ORIGINAL ARTICLE

Technology and Pregnancy

Kristin Castorino^{1*}, Moshe Hod², Lois Jovanović¹, Jennae Reken^{1*},
Maria E. Zepeda^{1*}, and Hayley Zyndorf^{1*}

Introduction

AMONG EXPERTS, THERE IS A GROWING AWARENESS THAT A PREGNANCY complicated by diabetes poses significant risks for both mothers and offspring. Accompanying this increased awareness has been an increase in related research. With over 1,700 relevant articles published in the last year, it was harder than ever to choose the most notable. After a systematic review, we decided on 13 articles addressing the most cutting-edge findings in the field of diabetes and pregnancy research. We have seen how early prediction plays a key role in treatment and maintenance of glycemic control for both the mother and the offspring. Several biomarkers and genetic factors have been identified as predictors of gestational diabetes. There has been an expansion of research pertaining to types of diabetes beyond just gestational diabetes mellitus. So much groundbreaking research is being conducted as this field moves toward a more holistic approach. We feel that the following articles best highlight the most recent and relevant findings, and will provide the most benefit when applied in a clinical setting.

Diabetes and pregnancy: an Endocrine Society clinical practice guideline

Blumer I¹, Hadar E², Hadden DR³, Jovanovic L⁴,
Mestman JH⁵, Murad MH⁶, Yorgev Y²

¹Charles H. Best Diabetes Centre, Whitby, Ontario, Canada;

²Helen Schneider Hospital for Women, Petach Tikva, Israel;

³Royal Victoria Hospital, Belfast, Northern Ireland, UK;

⁴Sansum Diabetes Research Institute, Santa Barbara, CA;

⁵University of Southern California, Los Angeles, CA; and

⁶Knowledge and Evaluation Research Unit, Mayo Clinic, Rochester, MN

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American Diabetes Association Standards of Medical Care in Diabetes

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Objective

Both articles formulate plans with the most updated suggestions for treatment of diabetes and pregnancy. American Diabetes Association (ADA) guidelines address diabetes in four clinical categories: type 1 diabetes, type 2 diabetes, diabetes due to genetic causes (MODY), and gestational diabetes mellitus. The purpose of the Endocrine Society guidelines is to specifically address diabetes and pregnancy in type 1 diabetes, type 2 diabetes, and gestational diabetes, and provide recommendations for clinical treatment.

Methods

The Endocrine Society team created a task force, which met once as a group, and communicated through conference calls and e-mails to reach a general consensus on the guidelines. The recommendations are evidence-based and were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. They are rated using a system of circles, where the number of cross-filled circles indicates the strength of the quality. The ADA has developed a grading system to provide evidence for their Standards of Care using the letters A, B, C, and E.

Results

The Endocrine Society developed guidelines with the most updated information for treating diabetes during pregnancy in areas pertaining to preconception care, gestational diabetes, glucose monitoring and glycemic targets, nutrition therapy and weight gain, blood glucose-lowering pharmacology, labor, delivery, lactation, and postpartum care. The ADA's Standards of Care are released annually. The Standards of Care are an exhaustive list of guidelines, formulated to address the treatment of diabetes in all forms, but the recommendations provided for pregnancy focus mostly on gestational diabetes.

¹William Sansum Diabetes Center, Santa Barbara, CA.

²Helen Schneider Hospital for Women, Rabin Medical Center, Petah Tikva, Israel.

*These authors have contributed equally to this work.

Conclusions

The guidelines established by the Endocrine Society and the ADA Standards of Care both address the same priorities for treating diabetes and pregnancy: maintaining a tight glycemic control to prevent embryopathy. The most recent guidelines are able to provide physicians with stringent expectations for treating a woman with diabetes preconception, during pregnancy, and postpartum.

Comment

The Endocrine Society clinical guidelines and the ADA Standards of Medical Care in Diabetes both aim to test mothers for diabetes during the first prenatal visit and achieve sufficient glycemic control throughout pregnancy. The Endocrine Society guidelines are extensive and cover recommendations for type 1 and type 2 diabetes preconception, throughout pregnancy, and after labor, as well as women diagnosed with gestational diabetes. The ADA Standards of Care mostly addresses the treatment and diagnoses of gestational diabetes, and only briefly touches on women who are diabetic preconception. For clinical use, the Endocrine Society guidelines appear to be more advantageous because of their thorough recommendations on all situations pertaining to diabetes and pregnancy.

Glycosylated fibronectin as a first-trimester biomarker for prediction of gestational diabetes

Rasanen JP, Snyder CK, Rao PV, Mihalache R, Heinonen S, Gravett MG, Roberts CT Jr., Nagalla SR

Departments of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, and the University of Washington, Seattle, WA; Department of Obstetrics and Gynecology, Kuopio University Hospital, and the University of Eastern Finland, Kuopio, Finland; Nizam's Institute of Medical Sciences, Hyderabad, India; and DiabetOmics, Beaverton, OR

Obstet Gynecol 2013; 122: 586–94

Objective

In order to assess glycosylated fibronectin as an early GDM maternal serum, potential GDM biomarkers such as adiponectin, sex hormone-binding globulin, high-sensitivity C-reactive protein (CRP), and placental lactogen were compared and evaluated.

Methods

In this case-control study of 90 pregnant women with GDM from the Finnish maternity serum bank, 92 control subjects were recruited between 2004 and 2010. Maternal serum concentrations were measured during the first 5–13 weeks of pregnancy after a 2-hour 75 g oral glucose tolerance test (OGTT). Enzyme-linked immunoassays were implemented to test five maternal serum concentrations: glycosylated (*Sambus nigra* lectin-reactive) fibronectin, adiponectin, sex hormone-binding globulin, high sensitivity CRP, and placental lactogen. They were compared using univariate and multivariate logistic

regression models and receiver operating characteristic (ROC) curves. A serial-measures analysis was used to compare glycosylated fibronectin variation throughout trimesters in each of the 35 pregnant women without diabetes.

Results

Statistical analysis between the control group and subjects with GDM resulted in a statistically significant p -value of <0.05 at $p=0.009$. All maternal serum concentrations excluding sex hormone-binding globulin were found to be significantly related to GDM. Glycosylated fibronectin had the strongest association under the multianalyte GDM screening panel and resulted with a higher area under the curve (AUC) of 0.93 compared to adiponectin (AUC=0.63), high-sensitivity CPR (AUC=0.68), and placental lactogen (AUC=0.67). Finally, glycosylated fibronectin levels greater than 120 mg/L correctly identified 57 GDM cases with a higher negative predicative value of 95% compared to the positive predicative value of 63% at a population prevalence of 12%, which showed the study being as good as “gold standard.”

Conclusions

Many observations associating maternal serums to GDM confirmed the importance of early predicative biomarkers. This retrospective study evaluated glycosylated fibronectin as the main predictor of GDM for women during the first-trimester pregnancy. Further studies comparing glycosylated fibronectin with maternal BMI changes, pregnancy hypertension, and postpartum diabetes will confirm glycosylated fibronectin as an early pregnancy biomarker replacing the OGTT.

Comment

One of the main concerns for a pregnant mother is to be notified of pregnancy complications as soon as possible to take immediate action. This study reveals the possibility of having a test that diagnoses GDM as soon as the first trimester. It was mentioned that the separation between case group and control group was not adequate for use as a screening test, but various analysis outcomes proved a good estimation because of the low GDM prevalence. There could be an overestimation of the relationship between design and cumulative sampling, but reference to other studies and justification of the statistical analysis proved the research hypothesis: the urinary biomarkers of glycosylated fibronectin have a positive future as testing method for GDM. One concern that may rise is the cost of this method. This procedure was completed through buffers and assays of the antibody, which can result as an expensive predicative screening test.

Early pregnancy urinary biomarkers of fatty acid and carbohydrate metabolism in pregnancies complicated by gestational diabetes

Qiu C¹, Enquobahrie DA^{1,2}, Frederick IO¹, Sorenson TL¹, Fernandez MAL³, David RM⁴, Bralley JA⁴, Williams MA^{1,3}

¹Center for Perinatal Studies, Swedish Medical Center, Seattle, WA; ²Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA; ³Department of Epidemiology, Harvard School of Public Health, Boston, MA; and ⁴Genova Diagnostics, Duluth, GA
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Objective

Organic acid biomarkers have been studied to show changes in insulin resistance, hyperglycemia, or type 2 diabetes. Considering GDM to be very similar to type 2 diabetes, this study investigates similar urinary biomarkers of fatty acid and carbohydrate metabolism that may be associated with GDM.

Method

This prospective study of a cohort of 25 GDM subjects and 25 control subjects measured fatty acid biomarkers, including adipate, suberate, and ethylmalonate, and carbohydrate metabolism biomarkers, including pyruvate, L-lactate, and β -hydroxybutyrate, during the first 17 weeks of gestation. Pregnant women were screened for GDM at 24–28 weeks of gestation using American Diabetes Association regulations for oral glucose tolerance tests. Urinary biomarkers were tested using liquid-chromatography mass spectrometry methods and urine creatinine concentrations. The creatinine concentrations were compared between biomarkers, maternal dietary macronutrient intake, and maternal and newborn characteristics.

Results

Of the 25 GDM cases, 16 were diet-controlled and 9 were insulin dependent. In all of the cases, total energy intake, maternal age, parity, and gestational age at delivery were similar. It was observed that the GDM group was more likely than the control group to have characteristics such as higher prepregnancy BMI, less likely to be non-Hispanic white, and more likely to have a family history. Women who were in the highest tertile for ethylmalonate had 11.4-fold increased risk of GDM, those in the highest tertile for pyruvate had 3.27-fold increased risk of GDM, and women with the highest tertile in adipate had 86% reduction in GDM risk compared to those in the lowest tertile. Median urinary concentrations of ethylmalonate, adipate, and pyruvate differed between the GDM group and the control group. Suberate, L-lactate, and β -hydroxybutyrate did not demonstrate significant difference between both groups.

Conclusions

This pilot study found a positive relationship between ethylmalonate with GDM risk, while adipate concentrations had an inverse relationship with GDM. From the results, changes in maternal fatty acid and carbohydrate metabolism could possibly be predicted at 16 weeks. These findings seem to match other studies done on nonpregnant patients with type 2 diabetes or hypoglycemia. In order to confirm the findings of this research, a larger sample size should be considered in the future. If confirmed, it will be significant to use urine as a biomarker, in revealing higher concentrations

of ethylmalonate and pyruvate and lower adipate in women with gestational diabetes mellitus.

Comment

This study supports the increasing possibilities of early diagnosis of GDM risk and of its complications. This study compares to the previous article, “Glycosylated Fibronectin as a First-Trimester Biomarker for Prediction of Gestational Diabetes.” It shows a weaker sample size but stronger time relationship between early organic acid excretion and GDM later in pregnancy. The previous research article illustrated a costly procedure. Though the fibronectin biomarker has its advantages of diagnosing in the first trimester, this current study demonstrates a more convenient and cost-effective method of urine testing. The urinary biomarker also has the advantage that GDM complications and risks can both be detected. Even though the detection would be in the early second trimester, this is still earlier than the timing of probable Doppler or the oral glucose tolerance test. It is beneficial for pregnant mothers to know other glucose abnormalities such as ketoacidosis.

Utility of superior mesenteric artery Doppler and maternal pancreatic size for predicting gestational diabetes mellitus

Tosun A¹, Duzguner S², Ozkaya E³, Korkmaz V⁴, Acar S⁵, Gultekin B², Altinboga O², Duzguner IN⁶, Kucukozkan T²

¹Department of Radiology, Giresun University School of Medicine, Giresun, Turkey; ²Department of Obstetrics and Gynecology, Dr. Sami Ulus Maternity and Children's Health Teaching and Research Hospital, Plevne Mh, Ankara, Turkey; ³Department of Obstetrics and Gynecology, Giresun University School of Medicine, Giresun, Turkey; ⁴Department of Obstetrics and Gynecology, Ankara Teaching and Research Hospital, Ankara, Turkey; ⁵Department of Internal Medicine, Giresun University School of Medicine, Giresun, Turkey; and ⁶Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Women Health, Teaching and Research Hospital, Ankara, Turkey

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Objective

Doppler ultrasonography and measurements of the pancreas have been used extensively as separate methods in assessment of diabetes. This study relates the superior mesenteric artery Doppler and the size of the pancreas as part of diagnosing gestational diabetes mellitus (GDM), abnormal glucose metabolism, and insulin deficiency during early pregnancy care.

Methods

From July 2012 to April 2013, this prospective study screened the fetuses of 258 pregnant women, who were 20–22 weeks in gestation and whose pregnancy was first and singleton. An ultrasound was taken of the maternal superior

mesenteric artery and the pancreatic size of the head, corpus, and tail. Subjects were excluded if BMI was greater than 30 kg/m² before pregnancy, height less than 1.55 m, gained less than 8 kg during pregnancy, had gastrointestinal abnormalities or surgeries, or if the subjects had diabetes before pregnancy. At 24–28 weeks, a 50 g glucose challenge test (GCT) was performed and those with abnormal GCT were required to take a 100 g GCT. Glucose levels higher than 140 mg/dL differentiated standard pregnancies from women with GDM. The peak-systolic and end-diastolic (S/D) flow velocities and the resistance index were measured to find a relationship between the Doppler and the pancreatic measurements.

Results

Out of the 258 subjects, about 11% were diagnosed with GDM. Age, BMI, gestational age, pancreatic head sizes, and pancreatic tail sizes were all similar between the GDM and normal glucose tolerance women. The measurement of the pancreas body, the superior mesenteric artery Doppler S/D, and the resistance index were different between women with GDM and women with normal glucose tolerance. In the GDM group, the Doppler and pancreatic body measurements were lower than in the normal pregnancies. These significant differences were further confirmed with the glucose challenge test and linear regression analysis displaying a correlation of GDM with the superior mesenteric artery Doppler S/D and resistance index.

Conclusions

The results emphasized how superior mesenteric artery blood flow can increase while fasting and decrease after glucose consumption. An ultrasound can illustrate a smaller sized pancreas, indicating diabetes. Overall, changes in superior mesenteric blood flow and pancreatic size can be used to detect abnormal carbohydrate metabolism before pregnancy routine screenings. These methods can be considered for early predictors of GDM for pregnant women.

Comment

The Doppler and pancreatic measurements could be efficient and noninvasive procedures to screen for GDM. Since ultrasounds are already part of routine pregnancy care, the early screening with the Doppler could be integrated into normal prenatal clinical visits. An earlier diagnosis of GDM could have positive effects on both antepartum and postpartum maternal care, and on the long-term health of the offspring. Though more research can be done to confirm these findings, this study reflects that the superior mesenteric artery Doppler and pancreatic size are reliable indicators of a woman being diagnosed with GDM through an OGTT.

The elevated gene expression level of the A_{2B} adenosine receptor is associated with hyperglycemia in women with gestational diabetes mellitus

Wojcik M¹, Zieleniak A¹, Mac-Marcjanek K¹, Wozniak LA¹, Cypryk K²

¹Department of Structural Biology, Faculty of Biomedical Sciences and Postgraduate Education Medical University of Lodz, Zeligowskiego, Lodz, Poland; and ²Diabetology and Metabolic Diseases Department, Medical University of Lodz, Rzgowska, Lodz, Poland

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Objective

Adenosine receptors denoted by A₁, A_{2A}, A_{2B}, and A₃ and encoded by *ADORA1*, *ADORA2A*, *ADORA2B*, and *ADORA3* genes, respectively, are adenosine-activated G-protein-coupled receptors that play an important role in obesity and type 2 diabetes mellitus. However, little is known about their significance in gestational diabetes mellitus (GDM). The purpose of this study was to investigate whether there are changes in leukocyte AR expression in GDM patients and whether these alterations are linked to well-known diabetic genes.

Methods

In this prospective cohort study, leukocytes were isolated from the blood of normal glucose tolerant (NGT; *n* = 35) and GDM (*n* = 82) pregnant women in their third trimester of pregnancy (24–33 weeks). All women were recruited during their first visit at a hospital in Lodz, Poland. The inclusion criteria included Caucasian ethnic background, age 18–40 years, no family history of diabetes in first-degree relatives, no GDM in previous pregnancy, absence of any form of prepregnancy diabetes, and not taking insulin. GDM was diagnosed if one or more plasma glucose levels were elevated during a 2-hour 75 g oral glucose tolerance test (OGTT). A semi-quantitative polymerase chain reaction (PCR) determined expression of ARs. Univariate correlation analysis was performed to investigate associations between expression of ARs and anthropometric and metabolic parameters of patients. Leukocyte gene expression profiles of women with GDM (*n* = 10) and women with NGT (*n* = 6; controls with highest leukocyte *ADORA2B* mRNA levels selected) were compared to determine if the overexpression of *ADORA2B* is accompanied by changes in expression of known diabetic-related genes. This was carried out using the human diabetes RT² profiler PCR arrays.

Results

ADORA2B mRNA expression was significantly higher in GDM versus NGT pregnant women (*p* < 0.05), and positively correlated with the glucose level at 1-hour 75 g oral glucose tolerance test (OGTT; *r* = 0.21, *p* = 0.044). Nineteen diabetic genes linked to leukocyte *ADORA2B* overexpression associated with hyperglycemia in GDM women were also identified. No significant differences were detected in anthropometric parameters between the GDM women and NGT controls. As expected, maternal serum glucose concentrations at 0, 1, and 2 hours during 75 g OGTT, as well as HbA_{1c} levels, were significantly higher in GDM participants compared to NGT controls. GDM patients also had significantly lower plasma HDL cholesterol levels than control patients. Other lipid metabolism markers, inflammation, and insulin resistance/sensitivity were not significantly different between the two groups.

Conclusions

There were significantly elevated levels of maternal leukocyte *ADORA2B* and of *ADORA2B* mRNAs in women with GDM in their third trimester of pregnancy. In women with GDM, there was a positive correlation between hyperglycemia and level of leukocyte *ADORA2B* mRNA. Furthermore, overexpression of leukocyte *ADORA2B* is accompanied by altered expression of 19 diabetes-related genes. These genes affect insulin action, glucose and lipid metabolism, oxidative stress, and inflammation.

Comment

This looks at genes already linked to diabetes to see if their transcriptions are altered in patients with GDM. Because altered leukocyte gene expressions were observed, this study is evidence that certain genes are associated with multiple forms of diabetes. Additionally, it is of note that history of diabetes in the patient and family is controlled for and that the participants were all Caucasian women from Poland, meaning ethnic background was likely quite similar between all women. Thus, the altered gene expression is unlikely affected by family history or differences between ethnicities.

Potential epigenetic dysregulation of genes associated with MODY and type 2 diabetes in humans exposed to a diabetic intrauterine environment: an analysis of genome-wide DNA methylation

del Rosario MC, Ossowski V, Knowler WC, Bogardus C, Baier LJ, Hanson RL

Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes, Digestive and Kidney Diseases, Phoenix, AZ

Metabolism 2014; **63**: 654–60

Objective

Offspring of mothers who had type 2 diabetes during pregnancy are at a higher risk of developing diabetes later in life. DNA methylation is called into question for facilitating the effects of diabetic intrauterine exposure. To better understand the role that methylation plays in later development of type 2 diabetes, DNA methylation was studied in groups born to mothers with and without type 2 diabetes.

Methods

Fourteen unrelated Pima Indians with diabetic mothers with an HBA1c of <6.5% and a PBL pellet available from a nondiabetic biennial exam were selected for study. Fourteen nondiabetics born to nondiabetic mothers were chosen for comparison. Samples of peripheral blood leukocytes were collected from both groups, and analyzed with a MeDIP-Chip assay to determine areas of differential methylation. KEGG pathway analysis was performed on genes with differential methylation in promoter regions.

Results

MODY, type 2 diabetes, and Notch signaling pathways make up the pathways that are most differentially methylated

between ODM and ONDM groups, all of which possess genes known to affect pancreatic development, beta-cell function, and insulin secretion. Data do not show that observed altered methylation is causative of diabetes through exposure *in utero*.

Conclusions

Though further studies outside of the Pima Indian population are needed, the hypothesis that epigenetic changes increase the risk of type 2 diabetes in ODM was substantiated. The differential methylation is likely to be caused by hyperglycemic exposure *in utero*. Promoter regions of genes causing type 2 diabetes and MODY are more likely to be differentially methylated.

Comment

The study is limited to a very specific population, the Pima Indians, and further longitudinal studies will be necessary to discover the prevalence of differential methylation in humans exposed to a diabetic intrauterine environment. Furthermore, the study only analyzed peripheral blood leukocytes, which may not be representative of all blood cell pathways in the body. However, the data provided show a connection between differential methylation and increased risk of diabetes. Because the identified genes are known to influence pancreatic development and insulin secretion, the data provided could be extremely valuable in understanding why offspring of women with diabetes have a higher risk of developing diabetes. Also, the identified pathways may be used in future investigations of diabetes occurrence, leading to better drugs and treatments.

Maternal diabetes, programming of beta-cell disorders, and intergenerational risk of type 2 diabetes

Chavey A, Ah Kioon MD, Bailbé D, Movassat J, Portha B

Unité BFA (biologie fonctionnelle et adaptative), laboratoire B2PE (biologie et pathologie du pancréas endocrine), université Paris-Diderot, Sorbonne-Paris-Cité, UMR 8251 Centre national de la Recherche Scientifique, Paris, France

Diabetes Metab 2014 **40**: 323–30

Objective

A mother with preexisting diabetes or GDM is usually concerned about fetal exposure to her diabetes. This review critiques important articles that outline fetal exposure to maternal diabetes (FEMD) models to identify critical periods and alterations that may lead to beta-cell disorders. Animal models are also reviewed, to outline possible mechanisms in humans showing intergenerational transmission.

Methods

Using a compare-and-contrast approach, an average of about 100 articles were evaluated. Of those 100 articles, 4 main topics, including epigenetic mechanisms, mechanisms for beta-cell mass (BCM) formation, and parental

physiology, were closely considered. This analytic review focused mainly on comparing each study and describing the significance by interpreting the biology as more comprehensive basic science.

Results

The development programming of beta-cell mass in rat studies of maternal protein restriction, caloric restriction, overnutrition, and diabetes demonstrated initial maternal insult gives rise to same programmed BCM outcome in the next offspring. Observations showed altered BCM phenotype in the daughter generation females to preventing normal BCM adaptation during pregnancy. Therefore, GDM passes on from one generation to the next. A significant observation mentions the intervention timing of treatments that may affect prenatal undernutrition. The uteroplacental insufficiency and fetal protein restriction models illustrated increased oxidative stress and impaired mitochondrial function. During the neonatal period, there was a reverse in the epigenetic silencing of the *Pdx1* gene and also reversed detrimental fetal programming of BCM when exposed to extendin-4, therefore inhibiting diabetes in adulthood. In addition, glucagon-like peptide-1 or extendin-4 treatment during neonatal prediabetic period shows an inhibition of adult type 2 diabetes in the Goto-Kakizaki rat model. Treatments utilized target chromatin remodeling, acetylation, and other histone modifications, indicating the important role of epigenetics in maternal diabetes.

Conclusions

This in-depth analysis of articles regarding animal and human studies on maternal diabetes, beta-cell mass programming, and intergenerational risk of type 2 diabetes mainly emphasized the importance of the expanding field of genetics. In maternal diabetes, similarities observed included altered BCM development and beta-cell disorders with possible genetic transmission. This review suggested further implications for public health, including adolescent obesity and nutrition control, especially in women with diabetes during pregnancy. Mothers who are obese have a higher risk of giving birth to offspring that will be obese and develop type 2 diabetes. The data collected pave a positive path toward potential postnatal therapeutic intervention to prevent development of “programmed” diabetes.

Comment

This careful review is a step closer in finding the answers to the role of advanced genetics in diabetes and pregnancy. Most of the medical approach to gestational diabetes mellitus has become narrowed to viewing it as a treatable disease usually identified in the second or third trimester in pregnancy. Newer studies have investigated advancements in technological devices to make diabetes easier to cope with during pregnancy. The various articles chosen illustrate a more preventable method that incorporates the public health perspective leading to an early revelation of diabetes even before pregnancy or can track transmission to future generations. Nutrition and lifestyle can influence epigenetically connecting genetics and public health. It is important to consider obesity

as part of lifestyle, because it could affect epigenetic mechanisms leading to gestational diabetes or type 2 diabetes. Overall, this can pose a broader view for the holistic approach of public health that considers lifestyle intervention, genetic approach, and diet plans for different therapies and techniques to help treat pregnant women with diabetes.

Prepregnancy dietary protein intake, major dietary protein sources, and the risk of gestational diabetes mellitus: a prospective cohort study

Bao *W*¹, Bowers *K*¹, Tobias *DK*², Hu *FB*^{2,3}, Zhang *C*¹

¹Epidemiology Branch, Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD; ²The Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA; and ³The Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Diabetes Care 2013; **36**: 2001–8

Objective

Dietary protein is an important modulator of glucose metabolism. However, studies regarding the association between dietary protein intake and gestational diabetes mellitus (GDM) risk are sparse.

Methods

This prospective cohort study included 21,457 singleton pregnancies reported among 15,294 participants of the Nurses' Health Study II cohort between 1991 and 2001. The participants were female nurses, aged 25–44 years at study inception in 1989. Included pregnancies were free of chronic diseases before pregnancy or of previous GDM. Beginning in 1991 and every 4 years thereafter, participants reported their food intakes using a semiquantitative food frequency questionnaire. Participants were divided into quintiles according to the cumulative average intakes of dietary protein (% of energy) or according to major protein sources (servings/day) in their diet. Generalized estimating equations were used to estimate the relative risks (RRs) and 95% CIs.

Results

Adjustments were made for age, parity, nondietary and dietary factors, and BMI prior to analysis. The multivariable relative risk (95% CI) for developing GDM, when comparing the highest and lowest quintiles of animal protein intake, was 1.49 (1.03–2.17). For vegetable protein intake, however, the multivariable RR (95% CI) was 0.69 (0.50–0.97). There was an estimated 51% lower risk of GDM associated with the substitution of 5% energy from vegetable protein for animal protein GDM (RR [95% CI], 0.49 [0.29–0.84]). When dividing participants based on major dietary protein sources, multivariable RRs (95% CIs) comparing the highest with the lowest quintiles were 2.05 (1.55–2.73) for total red meat and

0.73 (0.56–0.95) for nuts, respectively. The substitution of red meat with poultry, fish, nuts, or legumes showed a significantly lower risk of GDM.

Conclusions

Higher intake of animal protein, in particular red meat, was significantly associated with a greater risk of GDM. By contrast, higher intake of vegetable protein, specifically nuts, was associated with a significantly lower risk. Substitution of vegetable protein for animal protein, as well as substitution of some healthy protein sources for red meat, was associated with a lower risk of GDM.

Comment

Though much of this study relied on self-reported data, the large sample size strengthens the validity of the results, and indicates that the association between red meat intake and GDM risk is unlikely due to chance. The effect of substituting animal protein with vegetable protein was estimated based on reported data. A randomized control trial directly comparing animal and vegetable protein consumption with risk of GDM could confirm this calculated relative risk. Going forward, this study could be valuable in preconception care of women, especially those already at higher risk for developing GDM.

Assessment of cardiac functions in fetuses of gestational diabetic mothers

Balli S¹, Pac FA², Ece İ³, Oflaz MB⁴, Kibar AE⁵, Kandemir Ö⁶

¹Department of Pediatric Cardiology, Balıkesir Atatürk Hospital, Yıldız Mahallesi, Soma Caddesi, Balıkesir, Turkey; ²Department of Pediatric Cardiology, Türkiye Yüksek İhtisas Training and Education Hospital, Ankara, Turkey; ³Department of Pediatric Cardiology, Faculty of Medicine, Yüzüncü Yıl University, Van, Turkey; ⁴Department of Pediatric Cardiology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey; ⁵Department of Pediatric Cardiology, Mersin Children's Hospital, Mersin, Turkey; and ⁶Department of Obstetrics and Gynecology, Zübeyde Hanım Obstetrics and Children's Hospital, Ankara, Turkey

Pediatr Cardiol 2014; **35**: 30–37

Objective

Though the exact mechanism is unknown, gestational diabetes has been known to increase risk of fetal malformation. A combination of high glycated hemoglobin (HbA1c) levels and hyperglycemia induce placental genes that may play a role in embryopathy. The aim of the study was to examine the cardiac function of fetuses born from mothers with gestational diabetes (FGDM) to gain a better understanding of the influence of GDM on cardiac function.

Methods

In this prospective cohort study, 67 FGDMs and 122 fetuses from mothers without GDM were evaluated using Doppler, M-mode, and pulsed-wave echocardiography at weeks 24, 28, 32,

and 36. HbA1c levels were collected from all pregnant mothers at 24 weeks. IVS septum, left ventricular (LV), and right ventricular (RV) end-diastolic diameters were measured using M-mode echocardiography. End-diastolic and end-systolic dimensions of LV and RV were measured using M-mode, and used to calculate shortening fractions. Doppler imaging was used to acquire a four-chamber view of the heart.

Results

Birth weights were comparative in both groups and no pathological hypertrophy was detected. The study found that aortic and pulmonary flow velocities were greater in FGDM groups compared to the control group, suggesting alterations in myocardial compliance. LV and RV shortening fractions were equal in both groups (34%). Mitral and tricuspid E/A ratios were significantly lowered in the FGDM group. Velocities of RV E_a, A_a, S_a, and LV E_a waves were higher in the FGDM group, as well as RV E_a/A_a ratios. E/E_a ratios decreased throughout the pregnancy in the FGDM group, but there were no differences in LV and RV E/E_a ratios between the groups. At the end of the second trimester and beginning of the third trimester, MPI values were significantly increased in relation to IVRT in FGDM.

Conclusions

GDM was shown to cause diastolic dysfunction, increased left MPI, and impairment of ventricular diastolic function without pathological myocardial hypertrophy in fetuses. FGDM were asymptomatic, and further studies are required to determine the reason for this occurrence.

Comment

GDM's effect on fetal heart development is considered multifactorial, and effects were unclear before this study. The investigation provides data on cardiac function during weeks 24, 28, 32, and 36 of gestation. Since FGDM face additional risks, these cardiac risk factors can be checked during these specific times throughout pregnancy, which will aid in the overall health of the child before and after birth. The study also shows that tissue Doppler, M-mode, and pulsed-wave echocardiography are sufficient for detecting cardiac dysfunction in fetuses.

Effect of excess gestational weight gain on pregnancy outcomes in women with type 1 diabetes

Scifres CM, Feghali MN, Althouse AD, Caritis SN, Catov JM

The Department of Obstetrics, Gynecology and Reproductive Sciences, Magee Women's Research Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA
Obstetrics Gynecol 2014; **123**: 1295–302

Objective

To evaluate the prevalence and clinical effects of excess gestational weight gain on birth weight and other pregnancy outcomes in women with type 1 diabetes.

Methods

This was a retrospective cohort study of women with type 1 diabetes, who all delivered at the same hospital, between 2009 and 2012 ($n=175$). These women were classified into one of two groups: women with standard gestational weight gain and women with excessive gestational weight gain. The 2009 Institute of Medicine weight gain recommendations, adjusted for gestational age at delivery and prepregnancy body mass index (BMI), were used to identify excessive weight gain. Pregnancy outcomes were compared between the groups, and included gestational age at delivery, preterm delivery, LGA or small for gestational age status (based on U.S. national birth weight data), macrosomia, ponderal index, placental weight, cesarean delivery, shoulder dystocia, and stillbirth. Demographic and outcome data were obtained from patients' medical records and all patients were indicated to have received similar prenatal care.

Results

Excess gestational weight gain occurred in 114 of 175 women (65.1%). LGA birth weight occurred in 48 of 114 (42.1%) women with excess gestational weight gain and 5 of 61 (8.2%) women with recommended weight gain ($p<.001$). After adjustment for prepregnancy BMI, gestational age at delivery, nulliparity, vascular complications, and hemoglobin A1c measurements, the association between excess maternal weight gain and LGA birth weight remained significant (adjusted odds ratio 8.9, 95% confidence interval 3.1–26.2, $p<.001$). Stratified analyses demonstrated that excess maternal weight gain is associated with LGA neonates in both normal-weight and overweight or obese women.

Conclusions

Excess maternal weight gain leads to higher rates of LGA neonates in both normal-weight and overweight or obese women with type 1 diabetes. Apart from this, there were no other significant relationships between excess gestational weight gain and pregnancy outcomes. This study indicates that interventions designed to limit excess gestational weight gain may reduce the risk for fetal overgrowth in women with type 1 diabetes. As a result of the modest sample size, this study lacked statistical power to compare infrequent outcomes between those with expected and excess gestational weight gain.

Comment

Women with type 1 diabetes can have safe and healthy pregnancies; however, they are at greater risk for pregnancy complications such as LGA birth weight. This study gives insight into how monitoring weight gain in pregnant women with type 1 diabetes can both help prevent and indicate LGA. Only 3 of the 175 women (1.6%) in this cohort were considered underweight and were included with the normal weight women in analysis. Further studies could be done to establish the effects of an underweight prepregnancy BMI in women with type 1 diabetes.

Influence of gestational diabetes on circadian rhythms of children and their association with fetal adiposity

Zornoza-Moreno M¹, Fuentes-Hernández S¹, Prieto-Sánchez MT², Blanco JE², Pagán A³, Rol M-Á³, Parrilla JJ², Madrid JA³, Sánchez-Solis M¹, Larqué E³

¹Pediatric Service and ²Obstetrics and Gynecology Service, Virgen de la Arrixaca Hospital, Murcia, Spain; and ³Department of Physiology, Faculty of Biology, University of Murcia, Murcia, Spain

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Objective

Gestational diabetes has been associated with obesity in offspring. Obesity in adulthood has been shown to disrupt chronobiological rhythms, including circadian rhythms. Because circadian rhythms develop over the first year of life, offspring of GDM mothers were evaluated for circadian rhythm maturation, as well as influence of clinical treatment of GDM and programming of circadian rhythms.

Methods

A longitudinal prospective study analyzed the offspring of 21 women with GDM controlled with diet, 19 women with GDM controlled with insulin, and 23 pregnant women as controls. The criterion for the women was an age between 18 and 40 years old, nonsmoking, not consuming docosahexaenoic drugs, and singleton pregnancy. GDM was diagnosed between 24–28 weeks of pregnancy with a 50 g glucose challenge test. Positive results were followed by a 3-hour oral glucose tolerance test. Women were monitored by glycemic and ecographic control during pregnancy, and abdominal circumference was measured at time of diagnosis and during the third trimester. The skin temperature, rest-activity rhythms, and anthropometric parameters of the children were monitored throughout the first year of life.

Results

No significant difference existed in weight, length, BMI, or waist/hip index between groups. All babies were considered healthy according to anthropometric parameters. No GDM-related differences were found in mean skin temperature, $I<O$ index about concordance with parental sleep time or activity. Offspring of GDM mothers tended to have higher fetal abdominal circumference z -scores than control groups during the last trimester ($p=0.077$) and at delivery ($p=0.078$). Fetal abdominal circumference z -score was negatively correlated with circadian rhythm maturation parameters.

Conclusions

At 6 months of age, ODM insulin-treated babies demonstrated a disrupted pattern of the circadian function index of temperature. The study also showed that fetal adiposity lead to worse circadian rhythms in ODM. There were no significant differences in peripheral temperature or activity, though a significant shift was shown between 3 and 6 months of age in all groups.

Comment

The study was limited because only women of Spanish descent participated. Though the effects of GDM on offspring are well known, the extent of the effects is not well understood. The new connection between irregular circadian rhythms of GDM will be helpful in providing care to children of GDM mothers. This study begins to unravel the connection between GDM and disrupted circadian rhythms in children of mothers affected by GDM. Though the relationship is still unknown, the study paves the way for future research on other adiposity markers in children and chronobiological rhythm evaluation.

Gestational diabetes mellitus, maternal obesity, and adiposity in offspring

Page KA¹, Romero A¹, Buchanan TA¹, Xiang AH²

¹Department of Medicine, Keck School of Medicine, the University of Southern California, Los Angeles, CA; and

²Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

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Objective

This study aimed to determine the effects of maternal gestational diabetes mellitus (GDM) on offspring adiposity in a well-characterized cohort of Mexican American mother–child pairs.

Methods

This retrospective cohort study included 62 Mexican American (as defined by at least three-quarters of grandparents of Mexican descent) mothers and their index offspring. Mothers who had GDM and mothers who had normal glucose tolerance during the (singleton) index pregnancy were matched by age, body mass index (BMI), and parity. Mother–child pairs were recruited when offspring were between the ages of 5 and 16 years. Interviews with mother–child pairs were used to collect detailed medical history about the pregnancy and about maternal and child medical problems. Anthropometrics were measured. Main outcome measures were offspring BMI, BMI *z*-scores, BMI percentiles, and hip and waist circumferences.

Results

Mothers in the GDM (*n*=37) and non-GDM (*n*=25) groups did not have significantly different characteristics (age, BMI, diabetes diagnosis) at the time of testing for the study. GDM-exposed offspring had greater measures of BMI (all *p* ≤ .02) and greater waist and hip circumferences (both

p = .002), compared with offspring of non-GDM mothers. Adjustment for offspring age, sex, Tanner stage, birth weight, months of breastfeeding, maternal prepregnancy BMI, and pregnancy weight gain lessened the differences, but BMI *z*-score and BMI percentile were still significantly greater in the GDM-exposed group (*p* < .05). In the non-GDM-exposed group, offspring BMI *z*-score was 0.25 ± 0.2, and in the GDM-exposed group, the BMI *z*-score was 0.95 ± 0.2 (*p* = .02).

Conclusions

Intrauterine exposure to GDM is associated with greater adiposity in Mexican American children, and this relationship is not mediated by maternal obesity. In contrast to previous reports, this study included only Mexican Americans; thus, ethnic variations may influence the contributions of maternal GDM and maternal obesity to offspring adiposity.

Comment

The study does have limitations, such as a relatively small sample size and not considering possible confounding paternal factors on offspring. Still, this study is valuable in providing information on a specific group, Mexican Americans. Similar studies on various ethnic groups have been conducted, and these data could be used in comparing adiposity of GDM-exposed offspring between ethnicities.

Conclusion

Diabetes and pregnancy is about much more than 9 months and a GDM diagnosis. Any type of diabetes can complicate a pregnancy, and if the diabetes is not well controlled, offspring are at a higher risk for lifelong problems, such as increased adiposity, disrupted circadian rhythms, and defects in cardiac function. Experts have come to an agreement that treatment should not just begin 24 weeks into a pregnancy, after a failed oral glucose tolerance test. These studies suggest that diabetes is a part of preconception, prenatal, and perinatal care. As the field continues to broaden its scope, we are hopeful that earlier, more accessible and efficient means of detection and diagnosis can be applied in a clinical setting. Additionally, it is the potential clinical benefit of these studies that motivated our selection of human studies over animal studies. Nevertheless, many animal studies showed promise, and we look forward to seeing that research continue into human phases. More than anything, though, we are excited to see diabetes and pregnancy research continue to flourish.

Author Disclosure Statement

No competing financial interests exist.