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Primary Biliary Cholangitis: Shining Light on an "Invisible" Female Health Burden

Announcer:
Welcome to CE on ReachMD. This activity, titled Primary Biliary Cholangitis: Shining Light on an "Invisible" Female Health Burden is provided by Omnia Education and supported by Gilead Sciences, Inc.

This replay of a live broadcast reviews clinical features, diagnostic criteria, and treatment options for PBC, a chronic liver disease primarily affecting women over age 50.

Dr. Hirschfield:
Thank you very much for having us here today. You can see that I'm by myself. My colleague, Professor Mayo, unfortunately got stuck in Texas, so she's going to be Zooming in. But we'll be doing this together using technology.

This session is going to be Primary Biliary Cholangitis: Shining Light on an “Invisible” Female Health Burden. That's a liver disease—1 in 1,000 women over the age of 40 live with it.

My name is Gideon Hirschfield, and I'm a hepatologist from Toronto, and Professor Marlyn Mayo is a Professor of Hepatology from UT Southwestern Medical Center in Dallas.

These are our relevant disclosures with industry.

And with that, I'm going to hand over remotely to Marlyn.

Dr. Mayo:
Thank you, Gideon. I hope everyone can hear me. I just want to say I'm really disappointed that I can't be there in person. I always enjoy going to meetings which are not my exact specialty, not a GI or hepatology meeting, because that's where I learn the most. And of course, New York is just a fabulous location with all the restaurants and shows and everything, so I'm definitely going to miss it, but I'm pleased to be able to share with you this information.

So our learning objectives today are going to be to recognize the common phenotype of primary biliary cholangitis, or PBC, determine the clinical information that you need to make a diagnosis of PBC, and then how to use the available clinical information to determine when to refer to a specialist. And then we'll summarize the benefits of some recently approved therapies. It's a rapidly changing landscape.

So some of you who trained in the remote past may be familiar with the term primary biliary cirrhosis, which is what this disease was first called in the 1950s. And then the name changed around 2015. It's an interesting story that I always like to share, because it's really the only example that I can think of where patients were able to lobby to change the name of their disease. So the reason for the name

change is that we can now diagnose it earlier than we could in the 1960s and 70s, and therefore not everyone has cirrhosis at diagnosis.

And the way this process went is in 2014 there were some patient representative meetings, and they met with experts at some of the scientific meetings. And in 2015, there was a conference call of experts from around the world discussing what name could we use that would get rid of the stigma of the word cirrhosis. We wanted to keep the PBC moniker, but to take away the cirrhosis, and a bunch of names were thrown out. And then finally, primary biliary cholangitis is what won by popular vote. And what really sealed the deal was joint publications in all of the hepatology and gastroenterology journals at the same time in 2015.

And after that, you can see, if you do a Google trend on the term primary biliary cholangitis, that's when the term really took off. And then that was followed by, finally, Medicare services in the U.S. giving this an ICD-10 code.

So PBC is a chronic cholestatic liver disease that's characterized by this inflammatory destruction of the small and the medium sized bile ducts, and if it goes untreated for long enough, will progress to cirrhosis. It is a rare disease, although it's not an ultra-rare disease. In 2021 for every 1 million people, there were over 400 with PBC. So in the U.S., that means there are over 100,000 people living with PBC. And importantly for this meeting, 90% of these patients are women, and 3/4 of the people are diagnosed over the age of 50.

Men do get PBC—not as often, but when they do get it, they're usually diagnosed at an older age, usually because it goes unrecognized or not thought of.

Annually, the incidence is around 40 new women diagnosed with PBC for every 1 million individuals. And then survival after this diagnosis is around 20 years, which is an improvement; it used to be 10 years.

So if we look at epidemiological data, the prevalence is actually increasing over time. You can see the graphs from different studies showing the relative increase. The racial ethnic distribution is really unknown. The data that we have indicate a Caucasian bias, but that's probably because the data that we have are primarily from the U.S. and UK. The data in the U.S. comes from clinical trials which are biased towards Caucasians in enrollment, and the best quality geographic studies are also from fairly homogeneous Caucasian populations in the UK.

So the key clinical features often are none, right? So this is what can make this disease invisible, which is it is often asymptomatic. However, if they're going to have symptoms, the most common ones will be fatigue and itching. Dry eyes and dry mouth are also very common. They often complain of brain fog, and the minority, about 17%, will have some right upper quadrant pain.

Clinically, these patients often have hypercholesterolemia, which is a result of being cholestatic and not being able to get the bile out of the damaged bile ducts, which leads to buildup of the precursor of bile synthesis, which is cholesterol. They have increased rates and faster progression of osteoporosis. And then in more advanced stages, they actually have fat soluble vitamin malabsorption from the decreased bile acids in the gut which are required for fatty acid, or vitamins which are absorbed with fat.

So I mentioned that the most common disease symptoms are pruritus and fatigue. Up to 70% of patients will have itching, which we call cholestatic pruritus. It's important, particularly for patients, to know that the symptom severity doesn't correlate with the disease stage and it doesn't improve with our standard treatment, which is ursodeoxycholic acid.

Unfortunately, this is a symptom that often goes ignored, and less than 50% of patients are receiving appropriate therapy, according to recent studies. And if you ask patients to describe how the pruritus is for them, it can be really miserable. So here's some quotes for you: ‘I want to tear my skin off.’ ‘It messes with your mind.’ There are cases in the literature where patients even become almost suicidal from the severity of the itching.

The fatigue is also extremely common—50 to 75% of patients. It is associated with daytime somnolence. It often interferes with work, social activities, associated with poor sleep quality, depression. And patients often feel isolated, and this is a symptom which is often not appreciated by healthcare providers and dismissed as part of just aging. But patients will tell you it feels like you're really in a fog, and you can barely move one foot in front of the other.

So because the symptoms can be nondescript, laboratory findings can be extremely helpful in identifying these people. The most

important feature is that they are cholestatic, and so that is going to be evident by an elevated alkaline phosphatase and elevated GGT on the labs. They may get an elevated bilirubin, but that happens in later phases of the disease.

The hallmark of this disease is an autoantibody called antimitochondrial antibody, or AMA, and I'll talk a little bit about that. Most patients will have it. Antinuclear antibody, or ANA, is also quite common. They have a characteristic increase in IgM, which you don't see in too many other diseases. And as I mentioned before, they often have hypercholesterolemia.

So I mentioned these antimitochondrial antibodies, which are fairly specific for this disease. These are antibodies that are directed at the pyruvate dehydrogenase complex. And if you do immunofluorescence, which is kind of sort of your standard antinuclear antibody test, what you see is this fluorescence all throughout the cytoplasm on the left, which is lighting up all of the mitochondria in every cell in the body. You also see reactivity to this autoantigen, oddly, on the surface of the bile duct cells, which we think could be a clue as to the pathogenesis of the disease.

I mentioned that patients often have ANA—about 40 to 50% of patients with PBC will be ANA positive. There are lots of different kinds of ANAs. There's centromere, there's homogeneous, there's diffuse. There are some very specific types which happen to be speckled, which are highly specific for PBC, if you see them. And those are listed there below for you: the anti-GP210, anti-SP100, anti–Kelch-like 12, and anti-hexokinase 1. The latter two are really only available easily through the research studies, but the top two are commercially available in the U.S.

On immunofluorescence, if they have a GP210, they might say that there's a nuclear rim pattern. You can see that picture in the left side image. And the SP100 has an appearance that looks like multiple nuclear dots. And again, the picture there is on the right. These are not found in most PBC patients. Overall, about 20% of PBC patients will have one of those two antibodies. But it's very helpful to identify patients who happen to be AMA negative because of its very, very high specificity.

Now, the pathophysiology of this disease is really unknown, so I'm not going to spend a lot of time on it. We know that there is cholestasis and immune-mediated destruction of bile ducts, but we don't know which causes the other. It appears to be a combination of genetic risk factors, epigenetic changes, and environmental exposures. And my colleague, who you're going to hear from after me, Dr. Gideon Hirschfield, did a genome-wide association study to see what genes are most strongly associated with the disease. And they are indeed all immune regulation genes, such as major histocompatibility complex.

And then in terms of environmental exposures, there is some data that certain toxins may precipitate the development of PBC. For example, survivors of the Nagasaki bomb explosion have increased rates of PBC.

And then I thought, since this was in New York, you might be interested to see this study. This study looked at patients who are listed for transplant for PBC, and those are shown in the dark circles, and they seem to overlap fairly strongly with the New York toxic superfund sites, which are indicated in the arrows. So it's just—these are epidemiologic associations.

So the typical clinical progression of PBC is shown here. The AMA, or antimitochondrial antibody, is often the very first thing that pops up, and often even before you can detect the changes on biopsy, because the biopsy changes of inflammation of the bile ducts can be very patchy in the beginning. And then after a period of time—sometimes often many years— then we start to see the biochemical evidence of cholestasis with the elevated alkaline phosphatase.

The symptoms, as I said, don't tightly correlate with disease progression, but tend to pop up after the biochemical changes, and then eventually, over time, they get progressive fibrosis and eventually cirrhosis with portal hypertension. And once they reach that stage, they look quite similar to other patients who have cirrhosis from other causes.

So you can imagine if the main symptoms or features that you're going to see on these patients is things like fatigue, brain fog, osteoporosis, high cholesterol, some itching— if one of these patients walks through the door, PBC is probably not going to be the first thing that comes to mind, right? More common reasons for these symptoms are going to be anemia, depression, menopause, thyroid disease, and it's important to look for and evaluate these things.

But if I achieve anything in this talk, I hope it's to remind you that there is this potential zebra of PBC that could be responsible for all of these symptoms.

And I can't tell you the number of patients I've seen with PBC that said they complained of their symptoms to their provider and were told, 'Oh, you're just getting older. This is just part of menopause.'

There are a number of extrahepatic associations—other autoimmune diseases that are associated with PBC. Starting at the top and going around clockwise, hypothyroidism is quite common. We screen for it annually in these patients. There's also an association with limited scleroderma, what we used to call CREST, or calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, and telangiectasias. Some of these patients may have GERD. There's an association with autoimmune anemias. Raynaud's, by itself. A lot of these patients will have asymptomatic bacteruria. They can often get an autoimmune arthropathy or a reactive arthropathy. But even true rheumatoid arthritis has a strong association with PBC.

There's also a link to inflammatory bowel disease, particularly ulcerative colitis, and more so than Crohn's disease. A lot of these patients will have gallstones. It's a common story to hear that they presented with a little abdominal discomfort and a high alkaline phosphatase and had some gallstones, got their gallbladder taken out, and they still had the high alkaline phosphatase and the symptoms. And then later it was PBC that was found. There are a lot of PBC patients running around that do not have gallbladders anymore.

There's also association with lichen planus, psoriasis, and sicca syndrome is very, very common in 70 to 80%.

So if you see any of these symptoms in your patient, that might be a little flag to consider PBC. It's also not uncommon to see these symptoms or these conditions in relatives of the patient.

So now that I told you a little bit about what these patients look like, how do you actually make the diagnosis? Well, officially, the diagnosis requires two out of these three criteria. They should have an unexplained elevation of alkaline phosphatase, and generally we use a cutoff of about 1.5 times upper limit of normal. They should have a positive antimitochondrial antibody, or if they don't, then a positive PBC-specific ANA. And the third thing is they could have typical features on biopsy, which is this nonsuppurative destructive cholangitis. You see a picture of that on the right, with the circular area in the middle is this granulomatous inflammation that is destroying the bile duct. That's classic and very typical for PBC. It's called a florid duct lesion.

So based on the fact that you only need two out of those three criteria, you don't need to do liver biopsy if the patient is AMA positive and has had this high alkaline phosphatase that is chronic.

I want to add a couple caveats. That's based on a study where most of the patients were middle-aged women. So in men, there might be a little bit more consideration of doing a biopsy. It was based on women who all had transaminases that were less than 500, so if the patient has very high transaminases, that might also warrant a liver biopsy. And just in general, if there was some suspicion of other liver disease— here in Texas, we have a lot of fatty liver, now called metabolic-associated steatohepatitis, and so we're often having to do liver biopsy to differentiate PBC from MASH versus both.

Alright, so now it's my honor to turn over the program to my friend and colleague, Gideon Hirschfield. Professor Hirschfield is going to talk in more detail about diagnosing and particularly in treating PBC. And again, thanks for the opportunity to communicate via Zoom, even if the air traffic controllers in Dallas were having a lot of difficulty.

Dr. Hirschfield:
Thank you, Marlyn. I'll be the one to go to Raising Cane's to get some fried chicken while I'm here.

So it is a pleasure to be here, because I'm an adult hepatologist as well, and I look after a lot of patients with PBC. And over 90% of my patients are female, and therefore we spend a lot of time looking after this disease, but the intersection with some of their women's health needs. So talking to you today is really impactful for us as well.

I'm going to start with a case. It may not be the most common case, but it is another example of how I sometimes interact with women's health providers, because I'm sometimes interacting with obstetricians. This was a 32-year-old woman who was sent to me at 16 weeks pregnant because her obstetrician noted, and the patient noted, absolutely severe and devastating pruritus all over her body—palms and soles, arms and legs, perianal, perivaginal, no rash, and it was disfiguring. She does report pruritus between pregnancies, but had

not been investigated, and her first son had actually been born back in 2021.

The investigations by the OB team had shown a mild fatty liver. So that's very common nowadays, and that wouldn't explain this. And her labs put her into the really flashing red light for obstetric cholestasis, with bile acids at 75, elevated transaminase activity. But looking and digging around when I saw her, in fact, her alkaline phosphatase had been abnormal for many, many years and had just not been picked up. So here you can see evidence of cholestasis that actually went back more than five years, with an alkaline phosphatase of 419.

The OB had appropriately started some ursodeoxycholic acid, really thinking this was primary obstetric cholestasis, but only with some partial symptom relief, and had fast-paged us in hepatology because of the concern that this was quite early and quite severe and quite symptomatic.

We did some investigations, and knowing that she'd had abnormal liver tests before and had had pruritus outside of pregnancy, were suspicious that this wouldn't be classical primary obstetric cholestasis, but more, so to speak, a second obstetric cholestasis. And indeed, what you can see is a woman who's profoundly cholestatic, and even for pregnancy, has a very high alkaline phosphatase with exceedingly high bile acids that put her into the danger zone, but her immunology makes the diagnosis.

So this is an autoimmune liver disease. It is a lymphocytic cholangitis of the small bile ducts, and in more than 90 to 95% of patients, they are antimitochondrial antibody positive. So we can make a diagnosis quite efficiently, effectively, and usually without liver biopsy.

We obviously then co-managed the patient, managed her itch with some other therapies. In this case, we used some bezafibrate once we're in the second trimester, and I'm pleased that although she was delivered early because of the concern over her bile acids, she had a healthy baby, and now I'm looking after her with her primary biliary cholangitis. Her itch gets better as the pregnancy ends, but doesn't go away. The pregnancy had merely exacerbated the cholestasis, because estrogens seem to have an effect on the biliary epithelium.

So when we're diagnosing, and when you're diagnosing, and when primary care is diagnosing autoimmune liver disease, in particular, what you're doing is you're interpreting the serum liver tests, and that is the starting point for diagnosis. Patients who are cholestatic, who have biliary disease—small bile duct or large bile duct—will classically have elevated alkaline phosphatase that is accompanied by a gamma-GT rise. Okay? They can have elevations in transaminases, but in a sense, the alk phos is pulling up the transaminase activity so that the peak is less. Whereas the patients with hepatitis are, of course, characterized by very high transaminases and a much more trivial change in the alkaline phosphatase.

Our diseases do not have a known cause. They are autoimmune, and therefore we have to exclude alternate etiologies, and that means alcohol, viral, metabolic, and drug-induced.

One of the reasons, however, the name was changed from biliary cirrhosis to biliary cholangitis is the fact that many women with this disease will report having been asked about their alcohol intake multiple times over multiple months and not being believed that they were telling the truth before finally getting a diagnosis of PBC when finally their care provider agrees to do the AMA test. We will do other investigations—a baseline ultrasound will exclude biliary obstruction, but that's the way that we can make an efficient diagnosis.

So in a patient who's AMA positive with abnormal liver tests that are cholestatic, you have a 90 to 95% positive predictive value that you would find PBC on a liver biopsy. Hence, we make the diagnosis and we initiate treatment, and we initiate treatment for life.

We do have a pathway for those patients who are AMA negative—they would be referred to GI and hepatology. We would look for those antinuclear antibodies that Professor Mayo mentioned, because if we can spare a patient a liver biopsy, then that is much appreciated by our patients, and if we can make an efficient diagnosis on serology alone, we will. However, sometimes we need to do MRIs and sometimes we need to go on and do biopsies and other tests for alternate diagnoses that are even less common than primary biliary cholangitis.

Okay, so the five steps of PBC—and deliberately here for the non-expert audience—first and foremost, our treatment targets nowadays are aim for normal alkaline phosphatase, keep the bilirubin normal, and do everything we can to have a normal quality of life for our patients. We do this by effective diagnosis, confidently telling the patients they have a chronic disease that needs lifelong treatment, and

that we assure they have what they have, mainly using blood tests, occasionally using liver biopsy if there's concomitant disease, such as fatty liver or autoimmune hepatitis variants.

We then make a risk assessment. You heard that 75% of patients are over the age of 50. That means that 25% of patients are now diagnosed under the age of 50. We know that the younger the patient, the more significant the risk—and by that, I mean the more significant the risk that they will progress to cirrhosis and all the complications that I then told you about. So we are looking to understand the risk of our individual patient as we diagnose them, so that we are prompt in targeting therapy to them, and we are telling our patients that the best outcomes come if we can make their liver test normal.

We also use elastography. We use elastography in our practice of the liver. I know elastography is used in other parts of the body, and we measure liver fibrosis as a surrogate using this tool.

In the USA, there are now three FDA-approved therapies. One therapy was taken off the market—well, voluntarily withdrawn from the market about a week ago. Ursodeoxycholic acid is the mainstay treatment. All of your patients will be offered ursodeoxycholic acid and will be encouraged to take it for life. If they have insufficient response to urso—and urso is not designed for symptoms, but for preventing disease progression—they will now be offered one of two PPARs: elafibranor or seladelpar. Some of the data, which I will show you, previously offered obeticholic acid, but that therapy, although demonstrating some efficacy, was unable to meet some of the regulatory requirements of the FDA.

Alongside understanding the patient's risk, mitigating that risk of disease progression and end-stage liver disease and death from liver failure, will be symptom control. And symptoms are in parallel to disease severity—you can have a high symptom burden and have relatively mild liver fibrosis.

So we regularly ask our patients, listen, and are empathetic, but may not always have all the answers about pruritus, which is a biliary-specific symptom; fatigue, which is clearly a non-specific symptom; I heard a lot of talk about sleep apnea, so obviously fatigue has many causes, okay; and dryness, sicca complex, which is definitely a part of this disease. A dry gland syndrome was the description from one of the first academic descriptions of PBC.

And then alongside that, we work with our other providers—our primary care, our other women's health providers—to look after their cirrhosis if they have cirrhosis, to look after their bones to make sure that they're having osteoporosis screening, to signpost them to patient support groups, to survey for other autoimmune diseases—thyroid disease, celiac disease—and to provide the support in simple day-to-day things such as pain management, and then more complex as they may need over their long life.

So the therapeutic options that we have target the disease: ursodeoxycholic acid, first-line treatment, bile acid pool modifier given at gram quantities, makes the bile acid less toxic. That helps mop up some of the toxic bile acids that are causing injury. Obeticholic acid no longer available in the U.S. but still used in the UK, Canada, and Australia. It was an FXR agonist. And therefore, the mainstay of our second-line therapy in the U.S. is now what we call PPARs, and that’s elafibranor and seladelpar.

We have symptom management approaches that are medical and non-medical. The non-medical approaches are supportive. The medical approaches are a bit of a potpourri, but do help, including gabapentin and cholestyramine for itch. There will be, we hope, a new therapy for itch specifically in the future called linerixibat, which is an IBAT inhibitor. The reason I specifically mention this is that this is also a therapy that may one day actually be a specific therapy for the itch of obstetric cholestasis. There has, in fact, been clinical trials of IBAT inhibitors in obstetric cholestasis in the UK, and there are signs that it can really help significantly.

Clinical trials—again, I recognize that you're a general audience, you’re not hepatologists—but I want you to understand that there’s been a number of clinical trials in this rare disease, and what we look at is three things. We look at what's known as the composite response—we give the drug, compare that to placebo, we look to see whether the alkaline phosphatase drops beneath a threshold and the bilirubin stays normal. And we call that the composite response. That is a regulatory endpoint—that’s what the FDA wants.

We also look at our intuitive response—how many times does the patient get a normal alk phos? And how many times does their itch get better as compared to placebo? And that's how we are looking as we develop a bigger array of drugs, starting with OCA as the second line, and then there’s been the PPARs, and then combination therapies. And then there’s, at the very bottom, it’s just an abstract of another drug, but you can see that the composite response for OCA was running around 46 to 47%, for elafibranor it's running at 51%,

for seladelpar it's running at 61%.

And here, I'll show you some more of the details. So this was elafibranor; this was approved in the U.S. in 2024. You may come across it—you won't come across it in your younger patients, because a younger woman should be on contraception or not using elafibranor—but in the elafibranor in the ELATIVE clinical trial had a 51% composite response versus placebo of 4%. And this was the regulatory endpoint. The normalization rate for elafibranor—how often a patient's alkaline phosphatase went to normal after 12 months of therapy—reached 15%. So this was the results of normalization and the result: the alk phos drops rapidly and is sustained.

Elafibranor, when assessed for itch, did not meet its key secondary endpoint of improving itch in the pre-determined key secondary analysis of elafibranor versus placebo, but there were evidence of improvements in itch in some other secondary analyses. Adverse events occurred more frequently in patients receiving elafibranor, GI: abdominal pain, diarrhea, nausea, and vomiting.

The second drug on the market in the U.S., seladelpar, dosed at 10 mg, is a PPAR delta agonist. And in the RESPONSE clinical trial, had a 61.7% response by composite versus placebo of 20; 6 out of 10 patients reached the biochemical composite response at 12 months, with a difference of alk phos dropping by more than 40%. By normalization, seladelpar had a normalization rate of 25%—so 1 in 4 patients treated with seladelpar after 12 months normalized their ALP. So that is a significant improvement for the patients in this clinical trial.

Seladelpar did meet its key secondary analysis for pruritus. There was a clear separation between placebo and drug. This was in patients with moderate-to-severe pruritus, assessed at 6 months using a numeric rating scale, and seladelpar 10 mg significantly improved pruritus for our patients in this clinical trial.

So what about pruritus and its management itself? This is actually included partly because it's very important for adult patients in the liver clinic, but also partly because any of those of you who do manage patients during pregnancy will know that pruritus is a really devastating symptom.

We have the management of pruritus shown here from some European guidelines. I think the most important thing is really the conservative treatment in the middle: skin emollients, short nails, good hygiene, avoiding hot baths, certain fabrics. In children, largely, we're using UDCA and were previously rifampin. In some of the ultra-rare diseases, we're now using IBAT inhibitors. So there are some ultra-rare diseases called Alagille and PFIC, where IBAT inhibitors have been approved in the U.S. and have really made a huge difference for these children, who are scratching so much that their skin becomes scarred forever.

In the adult, we are using a mixture of approaches. UDCA, unlike during pregnancy, is not a treatment for pruritus. We have therefore been tending to use fibrates. In Europe and Canada, we use off-label therapies. The fibrates for PBC are not approved just for pruritus, so they are used in PBC, but only in those patients with an elevated alkaline phosphatase.

Other drugs that we do use: cholestyramine— a very safe drug, but not a very pleasant drug. It's a bile acid resin. Rifampin is a very effective treatment for pruritus, but does have a 5% hepatotoxicity risk, so is not as commonly used outside of specialist hepatologist providers. And then, very occasionally, we will need to transplant our patients for severe pruritus. It remains the case that most big transplant programs will do one or two people a year with transplant just for pruritus. We're hoping that the new drugs coming for pruritus, in particular IBAT inhibitors, will make a difference.

So to show you the data on why we're confident IBAT inhibitors will be relevant in the future, come next year, this is the clinical trial of linerixibat in primary biliary cholangitis in patients with moderate-to-severe pruritus, who over a 24-week period were randomized to placebo or linerixibat. And the linerixibat group had a rapid and a sustained, and statistically significant improvement in pruritus as compared to placebo.

And when you cross over—just to prove the point—from placebo to drug or drug to placebo, you can see the change in pruritus as expected—going up when you go on placebo, going down when you receive linerixibat. So we're hopeful that this will be a new agent for pruritus in the adult world, specifically for PBC.

I wanted to touch on some practice points for women with PBC. These are based on the questions that I get from my patients, and I get from their primary care providers, and from their obstetricians and gynecologists, which come up quite frequently and can cause some

anxiety.

So 25% of women are diagnosed before the age of 50; that means we do look after women with PBC who get pregnant, and we do have to navigate pregnancy, the risk of obstetric cholestasis, early delivery, and the management of pruritus, and the management of their drugs for their liver disease. The itch will and can get worse during pregnancy, and it can be very, very significant and very distressing. It can lead to significant sleep loss and really an inability to cope. So we are very proactive in managing itch in collaboration with our obstetric colleagues.

Ursodeoxycholic acid is safe in pregnancy. It is safe during conception, pregnancy, and breastfeeding. So that's why it's used. We encourage our patients to not stop the urso as they start a family, for fear that their PBC will flare and then everything will be that little bit harder for them.

Elafibranor is not recommended in pregnancy or in women not using effective contraception, and does require a negative pregnancy test before starting, and contraception in its use. Seladelpar, it is also recommended to make sure you're not pregnant, and contraception is used because there is no data for its safety during pregnancy.

Obeticholic acid is now taken off the market, so it is not relevant, but we would stop it if anyone got pregnant on obeticholic acid.

Bezafibrate, which we use off-label and which some people across America do access feno or beza, can be used in the second and third trimester of pregnancy. We now use it as our treatment of choice in severe obstetric cholestasis. So if we have a patient with severe obstetric cholestasis with intractable pruritus who is not responding to UDCA or cholestyramine, then we would use bezafibrate in the second or third trimester with really very, very good control of their bile acids and an improvement in their itch.

We also use rifampin with caution during pregnancy, and have also had very successful results with rifampin for obstetric cholestasis.

For women with PBC, the contraceptive pill is fine. It is very unlikely that they'll find any significant cholestatic side effects. So we tell our patients they can choose their contraception that works for them.

In women asking about HRT, HRT is also okay in our women with PBC. The only very unusual times we would be cautious is in our very few patients who got very advanced liver disease, who've got liver failure, and who've got ascites and jaundice, at which point we would ask you not to use estrogen replacement therapy.

Vaginal estrogens are safe. Women with PBC have frequent UTIs, frequently have bacteruria as part of the disease. And as you all know, vaginal estrogens reduces UTIs and reduce admissions. So we tell our patients there is absolutely no reason why they cannot use them if indicated from either our advice or their primary care advice.

Bone health is really important. For our women living with PBC, we have seen significant osteoporosis from the cholestatic liver disease, and we are very proactive in encouraging our patients to work with their primary providers to survey and treat as normal to prevent osteoporosis. Bisphosphonates can be used, can be used in advanced liver disease. We are just cautious with bisphosphonates in women with varices, but if taken correctly, it's okay. Although now with all the different choices in therapy for osteoporosis, if we did have someone with very advanced liver disease or someone with significant sicca complex who couldn't swallow because everything's too dry, they've got the options of Prolia and intravenous bisphosphonates. So they've got choices. But it's really important that, alongside calcium, vitamin D, different exercise, that their bone health is proactively treated with medical interventions.

Vitamin A, D, E and K deficiency is rare. It is only usually seen when patients are jaundiced, but in patients who've got chronic cholestasis who do have elevated bilirubin, we encourage them to buy ADEK supplementation—that's a vitamin that's got A, D, E and K, just to avoid any fat soluble vitamin deficiency.

Fatigue is a major problem for our patients. We recognize that this fatigue is not specific to PBC, it's common in cholestatic liver disease, but in fact, it's just common generally. It has both a central and a peripheral component. And by that, I mean you can do functional MRI and see differences in connectivity and oxygenation in women with PBC. And you can also do assessments of muscle and see different bioenergetic responses.

We treat holistically. Fundamentally, we believe that movement is medicine and in exercise is probably the most significant intervention we can offer our patients with fatigue; energy, pacing, exercise, diet, clearly cessation of smoking. Medical management is identifying alternative causes of fatigue, so we do tell our patients they can have depression treated, and there's no restriction on the therapies they use. We would also screen for obstructive sleep apnea. We would manage dry eyes. It's interesting, in our symptom survey, which we did last year in our clinic, there is a very strong correlation between sicca complex and fatigue. So it'd be interesting to see, again, this will be relevant to many of you, a condition called Sjogren's disease, where there's going to be new biologic therapies next year for Sjogren's disease, which improve the Sjogren Severity Scale, which includes how a patient feels, which includes fatigue. We'd also make sure there's no autonomic dysfunction.

Generally, medical treatments of fatigue are not recommended. There may be occasional patients who'd like to use modafinil. That's essentially a stimulant. We're not super keen on it, but we have had some patients who use it sparingly and sensibly to help them get through the day, and that's safe.

And then finally, actually multidisciplinary support really includes patient support groups who are very, very helpful in the management of symptoms and encouraging people to do physiotherapy and some kind of just support around psychology of living with chronic disease, which can be very hard for people to live with a disease which is silent, which is hidden, which you can't explain to people because it's rare. You're scratching, so people think you've got scabies when you haven't. And you're tired every afternoon, so your partner doesn't understand why you're having a nap every afternoon. So you can see how those kind of symptoms can really wear people down.

And that's why one of the approaches from one of my colleagues is known as the TRACE approach to managing fatigue. Treatment, yes, treat the treatable pruritus, other autoimmune diseases—celiac, thyroid, anemia. Make sure there's no comorbidities. Many of our patients are in their 60s and 70s might be on beta blockers. Ameliorate what you can ameliorate—sleep disturbance, depression, autonomic. Have coping strategies. So be positive, as their provider, that you can help them by listening to them and being pragmatic and show a little bit of empathy that says, whilst I may not understand everything, I validate your symptoms, and we'll work together to at least tackle what we can tackle.

Announcer:
You've been listening to a replay of a live broadcast reviewing clinical features, diagnostic criteria, and treatment options for PBC, a chronic liver disease primarily affecting women over age 50. This activity was provided by Omnia Education and is supported by Gilead Sciences, Inc.

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