2018

Are children of a diabetic mother in comparison to children of a nondiabetic mother at an increased risk for developing obesity in the first 10 years of life?

Chhorn Pho

Are children of a diabetic mother in comparison to children of a nondiabetic mother at an increased risk for developing obesity in the first 10 years of life?

By

Chhorn Pho, PA-S2

Meredith Wold, PA-C

Paper Submitted Partial Fulfillment

Of the Requirement for the Degree

Of Master of Science

Physician Assistant Studies

Augsburg University

August 10, 2018

Table of Contents

Abstract

Body weight, glucose, insulin, and leptin were studied in children of mothers with gestational diabetes, type 1 or type 2 diabetes. Breast milk of diabetic mothers was also analyzed to study its relationship to childhood obesity. In the first 2 years of life, infants of mothers with gestational diabetes have no significant difference in weight gain but by the age of 10, most of the children birthed by any diabetic mothers were either overweight or obese. Children of mothers diagnosed with diabetes mellitus type 2 have higher resistance to insulin than children of mothers with other diabetes types. Leptin was observed to be negatively correlated with insulin level in utero. Hyperinsulinemia was correlated with low leptin level in the fetal side of the placenta. Lastly, milk of mothers with diabetes was found to have higher glucose, insulin, and energy content than control group. By the age of 2, a significant number of breastfed children whose mothers had diabetes were either overweight or obese.

Keywords: pregnancy, diabetes, prepubescent, childhood obesity

Introduction

Since 1970, the number of children and adolescents with obesity have tripled.[1] Obesity is defined as having excess body fat and can be measured using body mass index (BMI) screening tools[1]. BMI is a person's weight in kilograms divided by the square of a person's height in meters. The World Health Organization (WHO) publishes the growth chart that measures BMI of infants less than 2 years old.[1] The WHO classify a child as having a high weight for length when the child BMI is greater than the 98th percentile.[1] Once the child is 2 years old or older, the BMI is then estimated using a growth chart issued by the Center for Disease Control (CDC) instead of the growth chart from the WHO. The CDC defines obesity as BMI at or above the 95th percentile for young people of the same age and sex.[1]

Childhood obesity has both immediate and long-term effects on physical, social, and emotional health. A child who is obese is at higher risk of having other chronic conditions such as type 2 diabetes, hypertension, metabolic syndrome, coronary heart disease, asthma, sleep apnea, and bone and joint problems.[1,16] An obese child is more likely to be bullied and teased, which increase their risk for depression and lower-self-esteem.[1] For these reasons, it is crucial to investigate if children of diabetic mothers are at an increased risk for developing obesity later in life. If so, then appropriate screening, monitoring, and intervention can be implemented to prevent the development of obesity in these young children.

There are many factors that influence childhood obesity such as poor dietary choices, sedentary lifestyles, and genetic predisposition to certain diseases. Whiles most childhood

obesity have resulted from poor eating habit and sedentary lifestyle, a significant amount of children have also become overweight or obese from familial disease such as diabetes as well.[1] Children who were born from mother with diabetes were thought to be at higher risk for overweight and obesity later in life.[13] There are several proposed mechanisms to help explain the relationship between diabetes in mothers during pregnancy and the development of overweight and obesity in the offspring later in life. One of the most notable hypothesis is the fuel-mediated teratogenesis. The fuel-mediated teratogenesis proposes that intrauterine exposure to an excess fuel such as glucose cause permanent fetal changes.[15,18,19] A child who is developing in a diabetic intrauterine environment is exposed to excess fuel (glucose). When a mother is diabetic, her body cells become resistant to insulin which impairs her ability to digest glucose.[18] This free-floating glucose easily crosses the placenta and stimulates the fetus to produce additional insulin to help take in the excess glucose.[18,21] The excess glucose is then converted into glycogen and stored muscles and liver cell.[15,18] Any excess glucose that is beyond storage is then converted into fat cells and is then stored as adipose tissues.[15,18] This leads to growth in muscle and adipose tissues in the fetus. Prolonged exposure to high level of glucose can then cause overgrowth of muscles and adipose tissues in the developing fetus and thus can result in a macrosomic baby.

The fuel-mediated teratogenesis hypothesis applies to three major forms of diabetes that a mother can have while she is pregnant. The three types of diabetes are gestational diabetes mellitus (GDM), type 1 diabetes mellitus (DM1), and type 2 diabetes mellitus (DM2). A diabetes diagnosis is given to an individual after he or she demonstrates a failure to digest glucose.[2] In a normal setting, an elevation in glucose prompt the pancreas to secrete insulin to mitigate

glucose.[2] Insulin reduces glucose level by stimulating glucose uptake by the muscles and adipose tissues.[15,18] Any dysfunction in this process will prevent glucose from being digested which result in elevated glucose level in the body.

Each type of diabetes has a different epidemiology, and characteristic. The disease pathology, presentation, and influence on pregnancy varies among each type of diabetes. Gestational diabetes mellitus affects about 6% of pregnancies in the United States.[3] The United States Preventative Service Task Force (USPSTF) recommends screening for GDM after 24 weeks of gestation in all women without known diabetes mellitus.[3] Screening involves a two-step approach, first administering a 50-g non-fasting oral glucose challenge test at 24 to 28 weeks, followed by a 100-g fasting test for women who have a positive screening result.[3] Alternatively, a one-step approach may be used where only a 75-g two-hour fasting oral glucose tolerance test is administered. Pregnant women with GDM are at risk for preeclampsia, macrosomia and shoulder dystocia in the child.[3] Both the mother and child also have an increased risk for developing diabetes mellitus type 2 in the future.[1,3] Similarly to gestational diabetes, type 1 diabetes mellitus (DM1) also affect a significant portion of the world population. Type 1 diabetes mellitus affects approximately 5% of the world population and is commonly diagnosed during childhood or adolescence.[2,5] DM1 is an autoimmune disease where the pancreas does not produce insulin. The bodies immune system attacks the insulin-producing beta cells in the pancreas rendering it nonfunctional.[2] A person with DM1 usually has unusual weight loss, polyuria, polydipsia, polyphagia, lethargy, and blurred vision.[2] In contrast to DM1, type 2 diabetes mellitus is more of an adult-onset condition and is associated with relative impairment

in insulin secretion. A person with DM2 are usually obese with BMI > 95th percentile, have acanthosis nigricans, hypertension, dyslipidemia, and polycystic ovary syndrome in female.[2] DM1 and DM2 are diagnosed based upon one of the four signs of abnormal glucose metabolism: glycated hemoglobin (A1C), fasting plasma glucose (FPG), random elevated glucose with symptoms, or abnormal oral glucose tolerance test (OGTT).[2] Whether it is type 1 or type 2, if not adequately controlled, diabetes mellitus can cause serious complications for the child. These complications include birth defects of brain, spine, and heart, stillbirth, miscarriage, macrosomia leading to shoulder dystocia during delivery, hypoglycemia after birth, jaundice, and obesity later in life.[2,5]

Although diabetes during pregnancy plays an important responsibility in changes in fetal development, other components in addition to diabetes were also found to contribute to overweight and obesity in children. Such factors are leptin and the mother's breast milk. Leptin is a hormone that is predominantly synthesized by adipose cells.[7,14] It helps regulate energy balance by inhibiting hunger. It is often referred to as 'the hormone of energy expenditure'. In obesity, there is a decrease in sensitivity or resistance to leptin.[7,14] This result in an inability to detect satiety despite excess in energy storage and elevated levels of leptin.[14] It is thought that children who are born from mother with diabetes have altered leptin protein which predisposes them to leptin resistance and thus obesity later in life.[10] Likewise, some research studies suggested that there may be a change in diabetic mothers' breast milk composition.[11] It is thought that breast milk from mother with diabetes has higher nutrient and fat concentration which contributes to rapid weight gain and overweight or obesity in infants.[11,12]

With that said, this research study investigates whether maternal diabetes status plays a role in fetal obesity during childhood and whether the different types of diabetes mellitus during pregnancy have any contribution to obesity in early childhood. Factors that are being observed include children weight gain, glucose tolerance, insulin sensitivity, leptin resistance, and the mother's breast milk composition. The result from this study may implicate future health awareness in children of mothers with diabetes.

Background

Gestational Diabetes Mellitus

Once a woman is diagnosed with gestational diabetes mellitus, a treatment plan is initiated soon after in order to reduce maternal and fetal complications. This is to prevent fetal prolonged exposure to hyperglycemia. Hyperglycemia exposure induces fetal metabolism to produce excess insulin to help digest the mother's glucose which, in turn, can cause overgrowth in fetal body cells. The excess nutrients get stored as fats and deposit in various areas of the body, thus increasing the fetal body weight and putting the fetus at risk for macrosomia (> 4,000 gm).

Many of the available research studies focus on GDM more than other types of diabetes mellitus. A large proportion of the studies found little to no abnormal increase in BMI in the first 4 years of life.[9,13,16,18,20] The largest predictor of childhood obesity in offspring of gestational diabetes mother was overweight or obesity in the first few months of life. A study from the University Medicine Berlin analyzed weight gain of 152 offspring of diabetic mothers in their

first 4 months of life.[20] They found that weight gain during the first 4 months of life was positively related to the childhood relative body weight later in life. Every 100-gram increase in weight increases a child's overweight risk by 65%.[20] In addition to that, the offspring of diabetic mothers with rapid early weight gain had more than a six-fold increased risk of later overweight.[20] One major drawback of this study is the ability to estimate how much milk intake a child is getting on a daily basis.

Another study published in the American Journal of Obstetrics and Gynecology investigated the risk of childhood obesity in toddler offspring of mothers with GDM.[16] They compared pre-pregnancy BMI, weight gain, demographic, birth weight, and follow up childhood BMI between 2-4 years. There were 203 women/toddler pairs with GDM to 2148 women/toddler pairs with no GDM.[16] It was found that there was no statistically significant difference in the rate of childhood obesity in this population than those with no GDM.[16] Interestingly, they noted that birth weights of GDM infants tended to be lower than those of non GDM mothers at 3388 grams versus 3448 grams in non-GDM. Although this may be due to mothers with GDM delivering their child earlier than those with no GDM. Mothers with GDM deliver a child on average at 39.4 weeks versus 39.8 weeks for non-GDM mothers.[16]

Furthermore, a third study research in Europe also found no significant increase in BMI in offspring of GDM mothers. This was a large family study in Belfast with a total of 1,165 offspring ages 22 to 30 months old from the Belfast, Northern Ireland center.[21] They acquired a very high rate of follow up. They found the overall correlation between maternal glucose during

pregnancy and BMI score of the children at age 2 years old to be weak.[21] The Belfast study concluded that with offspring of women with diabetes during pregnancy, the obesity associated with elevated maternal glucose concentrations resolves during the 1st or 2nd year of life.[21] They also found that offspring of diabetic women return to non-overweight or non-obese weight by their 2nd year of life.[21]

The studies mentioned above found little to no weight effect on offsprings of GDM mothers in toddlers up to 4 years old. As the investigation progresses to older ages, other studies reveal conflicting information in regards to diabetes mellitus and overweight or obesity in early childhood. In 2018, a systematic review and meta-analysis on obesity and abnormal glucose tolerance in offspring of diabetic mothers were published.[15] Initially, it was found that children of GDM mothers had a significantly higher risk of obesity or overweight, and higher than normal fasting plasma glucose than children of non-diabetic mothers.[15] Then a sensitivity analysis was conducted, where the mother's pre-pregnancy BMI was added to the statistical analysis. Once the mother's pre-pregnancy weight was adjusted, the association of overweight and obesity was no longer significant.[15] The systematic review and meta-analysis found no significant difference for fasting plasma glucose between mothers with GDM and control group in offspring ages 7 to 10 years old.[15] The systematic review and meta-analysis is consistent with the Belgium study, Belfast study, and the study from American Journal of Obstetrics and Gynecology.

In contrast to the systematic review and meta-analysis, a study from the United Kingdom stated otherwise.[9] They study the association of existing diabetes, gestational diabetes and

glycosuria in pregnancy with macrosomia and offspring body mass index and fat mass in later childhood. This was a prospective pregnancy cohort study. Data was collected from 10,591 mother/offspring pairs participants.[9] They found that women with existing diabetes, GDM, and those with at least two episodes of positive glycosuria have greater mean birthweight and greater odds for macrosomia than women without those characteristics.[9] Additionally, in 6,842 mother-offspring pairs for ages 9 to 11 years old, maternal GDM and glycosuria were associated with an increase in offspring odds for general and central overweight or obesity.[9] In mothers with GDM, such association was still insignificant once the mothers' pre-pregnancy BMI was adjusted for.[9]

In brief, the children of mothers with gestational diabetes during pregnancy were found to have no significant risk of abnormal weight gain during the first 8 years of life. The children may appear to be at risk for overweight or obesity during infantile stages through rapid weight gain but once they reach 3 years old as a toddler, the risk dissipates. It was also found that as the child of gestational diabetes mothers enters a pre-pubescent period, the increased risk for overweight and obesity returns.

Type 1 Diabetes Mellitus

Through the aspect of insulin exposure, unlike gestational diabetes where the infants may only be exposed to elevated glucose for half of the pregnancy period, in type 1 diabetes mellitus, infants would be exposed to elevated glucose throughout the entire pregnancy period. Since DM1 is an autoimmune disorder where the mother's pancreatic beta cells are being destroyed by

her own immune system, the mother's glucose level would continually be elevated on a daily basis. With that said, it is essential that the mother's insulin is well under control to prevent overgrowth of tissues in the fetus from the increase in glucose.[8,21] It was thought that continuous exposure to elevated glucose level may alter the infant glucose digestion and therefore affecting fasting glucose and plasma glucose. Two research studies found that offspring of DM1 mothers have a tendency to be more prone to becoming more overweight or obese than mothers with GDM or DM2, and the control group.[15,21] However, when both of the studies examine the offsprings fasting glucose and plasma glucose, they found no significant differences between offspring of DM1 and the referencing population.

One of the two studies that investigated the effect of DM1 in mothers on childhood obesity is a systematic review and meta-analysis.[15] They found a significantly higher BMI in offspring of DM1 mothers. Even with aggressive therapeutic intervention on the mother during pregnancy to control glycemic levels, there was still no reduction in the rate of childhood obesity or impaired fasting glucose in children ages 5 to 10 years old compared to control group.[15] When a sensitivity analysis was conducted using the mother's prepregnancy BMI, the significance in the rate of overweight and obesity did not change. The study hypothesized that this may be due to prolonged intrauterine exposure to hyperglycemia leading to offspring with higher birthweight or macrosomia. As a consequent, macrosomia has then predisposed a child to become overweight or obese later in life.[15] In contrary to that the study found no significant differences in fasting plasma glucose in children ages 7 -10 with a DM1 mother. They also found no significant 2-hour plasma glucose differences in children ages 7 - 10 with DM1 mother.[15]

The second study is a nationwide follow-up research study in the Netherlands. It also supported the results from the systematic review. This nationwide study followed infants born from Dutch hospitals between April of 1999 and April of 2000.[21] They collected information from 213 offspring of mothers with DM1 who were between the ages 6-8 years old. Their study results show that children who were born macrosomic become overweight twice as much as non-macrosomic children. The elevated BMI was present as early as 6 months of age along with an increase in insulin resistance.[21] Although, with adequate control and treatment of DM1 during pregnancy, the long-term effect on body composition in offspring and prevalence of overweight or obesity were not different compared to those of reference population. The study suggested that the only two independent predictors of early childhood overweight and obesity were fetal macrosomia and maternal overweight.[21] Similar to the results from the systematic review, this Netherlands study found that offspring of DM mothers who were severely macrosomic (> 97th percentile) at birth showed no increase in insulin resistance. However, insulin resistance was significantly higher in children that became overweight later in life around ages 6 - 8 years old.[21]

To sum up, infant of mothers with type 1 diabetes who were macrosomic at birth are at highest risk for overweight and obesity by the age of 10 years old. However, despite being macrosomic at birth, these children were found to have no significant difference in fasting plasma glucose and no difference in 2-hour plasma glucose. Although it was noted that children who do become overweight or obese by age 8 years old tend to have significantly higher insulin resistance than normal.

Type 2 Diabetes Mellitus

Alternatively, to type 1 diabetes, type 2 diabetes mellitus occurs when the pancreas produces insufficient amounts of the insulin hormone and the body's tissues become resistant to normal or elevated levels of insulin. As a result of insulin not being able to signal for glucose uptake into cells, glucose level rises. Since such increase insulin has suspected to be involved in the metabolic programming of the fetus, it is the focus of many research studies. Amniotic fluid is frequently used to measure insulin in study researches. Insulin can be measured in amniotic fluid because it crosses the placenta as part of antibody-insulin complexes.[6,7,8] This reflects both fetal insulin secretion and maternal insulin. It was hypothesized that maternal insulin could be a marker of insulin resistance in the mother and that there is some similarity in insulin resistance in the rest of the family.[7,8]

One small controlled study looked at the level of insulin sensitivity in offspring of DM2 ages 5 to 10 years old. They compared 17 offspring of DM1 mothers and 10 offspring of DM2 mothers.[8] Each child was given an infusion of IV dextrose and then 2 millimeters of blood was collected for insulin testing at increments of 1,2,5, and 10 minutes over a period of 90 minutes. They found that the BMI score and percentage fat mass in the children and in the mothers were negatively correlated with offspring insulin sensitivity.[8] However, children of mothers with type 2 diabetes were more overweight or obese with a tendency for a reduced insulin sensitivity.[8] The study suggested that adiposity is likely to have contributed to the lower insulin sensitivity in offspring of DM2 mothers, given the negative correlation between increased weight and insulin

sensitivity.[8] In addition to this finding, all of the mothers with DM2 were older and obese with BMI greater than 30 kg/m2 at the start of pregnancy.[8]

With that said, it was found that children of mothers with type 2 diabetes have the propensity to be more overweight or obese than normal. There was a hypothesis that maybe offspring of women with type 2 diabetes are exposed to a unique metabolic perturbation in addition to hyperglycemia that induces them to be more overweight or obese.[8] Currently, there are inadequate studies for rates of childhood obesity or overweight in offspring of DM2 mothers. There are no studies looking at diabetes and plasma glucose in children of DM2 mother.[15] More research on DM2 and early childhood obesity should be conducted to investigate further.

Leptin and Diabetes Mellitus

Leptin is a hormone that responds to appetite and weight control. Leptin is secreted by the placenta and from adipose tissues. It mediates long-term regulation of energy balance by suppressing food intake, and thus induces weight loss. During normal gestation, the placenta produces leptin. Increasing levels of leptin in the bloodstream are then compensated by the hypothalamic leptin resistance, which is required to increase food intake.[7,10,14] Then around mid-gestation, insulin resistance progressively increases and is mediated by increased in adiposity and placental hormones.[10]

The relationship between leptin levels and the intrauterine growth pattern and insulin level was observed in several studies. Leptin is also thought to counter-regulate insulin and may

be involved in obesity and energy distribution. One hypothesis proposed that high level of insulin in the fetal bloodstream during development can induce insulin and leptin resistance via downregulation of insulin and leptin receptors on cells.[10] Polyphagia or excessive hunger can be a result from insulin and leptin resistance, which can lead to hyperinsulinemia and growth of fat cells. Overgrowth in fat cells in utero and postnatally increases the risk of obesity early in childhood. [7,14]

Several studies found that when leptin was measured at birth, high levels of leptin was positively related to infant birth weight and fetal adipose tissues.[7,10,14] When comparing leptin and insulin levels between diabetic mothers and non-diabetic mothers, both leptin and insulin levels were significantly higher in diabetic mothers than in nondiabetic mothers. Leptin level was the only factor that was found to be positively correlated with insulin levels, the mothers' BMI, and the mothers' age.[7] In the diabetic mothers' group, only insulin levels showed a positive correlation with leptin. Whereas in non-diabetic mothers, age was the correlation with leptin levels.[7] These findings were supported by two other research studies, where GDM exposure was associated with both elevated leptin and insulin in the bloodstream of the newborn.[7,22]

It is still unknown as to what mechanism cause an elevated leptin level in diabetes. A study in 2014 from the American Journal of Obstetrics and Gynecology explored the concept of leptin DNA methylation in gestational diabetes and obese mothers. They observed that higher leptin DNA methylation was found in GDM placenta compared to non-GDM control.[10] There was also a report from studies that as glucose level rise in the placenta of the fetal side, leptin

DNA methylation in placenta on fetal side decreases.[10] In contrast to that, as glucose of the placenta on the mother side rises, leptin DNA methylation also tandemly increases.[10] With that said, the study postulated that their observation of higher leptin promoter DNA methylation in placenta from especially obese pregnancy could result in lower placenta leptin production due to a mechanism of resistance in response to basal excess leptin in the bloodstream of the mother.[10] Since there is an inverse relation between leptin and insulin in the developing fetus, low leptin across the placenta induces an increase in fetal insulin level. This programming could increase the risk of overweight and obesity during childhood.

In summary, it was found that infant of mothers with diabetes has low leptin level and high insulin level. A low leptin level would mean that these children are unable to detect satiety and suppress their hunger. Which in turn program themselves to overeat and cause them to gain more weight. The study of DNA methylation is one of the few types of researches that analyze leptin in relation to diabetes in pregnancy. Currently, the result of this study is not quite adequate to create any hypothesis. There are also many studies that associate leptin with various health conditions. So, more research is warranted to investigate its specific role in diabetes in pregnancy and childhood obesity.

Milk Composition of Mother with Diabetes Mellitus

Aside from insulin, glucose, and leptin affecting infant of mothers with diabetes, breast milk composition has also been questioned. Both the CDC and WHO suggested that breastfeeding may be protective against obesity and diabetes in later life.[4] The WHO even

recommends breastfeeding as the ideal way of providing nutrition to infants especially in the first 6 months of life.[4] But to date, the role of breastfeeding in offspring of mothers with diabetes has not been investigated closely. Only two studies seemed to show some evidence that challenges the CDC and WHO breastfeeding recommendations.

One of the two studies from the American Diabetes Association analyzed the composition of diabetic mother's milk[11] When energy content and macronutrient of breast milk from women with diabetes were characterized, an increase in the concentration of glucose and insulin and higher energy content was observed. Breast milk from non-diabetic mothers does not have as high of energy content found in breast milk of diabetic mothers.[11] Even when the diabetic mother has good metabolic control, significant modifications were found in the colostrum and transitional milk.[11,12] This study speculate that even a small increase in energy intake from altered breast milk composition may have a long-term effect on body weight and metabolism for offsprings of diabetic mothers later in life.[11]

A different study on long-term impact of neonatal breast feeding on body weight and glucose tolerance in children of diabetic mothers found that infants with high intake of breast milk from their diabetic mother had higher body weight at 2 years old than those of control.[12] This result was found to be independent of birth weight, gestational age, sex age, type of maternal diabetes, or maternal BMI.[12] Impaired glucose tolerance was also noted in children that breastfeed from diabetic mothers.[12] In contrast, there was a reduction in impaired glucose tolerance in children that received banked donor breast milk.[12]

To sum up, it was found that diabetic mothers' breast milk has more fat content, higher concentration glucose, and nutrients than non diabetic mothers' breast milk. Not only that, children that breastfeed by diabetic mothers have higher body weight and impaired glucose tolerance more than those breastfeed by donor breast milk. These are the only two studies that analyze the content of breast milk in diabetic mothers and its effect on childhood overweight and obesity. These research studies are also the first to identify a change in breast milk composition in diabetic mothers that increase the risk of overweight or obesity in toddlers. Further investigation should be conducted in the future before any conclusion can be made.

Method

The research articles for this research was selected using OneSearch online library database. The key words "diabetic mother and childhood obesity" yielded 2,878 results in relevant journals and peer reviewed articles. Inclusion criteria are gestational diabetes, DM1, and DM2, non-diabetic control, and singleton offspring. Exclusion criteria are variables known to affect infant birth weight such as hypertensive disorders, smoking, alcohol, and multiple gestations. Literature publication date was limited to those that were published from the year 2000 to 2018.

Fifteen articles were selected for this research. Articles that were selected were from the American Diabetes Association, Public Library Of Science, American Journal of Obstetrics and Gynecology, Biomed Central, Journal of Perinatal Medicine, and Royal College of Pediatrics

and Child Health. Resources are not limited to those only published in the United States. General information, facts, and current statistics were from government websites such as the Center for Disease Control and the World Health Organization. Specific recommendations for current practice to manage or screen for diseases are sourced from American Academy of Family Physician, American Academy of Pediatrics, and Uptodate.

Discussion

The primary purpose of this study was to examine whether children of diabetic mothers in comparison to children of nondiabetic mothers at an increased risk for developing obesity in the first 10 years of life. Previous research suggests that children of mothers with any type of diabetes mellitus are at increased risk for developing not only diabetes mellitus but central obesity later in life as well. The specificity of the timing when such an effect is to be expected is not very clear. There are also not many published works of literature explore the effect of diabetes mellitus during pregnancy on pre-pubescent children.

This study revealed no significant differences in weight gain in children of GDM mothers in the first 2 years of life than the control group.[20] A significant increase in weight gain is apparent only in offspring who are older than 7 years old when the mother pre-pregnancy BMI was not accounted for.[15] Once the mother's BMI was adjusted in some of the studies, it was found that there is no significant finding between children of GDM mothers and control group.[15] Not all research studies adjusted for the mother's pre-pregnancy weight. With that said, the results that were found have lower sensitivity factor. Overweight and obesity were more

prevalent among children ages greater than 6 years old in those with GDM mothers.[15,20]

In contrary, the offspring of DM1 and DM2 have significantly more weight gain than those of the control group. Offspring of DM1 were observed to have higher BMI at as young as 6 months of age.[21] Whereas offspring of DM2 tend to be larger for gestational age at birth and are heavier than offspring of nondiabetic mothers.[8] Overall, one predictive factor that confidently confirms risk for later overweight and obesity in children of a mother with any diabetes type is macrosomic infants.[8] This correlation was apparent in all studies and is considered an independent factor to predict overweight or obesity in early childhood supporting the thesis question above. Such results suggest that children of mothers with diabetes may have normal weight gain in the first few years of life, but as they age, they become more prone to be overweight or obese.

A number of speculations have been made to explain the GDM mother versus DM1 mother and childhood obesity phenomenon. It was thought that DM1 mothers expose the fetus to intrauterine hyperglycemia for the whole duration of pregnancy period while GDM mother exposed the fetus to hyperglycemia only during the second half of the pregnancy. Relating back to the fuel mediated teratogenesis, it was correlated that the longer a fetus is exposed to an elevated level of glucose, the higher risk for overweight and obesity. Other factors that support this finding are the children's glucose tolerance, insulin sensitivity, leptin level, and mother's milk composition.

An interesting finding was the relationship between each type of diabetes and its effect on the child's glucose level and glucose tolerance. There is no significant finding in fasting glucose but higher 2-hour plasma glucose tolerance tests were observed in offspring of GDM mothers.[15] There was no difference in fasting glucose and 2-hour glucose observed in children of DM1 mother. Significant finding for elevated glucose and insulin resistance, however, was higher in children of DM1 that become overweight or obese later in life around ages 6-8-year-old.[15,21] Whereas children of a mother with DM2 who were overweight or obese tend to have lower insulin sensitivity. It was proposed that maybe offspring of DM2 mothers are exposed to a unique metabolic disturbance than those in GDM and DM1 in addition to the elevated glucose level. This finding implicates that maybe fasting glucose or glucose tolerance test should be implemented as part of health maintenance of children with diabetic mothers. A specific conclusion cannot be made at this moment since there is a limited amount of information and literature published that studies glucose and insulin in prepubescent children.

In relation to insulin sensitivity, leptin hormone was also observed. A positive correlation was observed between insulin and leptin level in mothers with diabetes. As the women become more insulin resistant, her leptin level also increases. Leptin DNA methylation was specifically found to be the causes of elevated leptin level. As glucose concentration rise in the fetal side of the placenta, DNA methylation of leptin decreases in the fetus.[10,22] Low leptin level in the placenta in turn cause an increase in insulin level in the fetus in utero.[10] This relationship increases the risk for overweight and obesity in the child. Leptin not only was associated with obesity, other literature linked leptin to stress, reproduction, and even breast cancer to name a

few. Since leptin hormone is loosely associated with many variables in health disorder, further research should be implemented before any affirmation can be made.

Furthermore, only two research studies analyzed the relationship between breast milk of a diabetic mother and its effect on childhood weight gain. The result showed an increase in insulin, glucose, and higher energy content in breastmilk of diabetic mothers than mothers without diabetes.[11,12] Infants who acquire nutrients from diabetic mothers were observed to have higher body weight for height by age 2.[12] This study provides the association that breastmilk to have a negative effect on an infant's health. This information may not be well received by the general public because of the strong push with breastfeeding from both the WHO and CDC. With breastfeeding being so widely supported, it is not recommended to discourage diabetic mothers from breastfeeding their child.

All in all, many points of limitation were prominent in each literature. The sample size was extremely small for several studies; the majority of the research has samples size of fewer than 500 participants. Some of the studies had only had approximately 100 participants overall. The larger sample size was observed only in systematic reviews and meta-analysis. In one of the controlled studies, there were only 10 participants in each category under study. Not only that, the research groups were not proportionally sampled. There was a tendency to have a much larger sample for the control group than the diabetes group. Since pregnancies are generally healthy, it may be difficult to find research sample for diabetes groups. Not only that, it was not clear how many boys or girls were being analyzed. There were rare if any sort of distinction

between male and female children who were involved in the studies. Variation in sample size and absent in reports of sample population can significantly skew data result from one way to another. In addition to sample size, there were many lost to follow up. This further lowers the pool of sample size even more. Other limitation includes referencing previous studies that are very old and outdated. such from more than 30 years ago as those that were done in the late 1980s.

Certain confounding factors that were unable to exclude from the studies were noted as well. One confounding factor was obtaining the mother's pre-pregnancy BMI. Only half of the study cited in this article have pre-pregnancy BMI adjustment. Moreover, factors such as monitoring weight gain during pregnancy, duration or intensity of breastfeeding, children dietary intake, children physical activity level and intensity, and energy expenditure in comparison to caloric intake.

Conclusion

All in all, by the age of 10, most of the children given birth to any diabetic mothers were either overweight or obese. Children of mothers diagnosed with diabetes mellitus 2 have higher resistance to insulin than children with mother of other diabetes types and leptin was observed to be negatively correlated with insulin level in fetal circulation. Hyperinsulinemia was correlated with low leptin level in the fetal side of the placenta. Breast Milk of mother with diabetes was found to have higher glucose, insulin, and energy than the control group. Future research involving a large number of subjects that start prior to conception to birth to children age 10 are

needed.

An ideal prospective cohort study research design should include at least 2000 participants of mothers of all ethnic background in the Midwest region of the United States. In order to be able to obtain such a large quantity of participants, a collaboration between OBGYN clinical offices and pediatric clinics should be arranged. There should be an equal number in representative with 500 participants in each category of gestational diabetes, type 1 diabetes, type 2 diabetes, and control group. Inclusion criteria are gestational diabetes, DM1, and DM2, non-diabetic control, and singleton offspring. Exclusion criteria are variables known to affect infant birth weight such as hypertensive disorders, smoking, alcohol, and multiple gestations.

Data to be collected from the mothers are weight, glucose, insulin, and leptin level. Weights should consist of self-report pre-pregnancy weight, end of first trimester weight, end of second trimester weight, and end of third trimester weight. Glucose, insulin, and leptin level should be collected via venipuncture starting at 8 weeks gestation then every 4 weeks on after until the birth of the child.

Data to be collected from the children are also weight, glucose, insulin, and leptin level. Weights should be collected at 6 months, 1 year, and every year after until age 10. Glucose, insulin, and leptin level should be collected via heel poke or venipuncture starting at birth, then 1 year then yearly after until age 10. In order to control for consistent, follow up, these data should be collected at the time of annual well child check if possible.

Factors to be adjusted for in this ideal study are infant weight, caloric intake, and level of physical activity. Infant weights should be adjusted for breastfed versus formula fed infant ages 6 months and 1 year old. Since formula fed infant tends to gain more weight than a breastfed infant. Caloric intake should be measured based on an estimate of a daily amount of caloric intake in a typical week. Physical activity level should be classified using the MET for grading of metabolic equivalence. Low intensity activity includes walking around home, sitting at computer or TV, and eating. Moderate intensity includes brisk walking, vacuuming, and shooting basketball. High intensity includes running, swimming, soccer, and jump rope.

This study design is feasible because there are studies similar to this published in the past. Limitation for this study design is having mother self-report pre-pregnancy BMI, and daily physical activity recall and recording. Since a mother perspective on what is considered high intensity for the year may be different from each other. One may overestimate or underestimate their child level of energy expenditure.

References

1. Childhood obesity facts. www.cdc.gov Web site. https://www.cdc.gov/healthyschools/obesity/facts.htm. Updated 2018. Accessed July 19, 2018.

2. Barss V, Repke J. Care during pregnancy for women with type 1 or 2 diabetes mellitus. https://www.uptodate.com/contents/care-during-pregnancy-for-women-with-type-1-or-2-diabetes-mellitus-beyond-the-basics#H1 Website. . Updated 2017. Accessed July 19, 2018.

3. Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus. *Am Fam Physician*. 2015;91(7):460-467.

4. Benefits of breastfeeding; www.aap.org Web site. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Breastfeeding/Pages/Benefits-of-Breastfeeding.aspx. Updated 2018. Accessed July 19, .

5. Type 1 or type 2 diabetes and pregnancy; www.cdc.gov Web site. https://www.cdc.gov/pregnancy/diabetes-types.html. Updated 2017. Accessed July 18, .

6. Butte NF, Garza C, Burr R, Goldman AS, Kennedy K, Kitzmiller JL. Milk composition of insulin-dependent diabetic women. *J Pediatr Gastroenterol Nutr*. 1987;6(6):936-941.

7. Vela-Huerta MM, Amador-Licona N, Anaya-Aguirre S, Guizar-Mendoza JM, Velazquez-Bustamante A, Murillo-Ortiz B. Insulin and leptin levels in appropriate-for-gestational-age infants of diabetic mother. *Iranian journal of pediatrics*. 2012;22(4):475.

8. Hunter WA, Cundy T, Rabone D, et al. Insulin sensitivity in the offspring of women with type 1 and type 2 diabetes. *Diabetes Care*. 2004;27(5):1148-1152.

9. Lawlor DA, Fraser A, Lindsay RS, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: Findings from a prospective pregnancy cohort. *Diabetologia*. 2010;53(1):89-97.

10. Lesseur C, Armstrong DA, Paquette AG, Li Z, Padbury JF, Marsit CJ. Maternal obesity and gestational diabetes are associated with placental leptin DNA methylation. *Obstet Gynecol*. 2014;211(6):654. e9.

11. Rodekamp E, Harder T, Kohlhoff R, Franke K, Dudenhausen JW, Plagemann A. Long-term impact of breast-feeding on body weight and glucose tolerance in children of diabetic mothers: Role of the late neonatal period and early infancy. *Diabetes Care*. 2005;28(6):1457-1462.

12. Plagemann A, Harder T, Franke K, Kohlhoff R. Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. *Diabetes Care*. 2002;25(1):16-22.

13. Dabelea D. The predisposition to obesity and diabetes in offspring of diabetic mothers. *Diabetes Care*. 2007;30(Supplement 2):S174.

14. Tapanainen P, Leinonen E, Ruokonen A, Knip M. Leptin concentrations are elevated in newborn infants of diabetic mothers. *Hormone Research in Paediatrics*. 2001;55(4):185-190.

15. Kawasaki M, Arata N, Miyazaki C, et al. Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. *PloS one*. 2018;13(1):e0190676.

16. Pham M, Brubaker K, Pruett K, Caughey A. 266: The risk of childhood obesity in toddler offspring of gestational diabetic mothers. *American Journal of Obstetrics & Gynecology*. 2012;206(1):S130.

17. Patel S, Fraser A, Smith GD, et al. Associations of gestational diabetes, existing diabetes, and glycosuria with offspring obesity and cardiometabolic outcomes. *Diabetes Care*. 2011:DC_111633.

18. Kawasaki M, Arata N, Miyazaki C, et al. Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. *PloS one*. 2018;13(1):e0190676.

19. Logan KM, Gale C, Hyde MJ, Santhakumaran S, Modi N. Diabetes in pregnancy and infant adiposity: Systematic review and meta-analysis. *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 2017;102(1):F72.

20. Plagemann A, Harder T, Rodekamp E, Kohlhoff R. Rapid neonatal weight gain increases risk of childhood overweight in offspring of diabetic mothers. . 2012.

21. Rijpert M, Evers IM, de Vroede MA, de Valk HW, Heijnen CJ, Visser GH. Risk factors for childhood overweight in offspring of type 1 diabetic women with adequate glycemic control during pregnancy: Nationwide follow-up study in the netherlands. *Diabetes Care*. 2009;32(11):2099-2104.

22. Dabelea D. The predisposition to obesity and diabetes in offspring of diabetic mothers. *Diabetes Care*. 2007;30(Supplement 2):S174.

AUGSBURG
UNIVERSITY

Augsburg University Institutional Repository Deposit Agreement

By depositing this Content ("Content") in the Augsburg University Institutional Repository known as Idun, I agree that I am solely responsible for any consequences of uploading this Content to Idun and making it publicly available, and I represent and warrant that:

- I am *either* the sole creator or the owner of the copyrights in the Content; or, without obtaining another's permission, I have the right to deposit the Content in an archive such as Idun.
- To the extent that any portions of the Content are not my own creation, they are used with the copyright holder's expressed permission or as permitted by law. Additionally, the Content does not infringe the copyrights or other intellectual property rights of another, nor does the Content violate any laws or another's right of privacy or publicity.
- The Content contains no restricted, private, confidential, or otherwise protected data or information that should not be publicly shared.

I understand that Augsburg University will do its best to provide perpetual access to my Content. To support these efforts, I grant the Board of Regents of Augsburg University, through its library, the following non-exclusive, perpetual, royalty free, worldwide rights and licenses:

- To access, reproduce, distribute and publicly display the Content, in whole or in part, to secure, preserve and make it publicly available
- To make derivative works based upon the Content in order to migrate to other media or formats, or to preserve its public access.

These terms do not transfer ownership of the copyright(s) in the Content. These terms only grant to Augsburg University the limited license outlined above.

Initial one:

X I agree and I wish this Content to be Open Access.

___ I agree, but I wish to restrict access of this Content to the Augsburg University network.

Work (s) to be deposited

Title: Are children of diabetic mother in comparison to children of a nondiabetic mother at increased risk for developing obesity in the first 10yrs of life?

Author(s) of Work(s): Chhorn Pho, Meredith Wold

Depositor's Name (Please Print): Mike Bloomberg

Author's Signature: [signature] Date: 8/14/2018

If the Deposit Agreement is executed by the Author's Representative, the Representative shall separately execute the Following representation.

I represent that I am authorized by the Author to execute this Deposit Agreement on the behalf of the Author.

Author's Representative Signature: [signature] Date: 8/14 2018