**Assessing the outcomes of pregnancies of women with diabetes**

T. Cundy1,2 and R. I. G. Holt3,4

1Associate Editor, Diabetic Medicine

2Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

2Editor-in-Chief, Diabetic Medicine

3Diabetes and Endocrinology, Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK

*Correspondence to*: Tim Cundy. E-mail: [t.cundy@auckland.ac.nz](mailto:t.cundy@auckland.ac.nz)

Conflicts of Interest: The authors report no conflict of interest in relation to this paper

The discovery of insulin in 1921 meant for the first time that women with type 1 diabetes could contemplate and complete pregnancy, but until the 1960s it remained a high risk enterprise with perinatal mortality rates of up to 40%. The main causes of the high rate of loss were intrauterine death or birth trauma of large (‘macrosomic’) fetuses, neonatal hypoglycaemia, and major congenital malformations. In this era, simply the survival of a baby was a good outcome.

Developments in the 1960s, in particular, the understanding that high maternal glucose and fetal insulin concentrations were driving excessive fetal growth, led to substantial changes in practice. These were based on the dual principles of trying to maintain maternal glycaemia as close to normal as possible (particularly in the second half of pregnancy) and early delivery. The subsequent decline in perinatal mortality from about 10-20 times to about twice the rate in women without diabetes was one of the great triumphs of the last century (though the high rate of congenital malformations - related to poor early pregnancy glycaemic control - has proven harder to reduce). Excessive fetal growth, by the 1980s detectable with fetal ultrasound, and birth weight came to be accepted as surrogates of the adequacy of glycaemic control, and an important outcome measure.

But diabetes in pregnancy has changed in the past thirty years. Obesity has become endemic and type 2 diabetes is now prevalent in women of child-bearing age. Formerly a rare occurrence, pregnancy in women with type 2 diabetes is now more frequent than in women with type 1 diabetes in many parts of the world. Without entering the controversies about diagnostic criteria, maternal obesity is clearly a major driver of the increased rates of gestational diabetes, which is essentially a form of prediabetes.

Obesity itself has major effects on maternal and fetal outcomes. For the mother, these include pre-eclampsia, pregnancy-induced hypertension, respiratory, wound and urinary tract infections and venous thrombo-embolism. Through fetal overnutrition, obesity also causes macrosomic infants and is associated with all its familiar consequences: shoulder dystocia, perineal tears and increased rates of caesarean section, neonatal intensive care admission and perinatal mortality. Accelerated fetal growth can no longer be considered a problem specific to maternal diabetes.

In a paper in this edition of the journal, Hildén et al try to disentangle the impact of gestational diabetes (diagnosed by fairly liberal criteria) and maternal obesity on a number of serious pregnancy outcomes in the Swedish population (1). As expected the women with gestational diabetes were older, more overweight and more likely to be migrants, multiparous and to have chronic hypertension. Gestational diabetes was not associated with stillbirth or perinatal mortality, but was associated with premature delivery and lower Apgar scores. Increasing maternal body mass index (BMI) above 25 kg/m2 was strongly associated with both stillbirth and perinatal mortality, as well as premature delivery and lower Apgar scores that persisted after adjustment for diabetes status. Gestational diabetes was associated with an increased congenital malformation rate that persisted after adjustment for maternal BMI, but the difference was small (4.1% with *vs* 3.5% without gestional diabetes) and might be explicable by a proportion of the women with gestational diabetes having unrecognised type 2 diabetes. The authors conclude that the effects of gestational diabetes and maternal obesity were independent risk factors for the various outcomes studied, though the odds ratios were greatest for the higher degrees of maternal obesity. The associations of gestational diabetes and obesity with prematurity and low Apgar scores may in part be iatrogenic, through early induction of labour.

Missing from the paper is information on maternal weight gain in pregnancy. We know now that excessive gestational weight gain (another source of fetal overnutrition) is associated with all the same outcomes as maternal obesity and gestational diabetes. We also know that women who are overweight before pregnancy tend to gain more weight than average during pregnancy. The effect of gestational weight gain on fetal growth and birthweight is seen right across the spectrum of pre-existing and gestational. In type 1 diabetes, gestational weight gain is an important determinant of the amount by which insulin requirements increase during pregnancy.

The paper by Hauffe et al looks at outcomes of pregnancy in women with type 1 diabetes who managed their diabetes with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin (MDI) injections (2). CSII use in pregnancy has gained popularity and is commonly recommended to help women with persistent hyperglycaemia or troublesome hypoglycaemia obtain better glycaemic control, and so (in theory) reduce the incidence of macrosomia and other diabetes-associated problems. In their study, CSII was used was used in 59% of the 339 singleton pregnancies. The results were remarkably similar between the two groups in terms of glycaemic control, and obstetric and neonatal outcomes with the exception of birth weight which was on average 9% (300g) greater in the CSII group than in the MDI group. The HbA1c in the last trimester, CSII use and gestational weight gain were all significantly associated with birth weight. More CSII users than MDI users exceeded recommended weight gain in pregnancy. A recent analysis of data from the CONCEPTT trial also found that women using CSII had a higher mean HbA1c and higher rates of gestational hypertension, neonatal hypoglycaemia and neonatal intensive care admissions than women using MDI [3]; a salutary reminder that new technologies need careful evaluation and may not deliver all they promise.

The papers of Hildén et al and Hauffe et al [1,2] together add to the evidence that maternal obesity is a significant risk factor for serious adverse outcomes, independent of glycaemia, and that high birth weight, with all its attendant potential complications, is a complex phenomenon that cannot be equated simply with glycaemic control. Diabetes, maternal obesity and excessive gestational weight gain all increase birth weight, while factors such as smoking, inadequate weight gain, hypertensive disorders and placental insufficiency may all reduce birth weight. The secular trends toward population weight gain, less smoking and women having babies later in life mean that these issues are here to stay for the foreseeable future. It is worth noting that perceptions and practices concerning gestational weight gain vary substantially around the world. In Japan, for example, recommendations for weight gain in pregnancy for underweight and normal weight women are significantly lower than the widely used Institute of Medicine guidelines, and are largely adhered to, resulting in a very low rate of macrosomia [4]. For different reasons - 42% of prepregnant women are of low body weight - the mean gestational weight gain in India (7 kg) is also very low [5].

Egan and Simmons [6] discuss the relative ineffectiveness of intervention trials aimed at preventing GDM by diet and exercise. The disappointing results are probably because the differences in gestational weight gain between intervention and control groups are small, ranging from almost none to 2 kg, even when the intervention is started in the first half of pregnancy. A recently published trial shows the same result [7]. Egan and Simmons suggest that ‘at-risk women are often reluctant to engage in lifestyle changes’. The risk they refer to is the risk of GDM, which is not in itself an ‘outcome’, but a risk factor for various adverse pregnancy outcomes. So, while women at risk of a risk factor may indeed be reluctant to engage, there is ample evidence that once the risk becomes more immediate – that is, when GDM has been diagnosed – engagement is often good and gestational weight gain is commonly limited and, as demonstrated by Aiken et al [8], has clear effects on pregnancy outcomes. Of note in this paper was the relatively small proportion of women in the study who actually had weight measurements made at 28 weeks’ gestation, hinting perhaps at some reluctance of maternal care providers to engage in discussions of weight gain in pregnancy.

As Okely et al [9] discuss, once diagnosed with gestational diabetes, women are strongly motivated by an increase in risk perception, a strong affective response and a change in social identity (becoming a mother). In a further qualitative paper, McParlin et al describe how women with newly diagnosed gestational diabetes were happy to adopt a moderately reduce calorie diet in order to optimise the well-being of their baby [10]. However, these healthy behaviours are often not carried forward into the postpartum period for reasons that are explored by Parsons et al [11]. The same phenomenon is observed in women with type 1 and type 2 diabetes. With the motivation of pregnancy, even women with very poor early pregnancy glycaemic control often achieve excellent control in late pregnancy, but this is commonly followed by reversion to the prepregnancy pattern after delivery.

There is a tendency to regard and interpret the events and outcomes we count and record in the diabetic pregnancy as biological phenomena over which clinicians have relatively little influence; however, there is another major player that determines many of these outcomes, and that is variation in clinical practice. Obstetricians, for example, individually or at a given institution, have a set of beliefs about the indications to intervene to deliver a baby, and the timing and nature of that intervention. This is illustrated nicely in the paper by Abell et al [12] who tried to compare the effects on a number of obstetric and neonatal outcomes of ‘tight’ *vs* (slightly) more relaxed glycaemic treatment targets in women with gestational diabetes, from two centres in Melbourne. The most striking observation was that at the centre operating the regimen of tight glycaemic control, babies were also delivered a week earlier than at the other centre, with much higher rates of induction of labour and elective caesarean section. This undoubtedly says more about clinicians’ differing perceptions of risk (and probably other factors) than anything to do with the biology of diabetes and pregnancy. Another example can be found in the the HAPO study in which the rate of admission of newborns to neonatal intensive care differed by an order of magnitude across its study sites [13]. Remarkably few studies concerning pregnancy in women with diabetes ever go near the deep waters of how the outcomes we report are affected by variations in clinical practice.

1701 words

**References**

1. Hildén K, Hanson U, Persson M, Magnusson A, Simmons D, Fadl H. Are gestational diabetes and adiposity independent risk factors of perinatal outcome? Diab Med 2018 [this edition]. DME-2018-00272.R3
2. Hauffe F, Fauzan R, Schohe AL, Scholle D, Sedlacek L, Scherer KA, Klapp C, Ramsauer B, Abou-Dakn M, Henrich W, Schlembach D, Schaefer-Graf UM. Higher rate of large for gestational age newborns mediated by excess maternal weight gain in pregnancies with type 1 diabetes and use of continuous insulin infusion compared to multiple dose insulin injection. Diab Med 2018 [this edition]. DME-2018-00445.R1
3. Feig DS, Corcoy R, Donovan LE, Murphy KE, Barrett JFR, Sanchez JJ, Wysocki T, Ruedy K, Kollman C, Tomlinson G, Murphy HR. Pumps or multiple daily injections in pregnancy involving type 1 diabetes: a prespecified analysis of the CONCEPTT randomized trial. Diab Care 2018; dc181437. <https://doi.org/10.2337/dc18-1437>
4. Suzuki S. Optimal weight gain during pregnancy in Japanese women. J Clin Med Res 2016; 8: 787-92.
5. Coffey D. Prepregnancy body mass and weight gain during pregnancy in India and sub-Saharan Africa. PNAS 2015; 112: [11] 3302–7.
6. Egan AM, Simmons D. Lessons learned from lifestyle prevention trials in gestational diabetes mellitus. Diab Med 2018 [this edition]. DME-2018-00221.R1
7. Peaceman AM, Clifton RG, Phelan S, Gallagher D, Evans M, Redman LM, Knowler WC, Joshipura K, Haire-Joshu D, Yanovski SZ, Couch KA, Drews KL, Franks PW, Klein S, Martin CK, Pi-Sunyer X, Thom EA, Van Horn L, Wing RR, Cahill AG, and the LIFE-Moms Research Group. Lifestyle interventions limit gestational weight gain in women with overweight or obesity: LIFE-Moms prospective meta-analysis. Obesity 2018; 26: 1396-1404.
8. Aiken CEM, Hone L, Murphy HR, Meek CL. Improving outcomes in gestational diabetes: does gestational weight gain matter? Diab Med 2018 [this edition] DME-2018-00137.R2
9. Okely J, Mason C, Collier A, Dunnachie N, Swanson V. Educational and psychological aspects of the diagnosis of gestational diabetes: a ‘teachable moment’. Diab Med 2018 [this edition]. DME-2018-00163.R2
10. McParlin C, Hodson K, Barnes A, Taylor R, Robson SC, Araujo-Soares V. Views, experience and adherence of pregnant women participating in a study of weight loss in gestational diabetes (WELLBABE). Diab Med 2018 [this edition]. DME-2017-00825.R3
11. Parsons J, Sparrow K, Ismail K, Hunt K, Rogers H, Forbes A. A qualitative study exploring women’s health behaviours after a pregnancy with gestational diabetes to inform the development of a diabetes prevention programme, Diab Med 2018 [this edition]. DME-2018-00130.R2
12. Abell SK, Boyle JA, Earnest A, England P, Nankervis A, Ranasinha S, Soldatos G, Wallace EM, Zoungas S, Teede HJ. Impact of different glycaemic treatment targets on pregnancy outcomes in gestational diabetes. Diab Med 2018 [this edition]. DME-2018-00187.R2
13. HAPO Study Cooperative Research Group: Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008; 358: 1991–2002.