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## PDA's in Infants: To Close or Not to Close?

In preterm neonates with a patent ductus arteriosus, the standard of care has been to attempt to close the defect. Yet some experts have asked whether we need to treat PDA in most preemies at all. If we are to resolve the condition, there are various methods and protocols for treatment and even prevention. How do outcomes for PDA closure vary by treatment strategy? You are listening to ReachMD Radio on XM160, The Channel For Medical Professionals. Welcome to a special segment focused on heart health. I'm your host Dr. Jennifer Shu, practicing general pediatrician and author. Our guest is Dr. Darshak Sanghavi. She is at Pediatric Cardiology and assistant professor of pediatrics at the University of Massachusetts Medical School.

**DR. JENNIFER SHU:**

Welcome Darshak.

**DR. DARSHAK SANGHAVI:**

It's great to be here with you.

**DR. JENNIFER SHU:**

Now can you start of with just the definition of what a patent ductus arteriosus or PDA is?

**DR. DARSHAK SANGHAVI:**

Sure. As most people are aware, the lungs in a fetus don't accept a lot of blood flow because the pulmonary vascular resistance is very high. As a result, the blood has to bypass the lungs and in the fetus that has done through both the patent foramen ovale as well as the patent ductus arteriosus. Now this is a problem in preterm neonates because at birth, the patent ductus arteriosus simply does not close as often and some estimates are that approximately a third to approximately a half of preterm infants have a persistently patent ductus arteriosus and what this leads to and what neonatologists are often concerned about is that the flow actually becomes reversed after birth and so the lungs may be exposed to excessive blood at both high volume and high pressure. It's possible that this may then contribute to the difficulties that many preterm neonates face with respiration.

**DR. JENNIFER SHU:**

So normally you are saying before birth, the blood is flowing from the pulmonary artery to the aorta and bypasses the lungs and after birth that's the other direction?

**DR. DARSHAK SANGHAVI:**

Precisely so. In the fetus, it's referred to as right to left shunting and then postnatally you start to develop left to right shunting.

**DR. JENNIFER SHU:**

Now you mentioned that in preterm babies it's much more common, is that also more common in different genders or races or other conditions?

**DR. DARSHAK SANGHAVI:**

It is difficult to say; to my knowledge, there's not a lot of data on whether it varies by gender or by race. What it does vary by quite clearly is the gestational age and the weight of the infant. In other words, the more preterm the infant and the lower the birth weight, the more likely the infant is to have a patent ductus arteriosus.

**DR. JENNIFER SHU:**

Now what is the natural cause of a PDA in a preterm infant? Is it something like may be a VSD where you would watch it in hopes that it would close?

**DR. DARSHAK SANGHAVI:**

I think that's really an interesting question and the fact is that we don't really have a lot of data about the natural history of an untreated patent ductus arteriosus. However, it does appear, in some studies that approximately 70% of the time, they may spontaneously close. There are some studies most recently one published from Belgium last year that actually just watched patent ductus arteriosus in preterm infants and found that even in children in whom the duct is remained open, the 30% children in whom it remained open just conservatively treating it led to the majority of those actually closing within several days.

**DR. JENNIFER SHU:**

Now before we even talk about treatment, can we discuss may be other ways to prevent that open PDA

in infants? It definitely needs to be there in the fetus, but how can we increase the chances of it closing shortly after birth in these early preterm babies?

**DR. DARSHAK SANGHAVI:**

I don't know if anybody actually knows if there is a way to prevent this from happening and part of the issue is that many times when women deliver preterm infants, it really happens as a surprise. We don't really have a lot of time to prepare or administer any medical therapy to women ahead of time to prevent the ductus arteriosus from staying open. As a result, when the child is born, there is very little one can do right away to close the ductus arteriosus. Some people have advocated for administering medicines to close it right away at birth regardless of how the baby looks, the so called prophylactic strategy, but that's really the only message that are open.

**DR. JENNIFER SHU:**

So where as we might give steroids to the mother who then preterm labored to accelerate the lung maturity in a preterm baby, there's no equivalent for a PDA, that's what you are saying?

**DR. DARSHAK SANGHAVI:**

That's exactly right. I mean theoretically one could think that we could potentially give mothers ibuprofen or indomethacin, which are known to close the PDA if we suspect they are going to immediately deliver. Now the problem is we can only perfectly predict when women are going to deliver and so we really don't want to give a medication that should the child remain in utero that those medicines could actually be harmful.

**DR. JENNIFER SHU:**

So once the baby is born, how would be the PDA be diagnosed?

**DR. DARSHAK SANGHAVI:**

The standard of care in many places is that the infant receives surfactant or whatever else other therapy they need in order to achieve a stable respiratory status. If for some reason, the child is still hemodynamically unstable or if the neonatologist hears a heart murmur, they often will order an echocardiogram and that's what would actually demonstrate the patent ductus arteriosus.

**DR. JENNIFER SHU:**

Are there any other signs and symptoms besides the heart murmur that you might expect?

**DR. DARSHAK SANGHAVI:**

Some people refer to a widened pulse pressure; in other words, a big difference in the systolic and the diastolic pressure or sometimes they feel pulsations in the limbs, but really almost always it's the presence of the heart murmur. What's fascinating though is that several studies show that the presence or absence of a heart murmur is not very predictive of whether a PDA is actually present, so to really be honest, the only way to know is to do an echocardiogram routinely or screen children with an echocardiogram, but that's really not the standard of care.

**DR. JENNIFER SHU:**

So, are there some protocols that would prophylactically give something like indomethacin on the first day of life or I guess day of life is 0, might be how you would word it, to a preterm baby and what age cut off, what gestational age cut off would you use?

**DR. DARSHAK SANGHAVI:**

There is a body of literature because there are initially good randomized control trials where indomethacin was given prophylactically to infants who are very small. What's interesting is that the outcomes were not very impressive. There was no real long-term difference in mortality, chronic lung disease, or obvious developmental outcome in children who receive prophylactic indomethacin at birth to prevent the PDA from staying open. What we do know is that there was a slightly lower incidence of low-grade intraventricular hemorrhage or IVH, the so-called grade 1 and grade 2 IVH in children who are treated prophylactically with indomethacin. The problem is that there is also a bunch of side effects. Several studies show decreased gut perfusion, decreased urine output, and as a result, some centers have adopted this strategy because they would like to reduce the risk of low-grade IVH. Many other centers have chosen not to because there has been no long-term difference in the outcome and so the notion of using prophylactic indomethacin is very controversial still.

**If you have just joined us, you are listening to a special segment, focus on heart health from ReachMD Radio on XM160, The Channel For Medical professionals. I am your host Dr. Jennifer Shu. Our guest is Dr. Darshak Sanghavi. She is at pediatric cardiology at the University of Massachusetts Medical School. We are discussing prevention and treatment of patent ductus arteriosus in preterm infants.**

**DR. JENNIFER SHU:**

Now let's talk a little about therapeutic indomethacin on day of life 1, may be following an echocardiogram that confirms the PDA. What are recommendations regarding that?

**DR. DARSHAK SANGHAVI:**

There are no clear recommendations about treatment of PDA and so there's a lot of variation in practice. Some centers, for example, will prophylactically treat a PDA in preterm neonates as I mentioned because it reduces the risk of intraventricular hemorrhage, although in long term, there's no clear benefit in the medicine. Other centers will wait for a few days and see how the child responds to conventional therapy with face surfactant or ventilation. If the child does very well, weans off the ventilator, then they would probably defer treating the ductus arteriosus. Others would say well, if a PDA is present, even if the child is doing very well, has the so-called asymptomatic PDA, they would still treat that as well. I think the point I am making is that there is a vast amount of practice variation among centers in both how they diagnose PDAs and then subsequently how they choose to treat them.

**DR. JENNIFER SHU:**

Are there any centers that you would say go straight to a surgical approach if they are going to treat the PDA?

**DR. DARSHAK SANGHAVI:**

Well, there are certainly some centers that do that. They prophylactically will ligate PDAs in small infants. I think that again is something, which is not really supported by a great deal of data and also exposes the child to a risk of surgical complications. While there are centers that do surgically ligate immediately, I think that that it is outside the norm of practice now.

**DR. JENNIFER SHU:**

Do you know of any studies that compare the indomethacin treatment outcomes with the surgical ligation treatment?

**DR. DARSHAK SANGHAVI:**

Well, surgical therapy is felt to be definitive and so most of the studies look at whether indomethacin prevents the need for surgical ligation. I think that what we are getting at here is an interesting feature of how these studies are done. Most studies that are now done with the indomethacin and more recently ibuprofen, which is the supplanting indomethacin in many centers. The outcome measure they look at is do we avoid surgical ligation? The answer for that is that definitely yes. In other words, both indomethacin and ibuprofen are effective in closing a PDA, but that still does not get out with most parents and neonatologists care about long-term. In other words, does indomethacin therapy or ibuprofen therapy really reduce the risk of complications of prematurity such as chronic lung disease, necrotizing enterocolitis, developmental problems, and the like, and those are the questions that I think we should be asking.

**DR. JENNIFER SHU:**

So, have these studies not been performed is that what you are saying?

**DR. DARSHAK SANGHAVI:**

Well, I think that what is interesting is that the data really doesn't seem to show the aggressive therapy for PDA whether medical or surgical, it's not clear if that actually affects the long-term outcome in those neonates. The Cochrane Collaboration for example, and other investigators have looked at this in some detail and found that even aggressive therapy of PDA, the data is just not there to show that actually prevents necrotizing enterocolitis that it reduces the risk of developmental delays or that it reduces even the risk of mortality.

**DR. JENNIFER SHU:**

So should we be then watching and observing these patients to see if they get older and make sure that they don't go into heart failure before attempting to do some kind of intervention?



**DR. DARSHAK SANGHAVI:**

I think so. My opinion is that what's happened in the neonatology standards of practice is very similar to what happened with the widespread use of estrogen replacement therapy in women. In other words, people's intentions were good, but they were relying on a huge amount of retrospective cohort data that showed, for example, that in women having been on estrogen replacement reduces the risk of heart attack. Similarly, if you look a lot at the data, it does show that a lot of infants who have problems long term, in other words higher risk of mortality and so forth, did have the presence of a PDA, but the issue is, is that really a cause or is that an effect of being critically sick? In other words, babies that are sick seem to keep their PDAs open and so what I would argue for is that we simply don't have a large number of very good randomized controlled trials looking at ductal closure whether it is surgical or medical, and so we have gotten into a situation of is a widespread practice, which may or may not really be supported by subsequent long-term randomized trials, which we just don't have now.

**DR. JENNIFER SHU:**

So who would you propose do these randomized trials that are needed?

**DR. DARSHAK SANGHAVI:**

I think that there are a variety of individuals; these kinds of trials could be funded by a federal mandate or by a federal request for proposals. Nothing like that exists right now. The other individuals that could fund or perform a trial like this could be the makers of ibuprofen or indomethacin; that also is pretty dicey because they have invested in the widespread use of that. So, to my way of thinking, the last resort would be large neonatal research collaboratives. They also could undertake a randomized trial.

**DR. JENNIFER SHU:**

So in the meantime, is it okay to have such a variation on treatment protocols for these preterm babies with PDAs?

**DR. DARSHAK SANGHAVI:**

It is difficult to say because at this point in time, there are no clear evidence-based clinical guidelines that have been developed and widely adopted, and so I would hope that an institution whether it's the Cochrane Collaboration, the American Academy of Pediatrics, or other respected organizations that have experience in developing clinical guidelines, could actually sit down and review the literature and comprehensively issue with series of best clinical practice guidelines on the diagnosis and treatment of PDA. That's really what I think would be the optimal choice for the health of preterm children.

**I would like to thank our guest, Dr. Darshak Sanghavi. We've been discussing prevention and treatment of patent ductus arteriosus in preterm infants. I am Dr. Jennifer Shu. You have been listening to a special segment Focus on Heart Health from ReachMD Radio on XM160, The Channel For Medical Professionals. ReachMD, online, on demand, and on-air. Please visit us at reachmd.com and thank you for listening.**