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Understanding the Link Between Utero Diabetes & Heart Disease in Young Adults

Dr. Sorrentino:
Heart disease remains a leading cause of death in the United States, and while most of its victims are middle age or older, emerging research suggests that young adults and teenagers may also be at increased risk of heart disease. Could this threat begin even before they're born?
For ReachMD, this is Heart Matters, and I'm Dr. Matthew Sorrentino. Joining me today is Dr. Laetitia Guillemette, author of a recently published study in the Canadian Medical Association Journal that researched the relationship between exposure to diabetes in the womb and heart disease in young adults and teenagers. She also is a scientific reviewer for the Bureau of Cardiology, Allergy, and Neurological Sciences with Health Canada. Dr. Guillemette, welcome to Heart Matters.

Dr. Guillemette:
Thank you. I'm glad to be here.

Dr. Sorrentino:
To start us off, can you tell us how you became interested in researching the relationship between in utero diabetes exposure and the later development of heart disease?

Dr. Guillemette:
Of course, it started with my early research, which was done on gestational diabetes. And my research team at the time was interested in the impacts of gestational diabetes on the offspring, specifically on the offspring's metabolic parameters such as obesity and diabetes itself. And when I started my doctoral studies, which is where this paper came from, I was part of a team that was interested in cardiovascular outcomes. And that's where the link came from. Can gestational diabetes have an impact on the cardiovascular disease risk of the offspring, knowing diabetes and obesity themselves are cardiovascular risk factors.

Dr. Sorrentino:
So how did you design your study to look specifically at diabetes and determine that it may be a risk factor? And how does your study compare to previous studies that have tried to look at these factors?

Dr. Guilletmette:
Yes, in my studies, I took all of the birth that happened in the Province of Manitoba during a specified time frame, which was limited by the actual data that was in the repository. To follow up all of the offspring and follow up these individuals through the registry, and basically through their contacts with the health care system in the Province over the time frame to look at how and when they developed cardiovascular risk factors and cardiovascular diseases. In my definition of the exposure of diabetes, we decided to try to separate gestational diabetes, which is the form of diabetes that develops during pregnancy, after or during the second trimester, and naturally resorbs after delivery. We separated that from pre-existing type 2 diabetes, which, as the name says, is the type of diabetes that develops before pregnancy and unfortunately does not resolve after delivery. We excluded as much as we could all of the type 1 diabetes or other forms of diabetes that were not gestational or type 2. Because we were really interested in the metabolic effect of the intrauterine environment on the risk of cardiovascular disease in the offspring, we wanted to limit the confounding by genetic contributors to diabetes or cardiovascular disease. This study design was different from other studies that were done previously, specifically because many research on intrauterine exposure and long-term impacts in the offspring are typically limited by the duration of follow-up, because it's very rare to be able to link offspring with their intrauterine exposure and follow them up long enough with data of high quality to be able to assess their cardiovascular risk with reduced confounding being able to adjust for the confounding.

Dr. Sorrentino:
So in your cohort, about how many births were you able to collect and what percentage of those births had gestational or type 2 diabetes?

Dr. Guillemette:
We were able to collect a little less than 300,000 births that were considered valid records and that we could follow up throughout our entire time frame. So about 290,000 births, and most of them were not exposed to any type of diabetes, which is, as we would expect considering that the incidence of diabetes in pregnancy is about 10 percent. So, it's the same in Canada as in the U.S. so we had about 95 percent of the offspring who were not exposed to any sort of diabetes.

Dr. Sorrentino:
And then how long did you follow these children after the initial birth to see if there was the development of cardiovascular risk factors or cardiovascular disease?

Dr. Guillemette:
Our registry started in 1979 and we started the study in 2015. So we had access to 35 years of follow-up in the registry, and we tried to make the most of it. Unfortunately, there was a higher incidence of diabetes during the study. So most of our numbers come from later during the time frame, which means that we were not able to follow these offspring for as long of a period of time. And so that led to our average age at follow-up of being around 20 years old, which is not an age at which we would expect to see a lot of cardiovascular disease.

Dr. Sorrentino:
What were some of the other challenges of your study? Did you find that many of the children in the births were not well documented, or how well-documented were the records that you were able to be fairly certain if diabetes was present or not present?

Dr. Guillemette:
Excellent question. The assessment of diabetes was one of the main challenges, as well as the assessment of the outcomes. And that's what took the most time in setting up the study. The definition of gestational diabetes changed throughout time between 1979 and 20005, which was the cutoff for the eligibility for birth to be eligible for the cohort. We decided to not go with diagnoses codes for diabetes and gestational diabetes or at least not only rely on the codes, but we tried to establish the date of the diagnosis, and that's diabetes in the mother that I'm discussing here. The date of the diagnosis of the diabetes, irrespective of the type of diabetes, as long as it was like I mentioned, gestational or type 2 diabetes. And in relationship to the date of the pregnancy. And we as well confirmed the lack of diabetes diagnosis after delivery to ensure that it was not let's say, an undiagnosed type 2 diabetes that had been first diagnosed during the pregnancy but then did not resorb after delivery. So we did try to manually determine the diabetes exposure according to the dates and the diagnoses codes. And same thing for the outcomes. We triangulated the diagnoses based on drug prescription physician billing codes, so physician diagnoses as well as hospitalizations to try to confirm that what we saw were actual diagnoses and not simply screening or investigations that did not actually end up in an actual disease or risk factor in the offspring. So doing all of that helped us ascertain, as much as possible, the endpoints and the outcomes that we measured in this study without having to meet the actual participants to the study in person and take the actual measures.

Dr. Sorrentino:
For those just tuning in, this is Heart Matters on ReachMD. I'm Dr. Matthew Sorrentino. And today I'm speaking with Dr. Laetitia Guillemette about her study exploring the connection between diabetes exposure in the womb and the subsequent development of heart disease and heart disease risk factors at a young age. So let's jump right into the results of your study. What were your overall findings? Did gestational diabetes or having diabetes during pregnancy increase the risk of heart disease at a younger age?

Dr. Guillemette:
In fact, yes, we did find that not only being exposed to any sort of diabetes in utero led to a higher cardiovascular risk and a higher incidence of cardiovascular endpoints or so-called hard outcomes, but also there was a difference between exposure to gestational diabetes and pre-existing type 2 diabetes. And this was very interesting because it supported our hypothesis. It's really the intrauterine environment that influences the risk of cardiovascular disease later in life, as soon as 35 years of age. So those two findings were really interesting and also they were novel in the sense that it had not been determined prior to that that gestational diabetes or type 2 diabetes could have such a significant impact on the offspring's risk for cardiovascular disease early in life.

Dr. Sorrentino:
So looking at the results of your study, how much of the increased cardiovascular risk in the young adults can be attributed to the young adults developing diabetes themselves? Or is the development of cardiovascular disease and risk factors that is independent of the patient developing diabetes, but just due to the exposure of diabetes in utero?

Dr. Guillemette:
Yes, excellent question. In fact, we did include type 2 diabetes as part of the endpoints of interest of the study, meaning that as soon as an offspring could develop diabetes themselves, this counted as their endpoint, and then they could not be eligible to develop any other cardiovascular outcome as part of the study. This also means that any endpoint that we do see in the study was therefore independent, or so that happened in offspring who did not have diabetes at that point in time. We were also interested in the impact of the offspring having diabetes on the strength of our overall results. So we did conduct sensitivity analyses where we excluded any offspring who develop type 2 diabetes themselves, and re-ran the analyses so that we could confirm that diabetes in the offspring did not drive our results. And we did confirm that even by excluding all these offspring, we saw at the same trend and the same effect signs. I should probably mention as well that we excluded offspring who developed type 1 diabetes over the course of the study, since the link between people having type 1 diabetes and then developing cardiovascular risk and cardiovascular disease is already established. And we did not want that to confound our results either.

Dr. Sorrentino:
I wonder if you can speculate a little bit on the implications of your study. I'm sure in Canada as in the United States, we're seeing a surge of patients having diabetes with the obesity epidemic. Do you think your study is telling us that we're going to be seeing cardiovascular disease in younger and younger patients at larger and larger numbers?

Dr. Guillemette:
That is a possibility. By conducting this research, I had two goals in mind, and my results, I believe, do support these goals. The first one is the concept that going upstream can hopefully help us have long-term impacts, meaning that in this case, seeing that early exposure to gestational or type 2 diabetes can increase the incidence in cardiovascular risk. Hopefully we can prevent this by creating a healthier intrauterine environment for our next generation. So by treating earlier in life, hopefully we can prevent this rise. A second goal I had was looking at the big picture. One of the main tenants of cardiovascular, treatments is looking at the individual response, meaning somebody has a cardiovascular risk, so we're going to treat that individual. This person needs to do exercise, eat better, stop smoking. What my research is saying is that it seems that cardiovascular risk is much broader than the individual. The risk can come from things that the individual has no or very little control over. So I believe that as a society, we should look broader as well and try to create healthier environments for everyone because then that would increase our health care capacity by reducing the risk for everyone. Diabetes is fairly common and so is cardiovascular disease. I think by tackling them we would be in a good spot to help our health care systems.

Dr. Sorrentino:
Well, I think your important study has told us another cardiovascular risk factor for our patients that we certainly should be aware of. And with those important thoughts in mind, I want to thank Dr. Laetitia Guillemette for sharing her study with us and providing new insights on in utero diabetes exposure and the early development of risk for heart disease. It was great speaking with you today, Dr. Guillemette.

Dr. Guillemette:
Thank you for having me.

Dr. Sorrentino:
For ReachMD, I'm Dr. Matthew Sorrentino. To access this episode and others from Heart Matters, visit ReachMD.com/HeartMatters, where you can Be Part of the Knowledge. Thank you for listening.