Diabetes and pregnancy: Still lots more to do

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The recently published report of the Confidential Enquiry into Maternal and Child Health (CEMACH) titled *Pregnancy in women with type 1 and type 2 diabetes* (CEMACH, 2005) makes very disappointing reading.

The key findings of the report are that babies born to women with type 1 or type 2 diabetes are nearly five times as likely to be stillborn and nearly three times as likely to die in the first month of life as those of women without diabetes. The babies are also twice as likely to have a major (non-chromosomal) congenital malformation.

In the CEMACH study, type 2 diabetes was found to account for over 25% of all pregestational diabetic pregnancies and was strongly associated with social deprivation and being a member of a minority ethnic group. Pregnancy in women with type 2 diabetes carried as great a risk of an adverse outcome as in those with type 1.

Women with pregestational diabetes were shown to be poorly prepared for pregnancy and there is unequal access to robust education programmes and preconception care services in England, Wales and Northern Ireland. Far from narrowing the gap, there remains a yawning chasm of adverse pregnancy outcome for women with diabetes – much of which is amenable to early and appropriate intervention and treatment.

These sobering findings pose major challenges to front-line services. How will we redesign our services to meet the need? How will we develop new ways of engagement to deliver effective 'preparing for pregnancy' education for women with pregestational diabetes?

As if these challenges were not enough, the impact of unrecognised pregestational diabetes is also significant. The study from Martinez-Frias et al (see right) adds another insight.

In this large Spanish study, gestational diabetes mellitus (GDM) was also associated with an increased congenital malformation rate, and maternal obesity significantly amplifies the risk. Thus, the overall relative risk of a selected group of malformations, excluding neural tube defects, in the infant of an obese mother with GDM compared with an obese mother with normal glucose tolerance was 2.78 (95 % confidence interval [CI], 1.38–5.5; $P<0.001$). Within the group with GDM, maternal obesity (body mass index ≥30 kg/m^2) was associated with a significantly increased risk of cardiovascular defects compared with non-obese women with GDM (odds ratio, 2.82; 95 % CI, 1.31–7.04; $P<0.01$). There was no relationship between obesity and risk of congenital malformation in the women with normal glucose tolerance.

The authors review the accumulating data which point in this direction and suggest that the reason some previous studies have failed to show a relationship between GDM and malformation rates relates to the varying prevalence of maternal obesity (as a surrogate for severity of unrecognised pregestational diabetes) in the populations studied. It seems likely that the excess risk of congenital malformation in women with GDM relates at least in part to previously undiagnosed pregestational diabetes and the additive effect of obesity relates to the increased risk of previously undiagnosed pregestational diabetes in the more obese women.

This emphasises the importance of considering extending 'preparing for pregnancy education', and indeed screening for diabetes, to obese women contemplating pregnancy. This will permit appropriate intervention prior to pregnancy in an attempt to reduce the risk of congenital malformation and further improve pregnancy outcomes.

Confidential Enquiry into Maternal and Child Health (CEMACH; 2005) *Pregnancy in women with type 1 and type 2 diabetes.* CEMACH, London. Available at http://www.cemach.org.uk/publications/CEMACHDiabetesOctober2005.pdf (accessed 29.11.2005)

DIABETIC MEDICINE

Pregestational BMI predicts congenital malformations linked to GDM

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 It has been shown by recent studies that infants of women who have gestational diabetes mellitus (GDM) are at a greater risk of having congenital malformations.

2 This study aimed to establish predictors of a selected group of these congenital malformations.

3 Data were used from the hospital-based Spanish Collaborative Study of Congenital Malformations, and a number of characteristics of mothers with GDM were assessed.

4 Relative to obese mothers with normal glucose tolerance (NGT), those with GDM had a significantly increased risk of having infants with the selected group of congenital malformations (odds ratio [OR], 2.78; 95 % confidence interval [CI], 1.38–5.55; $P<0.001$).

5 Furthermore, for mothers with GDM but not mothers with NGT, being obese (body mass index ≥30 kg/m^2) was linked to a significantly increased risk of having infants with cardiovascular defects (OR, 2.82; 95 % CI, 1.31–7.04; $P<0.01$)

6 It is important, therefore, that women planning a pregancy who are obese be screened for the presence of diabetes.

Martinez-Frias ML, Frias JP, Bermejo E, Rodriguez-Pinilla E, Prieto L, Frias JL (2005) Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. *Diabetic Medicine* **22**(6): 775–81

'Vildagliptin improves beta-cell function through raising insulin secretion at any given level of glucose.'

JOURNAL OF CLINICAL EPIDEMIOLOGY AND METABOLISM

DPP-4 inhibitor shown to improve beta-cell function

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 It has already been shown that vildagliptin, a dipeptidyl peptidase (DPP)-4 inhibitor currently in clinical trials, raises intact glucagon-like peptide (GLP)-1 levels and glycaemic control in people with type 2 diabetes.

2 This study investigated vildagliptin's effect (100 mg twice daily for 28 days; n=9), relative to placebo (n=11), on beta-cell function in people with diabetes.

3 Given that vildagliptin does not affect plasma insulin levels in people with diabetes, the authors suggested that a relatively sophisticated method is needed to establish vildagliptin's beta-cell effect.

4 A mathematical model was employed that described the rate of insulin secretion as a function of glucose levels, temporal changes in glucose, and a potentiation factor (to represent other factors).

5 The results were consistent with those of previous studies.

6 The authors concluded that vildagliptin improves beta-cell function through raising insulin secretion at any given level of glucose – this could have clinical implications for the agent's effect in both fasting and fed states.

Mari A, Sallas WM, He YL et al (2005) Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed beta-cell function in patients with type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism* **90**(8): 4888–94

LANCET

Differences in new-onset diabetes seen among hypertension regimens

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 It has been suggested that the apparent shortcomings in the prevention of coronary heart disease (CHD) that have been seen in early hypertension trials could be overcome with newer agents.

2 Comparing the effect of amlodipine plus perindopril with that of atenolol plus a thiazide on fatal CHD and non-fatal myocardial infarction was an aim of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm.

3 This trial was multicentred, prospective, randomised and controlled, and it included 19 257 people with hypertension who were aged between 40 and 79 years and had three other cardiovascualr (CV) risk factors.

4 The amlodipine-based regimen (n=9639) involved adding perindopril 4–8 mg, as required, to amlodipine 5–10 mg; the atenolol-based regimen comprised atenolol 50–100 mg with bendroflumethiazide 1.25–2.5 mg and potassium as needed.

5 The trial was brought to an end early (median follow-up, 5.5 years), amassing 106 153 person-years of results.

6 The amlodipine-based regimen was found to prevent a greater number of major CV events.

7 Furthermore, a lesser incidence of new-onset diabetes was seen with the amlodipine-based regimen than the atenolol-based regimen ($P<0.0001$).

Dahlof B, Sever PS, Poulter NR et al (2005) Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* **366**(9489): 895–906

'The results demonstrate a potential benefit of pioglitazone treatment to the liver.'

DIABETIC MEDICINE

Pioglitazone has potential benefits for the liver

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Having type 2 diabetes increases people's susceptibility to liver damage and it is thus important to know about the hepatic effects of treatment for type 2 diabetes.

2 This analysis examined the results of liver tests from four 1-year, randomised, double-blind trials that compared pioglitazone, metformin and a sulphonylurea (gliclazide).

3 With pioglitazone, there were mean reductions in hepatic enzymes of 3–18 %; with gliclazide, there were mean increases of 3–13 %; and with metformin there were small increases or decreases.

4 At the end of treatment, liver test results within the normal range were seen in at least 87 % of people on pioglitazone, at least 80 % of people on metformin and at least 75 % of people on gliclazide.

5 An increase in alanine aminotransferase levels of greater than 3 times the upper limit of normal, at any time during treatment, were seen in 0.9 % of people on pioglitazone, 1.9 % of people on metformin and 1.9 % of people on gliclazide.

6 The results, the authors conclude, demonstrate a potential benefit of pioglitazone treatment to the liver.

Belcher G, Schernthaner G (2005) Changes in liver tests during 1-year treatment of patients with Type 2 diabetes with pioglitazone, metformin or gliclazide. *Diabetic Medicine* **22**(8): 973–9

DIABETIC MEDICINE

CSII may be superior to MDI in poorly controlled patients

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The aim of this randomised cross-over trial (n=40) was to compare the efficacy of continuous subcutaneous insulin infusion (CSII) with that of multiple daily injections (MDI) in obese people with type 2 diabetes who were poorly controlled on insulin therapy plus metformin.

2 In the intent-to-treat and completers' cohorts, the authors report a treatment advantage of CSII over MDI, but the only significant difference in outcome found was change in insulin dose in the completers' cohort (+20.1 IU/day with MDI and –15.5 IU/day with CSII; $P<0.0001$).

3 The authors use the findings to suggest that insulin pump therapy may have advantages in type 2 diabetes, but these advantages are small.

Wainstein J, Metzger M, Boaz M et al (2005) Insulin pump therapy vs. multiple daily injections in obese Type 2 diabetic patients. *Diabetic Medicine* **22**(8): 1037–46

BRITISH JOURNAL OF CANCER

Elevated risk of ovarian cancer seen with diabetes diagnosed before 30

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Studies of cancer risk in people with type 1 diabetes have been relatively small and therefore of limited power.

2 This one, though, involved 28 900 UK-based people with insulin-controlled diabetes; 23 834 of these were diagnosed before the age of 30 – the authors thus deduced that they would have almost all had type 1 diabetes.

3 Cancer incidence and mortality was compared against national expectations.

4 The only site for which a significantly elevated cancer risk was found in the 'type 1 diabetes' group was the ovary, for which there was a standardised incidence ratio of 2.14 (95% confidence interval [CI], 1.22–3.48; $P<0.01$) and a standardised mortality ratio of 2.90 (95% CI, 1.45–5.19; $P<0.01$).

Swerdlow AJ, Laing SP, Qiao Z et al (2005). Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study. *British Journal of Cancer* **92**(11): 2070–5

'While periodic screening for diabetes in women with PCOS is important, the interval could be more than a year.'

JOURNAL OF CLINICAL EPIDEMIOLOGY AND METABOLISM

Study adds to screening evidence in women with PCOS

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 This study assessed the changes in glucose tolerance over time in 67 women with polycystic ovary syndrome (PCOS) not on metformin.

2 At baseline, 25 women (37%) had impaired glucose tolerance (IGT) and 7 (10%) had type 2 diabetes.

3 After a mean follow-up of 2.5 years, there were no significant changes in the prevalence of glucose intolerance: 30 women (45%) had impaired glucose tolerance (IGT) and 10 (15%) had type 2 diabetes.

4 Annual conversion risks were 16% from normal glucose tolerance to IGT and 2% from IGT to type 2 diabetes.

5 The authors conclude that while periodic screening for diabetes in women with PCOS is important, the interval could be more than a year.

Legro RS, Gnatuk CL, Kunselman AR, Dunaif A (2005) Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. *Journal of Clinical Endocrinology and Metabolism* **90**(6): 3236–42

'For the primary outcome, comparing amlodipine or lisinopril with chlorthalidone, there was no significant risk difference in people with type 2 diabetes or normoglycaemia.'

ARCHIVES OF INTERNAL MEDICINE

Complications with diuretics not worse than those with antihypertensives

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 There is uncertainty about the optimal first-line antihypertensive to use for people with impaired fasting glucose (IFG) or type 2 diabetes.

2 The authors aimed to establish whether using a calcium-channel blocker or an angiotensin-converting enzyme (ACE) inhibitor led to fewer clinical complications than using a thiazide-type diuretic.

3 An intention-to-treat analysis was carried out in participants from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), of whom 13 101 had type 2 diabetes, 1399 had IFG and 17 012 had normoglycaemia.

4 For the primary outcome (fatal coronary heart disease or non-fatal myocardial infarction), comparing amlodipine or lisinopril with chlorthalidone, there was no significant risk difference in people with type 2 diabetes or normoglycaemia.

5 There was a significant increase in the risk of reaching the primary endpoint, though, for amlodipine relative to chlorthalidone in people with IFG (relative risk, 1.73; 95% confidence interval, 1.10–2.72).

6 There were also significant increases in the risk of heart disease in people with type 2 diabetes for amlodipine and lisinopril relative to chlorthalidone.

Whelton PK, Barzilay J, Cushman WC et al (2005) Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia. *Archives of Internal Medicine* **165**(12): 1401–9

JOURNAL OF CLINICAL EPIDEMIOLOGY AND METABOLISM

Intrauterine diabetes exposure associated with childhood HbA_{1c}

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 The intrauterine environment is known to be critical to programming the risk of type 2 diabetes and cardiovascular disease.

2 In this study (n=42), Pima Indians aged between 7 and 11 years were classified, retrospectively, as either infants from diabetic pregnancies or infants born before their mother developed diabetes (using maternal oral glucose tolerance tests).

3 A cross-sectional analysis was conducted for a range of parameters.

4 Intrauterine exposure to diabetes resulted in higher HbA_{1c} levels (5.7 %, compared with 5.0 % in infants born before their mother developed diabetes; P=0.002), higher systolic blood pressure (118 versus 107 mmHg; P=0.02) and lower LDL-cholesterol levels (41 versus 48 mg/dl; P=0.03) in childhood.

5 After adjustment for percentage body fat, the associations with HbA_{1c} and systolic blood pressure remained significant.

6 The results suggest, therefore, that diabetes in pregnancy confers risks that are independent of obesity.

Bunt JC, Tataranni PA, Salbe AD (2005) Intrauterine exposure to diabetes is a determinant of hemoglobin A(1)c and systolic blood pressure in pima Indian children. *Journal of Clinical Endocrinology and Metabolism* **90**(6): 3225–9

DIABETIC MEDICINE

Duration of insulin treatment predicts hypos

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This investigation aimed to establish frequency and predictors of hypoglycaemic events in people with type 1 diabetes and insulin-treated type 2 diabetes.

2 Two hundred and sixty-seven people were randomly recruited from a population-based register in Scotland; participants recorded hypoglycaemic events during a 1-month period.

3 For individuals with insulin-treated type 2 diabetes, rates of 16.37 hypoglycaemic events per person per year and 0.35 severe hypoglycaemic events per person per year were observed.

4 Ordinal logistic regression analysis revealed two significant predictors of hypoglycaemia in people with insulin-treated type 2 diabetes: a history of hypoglycaemia (P<0.0001) and duration of insulin treatment (P=0.014).

5 While the incidence of hypoglycaemia in insulin-treated type 2 diabetes was lower than that found in type 1 diabetes (42.89 hypoglycaemic events per person per year and 1.15 severe hypoglycaemic events per person per year), the authors felt the frequency is high enough to cause significant morbidity.

6 The authors state that educating people with type 2 diabetes about the risk of hypoglycaemia with insulin is thus merited.

Donnelly LA, Morris AD, Frier BM et al (2005) Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabetic Medicine* **22**(6): 749–55