REVIEW ARTICLE

Gestational diabetes

A window in the development of non-insulin-dependent diabetes mellitus

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Pregnancy has profound effects on maternal carbohydrate metabolism. In normal pregnancy fasting glucose declines to a nadir by 12 weeks which is sustained until term. Post-prandial glucose values are higher and peak later during pregnancy and have an attenuated fall to basal level.[1,2] Fasting and post-prandial insulin concentrations increase from about 20 weeks. Pregnancy therefore imposes a hyper-insulinaemic state, with more insulin being secreted for a given glucose load.[3] Insulin sensitivity, as measured by a variety of techniques,[4,5] declines by approximately 30 - 40% during pregnancy to levels equivalent to those in non-insulin-dependent diabetes mellitus.[6] For a woman to maintain normal glucose tolerance in pregnancy, there must be an adequate pancreatic beta-cell secretory reserve to overcome the pregnancy-related decline in insulin sensitivity.

Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance presenting during pregnancy; it is usual for GDM to abate after delivery.[7] A number of diagnostic criteria have been used to define GDM since its recognition by Bennewitz and its fuller description by Duncan, as reviewed by Hadden.[8] The chemical definition we apply is that recommended by the World Health Organisation. The diagnosis rests on the criterion for impaired glucose tolerance, i.e. 2-hour plasma glucose value after administration of 75 g glucose above 7.8 mmol/l.[9]

Some deny the existence of gestational diabetes as a specific clinical entity, considering that it is coincidental recognition of diabetes during pregnancy.[10,11] However, GDM has sufficient implications for pregnancy outcome and for the future health of the mother and child to regard it as a specific clinical problem.[12] GDM is a cause of large babies,[13,14] which are associated with an increased incidence of birth trauma and intervention.[15,16] Neonatal morbidity is increased with increased neonatal hypoglycaemia, hyperbilirubinaemia and polycythaemia.[17] An increased incidence of congenital anomalies has been reported.[18] However, this requires significant hyperglycaemia during organogenesis, and most cases of GDM occur after organogenesis is complete and when congenital anomalies no longer occur.[19] Perinatal mortality remains higher in pregnancies complicated with GDM, with an increased incidence of late intra-uterine deaths.[20]

It is increasingly apparent that GDM precedes the development of non-insulin-dependent diabetes mellitus (NIDDM) in the mother.[21-23] What is less certain is whether GDM increases susceptibility of the child to future development of NIDDM in later life, independently of any genetic influence. The strong familial associations of NIDDM imply that the child may inherit a genetic susceptibility to develop it. However, in addition to genetic factors, environmental factors in the form of the intra-uterine milieu also influence later development of NIDDM in the child.[24-26] Maternal hyperglycaemia during pregnancy predisposes to earlier presentation of diabetes in the child than if the mother develops diabetes subsequent to that pregnancy.[24,26] Recent work from the UK has shown that in an Europid population, small-for-date babies are at greater risk of developing diabetes or impaired glucose tolerance (IGT).[27,28] Animal work also supports these observations, as both experimentally induced intra-uterine growth retardation and maternal hyperglycaemia increase the incidence of diabetes in second and third generations in animals not otherwise at risk of diabetes.[29]

There are therefore several reasons to both identify and study gestational diabetes — firstly to improve the short-term outcome of the pregnancy, and secondly to study the development of NIDDM before overt biochemical changes have become established. Women who have had gestational diabetes also provide an unique opportunity to ascertain whether the natural history of NIDDM can be modified by changes in lifestyle.

The cause of NIDDM remains a subject of contention. The main arguments centre around whether the primary defect lies within the beta cell of the islet of Langerhans or in the sensitivity of the target tissues to insulin.[30-41] The major weakness of previous human studies addressing the causation of NIDDM has been that they were performed on subjects with established NIDDM, when hyperglycaemia and the other metabolic sequelae were already present. Glucose is itself a beta cell toxin[42] and disturbances of intermediary metabolism, e.g. raised free fatty acids, affect the action of insulin.[43,44] Reducing hyperglycaemia in NIDDM improves beta cell responsiveness.[45] Pro-insulin synthesis and pro-insulin conversion to insulin are stimulated by glucose metabolism;[46] in contrast, insulin release appears to be diminished by prolonged exposure to glucose.[47]

An additional problem has been the unreliability of previous insulin and pro-insulin assays, which were neither sufficiently sensitive nor specific.[48] In order to investigate the metabolic events that precede the development of NIDDM it is important to study subjects before hyperglycaemia and other metabolic sequelae become established.

The importance of gestational diabetes, apart from the obstetric consequences, is that these women will, over time, develop NIDDM. In our own follow-up study of 56 women investigated 6 - 12 years after a pregnancy complicated by gestational diabetes, 21 had developed diabetes, 13 had impaired glucose tolerance, and 17 were normal; 5 of the patients were pregnant again and had gestational diabetes.[49] By 12 years, therefore, only 30% of the original women still preserved normal glucose tolerance. Other studies have had similar findings.[23,50] In a follow-up study of 615 women, O'Sullivan[23] showed that after gestational diabetes there was a progressive accumulation of diabetes over 23 years, with earlier deterioration of glucose tolerance in obese individuals.

The reported incidence of gestational diabetes varies according to the diagnostic criteria used as well as the genetic susceptibility of the population under study. The incidences of GDM and NIDDM are similar, and are higher

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among non-Europid populations than among Europid populations.[51-53] The incidence of both NIDDM and GDM is increasing fastest among developing populations, probably owing to reduced physical activity and increased energy intake unmasking a previously unexpressed genetic susceptibility to diabetes.

The incidence and risk of developing gestational diabetes in our clinic in London, is highly dependent on ethnicity. The frequency among Europids is 0.4%, among people of Afro-Caribbean descent 1.5%, among Chinese 3.5%, among Asians (Indian subcontinent) 4.4% and among Arab/Mediterranean people 3.1%. Assuming a risk of 1 for the Europid group, women of Afro-Caribbean descent have a relative risk of 3.1, those of Arab/Mediterranean descent 5.9, Chinese 7.6, and those from the Indian subcontinent 11.3.[54]

Obesity, parity and maternal age[54] also influence the risk of developing GDM, but the effect varies according to ethnic group. Obesity influences the relative risk of GDM in ethnic Chinese less than in other groups. Increasing maternal age affects the risk of developing GDM only in women of Europid, Afro-Caribbean and Arab-Mediterranean descent, while increasing parity has its greatest influence on Chinese women. Extrapolating from these data, we suspect that the prevalence of GDM in South Africa, with its multi-ethnic mix, is underestimated. In addition the incidence is likely to rise with the adoption of a Western lifestyle.

Few hospitals have adopted universal screening policy for GDM on cost-benefit grounds, leaving most hospitals that do screen, screening only those women considered to be at risk. However, the recognised risk factors for GDM (previous GDM, baby > 4 100 g at birth, family history of diabetes, glycosuria)[55] do not address the influence of ethnicity, which in our clinic is the most important factor in determining overall risk for GDM. At St Mary's Hospital in London, where approximately 50% of the mothers are non-Europid, a universal screening policy is in place. All women attending the antenatal clinic at St Mary's Hospital are screened at 20 weeks with a 50 g oral glucose load in the non-fasting state. If the plasma glucose value at 1 hour is over 7.8 mmol/l, the patient automatically proceeds to a 75 g oral glucose tolerance test, interpreted according to WHO criteria. Women with an initial negative screening test but considered at high risk are retested at 28 weeks.

Not only do different ethnic groups have differences in the frequency of GDM, but there is evidence that there are metabolic differences between ethnic groups. Europid patients with gestational diabetes have low insulin and elevated pro-insulin concentrations.[56] In a separate study of 15 Europid gestational diabetics, intact pro-insulin concentrations were raised in comparison with an ethnic group-, age- and BMI-matched control population (I P Gray — unpublished data). The observation of raised pro-insulin concentrations in women with GDM is similar to that reported in subjects with impaired glucose tolerance (IGT)[57] and NIDDM.[48,58] Women with GDM who have high pro-insulin concentrations early in pregnancy are more likely to require insulin therapy later in pregnancy than women with lower pro-insulin values who can be controlled on diet alone.[59]

Europid patients studied within 1 - 3 years of pregnancy complicated by GDM have normal insulin sensitivity[60] as assessed by an insulin tolerance test,[61] and glucose production rates as estimated using (6.6-^{2}H)-glucose in an intravenous bolus technique[62,63] were similar to those in matched controls. In this study there was no significant difference in fasting glucose concentration or fasting insulin concentration. However, after a 75 g oral glucose load peak glucose levels were significantly higher and the total immunoreactive insulin response was significantly lower in the subjects with previous GDM.[60] These findings, while in agreement with studies on Japanese men,[64] contrast with studies of other ethnic groups studied before development of NIDDM. Studies on the Pima Indians,[39,65] a population greatly at risk of developing NIDDM, have shown abnormal insulin secretion to be present only when impaired glucose tolerance occurs, and not before.[66]

A study in which 20 Europid, 12 Afro-Caribbean and 10 Asian women who had previously had GDM were contrasted with 42 controls matched for age, body mass index and ethnicity has demonstrated differences in beta cell function within these ethnic groups.[67] Europid women had higher stimulated glucose concentrations after a 75 g glucose load and lower insulin responses than the normal controls. The women of Afro-Caribbean descent had glucose levels indistinguishable from the normal controls but significantly lower insulin levels. Beta cell dysfunction is thought to be the primary defect in NIDDM in South African blacks.[68] This suggests that impaired beta cell function is common to both ethnic groups at risk of developing diabetes. In contrast, the Asian women had higher fasting and stimulated glucose concentrations and higher insulin concentrations than the Europids with previous GDM. Other studies of Asian women including young Asian women living in South Africa,[69] have shown hyperinsulinaemia (albeit measured with nonspecific assays). First-degree relatives of Asian patients with NIDDM have insulin resistance, while relatives of Europids do not.[70] Thus the implication from our work and that of others is that women of Asian descent may behave differently metabolically from women of Europid or Afro-Caribbean descent. Asian subjects may be similar metabolically to the Pima Indians, in whom peripheral insensitivity to the action of insulin has been shown to be a more important contributor to NIDDM than impaired insulin secretion. Our data show in Europid and Afro-Caribbean women who are likely to develop NIDDM that there is a degree of insulin deficiency and hyperpro-insulinaemia, suggesting that the primary defect that precedes the development of NIDDM is more likely to be one affecting the beta cell.

We and others have shown that target tissue sensitivity to insulin is normal in women with previous GDM.[4,5,71] There is a large variation in insulin tissue sensitivity within glucose-tolerant individuals, which is influenced by both genetic and environmental factors.[5] An individual's glucose tolerance depends on a sufficient insulin secretory capacity to counter any change in insulin sensitivity. Pregnancy reduces insulin sensitivity in all women, but it is likely that GDM develops in those women whose beta cell reserve is insufficient to compensate for the physiological fall in insulin sensitivity. A woman with GDM can expect to remain glucose-tolerant after pregnancy provided that insulin sensitivity remains above the threshold for which her beta cells have reserves. However the future development of NIDDM is still likely, since an individual's insulin sensitivity and beta cell mass is not constant and insulin sensitivity will decline with increasing age, obesity, and decreased physical activity, while beta cell mass decreases with age and the influence of other factors.

Genetic and acquired influences determine beta cell mass and beta cell function, and both are likely to contribute to the development of NIDDM. Epidemiological studies on low-birth-weight infants,[27,72] supported by animal experiments,[29] strongly suggest that beta cell mass and the subsequent development of NIDDM can be influenced by intra-uterine events, independently of genetic factors. Animal work has also shown that insulin sensitivity is reduced when beta cell mass is sufficiently reduced *in utero,* implying that beta cell function as well as secretion can be influenced by acquired factors.[29] Although studies of concordance in identical twins and of first-degree relatives of patients with NIDDM strongly suggest genetic susceptibility,[73] a genetic cause remains elusive.[74] Linkage with genes or gene mutations have been identified in single pedigrees in both maturity-onset diabetes of the young and NIDDM, e.g. glucokinase[75,76] and adenosine deaminase gene.[77] In addition, single cases due to abnormalities of insulin, pro-insulin and the insulin receptor genes have been described.[74] None of these have been shown to be common to the majority of subjects with NIDDM, and it is naïve to assume that any single gene defect will be identified as the cause of NIDDM. What must not be overlooked is the fact that environment, both intra-uterine and after birth, is likely to be similar in twin and family studies. In addition, inheritance of a genetic susceptibility does not inevitably lead to development of the disease phenotype and requires interaction of environmental factors for expression. This is clearly demonstrated by the 10-fold increase, within a generation, in the prevalence of NIDDM in Nauruans, which has coincided with increased obesity, decreased exercise and the adoption of a Western lifestyle.[78]

Gestational diabetes is a clinical event with consequences for the mother and her child. Good obstetric management during pregnancy may minimise the immediate complications of pregnancy outcome. However, since the mother with GDM is at greatly increased risk of significant morbidity in the future, gestational diabetes provides us with an important health challenge — can health education hinder progression to NIDDM in these women? On theoretical grounds modification of lifestyle may attenuate the disease process, delaying or even preventing overt clinical diabetes. It is encouraging to note that lifestyle modification has proved successful in the reduction of cardiovascular disease in the USA[79] and has lowered the incidence of carcinoma of the lung in responsive groups. Recent studies from Tanzania[80] and from Sweden[81] have shown that lifestyle modification in the form of exercise has beneficial effects on glucose tolerance. Our own work has shown that dietary modification improves beta cell function.[82] Modification of maternal diet may in addition, have a beneficial effect on the intra-uterine milieu and thus subsequent susceptibility of the child to the later development of NIDDM.

Early recognition of gestational diabetes should provide us with an unique opportunity to lessen NIDDM and cardiovascular disease in the future.

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