**Episode 62: Diabetes in Pregnancy – Part 1**

By Dr. Joe Chappelle

Hello everyone, and welcome back. I’m Joe Chappelle and you’re listening to Episode 62 of the OB/GYN Podcast. Today I am finally getting the first episode on diabetes in pregnancy out to you. This one has been percolating since last December, but some things kept getting in the way of finishing it. You know, like children. As usual, what I thought would be a one-and-done episode has transformed into a three-part beast. And part of what delayed me recently was figuring out where to trifurcate that content. What I finally landed on was one episode on the history of diabetes in pregnancy and the risks that it poses to mother and baby, a second episode on the management of preexisting diabetes in pregnancy and the third on gestational diabetes. So, today we’ll tackle the first part.

As always, if you have comments, corrections, etcetera, then please contact me at [feedback@obgyn.fm](mailto:feedback@obgyn.fm). I love to hear from you. Also, recently, I’ve had a few people ask if they can do an episode, and the answer is always yes. I love guiding people through the process of researching, writing and creating a great topic episode. So, if you have a topic you’d love to hear about, well, then maybe you should be the one to make it. And if that seems like something that’s interesting to you, then drop me a line on the same email and we can get started. Anyone can do it –students, midwives, residents, attendings– it doesn’t matter. The show’s always been about bringing together people with different viewpoints and I really want to expand on this more.

The second thing I want to talk about today is sponsorship. As regular listeners know, I’ve been trying to bring in a little money to help support the show. Most of the cost of the show is really just my time, but it does cost something to keep it going as well. I’ve been reluctant to do advertising, and especially medical advertising, like a lot of podcasts do, because I don’t want any bias to creep into the show. This is a show about academic obstetrics and gynecology, and any time big business gets involved, there’s a potential for compromise. So, I’m not going to be doing any advertising right now. What I am going to announce today is the sponsorship from CooperSurgical. They decided to sponsor the podcast because they really believe in what we’re doing here –academic medicine. The letter of the contract explicitly states that I am not allowed to mention any of their products or services, so I only say that they make things that I use on a regular basis and I love, and that everyone I interacted with there really seems to care about helping us provide great care to women. So, with that I will say thank you to CooperSurgical for sponsoring the show.

All right. Well, let’s get started with today’s episode, and that’s Episode 62: Diabetes in Pregnancy – Part 1.

Diabetes has been documented since at least the 1st century. It was always described as a syndrome with polyurea and wasting. Later, others learned that the urine was sweet. These two facets would give rise to our naming of the disease. *Diabetes*, meaning “siphon” or “passing through” for the polyurea. And *mellitus*, meaning “honey,” for the sweet urine. Most or all these cases were likely caused by type 1 diabetes, which has a very severe presentation. Additionally, type 2 diabetes, as we’ll discuss, is usually reserved for those lucky enough to have access to abundant food, which is not something that most people had throughout human history. Today, type 1 diabetes, caused by autoimmune mediated destruction of beta-cells in the pancreas, occurs most frequently between ages 10 and 14. Unlike type 2 diabetes, there’s no reason to think that type 1 diabetes behaved any differently throughout history. And it was known from early Greek times to be a death sentence. A 1st century Greek physician, Aretaeus of Cappadocia, described it as such: “life with diabetes is short, disgusting and painful.”

After the collapse of the Roman Empire, the epicenter of medical learning shifted to the Arab world, and the 10th century Avicenna of Persia, was one of the first who documented the sweet taste of diabetic urine. He was also the first to document a real treatment, which included lupine, fenugreek and zedoary seeds, which are still used today as a way to decrease blood sugar in some parts of the world.

By 1776, Matthew Dobson had confirmed that it was the sugar of glucose that was found in urine and he argued that the disease didn’t originate in the kidney as most thought at the time. In any case, sweet urine, or later chemical tests to detect glucose, was the only diagnostic method and the two went hand in hand. By the 1800s, Western doctors began to recommend specific diets for those with diabetes, some of which were good –like eating more meats and fats– and some of which were bad –like eating more sugar. But how does all tie into obstetrics? Like I said, type 1 diabetes hits in the early reproductive years, especially in older times, because menarche happened later. With the rapid progression of the disease, few, if any of these women would make it to pregnancy.

As we became better nourished as a species, and some small amount of knowledge about diabetes was accumulated, two things occurred. One, is that women with type 1 diabetes lived long enough to get pregnant and people accumulated enough fat to start suffering from type 2 diabetes. As opposed to type 1 diabetes, type 2 is caused by unmasking of a preexisting genetic disposition by diet and lifestyle changes. This insulin resistance seems to have a competitive benefit in the low resource settings that we evolved in. But when we suddenly had access to greater numbers of calories on a daily basis, it came back to bite us. The massive urbanization of the 19th century led to less physically strenuous activity, increased wealth and a rise in access to food. All these factors led to the reversal of fortune for those with this genetic predisposition and led to how and why diabetes began to be noticed and discussed in obstetrics.

In 1882, Dr. J. Matthews Duncan, presented a paper to the London OB Society in which he described his experience with 16 women whose pregnancies were complicated by diabetes. Four died in “a coma or collapse within a few days of delivery.” Seven died from diabetes or tuberculosis within two years. And half of the children died. He argued that glycosuria was an important warning sign in pregnancy and should be treated seriously. Remember that in non-pregnant women the presence of glucose in the urine was pathognomonic for diabetes. Well, suffice it to say that not everyone in the OB world agreed. As prominent obstetricians started to test more women for glucose, they found that a lot of women had it at some point during the pregnancy, and that it most cases it didn’t seem to be associated with poor outcomes.

Dr. Williams, from Johns Hopkins and *Williams Obstetrics,* published a paper in 1909 describing his experience in review of 3,000 pregnancies from his hospital. Before we get into his findings, it important to understand the limitations of the day. Using the standard sugar reduction test of the time, one could only tell if there was sugar in the urine, not which sugar it was. This is important because other studies had already demonstrated that breastfeeding women and women in the last few weeks of pregnancy could spill lactose from breast milk into the urine, especially if they were engorged. Williams knew this, but his data did not contain this information. He was forced to assume that any sugar found in the urine close to term was in fact lactose and not glucose. He found a 5% rate of positive urine sugar reduction, with most occurring in the postpartum period, and only 24 cases during the pregnancy. After reviewing these 24 cases, he felt that only 2 represented diabetes. To be clear, he was not stating that diabetes was not concerning in pregnancy, but rather the presence of sugar in the urine alone did not mean that a woman had diabetes.

By the time he wrote the paper, a test was available to determine which sugar was present in the urine, and he concluded that when sugar is detected in the maternal urine, that one should determine whether it is glucose or lactose. If it is lactose, then it should be dismissed, and if it is glucose, then we are left with a conundrum. Because benign glycosuria and diabetes are hard to differentiate if glycosuria is the only finding. He does state that if a woman is known to have glucose in the urine prior to pregnancy, then it is definitely diabetes. If it is only recognized during pregnancy, then a diagnosis should be made if the glucose in the urine is present, enlarged or if she had other characteristic signs of diabetes.

Once a real diagnosis of diabetes was made, Williams knew from his own literature reviews that the prognosis could be just as bad as Duncan had described 20 years prior. He found in the 66 cases he studied that there was a 27% maternal mortality during or after delivery, and an additional 23% in the next two years. He found that most did well for the 7 to 8 months of the pregnancy and then rapidly deteriorated. This makes sense given the protodiabetic hormones that peak around this time of the pregnancy, and we’ll delve more into that later. He also found that many of the women who died became comatose, in what was probably diabetic ketoacidosis and, furthermore, that most of these women died. Additionally, the babies of these women were more likely to be large, have polyhydramnios and die in utero.

Unfortunately for the women of this time, there were few treatments available even if an accurate diagnosis could be made. He recommended that once the diagnosis was made, that women can be screened for symptoms and ketones in the urine. And that if either developed, that the pregnancy should be ended by either induction or termination depending on the gestational age. He then wraps up his paper with seven conclusions which may sound familiar. One, having sugar in the urine does not mean that women have diabetes. Two, lactose as a source should be excluded. Three, even if glycosuria is proven, it again does not mean that they have diabetes. Four, if a significant glycosuria occurs late in pregnancy it is not likely to cause significant harm to mother. Five, if it occurs early in pregnancy, we should be worried. Six, diabetes may be preexisting or developed during pregnancy. And seven, delivery or termination is indicated for severe disease. I think these findings hold up pretty well, even today. And I think they’re remarkable for having so little knowledge of the underlying etiology of diabetes.

By 1915, it was well-known that diabetes occurring before pregnancy was far more severe than it was if it started during gestation. Dr. Elliott Joslin of Harvard Medical School published a case series of women with diabetes in pregnancy in that same year –in 1915– and he advocated an approach of management that involved strict carbohydrate restriction and close monitoring of urine sugar, ketones and ammonia. By carefully adjusting the diet according to the urine findings, he found that he could keep the sugar to a minimum without raising the urine ketones. To give you an idea of the diet he proposed, here was the daily diet he gave to women under his care. Breakfast: bacon, two eggs, one orange, 30 g. of bread, 15 g. of oatmeal and 120 cc’s of milk. Lunch: 90 g. roast beef, carrots and peas, 120 cc’s of milk, 15 g. of nuts, one apple. Dinner: one egg, asparagus, 15 g. of oatmeal, 120 cc’s of milk, 15 g. of toast, half an orange and 60 g. of potatoes. That doesn’t sound too dissimilar to our modern diabetic diet, does it? With this diet and close monitoring, he was able to show good outcomes in women who developed glycosuria during pregnancy. Women with preexisting diabetes continued to do poorly overall, and even there, he was able to show better outcomes than had been reported before. This was great, but the world of diabetes was about to be rocked by the discovery of insulin.

That story starts in 1880, when Joseph von Mering and Oskar Minkowski discovered that by removing the pancreas in dogs, they could induce a diabetic state. Working off this, Dr. Eugene Opie narrowed down the area of interest to the Islets of Langerhans. And in 1910, Dr. Edward Albert Sharpey-Schafer suggested that there was only one chemical that was missing. He called it “insulin” from the Latin word *insula* meaning island for islets. Between 1911 and 1916 at least three independent labs made progress of extraction pancreatic material and injecting it into diabetic dogs with some success. In one case the lab was shut down by the university because it didn’t see the value in the work. In the other two, World War I interrupted the work and probably delayed our discovery of insulin by at least a decade.

After the war, Canadian surgeon Frederick Banting, hypothesized that the reason for the earlier failures was the pancreatic tissue surrounding the islets was producing enzymes that were destroying the insulin and making the extracts less potent. With some practice, he was able to tie off some of the pancreatic arteries and induce atrophy of the pancreas while leaving the islets intact. This is where his knowledge ended, and so he teamed up with the professor of physiology at the University of Toronto named J.J.R. Mcleod, who recruited two lab assistants for him. As a fun aside, Banting decided he didn’t need two, he really only needed one. And so, the two assistants flipped a coin to see who would stay on. Well, it ended up being a very faithful coin toss, because one would end up sharing the Nobel Prize and the other not. In any case, they worked fast, and within a year had produced an extract they called “insletin” and proved that it could reduce glycosuria.

This was a long and arduous work with dogs, though. Because each dog would need surgery to decrease blood flow to the pancreas to produce the atrophy we talked about. And then a second surgery to remove the pancreas before any extraction could take place. This took too long, and so Banting decided to use fetal calf pancreases instead, because they don’t develop the pancreatic enzymes until later in embryogenesis. This saved several steps and allowed them to decrease production times. With this new insletin, they began human trials in 1922, with a 14-year-old –presumably a type 1 diabetic– at Toronto General Hospital who was dying of his disease. The first dose was extremely impure, and he had a severe allergic reaction. Banting and his assistants spent two weeks purifying the sample and the second injection went off without a hitch. He would go on to live another 13 years before dying of pneumonia. This was a major breakthrough, because even in the 1920s, type 1 diabetes was still a death sentence.

I want to tell you about one more patient because I think it highlights how significant this discovery was. The second patient to get this insulin was Elizabeth Hughes, the daughter of the New York State governor at the time. She had been diagnosed with type 1 diabetes at age 11 in 1919. The only treatment at that time was to place them on a severe calorie-restricted diet of 800 calories per day to avoid hyperglycemia. When she was diagnosed, she was 4′11″ and weighed 75 lbs. By 1922, when she began treatment, she weighed just 45 lbs. She was put on a 2,200-calorie diet with her insulin injections and made a rapid recovery. She would go on to graduate college, get married, have three children, found the Supreme Court Historical Society and then finally die at the age of 73. In one year of work, Dr. Banting and his associates had managed to take a diagnosis that was universally lethal and turn it into a chronic disease. There are probably only a handful of times that can be said in the history of medicine, and so I hope you don’t mind me taking a few minutes to highlight it.

This amazing discovery of course had many knock-on effects. The most obvious is that we suddenly had people with diabetes living long enough and healthy enough to get pregnant. The rare cases that Dr. Williams had discussed in 1909 were about to get much more common, and the OB society was going to have to figure out how to manage these pregnancies. In one case series published by Dr. Titus in 1935, there were 43 cases of pregnancies complicated by diabetes, and of those, there were 9 fetal mortalities and no maternal deaths. This is in stark contrast to Dr. Williams’ experience where 50% of the mothers died. Dr. Titus recognized that there was a wide range of presentation of these women, but he did not have a way to categorize them yet. That would take another brilliant doctor from Boston and a colleague of Dr. Joslin who wrote that 1915 paper that we talked about.

Dr. Priscilla White started working with Joslin in 1924, two years after insulin became available, and she started to run into the Elizabeth Hughes of the world. Dr. White noted in a 1978 paper that between 1898 and 1917, Joslin had only seen 10 pregnancies and about 600 women with diabetes. Between 1924 and 1938, the clinic saw 128 live born infants. However, the survival rate was only 54%. Dr. White began to recognize that the severity and length of the diabetes predicted the pregnancy outcomes. She presented her findings at an OB meeting and was surprised that many of the other speakers were presenting data that contradicted hers. How could they be saying that diabetes in pregnancy was not concerning when she had all this evidence that it was resulting in stillbirth and neonatal death?

Upon reflection, she realized that the specialty clinic in which she worked was attracting women who were life-long diabetics, whereas most OBs were likely seeing only women who Dr. Williams had described earlier, the ones who developed diabetes later in pregnancy. So White stepped back and started to categorize these women by the severity of their disease. Throughout the ’40s, she developed a system and reported it in February 1953 in the second issue of the Green Journal that was ever published. In this paper, she outlined her classification scheme and reported on a series of patients that were managed based on it. Her classification took into consideration the age of onset, duration of disease and vasculo-renal complication.

Class A was for women who tested positive for diabetes but are euglycemic with diet alone. All the other classes require insulin therapy. B for women diagnosed after 20 years of age with less than 10 years of duration and no vascular disease. C for diagnosis between age 10 and age 19 or duration 10 to 19 years and no vascular disease. D for onset under 10 years or duration greater than 20 years with calcification in leg or retinitis. E for patients with calcified pelvic vessels and F for those with nephritis. This grading reflected the progressive nature of the hyperglycemic effects on the vascular system. The worst the vascular system, the worst the pregnancy outcomes. Later, R would be added for proliferative retinopathy, RF for both retinopathy and nephropathy, H for cardiac disease, and T for history of renal transplant. In White’s case series they found that the highest rates of morbidity and mortality followed these categories. While the overall neonatal survival rate was 86%, those in the F category had only 3% survival rate.

Reading the paper, you can see the major strides that had been made in the care of diabetic pregnancies, from the use of caesarean delivery in 70% of the women to the amnioreduction in those with polyhydramnios. In fact, in one case, they removed 3.5 liters of amniotic fluid. That’s a lot of fluid. To the management of prematurity related respiratory distress. To the recognition and management of neonatal hypoglycemia. In less than 40 years, we had gone from 50% maternal mortality to 0% maternal mortality, and only 10% neonatal mortality. A lot of the neonatal mortality is really attributable to great strides the neonatal care took during this time, but it is still a really remarkable amount of progress in a short time.

But let’s step back and look at what the underlying causes were for those high rates for maternal and neonatal mortality, because I think they will help us understand how and why we treat hyperglycemia today. The first contributor is one that was familiar to Dr. White –vascular disease. Women with longstanding hyperglycemia, with either type 1 or type 2 diabetes have microvascular changes. When they get pregnant, this starts right away when the trophoblasts invade the spiral arterials in the uterus. Hyperglycemia causes reactive oxygen species which damage placental tissue and arteries and can lead to shallow penetration of the trophoblast and reduce uteroplacental flow. This, in turn, can lead to early pregnancy loss, fetal growth restriction, preeclampsia and stillbirth. Some studies also suggested that these reactive oxygen species could be the cause of congenital malformations. These malformations, by the way, include spina bifida, anencephaly, cardiac abnormalities, anal atresia and renal anomalies. These all occur two to five times as often in women with preexisting diabetes. In addition, women with severe hyperglycemia in the first trimester are at severe risk of the fetus having situs inversus and caudal regression. Even in women with good control, the rate of malformations is higher than in the general population. However, women with poor control are twice as likely to have a malformation than women with good control.

Next up is hyperglycemia. Maternal glucose is transported across the placenta by facilitated diffusion. This is completely dependent on maternal glucose levels, which means, as maternal glucose levels rise, so do the fetal levels. This leads to a rise in fetal insulin levels. High insulin and glucose levels lead to excessive adipose deposition. This fat increases fetal oxygen demand, which as the fetus grows, can outstrip the maternal supply, leading to fetal hypoxia and acidosis. Prolonged hypoxia and acidosis lead to increase in vascular and epithelial growth factors and fibroblast growth factors. These cause hypervascularization in the placenta and increase the maternal-fetal exchange surface in an attempt to improve oxygen transfer. Nitrous oxide, a vasodilator, is also increased, which can inhibit the maturation of all these expanded blood vessels. Immature placental vessels cannot handle the rapidly growing fetus and eventually the fetus will outstrip even these adaptations, which can lead to stillbirth. Another cause of stillbirth –albeit one that is poorly understood– is hypoglycemia. Autopsies of these fetuses often show enlarged cardiac ventricles caused by increased glycogen deposition. But the exact mechanism here in unknown.

The last thing to talk about is neonatal mortality and morbidity. The most important contributor to neonatal mortality is prematurity. This explains the abysmal rates of neonatal survival in the ‘40s and ‘50s because our treatment options for pulmonary hyperplasia were non-existent. Even despite our modern advancements, these babies are still at increased risk and can cause significant morbidity. Part of this is because hyperinsulinemia inhibits the maturation of type 2 pneumocytes by reducing circulating glucocorticoids, which leads to a decrease in surfactant production. This means that even full-term neonates are still at risk for RDS in mothers that have diabetes.

Babies born to mothers with hyperglycemia get used to those high levels of glucose, and they compensate by producing large amounts of insulin. After delivery, when this exogenous glucose from the mother is cut off, this excess insulin can drop the blood glucose to dangerous levels. Extreme hypoglycemia can lead to brain injury. Even less extreme hypoglycemia can be associated with decreased IQ and therefore most neonatologists advocate for aggressive management. All neonates have a drop in their blood sugar after birth with occurring after about two hours. In normal neonates, it should not drop below 40 mg/dL. The blood sugar stabilizes by six hours and then rises over the next few days. This process is very dependent on when the first feed takes place. If the first feed is delayed three to six hours after delivery, then most neonates will not be able to maintain a level of 30 mg/dL. For these reasons, most neonatologists recommend aggressive treatment in babies at risk for hypoglycemia. This requires frequent heel sticks for blood glucose levels and supplementation with formula if the mother cannot or does not want to breastfeed.

The last things that these babies are at risk birth is birth related trauma. These babies are usually larger than their non-diabetic peers, and also have an abnormal fat deposition in the chest and shoulders. Macrosomic babies are especially at risk, with one third of all macrosomic babies born to diabetic women experiencing a shoulder dystocia. But even in non-macrosomic babies, there is an increased risk. So, a “normal-sized” fetus should not make us feel any better. Lastly, babies born to diabetic mothers are at risk for worse outcomes during a shoulder dystocia, with a higher percentage having broken bones and brachial plexus injuries.

Now that we have described what can go wrong, how do we prevent it? The first thing is obvious. The lower we keep the blood sugar, the better the outcome. In the next episode, we will talk about how we keep that blood sugar low. We’ll discuss why there are so many types of insulin and when to use them. And then we’ll go over the antenatal fetal monitoring and how and when to deliver women with type 1 and type 2 diabetes. I hope you enjoyed this first episode, and until next time, thanks for listening.