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Development of Diabetes and Obesity in Infants of Diabetic Mothers

Breanna Ritchie

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Breana Ritchie, BSN, RNC-NIC

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Abstract

Gestational diabetes mellitus (GDM), type two diabetes (T2DM), and obesity are on the rise in all populations and ethnicities throughout the United States causing serious health consequences. The foundation for this review was determined by an outpatient visit conducted at the clinical education center with a 45-year-old female who presented for complaints of fatigue and weight gain. It was then identified that this patient had poorly controlled T2DM, with a family history of T2DM, and who also had GDM with her last two pregnancies prior to her diagnosis of T2DM. This contributed to the systematic search for a correlation between GDM and the development of obesity and T2DM in the offspring and the current recommendations of management for these children. The literature review was conducted using CINAHL and PubMed. Multiple searches were completed using the keywords listed below. Upon further review, 15 were identified as relevant for this review. The findings of this literature review point to a correlation between GDM and the development of T2DM/obesity in their offspring. This implies that these children need closer monitoring when compared to children who were not exposed to diabetes in-utero.

Keywords: infant of diabetes, gestational diabetes, obesity, type two diabetes

Background

The incidence of GDM has been on the rise and is now affecting about 7.5% of all pregnancies (Riskin & Garcia-Prats, 2016). This increase in GDM is in direct correlation with the pandemic of obesity and T2DM seen worldwide (Osgood, Dyck & Grassmann, 2011). Gestational diabetes has been correlated with serious health concerns for both the mother and infant. Research has shown that about four to ten percent of GDM mothers will go on to develop T2DM within nine months after delivery (Osgood, Dyck & Grassmann, 2011). Furthermore, these women have a 35-65% risk of developing T2DM in the twenty years following their pregnancy (Grossman & Porth, 2014). The case report patient developed within five years. The consequences for the infant are high and include congenital anomalies, macrosomia, respiratory distress, metabolic complications, cardiomegaly, and prematurity with 47% of infant of diabetic mothers (IDM) requiring a neonatal intensive care unit admission (Riskin & Garcia-Prats, 2016). There is further risk in childhood of the IDM developing hypertension, dyslipidemia, obesity, and impaired glucose tolerance leading to T2DM (Mitanchez, Burguet & Simeoni, 2014).

A pioneering study in the Pima Indian population showed that children of mothers with a history of GDM had higher rates of obesity and T2DM. This specific population has one of the highest prevalence of GDM (Pettitt, Nelson, Saad, Bennett & Knowler, 1993). It was found that 45% of the children of mothers with a history of GDM developed T2DM between the ages of 20-24 when compared to their non-diabetic counterparts (Pettitt, Nelson, Saad, Bennett & Knowler, 1993). These adults were followed further and more than two-thirds of the children from the initial study had developed T2DM by the age of 34 (Riskin & Garcia-Prats, 2016).

With this knowledge and the research showing there is a trans-generational effect of experiencing hyperglycemia and hyperinsulinemia in-utero, there are applications that can be made to the case report patient and her family. This patient's children should be screened and managed differently than children who were not an infant of a diabetic mother.

Case Report

For the purpose of privacy in this specific case report, the patient will be referred to as Sally. Sally is a 45-year-old female who reports to the clinic as encouraged by her diabetes educator from a previous facility. She has complaints of fatigue and a 20-pound weight gain over the past six months. No history or physical information was on file and was all obtained during this visit.

History

Sally's medical history includes the following: GDM (in two of three pregnancies, managed poorly with diet), T2DM, hyperlipidemia, and hypertension. No environmental or drug allergies reported. No surgical history reported. The patient has a pertinent family history for heart disease and an acute MI in her father (died at age 55) and her mother has T2DM. She reports a negative family history for cancer or thyroid disease.

She reports that she does not remember the last time her hemoglobin A1C (HbA1C) was checked or the result. She also reports she is not taking her Metformin as prescribed because she had heard it could cause a heart attack and her father died of a heart attack. She is taking all of her other medications as prescribed. She does not follow her blood pressures at home but she has been checking her blood sugars in the morning prior to eating breakfast a couple times a week and results range from 150-200 mg/dL.

She feels that her diabetes management is going ok, as she doesn't feel any different from when she was on the Metformin regularly to now. She does not exercise and says that she eats fairly well but probably could continue to make improvements. She had her last vision exam about six months ago. She denies any recreational drug, tobacco, or alcohol use. The patient is prescribed the following medications: Metformin 500 mg twice daily, Aspirin 81 mg daily, Lisinopril 20 mg daily, Atrovastatin 20 mg daily, and Multivitamin daily.

Review of Systems

During her exam a review of systems was completed. The only abnormality Sally reported was chronic fatigue, which she reports to affect her daily and does not change regardless of the amount of sleep she gets. Some days she reports she leaves work to go home and nap. All other systems were reviewed with no abnormalities.

Physical Exam

Vitals were as followed: blood pressure 148/98 mmHg, heart rate 80 beats per minute, respiratory rate 20 breathes per minute, temperature 98.6 degrees Farenheit, weight of 230 pounds and height of 5 feet 4 inches. Her calculated BMI is 39.5. Vital signs are within normal limits except the patient's BMI, which places Sally in the obese III category and her blood pressure is elevated (American College of Cardiology, 2017; National Heart, Lung and Blood Institute, 2018).

Physical examination abnormal findings are as follows: monofilament exam performed and absent on the bottom, lateral aspect from heel to pinkie toe bilaterally. Minimal sensation noted at the tip of the left great toe. Normal assessment is as follows: visual inspection of both feet performed, no lesions or ulcers noted, left and right pedal

pulses present and no edema noted. S1 and S2 heart with no murmurs, clicks or rubs. Radial and carotid pulses +2, symmetrical without bruits. Lung sounds clear throughout lung fields. All other physical examination was unremarkable.

Management of Care

The following laboratory tests were obtained today: HbA1C, comprehensive metabolic panel, TSH with reflex, and Lipid Panel. The results are as follows: HbA1C 8.5, blood sugar (fasting) 178, TSH 6.4, T4 0.8, Total Cholesterol 187, HDL 43, LDL 133, and Triglycerides 180. The laboratory test results and positive exam for neuropathy were discussed with the patient at length. Sally was unaware of the neuropathy of her feet. Medication treatments for neuropathy were discussed but patient declines at this time. She wishes to work to lower her HbA1C first. Education provided on proper foot care. Plan to restart taking Metformin at 500 mg BID, if tolerating after two weeks increase to 1000 mg BID daily. Increase Lisinopril to 40 mg daily. Patient will start to check fasting blood sugars before breakfast daily and document results. Patient states that she will start to add more physical exercise into her daily routine. Patient would like to meet with a dietician, referral placed. In addition, referral placed for follow up appointment with a diabetes educator.

Follow up

Our diabetes educator will follow weekly with patient for the next four weeks via telephone. The patient will return to the clinic in two weeks for a nurse visit to recheck blood pressure. Medication adjustments will be made if needed. Patient will schedule a follow up appointment with this provider in one month to review medication compliance, fasting blood sugars and blood pressure. Patient was in agreement with plan.

Literature Search Strategies

The purpose of this literature review was to demonstrate the correlation between IDM and the development of obesity and T2DM later in life, which requires closer follow-up and management. Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PubMed databases were used.

The first search was completed using CINAHL with the keywords “infant of diabetes” and “type two diabetes”. This search resulted in 808 articles. The search was then limited to include articles that were printed within the last eight years, peer reviewed and the keywords “childhood obesity” were included. This resulted in 25 articles. A second search was completed using PubMed with the keywords “gestational diabetes” and “childhood obesity”. This search resulted in 356 articles. The search was then limited to include articles that were printed within the last five years, included only humans, with full text available, which resulted in 65 articles.

Furthermore, the Chester Fritz Library website was searched with the keywords of “infant of diabetes” and “childhood type 2 diabetes”. This resulted in 10,361 results. The search was then limited to the last five years and to include the topic of “gestational diabetes”. This resulted in 142 articles. Another search was completed with the keywords “childhood obesity screening” which resulted in 22,219 articles but was then limited to last five years with topic refined to include “type 2 diabetes”. This resulted in 144 articles. Three other articles that were not published within the last ten years were included in this literature review as the articles and study results were referenced multiple times within the other literature used for this discussion. Upon further review, 15 were

identified as relevant for this review as their research was directly related to GDM, T2DM, and obesity in children.

Literature Review

Gestational diabetes mellitus

Gestational diabetes is defined "as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy" (Hunt, Whitelaw & Gayle, 2014, p 238). The risk of developing GDM is higher when obesity is present and only increases as weight increases. For overweight women the risk of developing GDM compared to women of normal weight is 2.14-fold higher, for obese women the risk is 3.56-fold higher, and for severely obese women the risk is 8.56-fold higher (Mitanchez et al., 2015).

Screening recommendations for GDM varies by organization. In the United States, all pregnant women are screened between 24-28 weeks gestation. Women will first have a 50-gram oral glucose challenge where their blood glucose is tested at one hour. If their blood sugar is reported to be above the threshold, they then are required to do a three-hour oral glucose tolerance test (OGTT). The American Congress of Obstetricians and Gynecologist support this method. The International Association of Diabetes and Pregnancy Study Group (IADPSG) recommend a two hour 75-gram OGTT. If the IADPSG recommendations were adapted worldwide, it is estimated that the incidence of GDM could increase to over 16% (Hunt, Whitelaw & Gayle, 2014).

A longitudinal cohort study of U.S children found that exposure to maternal obesity was just as strong of a predictor for metabolic syndrome and large for gestational age (LGA) as GDM (Boney, Verma, Tucker & Vohr, 2005). They suggest that the

overweight/obese mothers without clinical GDM may experience hyperglycemia that is just below the threshold for diagnosis or occurs later in pregnancy (after screening), causing the fetus to be exposed to hyperinsulinemia and maternal hyperglycemia (Boney, Verma, Tucker & Vohr, 2005).

Carolan-Olah, Duarte-Gardea & Lechuga (2015) completed a thorough literature review of 31 research studies with the objective of finding evidence to link early life nutrition and fetal programming for adult disease. Four areas of fetal exposure were found to have an impact: under nutrition, over nutrition, GDM and infant catch up growth (Carolan-Olah, Duarte-Gardea & Lechuga, 2015). For the purpose of this review, over nutrition and GDM findings will be reviewed as it pertains to the case report patient.

Over nutrition includes LGA infants (macrosomia, > 90^{th} percentile) and increased adiposity. The fetal (in-utero) exposure to over nutrition causes permanent changes to the infant's appetite, satiety and energy regulation via the hypothalamus appetite regulatory system. One main hormone that is affected in this system is leptin (Carolan-Olah, Duarte-Gardea & Lechuga, 2015). In adults, leptin plays a vital role in energy homeostasis by reducing appetite and increasing energy expenditure when increased adiposity is present (Ojha, Saroha, Symonds & Budge, 2013). When leptin levels are high, it acts to suppress appetite however; this effect can become compromised (leptin resistance) and is what is seen in infants exposed to maternal obesity (Carolan-Olah, Duarte-Gardea & Lechuga, 2015).

Leptin is secreted by adipocytes in direct correlation to how many adipocytes are present. A study on sheep showed that maternal over nutrition during pregnancy caused down-regulation of leptin receptors (Ojha, Saroha, Symonds & Budge, 2013). In rodents,

a reduction of circulating leptin levels was seen in addition to the down-regulation of the receptors (Ojha, Saroha, Symonds & Budge, 2013). “These experiments suggest that postnatal over nutrition and rapid early growth lead to the resetting of the brain’s energy-sensing and appetite centers. Consequently, that individual becomes more prone to relative hyperphagia and obesity” (Ojha, Saroha, Symonds & Budge, 2013, p 820). If Sally’s mother was also a GDM (which is unknown), she would have been exposed to hyperglycemia and hyperinsulinemia prior to birth, placing her at risk for developing leptin resistance. Also, because Sally reports that she poorly managed her GDM, her two youngest children were also exposed to this environment.

Many initial studies were completed with Native Americans as the target population due to the higher prevalence of T2DM and GDM within this ethnic group. The Pima Indian data, discussed previously, was further supported by a study completed on Saskatchewan First Nations people. Osgood, Dyck & Grassmann (2011) completed a population study of inter- and intra-generational interaction of T2DM and GDM with data from 1956-2006. They found that within the Saskatchewan First Nations people, GDM may be responsible for 19-30% of all T2DM cases (Osgood, Dyck & Grassmann, 2011). Follow up studies have started to look at different ethnic groups to identify if there is also a correlation. One such study identified there is an increased prevalence of metabolic syndrome in LGA offspring in white adolescents. This prevalence was similar to previous data, which is discussed above (Boney, Verma, Tucker & Vohr, 2005). This is significant because it is the first study that showed this correlation in the general population in the U.S. (Boney, Verma, Tucker & Vohr, 2005).

Other studies have looked to compare sibling pairs where one sibling was born before the onset of maternal diabetes and the other born after the onset. “The risk of diabetes was significantly higher in siblings born after the mother developed diabetes than in those born before the mother’s diagnosis” (Mitanchez et al., 2015, p 261). A Swedish study compared male siblings born before and after the diagnosis of diabetes in their mother. At age eighteen, the BMI was higher in the sibling exposed to diabetes in-utero (Mitanchez, Burguet & Simeoni, 2014). With this data, Sally’s youngest two children are at a greater risk for developing T2DM and obesity then the older sibling.

Of other significance, a small cross-sectional study completed in a public hospital in Sydney, Australia looked to describe the body compositions of IDM whose mothers had well controlled GDM with mothers who did not have GDM. It was found that there was no significant difference in body composition of infants when the mothers had good glycemic control. This is one of the first studies to demonstrate that well controlled GDM can have minimal side effects on the infant’s growth in-utero and further emphasizes the importance of good glycemic control in GDM (Au, Raynes-Greenow, Tuerner, Carberry & Jeffery, 2013).

Obesity

Obesity rates in children are on the rise, starting with LGA infants. The occurrence of macrosomia is 5-20% but this is an increase of 15-25% in the last decade (Mitanchez et al., 2015). The CDC (2017) reports that obesity is affecting 12.7 million or 17% of children and adolescents in the United States. This prevalence is higher among Hispanics (21.9%) and non-Hispanic black (19.5%) when compared to non-Hispanic whites (14.7%) (Center for Disease Control, 2017). Children of low-income and who use

government services (e.g. Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)) are disproportionally affected. Additionally, children who are overweight or obese as preschoolers are five times more likely to be overweight or obese as adults (Center for Disease Control, 2017).

Zhao et al. (2016) completed a multinational cross-sectional study to examine the correlation that GDM had with childhood obesity. A study that was completed had 4,740 children ages nine to eleven years old in twelve countries around the world participate. Within the study population the prevalence of GDM was 4.3%. A correlation between GDM and childhood obesity (12.3%), central obesity (9.9%), and high body fat (8.1%) were found (Zhao et al., 2016). Once adjusted for variables this still remained statistically significant showing that children of GDM had increased odds of developing childhood obesity by the ages of nine to eleven (Zhao et al., 2016).

One cohort study reviewed the correlation of maternal obesity, excessive gestational weight gain (EGWG), GDM and breastfeeding to the impact of childhood obesity. In this review, 15,710 mother-child pairs were included and found that maternal obesity was associated more with the risk for childhood obesity than GDM. It was also found that mothers who were overweight or obese prior to pregnancy were more likely to have EGWD, GDM, and were less likely to breastfeed greater than six months (Bider-Canfield et al., 2016).

Breastfeeding has benefits for the long-term obesity risk. It has been found that the longer the duration of breastfeeding, the lower the tendency of obesity later in life for the infant. It is suggested that for every month the infant is breastfed, the risk for developing obesity decreases by four percent (Mitanchez et al., 2015). When

breastfeeding is compared to formula feeding, the following benefits are noted: glucose tolerance, hypertension, dyslipidemia, reduction of overall body size, and slows BMI growth both in infancy as well as childhood (Mitanchez, et al., 2015). Of greater importance when infants were breastfed for greater than six months, there was a decrease in the infant's adiposity levels associated with exposure to hyperglycemia in-utero (Mitanchez, Burguet & Simeoni, 2014).

A systematic review completed by Young, Johnson, and Krebs (2012) looked to identify the link behind infant weight gain and child obesity. The growth acceleration hypothesis suggests that the infant's metabolic profile can be programmed by early and rapid growth causing that infant to be more susceptible to obesity and metabolic syndrome (Young, Johnson & Krebs, 2012). A critical window for this growth includes the in-utero environment and programs the child's metabolic profile and risk for chronic disease. The first six months post-partum was deemed another critical window for metabolic programming in the child. This is a window that the provider has direct access to for management (Young, Johnson & Krebs, 2012).

Another study that was reviewed found that when growth was measured in the first two years of life, the infants who had accelerated growth in this time had a higher BMI and percentage of body fat at age five which then continued into adulthood with increased total and abdominal adiposity (Young, Johnson & Krebs, 2012). A prospective birth cohort study reviewed 851 children at the age of eight. The children who had greater weight gain between birth and three years of age had lower insulin sensitivity, higher BMI and waist circumference (Ojha, Saroha, Symonds & Budge, 2013).

Other studies have looked at this correlation over smaller intervals of time. A Chinese cohort study found that an increase in weight for age in the first three months of life was associated with a higher BMI at the age seven (Young, Johnson & Krebs, 2012). A multi-center cohort study in the U.S. also found that increased weight gain in the first four months of life was associated with a higher BMI at age seven (Young, Johnson & Krebs, 2012). Furthermore, an additional study compared infant weight gain from birth to six months and childhood weight gain between the ages of three and six years of age. The children were also assessed at age seventeen and the childhood weight gain was not associated with a metabolic risk whereas the infancy weight gain was (Young, Johnson & Krebs, 2012).

Current Screening Recommendations

What are the recommendations for screening for T2DM and obesity in children and adolescents? The American Diabetes Association (ADA) recommends testing children for diabetes in asymptomatic patients who are overweight or obese (BMI > 85th percentile) and meet two of the following criteria: T2DM in a first or second degree relative, a high risk racial/ethnic group, signs of insulin resistance or conditions associated with insulin resistance, and maternal history of DM or GDM (Laffel & Svorn, 2017). The ADA recommends testing begin at the age of ten years or the onset of puberty, whichever comes first. If results are normal then testing should be repeated every three years and annually in more high-risk patients (Laffel & Svorn, 2017). Sally's younger two children should be monitored for obesity closely as they meet two of the criteria for screening and her oldest meets one.

The ADA also recommends screening children who present with the typical symptoms of diabetes, such as polydipsia, polyuria, blurred vision or weight gain (Laffel & Svorn, 2017). Screening should include the use of FBS, HbA1C and OGTT (American Diabetes Association, 2010; Laffel & Svorn, 2017). The following results are considered diagnostic for pre-diabetes and diabetes respectively: HbA1C 5.7-6.4% and FBS 100-125 mg/dL and HbA1C ≥ 6.5% and FBS ≥ 126 mg/dL (Laffel & Svorn, 2017).

Screening of children and adolescents for T2DM usually has a low yield for identifying T2DM but a high yield in identifying pre-diabetes. One study examined a population of eighth graders and found that 43% met the criteria for pre-diabetes and only 0.5% met the criteria for diagnosis of T2DM (Laffel & Svorn, 2017). Diabetes can have an extended latency period where the patient is still asymptomatic but changes are occurring at a cellular level. This reinforces the need for screening of asymptomatic children so interventions can begin prior to the onset of symptoms (American Diabetes Association, 2000). It also strengthens the need to monitor children closely, especially IDM children, as their risk for developing T2DM is even higher.

Because of the debate on what is the best screening tool for diabetes in children, Barr, Mengwall, Franklin & Fierman (2014) sought to demonstrate the validity of screening for T2DM and pre-diabetes in children. The HbA1C of ≥ 5.7% and FBS ≥100 mg/dL and homeostatic model assessment of insulin resistance (HOMA-IR) were compared with OGTT to assess if combining screening options improved the ability to rule out diabetes and pre-diabetes. It was found that combined screening resulted in improved sensitivity. The combination of the HbA1C/FBS was more sensitive to rule out pre-diabetes than the HbA1C/HOMA-IR combination. HbA1C/FBS combination was

compared to the OGTT and was found to be just as sensitive as the OGTT in identifying glucose tolerance (Brar, Mengwall, Franklin & Fierman, 2014).

Many resources discuss that HbA1C should not be used solely for the diagnosis of diabetes in a child as it has not been adequately validated as a screening tool (Laffel & Svorn, 2017). However, one multicenter study (included 4848 children) found that HbA1C was a more reliable screening tool for this population when compared to the OGTT (Ehehalt et al., 2017).

Long-term prognosis for children who are diagnosed with T2DM is relatively unknown. What is known is that within two years of diagnosis, glycemic control deteriorates and it is estimated that these children may have a loss of up to fifteen years of life expectancy. This is coupled with the increase risk of serious health complications, worse cardiovascular risk profiles and risk for renal disease that are being seen by the time these children are in their forties (Mitanchez et al., 2015; Pulgaron & Delamater, 2014).

The USPSTF recommends screening all children for obesity starting at age six. Screening occurs by measuring height and weight then calculating BMI (Pulgaron & Delamater, 2014). The CDC defines overweight as a BMI that is at or above the 85th percentile and below the 95th percentile when compared to children of the same sex and age using the CDC's growth charts. Obesity is when the BMI is at or above the 95th percentile (Center for Disease Control, 2016). If the child is considered to be overweight or obese it is recommended that implementation be aggressive and include diet modification, physical activity and behavioral childhood obesity treatments (Pulgaron & Delamater, 2014).

Learning Points

When GDM is uncontrolled, the fetus develops hyperinsulinemia due to the mother's hyperglycemia. This environment has long-term consequences of macrosomia, childhood obesity, and early-onset T2DM. What is most concerning is the vicious circle this creates across generations. Maternal obesity/diabetes causes fetal over nutrition. This then places them at higher risk for early-onset T2DM and obesity, which places them at higher risk for adult obesity, T2DM and metabolic syndrome (Carolan-Olah, Duarte-Gardea & Lechuga, 2015).

- All pregnant women should be screened for GDM with the two-hour OGTT as recommend by the IADPSG between 24-28 weeks gestation.
- Weight loss should be recommended for all women of childbearing age who are overweight, obese, and severely obese with the goal of starting pregnancy at a healthy weight and subsequently encouraging a healthy weight gain during pregnancy.
- Continued encouragement of mothers to breastfeed for greater than six months.
- Screening for obesity in childhood should begin before age six. Furthermore, infants who were IDM, LGA at birth or whose growth places them in the 85th percentile or higher be monitored monthly for weight gain for the first six months of life.
- Aggressive screening for T2DM be completed in asymptomatic children according to the ADA recommendations.

- Comprehensive weight management programs be implemented for both the mother and child including dietician involvement, physical activity, family-based behavioral lifestyle intervention, internet delivered interventions, residential interventions and school-based interventions.

Primary care providers are in a unique position to implement these recommendations at every stage of life starting while the infant is still in-utero. The child's IDM status needs to be remembered throughout their life, especially in regards to primary prevention, screening and management of obesity and T2DM. It is estimated that the medical community is only beginning to see the tip of the iceberg and the generational impact of GDM will become more dominant. This trans-generational pandemic needs to be the target of prevention through aggressive screening and management throughout all generations.

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