

**ROBERT M.** What I'd like to do is-- I'm going to address-- obviously there are many different neurosurgical relevant diseases.  
**FRIEDLANDER:** I'm going to touch upon several of them, the ones that people usually ask me questions about, aneurysms, AVMs, cavernous malformations, and Chiari, for example. If there's other questions, we can address them at the end. But these are usually the ones that I get asked questions about.

So as I reviewed the literature for this, really, the literature is really poor on this, as to what to do, what the recommendations are, what the natural history. And over the past, I'm gonna say 10, 15 years, the natural history of these diseases that I talked about-- particularly the vascular ones, aneurysms, and AVMs-- not in pregnant patients, but just in the general population-- has improved significantly.

So it's not from, oh, it's an aneurysm, but rather, it's an aneurysm, and it's this location, and it's of this size. And again, I think the take home message is going to be at the end, is it we can't lump all these together, but rather we really need to tailor the recommendation on this specific patient. As well as, is the patient symptomatic from the disease, or not symptomatic?

One of the interesting things is clearly, there are lots of people walking around-- and I'll talk about that-- with aneurysms, again. But we don't get that many subarachnoid hemorrhage things during delivery, which I'm surprised about, but that's a good thing. So the question is what-- obviously there's a lot of people walking around with aneurysms that don't know it-- you can't make a recommendation on those. But with the ones that we know, what's the recommendation?

Part of the problem is that the stakes are extremely high. I mean, what level of risk do we take a patient-- again, going back to the aneurysm-- goes through delivery, and if they're OK, great. If they're not, who's taking the risk? Obviously it's not only about a medical legal issue, but it is as well. But also what's the safest thing to do for the patients?

So I just want to go over a couple of different aspects of the physiology, particularly that pertains to the nervous system during pregnancy. Overall, as you know, better than I do, there's an increase in total blood volume throughout pregnancy. Then starting about week 12, there's a mean cerebral perfusion pressure gradually increases as the resistance decreases. So lot of hemodynamic changes, clearly as well as a lot of hormonal changes.

Now one of the biggest changes, obviously, there are changes in the arterial side, but there's also very significant changes on the venous side. As the abdominal pressure increases, clearly there's issues with venous return, and with decreased venous return, that pertains to cerebral perfusion pressure, as well as with ICP in general. So ICP could be increased in these patients.

But it's not often that we see patients through pregnancy with problems with intracranial pressure, but certain kinds of patients certainly, it's something that can play a role. Also patients with elevated pressure, their cerebral perfusion pressure is decreased, and that's something that I know Dr. Fescu will touch upon, the ischemic side of this.

Now, as we think of the evidence, you know, traditionally you think of five levels of evidence, from one through five. One is the large, randomized control trials, with very clear-cut studies, and clearly we don't have that with patients with any neurological disease in pregnancy, as well. Then level two, small, randomized trials. And then three, four, and five, obviously is data that's less reliable from that point of view.

Once you see the levels of quality of the data, then you grade it. What's the recommendation that we have? So grade A is obviously a strong recommendation, when you have a randomized trial with very, very clear-cut results. Grade B is basically a recommendation with a randomized trials, with some controversy. And then C and D, as we call it, an option, where the data is really not very strong from that point of view. And really most of the recommendations are, some are B and most C and D for these kinds of diseases.

So with intracranial aneurysms, as you know, these are vascular weaknesses that occur, usually at branching points of arteries, where you can have a dilatation of the blood vessels. The feared complication is subarachnoid hemorrhage, when these aneurysms rupture. Now in general, mortality from a subarachnoid hemorrhage, a 30 day mortality, is around 50%, maybe 40% to 50% of the patients that survive, at least a third end up in fairly devastated manner. And the rest somewhere in between.

Now if we think of the prevalence of unruptured aneurysms, and you look at the age of relevance for pregnant females, you know, you can come up with a number somewhere around 1.8%, somewhere in that neighborhood. And you can do the math of how many patients you deal with every day through delivery, and 1.8%, not a huge number, but it's a pretty significant number. And clearly these complications don't happen that often.

Now, as I said, a number of studies have been done looking at the incidence of subarachnoid hemorrhages during pregnancy. And that the numbers that come up are between 3 and 31 per 100,000 in non-pregnant females. The number is 11.5 per 100,000. So again, it's somewhere within the ballpark, suggesting that pregnancy likely does not increase the risk of aneurysmal rupture. But that's, again, the quality of the data is not terrific there.

Now if a subarachnoid hemorrhage occurs, the likelihood that the fetus will die is about 17%, and maternal mortality, somewhere around 35%. As I told you, in non-pregnant females, mortality is closer to 40% to 50%. So again, likely in the similar ballpark. But now, of all fetal mortalities, subarachnoid hemorrhage accounts for 5%, so it's a reasonable number. But also, of all maternal mortalities, 12% are due to subarachnoid hemorrhage. So it's an important cause of maternal mortality.

Now the question, risk of vaginal versus c-section, and the data is all over the place, and again, not very strong. Early investigators recommended termination of the pregnancy, but obviously that's something that's not the current practice at this point with subarachnoid hemorrhages. 20, 30 years ago, we tended not to treat them acutely in the non-pregnant states, or in the pregnant state also. That was a lot of what was done as well.

But clearly, the thought is that during the delivery process is when there's the highest risk of hemorrhage. But that's not what occurs in practice. We don't see tons and tons of ladies that undergo delivery presenting with a subarachnoid hemorrhage. Of the bleeds, they tend to occur a little more often during the third trimester, and then the first few days after giving birth. In my personal experience, most of the ones that I've seen are usually one, two, three days after delivery. But it's not a huge number as well from that stand.

So a nice study was done by Brian Hoh-- who's a resident colleague of mine-- a number of years ago, where they looked at the Nationwide inpatient database sample. So it's all the patients, all the pregnancies within a certain group, between 1988 and 2009. So they found, they have a number of 20 million pregnancies. Of patients that went into the hospital, not with delivery, of these 20 million, was 2.7 patients. So before delivery there was 714 subarachnoid hemorrhages from ruptured aneurysms.

And I'll do a little bit of the math in the next slide. But in patients with delivery, out of 17 million patients, 172 patients presented with a ruptured aneurysm. So now if you look at the numbers here. So 2.7 million, 714 presented with a subarachnoid hemorrhage. If you think of an incidence of unruptured intracranial aneurysms of this 1.8%, there should have been 48,000 patients with unruptured aneurysms, and of these, 714 ruptured. So the risk of rupture is approximately 1.4% during the pregnancy.

And those numbers are sort of in line with the natural history of aneurysms. Again, I'll talk a little bit about different aneurysms, as I said, different sizes, or different morphologies of the aneurysm, but it's not it's not a number that's much, much higher than the natural history of an aneurysm. Although I think it's a little bit higher.

Now, during the delivery, the time of delivery-- and as I said, a couple of days around that-- they looked at 17 million deliveries, and they had 172 subarachnoid hemorrhages. Now, again, if the math is done, there should be-- actually, the numbers should be higher than 31,000, I'm sorry, that wrong-- but the rupture risk is 0.05%. So one in 2000 patients with unruptured aneurysms, the aneurysms would rupture. So if you say, OK, that number is pretty low. But if you say also that that's around the time of delivery, if that 0.05%, you multiply by 365, or somewhere a number there, you end up with a risk that is much higher.

So my gut feeling, with looking at the state, again, that there's a somewhat higher risk during the delivery period. Exactly what it is, and how much higher, and will all aneurysms be the same? That's where the key question is. When we evaluate patients with aneurysms-- not pregnant woman with it, but just in the general population-- we don't just say, you have an aneurysm, this my recommendation. But rather, we're able to stratify it.

And that's where the current studies, with the natural history of aneurysms, we're starting to delineate better in terms of what are the risk factors of these aneurysms to rupture? So the key question is, what is the likelihood of a certain aneurysm to rupture? There are two studies, that, again, not going to go into the detail, this is in, again, in the general population. But this is one of the first studies where we don't just say-- I remember during residency we used to say-- OK, risk of rupture of aneurysm, 3% per year. But we just kind of lumped everybody together. And that's clearly not the case.

What they did in this study is that they looked at aneurysms by location, and different locations appear to have different risks of rupture, as well as by size. The larger the aneurysm, the more likely that it is to rupture. So we might provide a recommendation to a patient with a three millimeter, five millimeter aneurysm, saying, just go ahead, the risk of rupture is pretty low.

If you think again, if it's one in 2,000, then it's one in 2,000, it's a real number, it's pretty low. But if we can further stratify, and be more delicate with the recommendation, it's something that would be useful. So this is, for example, one study that was done. This is an American study. Another study was a Japanese study, where they actually went and subdivided into categories of patients a little bit further with aneurysm morphology. Does the aneurysm have a daughter dome? Those are more likely to rupture.

So we're able to stratify better. So at this point, to provide a recommendation is not only based on the aneurysm, but also on the morphology in general. So my recommendations at this point is obviously, a patient with a ruptured intracranial aneurysm should be treated, no matter the stage of the pregnancy, due to the risk of a rerupture, and very, very high likelihood of mortality with rerupture.

The question is, with unruptured aneurysms, that there's no real, real good evidence that there is a greater risk with a vaginal delivery. And again, I'm not sure that a c-section is safe for either. So really, the decision needs to be tailored, consideration for elective treatment of aneurysms in a non-urgent manner can be done at a later time.

Second, the level of evidence, not good at our level, a three to five, and the greater recommendation is C in terms of an option. But in general, what I try to say is with aneurysms that I'm more concerned about-- a larger aneurysm, an aneurysm that's fairly irregular-- I would recommend a c-section. But again, it's just trying to be conservative there.

AVMs, again, just reviewing what they are. It's an abnormal conglomeration of blood vessels, essentially going from an arterial to a vein, with an intervening nidus. So you have veins carrying high arterialized pressure. And the prevalence of AVMs in general is at least tenfold less than patients with an aneurysm.

So again, just to show you an example of what these look like, this the carotid artery, this a feeding vessel aneurysm. These patients tend to form a significant number of aneurysms, given the high flow. If you could see, obviously, that this is the AVM here, with the draining vein, this is the size of one of her middle cerebral artery branches, almost the same size as her carotid. These are the size of all the rest of the vessels.

So again, very, very large flow. And with AVMs, you're going to have, again, both potentially increase flow going in during pregnancy, and increase the venous pressure. So there's increased pressure in the AVM. These are lesions that I'm much more concerned about during pregnancy.

Again, here is just a picture of that patient with that aneurysm there. That was treated, that's what the AVM usually looks like. So while the literature is mixed of what to do with AVMs during pregnancy, there is more and more evidence that these are higher risk of a hemorrhage type of situation. Rerupture in pregnancy is as high as 30%, so with a ruptured aneurysm, the likelihood that it will rerupture in the short term is actually very high with an AVM. And sometimes you just let them recover and you treat them later.

But in pregnant patients, the risk of rerupture is as high as 30%, versus the risk in the non-pregnant patients is more in the 5% range. And you can think of it, because there's high venous pressure, they're more likely to rerupture again. But really, there's no concrete data that suggests, that it looks at the risk during vaginal delivery with these patients.

Again, what you see here, this is a patient with an AVM, that arterialized vein, which, after removed, you can see, it goes to venous type of morphology. Now I have to show this, this study is a study done at the Brigham, by Rose Du, and the first author is Brad Gross, who is one of my faculty here now. So I had to review this study, although it was a good study. And I [INAUDIBLE] interest because of that.

So what they did is they followed patients with known AVMs over a period of time. So they had 121 known AVMs, 54 of them were pregnant, or females that went through pregnancy with a known AVM. So of these, a total of 62 pregnancies. And of these 54 females or 62 pregnancies, there were actually four patients with hemorrhages, one with rehemorrhage.

So looking at the annual rates of hemorrhage, you can see here in this table. So overall, the annual hemorrhage rate for non-pregnant females is 1.5%. The annual rebleed rate in this population was 7%. And the annual bleeding rate for females in general was 1.3%.

Now, the risk of hemorrhage with an AVM is 10%. Now we're talking, those are real numbers. Again, it's a small population, but it's one of those better studies, really looking at a population of patients with known AVMs that went through pregnancy. And I would say that 10% bleeding rates risk is way, way too high. And I believe, then, for patients with AVMs, a serious discussion needs to be had about potentially either treating the AVMS before.

There's another study looking at stroke risk in general. So out of these 58,000 pregnancies, that there was some ischemic, some hemorrhagic strokes. But of the 11 hemorrhagic strokes, four were from AVM. So again, the prevalence of AVMs is much lower than all the other pathologies. So the risk of hemorrhage with an AVM is clearly higher.

Treatment options are microsurgery, embolization, and in radiosurgery. The issue with a microsurgical resection of the AVM is that the AVM is cured once you leave the OR, if you take it all out. So it's an immediate cure. With embolization, often you don't-- it uses it as an adjunct to therapy. Usually you don't cure the most of the AVMS with embolization. And gamma knife radiosurgery takes one to five years for the treatment to obliterate the AVM.

So my recommendations in general, for patients with unruptured AVMS, is to consider intervention prior to pregnancy. And I believe that this is warranted, given the higher risk of hemorrhage within them. When I talked about aneurysms, we try to stratify them more a little bit, in terms of risks. The risk stratification with AVMS is not as clear-cut, although there clearly are some AVMS with slightly higher risk of a hemorrhage than in others.

So if the AVM ruptures, clearly you need to have a discussion about treating them at whichever stage of pregnancy the mother is at at that point. Radiosurgery, not a good option during pregnancy. As I mentioned, it takes three to five years for it to really cure the AVM. And embolization, there's a lot of radiation that's there, as well as all that contrast agent. So it's not a great option in and of itself.

You know, microsurgery is best performed, obviously, before pregnancy. But it could be done in the first trimester, or in the immediate postpartum period. Now, we don't have data showing that patients with a unruptured AVMS are at greater risk during vaginal delivery, but I'm not sure that we would catch that kind of information. So again, the level of evidence is so-so, but the recommendation, again, I think there's more and more evidence that these are higher risk lesions to follow throughout pregnancy.

Cavernous malformations, those are easy. They're venous blood vessel abnormalities, they're usually low pressure bleeds. There's really no well-documented data of risk of a hemorrhage, or increased risk of hemorrhage during pregnancy or vaginal delivery. So really, there's no need to alter the management of these patients, unless, obviously, if there's a bleed with them through the time of pregnancy, might want to consider c-section at that point. But again, these are lesions that are much lower risk.

Shifting gears a little bit, I get a lot of questions about patients with Chiari malformation. So Chiari malformation usually results from a herniation of the cerebellar tonsils through the foramen magnum. And what it does is just that it obstructs the flow of cerebrospinal fluid.

They're not that uncommon of a finding, but they're often asymptomatic, and you've got to follow them. The female to male ratio is 3:1, so it much more commonly occurs in females. And in some of the patients, particular symptomatic ones, present with syrinx, which is a cyst within the spinal cord.

Now, these patients, I'm a little bit more concerned about, because if a patient-- here, you could see that this patient has the cerebellar tonsil herniation below the foramen magnum. She has a pretty good sized syrinx there. If this syrinx expands further up, gonna cause more irreparable problems. I'm more concerned about the bearing down component of the delivery. Clearly increases intracranial pressure, and the cerebellum can herniate that further.

We worry about spinal taps with this, so epidurals, or spinals, or something that I would be concerned about with this population. So again, as I mentioned, the epidural anesthesia. You know, there are some case studies where they have done them and everything goes fine, but it's something that, at least in theory, I'm more concerned about.

There's a meta-analysis, a group-- well, not even a meta-analysis-- just putting together all the studies that have been done with deliveries in patients with Chiari. And they look at these number of patients here, it's not a huge number. You know, did have they did they have surgery beforehand? If I correct the Chiari, they ask when can they get pregnancy. I'd like for everything to heal up, so I say three to six months. But clearly that lots of patients, they didn't have surgery here.

So patients that have had a number of deliveries before and didn't have a problem with it. They've had both c-sections and vaginal delivery, but as you can see here, many of them have had spinals and epidural for pain control. And most of these patients are fine. So you know, it's something that, again, in theory I'm more concerned, but seems to be OK. They don't really talk about, are the patients symptomatic or not symptomatic before they started?

Because if a patient with a Chiari clearly has symptoms, you know, there's already compromised. But if somebody is not compromised, meaning that they have a Chiari by imaging, but they're asymptomatic at that point, the flow of CSF at that point is clearly OK. So here's to just to show you a specific case of this.

So this is a patient with a significant Chiari, and a syrinx. When you look at the foramen magnum-- so again, this is a little lower, you get the spinal cord and the CSF around it-- and that's how you want it to look at the level of the foramen magnum. And in this specific patient, you have, again, this is the whole foramen magnum. And I don't know if it projects well, but that's the spinal cord there, the upper part of the spinal cord.

And this is all cerebellum. So when this patient bears down, you can think of the cerebellum impacting more inferiorly, and her symptoms could worsen, that syrinx that she has is worse off. So again, I just wanted to show you, and I have to show one-- if it works-- one video of surgery, being a surgeon. There we go.

So this is the level of the foramen magnum here. And you can see the cerebellar-- this is the top, and that's the bottom-- these are the cerebellar tonsils. And you can see how low these cerebellar tonsils are, you don't see the spinal cord. And what we'll do is-- it's sort of playing-- when we spread out the cerebellar tonsils, you actually see the gush of CSF that comes out.

So there's already significant compromise with this patient. My hands are faster than that, so it's not playing well. And then one of the things that we do at the surgery, is we put a patch there, to give him a lot more room. And at the end, we coagulate the tonsils, just give it a lot more room in that area. I just wanted to show you that, so you could see, in the bottom, the spinal cord with this patient.

Everything is so tight there. So you could think through the process of delivery, if you have an epidural, if somebody who's mildly symptomatic, can she get a lot worse from this? And this is that same patient 18 months after. You can see the syrinx completely resolved, and you have that area with that space there.

So this is one that I'm a little more conflicted as to what to recommend. Both, clearly, are considerations towards the c-section of vaginal delivery. In my opinion, if a patient-- so you have the category of patients, it's symptomatic, to me that's an easier decision. I think those needs to be fixed before delivery, because those can get a lot worse, and have a more significant problem.

The issue is where the patient was asymptomatic, and you could say, well, you go through the liver, you have a spinal, can they become symptomatic? But again, it seems like the data doesn't necessarily support that. And obviously you want to avoid excessive bearing down during the delivery, and potentially, at least in theory, epidural anesthesia carries a higher risk.

So patients with Chiari, we even don't recommend for them to have lumbar punctures in general, or there's risk of lumbar punctures, even for non-pregnant patients. So this is one that I'm more concerned about, but the data's not there. So really, the level of evidence is the worst, and there's really no good recommendations from that point of view.

I wanted show this one case, because I know there's some anesthesiologists here. And it was this interesting, patient was a 29-year-old female, that during vaginal delivery-- this has nothing to do with Chiari or anything else-- had an epidural catheter placed, but they were unable to thread the catheter. And during the placement, the patient had severe leg pain and numbness, which improved over six weeks, but the symptoms recurred up afterwards.

And this patient had a big tumor in her conus, as you can see here. So obviously, it's going to be very hard to thread something up in that direction. Something to keep in mind, this is a patient, actually, that I had in Boston. We had a very similar patient like this a few months ago, one of my colleagues here, with a very, very almost identical kind of an image. This patient that had a subependymoma, as you can see, attached to the conus right there in the bottom. So anyway, I just wanted to show that.

So in conclusion, the existing literature is very poor. The problem in many of these studies, in trying to put them together is, you could say, it's not comparing apples to oranges, because those are both round fruits, or apples to bananas, those are both fruits. It's really comparing like, apples to trucks. I mean, it's just that the data is very, very, very different. And it's very hard to really compare them and make meaningful conclusions.

It's difficult, at least for me, to make blanket recommendations, you really have to tailor the recommendation based on the symptomatic nature of the disease. The question is also, for example, going back to aneurysms, what's the level of risk that is appropriate? One in 2,000, is that right? But that's the issue.

And clearly, we're in severe need of both prospective and retrospective high-quality data, and I'm not sure if that's one of the goals of this conference. But really, getting two very large institutions like UPMC and the Brigham, with so many deliveries, really, to follow, prospectively, these patients, I think would be a great service to the population.

I wanted to acknowledge one of my residents, Mike McDowell, who helped me put this together, as well as a medical student, Rajeev Sannan, Thank you very much.