Melissa Hayes

The Teratology of Diabetes During Pregnancy

Diabetes mellitus, commonly referred to as diabetes, affects more than 25.8 million children and adults in the United States, or 8.3% of our population (2011, American Diabetes Association). There are three basic types of this metabolism disorder: type I, type II and gestational. In all three types, there is a malfunction in the homeostasis of glucose in the blood and cells. The term diabetes literally means to siphon and mellitus comes from Latin origin meaning honey or sweet, referring to the “sweet” urine of diabetics, caused by the excess excretion of glucose in the urine as a result of hyperglycemia, or high blood sugar. All forms of diabetes are characterized by the presence of chronic and persistent hyperglycemia. Insulin, a hormone produced by the pancreas, is needed to transport glucose into cells to use as the body’s energy source. Diabetes is commonly a result of a malfunction in insulin action, production or secretion.

Type I is an autoimmune disease that causes the body’s own immune system to attack the insulin-producing beta cells in the pancreas (2011, Center for Disease Control and Prevention). In this form of diabetes, there is zero or very little insulin production and requires daily insulin injections to maintain blood glucose levels. Type I is more common in a younger population with an average onset age of 14 years. Type I is also known as insulin-dependent diabetes. According to numbers from National Diabetes Information Clearinghouse (NDIC), type II is the most common form making up 90-95% of diabetes diagnoses. The pancreas still functions, but the cells are no longer responding to the insulin or require more than is naturally secreted. This is known as insulin-resistant diabetes and is most commonly associated with obesity, lack of physical activity, diet, and family history of diabetes. If the first onset of diabetes is during pregnancy, it is called gestational diabetes. According to the National Institute of Health, this affects approximately 5% of pregnancies in the U.S. The mechanisms are similar to type II and in most cases, blood sugar levels return to normal after birth. However, mothers who have had gestational diabetes increase their risk of developing type II diabetes. Previously, diabetes type II was known as “adult onset,” but recently the average age of onset has begun to decrease every year along with an increase of diagnoses in women of reproductive age. This results in a growing number of pregnancies within the diabetic population, and with that comes the necessity to study the teratogenic effects of diabetes during pregnancy. The overall health effects of the teratology of diabetes in studies human models will be examined, then studies of specific mechanisms of teratogenic effects of diabetes using rat models.

Hyperglycemia during pregnancy has been shown to cause macrosomia (larger than average body at birth), jaundice, respiratory distress syndrome and may even increase the risk for obesity later in life. One study analyzes the cases from the Hungarian Congenital Abnormality Registry from 1980-1996, matching each of these cases with two controls with no congenital abnormalities. (2005, G.L. Nielsen et al.) The controls were matched to the cases by sex, birth week and parent residence. The purpose of this study is to determine if there is a correlation between pre-gestational diabetes and specific congenital abnormalities. Of the 22,843 cases of congenital abnormalities, 62 of those babies had mothers with diabetes. The control group is composed of 38,151 babies with no congenital abnormalities. Many different types of congenital abnormalities are examined in this study, among which are neural tube defects, cleft lip, renal and urinary tract problems, and cardiovascular problems. The congenital abnormalities most associated with maternal diabetes found in this study are renal dysgenesis, or dysfunction of
differentiation of renal tissue, (prevalence odds ratio of 14.8) obstructive urinary abnormalities (prevalence odds ratio of 4.3), cardiovascular abnormalities (prevalence odds ratio of 3.4), and multiple congenital abnormalities (prevalence odds ratio of 5.0) (2005, G.L. Nielsen et al.).

One effect that has been studied in relation to maternal diabetes is risk of macrosomia. The Pettit et al. (1983) study examines the effect maternal diabetes on body composition later in life. In this longitudinal study, the prevalence of obesity in offspring of mothers with diabetes at different ages is examined. The population that is examined in this study is mothers of the Pima Indian community in Arizona, which has a particularly high incidence of obesity and diabetes. The mothers in the study are split into three different categories: diabetic during pregnancy, those who developed diabetes after giving birth (pre-diabetics), and non-diabetics. Three age groups of the children of these groups of women are examined: 5-9 years, 10-14 years, 15-19 years. The total numbers of mother and child subjects studied are 625 mothers and 1935 children. Because of the longitudinal nature of the study, 1,068 children are included in data of at least two age groups, and 375 are included in all three. The results of this study show that in all age groups, children of diabetic mothers have a higher percentage of their desirable weight than both pre and non-diabetics (table below). Obesity, as defined by this study as a percent desirable weight of 140 or greater, was also greater in the maternal diabetes group. Because there are many factors that can lead to child obesity including environmental, correlations between maternal and child obesity are examined in two groups: offspring of non and pre-diabetic and offspring of diabetics. A positive correlation is found between maternal and child obesity in the offspring non and pre-diabetic, but no correlation was found with the offspring of diabetics group. The most important finding of this study is the risk of obesity is increased with maternal diabetes, and obesity in the offspring is a risk factor for developing type II diabetes.

Table 2. Mean Percentage of Desirable Weight in Offspring, According to Age and Mother’s Diabetes Status.

<table>
<thead>
<tr>
<th>Mother’s Diabetes Status</th>
<th>Age Group of Offspring</th>
<th>% desirable weight</th>
<th>95% confidence interval</th>
<th>no. in group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-9 years</td>
<td>10-14 years</td>
<td>15-19 years</td>
<td></td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>112 (111–114) 767</td>
<td>120 (118–122) 875</td>
<td>117 (114–119) 518</td>
<td></td>
</tr>
<tr>
<td>Pre-diabetic</td>
<td>114 (111–116) 296</td>
<td>123 (120–125) 430</td>
<td>125 (122–128) 336</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>132 (125–139) 48</td>
<td>149 (141–156) 51</td>
<td>145 (133–157) 24</td>
<td></td>
</tr>
</tbody>
</table>

The role of insulin is extremely important in the mechanisms of diabetes, and also has been shown to be involved in fetal growth. When a fetus is exposed to an excess amount of insulin in utero due to diabetes in the mother, it influences metabolic and growth mechanisms. As shown in the previous Pettit et. al. study, these impacts can continue past infancy and effect body composition and obesity in the offspring later in life. A study by Silverman et al. (1993) also examines the impact of diabetes during pregnancy, specifically hyperinsulinism, on the offspring and the continuing impacts between the ages of 6-14. All of the mothers chosen as subjects in this study had either gestational or pre-gestational diabetes. Amniotic fluid was tested for insulin levels and monitoring lung maturation. C-peptide, a byproduct of insulin production, and glucose levels are measured in the cord blood. After initial measurements of weight and length at birth, the offspring were examined at 3,6 and 12 months and then yearly. Fetal hyperinsulinism was seen in the offspring of diabetics with a mean amniotic fluid insulin level of 91.8 pM compared to a non-diabetic control group mean insulin level of 39 pM (1993, Silverman et al.). The high amniotic insulin levels reflect premature insulin secretion of the fetus in the
offspring of diabetic mothers. 50% of the diabetic offspring group were over the 90th percentile for birth weight. In the subsequent examinations of the 124 subjects, data show the macrosomia seen at birth resolves by about one year of age, however there is a sharp increase in BMI a few years later. Both male and female subjects are close to the reference population weight at 12 months, then have begin a period of weight gain at 6 years old. By the time they reach the age of 8, close to half are at the 90th percentile or above for weight. There are positive correlations between obesity during the ages of 6-8 and increased amniotic insulin levels, cord C-peptide and cord glucose levels. In subjects 8-14 years of age, the positive correlation between high amniotic insulin levels and obesity is still seen. The highest one-third amniotic insulin levels had a 48% incidence of “extreme obesity,” or greater than 140% of ideal body weight (1993, Silverman et al.). There is also a correlation between parental and child obesity, indicating the presence of environmental factors as well.

Insulin and insulin-like growth factor 1 (IGF-1) have been related to developmental and cognitive function of the central nervous system. “It has been shown that fetal hyperglycemia alters the expression of genes that are involved in the proliferation and differentiation of neural cells” (2012, Hami et al.). One mechanism of teratogenic effect of diabetes during pregnancy may be alteration of insulin and insulin-like growth factor 1 receptors (InsR and IGF-1R), leading to problems of expression of genes controlling proliferation and differentiation of neural cells. The Hami et al. (2012) study uses an animal model (rat) to examine the effect of maternal type I diabetes on the expression of these IGF-1R and InsR genes and subsequent central nervous system (CNS) function, specifically looking at the rat hippocampus. The 30 rat subjects were put into three different groups: 11 diabetic, 11 insulin-treated diabetic, and 8 control. Streptozotocin was used to induce diabetes in the diabetic and insulin-treated diabetic groups. The streptozotocin induced type-I diabetes by destroying the beta cells in the pancreas. This diagnosis of diabetes is then confirmed by a glucose tolerance test in the rat mothers and presence of hyperglycemia. All three groups of mothers were mated with non-diabetic males. The day the pups are born is postnatal day 0 (P0). Pups of the two diabetic groups were nursed by control females to avoid any effect of differences of milk. Only the hippocampi of male offspring were examined. The male pups of each group are randomly assigned to P0, P7 or P14, and are killed and hippocampus examined on their designated day. The IGF-1R mRNA expression in the right and left hippocampus is examined by using real-time PCR. The results show significantly increased mRNA expression in the right hippocampus of the untreated diabetic group at P0, and significantly decreased expression at P7 compared to the control and insulin-treated groups. At P14, the untreated diabetic group had slightly lower mRNA expression, but not significantly different than the other two groups. In the left hippocampus, expression of the untreated diabetic mRNA was significantly higher than only the control group at P0, significantly lower than both groups at P7, and significantly lower than only the control group at P14 (see figure 1 on page 5). An important finding in this study is the non-statistically significant differences at P14 between the control and insulin treated groups, indicating the importance of glucose monitoring and management during pregnancy for diabetics in minimizing the negative effects of diabetes during pregnancy on the offspring.

Babies born to mothers who had diabetes during pregnancy may have low arachidonic acid levels as a result, correlating with low arachidonic acid cord blood levels. Recent findings show that glucose and bone metabolism may be linked. A study by Zhao and Weiler (2010) examines the effect of arachidonic acid supplementation and maternal streptozotocin-induced diabetes on a rat population on body composition, glucose tolerance and liver fatty acids of the
offspring. The maternal rats are randomly put into one of six groups: two control non-diabetic groups and four streptozotocin-induced diabetic groups. One control groups is fed the control diet, and the other is fed the AA supplemented diet. The four diabetic groups are further split into two subgroups: well controlled glucose and poor controlled glucose defined as using insulin to maintain blood glucose levels of 13mmol glucose/l and 13-20mmol glucose/l respectively. Both subgroups have a control diet group and AA supplemented diet group. One week after the saline placebo or streptozotocin were administered, the female rats were mated with non-diabetic males, and they nursed their own pups until postnatal week four, at which time the pups were fed a normal chow. Rat pups were measured in the following areas: body composition, bone mass, oral glucose tolerance, liver fatty acid levels. The body mass areas examined at 4, 8 and 12 weeks are whole body, lumbar spine, femur and tibia. To take these measurements, the offspring are anaesthetized and examined with a dual-energy X-ray absorptiometry (2010, Zhao and Weiler). Data show more weight gain between day 3 and 12 weeks in the well-controlled diabetic group compared with the poorly controlled diabetic group with both diets. Data also show a large effect of diabetes and the extent of glucose control on bone area of the offspring. The poorly controlled diabetic group had less whole body bone area than the well-controlled diabetic and non-diabetic groups at 4 weeks. This low whole body bone area is negatively correlated with maternal glucose levels. The poorly controlled diabetic group also had less bone area of the tibia at 12 weeks. The bone area of the femur at 8 weeks was less in the poorly controlled diabetic group than the well-controlled diabetic group. The maternal diet group has no impact on bone area, bone mineral content or bone mineral density. All offspring of mothers assigned to the AA supplemented group show higher levels of liver AA at 4 weeks, but no difference is seen at 12 weeks. The raised level of liver AA at 4 weeks is associated with lumbar spine mineral density in males. The glucose tolerance tests of the offspring were not affected by the diabetic condition of the mother or diet. These data ultimately show that glucose control and hyperglycemia of the mother impact skeletal development in the offspring.

The mechanisms of the teratology of diabetes during pregnancy, whether it is type I, II or gestational, are quite complex and still have much to be discovered. With the research that we have today, the main mechanism seems to be the presence of hyperglycemia in the mother as a result of diabetes. Because these mechanisms cannot be examined or controlled completely in human models and the ethical issues regarding possible influences during pregnancy, there are not many variables that can be controlled or changed in these human models, we must turn to animal models and learn as much as we can by examining the mechanisms and their specific actions in detail. We are able to dissect the brain and examine the hippocampi of the rats to discover the importance of glucose monitoring during pregnancy and the impact on the insulin and insulin-like growth factor receptors. There are some differing results looking at the most common congenital abnormalities in the rat vs. human models. In humans, according to the G.L. Nielson et al. (2005) study, the most common congenital abnormalities associated with maternal diabetes are renal, urinary, cardiovascular and cases of multiple abnormalities. This does not reflect the skeletal impacts of hyperglycemia seen in rat models. The impact of hyperglycemia on the insulin and insulin-like growth factor receptors on the CNS in the rat models were also not reflected in the most prevalent congenital abnormalities in the G.L. Nielson et al. study. Obesity seen in rats overtime due to maternal diabetes in not examined in these studies, while this is a very big problem seen in the human cases studied. However, the lifespan and body composition of the two models are very different and the factors that influence the development of obesity are numerous and complicated. An interesting finding especially in the Hami et al. (2012) and Zhao
and Weiler (2010) studies, data show that careful blood glucose management is effective in reducing the teratogenic effects of diabetes during pregnancy. This is important when applying this information to the human diabetic population and demonstrates the importance of pre-pregnancy planning and readily available resources for pregnant women with diabetes to help them manage blood glucose levels. As the number of cases of diabetes increases and the onset age of diabetes decreases, the number of women with diabetes during reproductive years increases. With enough time and research, we will hopefully fully understand the specific mechanisms in which this metabolic disease enough to prevent the teratogenic effects on the children of diabetic mothers.

Figure 1.

**Right Hippocampus**

**Left Hippocampus**

Fig. 1 Effect of STZ-induced maternal diabetes and insulin treatment on IGF-1R mRNA expression in rat newborn hippocampus at P0, P7, and P14. Right hippocampus (a), left hippocampus (b). Values represent the mean ± SE (n = 7, for each time point). *Significant differences (P < 0.05)
Literature Cited


