, as you can see here, the blood that is circulating in our body is in a fluid state because there's this fine balance between the bleeding side and the clotting side. And if you have hemophilia, or factor VIII is missing, suddenly you're having more bleeding. If you have antithrombin deficiency, which is on the other side, so now you have a deficiency of an anticoagulant that is naturally occurring in our body, then you are on the clotting side. So, you have more thrombosis. So, what if both were to occur? Right? So, this is what we call as a rebalanced hemostasis. So, science has taken this a little bit further, so what if a hemophilia patient also had a low antithrombin level, and this can be achieved via pharmacology. And that drug is already under trials. It is known as Fitusiran. It is a – currently, it's an investigational agent, but it is an RNA interference therapy. That means it goes to the liver and shuts down the production of antithrombin itself to a level that is needed to rebalance this hemostasis. It's a subcut injection. It's in trials currently for patients with hemophilia A or hemophilia B, so this is fascinating for us because now we are not replacing the missing protein, but we're just making – altering the blood in a fashion that now you're coagulation is fixed, even though you didn't fix the actual problem there was. And then, beyond that, there's another molecule known as concizumab, which is made by Novo Nordisk, which is also based on the same rebalancing of hemostasis theory where the – on the clotting side, what is being targeted is something called a tissue factor pathway inhibitor. This is also a humanized monoclonal antibody and it's against a particular domain of the human TFPI, or tissue factor pathway inhibitor, and it selectively blocks the Xa binding to that. And because of that, the thrombin generation is increased in patients with hemophilia. So, basically, again, rebalancing. And lastly, there's a drug called – a drug which targets the activity in protein C, and this is an APC serpin that similarly rebalances hemostasis and, you know, causes – and makes patients with hemophilia, or any bleeding disorder, to have balanced hemostasis.

Dr. Singer:

Fascinating and wonderful that we have some emerging technologies to be able to use. As we wrap up our discussion, I just want to

revisit the importance of early referral for suspected bleeding disorders that we may all be seeing in the women's health care arena, and absolutely, teamwork.

Dr. Ahuja:

So, when gynecologists and family practice physicians and hematologists work together, we can achieve definitely much better outcomes. We don't need women to be admitted in the ICUs with hemoglobin of 4.4. We can identify them much earlier. We don't want women – we don't want women to have endometrial ablation and hysterectomies when they don't need them for heavy menstrual bleeding. We can do much better with medical therapies. We can identify these women, who may have a bleeding disorder, much earlier than at the time of repeated miscarriages or those hemorrhagic cysts that would bring them to the emergency departments. So, we can do all of this with teamwork and identify them much earlier so that they can be sent to the correct physicians and they can get a proper workup and treatment for those disorders.

Dr. Singer:

So, very important message with which we will leave you now. Dr. Ahuja, this has been a very enlightening discussion. I think you've given us much to think about on how to best care for our female patients with bleeding disorders and thank you so much for joining us today on this very valuable discussion.

Dr. Ahuja:

Thank you, very much.

Announcer:

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