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Gestational diabetes - Paradigm Lost?

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Abstract

Despite a prodigious number of publications on the subject of gestational diabetes, great uncertainty persists about its significance and how it should be diagnosed. We suggest that the problem lies with concepts introduced over thirty years ago: first that gestational diabetes is a distinct disease requiring 'diagnosis' and second that this entity should include all degrees of glucose intolerance in pregnancy, with the presumption of equal risk across the range. We argue that fetal risks clearly differ according to the degree of maternal glycaemia, being greatest for those with previously undiagnosed diabetes and lowest for those with minimally raised blood glucose. In the latter, 'gestational diabetes' is primarily a risk factor for macrosomia and hypertension in pregnancy, but probably not the most important: maternal obesity and excessive gestational weight gain are of greater significance. From this perspective, gestational diabetes is a risk factor rather than a disease, and while there are good reasons to reduce the incidence of large babies and hypertension, it is more logical to look at all risk factors involved. The excessive 'glucocentric' focus and the quixotic pursuit of perfect diagnostic criteria in much recent research are hindering rather than helping our understanding.

Key words: gestational diabetes, macrosomia, risk factor, diagnosis

Introduction

More than 7000 papers about gestational diabetes [GDM] and its diagnosis have been published in the last 15 years, but chaos reigns. The American Diabetes Association (ADA) now recommends three different ways of diagnosing gestational diabetes [1], the Canadian Diabetes Association two [2], the National Institute for Health and Care Excellence (NICE) recommendations differ from all others [3] and the World Health Organisation (WHO) is promulgating guidelines for which it acknowledges the quality of evidence is "very low" [4]. However did we arrive at such a point? In this paper we suggest that perhaps the current paradigm of GDM as a 'diagnosis' may be the root of the problem.

Some history

Before the discovery of insulin, the chances of a woman with diabetes dying in pregnancy were high and those of delivering a live healthy baby were close to zero. The introduction of insulin treatment transformed the life expectancy of women of child-bearing age, and restored fertility. Maternal mortality dropped sharply, but the prognosis for the fetus remained dismal. The major cause of perinatal mortality was the late intrauterine death of overgrown ('macrosomic') fetuses, but birth trauma, early neonatal death (particularly from severe hypoglycaemia) and major congenital anomalies also took their toll. In the middle decades of the last century advances in diabetes, obstetric, anaesthetic and neonatal care dramatically improved outcome of pregnancy for women with diabetes [5] and can be rightly considered one of the outstanding medical achievements of the age (although the incidence of major congenital malformations has proven more difficult to reduce). In the developed world, perinatal mortality and morbidity in women with diabetes has 'plateaued' at a relatively low rate, albeit still higher than for women without diabetes [6], and research into diabetic pregnancy has become increasingly focused on surrogate outcomes such as birth weight and fetal ultrasound measures.

The concept of gestational diabetes

Observations in the 1930s and 1940s suggested that women who later developed what we now call type 2 diabetes had a high incidence of large babies and fetal loss. Thus arose the concept of a pre-diabetic state that was harmful to the fetus [7]. Investigators described the effects of pregnancy on glucose tolerance and proposed diagnostic criteria for gestational diabetes (a term that came into use in 1961) that were based not on fetal outcomes, but on the ability of the oral glucose tolerance test (GTT) in pregnancy to predict later diabetes in the mother [7]. As one might expect, the subsequent risk of type 2 diabetes in the mothers is related to the degree of hyperglycaemia (and subsequent need of insulin) in pregnancy, maternal obesity, weight gain postpartum and the duration of follow up [8-10]. Women diagnosed with GDM are usually overweight and commonly have other features of the 'metabolic syndrome' such as dyslipidaemia and hypertension, and the prevalence of GDM reflects the prevalence of impaired glucose tolerance in any given community. Thus in the great majority of cases 'gestational diabetes' is simply a form of pre-diabetes [11].

Becoming a diagnosis

At the 1st International Workshop on Gestational Diabetes (1979) GDM acquired a formal definition: "Carbohydrate intolerance of variable severity recognized for the first time in pregnancy" and became established as a distinct form of diabetes - a position soon adopted by the ADA [12]. At the 2nd International Workshop (1984) the definition was qualified further to apply "irrespective of whether ... the condition persists after pregnancy (and) does not exclude the possibility that (it) antedated the pregnancy" [13]. These decisions have shaped two conceptual roadblocks with which we still struggle: first, the idea that gestational diabetes is a distinct disease requiring 'diagnosis' and second the conflation of all degrees of glucose intolerance in pregnancy into a single entity, with the presumption of equal risk across the range.

A serious flaw in the original concept of GDM was that it had no distinctive clinical features (other than later maternal diabetes) and so with only a biochemical definition, it was indeed

a diagnosis in search of a disease. Furthermore, despite the widespread introduction of testing for GDM in pregnancy in the 1980s, the benefits of screening and treatment were not established. Somewhat belatedly, trials to address these questions were started in the late 1990s.

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study

The HAPO study aimed to clarify the association of fetal morbidity and other pregnancy outcomes with the degree of maternal hyperglycaemia. 23,316 women had a 75g GTT performed at 24–32 weeks' gestation. Women whose fasting blood glucose ≤5.8 mmol/L and 2hr values ≤11.1 mmol/L were included, with clinicians blinded to the GTT results.

The study reported four primary endpoints: two of direct clinical importance (primary caesarean section rate and neonatal hypoglycaemia), and two surrogate measures (birth weight and cord-blood serum C-peptide level >90th centile). Continuous relationships between untreated maternal blood glucose (fasting, 1 hr and 2 hr post glucose load) and each of the outcomes were found. The surrogate measures, cord blood C-peptide level (a measure of fetal hyperinsulinaemia) and birth weight >90th centile, had the strongest association with maternal blood glucose, while neonatal hypoglycaemia, which occurred in only 2.1% of participants, had the weakest [14].

Randomised controlled trials (RCT) of treatment of mild gestational diabetes

A number of RCTs have examined the effects of treating mild GDM, defined as levels of hyperglycaemia that would not meet the diagnostic criteria for diabetes outside pregnancy. The two largest were the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the Maternal Fetal Medicines Unit Network study (MFMU) [15,16]. Meta-analyses of these trials conclude that the main effect of detection and treatment of GDM was a small reduction in babies weighing >4kg at birth (10% *vs* 13% in ACHOIS and 6% *vs* 7% in the MFMU trial). Presumably related to the lower birth weight, there was also a reduction in the (already low) rates of shoulder dystocia (1.4% *vs* 3.2% in ACHOIS and 1.5% *vs* 4.0% in the MFMU trial). There was also moderate quality evidence that treatment reduced the incidence of hypertensive disorders of pregnancy (12% *vs* 18% in ACHOIS and 8.6% *vs* 13.6% in the MFMU trial) [17,18]. In the ACHOIS study [15], the composite primary

outcome of 'any serious perinatal complication' was more frequent (4% vs 1%) in the subjects receiving routine-care. This difference was critically dependent on the 5 perinatal deaths in this group (1 %, vs none in the treated group). However, a number of the deaths cannot plausibly be attributed to the non-treatment of GDM; for example, one infant had a lethal congenital anomaly, while another had severe intrauterine growth retardation. The authors themselves acknowledged the lack of evidence that perinatal mortality is increased in mild GDM; and indeed there was no increase in perinatal mortality in either the HAPO study or MFMU trial [14,16]. What the HAPO study and the RCTs tell us then is that, rather than a specific diagnosis, mild GDM is primarily a risk factor for large babies and for hypertension in pregnancy. But are there other risk factors?

Fetal overnutrition – gestational diabetes, obesity and gestational weight gain

The traditional view of diabetes in pregnancy has been dominated by the concept of maternal hyperglycaemia providing excess nutrition that in turn accelerates fetal growth and inceases birth weight (the Pedersen hypothesis). However, both maternal obesity and excessive weight gain in pregnancy are also characterised by energy intake in excess of need. In the general obstetric population the marked secular trend toward increasing birth weight is largely explained by increased rates of maternal obesity and reductions in cigarette smoking [19].

GDM is of course strongly associated with obesity, but it seems little appreciated that almost all the morbidities commonly attributed to it are also seen with maternal obesity and excessive gestational weight gain, irrespective of changes in maternal glycaemia.

Maternal obesity is associated with an increased risk of and late fetal death, with the risk of the latter clearly related to the degree of obesity [20-21]. The risks for pre-eclampsia, pregnancy-induced hypertension, respiratory, wound and urinary tract infections, venous thromboembolism, large-for-gestational age infants, shoulder dystocia, perineal tears and rates of caesarean section and neonatal intensive care admission are all increased with maternal obesity [22-26]. Although gestational diabetes is associated with maternal obesity, the latter has a greater impact on these adverse outcomes [22,27,28]. Inter-

pregnancy weight gain is also associated with poorer outcomes in subsequent pregnancies [29,30].

These same pregnancy and neonatal morbidities are also associated with excessive gestational weight gain [27,28,34,35], and although gestational diabetes is associated with greater weight gain, particularly in early pregnancy [36], it is the weight gain that has the dominant effect on fetal growth [27,28]. In a randomised controlled trial of limiting gestational weight gain in obese women, the proportion of large-for-gestational age babies was reduced by 65% in the intervention group [37]. The same effects of gestational weight gain, independent of HbA_{1c}, are also seen in the pregnancies of women with type 1 and type 2 diabetes [38-40].

Thus maternal obesity and gestational weight gain are major risk factors for morbidities commonly attributed to mild GDM and important confounders to consider when assessing the impact of dysglycaemia. For example, when maternal BMI was taken into account in the HAPO cohort, the impact of maternal glycaemia on birth weight and caesarean section rates was substantially attenuated [41]. It is not clear from the intervention studies whether the between-group differences in birth weight and hypertension were primarily attributable to lower maternal blood glucose values or to lesser weight gain, since neither the ACHOIS nor MFMU studies reported between-group differences in achieved blood glucose measurements [15,16].

Is all gestational diabetes the same?

In the 1984 definition of GDM, all degrees of glucose intolerance in pregnancy were conflated into a single diagnostic entity, with the implication that the purported risks were similar across the spectrum of glucose intolerance. This is clearly not the case. At one end of this spectrum are women with previously unrecognised (mostly type 2) diabetes, who have rates of perinatal mortality and congenital malformation similar to those with known pre-existing diabetes [42-44]. The recent WHO and ADA guidelines have recently recognized this with their introduction of categories of “Diabetes in pregnancy” (WHO) or “Overt diabetes in pregnancy” (ADA) for women with a degree of hyperglycaemia in early pregnancy that would qualify as diabetes outside pregnancy [1,4].

In those with lesser degrees of glucose intolerance, perinatal mortality and congenital malformation rates do not differ from the general obstetric population [42-44]. Perinatal morbidity in the form of neonatal hypoglycaemia also shows a gradient of risk, being clearly increased only in the highest glycaemic band in the HAPO study [14]. At the lower end of the spectrum the risk is largely restricted to a somewhat greater birth weight - hence the disquiet about changing the diagnostic criteria to increase greatly the proportion of pregnancies diagnosed with GDM: all the new 'cases' would be at the very mildest end of the spectrum, where there is no proven benefit of intervention [45,46].

What are we trying to prevent?

Proponents of expanding the proportion of pregnancies diagnosed with and treated for GDM point to the reduction in shoulder dystocia and pregnancy-associated hypertension observed in the clinical trials [13,14]. Although these are potentially serious pregnancy complications, the population attributable risk of GDM is rarely addressed. The relative risks of shoulder dystocia and preeclampsia are indeed increased but >97% of deliveries complicated by shoulder dystocia occur in women without GDM [47], as do >95% of cases of preeclampsia [48]. As discussed above, both maternal obesity and excessive gestational weight gain are strongly associated with these outcomes and mildly elevated blood glucose levels may be only a minor player. Similar considerations apply to neonatal hypoglycaemia, which has many clinical associations not directly related to mild GDM, for example, preterm birth, small-for-gestational-age and large-for-gestational-age babies [49].

Reducing birth weight

GDM is a risk factor for macrosomia, but a large baby is not itself a disease or diagnosis, rather a risk factor for a number of adverse maternal and neonatal outcomes [50]. The maternal mortality and morbidity associations of macrosomia are in general more pronounced than the neonatal ones [50]. Thus one may view GDM as a risk factor for a risk factor, rather than a disease in its own right [45]. There may well be good reasons to reduce the incidence of large babies, but it would seem logical to look at all risk factors involved. In other branches of medicine such an approach is widely used. For example, when assessing the risk of cardiovascular disease we take into account age, blood pressure, diabetes and

smoking - not just the cholesterol level. Similarly, when assessing the risk of osteoporotic fracture we take into account age, falls, weight and previous fracture - not just the bone density measurement.

Such an integrated risk factor approach should consider, amongst other factors, the pre-pregnancy BMI, and strong recommendations and advice and support for all mothers to keep to recommended targets for weight gain in pregnancy [51], as well as testing for dysglycaemia in pregnancy.

Moving away from glucose?

Such an approach would be a shift away from the glucocentric view, but one that could lead us to think carefully about what we are trying to achieve and in whom, and not to exaggerate the importance of mild hyperglycaemia. Can we develop models that incorporate risk factors additional to glucose that better predict macrosomia and its associated adverse outcomes? Should treatment for GDM be targeted just to those with ultrasound evidence of impending macrosomia [52]? Are we really doing any good by lowering blood glucose, and introducing all the other interventions that go with a diagnosis of GDM, in women with mild hyperglycaemia whose fetuses are already growing slowly? There is an important research agenda here that will remain unexplored if researchers stay locked in to the existing GDM paradigm.

In the voluminous recent literature comparing GDM prevalence by various criteria, a common preoccupation is that 'cases' might be 'missed' unless the widest possible net is cast. What really matters, and is often missing from these papers, is information about the outcomes and risks, benefits and costs of the various approaches.

The next generation

The offspring of overweight parents commonly grow up to be overweight themselves. In much of the recent GDM literature there is a definite subtext, either implied or made explicit, that by detecting and treating GDM and reducing birth weight, obesity in children and adolescents can be prevented. There are a number of reasons to be sceptical about this inference. First, the original observations of the relationship between birth weight and the

later risk of obesity emphasised that low, not high, birth weight was the important risk factor [53]. Secondly, there is no sign that the rates of obesity or type 2 diabetes in young adults have been reduced in countries such as the USA, Canada, Australia and New Zealand, where screening for and treating GDM has been pursued the most enthusiastically over the past 30 years. Finally, if exposure to modest degrees of maternal hyperglycaemia was truly a significant driver of obesity and type 2 diabetes then the offspring of mothers with type 1 diabetes should be at particular risk– and there is no epidemiological data to suggest this is the case [54]. The studies that have focused closely on the relationship between childhood obesity and maternal glycaemia have rarely considered important confounding factors such as maternal and paternal BMI, family size and parental occupation [55] and so have tended to exaggerate the impact of GDM [54]. Again, future research examining the potential effects of GDM on the offspring needs to take a more holistic approach rather than remain narrowly focused on glucose.

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