Ozlem Goker-Alpan:

Hello everyone. Today we're going to be talking about reproductive system and pregnancy for lysosomal disorders.

We are going to actually start with the clinical consideration and impact of pregnancy, which actually is regarded a major event. But in general, the reproductive events in a woman's life also are major events that can actually change the trajectory of the disease. So in general, lysosomal diseases involve multi-organ systems that includes hematological, skeletal, visceral, and neuromuscular pathways. And as we all know, the pregnancy involves and imposes additional metabolic cardiovascular and respiratory stress and that can unmask or worsen symptoms. Enzyme replacement therapy or the therapies in general has improved the outcomes, but it requires individualized planning. And when a female becomes or contemplates a pregnancy when she has a lysosomal disorder, obviously early interdisciplinary involvement is crucial, which actually involves genetics, maternal-fetal medicine, anesthesia, and other departments when the need actually rises.

I would like to start with two publications. First is the disorder that I'm more familiar with, and the second is with another publication that we actually had in a few years ago on Pompe disease. So obviously first, Gaucher disease and pregnancy. Gaucher can affect reproductive events due to thrombocytopenia, organomegaly, and bone disease. Obviously, we're talking about undiagnosed and untreated patients here. But when you think about menorrhagia, which is increased bleeding, is significantly more common in untreated females. And also when you ask the question in any female in general, it's about 30%. ERT, as we know, that has improved pregnancy outcomes, which is spontaneous abortion is 13.8 versus 1.7 with ERT delivery complications similarly around 40% untreated and 6.5% with treatment and postpartum complications decreased from 21% to 7% with ERT. And we know that there has not been a proven evidence of fetal harm of ERT and breastfeeding, and it appears to be safe. However, the issue is the negotiated diagnosis can occur right after pregnancy, highlighting the heightened clinical suspicion.

Let's switch to another seemingly unrelated disorder, which is Pompe disease and pregnancy. We published this in 2020, but the research actually was almost a decade old. And what we did is we collected the clinical information from 45 or so females. In this cohort, the delayed diagnosis actually was the most prevalent, and most pregnancies actually occurred before the diagnosis of late onset Pompe disease. And obviously pregnancy acted as a metabolic stressor. Symptoms actually may worsen during pregnancy such as muscle weakness, or you have increased back pain, which may be related to Pompe disease and the pregnancy together. And 84% of these responders reported that back pain during pregnancy actually was worsened. And similarly, respiratory consideration is important in this group. It was rare, but critical when present. So if there is a respiratory and diaphragmatic involvement, and if there's a consideration for C-section, then the anesthesia needs to get involved.

So in this cohort, there were 86% live births and there was 12% miscarriage rate and stillbirth was slightly increased. When you compare with the others, it's the national, usually compared with the national data with the obviously otherwise healthy females. Several pregnancies, there was exposure to ERT and it showed no fetal adverse events. And symptoms often may worsen during the pregnancy and improve the patients when during postpartum period. That is all what I want to present during this introduction.

It is my utmost pleasure to introduce today's speaker, Dr. Asha Talati, who is the Assistant Professor and a tenure track faculty at the University of North Carolina at Chapel Hill School of Medicine. She's also the co-lead, obstetric and imaging services, and she's a faculty associate for Center for Bioethics. Before I invite and turn my camera off, I would like to actually remind that please fill out the evaluation forms.

Actually, the evaluations are very important for this program and also get the CME credit. Thank you very much. Asha, I give you the podium. Thank you.

Asha Talati:

Thank you so much for that introduction.

My name is Asha Talati. And as Dr. Goker-Alpan just mentioned, I'm an Assistant Professor in Maternal-Fetal Medicine and Clinical Genetics and Genomics. My clinical practice involves the care of high-risk pregnancies, and I particularly in my clinical practice care for individuals and parents with genetic conditions for which they require multidisciplinary management and care, many of whom have lysosomal storage disorders. Before we jump into the content of the talk, I will put my disclosures up here on the screen, and we'll take a second just to review them.

There are four key learning objectives that I would love for this audience to take away at the end of this lecture. The first learning objective is to describe the role of the gynecologist, obstetrician, and genetic counselor in the team approach to the care of people with lysosomal storage disorders. We'll also describe best practices for discussing pregnancy options for people with storage disorders, and then describe the best practices to manage a pregnancy in people with lysosomal storage disorders. Finally, we'll describe research trends involving pregnancy in people with these conditions.

We'll start first by talking in more detail about common lysosomal storage disorders that we're seeing in the adult reproductive time range. As many of you know, lysosomal storage disorders are single gene disorders that are mostly inherited in an autosomal recessive fashion. There are some conditions that we'll discuss today that are inherited in an X-linked fashion. About 70% of conditions are related to the loss or to the presence of a defect in enzyme activity. The remainder of the conditions are related to defects in enzyme activator or associated proteins that then will impact the function of the enzyme, or the ability of the enzyme to control substrate. Nearly 70 LSDs have been described so far, and we anticipate that more may be described given the trajectory of rare disease diagnosis and finding in our current era. There are variable ages at which an LSD can present, so like we've already alluded to, a high index of suspicion at different time points and interactions with healthcare are really important in order to make the most precise diagnosis and a timely diagnosis that could then impact healthcare at different critical time points.

Some LSDs will present as early as a prenatal period and have a prenatal phenotype. Other storage disorders will present much later, including presenting in the neonatal period, childhood, middle or late adolescence, and then even in early adulthood. Most conditions are going to present by early adulthood. Some diseases are related, most of the diseases, excuse me, are related to the accumulation of substrate and organs, and that then leads to a specific presentation, which increases our index of suspicion for a certain condition. We know that lysosomal storage disorders are individually rare, but given the number of conditions that we see, those individually rare conditions become cumulatively common. So again, a high index of suspicion, especially in high healthcare interaction time points like pregnancy, are really important.

There are different types of lysosomal storage disorders, as I've already alluded to. Some of the common categories include sphingolipidosis, mucopolysaccharidoses, lipofuscinosis, sialic acid-related disorders, mucolipidosis, and others. Some of the other conditions that Dr. Goker-Alpan has already alluded to include Pompe disease, which is often included in a glycogen storage disorder type category, but certainly has overlap in this scenario. We are going to focus on a few conditions that are particularly seen in the reproductive time point, including Niemann-Pick type B, which is a chronic visceral form; Gaucher disease type one, the most common form of Gaucher; Fabre disease, which as we mentioned

earlier is an X-linked condition; and then Pompe disease, which again, you've already gotten a small taste of from the prior slides.

In this moment, I do want to point out one particular condition which has a very specific prenatal phenotype, which is often on the radar of us as specialists in prenatal diagnosis. MPS type VII or Sly syndrome has a very unique presentation of hydrops fetalis, which is when a fetus will present with extra fluid accumulation in multiple body compartments. Most typically in the prenatal phenotype, this will present with skin edema, fetal abdominal ascites, pericardial effusion, or polyhydramnios. When we're seeing this particular phenotype, there's multiple causes that can lead to that diagnosis of hydrops. However, on the differential is the possibility of MPS type VII and an important diagnosis to make in the prenatal period, especially as we begin to think about in utero enzyme replacement therapy, which I'll talk about at the end of my talk today.

As we've already mentioned, again, there is significant multiple end organ impact that can come from having a storage disorder. As you can see from this particular image, depending on the particular variants that you have and enzyme that may be missing, or again, other mechanism of disease that may be causing loss of enzyme and accumulation of substrate, there is a variety of organs that can be impacted and a particular phenotype that may be derived from those end organ impacts. Some of the particular end organs that we worry most about in pregnancy, but certainly not limited to that and can still impact reproductive care include pulmonary and cardiac function, splenic function, liver function, GI function, and then certainly the hematologic system and the muscular system.

I want to now focus on certain specific conditions that are seen most commonly in the reproductive time range. The first condition that we'll talk about today is Niemann-Pick disease type B. Niemann-Pick disease type B is often referred to as a chronic visceral form of Niemann-Pick. It is resulting from a deficiency in acid sphingomyelinase, and typically is inherited related to biallelic variants in the gene SMPD1. Due to this particular condition and this enzyme deficiency, patients will have chronic visceral impact related to substrate accumulation in those particular organ systems. Often these patients are presenting with attenuated disease, and this is because of some residual enzyme activity that can carry them through the neonatal period and early childhood and then may present in late childhood or early adolescence with initial signs and symptoms such as mild pulmonary dysfunction or hepatosplenomegaly. For these patients, early recognition, referral to a specialist is incredibly important as they may have opportunity to receive therapy with recombinant enzyme therapy.

This type of therapeutic has been shown to be really beneficial, especially when it comes to improving pulmonary function and hepatic and splenic size, and reducing the need for additional therapeutics or worsening of those end organs.

Let's talk a little bit more about Gaucher disease type one now. Gaucher disease, like the other storage disorders, is an autosomal recessive condition, and it's associated with variants in GBA1, which results in a loss of glucocerebrosidase. Type one, which is the only type of Gaucher that I'll be referring to in this talk, is the most common, and it affects about 90% of patients that are diagnosed with the Gaucher spectrum disorders. Typically, this condition will result in multiorgan involvement, and some of the organs that we are thinking about are listed here. The conditions that I most worry about in pregnancy associated with Gaucher include the neurologic manifestations, the splenic manifestations, and hepatomegaly and hepatic function, and then finally, the hematologic abnormalities. Some patients will have some pulmonary involvement, which would also require additional assessment. Treatment for Gaucher disease type one is available with enzyme replacement therapy or substrate productive therapy, and we'll talk a little bit more about that as we're talking specifically about pregnancy.

I want to spend a little time talking about Fabry disease because Fabry especially in female reproductive populations, is often overlooked, but it's a growing area of recognition that these patients are

symptomatic. These patients can have poor disease control and can result in an increased female morbidity associated with lack of diagnosis and recognition of this condition. Fabry disease, as we mentioned before, is an X-linked condition. So females often will have variable presentation and variable severity. As such, they're often late to diagnosis, late to having access to treatment, or are undiagnosed, particularly in reproductive age populations. It is one of the most common of the lysosomal storage disorders, and it's related to a loss of alpha-galactosidase A. Typically, this condition is occurring due to pathogenic variants in the gene GLA, which again is inherited in an X-linked fashion. There is enzyme replacement therapy that is available with or without chaperone therapy, but again, the biggest barrier that we see here is a lack of recognition and a lack of referral in female populations.

I'm going to speak a little bit now about MPS disorders because they can be seen in reproductive time points, although more rarely than the other lysosomal storage disorders that I talked about. Patients with MPS disorders, especially with advent of therapy, are living longer life expectancies, particularly those that have undergone stem cell transplantation or enzyme replacement therapy. There is a growing number of reports of patients with MPS disorders that are approaching reproduction and have had spontaneous pregnancies. Patients with these conditions can have variable phenotypes depending on the type of MPS disorder they have, as well as how much residual enzyme function they have, and at the age at which they present.

But typically, for most of these conditions, we are seeing multiorgan involvement, including involvement in the skeletal system, multijoint involvement, we're seeing abnormalities of the spine, cardiopulmonary compromise, issues with airway and high-risk airways, issues with the development of hepatosplenomegaly, and often can be associated with impaired vision and hearing as well. As you can see on the right, patients will have a variety of symptoms depending on their type of MPS disorder. And so being aware of the need for multi-specialty care is really important for these patients, not just about their lifespan, but also during pregnancy.

As we've moved from these common disorders that we see in reproductive age population, I want to step back a little bit and think about puberty and some of the common issues that we see amongst patients broadly with lysosomal storage disorders as they're entering puberty. One of the most common issues that we see is delays in menarche, and that's been well described in many lysosomal storage disorders, but has been best described in populations such as females with Gaucher type one, and females that are diagnosed in Fabry disease most commonly diagnosed because they have an affected sibling. We know that delayed menarche can occur in up to 60% of patients in Gaucher type one, and this is an important consideration when we're thinking about the other pubertal changes that are coming along, such as growth plate closure, development of secondary sexual characteristics, and certainly the psychosocial changes and needs of patients that are of that sort of menarcheal and early puberty age.

This can also limit linear growth in many conditions, as I mentioned, and so some patients may benefit from a close eye on this in order to help impact linear growth as well. As Dr. Goker-Alpan has already mentioned, menorrhagia is also a significant issue for many patients with lysosomal storage disorders, and this may be related to the hematologic abnormalities that we see. As I've mentioned, some conditions have associated hematologic abnormalities like thrombocytopenia, and related to that thrombocytopenia, we can see a significant increase in menorrhagia spectrum disorders. So having an increase in the amount of bleeding, that leading to an iron deficiency anemia, and then poor growth and function of a teenage female patient. It can exacerbate existing anemia, particularly for other hematologic complications that are already present. You can think of that in Niemann-Pick type B. You can see that in Gaucher or some of the mucopolysaccharidosis, and it often is going to require active management to reduce the severity of bleeding.

When we're thinking about management of menorrhagia, we're not only thinking about management of the primary disease itself, but we're thinking about quick management to help stop bleeding when it is occurring during the cycle. There is a multidisciplinary team that will need to be involved for best care of these patients. Some of the individuals that we would often involve in our institution include a metabolic specialist, and this is where we think about enzyme replacement therapy or substrate therapies available to help reduce the impact, the hematologic impact of the condition, have better disease control, and by doing that, reduce the long-term prognosis that's associated with the menorrhagia. However, again, immediate control of bleeding can also be necessary. And so that is where having a pediatric adolescent and gynecology specialist, or having a gynecologist that is experienced in treating patients with rare conditions, or specifically with lysosomal storage disorders can be very helpful.

Patients, particularly patients that, excuse me, providers that are trained in pediatric adolescent gynecology, they will have experience with patients with rare disease. They'll also have experience taking care of patients that might have learning or developmental differences, which can be seen in the other LSD spectrum disorders, not necessarily the ones that I've discussed in detail today. They importantly will have pediatric equipment available. As we've noted, linear growth is often very limited in some of these patients. Other patients may have skeletal malformations that prevent them from being in lithotomy, and so having pediatric equipment available, or having sedation or an operating room setting available for better positioning or better placement and examination can be really helpful and is often more available in a tertiary care healthcare center, or with a subspecialist that's used to the care of these patients. Sometimes we can also consider partnering with endocrinology, and that can include the utilization of growth hormone in addition to enzyme replacement therapy as needed for some patients.

There are several methods that we use for menorrhagia management. Most of the published experience that we have is related to the use of oral contraceptive pills, so that's typically a combined estrogen and progestin pill, but that therapy certainly needs to be customized to individual needs. We'd be thinking about things like thromboembolism risk, if there's a presence of hypertension, if there's a presence of existing cardiopulmonary disease, or if someone has existing migraines with aura for which there is an increased risk of thrombotic or other cerebrovascular complications.

In those patients, OCPs may not be the best first step. Other methods of bleeding management may be necessary, like thinking about Depo-Provera, which is a progestin only method, or thinking about long-acting reversible contraceptive methods, most common of which include progestins only, but there are non-hormonal methods that can be utilized that are also long-acting methods. This is a nuanced conversation that often is going to require multidisciplinary care involving the metabolic specialist who may encourage receiving care with a gynecologic specialist, and helping to control, again, disease manifestations, but then also speaking to a gynecologist that can offer comfort and care to not only the patient themselves, but potentially also additional family members that, especially at adolescent ages, are going to be involved in the patient's care.

There is a significant lack of data in this area. Most data, again, has focused on oral contraceptive pills, but especially as long-acting methods have become available and are really useful in these particular patient populations, there needs to be an increase in data regarding safety, best practices around placement and efficacy, which currently are just not available.

I'm going to switch gears now to thinking a little bit about later in the reproductive time point and talk more about pregnancy. I have already alluded to the fact that certain lysosomal storage disorders will cause a myriad of end organ related issues. Those end organ related issues are really important for us as maternal fetal medicine specialists and obstetricians to be familiar with because we need to think about

how a patient with a lysosomal storage disorder is going to tolerate the physiologic changes of pregnancy in their current disease state and their current health status. As you can see here, there are many things that happen during pregnancy that are a change in female physiology that occur really quickly, often right at the start of pregnancy within the first trimester.

During pregnancy, we know that the cardiovascular system goes through major changes. There is a dramatic increase in blood volume by about two to three times. The two to three times increase compared to standard blood volume, cardiac output increases, and systemic vascular resistance drops. There's also a significant change in respiratory function. Pregnant patients are in a chronic state of hyperventilation and a chronic state of respiratory alkalosis. Their tidal volume increases, their minute ventilation increases, so pregnant women are often breathing harder, breathing faster.

And again, their systemic change includes a mild respiratory alkalosis that is a physiologic drive that's created by the fetus in order to facilitate the passage of fetal hemoglobin across the placenta and to the baby. There are also significant renal changes. There's a substantial increase in GFR so that there is more circulating through the kidneys at any time, and the kidneys often grow and expand during pregnancy to help adjust and deal with this increase in volume. There's increased blood flow to the kidneys, and we also see a physiologic hydronephrosis associated with the growing uterus and the compression it has on the kidneys.

There are several hematologic changes that we see. We see an increase in plasma volume. We see an increase in mass of red blood cells, and we see an increase in clotting factors. And finally, we see significant musculoskeletal changes. There's increased ligament laxity due to relaxin. We're also seeing an increased risk of musculoskeletal injury related to the changing of a patient's frame very dramatically, increase in weight gain, typically somewhere between 20 to 40 pounds during pregnancy, and diaphragmatic changes as well, especially when we think about the third trimester and how that diaphragm stays up to accommodate that growing gestation and growing uterus.

So as you can see, the physiologic changes of pregnancy are multi-organ system involvement. In that same way, LSDs also have multi-organ system involvement. And so when we're caring for a patient with a lysosomal storage disorder, we're thinking about how each organ system is functioning, what the current health status of that organ system is, and what changes are going to occur during pregnancy, and how we need to work together to best care for those systems so that the patient can successfully sustain the pregnancy, get to a place where she can deliver safely, and that her long-term end organ function is not compromised due to the physiologic changes of pregnancy. Oftentimes, the care team is going to include multiple people, some organ specific, and some overlooking the entirety of the patient's care plan and their wellbeing.

Some of the folks that are overarching and continuous in a patient's care plan include the clinical or metabolic geneticist. These are individuals that, in my role, I often pair with someone's primary geneticist or primary metabolic physician in order to make sure that I'm maintaining them on enzyme therapy, if that is the case for them, or having nuanced discussions with that provider about when to start or stop enzyme therapy depending upon their prognosis and their wellbeing during pregnancy. There's usually also a maternal fetal medicine specialist involved. These patients are high risk during pregnancy because of the risk of their end organ disease causing pregnancy complications, and so typically these patients should not be referred to a general obstetrician or midwifery. These are patients who are best going to be served by having care with a maternal fetal medicine specialist to help with organizing the multidisciplinary support the patient's need, but then also to help manage that chronic disease manifestation and how it's going to impact the pregnancy.

Genetic counseling is a really important piece of this puzzle, and I'll talk a little bit more about that when we talk about preconception counseling, but also during care during pregnancy. And the genetic

counselors can really help to facilitate decision making around carrier testing of a parent or around prenatal diagnosis, if that's indicated, or postnatal diagnosis, if that's indicated. Typically, patients are going to have to see an anesthesiologist early in pregnancy, and that might be related to a variety of conditions. For instance, patients with Gaucher disease who have hematologic concerns, severe thrombocytopenia can be a contraindication to neuraxial anesthesia and may require endotracheal anesthesia if the patient were to need cesarean delivery. Patients also have a right to know about what pain options are available to them if they don't qualify for neuraxial anesthesia. How we can treat that thrombocytopenia to make someone a candidate for neuraxial anesthesia are all things that our anesthesia colleagues can talk about and speak to and give the patient information about so that when they're in labor, they are prepared for what their pain management plan might be.

It's also important for them to be involved given the potential of cardiopulmonary risks. For patients that are in a situation in which an emergent delivery is required, which is frankly anytime in pregnancy, those are patients in which they may require general endotracheal anesthesia. And so understanding what current pulmonary and cardiac status is to safely provide general endotracheal anesthesia is a common reason that I refer to our anesthesia colleagues as well.

And finally, we may require subspecialist intervention as well, depending on disease status, and what chronic conditions the patient is dealing with related to their underlying storage disorder. Some patients may require ongoing care with physical medicine and rehabilitation therapy, particularly as bony structure and ligamentous laxity become an issue during pregnancy. PM&R physicians can offer a lot of support and can create a physical therapy regimen that can allow for ongoing retention of muscle function and provide best management of mobility related challenges that could affect some patients and maintenance of mobility during pregnancy despite the physiologic changes. Certainly cardiology, pulmonology, hematology are all also going to be involved related to the end organ dysfunction that we've already talked about.

And I want to highlight at the end of this, although it's the end of my slide, I would like to center it in the... I should have centered it in the middle of my slide for you all, but family supports and social work are a key aspect in how we best take care of patients during pregnancy. I really encourage my patients with genetic conditions and those with rare disease, including those with lysosomal storage disorders, to bring their family members with them that they live with and that are their support systems at home, or support systems in healthcare to come with them during their pregnancy and prenatal appointments. This could be individuals. This could be a spouse or a partner. It could be a mother or a father. It could be a sibling, but anyone who's been deeply involved in their healthcare, I highly recommend being involved in pregnancy care as well. Pregnancy can offer some unexpected challenges and some unexpected risks. And so having that support systems available as we're not caring for just one, but also two patients can be really meaningful to the patient themselves.

Finally, this can be a lot of appointments for patients. It could be financially stressful and pregnancy could offer a significant increase in the number of appointments and healthcare burden that patients are dealing with for that nine months of gestation. And so during that time, having additional resources, ability to access healthcare and sources of support is really important. And so this may be a place to get social work involved depending on what a patient's socioeconomic needs are or depending on what a patient's barriers to healthcare are.

I want to take a second now to talk a little bit about preconception counseling and care, and how important it is in these patient populations. Preconception counseling is integral to making sure that we have a safe pregnancy care plan for patients. It's often a first interaction with a healthcare space. What I typically recommend to my colleagues in pediatric genetics and to my colleagues in peds, genetics, and metabolism who are primary care physicians for patients with lysosomal storage disorders is to refer

early. As soon as patients are thinking about or interested in pregnancy, making sure that we ask about that, making sure we understand what their reproductive timeframe is. Refer early to have conversations with a maternal fetal medicine specialist and a genetic counselor to talk about what pregnancy would look like. There are several things that I discuss during preconception counseling.

The first things that I often discuss are looking in detail at a patient's current health status, and that includes looking at all of the organs that I know might be affected by a condition and understanding what current health status is of those patients. For some individuals that may have had a lapse in care, making sure that we are up-to-date to know what their current disease status is before we make a recommendation about pregnancy or not. For those that are up-to-date with care and are in excellent health status, we talk a lot about what pregnancy would look like and how health status may change with pregnancy. Preconception also allows for nuanced discussions and shared decision-making around enzyme replacement therapy. As we'll talk about soon, we'll see that for some conditions, enzyme replacement therapy is well studied, and has shown significant benefit even when continued during pregnancy.

However, for other conditions, enzyme replacement therapy is not as well studied, and so the impact on the fetus and what an individual's risk threshold is around that remains something to be discussed. That preconception time period allows us to make thoughtful decisions about when we're discontinuing enzyme replacement therapy, what the potential impact is of that, how that can affect long-term disease status and prognosis, how that can affect pregnancy outcomes, and recommendations to potentially stay on enzyme replacement therapy. Unfortunately, in pregnancy, when we don't have a significant amount of data of whether a medication is safe or not, there is often a trend to stop that medication. And so again, having these discussions early to talk about safety of continuing therapy can really be disease altering and lifesaving for these patients.

The other important part about preconception counseling is talking about genetic screening and genetic testing during pregnancy. And this is where a genetic counselor is an invaluable resource. I have all of my patients with genetic conditions, including those with lysosomal storage disorders, see a genetic counselor either in a preconception period, or if they come to me and are already pregnant, then during pregnancy itself. The genetic counselor, again, is invaluable at either time point. Genetic counselors will be able to talk through the risk that the fetus may have of inheriting the condition, offer carrier screening assessment for both the patient as well as her partner, and then certainly talk about options for either prenatal screening or diagnosis or postnatal diagnosis, whether that particular condition is captured on the newborn screen or not, or whether additional testing may be needed in the neonatal period.

Genetic counselors also help to facilitate that. Oftentimes at many institutions, a genetic counselor sits between multiple genetic service lines and so may serve as a connection between the obstetrician and the obstetric care pathway and the pediatric care pathway. Thereby letting the pediatric team know, "Hey, our patient with LSD whose fetus is at high risk is also delivering on this date that will allow the pediatric team to be available and aware and help facilitate care for that child after the child is born."

This counseling can be really nuanced, especially when we think about attenuated disease, adolescent onset disease, and adult onset disease. And so certainly having a genetic counselor that can help patients understand their own values, understand their own preferences, and then share in that decision-making can be really valuable. It's also important to think about prenatal screening and diagnostic options right now, given the possibility of in utero therapy or immediate postnatal therapy, which we'll discuss in a second.

When we are seeing patients, both either for their first visit in pregnancy or in a preconception evaluation, we are really reviewing the risks associated with pregnancy and outlining a safe care plan. So

again, I look organ system by organ system and think through what the potential impact of that condition will be on the pregnancy and how we should best care for that. This is an example of a patient that has Niemann-Pick type B and what particular organ systems I would be looking at and what their current disease status is, and what I would be thinking about in pregnancy. For example, that condition can be associated with cardiac risk factors. I would want to make sure that the patient recently has an echocardiogram within 12 months before proceeding with pregnancy, make sure I have a baseline assessment of their pulmonary function, and that their pulmonary function would be in a safe range to become pregnant.

We typically recommend that as pretty normal pulmonary function with an FEV1 of at least 80% for best outcomes in pregnancy. Certainly, we see patients with lower pulmonary function get pregnant, but that does certainly increase the risk, and that's a conversation I like to have either at the start of pregnancy or before a patient is pregnant. We discuss anesthesia risk. We discuss the risk of hematopoietic changes, and so assess a lot of those baseline function of end organs prior to the start of pregnancy to create the best care plan. We ideally like for patients to understand what the risks are and what adverse events can happen during pregnancy. And we know that there is an increased risk of a worsening of maternal disease, which we particularly can see for patients who were previously on enzyme replacement, who discontinued it during pregnancy, or patients who were recommended to start enzyme replacement and chose not to start enzyme replacement in the setting of pregnancy.

We know that some of the particular risks pregnancy-associated risks themselves include a risk of preterm birth, a risk of cesarean delivery, an increased risk of hemorrhage during delivery itself, regardless of mode of delivery, whether vaginal birth or cesarean, and then certainly an increased theoretical risk of other conditions, although this is not well documented in the literature. However, we know for patients that have preexisting cardiometabolic conditions or preexisting pulmonary conditions, there is an increased risk of hypertensive disorders of pregnancy.

For patients with baseline liver dysfunction, we know there's an increased risk of gestational diabetes, and certainly with any maternal condition in which there is long-term disease that affects end organs, there is a risk of fetal growth restriction. These extrapolations of pregnancy complications like hypertensive disorders, gestational diabetes, fetal growth restriction, these are extrapolations of patient populations with other disease. So if we think about a patient with cystic fibrosis with baseline pulmonary function abnormalities, the risks that we know come from that population are extrapolated for patients with lysosomal storage disorders. There is very limited data regarding outcomes of patients with lysosomal storage disorders broadly compared to other genetic conditions.

One of the best studied conditions when it comes to pregnancy is Gaucher disease, just given that Gaucher type one is the most common type of Gaucher disease and the availability of therapy that's pushed for us to study it in pregnancy. Gaucher disease is our model for how we think about the use of enzyme replacement therapy in pregnancy, and again, is the best studied of the lysosomal storage disorders as it relates to pregnancy, pregnancy impact on the condition and the value of continuing ERT during pregnancy. Although there's some limited data available broadly, when we think about Gaucher disease specifically, there is significant evidence to suggest that continuing enzyme replacement therapy in pregnancy leads to an improvement in maternal and fetal outcomes, including a reduced risk of hemorrhage and including a reduced risk of spontaneous abortion as we saw in previous papers. And the safety data around it demonstrates that there's no increased risk of birth defects and there's no increased risk of pregnancy loss, which are common safety and outcomes that we look at when we're evaluating the safety of a medication or drug in pregnancy.

When we look at Fabry disease by contrast, there is not a specific recommendation for use of enzyme replacement therapy in pregnancy, and just our experience with it is much more limited, often related

to the challenges and diagnosis that we see. We may have more patients with Fabry disease than are recognized, but either are not treated or evaluated or diagnosed when they enter pregnancy, or treated and diagnosed later after pregnancy such that we don't have data during pregnancy itself. However, amongst the limited data that we have, which is primarily in case reports and case series, there has been a suggestion of decreased progression of symptoms that do have a severe phenotype.

There are certain situations in which pregnancy is just not recommended, and these are situations which we anticipate is about a 50% risk of mortality for the mother. And so we strictly, when we have the opportunity to in a preconception visit, recommend against moving towards pregnancy. This also becomes an important discussion to discuss options for how else to grow a family. Some of the strict contraindications that we have include pulmonary arterial hypertension of any severity. We know that pulmonary arterial hypertension often will not accommodate, excuse me, the physiologic changes of pregnancy, and so the cardiopulmonary compromise that can happen for these patients in the third trimester, and particularly after delivery can be very challenging to manage even in a tertiary or quaternary care center, and with multidisciplinary planned care. These are patients who, due to the volume challenges that occur physiologically with pregnancy, unfortunately just don't have the reserve to be able to tolerate it, and often reach a successful gestational age to deliver a baby safely or get through the postpartum period. We see the first 24 to first week after delivery being a really high chance of mortality.

We also don't recommend pregnancy for individuals who have what we call the World Health Organization and WHO, maternal branch of the World Health Organization class four of heart disease. And this includes individuals who have severe left ventricular dysfunction with a very low ejection fraction or have severe mitral aortic stenosis. And this very similar to pulmonary arterial hypertension has a very significant risk of morbidity. The cardiac morbidity, such as MI, arrhythmia, or pulmonary edema, or has a significant risk of mortality. We often estimate, again, in some of these conditions, mortality is high as 50%. There are some relative contraindications that we think about and that are really applicable to this population. Some of the relative contraindications include sleep apnea. Sleep apnea can be common in patients with some lysosomal storage disorders, particularly the mucopolysaccharidosis and those that have atlantoaxial instability or spinal changes or have skeletal changes that can lead to a restrictive or obstructive sleep apnea condition.

We also think twice about pregnancy in patients that have heart failure with a preserved ejection fraction, although that doesn't meet our MW criteria that I've previously described. Patients with preserved ejection fraction can still have a lot of challenges with navigating the volume increase that can happen during pregnancy. And then finally, interstitial lung disease, particularly those that have a baseline oxygen requirement, or exacerbation six months prior to pregnancy or declining pulmonary function parameters. And finally, individuals that are a severe anesthetic risk. As I mentioned before, the risk of an acute delivery during pregnancy remains high, particularly throughout the late second and third trimester. Pregnancy can be unpredictable, particularly in those with rare disease. And so for those individuals with a severe anesthetic risk or severe critical airway, we may caution against pregnancy.

We talked a little bit about this already, but the best time for this type of counseling is in the preconception period, and particularly when we think about pregnancy risk counseling, and then branch to genetic counseling, that again is best done in that preconception period. What I want to highlight here is the value that expanded carrier screening can bring to the table, particularly for patients that are undiagnosed but have a high suspicion. Referring to reproductive genetics or reproductive genetic counselor can be a first step in terms of getting the patient to the right person for evaluation during pregnancy.

The American College of OB/GYN recommends screening for a few key conditions, including cystic fibrosis, spinal muscular atrophy, hemoglobinopathies, and if there's a history of intellectual differences in a family than Fragile X. However, that doesn't include any lysosomal storage disorder. Often larger carrier screening panels are including lysosomal storage disorders and are a little bit more reflective of what we see in newborn screening.

And so being able to talk to a genetic counselor, talking about options for larger carrier screening panels, which are more often ordered by a genetics professional can really offer the opportunity for screening, can offer the screening opportunity for diagnosis of a mother that was not diagnosed, and a more accurate fetal risk assessment when we can achieve both partner as well as maternal testing at the same time.

I have mentioned now some of the difficult conversations we often have in the preconception period, and so one of the things that we talk about after sometimes delivering challenging news like we don't recommend pregnancy or safe pregnancy is not feasible in this situation, is to think about other reproductive options. We may discuss the opportunities for IVF and for embryo selection for a couple that's at risk, or we might recommend seeking a gestational carrier, particularly for families that want to have their own biological children. For those that are less interested in that, we do talk about adoption and make appropriate referrals so patients can start the path of growing their family safely. Importantly, both during pregnancy and the preconception period, we do talk about termination of pregnancy and access to abortion because those might be something that are important and necessary for the life and health of the mother, or based on the personal values and preferences of a family.

I want to talk a little bit more about care during pregnancy itself. What I have outlined here is best guidance for best management and best practice. Again, we highly recommend that these patients are seen by a maternal fetal medicine specialist and that they are seen by a metabolic specialist in conjunction, particularly patients that are considering enzyme replacement therapy were previously on or continuing on enzyme replacement therapy. Patients should have routine screening for all end organs that are affected by their particular condition, and we want to make sure that that subspecialty care with individuals like pulmonology, cardiology, hematology continues during the pregnancy. Patients, as I mentioned before, need access to genetic counseling either before or during pregnancy itself. And again, need to be seen at a high risk pregnancy center that can offer specialized care. Some of that additional specialized care is what's mentioned on the bottom of my slide, and that includes a higher level ultrasound that can be than what is typically offered in general obstetrics and gynecology, so this is typically a targeted ultrasound or a fetal echocardiogram as indicated.

And then making decisions around how often we are assessing the fetus, including serial assessment of fetal growth or weekly assessment of fetal wellbeing, which typically occurs after 28 or 32 weeks. Those decisions are typically made around experience with disease severity or experience with the condition in itself. There is very little published about rates of stillbirth and lysosomal storage disorders. We know that there's a slightly increased risk in Gaucher for individuals that have enzyme replacement therapy versus those that don't, but we don't know how that truly compares in terms of individual stillbirth risk compared to the general population, or how disease control ends up modifying that stillbirth risk.

And so again, this is a big area of study and data for what should we be doing as it relates to fetal screening and fetal management for patients with lysosomal steroid disorders. And again, seeing a high risk professional is important because we are consistently screening for complications of pregnancy, including the risk of preterm birth, growth restriction, or maternal development of conditions like hypertensive disease or diabetes. Delivery care requires extensive planning, and this is where we are going to involve our OB anesthesia teams and often have a multidisciplinary meeting before delivery in

order to make sure that everyone's on the same page and what type of care we're providing at the time of delivery.

Some of the critical decisions that we're making include mode of delivery, should the patient labor and try for vaginal birth, or should we be opting for a primary cesarean section? What are the risks and benefits of each? And do we have the right teams available for this delivery with each? Is there a need for maternal cardiac monitoring? Is there appropriate plans around fluid management, particularly with the number of fluids that we administer during labor, with medications and NPO status, and then finally being prepared for bleeding risks.

We know that patients, particularly those with certain lysosomal storage disorders are at high risk of hemorrhage. What preparation are we going to take in order to make sure that if bleeding occurs, we're at the ready to immediately manage that bleeding. Postpartum care as well takes into consideration things like enzyme replacement therapy, breastfeeding, and what the timing of starting and stopping enzyme replacement therapy is as it relates to breastfeeding. We know that ERT and Gaucher, as I mentioned, very well studied, is considered safe with breastfeeding. However, it's less studied in other lysosomal storage conditions and so is something that needs to be discussed with shared decision making with the patient. And finally, for all of these patients that have a risk of lytic bone disease, I continue them on calcium and vitamin D supplementation given the risk of bone remodeling that occurs during the postpartum period.

I want to talk a little bit about research in the last few minutes we have left. As I mentioned throughout the talk, there are very few guidelines on how to best manage patients with lysosomal disorders during pregnancy. There's also limited data on the safety of enzyme replacement therapy and how it alters the course of disease. This in turn is going to affect every reproductive decision we make like what type of contraception should we be using? Are there any interactions? When should we be getting pregnant and how we manage that pregnancy?

As I mentioned before, the data around enzyme replacement therapy in pregnancy is overwhelmingly positive for Gaucher type one, but we're not really certain about how enzyme replacement therapy can be impactful in other conditions. And so for those of you listening, this is really an area that is active and right for research, and I highly encourage us to be thinking about how we can best study this. Well, for Fabry and Pompe, we have case studies that are suggestive of safety, but there is not clear guidance on how we can meaningfully recommend and whether we should be meaningfully recommending therapy in and around pregnancy or not.

There's also a significant gap in access to care to diagnosing in affected pregnancy. Like we mentioned, carrier screening is so important, but there are differences in guidelines between the American College of OBGYN and the American College of Medical Genetics. And as such, often pregnant patients are not receiving carrier screening that would include screening for lysosomal storage disorders and parents. And so we really are not often getting an accurate fetal risk assessment and by default of that, not able to refer on to the appropriate in utero or neonatal management that patients could have access to if they choose to. There's also issues that we consider when it comes to insurance coverage, particularly when we think about coverage of the partner and where the partner is able to access healthcare. And we see gaps in genetic testing in general. We see gaps in access to referral, gaps in access to CVS and amniocentesis, and this remains a big issue in terms of how we can get patients timely information around the health of their pregnancy.

I really want to say that the reasoning for prenatal diagnosis is actively changing. As you can see on this slide, this is the PEARL trial. This is an active clinical trial that's happening and being done by colleagues at the University of California and San Francisco. It's a multidisciplinary team, including pediatric surgery, maternal fetal medicine, metabolic disease specialist, genetic counseling, and this disease is offering a

trial of in utero enzyme replacement therapy for a variety of different conditions, including the MPS disorders, as well as lysosomal acid lipase disorder and Gaucher type two and three, which we know in infantile Pompe. So really an active area of research and really underscores the importance of prenatal diagnosis, active screening of the parents, diagnostic options for the fetus for the option for early in utero treatment. And what we see from these early trials is that there is a lot of promise. In utero therapy is feasible.

It has offered, especially in this first paper that's shown here, it is offered the first one of a liveborn affected child that is doing well at the age of two that has infantile onset Pompe disease, and that it can actually substantially improve immune tolerance of enzyme replacement therapy, which is an issue that we see ongoing when we're offering enzyme replacement therapy in young populations.

My last word about newborn screening, we know that the RUSP recommends screening for these four disorders. However, there's a lot of challenges with this, including when we're thinking about late affecting conditions, conditions that have variable presentations, timing, and phenotypes, how these results are interpreted. And then of course, when we find these results, what do we do about them? How do we get them to evaluation with the lysosomal storage disease provider and appropriate healthcare team?

So right on time, I would like to conclude and say that the care of patients with lysosomal storage disorders around the reproductive and pregnancy time points is complex and requires a multidisciplinary team, and a healthcare center that has experience with and is equipped to care for patients with LSDs. Management is best done in a team format with preconception being an important area of focus, and that this is an area with significant gaps in the literature, and so is an area that is ripe for additional research. With that, I say thank you, and I really appreciate everyone's time and tension, and please feel free to reach out to me with any additional questions, concerns, or research ideas, and ways that we can collaborate when it comes to best care for these patients. I'll stop sharing.

Ozlem Goker-Alpan:

We thank Dr. Talati for this very comprehensive presentation. Unfortunately, we do not have a lot of time for questions. I have one single question which is maybe helpful to the other OB-GYNs following this kind of patients, or genetic counselors. So what would you recommend for the carriers for the screening of the partners, either known disorders? Obviously, they're getting pregnant, especially with the conditions they have neuropathic involvement like NGD, NPS, such and such.

Asha Talati:

Yeah, thank you. When we have an affected mother and we're thinking about screening of the partner, there's a few pieces to this. The first is, I can't stress enough, preconception. We love to meet dad before they're even pregnant so that we can start thinking about best reproductive options even before the patient is pregnant. When we are offering carrier screening to the partner, we are often thinking about just sequencing of the affected gene.

The reason we move towards that as our carrier screening approach is because oftentimes when we're thinking about rare disease conditions, one, they're not often included on basic panels, and panels can be cost prohibitive. The second is that when carrier screening results are reported, they're often not reporting variants of uncertain significance. And in this particular situation, having a VUS can make a very big difference to disease stratification risk. And so we want to know about those VUSs when we have an effective parent and the risk is higher than general population carrier screening, and so that's what we're often recommending for the father of the baby.

Ozlem Goker-Alpan:

Thank you very much. I do appreciate this approach. Actually, we recommend a full sequencing to older fathers or the mothers with an affected father. So obviously that the other thing is the NGS sequences, next generation sequences actually may miss the large deletions and also recombinant alleles, which that's common in non-neuropathic Gaucher disease, also the other intronic alleles if it's not really included in the NGS screen. So as a personal experience, I have had actually seen patients with a neuropathic disorder when the parent's screening had been negative.

Asha Talati:

Yeah, we certainly run into that as well, and so we recommend skipping the carrier screening panel in this situation, but then talking about the other conditions.

Ozlem Goker-Alpan:

Okay. All right. Thank you very much. I think we are concluding this presentation. And before we close, I wish everyone a happy holiday and prosperous new year. We also would like to thank our sponsors that has actually made this CME presentations available to everyone. Thank you very much. Have a great day.