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TAPE: 2019-0232 PREMATURITYSYMPOSIUM_MICHAELPAIDAS

Jeanette Torres:	[00:00:01]	Good morning, again. My name is Jeanette Torres, and I am the director of programs at the Healthy Start Coalition of Miami-Dade. On behalf of our CEO and the coalition, we want to thank you for everything you did to be here on time and beating, right, Miami traffic. We know that's not easy. So, thank you so much for being here with us, to join us at the 2019 Miami-Dade Prematurity Symposium. We are so excited to see such a large and diverse group of people who wish to learn more about prematurity and making a difference in the community. It is definitely very rewarding.
	[00:00:39]	Before we begin, just a few housekeeping items. Number one, please make sure you have signed in. If you will need to leave early today, please sign out at the registration table, to ensure accurate provision of CEU credits. Also, digital copies of all presentations of today are posted on our website for your convenience, and I definitely need my glasses. Give me a sec. Yeah, I tried, no. And now, without further ado, please help me welcome our very own chief executive officer of the Healthy Start Coalition of Miami-Dade, Manuel Fermin.
[Applause]:	[00:01:21]	
Manuel Fermin:	[00:01:28]	Good morning, everyone. So, I have to stay on task and let me read this. If not, everybody knows I'm hyper and I'm going to go all over the place. The Healthy Start Coalition Miami-Dade is pleased to welcome you to the 2019 Prematurity Symposium, which has been made possible by our signature sponsor, Aetna Better Health of Florida. So, please join me in acknowledging and thanking them.
[Appluase]:	[00:01:50]	
Manuel Fermin:	[00:01:54]	We appreciate you taking the time to – from your busy schedule to join us today. We had a great event last night. We had approximately 50 individuals for last night's presentations. And we have a great line up of presenters today, who will lead us in discussions of known causes, potential and evidence-based

interventions, and the best practices to address prematurity. I also wanted, quick housekeeping notes. If everyone can make sure that you get – it was just released this past week, the March of Dimes Report Card that discusses about how Miami-Dade, Florida, and in the nation, comparing the prematurity rates. I also wanted to acknowledge, it was just some important news, Dr. Bill Sappenfield, say hi, Bill – there we go, is the 2019 March of Dimes Lawton Child's Service Award Winner.

[Applause]: [00:02:45]

Manuel Fermin: [00:02:51] The award recognizes an individual whose work has positively influenced the advancement of maternal and child health in the state of Florida in the areas of leadership, advocacy, evidence-informed interventions, collaboration, and or reducing health disparities. The March of Dimes created the Lawton Child's Advocacy and Service Award in 1999 to honor the memory of one of Florida's finest advocates for mothers and babies, the late Governor and Senator Lawton Childs. So, join me again in recognizing Dr. Bill Sappenfield for getting this award.

[Applause]: [00:03:24]

Manuel Fermin: [00:03:26] Thank you. Now, please help me and welcome Dr. David Gilchrist, senior medical director of Aetna Better Health.

[Applause]: [00:03:36]

Dr. David Gilchrist: [00:03:47] Good morning, everybody. My name is Dr. David Gilchrist, I am the chief medical officer over at Aetna Better Health of Florida, the Medicaid program. Welcome to all of you to the Miami-Dade Prematurity Symposium, and by – and I'd like to open by thanking Manny Fermin and the Healthy Starts Coalition of Miami-Dade for working with Aetna on this very important symposium. As you know, the state of Florida has been the forefront of the effort to improve birth outcomes by reducing preterm births. The Agency for Healthcare Administration has charged the health plans with improving birth outcomes, by improving the primary C-section rates, preterm births, and NAS babies. We have a panel of speakers today who are committed to these same goals and I want to express our gratitude to each of these speakers for taking the time out of their busy schedules to come and speak with us.

[00:04:48] The goal of this symposium are to provide both education and an opportunity to share evidence-built – based strategies to truly impact the health of each baby and mother throughout

the state. I'd like to also thank Dr. Sappenfield and the Florida Perinatology, Perinatology Quality Collaborative for being in the role model in perinatal healthcare, advancements and nationally recognized leader in ensuring every mother and infant receives the highest quality of care and the safest possible outcomes.

[00:05:16] This symposium demonstrates a true partnership and a collaboration between the healthcare plans, the community stakeholders, healthcare providers, even more importantly the Agency for Healthcare Administration, and, and such. We can achieve great things if we all come together and this is a perfect example of such. Thank you again for your attendance and please be sure to join in the discussion as this is supposed to be an interactive experience. This symposium is here so we can all participate. Thanks, and again, welcome.

[Applause]: [00:05:51]

Jeanette Torres: [00:05:57] Now, thank you very much, Dr. Gilchrist and Aetna for all your support, thank you. I'd like to introduce our first speaker of the day, Dr. Michael Paidas. Dr. Paidas is professor and chair of the Department Obstrec [sic] and gynecology at the University of Miami, Miller School of Medicine. And chief of service at University Health Tower and Jackson Hill system. Dr. Paidas re-established and serves as program director, maternal-fetal medicine program of the University of Miami, Jackson Health System. Dr. Paidas recently arrived at the University of Miami, following a 16-year career at the Yale Medical School where he held several positions including professor and vice-chair obstetrics and director of the maternal-fetal medicine fellowship.

[00:06:55] Dr. Paidas is recognized as an international authority in hemostasis disorders and women's health. Dr. Paidas will presenting, will be presenting high-risk obstetrics leading to preterm birth. Please help me welcome Dr. Michael Paidas.

[Applause]: [00:07:13]

Dr. Michael Paidas: [00:07:20] Hi, good morning, everyone. It's really terrific to be here. I want to thank Manny for the invitation, the Healthy Start Coalition, and our sponsors with Aetna. So, thank you again. So, I was asked to talk about high-risk obstetrics that lead to preterm birth, and so that's what I intend to do this morning. Here are my federal and non-federal disclosures and just to point out some of the areas of interest, the NICHD, the perinatal brain injury program, and the radiation syndrome related to one of

the synthetic peptides that I will describe at the end of my talk to, to conclude.

[00:08:04] So, we all know what preterm birth is about and we know we're talking about delivery less than 37 weeks gestation. We know that ever increasingly, it's accounting for a significant financial burden but more importantly, the stress that this is causing both for the, the patient and the family, and societies in our community. And I think all of these details are well documented and I don't need to dwell on this anymore. But let me just give you some of the latest news that's just recently broken. I think it's important that we have some – this conversation and just highlight what's going on at the moment. So, quite recently, in fact, you can see here this is November 8th, so we're talking very recently, following a, an international trial looking at one of our main prevention strategies for preterm births, 17P, the FDA Advisory Panel, and I want to make clear about this. So, the FDA has an advisory panel that recommends or counsels on medications, and you know, special, special bodies.

[00:09:19] And so, the advisory recommended that, based on the results of this data in total, that they recommend that they withdraw app, approval, a provisional approval for the 17P, which we've all been using. So, how did we get there? I just want to sort of highlight this. And I just want to emphasize that the FDA has not made a decision about this but this was the advisory panel. And so, so there we are. And then, following that, the Society for Maternal-Fetal Medicine had to issue a statement basically saying that, you know, care should be individualized and multiple factors should be taken into account. And similarly, ACOG also came out with a statement. So, just to alert you that there's some discussions, active discussions going on in, in this area. And so, just to frame this initial conversation, we had the first randomized trial done in the United States, what we call the Meis trial where we looked at – these investigators looked at the use of progesterone 17P injections in women that had a history of spontaneous preterm birth.

[00:10:39] And the results were such that there was a benefit to the progesterone and reducing the risk of preterm birth. And when we look at that, we know some – we, we realize and, and acknowledge that the rates of preterm birth in the placebo or the group that did not get the medication was quite high. And so, maybe a little higher than what we would normally expect. So, anyway, that was a positive study and the FDA had asked for a larger study to sort of confirm these results before it, it provides, you know, final approval. And so, finally, so a trial was undertaken which began in 2012 and concluded in 2018 and

was recently published. And just to point out that this, that while the study design was based on the Meis trial, it turns out that there were some important differences in, in the, in the group, when we compare these two populations.

[00:11:50] And so, the, the, the bottom line about this trial that's come out is that it was a negative trial. And the, the preterm delivery rates, in general, were lower it turns out in this trial than in the first positive trial, the Meis trial. And even though it was quite a large study, it might be underpowered to detect the true difference. But nonetheless, in essence, it was a negative trial for the use of 17P. We did also, I should just say, just to find out that there was a, a good safety signal with this trial which is, of course, extremely reassuring. So, just to, just to point that out in this group, that the safety trial was, was reassuring. And one of the only differences that showed up was that in the 17P group, the, the rate of miscarriage was less in this group, than in the placebo group, but this really was not involved with any of the primary outcome for the study. So, anyway, a negative trial but safe.

[00:13:03] And so, so that's where we find ourselves right now and I bring this up because we're, we're at a point where we're looking for, you know, effective therapies and safe therapies to prevent preterm birth. Alright, so with that sort of highlight, let's just go onto the, onto the next steps. And so, I'm going to emphasize today, the effects of maternal age among other things related to the issues of pregnancy outcome because age and obesity are two of the common factors that we are dealing with, right, in our, in our delivery of women's healthcare and particularly in obstetrics. So, I chose to just show you the most recent data that we have, national data. When you look at this is 2016 and 2017 data looking at the distribution of preterm birth across the spectrum of gestational age here on the bottom. And then – so one is just to point out that there is an uptick in the extremes of age, the older age, which I think is an important consideration. And secondly, just to highlight also that the late preterm birth accounting for a significant proportion of preterm birth. So, just to emphasize those two things.

[00:14:36] And then, nationally, when you look at our, our data, there's a map of all of this. As you know, we're struggling here in Florida and in many states about preterm birth. And this is also in the southern United States, what we also consider as the preeclampsia belt. So, if you can imagine sort of parts of the south have both high risks for preterm birth and preeclampsia, and that's going to be one of the topics I'm going to share with you this morning. Important to highlight that we have still the

issue on disparity that many investigators and, and, you know, agencies are, are working on to try to address and we really, really need to make good headway in this area but, but it's important for us to recognize this.

[00:15:38] Now, just a few comments for those of you, I just want to share with you, kind of a mindset approach about some of the research that's gone into preterm birth and where we are now and where we might be heading. So, if you think about some of the changes that could occur during the course of the uterus, the cervix, over the course of a pregnancy, one general concept is maybe the same sorts of things are happening in women that deliver preterm. It's just pushed earlier, right. So, we know that there are things that happen to soften the cervix, ripen, and then eventually, dilate, and is this something that is just happening earlier or, or not? And when – about – a few decades ago, when folks started looking at trying to tease away pathways, we, we had sort of a simple, simplified kind of construct and I'll just explain it to you. And this is oversimplified but it's, it's helped us kind of tackle predictors and, and ways to try to understand mechanisms that would hopefully lead to interventions. So, you can just sort of think of broad categories.

[00:16:57] And we have concerns about maternal stress, maternal and fetal stress. And there's some biomarkers that we can look at in that arena. We can look at the inflammatory path, cas, cascade, and like, for example, with chorioamnionitis. We could look at markers that can, that are reflective of that. We can look at bleeding or hemorrhage or abruption, and we look, we can look at markers in that area. Or we can think about in other cases, uterine distention where the uterus is kind of overstretched and I'm sure you can imagine, you have a muscle and you stretch it may be more than it should be, the natural inclination is that it's going to contract, right. So, what are some of the things that go on there? But ultimately, what, what happens is that these processes tend to converge right where the membranes, the amnion core membranes meet the uterus and it happens that processes occur that breakdown the clue that attaches the membranes to the uterus. And between that and contractions, you end up having a situation where you lead to ruptured membrane, cervical change contractions and, and ultimate delivery. So, that's kind of been like a working contract, construct.

[00:18:22] And then, so there are biomarkers that have been developed to try to look at that area, and one of the other tools that we have is to look at the cervix, the idea being that we can look at the characteristics of the cervix, the shorter the cervix is, the higher

the risk for preterm birth. And there's a reason for just sort of highlighting a couple of these areas. And what I would like to just point out is that while we've had several studies looking at using these kinds of things for intervention, here you can look just most recently in JAMA in 2017, looking at, you know, well perhaps, you know, we shouldn't be routinely using these tests in certain populations. So, really, we're not getting enough bang for our buck in, in this area, if I could paraphrase. And there are health economic arguments about all this.

[00:19:21] So, you know, the, the message is we're trying to actually find the right interventions and diagnostic tests and making sure that we're implementing tests that we know are effective and, and will help also on the, on the, on the cost side of things. So, if you – at the moment, if you were to look at ACOG for our guidance for preterm birth, and when you look at this process of measuring cervical length during the course of a pregnancy, we have kind of an algorithm that is often accepted by many practitioners. And so, the, the sort of the paradigm just for you to understand is if someone – if a woman has given birth preterm in a prior pregnancy, sort of spontaneously, these patients have been recommended to take 17P, the medicine that I initially described to you. And women that have a shortened cervix on ultrasound without any of that prior history, we recommend vaginal progesterone as a way to prevent preterm birth. And then, as, as you can imagine, sometimes cases get a little bit more complicated and there are other interventions that we look at, for example, placing a cerclage or a suture to keep the uterus closed, and that is either a primary procedure when we know that what we call cervical insufficiency or cervical incompetence, where the cervix just really doesn't stay shut for some reason.

[00:20:59] And maybe surgery, maybe another medical condition, and therefore, we use that primarily. But we also use it as kind of a rescue to prevent preterm birth. And there, there are other things that we've used as well such as perhaps pessary. So, alright, so with the, with that sort of background, we have come to learn that in certain situations, these medications work and sometimes we don't, and, and they don't. And so, what we try to do as clinicians is to say alright, do we have evidence that an intervention is going to work, therefore we're going to offer that to our and recommend that to our patients. So, for example, our patients that have a multiple gestation where you would think the progesterone, the 17P might be beneficial in reducing preterm birth, it doesn't work. And so, we don't offer that. It works in a different setting. So, so this is what we, as

clinicians, find our, ourselves. So, we have positive and negative data for different interventions.

[00:22:15] But we know that there are some things that, you know, kind of unequivocally are, are really helpful in preventing preterm birth. So, it's important that as we are looking at interventions and deciding on what, what we should be offer, remember some of the real basics that can make real great int, impacts. So, for example, you know, timing the deliveries for a patient. So, the shorter that you have of your deliveries, less than 18 months, the increased risk you have for preterm birth. We want to minimize things like smoking, drug use. We want to address weight issues like low pre-pregnancy weight, poor nutritional status. We want to use contraception to prevent unintended pregnancy as much as we can. You know, these are really great public health interventions that we can do. Now, I'm not going to dwell on this a lot but at the, if you were at the Rippick [ph] presentation that we had a few months ago, where we were highlighting on maternal mortality and you're going to hear more about that, but this is another area that we're concerned with about preterm birth.

[00:23:27] So, because primarily of the very high caesarian section rate that we have, the consequences of that with the damage, the scar on the uterus is setting in motion a scenario wherein subsequent pregnancies, the placenta sticks to the uterus too much, and the placenta invades through the uterus and it can go into other organs, for example. But this is responsible for major morbidity and mortality for us that we, we deal with on a regular basis. And so, the point that I'm making, because I'm talking about the preterm birth aspect, is that this also is a contributor to part of preterm birth. It's not a, a big part like some of these other risk factors but it is yet another risk factor because in cases where we know this occurs, we have a planned delivery. So, this could be accounted for in some cases early in preterm birth, but certainly in the late preterm birth. So, you can see how now imagine that as we tackle the preterm the – pardon me, the caesarian section rate, how it's also going to improve in another, in a number of other areas. So, just keep that in mind.

[00:24:47] And, and this condition has really – we really consider it an epidemic for, for us. In fact, to put it in perspective, at the University of Miami, at Jackson, there is not a time where I don't have a patient who's about to have surgery for accreta, is having one or has just recovered one. So, just to give you a sense about how frequently this is occurring. Okay. And so, what are other contributors? High-risk obstetric conditions that

are contributing to preterm birth. Well, this is a cartoon about using laser ablation in the placenta, and certain twin complications as in twin to twin transfusion syndrome. So, again, multiple gestation and complications are contributing to preterm birth. And then you can get a little bit more involved and look at fetal surgery, in utero repair. So, this is an example here of in utero repair. This is the uterus and this is the surgeons about to close the defect for, for spina bifida, an open neuro defect. This also is – these types of surgeries also pose a risk for preterm birth.

[00:26:10] And so, if you kind of collectively look at some of the risk factors that we're concerned about, here I've kind of highlighted them into two major categories, just so that you have an appreciation of what we're looking at. So, we have historical, genetic, social, obstetrical, environmental risk factors. As I mentioned to you, history, and I'm going to come back to history in a moment. Uterine malformations, family history, short interval between delivery, no prenatal care, the issues with respect to weight gain, fertility treatments, I'm going to address that for you momentarily, the issue of birth defects, drug and smoking use. Lower socioeconomic status, and then in an area that, you know, is increasingly getting attention is this notion of pollution and you know, environmental causes, and contributors. And then, the medical risk factors. So, BMI, and then there are some, believe it or not, there are genetic disorders that can predispose to preterm birth because it affects some of the components of the tissue. So, you can have elastane type disorders that can contribute to the cervix and uterus not behaving as you would ideally like.

[00:27:35] And then, diabetes, of course, hypertension, preeclampsia, infection, and then some other conditions that predispose such as blood clotting related issues. So, but being a practical person as well, I think it's really important to start out with a history and you can get an awful lot of information and risk stratification with history and I'm going to just share with you briefly about that, just to give you a sense. And this is our U.S. data looking at the contribution of when you have a preterm birth, you have an increased risk in a following pregnancy. But then, as you imagine, if you have multiple or recurrent preterm birth, your risk goes up. And so, if you've had two preterm births, you're over 30%. Now I'm going to segue a moment and, and give you part of my experience in this journey for almost 20 years. And when we've been trying to develop interventions to treat pregnancy-related complications, we've always been struggling with well what is the, what is the chance of this occurrence going to happen again? What is the chance of

someone having, for example, if you had preeclampsia, what's the chance of you having it a second time?

[00:29:01] Because that will affect, you know, sort of what will – how you might model a study and how you might look at your endpoints, and determine whether or not an intervention works. And so, I was particularly interested in two big areas. One is what does it mean for a woman's health when you have a pregnancy complication, what does that mean in their longer-term? And, and we were particularly interested in, not in like 30 or 40 years, but essentially what's happening right after your pregnancy and then moving forward. And what I elected to do is to try to use large cohorts and we ended up working with the Scandinavian cohorts and so we, we have sort of terrific linkages of all the databases. So, birth certificate, death certificate, when you go to your pharmacy. You know, all of these things are, are literally linked. And we thought about looking at homogenous population to start with, to understand what the risks were.

[00:30:11] So, so we chose the Danish cohort, they're pretty cardiovascularly [sic] fit, they don't smoke. You know, they ride bikes, they're – you know, it's all, it's quite uniformed population. So, when you're trying to look to see about an exposure and then what an effect may be when you limit all these variables, it's quite helpful. Alright, so long story short with that is we looked at almost 12 million patient-years' worth of data, it's the largest study that have been published for pregnancy complications in healthy women, first and second pregnancies. 800,000 women, roughly, across the entire country. And showed that basically, if you're healthy, if you screen out as best you can, all women have pregnancy – that have medical complications as best you can, if you have a pregnancy complication, you're at increased risk subsequently for cardiovascular and non-cardiovascular disease. The reason for just bringing that up is that we were quite interested in looking at well what about the pregnancy complication itself? And the stories are pretty uniform. So, let me just explain for a moment.

[00:31:27] So, so imagine these are healthy women as best as you can tell. So, screened out for diabetes, high blood pressure, etcetera. And so, here's the idea. So, if you have a preterm birth in, in a pregnancy, but you have a preterm birth that is quite early, under 28 weeks, in your next pregnancy, you have about – in this population, important to say that, in this predominantly white population, you have 26% risk of a preterm birth which is higher than if you had delivered between 32 to 36 weeks. So, you get the idea. The more severe the complication, the higher

the risk in a subsequent pregnancy. But not only are you at increased risk for a preterm birth in a subsequent pregnancy, you're also at increased risk for preeclampsia or gestational age or abruption in subsequent pregnancy. They're all statistically significant, just to point out.

[00:32:29] So, and the P values are all down here. Now, you can flip the chart and say well, what about preeclampsia instead of preterm birth. Suppose instead of delivering from preterm birth, you deliver from pre, preeclampsia, and you make this preterm birth, SGA, abruption, and add even stillbirth, and they're all significant. So, the message I just want to get out is when you have pregnancy complication, you need to think that woman is at risk in a subsequent pregnancy, that's, that's point number one. Point number two, and particularly for women that have a preterm birth or preeclampsia, we need to be thinking especially preeclampsia, about subsequently afterwards. So, preeclamptic patients, when they come back for their check-up, it's not typical like, oh, come back in a year, right. So, these patients need to be followed for things like diabetes and, and blood pressure control. And we're getting more and more of this information, which is helping to guide us. In fact, right now, when you look at the cardiovascular trial interventions. Now, the American Heart Association recognizes pregnancy complications as a risk factor, right?

[00:33:46] It's in their, it's in their algorithm. So, amazing that we've come all this way for women's health. So, very happy about that. Okay, so, so I've given you some smaller contributors to preterm birth, but what are some other ones? What are the ones that we really struggle with? Okay, preeclampsia. 6 to 8% of all pregnancies, greater than 200,000 pregnancies per year in the United States. To put it in perspective, 70 maternal deaths, about 50,000 deaths worldwide. And in particular, we're, we're quite interested in the very early preterm birth spectrum. So, 6 to 8,000 pregnancies in the United States per year. So, trying to make a difference in this very early preterm setting. So, what data do we have? So, this is data that we put together not long ago for – as a basis for an interventional trial, and we showed that PIH is what's – pregnancy-induced hypertension. This is one of the older terminologies that have been – we've been using, and you can see that our risk for preeclampsia for – in these disorders are increasing over time. And, and if you look at early-onset preeclampsia or the more severe variants early on, that's rising significantly. 143% from 1990. So, we're going in the wrong direction.

[00:35:22] So, just to realize that we have recognized risk factors and it's important as clinicians and care providers that when we, we are assessing a patient, we want to think about okay, what are, what are some – does this patient have risk factors that we might – that might alert us to potential causes for or associations with? For example, with preeclampsia. So, nulliparity, partner-related issues, multiple gestation, pre-existing medical conditions, hypertension, diabetes, antiphospholipid antibody syndrome. There, there are more. Their personal and family histories and smoking curiously actually is associated with a lower risk for, for preeclampsia. I think it might relate to the compensatory mechanisms for smoking that, that tend to mitigate some of the preeclamptic related effects but anyway, but we certainly don't encourage smoking for so many reasons as, as you, all know. Alright, and the extremes of age. Alright, so, so what about this real conundrum because you will hear that a small – and you heard last night, and I suspect you're going to hear more about it today, is that what also we're struggling with as a – in terms of our healthcare is that sometimes the very sickest, early pregnancy, these fetuses, neonates, from these pregnancies really account for a significant proportion of healthcare expenditure, etcetera.

[00:37:04] And so, you know, if we can make some dents in trying to reduce this very severe prematurity that would be overall. So, just to point out that in this very early preterm preeclampsia variety which has been increasing, and we'll get into that in a moment, you know, what can we do? Many of you who have had some experience with preeclampsia, know that when you have this condition really, it's almost a one-way street, in that you end up leading for delivery or need to be delivered. And it turns out that in this type of patient, what ends up happening is that you, you end up delivering in the majority of cases, not all, for maternal indications, mostly related to blood pressure. But not completely, but mostly. And why we try to look at interventions to try to reduce this risk is demonstrated in this slide which is that we know that the earlier the babies are born, the higher the mortality and the higher the risk that they're going to have significant long-term morbidity. And so, what are some of these? And here's a simple graph that kind of really illustrates how, if we can get babies a little farther along in this setting, we'll do a lot better.

[00:38:29] So, here on the right is 32 weeks and you can see that a lot of the serious morbidities are quite low, whereas if you're under 29 weeks, they're quite high. So, we have a lot of motivation to drop that and, and this slide demonstrates the contribution

about blood pressure for indications for delivery. There are other indications but that's the lions share, and then there's some that include both maternal and fetal, and some that are uniquely maternal. And we know, and not to belabor because you're going to hear more I think about the neonatal outcome, is that these babies have a number – they have short-term risk but they also have long-term risk. So, we're really trying to address the, the longer-term ones as well. So, what's in our toolkit and how do we approach patients like this?

[00:39:15] Well, really important ideally to see our patients ahead of time to plan a pregnancy, right. So, you'd like to be able to identify risk factors preconceptually, you know, optimize maternal health, that's what it's all about. Folic acid, really important, and then what do we do in the early, in the first trimester, and then I'll share with you some of our recommendations. This is a strategy actually for prevention of preterm birth and with this kind – that for women that are at risk for preeclampsia, I'll describe that. And then what do we do in monitoring in the second and third trimester? So, you know, toolkits, really helpful. And so, where we are on the biomarkers? So, do we have a test that tells us, you know, yes or no? Well, we have some areas emerging, biomarkers, but we all have to say, right, that these are not in everyday use for everyone. They're either blood markers or, or ultrasound related studies. We just don't have a simple, like a urine pregnancy test right now, right. So, that's kind of – and we, we may have to have a, an algorithm that takes into account a lot of stuff. But the point is we don't have one that's routinely being used at the moment.

[00:40:33] So, how do we manage our patients? Just so you have a sense, you know. If you reach a certain gestational age and you have preeclampsia, we deliver you. If you're not, and that's at 37 weeks. If you're earlier than that and there are some reassuring signs that you don't need to be delivered, okay, we'll hold. But, but short of that, we're going to move toward delivery. And, and then there are some considerations where when you're in – when you're very early and there are interventions that we give that are quite important, so all babies that are delivered preterm, we want to be able to, you know, give them corticosteroids, we use mag for neuroprotection seizure prevention, and then controlling blood pressure. Okay. So, on the topic about what we call latency, which is when you have preeclampsia, how long can you get if you try to hold out and not be delivered? The majority deliver between 24 and 48 hours but if you try carefully, to try to extend gestation, the average is somewhere around a week or so. And so, we're trying to really –

a lot of efforts to try to move the dial on all of this. So, what, what do we have right now?

[00:41:57] So, this is the United States Preventative Task Force that describes criteria for using aspirin. So, I want to highlight, you know, this is one preventive strategy. So, if you've had a history of preeclampsia, if you have multiple gestation, chronic hypertension, diabetes, renal disease, autoimmune disease, and then two – more than two moderate risk factors for – it might be another indication, and just to point out that there are, there is more than one guidance. There is the guidance from the U.S. Task Force, there's also ACOG guidance which is a little bit more conservative, but the message is that we have an intervention to try to reduce the risk of recurrence or occurrence of preeclampsia. And for those of you in the health economic arena, there has been data published about – from colleagues at Brown on looking at what would happen in terms of using aspirin. So, what's kind of on the immediate horizon?

[00:43:04] So, one of the statins that you use to control cholesterol, one of them pravastatin is safe in pregnancy and has been used and preliminary studies and there's a lot of reasons why it might work. In a small group of patients that were at high risk for preeclampsia, it was shown to reduce the risk. And so, now there's interest in doing a larger study to test this. We just completed the largest randomized trial in preterm preeclampsia that's been finished. It was a negative study and it's in review right now and that's for looking at recombinant antithrombin. And it's, it's a cautionary note because we had three randomized trials prior to our large U.S. trial we, we finished, that was positive. And then, eventually, some negative data, and a lot of animal work, and a lot of work that in the lab suggested it would be the right thing, but the point is, you have to put it to the test. So, I, I, you know, personally, really want to thank our patients and you know, our investigators here in the United States that really see the value of committing to clinical research here to help improve their care and, and, and the care of others down the road. It's really wonderful to see.

[00:44:32] Okay. So, as a clinician, we're faced with really two big areas apart from certain medical conditions and obstetric complications, and that is really the increasing maternal age for pregnancy and obesity. So, I think it's worthwhile that you have a, a sense about this. So, one is our fertility rates are dropping and that should be no surprise based on everything. And if you look at the, the rates, the success of IVF and BMI, they tend to go down with, with increasing BMI, right. So, so there's, there's an important effect. So, that's why controlling blood pressure,

really important. And just to give you a construct so the folks that are dealing in the IVF world, that are dealing with patients that are coming out the extremes of age, there's different sets of concerns that we have when we're trying to address how do we help these?

[00:45:37] So, so someone who's infertile very young might have a certain group of considerations, you know, whereas patients that are quite older, might have another set. So, and our IVF colleagues are trying to, to deal with these kinds of complications. So, what do we know about now, about increasing maternal age? So, one is it's – there is a risk for stillbirth and age. And even when you control for diabetes and hypertension, it exists. So, that's one message I want you to understand. And then, you can look at, you know, the extremes of age and they really do persist. Now, what about the impact of like reproductive technologies? Suppose you're older but it's just spontaneous pregnancy or suppose you have an IVF pregnancy or you're having ovulation induction? So, I tried to give you the most recent data that we have in this. This is a large study that's come out of Israel and basically, what it demonstrates is that the patients that are older are – have an increased preterm birth risk when they're having pregnancies from IVF.

[00:46:59] So, 23% versus 10 versus ovulation induction and spontaneous pregnancy. But there are other considerations that these patients will have, complications that we need to pay attention to. This is – their inception rate is higher, the diabetes rate is higher, etcetera, important considerations. And some of the other ones as well. Then, this is a busy slide but I put it up for one reason, which is kind of the good news about advanced maternal age. And this is looking at, in a large collection of studies, 63 studies. So, when you look at the breakdown between age 35, under 40, 40, 40 to 50, you know, this kind of stratification, all of these complications, preeclampsia, diabetes, low birthrate, small for gestational age, they're all significant when compared to under 35 years old. But when you start looking beyond, the risks aren't – not that much different. They're not different in this collection of studies if you were say 35 versus 45. So, another important consideration for us.

[00:48:12] And then, we have another data set from the U.K., a population-based study where they looked at women that were on average 49, so the range was about 48 to 61 years of age and they compared it to younger age women. And you know, it was no surprise that these women had higher risks for, for medical conditions. They were at higher risk for multiple gestations and complications associated with assisted reproductive

technologies but what I would – just want to call your attention to and again for our clinicians that are taking care of patients, is that one is the risk for postpartum hemorrhage are higher in this group. Not so much for, for preterm birth but in the hemorrhage related area and also for diabetes. So, more of these older women are coming to us, and so we need to be ready to deal with this.

[00:49:12] And then, I would just mention that you can even look at that next step, so you look at intertidal plasmic sperm injections, so that when we're actually injecting the sperm into the egg, so that procedure, ICSI, there's national data about this and it's, it's important to just understand that there is an association with increasing risks of miscarriage as you get older. And not an increased risk for preterm birth in this, in our U.S. cohort. But sort of in winding up in this area, I, I started by describing the kinds of conditions that – and the construct that we think about for preterm birth, the different areas, bleeding, infection, stress. And now I just want to give you sort another view about things. So, this is a very recent study, just published a few months ago from the Brazilian cohort on preterm birth. And you can identify multiple conditions that might be related, but let me explain basically, there's three buckets that these patients tend to fall in. And one is the spontaneous preterm birth, and the other is kind of a mix of ruptured membranes in preterm birth, so this is about 35%, 28%, and then like physician indicated preterm birth, for some reason. For example, like preeclampsia, about 35%.

[00:50:53] And that's pretty similar to what, you know, we're seeing. But what I would call your attention to is in that mixed group, that patients that deliver from spontaneous preterm birth or rupture of membranes, that's accounting – infection is accounting for over 40% of these patients, but they also have coexisting, a number of other complications for us. So, this kind of information is also useful for us as we try to address strategies to, to try to prevent these areas, these complications. So, what are the key points? I've taken you through a tour about preterm birth, and I say, so the use of progesterone as a treatment, preventive strategy is uncertain and I think you can appreciate that we're still navigating this area. I'd also highlight that advancing maternal age, reproductive technologies, and common health issues, obesity, metabolic syndrome, will continue to have a significant impact on reproductive health, including preterm birth and preterm preeclampsia. And that innovative research is required to better understand disparities, underlying pathogenic mechanisms, prevention, and treatment strategies for preterm birth.

[00:52:13] And I'll just share with you kind of an 18-year effort where we've been – areas of interest to try to address some of these issues, I'll just share with you. My work and what we're doing now, beginning at, at University of Miami, and I've always been intrigued with the maternal acceptance of pregnancy, what's regulating this? Why is it that women that have autoimmune diseases tend to do better in pregnancy? What is responsible for all of that? And long story short, we've identified a peptide from the embryo that we've gone ahead and synthesized. So, we have a synthetic version that we've now developed and tested and this is the factor. It's called Preimplantation Factor. It's present, you can detect it from the two-cell stage of all mammals. And we have it developed for diagnostics and, and therapeutics, both in the human and animal, civilian, and military applications. And why it might be interesting to this group, is I'll explain to you in addressing some of the effects of brain injury that we're, we're working on. And so, it turns out that it has a number of interesting effects related to immunity and how the embryo interacts with the, the uterus.

[00:53:38] And so, really quick, just to give you a sense about this, if you induce in the animal a stroke, so you cut off the blood supply of a major brain artery, you give infection, and you take away oxygen, you can induce a really severe hemorrhage in the brain. But if you give the peptide early on, we've actually been able to restore and this is what the treated look – this is the normal, and this is the damaged one, and I think you could pretty much see the difference. Anyway, so that we've been able to restore that and through this work, we've uncovered a new pathway that exists, that is responsible for, for why this all happens and in the end, you're, you're able to regenerate brain, decrease the brain, the neuronal loss, and, and reduce the inflammatory aspects that mitigate at the blood-brain barrier. So, we are proceeding forward and looking at this in a model to treat hypoxic, ischemic, and encephalopathy [sic], and that's the work that's been funded now from the NICHD, to try to address that. And the NCATS bridging program, we're working with the NIH, so they work with the peptide internally, and we work with it externally as well.

[00:55:04] And so, we hope that there's potential treatments, both for pregnancy complications and perhaps in the, in the realm of reducing preterm birth. These are my collaborators that have existed in Yale and I would acknowledge my new collaborators here in, in Miami. So, I thank you for your attention and I'm so happy to be here in Florida and I hope that we continue to work together to make a difference for this state. So, thank you for your attention.

[Applause]:	[00:55:34]	
Jeanette Torres:	[00:55:43]	Thank you, Dr. Paidas. We have a few minutes for questions from the audience. Are there any questions that you will like to ask?
Rebecca Antoine:	[00:55:53]	Hello, good morning. Thank you for your wonderful presentation. My one question – well, my name is Rebecca Antoine, I'm from the – I used to work for Miami-Dade Healthy Start, now I work with the Broward Health Start Coalition. So, my one question related to when you talked about the preeclampsia belt in the south, what is the factors relating to the concentration in that specific area? Could you give more details on that?
Dr. Michael Paidas:	[00:56:25]	Sure, good morning, and thank you for the comment. Yeah, so I, I think it's a mix of things. It's disparities that we are dealing with. I think it's the nutritional status, the underlying medical conditions, socioeconomic status, access to care. So, the point is, it's, it's going to take a lot to address [audio cuts out] but I think nutrition, diet, and underlying health play a big role in that. Okay, well, thank you.
Jeanette Torres:	[00:57:05]	Thank you, thank you so much.
[Applause]:	[00:57:05]	
	[00:57:09]	[End of tape]