Technology and Pregnancy

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Introduction

THE 10 MANUSCRIPTS CHOSEN FOR this year's article reflect some key advances in the field of diabetes pregnancy, with large-scale national and international collaborations pulling together to establish an evidence base for improving the health outcomes of pregnant women with diabetes and their children. A major advance in the management of pregestational diabetes has been to collect and publish contemporary pregnancy outcome data in a timely fashion. The United Kingdom's National Pregnancy in Diabetes (NPID) audit has published maternal characteristics and obstetric and neonatal outcome data on over 3000 pregnancies (1). This large sample size allows for statistical comparison of serious adverse events and documents a sustained 2.5-fold reduction in the rate of stillbirth for pregnant women with both type 1 and type 2 diabetes. While there is a small decline in stillbirth in the general maternity population, the reduction in diabetes pregnancy is substantial and is most likely related to improvements in pregnancy preparation, fetal surveillance, and earlier delivery. Unfortunately, there are no changes in rates of congenital anomaly or neonatal death. The audit also highlights suboptimal glucose control in type 1 diabetes and unacceptable clinic to clinic variation in the care of pregnant women with type 1 and type 2 diabetes. The expectation is that by publishing these data there will be more collaborative work to ensure that services that are currently struggling are supported to improve. The audit highlights the need for new technologies to improve glucose control in late gestation type 1 diabetes pregnancy. The first automated insulin delivery, overnight closed-loop, in a pregnancy trial reported a 15% increase in overnight time in target compared with the best available comparator of sensor-augmented pump therapy (2). The lived experiences of women with diabetes who used closed-loop technology are reported separately and serve to remind us that as with all new treatments there are both benefits and burdens to be considered (3). Not surprisingly individuals weigh these up differently, as some women with biomedical improvements were quite ambivalent about closed-loop, while others with minimal objective improvement were far more positive about the impact of closed-loop on quality of life and reduced burden of diabetes self-management. Longer-duration randomized trials comparing closed-loop and usual care with detailed biomedical and psychosocial outcomes are now required. Law et al. urge us to look beyond traditional markers of glucose control like glycated hemoglobin (HbA1c) and estimated average glucose (eAG). A novel pregnancy-specific estimated average glucose (PeAG) is proposed, with the suggestion of aiming for a PeAG of 6.4–6.7 mmol/mol (4). Abell and colleagues remind us not to assume that increasing use of technology is necessarily associated with improved pregnancy outcomes and recommend larger-scale, high-quality trials of insulin pumps in pregnancy (5). The diabetes pregnancy community need to consider whether this is still feasible given the widespread use of pumps before and during pregnancy and/or whether trials of automated insulin delivery are more relevant.

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A landmark collaboration from the International Weight Management in Pregnancy (i-WIP) Collaborative Group provides the first individual patient data meta-analyses of diet and exercise interventions to reduce obstetric and neonatal risks in obese pregnant women (6). These data confirm that dietary and physical activity interventions are not harmful and work for women of all weights. Even modest weight loss, approximately 0.7 kg, is associated with reduced risk of caesarean delivery. Interventions based on increased physical activity may be particularly effective for reducing risk of gestational diabetes (GDM). Hodson et al. suggest that in women with GDM, greater weight loss (0.4 kg per week) can be safely achieved with a hypo-energetic diet of 1200 kcal/day, with 50% reduced liver triacylglycerol and reduced need for additional insulin and/or metformin (7). As uncertainty remains about the use of glyburide and to a lesser extent metformin (8), a stronger evidence base for more rigorous, well-described dietary interventions in GDM is required and likewise for antenatal breastmilk expressing, which seems intuitively sensible for management of neonatal hypoglycemia (9). While this does not seem to cause harm, larger trials of higher-risk women are needed before this can be routinely recommended for all women with diabetes. Finally, a French group have reported the potential for good pregnancy outcomes in women with cystic fibrosis (CF). Furthermore, with improved treatment protocols, cystic fibrosis-related diabetes (CFRD) was not associated with decline in lung function or maternal nutritional status after pregnancy (10).

Key Articles Reviewed for the Article

Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study

Murphy HR, Bell R, Cartwright C, Curnow P, Maresh M, Morgan M, Sylvester C, Young B, Lewis-Barned N

Diabetologia 2017; **60**: 1668–1677

Closed-loop insulin delivery during pregnancy in women with type 1 diabetes

Stewart ZA, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP, Simmons D, Law GR, Scott EM, Hovorka R, Murphy HR

N Engl J Med 2016; **375**: 644–654

Experiences of closed-loop insulin delivery among pregnant women with type 1 diabetes

Farrington C, Stewart ZA, Barnard K, Hovorka R, Murphy HR

Diabet Med 2017; **34**: 1461–1469

Translating HbA1c measurements into estimated average glucose values in pregnant women with diabetes

Law GR, Gilthorpe MS, Secher AL, Temple R, Bilous R, Mathiesen ER, Murphy HR, Scott EM

Diabetologia 2017; **60**: 618–624

Pregnancy outcomes and insulin requirements in women with type 1 diabetes treated with continuous subcutaneous insulin infusion and multiple daily injections: cohort study

Abell SK, Suen M, Pease A, Boyle JA, Soldatos G, Regan J, Wallace EM, Teede HJ

Diabetes Technol Ther 2017; **19**: 280–287

Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials

International Weight Management in Pregnancy (i-WIP) Collaborative Group

BMJ 2017; **358**: j3119

Liver triacylglycerol content and gestational diabetes: effects of moderate energy restriction

Hodson K, Dalla Man C, Smith FE, Barnes A, McParlin C, Cobelli C, Robson SC, Araújo-Soares V, Taylor R

Diabetologia 2017; **60**: 306–313

Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: a randomized controlled study

Nachum Z, Zafran N, Salim R, Hissin N, Hasanein J, Gam Ze Letova Y, Suleiman A, Yefet E

Diabetes Care 2017; **40**: 332–337

Advising women with diabetes in pregnancy to express breastmilk in late pregnancy (Diabetes and Antenatal Milk Expressing [DAME]): a multicentre, unblinded, randomised controlled trial

Forster DA, Moorhead AM, Jacobs SE, Davis PG, Walker SP, McEgan KM, Opie GF, Donath SM, Gold L, McNamara C, Aylward A, East C, Ford R, Amir LH

Lancet 2017; **389**: 2204–2213

Pregnancy outcome in women with cystic fibrosis-related diabetes

Reynaud Q, Poupon-Bourdy S, Rabilloud M, Al Mufti L, Rousset Jablonski C, Lemonnier L, Nove-Josserand R, Touzet S, Durieu I; and participating centers of the French Cystic Fibrosis Registry

Acta Obstet Gynecol Scand 2017; **96**: 1223–1227

Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study

Murphy HR^{1,2}, Bell R³, Cartwright C⁴, Curnow P⁴, Maresh M⁵, Morgan M⁶, Sylvester C⁴, Young B⁴, Lewis-Barned N⁷

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Diabetologia 2017; **60**: 1668–1677

Objectives

This prospective nationwide study examined outcomes of pregnant women with pregestational diabetes in England and Wales and compared changes over the decade since the 2002–2003 Confidential Enquiry in Maternal and Child Health.

Methods

Data were collected as part of a national audit whereby maternity clinics are required to complete web-based data entry forms for all pregnant women with diabetes who had a

pregnancy that ended in 2015. Outcomes of interest such as pregnancy preparation (5 mg folic acid, first trimester HbA1c); perinatal morbidity (delivery prior to 37 weeks, large-for-gestational-age infants); congenital anomaly; stillbirth; and neonatal death were collected and analyzed.

Results

A total of 3036 women from 155 maternity clinics were included. Most women had type 1 diabetes (51%) or type 2 diabetes (46%), with other types of diabetes comprising 3% of women. The level of glycemic control (HbA1c <6.5% or 48 mmol/mol) achieved by women differed by clinic attended (median for women with type 1 diabetes 14.3% [interquartile range 7.7–22.2], type 2 diabetes 37.0% [27.3–46.2]). In comparison with women with type 2 diabetes, women with type 1 diabetes had more preterm births (39.7% vs. 21.7%, $P < 0.001$) and more large-for-gestational-age infants (46.4% vs. 23.9%, $P < 0.01$). The rates of congenital anomaly and neonatal death were unchanged since 2002/2003. However, stillbirth rates following pregnancies complicated by both type 1 diabetes (10.7 vs. 25.8/1000 births, $P = 0.0012$) and type 2 diabetes (10.5 vs. 29.2/1000 births, $P = 0.0091$) were significantly lower in 2015 compared with 2002/2003.

Conclusions

There is substantial clinic-to-clinic variation in proportion of women achieving target HbA1c and in rates of 5 mg pre-conception folic acid supplementation. While there was no change in rates of congenital anomaly or neonatal death between 2002/2003 and 2015, there were 2.5 times less stillbirths. There were also improvements in the perinatal morbidity among newborn infants of mothers with type 2

diabetes, with lower rates of preterm birth and large-for-gestational-age birthweight.

Comments

This study found a significant 2.5-fold reduction in the rate of stillbirth in patients with both type 1 and type 2 diabetes. The reasons for this are unclear, especially as neonatal death rates are unchanged. Furthermore, glycemic control before and during pregnancy remains suboptimal, especially among women with type 1 diabetes. There have been some improvements in glucose control and neonatal outcomes in type 2 diabetes. The substantial clinic-to-clinic variation suggests that there are opportunities for improvement in both type 1 and type 2 diabetes pregnancies.

Closed-loop insulin delivery during pregnancy in women with type 1 diabetes

Stewart ZA¹, Wilinska ME¹, Hartnell S², Temple RC³, Rayman G⁶, Stanley KP⁴, Simmons D², Law GR⁷, Scott EM⁷, Hovorka R¹, Murphy HR^{1,2,3,5}

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N Engl J Med 2016 375: 644–654

This manuscript is also discussed in the article on Closing the Loop, page S-41.

Objective

Women with type 1 diabetes mellitus in pregnancy continue to have an increased risk of serious complications despite significant advances in diabetes care over time. Closed-loop insulin delivery uses an insulin pump, continuous glucose monitor, and a computer algorithm to adjust insulin delivery in real-time; however, data regarding its use in pregnancy are limited.

Methods

This was a multicenter, open-label, randomized crossover study of pregnant women with type 1 diabetes. Women were randomized to 28 days of overnight closed-loop insulin delivery vs. sensor-augmented pump therapy followed by a 2-week washout period prior to crossing over. This was followed by a nonrandomized extension period allowing participants to choose to use injections, an insulin pump, continuous glucose monitor or closed-loop, day and night until delivery.

Results

In total, 16 women completed the study and were included in the analysis. The primary outcome, percentage of time overnight within the target glucose range, was significantly higher during the closed-loop phase compared with sensor-augmented pump phase (75% vs. 60%, [95% CI 6.1–24.3]). There was no significant difference in hypoglycemia and no episodes of severe hypoglycemia in the study period. Fourteen women chose to keep using closed-loop after the crossover period was complete. Women using day-and-night closed-loop achieved 68% time in target during pregnancy and a high percentage time in target (86%) when closed-loop was continued during labor and delivery.

Conclusions

This study demonstrated that when compared with sensor-augmented pump therapy, closed-loop insulin delivery resulted in superior overnight glucose control without increasing hypoglycemia. The continuation phase of this trial demonstrated the ability of the closed-loop system to perform day-and-night until 48 hours postpartum, which included hospitalizations as well as labor and delivery.

Comments

This study of women with type 1 diabetes in pregnancy demonstrated the ability of closed-loop insulin delivery to improve time in target overnight when compared with sensor-augmented pump therapy. The women included had a mean duration of diabetes of 23.6 ± 7.2 years and many had a substantial history of pregnancy-related complications. The continuation phase highlighted the adaptability of closed-loop insulin delivery during the changing demands of pregnancy: increasing insulin resistance, changing glucose utilization, antenatal steroid administration, labor, and delivery as well as the immediate postpartum period. Larger-scale clinical trials are needed to study the closed-loop system in various populations as well as to assess the impact of closed-loop delivery on obstetric and neonatal outcomes.

Experiences of closed-loop insulin delivery among pregnant women with type 1 diabetes

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Diabet Med 2017; 34: 1461–1469

Objective

Closed-loop insulin delivery has shown potential as a valuable tool in the management of type 1 diabetes during pregnancy. However, the attitudes of women with diabetes toward this emerging technology had not been reported. This

study aimed to evaluate the psychological aspects of the closed-loop insulin therapy in pregnancy.

Methods

Participants in this analysis were part of an open-label, randomized, crossover study comparing closed-loop insulin delivery with sensor-augmented pump therapy in pregnant women with type 1 diabetes. Mixed methods were used to analyze participant questionnaires and semistructured interviews.

Results

A total of 16 participants were included in the study. Of the 16 women who were randomized, 14 chose to continue the closed-loop system after the crossover was complete. The questionnaire and interview data were consistent, both highlighting perceived benefits such as improved glucose control, feeling more “normal,” and “time off” from diabetes. Interviews also revealed themes of excitement and empowerment regarding the potential of the closed-loop system for future management of diabetes. Many women identified drawbacks regarding closed-loop therapy such as spending more time thinking about diabetes, the bulkiness of the system, device challenges, and possible “deskilling” regarding alertness for symptoms of hyper- and hypoglycemia. Women’s perception of glucose control and directly measured continuous glucose monitoring time in target sometimes differed.

Conclusions

This study describes the benefits and burdens experienced by women with type 1 diabetes using closed-loop insulin therapy in pregnancy.

Comments

Closed-loop insulin delivery is on the forefront of the management of diabetes in pregnancy. This study explores the psychological aspects of the closed-loop system on women using it as part of a randomized study. Not surprisingly, participants noted both benefits and burdens associated with using the system. Some participants also revealed feelings of excitement and empowerment, a promising sentiment for women with diabetes. While the technology is likely to improve in terms of its cumbersome nature, the concern for potential “deskilling” with regard to daily diabetes self-management will need to be further considered as studies with the artificial pancreas advance.

Translating HbA1c measurements into estimated average glucose values in pregnant women with diabetes

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Diabetologia 2017; **60**: 618–624

Objective

Continuous glucose monitoring has been used to assess the relationship between average glucose and HbA1c in various studies outside of pregnancy. Given the various physiologic changes throughout pregnancy and the known limitations of HbA1c in this population, estimates outside of pregnancy may not be accurate in pregnant women. This study sought to define the relationship between estimated average glucose (eAG) and HbA1c throughout pregnancy in women with type 1 and type 2 diabetes mellitus.

Methods

Data from two previous randomized, controlled trials examining continuous glucose monitoring (CGM) in women with type 1 and type 2 diabetes in pregnancy were used for this study. The average glucose, defined as the mean glucose values from CGM for a 5- to 7-day period, was compared with HbA1c values taken within 1 week. Regression modeling was used to determine this relationship.

Results

Data from 117 patients (89 with type 1 diabetes and 28 with type 2 diabetes) were included. An analysis of 688 CGM profiles and 688 HbA1c values was performed. Using CGM data, the authors calculated an eAG at various times in pregnancy using the formula: $\text{glucose (mmol/L)} = 6.78 + [0.43 \times (\text{HbA1c [\%]} - 6.3)] + [0.004 \times (\text{gestation [weeks]} - 21)] - [0.001 \times (\text{gestation [weeks]}^2 - 528)]$. They found that in pregnancy, a 1% difference in HbA1c is equivalent to 0.67 mmol/L in average glucose levels. More specifically, HbA1c during pregnancy is associated with lower estimated average glucose levels than outside of pregnancy. This difference between the pregnancy-specific and nonpregnancy average glucoses increased with increasing HbA1c values.

Conclusions

The drop in HbA1c in pregnancy represents a smaller change in average glucose than the equivalent drop outside of pregnancy.

Comments

HbA1c plays a central role in the assessment of glucose control in patients with diabetes in pregnancy. While studies have demonstrated an association with HbA1c and various pregnancy outcome data, HbA1c has the potential to be unreliable due to the dynamic physiology of pregnancy. The authors note some limitations such as the narrow patient population and the different methods of determining average glucose from the comparative study outside of pregnancy. However, overall this study demonstrates a difference in the relationship between average glucose and HbA1c and offers clinicians a practical method of assessing glucose based on aiming for average glucose levels of 6.4–6.7 mmol/L.

Pregnancy outcomes and insulin requirements in women with type 1 diabetes treated with continuous subcutaneous insulin infusion and multiple daily injections: cohort study

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Diabetes Technol Ther 2017; **19**: 280–287

Objectives

The importance of achieving tight glycemic control throughout pregnancy in women with type 1 diabetes is well established. This study examined glycemic control and pregnancy outcomes in women with type 1 diabetes using continuous subcutaneous insulin infusion (CSII) vs. multiple daily injections (MDI).

Methods

This was a retrospective cohort study of women with type 1 diabetes receiving care as part of a public health service in Australia. It included women with singleton pregnancies and births after 20 weeks of gestation. Data were collected by chart review and from a Birthing Outcomes System database.

Results

In total, 40 pregnancies using CSII and 127 using MDI were included in the analysis. There was no statistically significant difference in baseline diabetes characteristics between the two groups. There was no evidence of a difference in glycemic control achieved (as measured by HbA1c) or in obstetrical outcomes between women using CSII vs. MDI. When compared with women using MDI, women with CSII were prescribed less insulin preconception and throughout pregnancy as well as a smaller percent change of insulin requirements (in units/kg) in early compared with late pregnancy (40% vs. 52%).

Conclusions

In this cohort of pregnant women with type 1 diabetes, there were no significant differences in glycemic control or obstetrical outcomes in treatment with CSII vs. MDI.

Comments

The cohort study adds to the literature on CSII vs. MDI in the management of type 1 diabetes in pregnancy. This study had a small sample size and was not powered to show a difference in glycemic control and obstetrical outcomes. In contrast, Kallas-Koeman et al. demonstrated a significantly lower HbA1c throughout pregnancy in their larger study of 113 pregnancies managed

with CSII vs. 218 pregnancies with MDI (11). They noted a higher proportion of large-for-gestational-age neonates in the CSII group (55.0% vs. 39.2%, $P=0.007$) but no difference in other obstetrical outcomes. The literature examining the effect of CSII is made up primarily of cohort studies which are subject to bias (i.e., women who are on pumps may be different from women on MDI). With the introduction of closed-loop, we may not see high-quality randomized trials of CSII and MDI in pregnancy, although these are needed to evaluate the safety and efficacy of pumps in pregnancy.

Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials

International Weight Management in Pregnancy (i-WIP) Collaborative Group

BMJ 2017; **358**: j3119

Objectives

Approximately one in two women of reproductive age are now overweight or obese with short and longer-term health implications for both mother and child. The impact of dietary and physical activity (PA) interventions starting during pregnancy have generally been disappointing. The aim of this meta-analysis of individual participant data (IPD) was to synthesize the published evidence and work out the effects of diet and PA on maternal gestational weight gain and maternal/infant health outcomes.

Methods

IPD was obtained from 36 randomized trials involving >12,500 women in 16 countries. This included 22 studies from Europe; 4 each from the United States, Australia, and Brazil; and 1 each from Egypt and Iran. In 23 studies women of any weight were included, while 6 studies included overweight and obese women and 7 included only obese women. The interventions were mainly based on diet ($n=4$), PA ($n=16$), or a combination of diet and lifestyle ($n=15$). Women with gestational diabetes (GDM) and known hypertensive disorders were excluded. The primary outcome was gestational weight gain (GWG), defined as the difference between maternal weight at booking and the last weight before delivery. Key secondary outcomes were GDM, hypertensive disorders, preterm and caesarean delivery (mothers) and stillbirth, large or small for gestational age, and neonatal intensive care unit (NICU) admission (infants). The overall effects of interventions were examined for composite and for individual maternal and infant outcomes.

Results

The women were mostly (>80%) white, 45% primiparous, 40% obese, and 40% sedentary. Approximately 50% were classified as having high socioeconomic status. Data for approximately 50% of eligible women was not available. The largest data sets were available for gestational age

(34 studies, >12,000 women), with similarly high numbers (<11,000) for preterm delivery, and small numbers for gestational age (SGA) and caesarean section. For GWG, hypertensive disorders of pregnancy, and GDM there were data from approximately 9500 women. Slightly smaller data sets were available for the maternal and infant composite outcomes (8800 and 7900 respectively). Both diet and PA interventions were effective in reducing GWG by approximately 0.7 kg, which did not differ according to maternal normal weight, overweight, or obesity. Likewise, there was no evidence of differential effects for maternal baseline demographic characteristics such as age, parity, ethnicity, and preexisting medical conditions. There was also a significant reduction in caesarean section, with summary estimates that favored the interventions for both the maternal and infant composite outcomes, but these did not reach statistical significance. The reduction in other individual outcomes such as GDM and preterm delivery were also not statistically significant. When study-level data from non-IPD studies were meta-analyzed with IPD, there was stronger evidence for GDM reduction (59 studies in 16,885 women). Interventions based on PA showed a reduction in GDM in both IPD and combined IPD and non-IPD meta-analysis (OR 0.67 and 0.66 respectively). Likewise, for the impact of PA on reduction in caesarean section and hypertensive disorders, the combined IPD and non-IPD meta-analysis suggested stronger evidence of benefit with reductions by 17% for caesarean section and 32% for hypertensive disorders. For diet-only interventions there was a strong effect for reduction in preterm delivery in both the IPD alone and the combined IPD and non-IPD meta-analysis, but these analyses were limited to 4 and 7 studies with approximately 1300 and 1700 women respectively.

Conclusions

This large collaborative IPD meta-analysis confirms that diet and PA interventions are effective for reducing GWG in all women and did not vary according to maternal weight. However, the effect is clinically modest (0.7 kg), and impact on postpartum weight retention and longer-term health outcomes is unknown. The only individual outcome impacted was reduced odds of delivery by caesarean section. The addition of study level data from non-IPD studies showed benefit for reduction in GDM, in particular for PA-based interventions. The lack of harm (for example, no increase in preterm delivery or small for gestational age) should provide reassurance to mothers and clinicians that diet and PA are safe during pregnancy.

Comments

This large collaborative undertaking is the first to evaluate the differential effects of diet and PA on a range of clinically important outcomes. This provided statistical power for estimating covariate interactions and adjusting for maternal age, weight, and important baseline characteristics. Because of the speed of new publications in this area, it was not possible to perform IPD meta-analysis for all published trials. They therefore also reported on outcomes from combined IPD and non-IPD meta-analysis.

Liver triacylglycerol content and gestational diabetes: effects of moderate energy restriction

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Diabetologia 2017; **60**: 306–313

Objectives

Energy restriction, while effective for improving glucose control and liver triacylglycerol in type 2 diabetes, remains controversial during late pregnancy. The aim of this Weight Loss Looking for Mother and Baby Better Outcomes (WELLBABE) study was to quantify the impact of a 4-week calorie restricted diet in women with GDM.

Methods

Sixteen women with GDM (gestational age 27 ± 3.3 weeks) were recruited to a 4-week hypo-energetic diet (1200 kcal/day) with a magnetic resonance spectroscopy scan and standardized meal test performed before and after the intervention and between 12 and 28 weeks postpartum. The dietary intervention was delivered by trained research dietitians (50% carbohydrate, 25% protein, 25% fat) supported by portion size cups and a smartphone application (MyFitnessPal). After the 4-week dietary intervention, women were recommended to continue on approximately 1500 kcal/day. The data from 28 matched comparators with GDM were compared with those of women in the intervention group.

Results

Women in the intervention group (mean age 31.5 years, mean weight 93.1 kg, mean body mass index [BMI] 34.6) lost 0.4 kg/week or 1.6 ± 1.7 kg in total compared with weight gain of 0.3 kg/week or 1.4 ± 1.2 kg in the comparator group. Six women lost >2 kg, five women lost 0.3–1.2 kg, and three had a small weight gain (<0.5 kg). Two women dropped out. The mean liver triacylglycerol was halved (from 3.7% to 1.8%) after 4 weeks of dietary restriction and returned to baseline by 12–28 weeks postpartum. Fasting plasma glucose, postmeal glucose, fasting insulin and C-peptide and markers of insulin resistance were unchanged pre- and postintervention. Lipid levels and fasting non-esterified fatty acids (NEFA) were unchanged. Insulin resistance was reduced postpartum. The numbers of women requiring treatment were 0 for insulin and 2 for metformin compared with 6 and 8 respectively in the comparator group. Glucose control and maternal fetal outcomes did not differ between the two groups.

Conclusion

Dietary intervention was well tolerated by women and was associated with weight loss of 0.4 kg/week and a 50% reduction in liver triacylglycerol. The finding that liver triacylglycerol levels were normal and not elevated, as suggested in previous pregnancy literature, was unexpected given the central role of lipid metabolism in the pathogenesis of GDM and type 2 diabetes. The authors speculate that liver triacylglycerol levels decrease reciprocally with elevated plasma triacylglycerol levels in GDM pregnancy.

Comments

The study provides further reassurance for women and clinicians regarding the potential for benefit from a more aggressive hypo-energetic dietary intervention. In particular it suggests that an effective dietary intervention reduces the need for additional pharmacotherapy with insulin and/or metformin. Larger randomized clinical trials of a more sustained hypo-energetic diet in women with GDM are required.

Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: a randomized controlled study

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Diabetes Care 2017; **40**: 332–337

Objective

The mainstay of treatment of gestational diabetes mellitus is lifestyle modification; however, pharmacotherapy is often needed to achieve target glucose control. The aim of this study is to assess the use of glyburide vs. metformin vs. glyburide plus metformin in the management of gestational diabetes.

Methods

This was an open-label, single center, randomized controlled trial in women with gestational diabetes diagnosed at 13–33 weeks gestation. Women were initially randomized to either glyburide 2.5–5.0 mg/day or metformin 850–2550 mg/day. If glycemic targets were not achieved on monotherapy, the alternative medication was started. Patients who experienced adverse events were placed on the alternative medication. If glycemic targets were not reached on two drug therapies, patients were started on insulin. The primary outcomes were inability to achieve glycemic targets and glycemic control on the medication to which the patient was originally randomized.

Results

This study randomized 104 women to glyburide (53 women) or metformin (51 women). Of the participants randomized to

receive glyburide, 12 (23%) required the addition of metformin and 6 (11%) were switched to metformin because of an adverse effect. Of the participants randomized to metformin, 14 (28%) required the addition of glyburide and 1 (2%) were switched to glyburide because of an adverse effect. There was no statistically significant difference in adverse effects between glyburide and metformin ($P=0.11$). A total of 11 patients required insulin therapy: 4 for adverse effects to oral medication and 7 due to inability to meet glycemic targets. There was no significant difference in pregnancy outcomes reported.

Conclusions

Glyburide and metformin perform similarly in terms of the treatment and adverse effects of gestational diabetes diagnosed between 13 and 33 weeks gestation.

Comments

This trial is too small to provide adequate reassurance regarding use of glyburide. Both metformin and glyburide have been shown to cross the placenta. In their large trial of metformin vs. insulin in the treatment of gestational diabetes, Rowan et al. did not demonstrate a concern for adverse events with metformin (12). However, a large observational cohort suggested glyburide may be associated with increased neonatal complications when compared with insulin (13).

Advising women with diabetes in pregnancy to express breastmilk in late pregnancy (Diabetes and Antenatal Milk Expressing [DAME]): a multicentre, unblinded, randomised controlled trial

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Objectives

A trial was conducted to determine the safety and efficacy of antenatal milk expressing in women with diabetes. The rationale behind this advice is that expressing and storing colostrum during late pregnancy would provide

breastmilk for infants who are admitted to neonatal intensive care units (NICU) after delivery and thus facilitate exclusive breastfeeding during the early neonatal period. It has also been suggested that colostrum may be more effective for stabilizing neonatal glucose levels than formula milk.

Methods

An open-label, multicenter, randomized controlled trial of 635 women with diabetes was carried out in six Australian maternity hospitals. Women with a singleton pregnancy were randomized between 34 and 37 weeks gestation to hand expressing of breastmilk for up to 10 minutes twice daily from 36 weeks gestation or to standard antenatal care. Women with evident fetal growth restriction or fetal growth acceleration (ultrasound estimated fetal weight $\geq$ 95th percentile with abdominal circumference $>$ 97th percentile, polyhydramnios), and breech presentation were excluded. Women were taught how to express while having cardiotocography (CTG) surveillance and asked to monitor their capillary glucose levels on the first three occasions. The primary outcome was the proportion of infants admitted to the NICU. Key secondary outcomes were gestational age at birth, neonatal hypoglycemia defined as <2.6 mmol/L before feeding and exclusive breastmilk feeding.

Results

Most women ($>90\%$) had gestational diabetes (GDM) and approximately half were insulin treated. Metformin was not commonly used ($<1\%$). Only small numbers of women with pregestational diabetes were included (3%–4% with type 1 and type 2 diabetes). Approximately half were overweight or obese and just over half were primiparous (57.5%). During the 18 days from randomization until delivery, $>40\%$ of women in the intervention group expressed more than 20 times with 25% expressing 6–19 times. The mean volume of colostrum obtained was 5.5 mL. A small number of control group women ($<10\%$) reported some breastmilk expressing before delivery. There were no between-group differences in the proportion of infants admitted to NICU (15% vs. 14%), gestational age at delivery (38.6 vs. 38.7 weeks) or reasons for NICU (neonatal hypoglycemia 42% vs. 36%, infection 42% vs. 41%, and respiratory distress 27% vs. 23%). The proportion of infants requiring IV dextrose also did not differ (11% vs. 9%). The rates of exclusive breastfeeding for the intervention vs. control group were as follows; 69% vs. 60% day 1; 57% vs. 49% day 7; and 60% vs. 55% at 3 months postpartum, with $>80\%$ mothers in both groups reporting some breastmilk feeding at 3 months. During CTG surveillance there was some transient increase in uterine activity but no evidence of any fetal compromise.

Conclusions

There was no evidence of harm from advising women with diabetes to express breastmilk from 36 weeks' gestation with no increase in rates of NICU admission or preterm delivery. Antenatal colostrum expressing was associated with slightly higher rates of breastmilk feeding during the first day and throughout hospital admission, but this effect was not sustained at 3 months postpartum.

Comments

This high-quality randomized controlled trial shows no evidence that antenatal breast stimulation leads to earlier onset of labor or higher rates of NICU admission in offspring of women with hyperglycemia. It should be noted that these were mostly women with low-risk GDM pregnancy and that these data cannot be extrapolated to women with higher-risk type 1 and type 2 diabetes pregnancy. Furthermore, women with fetal growth acceleration, which is widespread in pregestational diabetes pregnancies, were excluded. The authors suggest that future trials of higher-risk women are required.

Pregnancy outcome in women with cystic fibrosis-related diabetes

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Objectives

With advances in care for people with cystic fibrosis (CF), more are surviving into their fourth and fifth decades and developing cystic fibrosis-related diabetes (CFRD). The number of pregnancies in CF women is also increasing. The aim of this study was to examine the pregnancy outcomes of women with CF.

Methods

A multicenter retrospective cohort study was conducted using data from 49 French CF study sites between 2001 and 2012. Women were separated into those with and without CFRD and studied for 4 years before and up to 2 years following pregnancy. Pregnancies in CF women with lung transplants were excluded. Key maternal outcomes were decline in forced expiratory volume in one second (FEV₁) and body mass index (BMI) during follow-up. Other data collected included method of conception, mode of delivery, preterm birth (<37 weeks), and neonatal birthweight.

Results

In all, 294 pregnancies in 232 women with CF were reported; this included 180 women with 1 pregnancy, 42 women with 2 pregnancies, and 10 with 3 pregnancies, resulting in 234 livebirths. Women had a median age of 27 years (range 15–42) and a median BMI of 20 (range 15–34). Eighty

percent had pancreatic insufficiency and over one-third were homozygous for the F508 deletion mutation. Only a small proportion received enteral feeding (<4%). There were 29 documented miscarriages and 29 terminations of pregnancy (16 therapeutic and 13 for other indications). There were no stillbirths or neonatal deaths. Three infants were diagnosed with CF. The overall rate of preterm delivery was 30%, with 27% of infants delivered by caesarean section. The median birthweight was 3000 g. Most women (85%) did not have CFRD. Among women with diabetes (n=29), maternal age was higher (29 vs. 26 years), FEV₁ was lower (50% vs. 67%) and they were more likely to have had a medically assisted conception (54% vs. 34%). No specific data regarding glucose control or diabetes treatment were available. Participants' BMI (19.9 vs. 21.1), rate of BMI decline, and rate of FEV₁ decline was not statistically different than women without CFRD. The infants of CFRD mothers were more likely to be delivered by caesarean section (48% vs. 21%; *P*=0.005). Gestational weight gain (GWG) and infant birthweight was comparable between women with and women without CFRD (GWG 19.9 vs. 21.1 kg; median birthweight 2950 vs. 3000 g).

Conclusions

The pregnancy outcomes of women with CF are generally favorable. CFRD is associated with a higher rate of delivery by caesarean section but it is not associated with decline in maternal lung function or nutritional status. Early and aggressive treatment of CFRD may have minimized the potential negative impact of CFRD on lung function and maternal nutritional status.

Comments

The number of CF women of reproductive years with good lung function and nutritional status is expected to further increase as cystic fibrosis transmembrane conductance regulator (CFTR) modulators are introduced. This study emphasizes the potential for good pregnancy outcomes in CF women with and without CFRD. More details on the glucose control and pregnancy outcomes in women with CFRD is needed. Meanwhile, these data will provide some reassurance to women with CF who are pregnant or planning for pregnancy.

Author Disclosure Statement

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