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Diabetes and pregnancy: beyond glucose?

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Many readers will know what it is like to be called to a delivery room when one of your patients with type 1 diabetes has just given birth to a macrosomic baby. The eyes of all around will accuse you of poor glucose control. So you go back to scan the file and find that this patient had a set of excellent HbA_{1c} results. You may now be ready to believe that glucose control, especially mean glycaemic control, is not the only factor that determines the outcome of pregnancy in a woman with diabetes.

The notion that glucose levels as close to normal as possible are essential in women with diabetes who wish to become pregnant has long since pervaded the scientific and clinical community. Data from epidemiological and intervention studies clearly demonstrate that women with tight glycaemic control before and early in pregnancy have fewer congenital malformations in their offspring and lower neonatal morbidity and mortality than women with high mean glucose levels [1, 2]. Even in the DCCT, which was not designed to look at pregnancy outcomes but nonetheless recorded 270 pregnancies, the congenital malformation rate was 5.9% in the conventionally treated women and 0.7% in the intensively treated group [3]. Such clinical observations are supported by overwhelming experimental evidence from animal models that glucose is directly toxic to the developing foetus [4]. Later in pregnancy, as we have also learned, glucose should be kept as close to the norm as possible to avoid macrosomia and further neonatal morbidity [5]. Macrosomia is especially important, not only because of the obstetric problems it gives rise to, such as dystocia and need for Caesarian section, but also because it predisposes to problems in later life, such as an increased risk of the metabolic syndrome [6, 7]. The policy of good glycaemic control throughout pregnancy is now applied

around the world, and women with diabetes are urged to attend pre-pregnancy diabetic clinics and to intensify their treatment to reach this level of control. The recent Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) demonstrated that tight glycaemic control also reduces perinatal morbidity and mortality in women with gestational diabetes, in whom glycaemic control only becomes a major issue during the latter part of pregnancy [8].

The St Vincent Declaration set out to lower the risk for mother and child in diabetic pregnancy to that of a non-diabetic pregnancy [9]. Although major efforts have been made by means of improved glucose control, several studies have shown that this goal has not yet been achieved [10]. Why? One reason is that many women still fail to plan their pregnancies, do not attend a pre-pregnancy clinic, and thus have suboptimal glycaemic control in early pregnancy [11]. However, this is not the whole story, for problems remain even when near-perfect mean glycaemic control appears to have been achieved. HbA_{1c} or fructosamine provide a useful global index of glucose control in the non-pregnant, but avoidance of postprandial hyperglycaemia may prove more important in pregnancy, and has been shown to limit neonatal macrosomia, morbidity and mortality [12, 13].

Macrosomic children continue to be born, with a corresponding increase in neonatal morbidity, to women with near-perfect glycaemic control and no underlying vascular problems. Two papers in the present issue of *Diabetologia* address these non-glycaemic contributors to pregnancy outcome [14, 15]. Kerssen et al. demonstrate that when women with diabetes achieve HbA_{1c} levels within the 'acceptable' range during pregnancy, variations around such values contribute only minimally to the birthweight of the child [14]. In this near-normal range, a difference in HbA_{1c} of 0.5% made no measurable difference in terms of outcome. There are two reasons for this. First, HbA_{1c} is not a good measure of glucose control in pregnancy, since the goal is to avoid glycaemic overload of the foetus. Mothers with similar HbA_{1c} levels may have different outcomes because of differences in the waves of glucose that cross the placenta after meals. The authors therefore propose, as

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others have done before, that self-monitored blood glucose before and after meals offers a far better means of estimating glucose control in pregnancy, at least when it comes to avoiding macrosomia. A second reason for the difference in outcome is that other non-modifiable factors, such as genes, may enter the picture: parental and—as shown in this study—sibling birthweights are also good indicators of macrosomia.

The study by Ricart et al. takes the same story into the general population [15]. This Spanish population study demonstrates that pre-pregnancy BMI is a more important predictor of foetal macrosomia than gestational blood glucose control, although this, too, is important. These findings are consistent with studies of gestational diabetes, suggesting that the impact of the metabolic syndrome, obesity included, is greater than that of glucose control alone.

So, where do we go from here? It is clear that glycaemic control is the first hurdle to overcome in women with overt diabetes. Poor glucose control in early pregnancy causes foetal malformations, termination of pregnancy and pregnancy complications, and is dangerous for both mother and child. It is essential to achieve tight glycaemic control as early as possible, and thus before pregnancy, whenever this can be organised. However, once good overall control is achieved, we should not rest. Tight control should be maintained throughout pregnancy, given the overwhelming literature showing that high glucose levels result in macrosomic and dysmature infants. Good overall control is not enough, however, and postprandial peaks should also be avoided. Many authors therefore suggest routine postprandial glucose measurements in pregnant patients with diabetes [16], and recent data suggest that 90 min after a meal is the most sensitive time to measure [17]. Glycaemia apart, other factors, such as smoking, BMI and weight gain, must also be taken into account, as in non-diabetic women. This having been done, we are left with non-modifiable factors such as genes or pre-existing diabetic complications. Indeed, both maternal and foetal outcome are affected to a major extent by the presence of microvascular or macrovascular complications in the mother before pregnancy. Normal pregnancy is accompanied by expansion of the vascular bed, and vasculopathy prevents a normal expansion, thus increasing the risk of pre-eclampsia, eclampsia and adverse maternal outcome [16]. This issue becomes increasingly important as women opt for later pregnancy.

In conclusion, our patients with diabetes should know as they prepare for pregnancy that optimal glycaemic control is essential to avoid malformations and to limit macrosomia, but we should bear in mind that other players may come into the picture, not all of which can be affected by our treatment. There is more to diabetic pregnancy than good glycaemic control, but this is still the right place to start.

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