

## COMMENTARY

# Rethinking Research Conventions of Perinatal Complications in Diabetic Pregnancy

Ariel Lee<sup>1</sup>, Logan Vander Woude<sup>1</sup> and Cyril Blavo<sup>1</sup>

<sup>1</sup>Nova Southeastern University College of Osteopathic Medicine, 3301 College Avenue, Ft. Lauderdale, FL 33314-796 USA

### ABSTRACT

This commentary discusses how the traditional approach for the majority of research studies involving complications of diabetic pregnancy have shared several common assumptions that may have decreased the accuracy of their conclusions. Specifically, there should be a focus on correcting two conceptual errors concerning the nature of diabetes with regard to pregnancy. The first assumption is that fetal complications are necessarily related to glycemic control. Although significant evidence exists proving glycemic control is a major factor in prenatal and perinatal complications, other possible factors such as those presented in the modified Pederson hypothesis should be addressed as well. However, these have gone largely overlooked in any major study to date. In addition to this, the differing types of diabetes including diabetes mellitus type 1, diabetes mellitus type 2, and gestational diabetes are often not properly differentiated despite having differing etiologies, onsets, and outcomes that should be properly acknowledged in order to minimize inaccuracy of data and conclusions. By correcting these two fallacies, future research into diabetic pregnancy can be optimized to reflect both more accurate explanations of mechanisms behind fetal complications as well as better recommendations for prenatal care for women who are facing the obstacles presented by a diabetic pregnancy.

### INTRODUCTION

Fetal complications resulting from maternal diabetes are well known and have been documented as far back as the 19<sup>th</sup> century (Negrato & Gomez, 2013). The introduction of insulin in 1922 hailed the end of an era in which diabetes often proved fatal; however, diabetes in pregnancy remains a stubbornly elusive problem. As illustrated in Table 1, the rates of diabetic pregnancy have risen rapidly over the past ten years and continue to rise. Despite the many avenues for regulating blood sugar available today, neonates of diabetic mothers suffer a 34% rate of respiratory distress, 47% rate of admission to NICU after birth (Allen & Armson, 2007), and a perinatal mortality rate with a range of 0.6 – 4.8% (Riskin & Garcia-Prats, 2016). Patient adherence notwithstanding, there are structural and categorical weaknesses when it comes to how perinatal complications of diabetic pregnancy have been traditionally studied. Discussed here are two major conceptual errors. The first is the assumption that all fetal complications from diabetes are directly related to glycemic control. The second is the tendency to group all types of diabetes under the vague umbrella term “maternal diabetes” when in fact they consist of three separate categories with differing etiologies, onsets, and disease courses: Diabetes Mellitus Type 1 (T1D), Diabetes Mellitus Type 2 (T2D), and Gestational Diabetes (GDM). These two errors when put together skew not only the accuracy of data, but also obscure the best methods of prevention, management, and treatment that might result in improved outcome of the neonate.

## **BEYOND GLYCEMIC CONTROL**

Research has begun elucidating the mechanisms behind perinatal complications of diabetic pregnancies, which affects more than 171 million pregnancies worldwide, with a large-scale study in Norway (Engeland, Bjorge, Daltveit, 2011) projecting 366 million affected by 2030. Much of this research has focused on poor glucose control during pregnancy, suggesting that this factor alone is responsible for the majority of prenatal and perinatal anomalies. While there are numerous examples indicating that both hypoglycemia and hyperglycemia play significant roles in fetal complications, glucose alone cannot be responsible for what is a truly multifaceted disease. By reducing a polygenetic endocrine disorder to a single problem—glucose—one vastly oversimplifies and ultimately fails to fully account for the effect of different types of diabetes on pregnancy. In order to be properly studied and effectively treated, diabetes needs to be first, specified, and second, researched in the context of an entire physiological system instead of a single hormone deficit.

The Pedersen hypothesis has historically played a major role when guiding research on the manifestations of maternal diabetes in the fetus. The theory, originally posited by internist Jorgen Pedersen in the 1950s and still recently cited in commentary and studies (Lindsay, 2009), states that hyperglycemia in the mother triggers hyperinsulinemia in the fetus which results in accelerated lipogenesis and growth of the tissues (Macfarlane & Tsakalagos, 1988). The macrosomia, in turn accounts for higher rates of stillbirth, fetal oxygen deprivation, respiratory distress syndrome, hypoglycemia, and shoulder dystocia of the newborn. The premise of the Pedersen hypothesis is contingent on the fact that although maternal insulin cannot cross the placental barrier, glucose crosses the placental barrier, thus stimulating the fetal pancreas to produce excess insulin which acts as a growth factor. This widely-accepted hypothesis was later modified by doctors Freinkel and Metzger in the 1970s in the extended hypothesis (Macfarlane & Tsakalagos, 1988), theorizing that the fetus early on has an exaggerated pancreatic response that enhances hyperglycemia regardless of the mother's glucose control. In addition, it has been postulated that this pancreatic response may also be triggered by "alternate fuels," such as lipids or polypeptides.

While the first half of this "modified Pedersen hypothesis" has become the modern-day standard of how we account for the majority of complications found in infants of diabetic pregnancy, a substantial amount of research is still lacking on the "alternate fuels" portion of the modified theory. A 2001 study (Szilagyi & Szabo, 2001) comparing obstetrical and perinatal outcomes of diabetic pregnant women with tight metabolic control found that while perinatal mortality could be greatly improved by tight metabolic control, maternal morbidity was still higher despite excellent glucose control. If we are to accept that there are complications beyond those attributed to hyperglycemia, the next logical step would be to stratify the types of diabetes and look beyond their shared symptom of aberrant glucose metabolism to determine what else may be the driving force behind these complications.

## **DIFFERENTIATING DIABETES IN PREGNANCY**

In order to understand why it is important to separate the different types of diabetes in pregnancy it is helpful to first have some background information on why and how these diseases manifest.

### *Type 1 Diabetes Mellitus*

In Diabetes Mellitus Type 1 (T1D) there is autoimmune destruction of the pancreatic beta cells, which the body uses to produce insulin. Without insulin, glucose is unable to enter cells and serve as fuel. T1D is caused by genetic polymorphisms associated with an environmental stressor (Pietropaolo, 2016). This

etiology is unique to T1D, and one might assume that the complications from pregnancy with T1D might differ from pregnancies of women with other forms of diabetes. Although there is a paucity of research specifically regarding this subject, available evidence seems to support this theory. In a prospective study of 330 women with T1D and 540 with T2D (Cundy & Gamble, 2007), both the rate of pregnancy loss and the HbA1c at presentation near term were similar, but the cause of loss differed, with >75% of losses in T1D attributable to major congenital anomalies or prematurity and >75% losses in T2D attributable to stillbirth or chorioamnionitis. The only other measured difference between the two groups of women was that the T2D women were generally older ( $P < 0.001$ ) and more obese ( $P < 0.0001$ ). Despite these differences, few studies have been conducted distinguishing the complications of T1D and T2D pregnancies. Not only could distinguishing these disparate types change the active management of these pregnancies, recognizing the different pathophysiology leading to these two diseases and during the disease processes is vital to the understanding of the accuracy of measurement tools used in studies as well as the outcomes.

Besides glucose, other changes have been detected in the pregnancies of women diagnosed with T1D and T2D. A 2010 study of 173 diabetic pregnancies and 137 healthy pregnant women (Gobl, et. al, 2010) which differentiated T1D and T2D demonstrated that lipid profiles of the two diabetic groups differed significantly, with T1D women having consistently higher lipid levels than T2D women. Additionally, the study also found that there was a positive association between higher maternal triglycerides and macrosomia that was independent of glycemic control. Although lipids have been postulated to serve as an “alternative fuel” in the modified Pedersen hypothesis, there is simply not enough research available to reach any solid conclusion at this time. Nevertheless, there may be other factors yet unaccounted for. A 2002 nationwide cohort study in the Netherlands (Evers, Valk, Mol, 2002) identified the risk of macrosomia in women with only T1D despite good glycemic control (HbA1c under 7%). After stratifying for multiple factors, the study concluded that HbA1c had a weak predictive value for “Large for Gestational Age” (LGA) infants with a variance of  $< 5\%$ .<sup>11</sup> It is of important note that HbA1c becomes a steadily less efficacious marker in pregnancy due to hormonal changes. However, if glucose is not the exclusive factor, further investigation is necessary to determine the other causes. In order to postulate other potential causes, it is important to look at the other types of diabetes in which macrosomia or LGA of the neonate is common.

### *Type 2 Diabetes Mellitus*

Unlike T1D, in which the majority of onset is before age 19, T2D is a condition often acquired later in life (Levitsky & Misra, 2016). T2D does not appear to be overtly autoimmune in nature and is thought to be the result of a burgeoning resistance of cells to the influence of insulin, which becomes chronically elevated in response. While T1D patients cannot make any insulin, T2D initially make large quantities of insulin to stimulate cells, until the pancreas burns out and is no longer able to keep up the rate of insulin production. T2D has a clear association with obesity, so strong in fact that current statistics (Leffel & Svoren, 2016) show that up to 80% of adolescents diagnosed with T2D were comorbid for obesity. Ultimately a definitive answer for the cause of T2D is still under investigation. Current areas of research include the GLUT-2 receptors, which let glucose into the cell, as well as adipokines, which are produced by adipocytes, and defects in the processing of proinsulin into insulin. Along with the problem of insulin resistance (as opposed to the deficit of insulin seen in T1D), obesity has a different impact on the fetal environment. In an article calling for a re-examination of the Pedersen hypothesis (Catalano & Hauguel-De Mouzon, 2011), it is suggested that obesity carries with it its own pregnancy risks including early pregnancy loss, congenital anomalies, and neural tube defects. There is mounting evidence that the maternal metabolic environment directly affects metabolic programming of the infant. Although adipose tissue has been thought of in the past as an inert form of energy storage for the body, more recent research indicates that it is an active metabolic tissue. When in

excess, adipose tissue may create an "inflammatory milieu" involving cytokine production by macrophages, effecting post-receptor insulin receptors resulting in increased insulin resistance (Catalano, 2011). As a result, even with perfect glucose control, obese women with T2D may begin their pregnancy with more inflammation and an excess of nutrients and cytokines that can affect the fetal outcome in the postnatal period.

A 2014 study of 156 subjects (Mitrovic, Stojic, Tesic, 2014) found striking differences between fetal outcomes based on categorizations of T1D versus GDM and T2D (which were grouped together). The study found that pregnancies of women with T1D were more likely to have pre-term birth and a higher rate of Cesarean section than those without T1D. It also found that T1D pregnancies manifested in neonatal hypoglycemia more frequently than the T2D/GDM group, while the T2D/GDM group were more likely to experience macrosomia. The study also found no differences in the HbA1c levels of either group relative to macrosomia or fetal abnormalities. This should call into question the validity of the Pedersen hypothesis and highlight the need for further research into alternate mechanisms.

### *Gestational Diabetes*

Confounding T2D and Gestational Diabetes Mellitus (GDM) is another common error in research. Although there is a correlation between the two, they are not the same disease and should not be treated as such. Of the three types of diabetes, GDM remains perhaps the most puzzling in terms of etiology. While GDM shares some characteristics with both T1D and T2D, it is unique in that it usually occurs at the third trimester of pregnancy and ends at birth. An article detailing gestational diabetes (Hick, 2000) explains that GDM is associated with the hormones of pregnancy including human placental lactogen, that are produced after the 20<sup>th</sup> week of gestation. GDM appears more commonly but is less frequently affiliated with poor perinatal outcomes than T1D and T2D. The large and well-organized Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (Lowe, Dyer 2012) showed that GDM carries an increased risk of new-onset T2D diagnosis postpartum, even in women who were asymptomatic and euglycemic before pregnancy. A 2014 retrospective study of 169,428 subjects (Fong, et. al, 2014) examined the differences in outcomes of GDM versus pre-existing diabetes using ICD-9 code identification and logistic regression. The study concluded that those with pre-existing diabetes were far more likely than those with GDM to have fetal CNS malformation, fetal demise, shoulder dystocia, failed induction of labor, and Cesarean section delivery. This study had several relative weaknesses, one being that it failed to differentiate between T1D and T2D, grouping them together as "pre-existing," and did not mention glycemic control or HbA1c among the subjects with regard to fetal outcomes.

Yet another distinguishing factor of GDM, especially in comparison to T1D and T2D, was shown in the HAPO study (Lowe, 2012) when analyzing the use of A1C levels in place of glucose levels. They found that A1C levels did not well separate women with normal pregnancy from those with GDM, although A1C is useful in other types of diabetes. The trial also found no independent association of neonatal birth weight with mother's A1C level and in fact found lower odds of neonatal hyperglycemia in the highest category of A1Cs. In fact, HbA1C can be a poor predictor in pregnancy in general due to erythrocyte turnover.

Euglycemic ketoacidosis is not unheard of during diabetic pregnancy. While it is most frequently caused by cases of T1D, which tend to be the most serious, one study (Dalfra, Burlina, Sartore, 2015) showed fewer and milder cases of T2D and GDM being reported as well. Ketoacidosis in pregnancy can often be triggered by the increased insulin resistance as a consequence of elevated human placental lactogen, occurring both faster and at lower levels of glucose than in non-pregnant individuals. Euglycemic ketoacidosis compromises maternal health and fetal outcome. A peer-reviewed article

reviewing diabetic ketoacidosis in pregnancy (Kamalakannan, Baskar, Barton, 2003) showed that there is a 30% fetal loss rate, and maternal DKA soars to 64% if the mother remains untreated long enough to become comatose.<sup>20</sup> This again should call into question the assumption that if glucose is within normal limits at pregnancy, there is nothing to be concerned about. Not only does this presumption give the clinician a false sense of security when following this type of high risk pregnancy, but it may also result in unexpected tragedy for the expectant mother if she is made to believe early on that well controlled glucose assures that her child will not suffer complications.

## CONCLUSION

Several conclusions may be drawn from this discussion. First and foremost, the evidence suggests that future research needs to be structured to differentiate the types of diabetes in pregnancy. Secondly, more attention must be focused on the physiology of diabetes as a whole, beyond addressing it as a simple “glucose disorder.” Finally, this information should be a call to future researchers and clinicians to pay attention, not only to the type of diabetes an obstetrics patient has, but to go beyond the gold standard of excellent glycemic control and address potential perinatal and postnatal risks with the ultimate goal of giving patients the most comprehensive evidence of risk available and making a compliant diabetic pregnancy as safe as possible.

**Corresponding Author:** Ariel Lee ([al1317@nova.edu](mailto:al1317@nova.edu))

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**Keywords:** pregnancy, gestational diabetes, diabetes mellitus, modified Pederson hypothesis, glycemic control, prenatal complications, diabetic pregnancy

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**Table 1: Rising Prevalence of both Gestational and Pre-Gestational Diabetes During Pregnancy**

Prevalence	Pre-Gestational Diabetes (T1D and T2D)	Gestational Diabetes
1996	0.7%	2.7%
2010	1.5%	5.6% - 9.2%

**Table 1:** A large-scale Canadian population based cohort study (Feig DS, Hwee J, Shah H et al 2014) of 1,109,605 was followed from 1996-2010 with the following results for the first and last years listed in the table above. In a similar study following 23,479 pregnancy outcomes from 2007-2010 (De Sisto CL, Kim SY, Sharma AJ et al, 2014), a 9.2% prevalence GDM was recorded from evidence reported on the birth certificate or PRAMS questionnaire in the US population. Despite there being insufficient new data available, continuing to project this trend points towards a burgeoning health crises regarding diabetes of all types during pregnancy. Unfortunately, without any available large-scale studies that differentiate T1D and T2D during pregnancy and without any new large-scale studies between 2010 and 2017, there remains the need for more specific evidence regarding both the cause and prevention of this escalating problem in the gravid population.