ARUNDHATHI JEYABALAN: So we have a fairly large topic today to cover pre-eclampsia and eclampsia. So I'll do my best to hit the highlights.

As an outline, I hope to cover the impact of pre-eclampsia, classification and definitions, which have recently changed, the pathophysiology, evaluation, and management, as well as eclampsia, in particular for this audience, as well as later life impact.

So the hypertensive disorders of pregnancy as a group encompass about 10% of all pregnancies. And it's a really big cause of maternal as well as fetal and newborn morbidity, as well as mortality worldwide. Pre-eclampsia, a subset of the hypertensive disorders of pregnancy, affects about one out of every 12th pregnancy. It is a pregnancy specific disorder that tends to occur in the second half of pregnancy, often recognized by hypertension and proteinuria. But it really is a systemic disorder that can affect multiple organs.

The term "eclampsia" itself comes from the Greek. It means "sudden flashing" or "lightning," which refers to the sudden onset of a eclamptic fits that can occur. It was first described over 2,000 years ago by the Egyptians and the Indians. At that time the cure for this condition was delivery. And now in 2018, that continues to be the mainstay of care in pre-eclampsia.

Globally, there are about 76,000 maternal deaths a year and over 500,000 infant deaths annually. And the actual numbers are probably higher, because the monitoring of this is less well done in developing countries. That's a little over 200 women a day. So it's a pretty serious number. And in developing countries, mortality is very high. Fortunately, in more developed high income countries, mortality is lower, but the morbidities continue to remain high.

The fetal/neonatal effects are stillbirth, and neonatal death, fetal growth restriction, as well as indicated preterm delivery, and all of the short and long-term consequences that can come as a result of delivering prior to full-term.

As we move to definitions and diagnostic criteria, this is a hodgepodge of different societies using different definitions. The NICE guidelines from the UK are slightly different from the International Society for the Study of Hypertension and Pregnancy guidelines, which is slightly different from the American College of Obstetricians and Gynecologists definitions.

We live in the United States, so we use the ACOG recommendations. And I was honored to serve on that task force which came out with this publication in 2013 with the new definitions and guidelines. And for those of you who are interested, it's about a 100-page document with a five-page executive summary. And it's available online for free if you want to Google it.

The classification, based on this 2013 document, consists of gestational hypertension, pre-eclampsia with or without severe features, eclampsia, HELLP syndrome, pre-gestational hypertension-- also referred to as chronic hypertension-- and superimposed pre-eclampsia. I will point out to you that terms like "toxemia," "pregnancy induced hypertension"-- which is what we used when I was a resident-- and even the term "mild pre-eclampsia" are now outdated.

So just in terms of definitions, gestational hypertension is the new onset of elevated blood pressure after 20 weeks in the absence of proteinuria. The blood pressure criteria that we use is a systolic of greater than or equal to 140, or diastolic of greater than or equal to 90. And these are in women who were previously normotensive. Chronic hypertension, hypertension prior to pregnancy or newly diagnosed prior to 20 weeks.

The diagnostic criteria for pre-eclampsia are slightly different from the 2000 version that came out through ACOG and the NHLBI. And I will point out to you that while blood pressure and proteinuria continue to be criteria for pre-eclampsia, the diagnosis can be made even in the absence of proteinuria, as long as some of these other features below are present.

So let's just go over these for a second. The blood pressure criteria are greater than or equal to 140 systolic, 90 diastolic at least four hours apart in a woman who was previously normotensive, or, alternatively, greater than or equal to 160 systolic or 110 diastolic in a shorter period of time. This is to avoid obstetricians waiting for the full four hours before effecting a blood pressure treatment. For proteinuria, that's generally through a 24-hour urine collection with greater than or equal to 300 milligrams per 24-hour urine collection; or what's more commonly used now, the protein to creatinine ratio of greater than or equal to 0.3; and as a last resort, the dipstick of 1 plus.

So again, in the absence of proteinuria, you can have pre-eclampsia with new onset blood pressures and any one of the following-- thrombocytopenia, so platelets lower than 100,000; renal insufficiency, serum creatinine of greater than or equal to 1.1, or a doubling of the serum creatinine; impaired liver function; pulmonary edema; persistent and severe cerebral or visual symptoms.

I point this out and want to highlight, the reasoning behind the change in this definition is that obstetricians and other obstetric providers were actually missing pre-eclampsia, even in situations of very severe systemic disease, just because a woman didn't have that proteinuria criteria. So this actually is a common feature in all of the newer classification systems.

So the criteria that make pre-eclampsia severe include severe hypertension, the thrombocytopenia that I mentioned, progressive renal insufficiency, the impaired liver function, also severe right upper quadrant or epigastric pain that's unresponsive to medication and not attributable to other diagnoses, pulmonary edema, or new onset cerebral/visual symptoms. So as you can see, in severe pre-eclampsia multiple different organs can be affected, as it is a systemic disorder. And different organs are differentially affected in different women.

Eclampsia are generalized seizures occurring in a woman with pre-eclampsia that cannot be attributed to other causes. HELLP syndrome, the letters essentially stand for Hemolysis, Elevated Liver transaminases, and Low platelets. This is often considered to be along the pre-eclampsia spectrum of disorders. But it actually can occur in about 15% without hypertension or proteinuria.

Superimposed pre-eclampsia, this is often a little bit of a diagnostic dilemma. Because we know that blood pressure increases in the third trimester, as does proteinuria. And so the definition is a little bit more vague-- sudden and sustained increase in blood pressure with or without substantial increase in proteinuria. It becomes a little bit more apparent when other organs become a part of the syndrome.

Again, some notable differences from prior classifications-- non-dependent edema, hyperreflexia, the change in systolic blood pressure of 30 millimeters of mercury, the change in diastolic blood pressure of 15 millimeters of mercury-- while may be considered important, are not part of the diagnostic criteria. As I said, the term "mild" has been discarded, because it starts to make obstetric providers, as well as patients, a little bit complacent. And really, the task force wanted to highlight that pre-eclampsia can be progressive, and it can be unpredictable. And in no way, shape, or form is it ever mild.

Again, proteinuria is no longer necessary for the diagnosis, and oliguria, and fetal growth restriction, oligohydramnios, and abruption are not included in the ACOG definition, but still very, very important for management.

The pathophysiology even here in 2018 is incompletely understood. Probably the most popular hypothesis is the two-stage hypothesis that was put forth by our very own Jim Roberts here at the University of Pittsburgh and one of the gurus of pre-eclampsia. This is a two-stage hypothesis, where the first stage consists of abnormal trophoblast placental invasion into the uterus, abnormal vascular remodeling of the spiral arterioles, and then resulting in reduced profusion of the placenta, then resulting in the maternal syndrome, with the big question marks highlighting our incomplete understanding of how the two are connected.

This is a picture that kind of represents this stage one hypothesis. On the left is normal pregnancy. You can see the spiral arterioles coming off of the uterine artery, going through the endometrium and myometrium of the uterus. And on the far right is what happens in normal pregnancy, which is the trophoblast cells start to remodel the spinal arterioles to result in very dilated, high caliber, low resistance blood vessels that can easily feed and profuse the placenta.

In the middle is pre-eclampsia, where you can see this remodeling is incomplete or abnormal compared to normal pregnancy.

Stage two is the maternal syndrome. And it's a lot more than just blood pressure and proteinuria. It's actually manifested by systemic vascular dysfunction with increased peripheral vascular resistance, endothelial activation, vasospasm, activation of the coagulation cascade, including platelet aggregation, capillary leak, increase in inflammatory markers, ischemia, and reduced perfusion, which results in the clinical manifestations that we have as a part of our diagnostic criteria.

It's clearly a little bit more than the two-stage hypothesis. And you can add onto it the fact that maternal constitutional factors, such as underlying vascular disorders, genetics, and obesity can actually affect placental implantation, and maternal factors can affect the clinical manifestation of the disease, as it affects later life cardiovascular disease.

So there's a lot going on in pre-eclampsia, a lot of contributors, a lot of manifestations. One of the most popular theories that is very current is associated with angiogenic factors. And just in the way of background, angiogenic factors are at very high levels over pregnancy, increasing dramatically in the second and third trimester. The pro-angiogenic factors are vascular endothelial growth factor and placental growth factor. The anti-angiogenic factors are sFlt-1 or VEGF receptor, the soluble VEGF receptor.

And on the top diagram, which is a normal pregnancy blood vessel, you can see that the green dots-- the vascular endothelial growth factor-- and the blue dots-- the placental growth factor-- are in nice harmony with the VEGF receptor on the endothelial cells, as well as the little soluble parentheses shaped soluble VEGF receptor.

In pre-eclampsia, the soluble Flt receptor is at higher levels compared to normal pregnancy. It binds up all the placental growth factor and vascular endothelial growth factor, resulting in vasoconstriction. And these mediators, these angiogenic factors, are released from the placenta and can result in hypertension, proteinuria, multi-organ dysfunction, including cerebral edema.

So essentially, this imbalance-- low placental growth factor and high soluble Flt-1-- is associated with pre-eclampsia. And one of the reasons that this particular aspect is gaining a lot of attention in the pre-eclampsia world is that these can be detected in the maternal serum and have high potential for being biomarkers to predict and risk stratify a pregnant woman's risk for pre-eclampsia. Moreover, it is a potential target for therapy. And there are currently trials in place that are testing apheresis-- basically a plasma pheresis-- to remove that excess soluble Flt, to see if a pregnancy can be prolonged in the setting of severe pre-eclampsia, as well as VEGF therapy to give back VEGF.

All that said, pre-eclampsia remains challenging. It's a disease of theories. It's a syndrome with multiple organs involved. We still don't know the exact cause, except that you have to have a placenta. Preventative strategies, many millions of dollars have been spent on this, with primarily low dose aspirin providing a modest risk reduction in high risk women. The interventions that we have are limited. And there's not an ideal animal model to study this condition, because animals don't get pre-eclampsia. It's only a disease of humans. And of course, the only known cure is delivery.

In terms of the practical approach to taking care of the patient, the care really starts at the prenatal time frame with a high degree of suspicion. This is one of the reasons for the frequent visits in the third trimester. We check blood pressure and urine protein at every visit. Particularly in the second half of pregnancy, ask about symptoms and signs-- neurologic symptoms, headache, vision changes, scotomata, flashing lights, new epigastric or right upper quadrant pain, new onset of nausea, vomiting, shortness of breath, decreased urine output, vaginal bleeding, which could be a sign of abruption, and decreased fetal movement.

There are clearly a number of risk factors for pre-eclampsia both pregnancy specific-- such as first pregnancy, multi-fetal gestations, twins, triplets, assisted reproductive technologies-- as well as maternal risk factors, such as underlying chronic medical conditions. But the real take-home message from this slide is that any woman can get pre-eclampsia in any pregnancy. So high degree of suspicion.

Evaluation and management of pre-eclampsia really needs to happen side by side, especially in severe cases, and often needs to be a multidisciplinary team. We often will bring in our OB anesthesia colleagues, our neonatology colleagues, and ICU physicians, and then, based on the particular aspects of the disease, often our neurology colleagues, et cetera.

So the initial evaluation if pre-eclampsia is suspected is recommended to take place in a triage or hospital setting-- history, presenting signs or symptoms, physical exam with a focus on the cardiopulmonary, and neuro exam. The classic laboratory studies that we order are complete blood count, specifically with a focus on the platelet count, as that could be reduced in severe pre-eclampsia, liver transaminases, creatinine, and LDH as marker of hemolysis.

Fetal assessment-- as obstetricians, we have our second patient to worry about-- and fetal well being is assessed with non-stress test or ultrasound biophysical profile, as well as a growth assessment by ultrasound to evaluate for intrauterine fetal growth restriction.

Key aspects of management, again happening side by side, are thinking about the classic ABCs. And then the other important tenets of management are seizure prophylaxis and treatment, blood pressure management, antenatal steroids for fetal benefit, supportive care, and thinking about timing of delivery.

Importantly, recognition of the problem is the key to treatment. Pre-eclampsia is very frequently unrecognized in ERs and clinics across the country. So recognition is key. If you are taking care of a pregnant woman, think about pre-eclampsia somewhere in the back of your mind.

The definitive treatment, as I said multiple times, is delivery. It, however, is not that simple, because delivery certainly is always beneficial for the mom to prevent disease progression and endorgan damage. But a preterm delivery can be harmful for the baby. And so the decision is made based on a combination of gestational age, severity of the disease, maternal and fetal well-being, as well as the ability of a particular medical center to care for the mother, baby, diet.

So let's talk a little bit about magnesium for seizure protection. The ACOG guidelines recommend that magnesium intravenously be administered to women who have severe pre-eclampsia, neurologic symptoms or signs as a part of their pre-eclampsia syndrome, or worsening course. It's generally recommended that it be administered as soon as possible after the diagnosis and ideally prior to transfer, and continued during that initial evaluation of stability, and then continued intrapartum and 24 hours post delivery. We here in the US generally use an initial bolus, classically 4 grams an hour, and then 1 to 2 grams per hour continuous infusion.

If an IV is not available, then intramuscular magnesium can be used. It's 10 grams. It's two big shots, one per buttock, and your patients won't like you very much after you give them that shot.

Magnesium, obviously, at these doses has potential for toxicity and harm. So we generally use very well marked magnesium bags at Magee. These are with red writing, so as not to mix them up with a lactated Ringer's or normal saline. They're always hung on a pump. And our intramuscular magnesium is available on all the crash carts.

Monitoring for toxicity is imperative once the magnesium is started, including respiratory status and patellar reflexes. As the serum magnesium level increases respiratory and cardiovascular collapse are potential toxicities which are generally treated by stopping the magnesium, giving calcium gluconate, and then supportive care. Back in the day when I was a resident, these were not hung on IV infusion pumps. And sometimes when we needed to bolus a woman with normal saline or lactated Ringer's, the magnesium would be opened wide open. And needless to say, there were a lot of emergencies related to that. So those are good changes that have happened over time.

In the setting of renal dysfunction with the potential for decreased magnesium clearance, we will often administer the loading dose bolus, and then reduce the infusion rate, or continue intermittent boluses, and consider magnesium levels. This is not a well tolerated medication. And so a lot of education and supportive care is required when patients are on this medication.

So for obstetricians, we use magnesium for just about everything, whether it was preterm labor in the past, neuroprotection, or seizure prophylaxis. It's not a commonly used medication in other specialties, or for seizure treatment or prevention. And there have been a number of studies that have actually looked at magnesium for seizure prevention in the setting of pre-eclampsia and this is a battle in the mid-1980s between the US and our colleagues in the UK and Europe, with the US folks rooting for magnesium and our colleagues across the pond advocating phenytoin. And in 1995, there was a Sentinel study, an RCT done, comparing the two directly for pre-eclampsia prevention. And magnesium was shown to be superior.

Our colleagues still did not completely believe that study and went on to do perhaps the most definitive study, which is the Magpie Study that was carried out in multiple countries around the world with thousands of women. Based on the most recent Cochrane systematic review, magnesium has been shown to be superior to no treatment or placebo, Dilantin, and just anti-hypertensive therapy alone. So pretty clear when combining it with the landmark Magpie Study.

It's preferred over benzodiazepines, as well as other leaded cocktails. It has not been compared against some of the newer anti-epileptic agents such as Keppra. We also have an additional use for magnesium, which is its neonatal benefit prior to 32 weeks in terms of neural protection for the fetus and reducing the risk of cerebral palsy.

The mechanism by which magnesium prevents seizures is not well defined. There are a couple of thoughts behind that-- increasing the seizure threshold, membrane stabilization through a calcium channel blockade, decreased acetylcholine transmission at the level of the motor neurons, as well as a vasodilatory effect.

As I mentioned, there are not great animal models. But one of the most common models used in pre-eclampsia studies is the rodent model, reduced uterine perfusion pressure model, whereby the uterine arteries are surgically clipped, reducing perfusion to the uterus. The rats have various systemic manifestations of pre-eclampsia. And very elegant studies, they linked blood-brain barrier dysfunction to neural inflammation as well as increased seizure susceptibility. And the seizure threshold was restored with administration of magnesium, as well as a reduction in neural inflammation, kind of suggesting one of the mechanisms by which magnesium is beneficial.

We're going to switch gears to anti-hypertensive therapy, and very briefly. The main goal of anti-hypertensive therapy is to treat severe blood pressures and prevent cerebrovascular accidents and coronary events. That threshold, at least based on current data, is fairly high based on the ACOG studies. Many advocate lower thresholds, including the NICE guidelines advocating a 150 over 100 threshold. Alternatively, we do not want super duper tight blood pressure control. And we don't want to drop their blood pressures much more than 140 over 90, as these can have both maternal and fetal effects, including decelerations, drops in the fetal heart rate on fetal monitoring, fetal distress and even demise, as well as maternal risks with rapid blood pressure reduction.

The most commonly used agents for acute management of hypertension and pregnancy and pre-eclampsia are IV labetalol and IV hydralazine. Oral nifedipine can also be used. If drips are needed, we generally get our ICU colleagues involved in the management.

In comparing these different anti-hypertensive, no one agent has been shown to be superior. But one of the landmark systematic reviews recommends that providers should use the anti-hypertensive agent with which they're the most familiar. And this is a safety issue, as well as an effectiveness issue.

Oral agents can also be used. The most commonly used in obstetrics are labetalol and nifedipine. Methyldopa, while traditionally used, is not a very good anti-hypertensive agent. So we use that less commonly. Other agents can also be used with the exception of ACE inhibitors and ARBs.

In thinking about our second patient, our baby, often we will recommend steroid administration if less than 34 weeks in the setting of pre-eclampsia. Antenatal steroids, particularly betamethasone and dexamethasone have benefits, decreasing the risk of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, as well as neonatal death in the very premature infant. We give betamethasone or dexamethasone. Betamethasone is most commonly used in the United States.

Fluid management, very important. I mentioned that with the systemic vascular dysfunction often comes capillary leak. It's one of the reasons for much of the edema that can be seen with pre-eclampsia, including non-dependent edema. And so iatrogenic fluid overload can put patients at high risk.

ACOG, as a part of the Safe Motherhood Initiative, has come out with a number of checklists to assist with safe management of mothers with pre-eclampsia. Timing of delivery. This is often a very detailed discussion. But the quick and dirty is that without severe features, delivery is generally by 37 weeks, with severe features by 34 weeks, and if a mom is unstable with progressive conditions, mom's status is stabilized and delivery is effected. If expectant management is undertaken, that should occur at a tertiary facility. And we get a lot of women from the surrounding areas transferred to us for pre-eclampsia concerns.

This is a little bit more detailed table of the nuances of expectant management. Vaginal delivery is generally preferred, with c-section on the back burner for all the usual obstetric indications for c-section. And neuraxial analgesia is generally preferred. And I think Dr. Jonathan Waters will be talking about that in a couple minutes.

Post delivery management. Magnesium is generally continued for 24 hours after delivery with control of blood pressures. Importantly, blood pressures can often go down immediately after delivery, with a subsequent increase five days postpartum. Ongoing blood pressure management is recommended.

I'm going to just quickly switch gears to pre-eclampsia. This case is a classic case. In fact this summer, we saw a woman at 32 weeks, first pregnancy, who came to a local clinic, had elevated blood pressures and headache, was sent home asked to come back the next day, take some Tylenol to help with the headache, had elevated blood pressure, was told to go to the hospital in a car. She had a seizure in the car and was brought into the hospital where she seized again.

Eclampsia is very high in low and middle income countries, where it's a major cause of death, and can occur in 2% to 3% of women with severe pre-eclampsia in absence of magnesium. It can occur at any time. In this very large systematic review, 60% occurred prior to delivery, 20% intrapartum, and 21% postpartum. And that postpartum can be up to six weeks out, with most occurring in the first two weeks after delivery.

The clinical presentation, meaning antecedents-- headache, hypertension, visual disturbances, and right upper quadrant or epigastric pain have been reported. But importantly, at least a quarter of these women don't have any symptoms at all, which can actually be quite frightening.

The mechanisms are thought to be reduced cerebrovascular resistance, increased cerebral perfusion pressure, blood-brain barrier disruption, and edema formation. And this can occur even if autoregulation is maintained. It's supported by a number of ex vivo animal and human studies. And I mentioned the angiogenesis factor imbalance. There's emerging evidence that that may affect permeability of the brain-blood vessels, as well.

While not pathognomonic for eclampsia or pre-eclampsia, PRES, the Posterior Reversible Encephalopathy syndrome, is a common finding on MRI, with these white areas seen in the occipital and parietal areas. It can be seen in up to 98% of eclamptic women. This is based on a study out of Memphis. Again, as indicated in the title, generally in pre-eclampsia this is reversible with time and treatment.

The eclamptic seizure is fairly classic, with a tonic phase, clonic phase, and postictal phase. Generally, the seizures are no more than one to two minutes. But it may take about 20 minutes for recovery. Fetal bradycardia is not uncommon during the seizure, and can persist for a couple minutes after. This makes all of us obstetricians and obstetric nurses very, very nervous, with an urge to rush towards delivery when really we just need to treat the seizure.

The management of eclampsia is similar to the management of other seizures-- calling for help, ABCs, et cetera. Key different feature is initiating the magnesium sulfate as soon as possible with a standardized protocol. We generally use, again, a little bit of a higher dose for our bolus-- about 6 grams IV-- and use this consistent regimen, as well as a checklist. We often have drills and education to make sure that there is not complete mayhem in the setting of an eclamptic seizure, and that there is an organized, effective, and efficient approach to care.

With recurrent seizures, we often will give an additional magnesium bolus. Certainly other agents can be considered at that point. Rarely is intubation required, but does need to be a consideration for maintaining the airway. Neuroimaging is often considered in these scenarios.

And of course, other causes of seizures need to be considered. But generally speaking, it's eclampsia until proven otherwise in the third trimester.

Just two words, a couple of words, about long-term effects of pre-eclampsia. It doesn't just end after delivery and the six weeks' visit with the obstetrician. There's very, very good data about the long-term risk of heart disease, stroke, and elevated blood pressure. The American Heart Association in their 2011 guidelines recommend that pre-eclampsia be used as a risk factor for future cardiovascular disease.

Neurologic long-term effects are less well described. There certainly has been reports of persistence of white matter lesions thought to be a result of small vessel disease, higher in pre-eclamptic women and eclamptic women, but also seen in women who've had normal pregnancies. It's more frequent with the early onset and severe pre-eclampsia. The precise implications are not completely known. And a very recent study published in 2017 also suggests a decrease in cortical volume in women with pre-eclampsia compared to normal controls.

The issue of cognitive effects has been a little bit messy. Certainly self report-- perception of cognition, emotional, and mood changes-- are common in multiple studies. The objective data, however, are limited, with one study showing no evidence after pre-eclampsia/eclampsia, and another showing no evidence of impaired cognitive executive function, but other aspects of impairment, including auditory/verbal memory, less word learning, and recall.

Clearly there's more work that needs to be done in this area, including studies outside of the Scandinavian countries, which is where most of these were done, for generalizability, as well as considering options for intervention.

I'm going to end there. Our goal is obviously a healthy mom and baby. And we'll break for our next speaker and then questions after. Thank you.