Technology and Pregnancy

Jennifer M. Yamamoto^{1,2} and Helen R. Murphy^{3,4,5}

Introduction

THE MANUSCRIPTS CHOSEN for this year's technology and pregnancy article provide new insights into fetal exposure to maternal glucose during pregnancies complicated by gestational diabetes, and type 1 diabetes. The increasing use of continuous glucose monitoring (CGM) both in research studies and in real-world settings provide data relating maternal glucose profiles to neonatal health outcomes. These data confirm the well-recognized gestational limitations of glycated hemoglobin (HbA1c), which is inadequate for assessing short-term changes in maternal glycemia during pregnancy.

Data from Sweden confirm that we are far from achieving the stringent international consensus target of $\geq 70\%$ time in range (TIR) 63–140 mg/dL during type 1 diabetes pregnancy (1). Kristensen et al. demonstrate that despite 70% of women achieving HbA1c $< 6.5\%$ (48 mmol/L) in late pregnancy, time in range (63–140 mg/dL) increased from on average 50% in the first to 60% in the third trimester (2). The international consensus target of $\geq 70\%$ TIR 63–140 mg/dL was achieved only in the final few weeks of pregnancy, too late for optimal neonatal outcomes. Importantly, small second and third trimester TIR increments of 5%–7%, were associated with decreased risk of large for gestational age (LGA) and neonatal complications. These data are comparable to an ancillary study from the Continuous Glucose Monitoring in Type 1 Diabetes Pregnancy Trial (CONCEPTT) (3). During CONCEPTT fetal hyperinsulinemia, LGA, and newborn adiposity and were all increased in mothers with 5%–7% higher TIR (63–140 mg/dL) and 5%–7% lower time above range (TAR > 140 mg/dL). Taken together, these data suggest that healthcare providers should focus on increasing CGM TIR and decreasing TAR in small achievable increments.

Another CONCEPTT ancillary study demonstrated that insulin pump users had a 5% lower (TIR 63–140 mg/dL 53 vs 48%) at 24 weeks, despite comparable first and third trimester CGM glucose measures (4). These findings suggest that clinicians and insulin pump users need to be more aggressive with their insulin dose increments, as gestational insulin resistance increases from around 18–20 weeks (5). Data from the T1D Exchange clinic registry confirms increasing diabetes technology use, with 74% of recently pregnant women using insulin pumps and 36% using CGM (6). Despite increased diabetes technology use, glucose control and pregnancy outcomes remained suboptimal, with LGA rates of 65%. Given the high rate of insulin pump use before and during pregnancy, more data are needed to inform optimal implementation of insulin pump therapy, especially during the second and third trimesters.

Current recommendations advise women with gestational diabetes mellitus (GDM) to perform glucose testing at least four times daily, with increasing use of CGM expected as sensors become more affordable, accurate, and user friendly. Using

¹Departments of Medicine and Obstetrics and Gynecology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

²Alberta Children's Hospital Research Institute, Calgary, Canada

³Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

⁴Women's Health Academic Centre, Division of Women's and Children's Health, King's College London, London, UK

⁵Norwich Medical School, Floor 2, Bob Champion Research and Education Building, James Watson Road, University of East Anglia, Norwich Research Park, Norwich, UK

functional data analysis, Law et al. demonstrated that a higher mean glucose level is driven by suboptimal nocturnal glucose control and that small differences in nocturnal CGM measures are associated with offspring LGA (7). Another team used spectral clustering approaches to develop a new glucose variability metric, the “glucotype” (8). Hall et al. describe three glucotypes of increasing variability (low, moderate, and severe), which together with mean CGM glucose explain > 70% of temporal glucose variability. This methodology could detect earlier preclinical forms of dysglycemia and identify those most at risk for type 2 diabetes or prediabetes, which is very relevant for women with GDM. Interestingly it also highlighted the limitations of the oral glucose tolerance test (OGTT), which was seemingly normal in one-quarter of participants categorized as having severe glucotypes. Retnakaran et al. describe the impact of higher environmental temperatures on OGTT results, although unfortunately lacked CGM data, to establish whether or not environmental temperatures impact on CGM measures (9).

The follow-up study of over 4,700 mother–child pairs from the Hyperglycemic and Adverse Pregnancy Outcomes (HAPO) study confirmed that, women with GDM were more likely to develop type 2 diabetes or prediabetes (52.2 vs 20.1%) than those in the general maternity population (10). Another study not directly involving pregnant women with diabetes but very relevant to maternity and pediatric populations describes the long-term impact of being born LGA (11). In a large German cohort of over 50,000 participants, almost half of all LGA newborns continued to be overweight or obese into adolescence. This highlights the importance of optimizing maternal glucose control in the second and third trimesters to reduce neonatal LGA and the longer-term consequences of overweight and obesity persisting into adolescence.

Key Articles Reviewed for the Article

Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies

Kristensen K, Ögge LE, Sengpiel V, Kjölhede K, Dotevall A, Elfvin A, Knop FK, Wiberg N, Katsarou A, Shaat N, Kristensen L, Berntorp K

Diabetologia 2019; **62**: 1143–1153

Maternal glycaemic control and risk of neonatal hypoglycaemia in type 1 diabetes pregnancy: a secondary analysis of the CONCEPTT trial

Yamamoto JM, Corcoy R, Donovan LE, Stewart ZA, Tomlinson G, Beardsall K, Feig DS, Murphy HR; on behalf of the CONCEPTT Collaborative Group

Diabet Med 2019; **36**: 1046–1053

Pumps or multiple daily injections in pregnancy involving type 1 diabetes: a prespecified analysis of the CONCEPTT randomized trial

Feig DS, Corcoy R, Donovan LE, Murphy KE, Barrett JFR, Sanchez JJ, Wysocki T, Ruedy K, Kollman C, Tomlinson G, Murphy HR; on behalf of the CONCEPTT Collaborative Group

Diabetes Care 2018; **41**: 2471–2479

Diabetes technology use among pregnant and nonpregnant women with T1D in the T1D Exchange

Polisky S, Wu M, Bode BW, DuBose SN, Goland RS, Maahs DM, Foster NC, Peters AL, Levy CJ, Shah VN, Beck RW

Diabetes Technol Ther 2018; **20**: 517–523

Suboptimal nocturnal glucose control is associated with large for gestational age in treated gestational diabetes mellitus

Law GR, Alnaji A, Alrefaii L, Endersby D, Cartland SJ, Gilbey SG, Jennings PE, Murphy HR, Scott EM

Diabetes Care 2019; **42**: 810–815

Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity

Lowe WL Jr, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, Catalano PM, Linder B, Brickman WJ, Clayton P, Deerochanawong C, Hamilton J, Josefson JL, Lashley M, Lawrence JM, Lebenthal Y, Ma R, Maresh M, McCance D, Tam WH, Sacks DA, Dyer AR, Metzger BE; HAPO Follow-up Study Cooperative Research Group

JAMA 2018; **320**: 1005–1016

Glucotypes reveal new patterns of glucose dysregulation

Hall H, Perelman D, Breschi A, Limcaoco P, Kellogg R, McLaughlin T, Snyder M

PLoS Biol 2018; **16**: e2005143

Impact of daily incremental change in environmental temperature on beta cell function and the risk of gestational diabetes in pregnant women

Retnakaran R, Ye C, Kramer CK, Hanley AJ, Connelly PW, Sermer M, Zinman B

Diabetologia 2018; **61**: 2633–2642

Acceleration of BMI in early childhood and risk of sustained obesity

Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, Pfäffle R, Kiess W, Körner A

N Engl J Med 2018; **379**: 1303–1312

Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies

Kristensen K^{1,2,3}, Ögge LE^{4,5}, Sengpiel V^{4,5}, Kjölhede K^{4,5}, Dotevall A^{5,6}, Elfvin A^{5,7}, Knop FK^{8,9}, Wiberg N^{1,3}, Katsarou A^{10,11}, Shaat N^{10,11}, Kristensen L², Berntorp K^{10,11}

¹Department of Clinical Sciences Lund, Lund University, Lund, Sweden; ²The Parker Institute, Copenhagen University Hospital, Copenhagen, Denmark; ³Department of Obstetrics and Gynecology, Skåne University Hospital, Malmö, Sweden; ⁴Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Gothenburg, Sweden; ⁵Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; ⁶Department of Medicine, Östra/Sahlgrenska University Hospital, Gothenburg, Sweden; ⁷Department of Pediatrics, Sahlgrenska University Hospital, Gothenburg, Sweden; ⁸Clinical Metabolic Physiology, Steno Diabetes Center Copenhagen, Gentofte Hospital, Hellerup, Denmark; ⁹Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ¹⁰Department of Endocrinology, Skåne University Hospital, Malmö, Sweden; ¹¹Department of Clinical Sciences Malmö, Lund University, Lund, Sweden

Diabetologia 2019; **62**: 1143–1153

Background

Data relating continuous glucose monitoring (CGM) in type 1 diabetes pregnancy to neonatal outcomes are scarce. This real-world analysis of glycemic profiles from pregnant women using either real-time continuous glucose monitoring (rtCGM or intermittent CGM [iCGM]) aimed to better understand the associations between maternal CGM profiles throughout pregnancy and neonatal complications.

Methods

Data from 92 rtCGM and 94 iCGM pregnant users, were combined to provide detailed glycemic profiles in 186 Swedish women from two tertiary hospitals. Women made their own choice of which CGM device to use. 38% of iCGM users and 72% of rtCGM users were new to CGM during pregnancy. Maternal glycemic control was assessed by HbA1c in each trimester and CGM measures throughout pregnancy. The main neonatal outcomes were large for gestational age (LGA, defined as >2 SD above the expected birthweight), and at least one neonatal complication (macrosomia, shoulder dystocia, neonatal hypoglycemia, or admission to NICU >24 hours).

Results

Of 186 women in the study, 155 (83%) had CGM glycemic profiles in the first trimester, 165 (89%) in the second trimester, and 167 (90%) in the third trimester. The proportion of women with target HbA1c <48 mmol/mol (6.5%) was 37% in the first trimester and increased to 71% and 68% in the second and third trimesters. TIR (3.5–7.8 mmol/L or 63–140 mg/dL) for women in early pregnancy was 50%, increasing to 60% in the third trimester, with 33% TAR (>7.8 mmol/L or 140 mg/dL). Real-time CGM users spent significantly less time below range (3.5–7.8 mmol/L or 63–140 mg/dL) throughout pregnancy, with iCGM users spending strikingly high time below range in the late first and third trimesters. Overall, 52% and 53% of infants were born LGA with significant associations between mean second and third trimester CGM glucose and LGA (odds ratio [OR] 1.53 and 1.57, respectively). Higher second and third trimester TIR was associated with lower risk of LGA (OR 0.96 and 0.97). Higher second trimester glycemic variability (glucose SD) was associated with LGA and higher third trimester SD with neonatal complications.

Conclusions

Despite 70% of women achieving target HbA1c levels, CGM data confirmed suboptimal day-to-day glucose control throughout pregnancy. A 5%–7% higher TIR during the second and third trimesters, was associated with decreased risk of LGA and neonatal complications, including macrosomia, shoulder dystocia, neonatal hypoglycemia, or NICU admissions of > 24 hours in duration.

Comment

Objectively measured glucose control was suboptimal in this real-world cohort of iCGM and rtCGM users. A TIR target of 70% was achieved only in the final weeks of the third trimester, too late for optimal neonatal outcomes. Pregnant women with type 1 diabetes should be encouraged to aim for a TIR target of 70% and a TAR target of < 25% as early as possible during the second and third trimester. For those who cannot reach 70%, small 5%–7% differences are associated with improved neonatal outcomes. More work is needed to support women and healthcare professionals to optimize use of technology before and during pregnancy.

Maternal glycaemic control and risk of neonatal hypoglycaemia in type 1 diabetes pregnancy: a secondary analysis of the CONCEPTT trial

Yamamoto JM^{1,2}, Corcoy R^{3,4}, Donovan LE^{1,2}, Stewart ZA^{5,6}, Tomlinson G⁷, Beardsall K^{8,9}, Feig DS^{10,11,12}, Murphy HR^{5,13,14} on behalf of the CONCEPTT Collaborative Group

¹Departments of Medicine and Obstetrics and Gynaecology, University of Calgary, Calgary, Canada; ²Alberta Children's Hospital Research Institute, Calgary, Canada; ³Servei d'Endocrinologia i Nutrició, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; ⁴CIBER-BBN, Madrid, Spain; ⁵Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge, UK; ⁶Department of Cardiovascular Sciences, University of Leicester, UK; ⁷Department of Medicine, University Health Network, Toronto, Canada; ⁸Department of Paediatrics, University of Cambridge, Cambridge, UK; ⁹Neonatal Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ¹⁰Department of Medicine, University of Toronto, Toronto, Canada; ¹¹Mount Sinai Hospital, Sinai Health System, Toronto, Canada; ¹²Lunenfeld-Tanenbaum Research Institute, Toronto, Canada; ¹³Women's Health Academic Centre, Division of Women's and Children's Health, King's College London, London, UK; ¹⁴Norwich Medical School, University of East Anglia, Norwich, UK

Diabet Med 2019; **36**: 1046–1053

Background

Continuous glucose monitoring (CGM) provides a more detailed assessment of glycemic control than standard capillary glucose monitoring. This secondary analysis of CONCEPTT used CGM measures to examine the association between maternal glycemic control and neonatal hypoglycemia, a common complication of type 1 diabetes pregnancy.

Methods

CONCEPTT was a multicenter randomized trial of CGM in women with type 1 diabetes who were pregnant or planning a pregnancy. Women from both the pregnant and planning pregnancy trials with a live birth were included in this cohort study ($n = 225$). Glycemic control was assessed in the first, second, and third trimesters using HbA1c and CGM measures. Additionally, intrapartum glycemic control was assessed for women with available CGM data in the 24 hours prior to delivery. Measures of infant size, adiposity, and fetal hyperinsulinemia (as assessed by cord blood C-peptide concentrations) were also examined for associations with neonatal hypoglycemia (defined as a glucose < 2.6 mmol/L and requiring intravenous dextrose).

Results

Neonatal hypoglycemia was diagnosed in 25% of infants in this cohort. Glycemic control as assessed by both HbA1c and TIR was associated with neonatal hypoglycemia in the second and third trimesters. There were no significant associations with CGM measures during the intrapartum period and neonatal hypoglycemia, though the number of women with intrapartum CGM data were small ($n = 33$). Infant size (extreme large for gestational age), adiposity (skinfold thickness), and fetal hyperinsulinemia (cord blood C-peptide concentration) were significantly higher in neonates with hypoglycemia compared with those without.

Conclusion

The association between both glycemic control the second half of pregnancy and measures of infant size and adiposity with neonatal hypoglycemia suggest that antepartum glycemic control plays an important part in the development of neonatal hypoglycemia. Additional studies are needed to determine the relative contribution of maternal antepartum versus intrapartum glycemic control to the risk of neonatal hypoglycemia.

Comment

Neonatal hypoglycemia remains a common complication following type 1 diabetes pregnancies. This study is consistent with other studies that demonstrate the importance of antenatal glycemic control in reducing the risk of neonatal hypoglycemia. Additionally, the association of infant size and adiposity with neonatal hypoglycemia further supports this. Using CGM, this study demonstrated that small improvements in TIR (5%–7%) are associated with less neonatal hypoglycemia. Healthcare providers and women with diabetes can focus on increasing CGM time in range during the latter half of pregnancy to reduce the risk of neonatal hypoglycemia.

Pumps or multiple daily injections in pregnancy involving type 1 diabetes: a prespecified analysis of the CONCEPTT randomized trial

Feig DS^{1,2,3}, Corcoy R^{4,5}, Donovan LE⁶, Murphy KE^{1,2,3}, Barrett JFR⁷, Sanchez JJ⁷, Wysocki T⁸, Ruedy K⁹, Kollman C⁹, Tomlinson G^{3,10}, Murphy HR^{11,12,13} on behalf of the CONCEPTT Collaborative Group

¹Mount Sinai Hospital, Sinai Health System, Toronto, Canada; ²Lunenfeld-Tanenbaum Research Institute, Toronto, Canada; ³Department of Medicine, University of Toronto, Toronto, Canada; ⁴Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; ⁵CIBER-BBN, Zaragoza, Spain; ⁶University of Calgary, Calgary, Canada; ⁷Sunnybrook Research Institute, Toronto, Canada; ⁸Nemours Children's Health System, Jacksonville, FL; ⁹Jaeb Center for Health Research, Tampa, FL; ¹⁰University Health Network, Toronto, Canada; ¹¹Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ¹²Department of Women and Children's Health, King's College London, London, UK; ¹³Department of Medicine, University of East Anglia, UK

Diabetes Care 2018; **41**: 2471–2479

Background

Tight glycemic control is associated with improved pregnancy outcomes in women with type 1 diabetes. However, the effectiveness of insulin pump therapy versus multiple daily injections (MDI) in achieving tight glycemic control in pregnancy has not been clearly established.

Methods

In this prespecified secondary analysis of CONCEPTT, women using an insulin pump versus MDI were compared. The primary outcome was change in HbA1c from baseline to 34 weeks gestation. Additional outcomes included CGM measures, patient-reported outcome measures, and pregnancy complications.

Results

A total of 248 pregnant women (125 and 123 using a pump and MDI respectively) were included in this cohort study. Individuals using insulin pump therapy were more likely to be married or common-law (94% vs 81%; $P=0.003$), less likely to smoke (10% vs 21%; $P=0.02$) and more likely to be taking a preconception multivitamin (39% vs 25%; $P=0.03$). In the first trimester, there was no significant difference in HbA1c between individuals on pump or MDI ($6.84 \pm 0.71\%$ vs $6.95 \pm 0.58\%$; adjusted $P=0.23$). However, at 34 weeks individuals on pump therapy had a significantly larger decrease in HbA1c from randomization to 34 weeks than those on MDI ($-0.32 \pm 0.65\%$ vs $-0.55 \pm 0.59\%$; adjusted $P=0.001$). Infants of pump users were more likely to be admitted to the neonatal intensive care unit ($P=0.02$) and slightly more likely to have neonatal hypoglycemia requiring intravenous dextrose ($P=0.05$).

Conclusions

In this cohort study of CONCEPTT participants, women on pump had significantly higher HbA1c in the second half of pregnancy and a smaller change in HbA1c from early to late pregnancy.

Comment

This is one of the largest cohort studies comparing pump to MDI in pregnancy. Even with adjustment for confounders,

cohort studies in pregnancy are subject to bias because of the differences between women who choose pump versus MDI. However, it is one of the few contemporary studies to suggest potentially less favorable neonatal outcomes between pump and MDI users. The increased neonatal hypoglycemia was likely related to a 5% lower TIR at 24 weeks. This contrasts with a previous Canadian cohort study, which found women using pump therapy had a lower HbA1c compared with those using MDI in the third trimester ($6.5 \pm 0.5\%$ vs $6.8 \pm 0.8\%$; $P=0.002$). However, women using pumps started pregnancy with lower HbA1c than those on MDI ($6.9 \pm 0.7\%$ vs $7.6 \pm 1.4\%$; $P=0.001$). Interestingly, insulin pumps users also had less of a change in HbA1c from early to late pregnancy (-0.4% vs -0.8%). In CONCEPTT, pump users had a 5% lower (TIR 63–140 mg/dL 53 vs 48%) at 24 weeks, despite comparable first and third trimester CGM glucose measures. The difference between pump and MDI users could be related to different eating patterns, and/or inadequate insulin dose adjustment in pump users during pregnancy. Regardless of the underlying cause, insulin pump users and their clinicians need to be more aggressive with insulin dose increments, as insulin resistance increases. Since only 25 women used pumps with low glucose suspend features in CONCEPTT, it remains to be seen if the newer pumps with partially automated features, or hybrid closed-loop systems will facilitate more aggressive insulin dose adjustment in the second and third trimesters.

Diabetes technology use among pregnant and nonpregnant women with T1D in the T1D Exchange

Polsky S¹, Wu M², Bode BW³, DuBose SN², Goland RS⁴, Maahs DM⁵, Foster NC², Peters AL⁶, Levy CJ⁷, Shah VN¹, Beck RW²

¹Barbara Davis Center for Diabetes, Aurora, CO; ²Jaeb Center for Health Research, Tampa, FL; ³Atlanta Diabetes Centers, Atlanta, GA; ⁴Naomi Berrie Diabetes Center at Columbia University Medical Center, New York, NY; ⁵Department of Pediatrics, Stanford University, Stanford, CA; ⁶Department of Internal Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, CA; ⁷Department of Medicine, Division of Endocrinology, Diabetes, and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, NY

Diabetes Technol Ther 2018; **20**: 517–523

Background

Little is known about the glucose monitoring and insulin delivery systems that women with type 1 diabetes use to optimize glucose control before and during pregnancy. Data from the T1D Exchange clinic registry were combined with self-reported maternal and fetal health outcomes of women with a delivery in the previous year to examine contemporary diabetes technology use in a real-world setting.

Methods

Data collected from 4,340 female participants aged 18 to 45 years from 68 T1D Exchange centers during 2010–2013 were

categorized as recently, previously, or never pregnant. Demographic data, details of diabetes technology use, and biomedical details were collected through self-reported questionnaires, chart reviews, and clinic medical records. Delivery and postpartum maternal infant outcomes among recently pregnant women were collected through self-reported questionnaires.

Results

There were 214 (4.9%) recent pregnancies, 1,540 (35.5%) previous pregnancies, and 2,586 (59.6%) women who were never pregnant. Women were 28 ± 9 years old, 84% white non-Hispanic, median (inter quartile range [IQR]) diabetes duration 13 years (8–20), median (IQR) HbA1c 7.9% (7.0–9.0%), and median (IQR) total daily insulin dose 0.6 units/kg (0.5–0.8). Women who were recently or previously were older (29.2 and 32.8 years) and had longer duration of diabetes (15 and 16 years) than women who were never pregnant (24.3 years old and 12 years duration). They also had higher rates of diabetes technology use (74%, 60%, and 58% for continuous subcutaneous insulin infusion) and (36%, 17%, and 12% for CGM) for recently, previously, and never pregnant women, respectively. Recently pregnant women had lower HbA1c levels (6.5%, 7.8%, and 8.0%) for recently, previously, and never pregnant. Rates of fetal loss were particularly high among recently and previously pregnant women (46% and 34% reported miscarriages; 6% and 3% reported stillbirths). Data from 130 recently pregnant women confirmed high rates of neonatal morbidity among liveborn infants (65% LGA, 43% neonatal intensive care unit admission, and 27% delivered at <37 weeks).

Conclusions

Adverse maternal and fetal outcomes were common in this small cohort of recently pregnant women with type 1 diabetes, suggesting that insulin pump therapy in particular, and to a lesser extent CGM, were not used optimally during pregnancy. However, these data were collected between 2010 and 2013, and diabetes technology usage in particular access to CGM has changed since that time.

Comment

Although limited by small numbers these data suggest that despite widespread use of insulin pumps, suboptimal maternal glucose control and infant outcomes persist. Patients and clinicians need to focus on optimizing insulin dose adjustment in pump users during the pregnancy. The number of recently or previously pregnant CGM users in this study were small and the CGM systems used during 2010–2013 have been superseded by more accurate, longer duration CGM. Further follow up in a larger contemporary cohort will be of interest.

Suboptimal nocturnal glucose control is associated with large for gestational age in treated gestational diabetes mellitus

Law GR¹, Alnaji A², Alrefaii L², Endersby D³, Cartland SJ^{2,3}, Gilbey SG³, Jennings PE⁴, Murphy HR⁵, Scott EM^{2,3}

¹School of Health and Social Care, University of Lincoln, Lincoln, UK; ²Division of Clinical and Population Sciences, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK; ³Leeds Teaching Hospitals NHS Trust, Leeds, UK; ⁴York NHS Foundation Trust, York, UK; ⁵Division of Maternal Health, St Thomas' Hospital, King's College London, London, UK

Diabetes Care 2019; **42**: 810–815

Background

Gestational diabetes is associated with an increased risk of pregnancy complications including LGA neonates. With detailed information on day-to-day glycemic control, CGM can provide insight into specific temporal glycemic patterns that may be associated with large for gestational age neonates.

Methods

In this prospective observational cohort study, pregnant women with gestational diabetes were recruited. Participants wore masked CGM (iPro2 with the Enlite sensor) for 7 days at 30–32 weeks of gestation. Summary statistics were used to compare measures of glycemic control between women with and without LGA infants. Functional data analysis was used to examine if temporal glycemic patterns were associated with large for gestational age infants.

Results

A total of 162 participants were recruited in this cohort. Women with an LGA infant had significantly higher CGM fasting glucose levels (6.2 ± 0.6 vs 5.8 ± 0.6 mmol/L; $P = 0.03$) and significantly higher CGM nocturnal glucose levels (6.0 ± 1.0 vs 5.5 ± 0.8 mmol/L; $P = 0.005$) than women who did not have a large for gestational age infant. Functional data analysis demonstrated that women with a large for gestational age infant had significantly higher glucose levels from 0030 to 0630 hours compared with those without a large for gestational age infant. There was no difference in glucose variability measures (SD or coefficient of variability), daytime CGM glucose profiles or mean fasting capillary glucose between the two groups.

Conclusions

Using CGM, this study demonstrated women with an LGA neonate have significantly higher nocturnal and fasting glucoses. Targeting overnight glucoses may allow women with GDM and their clinicians to reduce rates of LGA.

Comment

This study demonstrates that CGM can be used to identify specific glycemic targets associated with infant outcomes in women with gestational diabetes (GDM). It demonstrates that women with GDM spend a high percentage Time in Range (90% TIR 70–140 mg/dL) with minimal time above range (10% TAR > 140 mg/dL). It also confirms that small differences in maternal overnight glucose levels are associated with neonatal outcomes and adds to the growing literature of the objective

CGM measures in the development of pregnancy complications. It explores the use of functional data analysis to analyze time-series CGM data at a population level in order to maximize the temporal information obtained. These techniques may be particularly applicable for women with GDM and those with less severe glycemic conditions for whom conventional CGM summary statistics and time-in-range measures may be insufficiently sensitive.

Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity

Lowe WL J¹, Scholtens DM¹, Lowe LP¹, Kuang A¹, Nodzenski M¹, Talbot O¹, Catalano PM², Linder B³, Brickman WJ^{1,4}, Clayton P⁵, Deerochanawong C⁶, Hamilton J⁷, Josefson JL^{1,4}, Lashley M⁸, Lawrence JM⁹, Leberthal Y¹⁰, Ma R¹¹, Maresh M¹², McCance D¹³, Tam WH¹¹, Sacks DA⁹, Dyer AR¹, Metzger BE¹, HAPO Follow-up Study Cooperative Research Group

¹Northwestern University Feinberg School of Medicine, Chicago, IL; ²MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH; ³National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; ⁴Ann and Robert H. Lurie Children's Hospital, Chicago, IL; ⁵Royal Manchester Children's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, School of Medical Sciences, Faculty of Biology, Medicine, and Health, University of Manchester, Manchester, UK; ⁶Rajavithi Hospital, Bangkok, Thailand; ⁷Hospital for Sick Children, University of Toronto, Toronto, Canada; ⁸Queen Elizabeth Hospital, School of Clinical Medicine and Research, University of the West Indies, Barbados; ⁹Kaiser Permanente of Southern California, CA; ¹⁰Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ¹¹Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; ¹²St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, England; ¹³Royal Victoria Hospital, Belfast, Ireland

JAMA 2018; **320**: 1005–1016

Background

Gestational diabetes is common, and its incidence continues to rise. Increased adiposity in the children of women with gestational diabetes has been shown in some but not all studies.

Methods

This was a follow-up study of mothers and their offspring from Hyperglycemic and Adverse Pregnancy Outcomes (HAPO) cohort. The primary exposure was untreated gestational diabetes, defined post-hoc by the International Association of Diabetes and Pregnancy Study Groups. A

composite of type 2 diabetes and prediabetes was the primary maternal outcome of interest. The primary outcome for offspring was being overweight or obese. Secondary offspring outcomes included body fat percentage, waist circumference, and sum of skinfolds.

Results

A total of 9,322 mother–child pairs of the 15,812 eligible pairs were screened for inclusion in the study. Of those, 4,832 children (mean age 11.4 ± 1.2 years) and 4,697 mothers (mean age 41.7 ± 5.7 years) were included in this cohort. Women with gestational diabetes were more likely to develop type 2 diabetes or prediabetes than women without gestational diabetes (adjusted OR 3.44 [95% CI 2.84, 4.14]). Offspring of mothers with gestational diabetes compared with those without were more likely to be overweight or obese (39.5 vs 28.6%). However, when this was adjusted for maternal BMI during pregnancy, this association was no longer apparent (adjusted OR 1.21 [95% CI 1.00, 1.46]). Maternal gestational diabetes was associated with secondary offspring outcomes including obesity (adjusted OR 1.58 [95% CI 1.24, 2.01]), body fat percentage (adjusted OR 1.35 [95% CI 1.08, 1.68]), waist circumference (adjusted OR 1.34 [95% CI 1.08, 1.67]), and sum of skinfolds (adjusted OR 1.57 [95% CI 1.27, 1.95]).

Conclusions

Women with gestational diabetes were more likely to develop disorders of glucose metabolism compared with those without (52.2 vs 20.1%). There was no significant difference in the primary offspring outcome, childhood overweight or obesity, after adjustment for maternal BMI and other covariates. There was a significant association with maternal gestational diabetes and secondary measures of offspring obesity and adiposity.

Comment

This large cohort study of women with untreated gestational diabetes further supports gestational diabetes as an important risk factor for the development of maternal disorders of glucose metabolism. This study benefits from its large sample size, diverse racial/ethnic population, and rigorous data collection. Interestingly, adjustment for maternal BMI attenuated the strength of association between offspring exposure to gestational diabetes and all measures of offspring obesity and adiposity. This highlights the importance of obtaining maternal BMI when conducting follow-up studies examining offspring obesity.

Glucotypes reveal new patterns of glucose dysregulation

Hall H^{1,2}, Perelman D², Breschi A², Limcaoco P², Kellogg R², McLaughlin T³, Snyder M²

¹Stanford University, Stem Cell Biology and Regenerative Medicine, Stanford, CA; ²Stanford University, Department of Genetics, Stanford, CA; ³Stanford University, Department of Medicine, Division of Endocrinology, Stanford, CA

PLoS Biol 2018; **16**: e2005143

Background

Current CGM metrics measure individual aspects of the time-series data, but do not adequately characterize the temporal glucose profile or the shape of continuous glucose curves. Analyzing the shape of the continuous glucose time-series data, allows for a more complete assessment of glucose variability.

Methods

Fifty-seven healthy participants (32 female, 25 male), median age 51 years (range 25–76), without known diabetes were characterized by CGM, fasting glucose, HbA1c, 75-g OGTT, and steady-state plasma glucose testing as a marker for insulin resistance. Five participants had undiagnosed type 2 diabetes, 14 had prediabetes, and 38 had normal glucose tolerance. The temporal glucose profiles were segmented into overlapping sliding 2.5-hour windows to characterize the magnitude and degree of glucose variability. Spectral clustering was applied to capture high similarities between windows with similar glucose profiles and to classify three patterns of low, moderate, and severe variability. Thirty participants ate three standardized breakfasts consisting of cornflakes and milk (high sugar), a peanut butter sandwich (high fat and protein), and a protein bar (moderate fat and protein), all with similar calories.

Results

Some participants stayed predominantly in the low variability range, whereas others were predominantly in the moderate or severe variability range, with clear intermediates. The three patterns increased in both glucose variability and mean glucose concentration (77, 96, and 122 mg/dL for low, moderate, and severe). There were significant positive correlations between the time spent in low and high glycemic signatures with lower and higher values for fasting glucose, HbA1c, OGTT, steady-state plasma glucose, BMI, and age. Severe variability glucose patterns after high sugar breakfasts were seen in 80% of participants, whereas the responses to moderate and higher fat and protein intake varied between individuals. Twenty-five participants (44%) had higher glycemic responses measured by CGM compared with OGTT despite similar carbohydrate loads. Among participants with “normal” glucose tolerance, 42% (16/38) had CGM glucose levels in the prediabetes or diabetes range.

Conclusions

Spectral clustering revealed three glucotypes of increasing variability (low, moderate, and severe) accompanied by increasing mean glucose that explained >70% of the glycemic variability. The proportion of time spent in each glucotype pattern was correlated with clinically relevant metabolic measures. The prototype software for viewing and categorizing 2–3 weeks of CGM data is available at glucotype.

Comment

This study describes the development of a new glucose variability metric, the glucotype, which could detect earlier preclinical forms of glycemic dysregulation and

allow for targeted personalized diet and lifestyle interventions to prevent progression to type 2 diabetes. It also highlights the limitations of conventional glycemic classifications based on fasting glucose, HbA1c, and OGTT, with 25% of “normoglycemic” participants demonstrating severe glucose variability. These data are particularly relevant for pregnant women at risk for developing gestational diabetes (GDM), for whom conventional glycemic tests are further influenced by changes in gestational physiology.

Impact of daily incremental change in environmental temperature on beta cell function and the risk of gestational diabetes in pregnant women

Retnakaran R^{1,2,3}, Ye C¹, Kramer CK^{1,2}, Hanley AJ^{1,2,4}, Connelly PW^{2,5,6}, Sermer M⁷, Zinman B^{1,2,3}

¹Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Canada; ²Division of Endocrinology, University of Toronto, Toronto, Canada; ³Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada; ⁴Department of Nutritional Sciences, University of Toronto, Toronto, Canada; ⁵Keenan Research Centre for Biomedical Science of St Michael's Hospital, Toronto, Canada; ⁶Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada; ⁷Division of Obstetrics and Gynecology, University of Toronto, Toronto, Canada

Diabetologia 2018; **61**: 2633–2642

Background

Previous studies have identified a higher prevalence of GDM in summer compared with winter. However, a mechanism connecting environmental temperature and GDM has not been established.

Methods

In this prospective cohort study in Toronto, Canada, women were recruited at the time of screening for GDM. Environmental temperature data were obtained from Environment Canada. Mean temperature and temperature changes at eight time points up to 56 days prior to the oral glucose tolerance test (OGTT) were obtained. Multiple linear regression was performed to examine for associations between temperature variables and glycemic measures as well as measures of insulin resistance after adjustment for important covariates.

Results

Of the 1,464 individuals who participated in this study, 318 women were diagnosed with GDM. In the adjusted analysis, temperature changes in the 1 to 8 weeks before the OGTT were associated with gestational diabetes during the months when the temperature was increasing. Adjusted ORs demonstrated a significant association between temperature changes in the preceding 1-, 2-, 3-, and 4-week periods prior to the OGTT, but no significant associations with mean temperature during the same period. Temperature changes in the preceding 4- and 5-week period prior to diagnosis were

inversely associated with measures of beta cell function (insulin secretion-sensitivity index-2 and insulinogenic index/homeostatic model assessment of insulin resistance).

Conclusions

Increasing temperatures in the weeks preceding the OGTT rather than mean temperature were associated with diagnosis of gestational diabetes. The inverse association between temperature changes and measures of beta cell function suggest beta-cell dysfunction as the etiology of temperature related patterns in GDM diagnosis.

Comment

A growing number of studies have identified an association between environmental temperature and glucose metabolism. This cohort study demonstrated that increasing temperatures in the time prior to diagnosis of GDM, rather than mean temperature, was associated both with diagnosis of gestational diabetes and with beta-cell function. This has important implications at a public health and resource utilization level and can help us better understand how beta-cell adaptation during pregnancy may be adversely affected by increasing environmental temperatures. More data are needed to understand whether increasing environmental temperature is associated with obstetric and neonatal outcomes. Also, it would be interesting to evaluate the impact of environmental temperature on direct CGM glucose measures.

Acceleration of BMI in early childhood and risk of sustained obesity

Geserick M^{1,2}, Vogel M², Gausche R³, Lipek T^{1,4}, Spielau U^{1,4}, Keller E³, Pfäffle R^{1,3}, Kiess W^{1,2}, Körner A^{2,4}

¹Center for Pediatric Research, University Hospital for Children and Adolescents, Leipzig, Germany; ²Leipzig Research Center for Civilization Diseases (LIFE Child), Leipzig, Germany; ³CrescNet, Medical Faculty, University Medical Center, University of Leipzig, Germany; ⁴Integrated Research and Treatment Center (IFB), Adiposity Diseases, University Medical Center, University of Leipzig, Leipzig, Germany

N Engl J Med 2018; **379**: 1303–1312

Background

The prevalence of childhood obesity is high and rising. Understanding the time points when children are most susceptible to becoming overweight and obese may help to develop more effective public health strategies. The aim of this study was to examine the specific ages at which children are most prone to developing sustained obesity.

Methods

A population-based study of 51,505 children (aged 0–14 years) and adolescents (aged 15–18 years) with prospective and retrospective analyses. BMI and height were collected

prospectively with at least 2 and up to 16 visits per participant and converted to BMI standard deviation scores (BMI SDS) using German reference data. The rate of weight gain was evaluated in yearly intervals from 0 to 18 years. The percentage of children in each group were retrospectively categorized as underweight (BMI SDS -5 to < -1.28), normal weight (BMI SDS -1.28 to $< +1.28$), overweight (BMI SDS 1.28 to < 1.88), and obese (BMI SDS 1.88 to < 5).

Results

A total of 51,505 children and adolescents with 241,715 data points were included in the study. A majority of normal weight adolescents had normal weight trajectories throughout childhood. A majority of obese adolescents had already become overweight or obese by 5 years of age. Approximately 50% of children who were overweight at 2 years of age returned to normal weight in adolescence, but 90% of children who were obese at 3 years of age continued to be overweight or obese into adolescence. These patterns were similar in boys and girls. The greatest acceleration of BMI SDS occurred between 2 and 6 years of age, in both boys and in girls. Almost half (43.7%) of LGA newborns were overweight or obese adolescents compared with a third of appropriate or small for gestational age neonates. Maternal overweight rates were, as expected, an independent risk factor for childhood obesity.

Conclusions

Children born to overweight mothers and LGA newborns have a sustained increased risk of adolescent overweight and obesity. The tracking of growth and weight patterns in early childhood especially in LGA and children of overweight mothers is crucial for identifying the children at risk for sustained overweight and obesity.

Comment

This study highlights the long-term consequences of LGA and underlines the importance of optimizing maternal glucose control in the second and third trimesters in women with diabetes to reduce the longer-term health consequences of overweight and obesity persisting into adolescence.

Author Disclosure Statement

H.M. is on the Medtronic (insulin pump and CGM manufacturer) European scientific advisory board. There are no other competing financial interests.

References

1. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019; **42**: 1593–1603.
2. Kristensen K, Ogge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. *Diabetologia* 2019; **62**: 1143–1153.
3. Yamamoto JM, Benham J, Mohammad K, Donovan LE, Wood S. Intrapartum glycaemic control and neonatal hypoglycaemia

- in pregnancies complicated by diabetes: a systematic review. *Diabet Med* 2018; **35**: 173–183.
4. Feig DS, Corcoy R, Donovan LE, et al. Pumps or multiple daily injections in pregnancy involving type 1 diabetes: a prespecified analysis of the CONCEPTT randomized trial. *Diabetes Care* 2018; **41**: 2471–2479.
 5. Feig DS, Corcoy R, Donovan LE, et al. Response to “Comment on Feig et al. Pumps or multiple daily injections in pregnancy involving type 1 diabetes: a prespecified analysis of the CONCEPTT randomized trial.” *Diabetes Care* 2019; **42**: e98–e99.
 6. Polsky S, Wu M, Bode BW, et al. Diabetes technology use among pregnant and nonpregnant women with T1D in the T1D exchange. *Diabetes Technol Ther* 2018; **20**: 517–523.
 7. Law GR, Alnaji A, Alrefaii L, et al. Suboptimal nocturnal glucose control is associated with large for gestational age in treated gestational diabetes mellitus. *Diabetes Care* 2019; **42**: 810–815.
 8. Hall H, Perelman D, Breschi A, et al. Glucotypes reveal new patterns of glucose dysregulation. *PLoS Biol* 2018; **16**: e2005143.
 9. Retnakaran R, Ye C, Kramer CK, et al. Impact of daily incremental change in environmental temperature on beta cell function and the risk of gestational diabetes in pregnant women. *Diabetologia* 2018; **61**: 2633–2642.
 10. Lowe WL, Jr., Scholtens DM, Lowe LP, et al. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. *JAMA* 2018; **320**: 1005–1016.
 11. Geserick M, Vogel M, Gausche R, et al. Acceleration of BMI in early childhood and risk of sustained obesity. *N Engl J Med* 2018; **379**: 1303–1312.