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The Future of Type 1 Diabetes Mellitus and Pregnancy

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For many women, conceiving and birthing a child is the ultimate dream – the culmination of womanhood. For others, however, it is an uphill battle wrought with both physical and emotional struggle. The latter is more likely to be true for women with type 1 diabetes mellitus. Type 1 diabetes (also known as juvenile or insulin-dependent diabetes) is an autoimmune disease in which the body's white blood cells attack the beta islet cells of the pancreas, resulting in an absolute insulin deficiency (Wisse, 2015). The autoimmune destruction is what differentiates type 1 from type 2. In type 2 diabetes, the body has grown resistant to insulin, but the condition can reversed with diet and exercise; in type 1, there is no reversal. There is no cure.

How does this disease obstruct the prospect of pregnancy? Research over the past century has demonstrated that women with type 1 diabetes experience dramatically higher rates of complications of pregnancy and labor. The mother's high levels of glucose cross the placenta, causing the fetus to grow much larger than is safe. Fetuses of diabetic mothers are far more likely to die in utero or to have major congenital anomalies. If the baby survives to term, he or she is likely to have hypoglycemia, respiratory distress syndrome (RDS), polycythemia, and/or dangerous electrolyte imbalances (Potter, 2016). On the maternal end, diabetic women have an increased risk for preeclampsia and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, lacerations associated with shoulder dystocias, imbalanced glycemic control, and worsening of diabetic complications such as retinopathy and renal disease (Moore, 2014). In the past, pregnancy was considered a contraindication with diabetes, for reasons that are easy to see. However, in the past few decades, diabetic women have been successfully giving birth with significantly decreased rates of complications. To determine the specific impact of medical technology and the advancement of diabetes care in pregnancy, three areas can be examined: 1)

the time frame in which pregnancy become safe for type 1 diabetics, 2) the technological innovations that facilitated this change, and 3) the future of technology in diabetic pregnancies.

The first documentation of diabetes was in Egypt, circa 2,000 B.C. However, it was the Greeks who first gave it the name diabetes mellitus – diabetes meaning "siphon" (referring to the fact that hyperglycemia causes frequent urination) and mellitus meaning "honey." The physician would diagnosis the disease by tasting the person's urine. Because of the body's attempt to excrete the excessive glucose in the urine, it would taste sweet ("Diabetes Mellitus History – From Ancient to Modern Times," 2015).

It wasn't until the beginning of the 20th century that any real progress was made in the treatment of diabetes mellitus. Up until that point, diabetes was essentially a death sentence. Parents would watch their children slowly waste away to a miserable death. Pregnancy wasn't an issue because either the young women wouldn't live long enough to reach sexual maturity, or if they did, their bodies were too weak for normal ovulation. They were considered to be sterile.

The first major discovery regarding diabetes occurred in 1909 when Sir Edward Albert Sharpey-Shafer discovered the insulin hormone while studying the pancreas. In 1921, Frederick Banting, MD, and Charles Best, MD, took the discovery a step further by extracting the insulin from dogs. They then injected the hormone into a dog whose pancreas had been removed, and they noted that the dog's blood glucose levels decreased. This was arguably the most important revelation in the history of diabetes. Two years later, insulin was purified and readily available for use in humans. Another vital advancement in the treatment of diabetes occurred in the 1950s, at which time testing methods for blood and urine glucose were made to be more user-friendly and accessible to all. The real innovation was the urine dipstick, which was a simple and

inexpensive means by which individuals could test their own glucose ("History of Diabetes," 2014).

The 1970s were also important years in the development of diabetes treatment. They saw the advent of the first glucose meter, insulin pump, and continuous glucose monitoring. All three of these innovations would continue to improve in accuracy and portability in the years to come. Also in the decade, the bacteria *E. coli* was genetically modified to produce human insulin, driving down the costs of insulin and allowing more efficient production. In the 1980s, 1990s, and 2000s, medical technology related to insulin delivery grew more diverse and mainstream. Time-released insulins were produced, pumps became smaller, continuous glucose monitoring became more precise, and glucose meters become more interactive ("Innovation Milestones," 2016). With each new innovation in medical technology, glucose control became a more accessible outcome to those with diabetes, which had a direct result in the outcomes of diabetic pregnancies.

Dr. Frederick Taylor was among the first physicians to document the outcomes of diabetic pregnancies. In his 1899 publication, he described twenty-two pregnancies in fifteen women with diabetes. His sample size was small by modern standards, but it is important to note that, as previously mentioned, pregnancy in diabetic women was then considered to be a rarity. The outcomes of Dr. Taylor's pregnant women were bleak. There were seven intrauterine fetal deaths, four maternal deaths in labor, and two additional infant deaths within twenty-four hours of birth. Thus, in this group of women, there was a 47% occurrence of infant death and a 27% chance of maternal death (Taylor, 1899).

Jumping ahead nearly fifty years, beyond the discovery of insulin and glucose testing, two women in the field published their own literature on the subject. Mary Petkauskos, RN, and

Priscilla White, MD, found that 33% of diabetic pregnancies ended in spontaneous abortion and another 30% were either stillborn or passed away before reaching twenty-four hours of age. These infants tended to be overdeveloped, toxemic, or had congenital abnormalities (Petkauskos & White, 1948). Although these rates were significantly improved from the documented cases of Dr. Taylor, they were still not favorable. However, as technology continued to become more advanced, the success rates of pregnancies progressed in step. There were also more instances of pregnancy in women with type 1 diabetes because of the increased survival rates of the disease in general.

In 1984, a new study including 232 pregnant women with diabetes resulted in zero maternal deaths. There were thirteen intrauterine fetal deaths (5.6%), thirteen major congenital malformations (5.6%), and a 60% Caesarean delivery rate (Plehwe, Shearman, & Turtle, 1984). Then, in 1996, 75 years after the discovery of insulin, the rates of successful pregnancies reached an all-time high. In a sample size of 175 diabetic women, there were no maternal deaths and only four infant deaths (2.3%). The rate of Caesarean delivery was 16.6%. The primary complication among the newborn infants was hypoglycemia, which occurred in 39.8% of the neonates. Other characteristics of the infants were not commented upon (Penza, Banaczek, & Szatane, 1996).

Though it is difficult to compare these studies side by side due to the inconsistencies in which outcomes were included, methods of data analysis, and different sample sizes, it is clear that the progress in medical technology had a significant benefit on the ability of women with type 1 diabetes to bear and deliver healthy infants. Based on the timeline of technology and the outcomes of pregnancy over the years, the original question regarding the time frame in which pregnancy became safe for diabetic women doesn’t have one simple answer. It could have been the discovery and production of insulin in 1921. It could have been the invention of urine

glucose testing in 1953 or the glucose meter in 1970. It could have been the research in 1993 that demonstrated how normoglycemia slows the progression of diabetic complications. The best answer, however, is probably all of the above. Medical technology is always a work in progress, always seeking to find more efficient and effective ways to cure or treat disease. In the case of diabetes, the discovery of the hormone for treatment, the means of testing for individual improvement, and the knowledge that tight glucose control results in more positive outcomes were all necessary to reach where we are today. If any pieces were missing, the treatment process of diabetes would not be whole. Furthermore, the increasingly positive outcomes of pregnancy would likely not have occurred, for is it clear that the glucose control of the mother has a direct influence on the pregnancy.

The modern-day diabetic pregnancy is still not without its risks. According to a study in 2012, women with type 1 diabetes have a 15% risk of spontaneous abortion (approximately double that of a non-diabetic pregnancy), which has been shown to be even higher for women with less than ideal blood sugar control. The perinatal mortality rate is demonstrated to be 3.3%, which is much higher than the non-diabetic rate of 0.9%. There is also a 13% preterm delivery rate, and the newborns have a 2.2% rate of congenital anomalies. In addition, approximately 29% of infants have macrosomia (Al-Agha, Firth, Byrne, Murray, Daly, Foley, Smith, & Kinsley, 2012).

Currently, the blood glucose goal for non-pregnant diabetics set by the American Diabetes Association is to have a hemoglobin A1C of 7% or below. Hemoglobin A1C is a method of testing one's glucose range over a period of about three months. An A1C of 7% correlates approximately with an average blood sugar of 154 mg/dl. During pregnancy, the recommended A1C is 6% (Barss & Repke, 2015). Is this sufficient glycemic control to prevent

maternal and fetal complications? According to a study recently completed in 2015, the answer is no. It was found that A1C levels of 6.0-6.4% still correlate with an increased risk for infants who are LGA, or large for gestational age (Maresh, Holmes, Patterson, Young, Pearson, Walker, & McCance, 2015). Nevertheless, episodes of hypoglycemia during pregnancy can also be precarious, so a significantly lower A1C is not necessarily a good thing. In short, glucose control during pregnancy is a dangerous game of tug-of-war.

The American College of Obstetricians and Gynecologists (ACOG) has published other, more specific recommendations for diabetic pregnancies. It states that a woman's fasting glucose should be less than or equal to 95 mg/dl, postprandial glucose should be less than or equal to 140 mg/dl, and glucose levels during the night should not drop below 60 mg/dl . These recommendations were designed to address the problem of glucose tug-of-war – to reach a level of glycemic control that is safest for both mother and baby.

Glycemic control during pregnancy is no easy feat. It is more complex than typical diabetic treatment. Management involves dietary planning, exercise, and an insulin regimen that is constantly evolving. Inulin needs change throughout pregnancy due to rising levels of hormones. In the first trimester, insulin needs may decrease because of the body's hypermetabolic state. In the second trimester, insulin requirements start to rise, and they rise even further in the third trimester. For this reason, frequent glucose monitoring and A1C testing is imperative. It is also important for the woman to have frequent prenatal care and ultrasounds and to continue having regular eye exams, blood pressure monitoring, and kidney function tests to determine if diabetic complications are progressing (Barss & Repke, 2015).

Having type 1 diabetes and attempting a pregnancy clearly involves many obstacles and hoops to jump through, which begs the question – what does the future hold for these women? In

years to come, two changes will probably occur. The first is tighter recommendations for glucose control. The second is more accurate means of controlling blood sugar levels. Today, insulin pumps and continuous glucose monitors (CGMs) are the most state-of-the-art technology available to diabetics. CGMs allow for a graph and trend-line of glucose levels to appear on a screen, which eliminates the need for constant finger-pricking. Pumps deliver continuous insulin and meal boluses at the push of a button, so no needles or vials are necessary. Insulin pumps allow for greater accuracy because they can deliver partial units, unlike the syringe and needle method. Although research hasn't been able to confidently say that insulin pumps afford better control than multiple daily injections, studies have shown that pumps provide diabetics with a higher quality of life and decreased stress, which is a very positive effect in and of itself, particularly for pregnant women (Bode, 2007).

There are other very exciting advancements in the field of diabetes management that may come to play in the next ten years. One of these developments is Ins-PBA-F, or "smart" insulin, which is currently being researched at the University of Utah. Ins-PBA-F must only be injected once every fourteen hours. It isn't activated until it senses rising blood sugar, thus eliminating the probability of human error associated with administering too much or too little normal insulin. It mimics how the beta islet cells are supposed to work in a healthy pancreas ("Novel 'Smart' Insulin," 2016). Another new advancement with the same idea is the "smart" insulin pump. It uses the same technology as a typical insulin pump except that it has a smart phone application with computer algorithms to determine insulin need. The CGM communicates with the pump, and they work together so that no human input is needed to administer insulin. Long term trials of smart insulin pumps will begin this year (Karoff, 2014).

Some researchers have gone a slightly different route, such as with the insulin patch. The insulin patch is simply an adhesive patch that contains hundreds of microneedles which release insulin in response to high interstitial blood sugar (Veiseh & Langer, 2015). Another example is the artificial pancreas, an implantable devise with a gel layer that liquefies and solidifies, releasing and holding the output of insulin as determined by sensed blood sugar levels (Newmarker, 2014). Neither of these two devices is yet in human trials, but people with diabetes could very well have access to them in the next ten years.

There is no easy answer when it comes to type 1 diabetes and pregnancy. Though once considered a life-threatening situation, it is now a relatively common and safe occurrence. Nevertheless, pregnant women with diabetes still face more potential for risks than typical pregnancies, and they must exhibit strict glucose control over the duration of their gestation. The change that allowed diabetic women to carry children was not a sudden, silver bullet in the history of medical technology. Rather, it was a process that slowly evolved over the 20th century, and is still evolving today. There are many new technologies in the works to provide an even brighter for future for the diabetic women who wish to become mothers. In time, it is entirely possible that diabetic women will face no greater risks than those of their non-diabetic counterparts. One day, there will be a way to control type 1 diabetes as if the disease never existed.

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