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Exploring the Prevalence of Congenital Heart Disease in Conjoined Twins

Dr. Sorrentino:
Congenital heart diseases are the most common type of birth defects resulting in lifelong disability and in some cases, even death. But when a patient is expecting more than one child, could that double the risk of congenital heart disease, especially when it's paired with anther birth defect?

Welcome to Heart Matters on ReachMD. I'm Dr. Matthew Sorrentino and joining me to discuss the results from their recent study published in the American Journal of Cardiology focusing on the prevalence of congenital heart disease in conjoined twins and higher order multiple births are Drs. Anita Moon-Grady and Dr. Laxmi Ghimire. Dr. Moon-Grady is a Professor of Pediatrics and Director of the Fetal Cardiovascular Program at UCSF. Dr. Moon-Grady, welcome to the program.

Dr. Moon-Grady:
Thank you for having me.

Dr. Sorrentino:
And Dr. Ghimire is a pediatric specialist. His specialties include pediatric internal medicine and pediatric cardiology. He is currently at Lake Region General Hospital in Laconia, New Hampshire. Dr. Ghimire, thanks for being here with us today.

Dr. Ghimire:
Thank you for the invitation. I am very glad to be here.

Dr. Sorrentino:
So, let's begin with you, Dr. Ghimire. Can you give us a better understanding of the prevalence of congenital heart disease in the overall general pediatric population?

Dr. Ghimire:
Absolutely, congenital heart diseases are the most common congenital anomalies. Many believe that the incidence is around 8 per 1,000 live births, that's 0.8%, and we're able to verify the incidence in our study, as well. So, early studies, before 2000s showed a low incidence of congenital heart disease, potentially from the lack of good diagnostic tools like counting only the CVR defects and not counting the milder forms of the defects. But the last two decades, the incidence of congenital heart diseases has remained stable. The incidence of congenital heart diseases is similar even in different geographical locations, countries, races, and socioeconomic conditions. Let me introduce two terms here. First one is CVR congenital heart disease, that's a term that we use for the ones who present as severely ill in the newborn period or infancy, and the second term is called Critical Congenital Heart Disease, those who need surgical or cardiac catheterization intervention in the first year of life and these lesions represent around 1/3 of all congenital heart diseases. I would like to briefly mention certain conditions or circumstances that increase the risk of congenital heart diseases at the population level, like the incidence of congenital heart diseases are higher in many chromosomal and genetic abnormalities, infants of mothers who have diabetes, and certain maternal medications like ACE inhibitors and acne medication like Isotretinoin. Also, maternal smoking and alcohol can increase the risk of congenital heart disease. Another interesting fact is there are recent reports of higher incidence of congenital heart diseases at higher altitudes, specifically for the non-CVR heart defects. The reports of South America from Peruvian Andes show that, as the altitude increases, the incidence of congenital heart diseases also increased.

Dr. Sorrentino:
Dr. Moon-Grady, with that background, knowing the general population incidence of congenital heart disease, we had more limited

information on the prevalence in twins and triplets and higher order multiple births. So, how did you conceive of and design a study to look at this more special population to determine the incidence of congenital heart disease in those patients?

Dr. Moon-Grady: In my work as a fetal cardiologist, I do a lot of education of, not only cardiologists but our maternal-fetal medicine colleagues and I've also been privileged to be on working groups that produced guidelines documentation for a variety of different organizations nationally and internationally. As part of this, I have extensively reviewed the literature on indications for fetal echo and that's where this becomes pertinent to this work because there were a few large studies on twins and congenital heart disease, but limited, or no good information on conjoined twins and triplets in higher-order multiple births. We'd been using the KID database, Dr. Ghimire and I, which is a national database including more than 3 million births per year in the U.S.; we'd been using these to perform research studies on infants and children with congenital heart disease. The database, I thought, would be ideal as far as one to study for rare diseases like congenital heart disease and especially in rare populations, like conjoined twins and triplets, quads, and higher-order multiples where there really was a dearth of information in the literature. The congenital heart diseases and procedures and whether the baby was part of a multiple birth are fairly robustly coded, and we know this because of our use of it in our prior projects. The downside, as pointed out in the study that we could not look at other factors, such as chorionicity or zygosity, we could not look at the use of infertility treatments for the pregnancy and that may all have impacted the findings and may have been important. Those details just aren't there, the database can't answer those questions, but it can ask the question that we asked. So, our study design allowed us to include more than 19 million newborns; out of these, more than 600,000 were twins, 238 were conjoined twins, and almost 26,000 triplets and higher-order multiple births, that's quads, quintuplets, sextuplets. So, this makes ours the largest study on the incidence of congenital heart disease in twins, conjoined twins, and triplets, and higher-order multiples.

Dr. Sorrentino:
So, with that being said, Dr. Ghimire, can you tell us a little bit about the results of your study? How did the incidence of congenital heart disease differ for the twins and triplets, conjoined twins, and higher-order multiple births in your study compared to the general population?

Dr. Ghimire:
Sure. In our study, the incidence of congenital heart disease in twins was 2.35%, that's 3 times higher compared to the singletons and that's also similar to the prior literature. And we found the incidence in triplet and higher-order births as 5.1%, that's 6 times higher. Very interestingly, the incidence of congenital heart disease in conjoined twins was 27%, that's 34 times higher.

Dr. Sorrentino:
For those just tuning in, you're listening to Heart Matters on ReachMD. I'm Dr. Matthew Sorrentino and with me today are Drs. Anita Moon-Grady and Dr. Laxmi Ghimire. Together, we're talking about their recent study on the prevalence of congenital heart disease in twins and higher-order multiple births. Dr. Moon-Grady, is there any understanding of why this group of patients has such a high incidence of congenital heart disease?

Dr. Moon-Grady:
I suspect that the minor heart disease, that's ASDs, VSDs, and so forth, may have been picked up in these populations due to an increase in surveillance of both the pregnancies and the newborns; the higher-order multiples, especially, are more likely to be born prematurely, and we have a higher pickup rate for minor heart disease as well as major heart disease. But it is very important that the major heart disease is so much higher with twinning and multiple births. It's not a surprise to me, but because we have published single-center data, as have others, on serious congenital heart disease and identical twins who interestingly enough don't usually have the same heart problem, usually one twin is normal and the other has serious heart disease and this data suggests that since they do share common DNA that there must be other epigenetic factors controlling right/left patterning and flow-dynamic differences that help to shape the developing heart that may be different in twins, especially those who share a placenta. Our work in higher-order multiples that we've done here supports that these observations that we see in twins are also the case in triplets and, sort of, puts a general number to what the extent of the problem is, but I don't think that it answers the question at all. I do think the most surprising thing was actually the high rate in triplets; most triplet pregnancies are not identical triplets, but either they're all different genetically or at least one is different, so I would've expected a rate similar to that in twins, but that's not what we saw. Now, the conjoined twins is a little bit easier to explain in terms of the right/left patterning and the very late splitting of the early embryo.

Dr. Sorrentino:
Does prematurity play a role in this increased incidence of congenital heart disease or is this something from conception that leads to the problem, do you think?

Dr. Moon-Grady:
Well, we did our best to exclude Patent ductus arteriosus and PFO, and so, along those lines, we really took a great deal of care to only

have embryologic, true congenital heart disease and not disease that was the result of prematurity. As I said before and maybe it bears repeating that some of the increase in congenital heart disease over the 0.8% could be attributed to increase surveillance since these babies are premature, they're in an intensive care nursery, they're seeing doctors every day, there's a high level of suspicion, and so they may have more echo-cardiography or other diagnostic testing done than the general population, but it does not account for the serious heart disease that would really only be expected to increase the incidence of PDA, which we excluded and maybe small muscular VSDs, which were put into the minor heart disease group.

Dr. Sorrentino:
Dr. Ghimire, with your results showing this increased incidence in twins and triplets and others, what implications does that have for screening. Should we be doing more careful screening of our multiple birth moms?

Dr. Ghimire:
Absolutely. I think that will be the take-home message from this study. I think the managing team, specifically obstetrics and pediatric cardiology team should do a fetal echo to identify cardiac lesions in utero. And when the babies are born, they also need to be thoroughly examined, like they need to have clinical evaluation along with echocardiogram, if indicated in the post-natal period so that we can identify the congenital heart disease earlier because a number of studies have shown that early diagnosis improves outcomes in children with congenital heart disease. So, that would be my take-home message that they need to be carefully evaluating prenatal period and immediately they are born.

Dr. Sorrentino:
And Dr. Moon-Grady, I'll give you, a final word for our audience. Thinking about your study, what are future implications, future directions, and advice that we should be giving to our patients about these results?

Dr. Moon-Grady:
Well, I think that the information benefits both the patients and the practitioners. There's a little bit of a practice change necessary, here that would be in the prenatal counseling and care. These higher-order multiples should be counseled that the congenital heart disease risk is higher than it would be for just one baby and they should be referred in a timely manner for fetal echo. It also suggests the importance of evaluating the fetal heart prior to multi-fetal pregnancy reductions, which are often at least considered in higher-order multiples, very early in gestation and before we would usually look at the fetal heart in detail. So, we can look at the fetal heart at 12 to 14 weeks, and probably, based on this information, they should be looked at before any decisions are made about the pregnancy. There's still a lot we need to learn about congenital heart disease and so beyond just the immediate practice change and patient-facing information, this increased incidence in multiples should really be hypothesis-generating and I really look forward to seeing our science colleagues take this information and use it to further our understanding of heart disease and heart development. This is something that we don't see in animal models and it's just a wealth of information that could be gained from these twins, triplets, and other multiple births.

Dr. Sorrentino:
Well, based on our discussion today, it's clear there's still a lot to discover about congenital heart disease, especially in these more high-risk populations. I want to thank my guests, Dr. Moon-Grady and Dr. Ghimire for joining me to discuss their research that is helping to fill in some of these gaps. It was really great having both of you on the program today.

Dr. Moon-Grady:
Well, thank you for having us.

Dr. Ghimire:
Thank you.

Dr. Sorrentino:
I'm Dr. Matthew Sorrentino. To access this and other episodes in our series, visit ReachMD.com/programs/HeartMatters, where you can Be Part of the Knowledge, and thanks for listening.