Technology and Pregnancy

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Introduction

THE MANUSCRIPTS CHOSEN FOR THIS YEAR'S article on technology and pregnancy reflect some key advances in the field of diabetes technology that is increasingly used in the clinical management of diabetes before and during pregnancy. From over 2300 published articles, we have selected 10 papers describing the potential impact of currently available on-demand and real-time continuous glucose monitoring and emerging closed-loop or automated insulin delivery systems. Large population-based studies remain crucial for understanding changes in maternal demographics and pregnancy outcomes—in particular, the serious but relatively uncommon adverse outcomes of congenital anomaly, stillbirth, and neonatal death. Data from Scotland including over 2300 type 1 and 1400 type 2 diabetes pregnancies serve as a timely reminder that the serious adverse outcomes and newborn complications attributed to maternal glycaemia show little improvement over the past 15 years (1).

The trials include women with gestational, type 1, and type 2 diabetes and range from the first descriptions of closed-loop insulin delivery use during labor, delivery, and postpartum to pivotal phase 3 trials of masked intermittent and real-time continuous glucose monitoring (CGM). The Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) demonstrates the impact of real-time CGM on neonatal health outcomes in a high-quality multicenter international randomized trial from Canada, England, Scotland, Spain, Italy, Ireland, and the United States (2). Its results are in stark contrast to the evaluation of intermittent masked CGM in Gluco-MOMs (3). While masked CGM remains an important direct measure of fetal glucose exposure for research purposes, it was not successful as a clinical intervention in this trial. The first home study of day-and-night closed-loop in pregnancy suggested the potential for automated insulin delivery (real-time CGM, insulin pump, and control algorithm) to maintain satisfactory glucose control with minimal time spent hypoglycemic (4).

Outside of pregnancy, the Freestyle Libre has emerged as a potential game changer in the clinical management of diabetes, paving the way for more affordable accessible glucose monitoring. It is the first sensor specifically licensed for use during pregnancy with initial data suggesting that it is accurate, acceptable, and safe in pregnancy (5). Real-world data are becoming increasingly important to health-care providers and regulators. Data from Belgium provide some insights into the “real-world” use of CGM in insulin pump users use before and during pregnancy (6). While hypoglycemia and suboptimal glucose control were the most common indications for CGM, 66 participants were included for pregnancy.

Clinical trials, whether positive or negative, lead to changes in practice, with a large French study confirming that the oral glucose lowering agent gliburide (glibenclamide) is associated with increased neonatal hypoglycemia and should not be used as first-line therapy in the treatment of gestational diabetes mellitus GDM (7). In early pregnancy, the appropriate diagnostic criteria for GDM are poorly defined. This is particularly important in high-risk obese women, in whom fetal growth acceleration

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precedes GDM diagnosis. Metabolomic data from the UK describe the metabolite disturbances in obese women 10 weeks prior to GDM diagnosis, offering the potential of identifying and targeting clinical and/or research interventions more effectively (8).

During pregnancy, DNA fragments from the placenta are released into the maternal plasma in sufficient quantities for genetic analysis from about 10 weeks gestation. Hughes and colleagues demonstrate how testing of fetal DNA will lead to new biological insights into variation in fetal growth and large for gestational age (LGA) (9). Fetal genetics influenced neonatal birthweight independently of fasting glucose concentration and across all levels of maternal glycaemia. These data provide some reassurance for women and clinicians that maternal glucose is not the only contributor to offspring LGA.

Key Articles Reviewed for the Article

Diabetes and pregnancy: national trends over a 15 year period

Mackin ST, Nelson SM, Kerssens JJ, Wood R, Wild S, Colhoun HM, Leese GP, Philip S, Lindsay RS; on behalf of the Scottish Diabetes Research Network Epidemiology Group

Diabetologia 2018; **61**: 1081–1088

Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial

Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, Asztalos E, Barrett JFR, Sanchez JJ, de Leiva A, Hod M, Jovanovic L, Keely E, McManus R, Hutton EK, Meek CL, Stewart ZA, Wysocki T, O'Brien R, Ruedy K, Kollman C, Tomlinson G, Murphy HR

Lancet 2017; **390**: 2347–2359

Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): a multicentre randomized controlled trial

Voormolen DN, DeVries JH, Sanson RME, Heringa MP, de Valk HW, Kok M, van Loon AJ, Hoogenberg K, Bekedam DJ, Brouwer TCB, Porath M, Erdsieck RJ, NijBijvank B, Kip H, van der Heijden OWH, Elving LD, Hermesen BB, Potter van Loon BJ, Rijnders RJP, Jansen HJ, Langenveld J, Akerboom BMC, Kiewiet RM, Naaktgeboren CA, Mol BWJ, Franx A, Evers IM

Diabetes Obes Metab 2018; **20**: 1894–1902

Day-and-night closed-loop insulin delivery in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial

Stewart ZA, Wilinska ME, Hartnell S, O'Neil LK, Rayman G, Scott EM, Barnard K, Farrington C, Hovorka R, Murphy HR

Diabetes Care 2018; **41**: 1391–1399

Accuracy, user acceptability, and safety evaluation for the FreeStyle Libre Flash glucose monitoring system when used by pregnant women with diabetes

Scott EM, Bilous RW, Kautzky-Willer A

Diabetes Technol Ther 2018; **20**: 180–188

Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: a real-world study

Charleer S, Mathieu C, Nobels F, De Block C, Radermecker RP, Hermans MP, Taes Y, Vercammen C, T'Sjoen G, Crenier L, Fieuws S, Keymeulen B, Gillard P; for the RESCUE Trial Investigators

J Clin Endocrinol Metab 2018; **103**: 1224–1232

Adaptability of closed-loop during labour, delivery and postpartum: a secondary analysis of data from two randomized crossover trials in type 1 diabetes pregnancy

Stewart ZA, Yamamoto JM, Wilinska ME, Hartnell S, Farrington C, Hovorka R, Murphy HR

Diabetes Technol Ther 2018; **20**: 501–505

Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial

Sénat MV, Affres H, Letourneau A, Coustols-Valat M, Cazaubiel M, Legardeur H, Jacquier JF, Bourcigaux N, Simon E, Rod A, Héron I, Castera V, Sentilhes L, Bretelle F, Rolland C, Morin M, Deruelle P, De Carne C, Maillot F, Beucher G, Verspyck E, Desbriere R, Laboureau S, Mitanchez D, Bouyer J; for the Groupe de Recherche en Obstétrique et Gynécologie

JAMA 2018; **319**: 1773–1780

Metabolic profiling of gestational diabetes in obese women during pregnancy

White SL, Pasupathy D, Sattar N, Nelson SM, Lawlor DA, Briley AL, Seed PT, Welsh P, Poston L; on behalf of the UPBEAT Consortium

Diabetologia 2017; **60**: 1903–1912

Fetal genotype and maternal glucose have independent and additive effects on birth weight

Hughes AE, Nodzenski M, Beaumont RN, Talbot O, Shields BM, Scholtens DM, Knight BA, Lowe WL Jr, Hattersley AT, Freathy RM

Diabetes 2018; **67**: 1024–1029

Diabetes and pregnancy: national trends over a 15 year period

Mackin ST¹, Nelson SM², Kerssens JJ³, Wood R⁴, Wild S⁴, Colhoun HM⁵, Leese GP⁶, Philip S⁷, Lindsay RS^{1,8}; on behalf of the Scottish Diabetes Research Network Epidemiology Group

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Diabetologia 2018; **61**: 1081–1088

Background

Understanding the trends in perinatal outcomes in diabetes pregnancies is essential to focus health-care resources for improving health outcomes in women with diabetes and their offspring. The aim of this cohort study was to evaluate the trends in obstetric and neonatal outcomes in Scotland.

Methods

All women discharged from Scottish maternity hospitals for a 15-year period (April 1, 1998, to March 31, 2013) were identified and linked with the Scottish Care Information–Diabetes database. Women with diabetes who delivered between 24 and 44 weeks' gestation were included. Obstetric and neonatal outcomes of women with type 1 (T1D) and type 2 diabetes (T2D) were compared to women without diabetes.

Results

The study included 3229 women with T1D and 1452 women with T2D. There was a 44% increase in the number of deliveries to women with T1D and a 90% increase in women with T2D. Compared to pregnancies without diabetes, stillbirth rates in diabetes pregnancies were approximately five times higher (T1D 19.5 per 1000 births, T2D 24.8 per 1000 births, women without diabetes 4.9 per 1000 births). LGA and preterm delivery were more common in pregnancies with diabetes, especially in T1D women, who continued to have the highest rates of preterm delivery (35.3%, n=1126) and LAG neonates (50.9%, n=1632).

Conclusions

The prevalence of pregestational diabetes in pregnancy is increasing in this population. The elevated risk of serious and common complications shows little improvement over the 15-year period.

Comments

This large national cohort study highlights the persistent increased risk associated with pregestational diabetes in pregnancy. Unlike comparable data from women in England and Wales, which reported an over 2-fold reduction in stillbirths during the past decade (11), Mackin et al. report no improvement in stillbirths despite a decrease in stillbirth in the general population. Further research is needed to understand whether this relates to differences in maternal demographics, antenatal glycaemic control, and/or obstetric practices. Although not directly comparable due to different birthweight centiles, there were seemingly higher rates of LGA in Scotland (most notably in T2D) and lower rates of preterm delivery in T1D (35% vs 40% in England and Wales).

Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial

Feig DS^{1,2,3}, Donovan LE⁴, Corcoy R⁵, Murphy KE^{2,3,6}, Amiel SA⁷, Hunt KF^{7,8}, Asztalos E⁹, Barrett JFR⁹, Sanchez JJ⁹, de Leiva A⁵, Hod M¹⁰, Jovanovic L^{11,12}, Keely E¹³, McManus R^{14,15}, Hutton EK¹⁶, Meek CL¹⁷, Stewart ZA¹⁷, Wysocki T¹⁸, O'Brien R¹⁹, Ruedy K¹⁹, Kollman C¹⁹, Tomlinson G^{3,20}, Murphy HR^{17,21,22}

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Lancet 2017; **390**: 2347–2359

This manuscript is also discussed in the article on Continuous Glucose Monitoring in 2018, page S-13.

Background

Continuous glucose monitoring has been associated with improved glycemic control outside of pregnancy. During pregnancy, the use of intermittent masked CGM was associated with decreased glycosylated hemoglobin (HbA1c) and reduced risk of macrosomia in one study. However, the effectiveness of real-time CGM worn throughout pregnancy, rather than intermittently, is unknown.

Methods

CONCEPTT was a multicenter, open-label, randomized controlled trial in 31 sites from Canada, the United Kingdom, Spain, Italy, Ireland, and the United States. It comprised of two parallel trials, one in pregnant women and the other in women planning pregnancy. Women with T1D of at least 1-

year duration were randomized to CGM plus capillary glucose testing vs capillary glucose testing alone. Women were stratified by method of insulin delivery (multiple daily injections or pump) and baseline HbA1c. In the pregnancy trial, the primary outcome was change in HbA1c from randomization to 34 weeks. In the prepregnancy trial, it was change in HbA1c to 24 weeks of conception. Multiple prespecified CGM glycemic and neonatal health outcomes were assessed.

Results

A total of 215 pregnant women and 110 women planning pregnancy were randomized. The use of CGM was reasonably high: median sensor use of 6.1 days (interquartile range [IQR] 4.0–6.8) in pregnant women and 6.2 days (IQR 5.2–6.9) per week in women planning pregnancy. For the primary outcome, women in the pregnancy trial randomized to CGM had a greater change in HbA1c from baseline (–0.54% vs –0.35; $P=0.037$). Pregnant CGM participants also spent an extra 100 minutes per day in the glucose target range compared to the control arm participants. The treatment effect of CGM was consistent across sites and independent of insulin delivery modality. Importantly, neonates of CGM participants were less likely to be large for gestational age (53% vs 69%; $P=0.021$), less likely to have hypoglycemia requiring intravenous dextrose (15% vs 28%; $P=0.025$), and spent less time in hospital (3.1 days vs. 4.0 days; $P=0.016$). There were no significant differences in maternal or neonatal outcomes among the prepregnancy trial participants.

Conclusions

The use of real-time CGM during pregnancy is associated with improved maternal glycemic control as measured by both HbA1c and CGM time in target range. The treatment effect was comparable for insulin pump and multiple daily injections users. Neonatal complications related to maternal hyperglycemia were significantly reduced.

Comment

The CONCEPTT study is a large, multicenter, robust study. It unequivocally demonstrates that continuous wear CGM improves both glucose control and infant health outcomes (a halving in the odds ratio for large for gestational age infants, neonatal intensive care admissions, and neonatal hypoglycemia) and reduces length of hospital stay by a day. The number of women needed to treat with CGM to avoid an adverse infant health outcome is six, suggesting that the additional costs of CGM use during pregnancy may be offset, at least in part by reduced infant health-care costs.

Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): a multicentre randomized controlled trial

Voormolen DN¹, DeVries JH², Sanson RME³, Heringa MP¹, de Valk HW⁴, Kok M⁵, van Loon AJ⁶, Hoogenberg K⁷, Bekedam DJ⁸, Brouwer TCB⁹, Porath M¹⁰, Erdsieck RJ¹¹, NijBijvank B¹², Kip H¹³, van der Heijden OWH¹⁴, Elving LD¹⁵, Hermesen BB¹⁶, Potter van Loon BJ¹⁷, Rijnders RJP¹⁸, Jansen HJ¹⁹, Langenveld J²⁰, Akerboom BMC²¹, Kiewiet RM²², Naaktgeboren CA²³, Mol BWJ^{24,25}, Franx A¹, Evers IM²⁶

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Diabetes Obes Metab 2018; **20**: 1894–1902

This manuscript is also discussed in the article on Continuous Glucose Monitoring, page S-13.

Background

Diabetes increases the risk of adverse pregnancy outcomes. This study assesses the effectiveness of intermittent masked CGM in women with type 1, type 2, and gestational diabetes.

Methods

This was an open label, multicenter, randomized controlled trial in 22 hospitals in the Netherlands and 1 hospital in Belgium. Women with preexisting diabetes prior to 16 weeks and women with GDM prior to 30 weeks who required insulin were randomized to masked CGM worn for 5–7 days every 6

weeks vs standard capillary glucose testing. The primary outcome was macrosomia defined as gestational age and sex-adjusted birth weight above the 90th centile. An estimated sample size of 300 women was required to find a reduction in macrosomia from 45% to 35% regardless of type of diabetes.

Results

Three hundred participants were enrolled (109 T1D, 82 T2D, and 109 GDM). Outcome data were available for 290 women (143 randomized to CGM and 147 randomized to control). The intention-to-treat analysis found no difference in macrosomia between women randomized to intermittent masked CGM vs control (44 [31%] vs 42 [28%], respectively; relative risk 1.08 [0.76–15.4]). There was less preeclampsia in the CGM group compared with the control group (5 [3.5%] vs 27 [18.4%]; relative risk 0.30 [95% confidence interval (CI) 0.12–0.80]). Of the 290 women included in the intention-to-treat analysis, 44 women in the CGM group did not adhere to the study protocol. Seven women with T1D (4 CGM, 3 control) were switched from masked-intermittent to continuous real-time CGM.

Conclusions

No difference in antenatal glucose control or macrosomia was found between women randomized to intermittent masked CGM vs standard of care.

Comments

The trial included a mixed group of women, approximately one-third with T1D, one-third with T2D, and one-third with GDM, meaning that it lacked statistical power to detect between-group differences in maternal glycemia and/or neonatal outcomes in T1D. Details of the objective CGM measures were not provided. The assumption of a baseline macrosomia rate of 45% in all participants represents a large overestimation for two-thirds of the study population. The expected macrosomia rates approximate 25% in T2D and 10% among women with GDM (11,12). Interpretation of the results is also limited by the relatively high proportion of women who did not adhere to the study protocol. Taken together, data from CONCEPTT and GlucoMOMs suggest that continuous use of real-time CGM is the most effective intervention for reducing excessive fetal growth acceleration and rates of large for gestational age in T1D pregnancy.

Day-and-night closed-loop insulin delivery in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial

Stewart ZA^{1,2}, Wilinska ME¹, Hartnell S², O'Neil LK³, Rayman G⁴, Scott EM⁵, Barnard K⁶, Farrington C⁷, Hovorka R¹, Murphy HR^{8,2,3,9}

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Background

Overnight closed-loop insulin delivery has been previously shown to improve overnight time-in-target during pregnancy. However, the safety and efficacy of hybrid closed-loop insulin delivery used day and night in T1D pregnancies have not been evaluated.

Methods

In this open-label randomized crossover trial, women were randomized to start with either day-and-night hybrid closed-loop or sensor-augmented pump therapy. After completing 4 weeks in their respective groups, there was a 1- to 2-week washout period before crossing over to the alternate arm. Following the completion of the randomized trial, women could choose to continue closed-loop for up to 6 weeks postpartum.

Results

Of the 19 women recruited, 16 women completed the randomized trial. They had a diabetes duration (mean $\pm$ standard deviation) of 19.4 ± 10.2 years and booking HbA1c of $8.0 \pm 1.1\%$. Eight participants (50%) were on the insulin pump at booking and nine (56%) had a booking HbA1c $> 7.5\%$. Closed-loop achieved a similar time-in-target compared with sensor-augmented pump therapy (62% vs 60%; $P=0.47$). However, participants experienced less hypoglycemia while on closed-loop in terms of time $< 63\text{mg/dL}$ (3.5 mmol/L); 1.6 vs 2.7% ; $P=0.02$, time $< 50\text{mg/dL}$ (2.8 mmol/L); 0.2 vs 0.5% ; $P=0.03$, number of hypoglycemic events (8 vs 12.5 per 28 days; $P=0.04$) and low blood glucose index (1.0 vs 1.4 ; $P=0.01$). All 16 participants chose to continue closed-loop for varying periods of time after completion of the randomized crossover trial and achieved a median time-in-target of $> 70\%$ up until delivery.

Conclusions

Day-and-night closed-loop is safe and effective in pregnancy. While there was no significant improvement in time-in-target, participants experienced less hypoglycemia while using the closed-loop system. The differences in the level of glycemic control obtained between women who started pregnancy with higher and lower HbA1c suggest that diabetes self-management practices including accuracy of carbohydrate counting, precision and timing of premeal boluses, and maternal dietary intake are all still relevant during hybrid closed-loop use. More research is needed to understand which women with T1D are candidates for closed-loop insulin delivery and which women achieve satisfactory glucose control with existing CGM and insulin pump therapy.

Accuracy, user acceptability, and safety evaluation for the FreeStyle Libre Flash glucose monitoring system when used by pregnant women with diabetes

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Diabetes Technol Ther 2018; **20**: 180–188

Background

Effective glucose monitoring is essential in the management of diabetes in pregnancy. Flash glucose monitoring (the FreeStyle Libre) uses a sensor that is worn for up to 14 days. Glucose results are displayed after scanning the sensor. Flash glucose monitoring does not require finger stick calibrations, nor does it have automatic alarms. The study sought to determine the safety, accuracy, and user acceptability of Flash glucose monitoring in diabetes pregnancies.

Methods

This prospective cohort study included participants with type 1, type 2, and gestational diabetes from the United Kingdom and Austria. Women were eligible for inclusion if they were over 18 years of age with a singleton pregnancy after 12 weeks gestation. Participants wore the masked sensor for 14 days and were required to perform four pre-meal capillary glucoses immediately before taking a masked sensor glucose reading. The only device training provided included the product labeling information and how to use the device in masked mode.

Results

A total of 74 participants were included: 39 GDM, 24 T1D, and 11 T2D. Self-reported frequency of capillary glucose monitoring (mean $\pm$ standard deviation) was 4.7 ± 1.1 , 7.9 ± 1.8 , and 4.8 ± 1.1 for women with GDM, T1D, and T2D, respectively. The accuracy of the Flash glucose monitor was assessed using 5031 paired capillary and sensor glucose values. The overall mean absolute relative difference was 11.8%. For lower glucose concentrations ($< 5.6\text{ mmol/L}$ [100 mg/dL]), the mean absolute difference was 0.53 mmol/L (9.6 mg/dL). There were no unanticipated adverse events related to the study device, which was highly acceptable to the participants.

Conclusions

Flash glucose monitoring using the Freestyle Libre appears to be accurate, acceptable, and safe in pregnancy.

Comment

On-demand glucose monitoring is attractive due to its relatively long sensor time (14 days), lack of calibration

tests, affordability, and user acceptability. This study suggests Flash glucose monitoring has the potential for use as an alternative to capillary glucose testing in pregnancy. Caution should be taken when sensor glucose measurements are below 5.6 mmol/L, when accuracy is unclear. Future studies should assess if the use of Flash glucose monitoring is as effective as real-time CGM for improving maternal glycemic control and neonatal health outcomes.

Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: a real-world study

Charleer S^{1,2}, Mathieu C¹, Nobels F³, De Block C⁴, Radermecker RP⁵, Hermans MP⁶, Taes Y⁷, Vercammen C⁸, T'Sjoen G⁹, Crenier L¹⁰, Fieuws S¹¹, Keymeulen B¹², Gillard P¹; for the RESCUE Trial Investigators

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This manuscript is also discussed in the article on Continuous Glucose Monitoring, page S-13, and the article on Practical Implementation of Diabetes Technology: It Is Time, page S-148.

Background

The Belgian health-care authority authorized reimbursement of real-time CGM for insulin pump users with T1D treated in selected specialized diabetes centers. Participating centers were required to report on the effectiveness of this policy under real-world conditions with data on HbA1c, admissions for severe hypoglycemia and/or ketoacidosis, quality of life, and time spent hypoglycemic.

Methods

Seventeen specialized diabetes centers (each with ≥ 50 insulin pump users) were offered reimbursement of real-time

CGM for 25% of insulin pump users (clinician decided). Suggested inclusion criteria included T1D ≥ 12 months duration, pump therapy ≥ 6 months duration, suboptimal glycemic control, and motivated to wear CGM sensors $\geq 70\%$ of the time. The primary endpoint was evolution of HbA1c over time between baseline and 12 months after reimbursement.

Results

A total of 515 adults (including 66 women who were pregnant and/or planning pregnancy) with T1D were included. Selected participants were female (59%), well educated (64% post-secondary school education), and had long duration T1D (22.3 ± 11.6 years). The main indications for CGM were hypoglycemia (56%), suboptimal glycemic control (26%), and pregnant/or planning pregnancy (13%). Of the 515 participants, 417 (81%) continued real-time CGM for at least 12 months, 46 (9%) for less than 12 months, and 52 (10%) stopped. Impaired awareness of hypoglycemia was common (47%) in this population of pump users, with a mean baseline HbA1c of $7.6 \pm 0.9\%$ (60.0 ± 9.8 mmol/mol). The largest decline in HbA1c was observed in those with highest baseline levels $8.2 \pm 0.9\%$ (66.0 ± 9.8 mmol/mol) to $7.6 \pm 0.8\%$ (60.0 ± 8.7 mmol/mol). Women who were pregnant and/or planning pregnancy had the lowest baseline HbA1c ($7.2 \pm 0.7\%$ [55.0 ± 7.7 mmol/mol]), with further reductions after 4 and 12 months, $6.6 \pm 0.7\%$ (49.0 ± 7.7 mmol/mol) and $6.9 \pm 0.9\%$ (52.0 ± 9.8 mmol/mol), respectively. Admissions for severe hypoglycemia and/or ketoacidosis decreased (16% to 4%) as did diabetes-related work absenteeism (123 vs 36 participants).

Conclusions

Participants were highly motivated with sensor usage of 87.5%, which is higher than in many randomized controlled trials. A similar magnitude of HbA1c reduction of approximately 0.3% (3.3 mmol/mol) was observed in this real-world setting as reported in randomized controlled trials.

Comments

The authors concluded that clinical teams selected motivated patients, mainly those with hypoglycemia, who derived a high benefit from the technology. Sixty-six women who were pregnant and/or planning pregnancy were included, providing some of the first “real-world” data on CGM use before and during pregnancy. Further subgroup analysis of these women, including their gestational status and age at entry as well as obstetric and neonatal outcomes, would be of interest.

Adaptability of closed-loop during labour, delivery and postpartum: a secondary analysis of data from two randomized crossover trials in type 1 diabetes pregnancy

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Diabetes Technol Ther 2018; **20**: 501–505

Background

Labor and delivery is a difficult time to achieve guideline-recommended glycemic control. Closed-loop insulin therapy may help women with T1D achieve these targets without excessive hypoglycemia. This observational cohort study aimed to evaluate the adaptability of hybrid closed-loop in the peripartum period among women with T1D.

Methods

This was a secondary analysis of two randomized crossover studies of hybrid closed-loop in T1D pregnancy. In brief, participants were randomized to closed-loop system therapy or sensor-augmented pump therapy for 4 weeks. After a washout period, they switched to the other alternative intervention. Afterward, participants could choose either closed-loop or sensor-augmented pump therapy for the remainder of their pregnancy. The glucose target range during pregnancy, including labor and delivery, was 3.5–7.8 mmol/L (63–140 mg/dL) and 3.9–10.0 mmol/L (70–180 mg/dL) postpartum.

Results

Eighty-four percent of women opted to use closed-loop during labor and delivery. During labor and delivery (defined as the 24 hours prior to delivery), women using closed-loop achieved 82% time-in-target (IQR 49.3–93.0) with minimal time spent below target (median 0, IQR 0–2.2). Immediately postpartum (48 hours after delivery), women spent 83% (IQR 75.2–94.6) time-in-target with a median time below target of 2.5% (IQR 0.9–5.8). There were no episodes of severe hypoglycemia or serious adverse device-related events.

Conclusions

Closed-loop insulin therapy allowed women to avoid invasive insulin infusion regimens and to self-manage their diabetes during labor, delivery, and the immediate postpartum period. Women using closed-loop achieved a high, over 80%, time-in-target range, with minimal hypoglycemia for all types of delivery (vaginal, emergency caesarean section, elective caesarean section). Randomized trials are required to compare glycemic control and women's and obstetric ward staff's experiences of using closed-loop and intravenous insulin infusion regimens during hospital admissions.

intravenous insulin infusion regimens. Larger trials are needed to assess if closed-loop can improve longer-term glycemic control, neonatal health outcomes, and reduce the burden of diabetes-related care among women with T1D and their antenatal health-care providers.

Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial

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Comments

Closed-loop insulin delivery is an exciting and promising tool in the management of type 1 diabetes during pregnancy. It appears to be safe and acceptable in the small studies to date (13,14,15). It adapts to the unique demands of pregnancy, including labor and delivery, potentially allowing women to avoid more invasive

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Background

Gestational diabetes (GDM) is a common and increasing health concern worldwide. Insulin continues to be a commonly used first-line pharmacological therapy. Metformin can also be used; however, it is not licensed in pregnancy, and insulin is still required in almost half of women started on metformin (16). Glyburide (also known as glibenclamide) could be an alternative oral agent for clinical management of women with GDM.

Methods

This was a multicenter randomized controlled trial of 13 tertiary care university hospitals in France. Participants with GDM and gestational age 24–34 weeks were randomized to receive glyburide or insulin after 10 days of lifestyle intervention. For those randomized to glyburide, a starting dose of 2.5 mg was initiated and titrated up to a maximum of 20 mg/day. The primary outcome was perinatal complications, which was a composite of macrosomia, hyperbilirubinemia, and neonatal hypoglycemia. The primary outcome was analyzed as noninferiority on a per-protocol basis, excluding participants who were switched to insulin therapy.

Results

Of the 914 randomized participants, 460 were randomized to glyburide and 454 to insulin. After removal of women not meeting inclusion criteria ($n=18$), women without primary outcome data ($n=6$) and women randomized to glyburide who switched to insulin ($n=81$; 18%), 809 participants (367 glyburide, 442 insulin) were included in the per-protocol analysis. The composite neonatal outcome occurred in 27.6% of glyburide participants, and 23.4% of insulin participants (absolute difference=4.2% [one-sided 97.5% CI 10.5%]; $P=0.19$). The upper limit of the 95% CI exceeded the noninferiority margin of 7%. Post hoc analysis revealed neonatal hypoglycemia occurred in 45 (12.2%) neonates of mothers on glyburide compared to 32 (7.2%) of mothers treated with insulin ($P=0.02$).

Conclusions

This large multicenter randomized controlled trial failed to show noninferiority of glyburide compared to insulin in the treatment of GDM.

Comments

This adequately powered trial failed to show noninferiority of glyburide. Importantly, neonatal hypoglycemia and

maternal hypoglycemia were more common with glyburide than insulin. This trial adds to existing systematic review evidence (17) that glyburide should not be used as first-line therapy in the treatment of GDM.

Metabolic profiling of gestational diabetes in obese women during pregnancy

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Diabetologia 2017; **60**: 1903–1912

Background

The aim of this study was to examine the possible differences in metabolic profiles in obese women with and without gestational diabetes (GDM).

Methods

This was a secondary analysis of data from the randomized controlled UK Pregnancies Better Eating and Activity Trial (UPBEAT). The aim of UPBEAT was to assess the efficacy of a complex lifestyle intervention in the prevention of GDM and LGA neonates in obese women. Participants required a diagnostic oral glucose tolerance test, blood samples taken at recruitment and at time of oral glucose tolerance test testing (typically 24–28 weeks gestation), and complete analyte data for inclusion. A metabolic profile was generated by evaluating 163 analytes at the time of GDM diagnosis and 10 weeks prior. Multivariate logistic regression was used to compare obese women with and without GDM after adjustment for potential confounders.

Results

Of the 646 eligible women, 198 (30.7%) developed GDM. Women with GDM had different metabolic profiles from women without diabetes from as early as 10 weeks before GDM diagnosis. Specifically, women with GDM had higher total lipids in most very low density lipoprotein subclasses at and before diagnosis; marginally higher total fatty acids at diagnosis but substantially higher before diagnosis; higher glucose and HbA1c before diagnosis; and higher fructosamine, C-peptide, and insulin at and before diagnosis. Women with GDM also had higher branched-chain and aromatic amino acids and had differences in liver, adipokine, and inflammatory markers.

Conclusions

In women with obesity in pregnancy, those with GDM have differing metabolic profiles both at time of diagnosis

and 10 weeks prior compared with women with normal glucose tolerance. The metabolic profiles of obese women with GDM were remarkably similar before and at the time of diagnosis.

Comment

The similarity between the metabolic profiles in obese women with GDM at time of diagnosis and at 10 weeks earlier suggests that the metabolic disturbances are evident many weeks prior to GDM diagnosis. Additional studies are required to determine the role of metabolic profiles in stratifying women at risk for GDM, both in clinical and in research settings.

Fetal genotype and maternal glucose have independent and additive effects on birth weight

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Background

Maternal glucose is an important contributor to neonatal birthweight with the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study confirming a strong, continuous association between maternal glucose levels and newborn birth weight (18). However, other nonglycemic factors, including the fetal genotype, may also be relevant. The aim of this study was to determine the relative contribution of fetal genotype on neonatal birthweight in the presence of maternal hyperglycemia.

Methods

A genetic score for birthweight was calculated using fetal single nucleotide polymorphisms (SNPs) associated with birthweight. The study included 701 mother–offspring pairs from Exeter, UK, and 1350 European mother–offspring pairs from HAPO. The fetal genetic score was calculated by taking into account the known effect sizes of SNPs in relation to birthweight.

Results

Maternal glycemia and fetal genetic score for birthweight were both positively associated with rate of LGA newborns. However, maternal glycemia was not associated with the fetal genetic birthweight score. Combining maternal glycemia and fetal genetic birthweight score had an additive effect on birthweight in both European and non-European participants. Among mothers with comparable glycemia (fasting glucose 4.9 mmol/L), the rate of LGA newborns increased

from 14% to 31% as the fetal genetic birthweight score increased from the lowest to the highest tertile. Among mothers with GDM (fasting glucose ≥ 5.1 mmol/L) the LGA rates increased from 21% to 43% as the fetal genetic birthweight score increased from the lowest to the highest tertile.

Conclusions

Fetal genetics influenced neonatal birthweight independently of fasting glucose and across all levels of maternal glycemia. The fetal SNPs associated with birthweight are also associated with newborn skin-fold thickness but not associated with maternal glycemia and fetal insulin secretion.

Comment

Fetal genetics make an important contribution to variation in neonatal birthweight and offspring LGA. Sequencing of fetal DNA will allow new insights into the biological mechanisms of LGA.

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.

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