Technology and Pregnancy

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Articles Reviewed for the Chapter

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 and Lewis-Barned N

Diabetologia 60 (9); 1668-77 2017 (1).

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 and Murphy HR

N Engl J Med 375(7): 644-654 2016 (2)

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

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

Diabet Med. 2017 Jun 20. doi: 10.1111/dme.13406 (3)

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 and Scott EM

Diabetologia 60(4): 618-624 2016 (4).

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 and Teede HJ

Diabetes Technol Ther 19(5): 280-287 (5)

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 Jul 19;358:j3119. doi: 10.1136/bmj.j3119 (6)

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 Feb;60(2):306-313 (7)

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 and Yefet E

Diabetes Care 40(3): 332-337 (8)

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 SM7, Gold L, McNamara C, Aylward A, East C, Ford R, Amir LH

Lancet Volume 389, Issue 10085, 3–9 June 2017, Pages 2204-2213 (9)

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; participating centers of the French Cystic Fibrosis Registry.

Acta Obstet Gynecol Scand. 2017 Jun 24. doi: 10.1111/aogs.13185 (10)

The ten articles chosen for this year's chapter 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 pre-gestational 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, obstetric and neonatal outcome data on over 3,000 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 both in type 1 and in type 2 diabetes pregnancy. Whilst 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. The expectation is that by publishing these data there will be more collaborative working to ensure that services which 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 pregnancy trial reported a 15% increase in overnight time-in-target compared to the best available comparator of sensor-augmented pump therapy (2). The lived experiences of women with diabetes who used closed-loop 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 randomised trials of closed-loop compared to 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 HbA1c and estimated average glucose (eAG). A novel pregnancy specific estimated average glucose (PeAG) is proposed, with the suggestion that aiming for a PeAG of 6.4-6.7mmol/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.

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 0.7kg 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 (0.4kg per week) can be safely achieved with a hypo-energetic diet of 1200kcal/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. Likewise, for antenatal breastmilk expressing which seems intuitively sensible for management of neonatal hypoglycaemia (9). Whilst 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).

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 R[3], Cartwright C[4], Curnow P[4], Maresh M[5], Morgan M[6], Sylvester C[4], Young B[4] and Lewis-Barned N[7]

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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 2002-03 Confidential Enquiry in Maternal and Child Health (CEMACH).

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 which ended in 2015. Outcomes of interest such as pregnancy preparation (5mg 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 analysed.

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 glycaemic control (HbA1c <6.5% or 48mmol/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 to women with type 2 diabetes, women with type 1 diabetes had more preterm births (39.7% versus 21.7%, p<0.001) and more large-for-gestational age infants (46.4% versus 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 versus 25.8/1000 births, p=0.0012) and type 2 diabetes (10.5 versus 29.2/1000 lives births, p=0.0091) were significantly lower in 2015 compared to 2002/2003.

Conclusions: There is substantial clinic-to-clinic variation in proportion of women achieving target HbA1c and in rates of 5mg preconception 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.

Commentary: This study found a significant 2.5 fold reduction in the rate of stillbirth both in type 1 and in type 2 diabetes. The reasons for this are unclear especially as neonatal death rates are unchanged. Furthermore, glycaemic 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 ZA[1], Wilinska ME[1], Hartnell S[2], Temple RC[3], Rayman G[6], Stanley KP[4], Simmons D[2], Law GR[7], Scott EM[7], Hovorka R[1] and Murphy HR[1,2,3,5]

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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, the data of its use in pregnancy are limited.

Methods: This was a multicentre, open-label, randomized crossover study of pregnant women with type 1 diabetes. Women were randomized to 28 days of overnight closed-loop insulin delivery versus sensor augmented pump therapy followed by a 2-week washout period prior to crossing over. This was followed by a non-randomised 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 to sensor-augmented pump phase (75% versus 60%, 95% CI [6.1, 24.3]). There was no significant difference in hypoglycaemia and no episodes of severe hypoglycaemia 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 labour and delivery.

Conclusions: This study demonstrated that when compared to sensor-augmented pump therapy, closed-loop insulin delivery resulted in superior overnight glucose control without increasing hypoglycaemia. 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 labour and delivery.

Commentary: 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 to 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 during the changing demands of pregnancy: increasing

insulin resistance, changing glucose utilization, antenatal steroid administration, labour 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 on obstetric and neonatal outcomes.

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

Farrington C[1], Stewart ZA[2], Barnard K[3], Hovorka R[2] and Murphy HR[2,4]

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Objective: Closed-loop insulin delivery has shown potential as a valuable tool in the management of type 1 diabetes in pregnancy. However, the attitudes of women with diabetes towards this emerging technology had not been reported. This study aimed to evaluate the psychological aspects of the closed-loop in pregnancy.

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

Results: A total of 16 participants were included in this 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 closed-loop 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 hypoglycaemia. Women's perception of glucose control and directly measured CGM time in target sometimes differed.

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

Commentary: Closed-loop 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 patients with diabetes. While the technology is likely to improve in terms of its cumbersomeness, the concern for potential 'deskilling' with regards 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

Law GR[1], Gilthorpe MS[2], Secher AL[3], Temple R[4], Bilous R[5], Mathiesen ER[3], Murphy HR [4,6] and Scott EM[2]

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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 to 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's was performed. Using CGM data, the authors calculated an eAG at various times in pregnancy using the formula: "glucose (mmol/L) = 6.78 + [0.43 x (HbA1c [%] – 6.3)] + 0.004 x (gestation [weeks] – 2)] – 0.001 x (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 glucoses than outside of pregnancy. This difference between the pregnancy specific and non-pregnancy 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

Commentary: 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 between the relationship between average glucose and HbA1c and offers clinicians a practical method of assessing glucose based on aiming for average glucose levels of 6.4-6.7mmol/L.

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[1,2], Suen M[2], Pease A[2], Boyle JA[1,3], Soldatos G[1,2,] Regan J[3], Wallace EM[3,4] and Teede HJ[1,2]

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

Methods: This was 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 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 characteristic between the two groups. There was no evidence of a difference in glycaemic control achieved (as measured by HbA1c), or obstetrical outcomes between women using CSII versus MDI. When compared to 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 to late pregnancy (40% versus 52%).

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

Commentary: The cohort study adds to the literature on CSII versus 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 glycaemic 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 versus 218 pregnancies with MDI (11). They noted a higher proportion of large-for-gestational-age neonates in the CSII group (55.0% versus 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 randomised 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

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Objectives: Approximately one in two women of reproductive years 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 being disappointing. The aim of this meta-analysis of individual participant's data (IPD) was to synthesise 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 randomised trials involving >12,500 women in 16 countries. This included 22 studies from Europe, 4 each from USA, Australia, Brazil and 1 each from Egypt and Iran. 23 studies included women of any weight, 6 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 of high socioeconomic status. Data for approximately 50% eligible women was not available. The largest data were available for large for gestational age (LGA) with 34 studies (>12,000 women), with similarly high numbers (<11,000) for preterm delivery, small for gestational age (SGA) and caesarean section. For GWG, hypertensive disorders of pregnancy and GDM there were data from approximately 9,500 women. Slightly smaller datasets were available for the maternal and infant composite outcomes (8,800 and 7,900 respectively). Both diet and PA interventions were effective in reducing GWG by approximately 0.7kg, 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 pre-existing medical conditions. There was also a significant reduction in caesarean section with summary estimates that favoured 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, preterm delivery were also not statistically significant. When study level data from non-IPD studies were meta-analysed with IPD, there was stronger evidence for GDM reduction (59 studies in 16885 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). 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 (0.7kg) 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.

Comment: 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.

Hodson K[1,2,3], Dalla Man C[4], Smith FE[5,6], Barnes A[7], McParlin C[5,8], Cobelli C[4], Robson SC[5,8], Araújo-Soares V[7], Taylor R[5,6,8].

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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: 16 women with GDM (gestational age 27±3.3 weeks) were recruited to a 4-week hypo-energetic diet (1200kcal/day) with a magnetic resonance spectroscopy (MRS) scan and standardised meal test performed before and after the intervention and between 12-28 weeks post-partum. 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 1500kcal/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 (age 31.5, weight 93.1kg, BMI 34.6) lost 0.4kg/week or 1.6±1.7kg in total compared to weight gain of 0.3kg/week or 1.4±1.2kg in the comparator group. Six women lost >2kg, five women lost 0.3-1.2kg and three had a small weight gain (<0.5kg). Two women dropped out. The mean liver triacylglycerol was halved (3.7 to 1.8%) after 4-weeks of dietary restriction and returned to baseline by 12-28 weeks postpartum. Fasting plasma glucose, post-meal glucose, fasting insulin and C-peptide and markers of insulin resistance were unchanged pre and post intervention. Lipid levels and fasting NEFA were unchanged. Insulin resistance was reduced post-partum. The numbers of women requiring treatment were 0 for insulin and 2 for metformin compared to 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 associated with 0.4kg weight loss per 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.

Comment: 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 randomised 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

Nachum Z[1,2], Zafran N[1,2], Salim R[1,2] Hissin N[1], Hasanein J[3], Gam Ze Letova Y[1], Suleiman A[1] and Yefet E[1]

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

Methods: This was on open-label, single centre, randomized controlled trial women with gestational diabetes diagnosed at 13-33 weeks gestation. Women were initially randomized to either glyburide 2.5-5.0 mg/day versus metformin 850-2550 mg/day. If glycaemic targets were not achieved on monotherapy, the alternative medication was started. Patients who experienced adverse events were placed on the alternative medication. If glycaemic targets were not reached on two drug therapy, patients were started on insulin. The primary outcomes were inability to achieve glycaemic targets and glycaemic 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: four for adverse effects to oral medication and seven due to inability to meet glycaemic targets. There was no significant difference in pregnancies 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.

Commentary: 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 versus 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 to 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: To determine the safety and efficacy of antenatal milk expressing in women with diabetes. The rationale 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 breast-feeding during the early neonatal period. It has also been suggested that colostrum may be more effective for stabilising neonatal glucose levels than formula milk.

Methods: An open-label, multicentre randomised controlled trial of 635 women with diabetes in six Australian maternity hospitals. Women with a singleton pregnancy were randomised between 34-37 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 ≥95th percentile with abdominal circumference >97th centile, 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 hypoglycaemia 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 pre-gestational 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 randomisation 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 5.5ml. 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 hypoglycaemia 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 breast feeding 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 post-partum 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 post-partum.

Comment: This high quality randomised controlled trial shows no evidence that antenatal breast stimulation leads to earlier onset of labour or higher rates of NICU admission in offspring of women with hyperglycaemia. 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 pre-gestational 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-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 multicentre retrospective cohort study using data from 49 French CF study sites between 2001-12. 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 (FEV^1) 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: 294 pregnancies in 232 women with CF were reported; 180 women with 1 pregnancy, 42 women with 2 pregnancies and 10 with 3 pregnancies, resulting in 234 livebirths. Women were aged 27 years (range 15-42) and had a BMI of 20 (range 15-34). 80% 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% infants delivered by caesarean section. The median birthweight was 3000g. Most women (85%) did not have CFRD. Among women with diabetes (n=29), maternal age was higher (29 vs 26 years), FEV^1 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. Their BMI (19.9 vs 21.1), rate of BMI decline and rate of FEV^1 decline was not statistically different to women without CFRD. The infants of CFRD mothers were more likely 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 3000g.

Conclusions: The pregnancy outcomes of women with CF are generally favourable. 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.

Comment: The number of CF women of reproductive years with good lung function and nutritional status is expected to further increase as CFTR modulators are introduced. This study emphasises 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.

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