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Clinical controversy

Diabetes in pregnancy 1985

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The art of obstetrics is not a subject which is often discussed in the pages of *Diabetologia*. However, as the care of the diabetic mother and her offspring is rightly an interdisciplinary responsibility between obstetrician, diabetologist and neonatologist, it is important that each has a close understanding of the various problems. Dr. M. I. Drury (Dublin), speaking as an internist, raises a question on the optimum time and method of delivery of the baby; this has more than purely obstetrical implications. Drs. L. Mølsted-Pedersen (Copenhagen) and C. Kühl (Copenhagen and Klampenborg), obstetrician and internist from the longest-established joint obstetric/diabetic service in the world, present a Scandinavian view on the management of pregnancy. Both centres have distinguished records in the management of diabetic pregnancy. The different viewpoints in Denmark and in Ireland are clear - in Copenhagen, therapeutic abortion is practiced in a pregnancy at risk of severe congenital malformation; in Dublin it is not. Dr. Drury quotes a perinatal loss of 13 of 285 pregnancies (4.5%) in the past 5 years, but does not include the recognised spontaneous abortions which, on his overall figures, are about 10% of conceptions. Dr. Mølsted-Pedersen reports a perinatal loss of 3 of 201 infants (1.5%), excluding 17 spontaneous and 9 induced abortions. If these 9 aborted pregnancies, which were performed due to a risk of severe congenital malformation, were included as fatalities, the Copenhagen figure would be 12 of 210 (5.5%). Of course, we do not know if all those 9 fetuses were affected. The spontaneous abortion rate was 17 of 223 (8.0%). Thus, if total fetal loss is taken as the index, there appears to be little difference between the two centres. The clinical controversy on the timing and method of birth in the different centres will continue - pundits can be conservative as well as radical, and, as Dr. Drury remarks, the truth probably lies somewhere in between.

The bottom line in reports on the management of diabetes in pregnancy used to be the perinatal mortality (from 28 weeks gestation to the end of the first week of life). With the continuing improvement in neonatal care, more babies who would have died during the perinatal period are surviving beyond the seventh day of life. As a result, their subsequent deaths are not recorded in many publications. Even greater emphasis will fall on the quality of life for those infants surviving with a major congenital abnormality (heart and neural tube defect) which produces profound childhood morbidity. Prevention of these congenital abnormalities is the most important aim of pre- and early conceptional care of the diabetic mother. Both centres which report their recent results in this issue would agree that there has been an improvement even in the past 5 years - the problem is to define exactly which developments account for the change for the better, and which previously-trusted techniques can safely be allowed to fall by the wayside.

Key words: Diabetes in pregnancy, perinatal loss, total fetal loss.

There have been at least eight books published in the past 10 years on diabetes in pregnancy. Seven of these are the proceedings of conferences, and are, therefore, diffuse and multicentred in outlook. One, the second edition of the late Jorgen Pedersen's "The Pregnant Diabetic and her Offspring" [1], while the basic reference to the whole subject, was first conceived in 1965 and does not always represent modern practice. Because of the four main disciplines involved in the field of diabetic pregnancy - obstetrics, paediatrics, internal medicine and experimental animal models, each of which has the opportunity to publish in journals not often seen by the others - it is difficult to obtain a comprehensive view of the field from the aspect of an interested clinical scientist. This review will be selective rather than comprehensive, will try to point out the problems rather than dwell on the successes and will adopt an international and trans-speciality approach [2-8].

Delivery of health care

There are now many reports from centres specialising in the care of diabetic pregnancy which show that the expectation of a live normal baby is very much greater

than it was even 10 years ago [9–12]. Concern exists that these centres of excellence may not represent the clinical practice in all areas, and the next stage of the process is to ascertain the outcome of diabetic pregnancy at national levels. While this might be possible in a country with a suitable central organization or where a national registry of diabetic patients exists, as in Denmark, it is virtually impossible elsewhere. In particular, in countries with a tradition of independent or private practice both for diabetes care and for obstetrical management, it is difficult for some of the concepts implicit in the team approach to be adopted. As the good news spreads among our patients, it is likely that some further adjustments in clinical practice will be needed. There is no doubt that close proximity of the obstetrician, diabetologist and neonatologist is most desirable. As the maternity clinic will be the scene of action from the mother's point of view, it is normally best for the diabetes supervision to take place there with a joint diabetes/antenatal team [13]. There is evidence from Denmark [14] that the fetal malformation rate was significantly higher for diabetic mothers who had not been controlled at a diabetes centre before the onset of pregnancy, which is consistent with the fact that most women do not seek medical attention for pregnancy until after the critical period of organogenesis [15].

In the United Kingdom, a confidential enquiry into the outcome of babies born to diabetic mothers during 1979–80 was carried out by the Royal College of Obstetricians and Gynaecologists. Although 188 hospitals participated and notifications were received for 773 mothers with established diabetes, it is still uncertain how complete an ascertainment was achieved [16]. Full details of this study have not yet been published, but the concepts that perinatal mortality decreased with increasing gestational age of the infant and decreasing mean maternal third trimester blood glucose were confirmed. The very poor control of maternal blood glucose achieved in the relatively small number of mothers who had sufficient data in the first trimester emphasises the need for better and earlier communication between the potential mother and her physician [17].

A problem with many long-term obstetrical reviews of clinical practice arises from the epidemiological definition of "perinatal death". Traditionally, this was a useful index of obstetrical results and included all losses of viable fetuses (28 weeks to delivery) and all deaths of live born babies in the first week of life. With improved neonatal intensive care facilities, many babies born before 28 weeks now survive, and some seriously deformed or very premature babies who would previously not have lived for a week are maintained under intensive care only to die some weeks later. A very low perinatal death rate will also conceal the number of pregnancies which were terminated. In the future, for a specific problem such as pregnancy in diabetes, the total conceptions, total fetal loss and neonatal deaths in the first year should be recorded.

Internal medical aspects

From the point of view of the physician responsible for diabetes care there are three main issues – attendance, monitoring and insulin administration. A formal pre-pregnancy interview at a joint antenatal/obstetric clinic is unlikely to achieve the desired aim except in highly motivated patients. Much more important is the constant awareness of the possibility of pregnancy and the ability to discuss this at routine diabetic clinic attendance. The logic of pre-pregnancy counselling was first pointed out by Steel et al. [18], and the need for this to take place more or less continuously in those who are actively trying to achieve pregnancy is now established [19–21]. A suitable pamphlet explaining the idea and the reasons behind it is a useful adjunct, especially in a large diabetic clinic where the patient may not always be seen by the same physician. It would seem important to aim for blood sugar control or glycosylated haemoglobin values within the normal range before conception, but even with the best motivation this goal may be difficult to achieve.

Self-monitoring of capillary blood glucose is now a well-established patient-oriented technique. Although there may be discussion as to the frequency and times of measurement, and as to which strip and meter to use, there is really no debate on the improvement of the quality of care for diabetes which has followed. This is not to say that good compliance is not possible in some patients even with simple urine testing [22], but to emphasise that the special motivation that occurs during, and hopefully before pregnancy, demands the reassurance and flexibility that only immediate knowledge of the blood glucose value can provide. The cost of the glucose oxidase impregnated strips, however, whether paid for by a national health service, health insurance scheme or individually by the patient herself must surely be reduced with the increased demand.

The Stockholm group [23] have carried out a prospective randomised multicentre study between 1979 and 1982 with patients assigned to alternative treatment groups: either hospitalisation from week 32 to delivery, or self monitoring from weeks 32 to 36 with hospital admission at week 37. The incidence of neonatal complications was not much different between the two groups, and neither was the degree of maternal blood glucose control or evidence of fetal hyperinsulinism. This accords with the experience in Nottingham [24], where it was found that the cost of meters and strips was repaid many times over in the saving of hospital costs, to say nothing of patient popularity.

The perfect system of insulin administration for diabetic patients does not yet exist. Twice daily mixtures of short and medium-acting insulins are now widely used, and often achieve satisfactory control with careful self-monitoring and patient adjustment of the insulin dose. That the dose will need to be increased as pregnancy proceeds is well worth emphasising at an early stage.

This practical problem of blood glucose control in pregnancy, with an increased hypoglycaemic tendency in the first trimester and increased insulin resistance in the third trimester, may often be approached by splitting the usual evening dose of short and intermediate-acting insulin and giving most of the intermediate-acting dose with the late night snack. The concept of 'maximal tolerated insulin dose' which was introduced by Roversi [25] over 20 years ago did much to encourage the more enthusiastic use of insulin, and in particular demonstrated the often very considerable increase in insulin dose needed in the pregnant diabetic mother to achieve normoglycaemia. The ability to self-monitor blood glucose has simply improved the ability to demonstrate normal glucose values. The use of subcutaneous glucagon for severe hypoglycaemia in early pregnancy has been shown to be effective and safe. Measurement of postprandial as well as preprandial capillary glucose will demonstrate the post-breakfast peak, which may require more attention if true normoglycaemia is to be achieved.

Continuous subcutaneous infusion of insulin by an external pump is now well-established and can be used throughout pregnancy. There do not appear to be any particular advantages or disadvantages related to the pregnancy; but it is interesting how often the mother is inclined to "deliver the pump with the baby" and revert to insulin by injection post-partum. The theoretical rationale for the use of the recently-introduced human insulin preparations depends on the possible adverse effects of transplacental passage of maternal anti-insulin antibodies to the fetus [26]. Until more is known, both of the antigenic potential of the human insulin preparations and of the immunological role of maternal antibodies in the fetus, it is not possible to make a definitive statement. Human insulin of recombinant DNA origin given during pregnancy has been shown to produce antibodies which were also detectable in the fetal circulation, although they were not associated with any effect on neonatal metabolism [27].

Obstetrical aspects

The art of obstetrics is learned at the bedside, and there is surprisingly little documentation of different practices in diabetic pregnancy in contrast to the voluminous literature on research and investigational aspects. Gillmer [28] has encapsulated some of the basic precepts of the past 50 years, and gives good evidence that the rigid management protocols embodied in recent standard obstetrical textbooks [29, 30] may soon be altered. Admission at 32–34 weeks, with routine amniocentesis and delivery at 37–38 weeks was introduced at a time when maternal blood glucose control was poor and there was a real risk of unexpected intrauterine death in the last month of pregnancy. New editions of textbooks will take note of these changes.

The influence of self-monitoring of capillary blood glucose has already been discussed. More than any other factor, this has made possible delayed hospital admission. There is no theoretical reason why a perfectly-controlled diabetic mother with no other obstetric complication, in whom routine pregnancy monitoring is satisfactory, should not be managed as for any other normal pregnancy. Understandably, obstetricians are reluctant to change a well-tried protocol, and there is still sufficient concern overall to allow individual opinion based on experience to override a doctrinaire approach. Admission to the hospital merely to allow daily fetal monitoring in late pregnancy may not be necessary.

Early booking and dating of the pregnancy is important. There is now widespread confidence in the use of ultrasound for fetal assessment, and no evidence of harm even to the fetus of the diabetic mother, which is already at risk for early embryological abnormality. Ultrasound measurement of the biparietal fetal skull diameter will allow an accurate gestational age and will also demonstrate major skeletal or other malformations. There is still some doubt about the reliability of crown-rump measurements [31], which may reflect early growth delay in some diabetic pregnancies, or may simply reflect the difficulty of true dating of the conceptus at these early stages. Routine antenatal care every two weeks, which is also needed for close supervision of blood glucose, is generally advised. Simple ultrasound measurements of fetal growth may be helpful. Measurement of urinary oestriol and plasma human placental lactogen to assess placental function has been discarded. Admission in late pregnancy would thus depend on other obstetrical complications.

Measurements of insulin, proinsulin and C-peptide in amniotic fluid sampled during the third trimester have been reported [32]. These products are thought to be solely of fetal origin, reaching the amniotic fluid via fetal urine. They were all present in considerably increased amount in diabetic pregnancy, suggesting increased fetal B-cell activity. There was some suggestion that C-peptide concentration was even higher in those pregnancies associated with neonatal morbidity, but this may simply reflect the effect of inadequate maternal blood glucose control earlier in the pregnancy. It does not seem likely that this measurement will be a useful guide to management.

The timing and mode of delivery is also not as rigid as previously. Beard [33] suggested that the practice of premature delivery might have caused more problems than it solved, particularly fetal prematurity and failed induction of labour. Drury [34] has shown that in Dublin it is often possible to follow a policy of allowing pregnancy to proceed to full term (40 weeks), which allows many mothers to go into spontaneous labour and deliver vaginally, and a similar policy in Cleveland, Ohio, USA [35] has also been successful. Amniocentesis may therefore only be necessary for those pregnancies

where delivery is deemed necessary before 38 weeks, or the dates are unreliable. If so, the phosphatidyl glycerol level provides a better index of fetal lung maturity than the lecethin-sphingomyelin ratio in diabetic pregnancy [36]. The fear of intrapartum trauma consequent on macrosomia, with shoulder dystocia, will still indicate the need for Caesarean section when cephalopelvic disproportion is suspected from ultrasound or other techniques [37]. Intrapartum management of diabetes either for vaginal or operative delivery is considerably facilitated by monitoring of capillary blood glucose in the labour suite [28]. There is now a greater enthusiasm for normal vaginal delivery at term both from obstetrician and patient, and this concept, which may have become possible because of better blood glucose control by the internist, will certainly find favour with the neonatologist (see Clinical Controversy in this issue).

In spite of the best efforts of the diabetologist to present his or her obstetrical colleague with a normoglycaemic diabetic mother at the first obstetric consultation, there are other factors over which he has less immediate control. The presence of complications - retinal, vascular, renal - of long-term diabetes has always been recognised to increase the obstetric risk. However, better treatment for these complications is also available. The prevalence of diabetic retinopathy in pregnancy has variously been reported at between 27% and 10% in the past five years. The availability of laser photocoagulation therapy has made it difficult further to test the hypothesis that the retinopathy is worsened by the pregnancy, but there is no doubt that progression may occur and that frequent ophthalmic assessment and treatment may be needed [38]. The good visual results of this treatment mean that retinopathy alone, even in a proliferative phase, is not an indication for termination of pregnancy, although it certainly remains a significant fetal risk factor. Diabetic nephropathy is still a serious pregnancy complication, with a major risk of associated hypertension [39]; evidence exists that patients with severe renal failure should be carefully counselled and aided in the avoidance of pregnancy. However, renal transplantation in this situation is both feasible and has been followed by successful pregnancy [40].

It is customary in textbooks on obstetrics to discuss diabetic pregnancy from two standpoints - the effect of the diabetes on the pregnancy and the effect of the pregnancy on the diabetes. This former has tended to occupy the main body of this review, but the disastrous effect of becoming pregnant on the mother before insulin treatment must not be forgotten and must still represent a real risk in third world countries. Maternal mortality in western countries is now rare, but real morbidity related to diabetes complications (retinal, renal and myocardial) still exists. This may even become more common with the increasing possibility of successful pregnancy in women who have severe complications.

The White classification (Classes A, B, C, D, F) has achieved an almost hallowed acceptance among obstetricians, but it must be pointed out that it is less than satisfactory from an epidemiological viewpoint [41]. In particular, it does not distinguish between the age of the mother and the duration of her diabetes, and the additional classes (F, R) for mothers with specific complications disregard both age and duration of diabetes. Class A is defined only by the absence of insulin treatment, but does not relate to any recognised diagnostic criterion for diabetes. Although in its simplest form it is of clinical help in denoting grades of obstetrical risk, as recognition of retinal, renal and vascular complications become more sophisticated the whole classification will become redundant. It would be more useful if an accepted system to indicate the level of blood glucose control before and during the pregnancy were established and the well-recognised obstetrical risks of increased age, renal disease and hypertension were considered at the antenatal clinic in the normal manner. A simple classification for duration of diabetes is: (1) impaired glucose tolerance; (2) Type 1 diabetes duration less than 10 years; (3) Type 1 diabetes 10–19 years; (4) Type 1 diabetes 20 years or more.

Neonatal and paediatric aspects

The neonatal paediatrician must be an integral part of the team approach to caring for the diabetic pregnancy, and yet if all went according to plan from the diabetes control and obstetric viewpoints, his function should not be different from that of supervising a well baby. Nevertheless, the pattern of neonatal morbidity is less severe than it used to be [23], and the problems arise due to prematurely born infants. The premature low birthweight baby, or the severely growth-retarded, or the growth-accelerated baby each have various types of neonatal complications. New non-invasive techniques which allow monitoring of vital functions inside an incubator, including transcutaneous measurement of blood gases and bilirubin, cardiac and cerebral monitoring, transfontanelle pressure recording, as well as simple body and skin temperature, and heart and respiration rates, have been developed.

The detection of neonatal hypoglycaemia has always been of interest, although routine glucose treatment of short term (less than 4 h) plasma glucose levels less than 2.0 mmol/l is no longer practiced. Early and more frequent high calorie low birthweight formula feeds should suffice [42] but are not always possible, even in relatively well-staffed units. The reasonable desire to reunite mother and child as quickly as possible would meet with universal approval. Better antenatal and intrapartum control of maternal blood glucose, which many would ascribe in large part to the means of frequent self-monitoring by the mother or her attendants, must play a large part in the improved neonatal outlook for full-term infants. The pathophysiological arguments [43, 44] about the exact mechanism of the hypoglycaemia and how best to treat it have become less

important. One new aspect of the disordered growth pattern of the fetus of the hyperglycaemic diabetic mother is the recognition of fetal cardiomyopathy which may require cardiogenic therapy on delivery [45]. The concept of fetal medicine should serve to allow greater co-operation between the neonatologist and the maternal antenatal team. Closer analysis of the relation between pregnancy duration, maternal diabetes duration, vascular complications and blood glucose control, and the degree of fetal hypoglycaemia and hyperinsulinaemia is still necessary.

With the welcome return to breast feeding comes the rediscovery of the increased glucose content of the breast milk during uncontrolled maternal hyperglycaemia. Perhaps of greater importance is the suggestion that there might be a retarded brain growth and subsequent lower intelligence in children whose diabetic mothers had poor blood glucose control or even episodes of ketacidosis. Careful study of the very large US Collaborative Perinatal Project data with respect to diabetic pregnancies showed that lower intelligence quotient (IQ) values at age four years were found when the mother was ketotic during the pregnancy, but that this was more likely due to complications or associated amniotic fluid infection than to ketosis alone [46]. In a controlled study of 123 children of diabetic mothers, all delivered before 38 weeks, no difference was found at paediatric assessment or by a psychologically-based maternal and teacher questionnaire of emotional state and academic achievement [47]. This finding is supported by other studies of the intellectual ability of children born to non-diabetic high-risk pregnancies [48]. Finally, in the genetically and environmentally unique Pima Indian tribe, it is possible to demonstrate that the hyperglycaemic prenatal environment of the offspring of diabetic women results in the later development of childhood obesity, which may be one reason for the perpetuation of the diabetic trait in this population isolate [49].

Fetal abnormalities

The definitive clinical observations on the increased incidence of congenital fetal malformations in diabetic pregnancy were not made until 1964 by Mølsted-Pedersen, Tygstrup and Pedersen [50]. This relatively delayed recognition of what is today the major residual clinical problem in this field must have been due to the overriding effects of the many other difficulties faced by the pregnant diabetic woman up to that time. These observations were fully confirmed in many centres, both retrospectively [51–55] and prospectively [56]. Epidemiological objections [57] to the different groups analysed retrospectively as normal or "control" populations do not overcome the increasing recognition by clinicians that, in spite of the many improvements in obstetrical and neonatal care, very little progress has been made in reducing the risk of a fetal abnormality. Experimental work (see below) has suggested that the responsibility for this risk must rest with those caring for the mothers' blood glucose control before and at the time of conception and during the very early weeks of gestation.

The epidemiological approach to this problem is difficult because of the considerable differences in both mortality and morbidity from congenital malformations in different countries [58, 59]. The WHO reports show that recorded overall mortality from spina bifida and hydrocephalus, the commonest neural tube defect, varies from less than 1 per 100,000 births in Scandanavian countries to over 50 per 100,000 in the United Kingdom, with the USA and other European countries intermediate. The data for total morbidity, although even less complete [60], shows a variation within Europe from 45 per 100,000 births in Denmark to over 250 per 100,000 in Northern Ireland. It is clear that these international differences do not closely reflect the prevalance of maternal diabetes in those countries. The mortality data for congenital heart abnormalities, however, shows surprisingly little difference between the same countries. Other potential sources of bias include the likelihood that in centres specialising in diabetic pregnancy, the degree of ascertainment of anomalies in the children of diabetic mothers will be greater than in those of non-diabetic mothers. The definition of congenital malformation used in the diabetic studies has usually been that of Mølsted-Pedersen et al. [50], as structural abnormalities present at birth and recognisable by external examination or by X-ray studies when clinically indicated before the 10th day of life. Malins [54] has drawn attention to the fact that very few published series indicate the extent to which termination of pregnancy has been permitted, encouraged or firmly advised. Exclusion of unpromising pregnancies of women with severe diabetic complications or a previous fetal abnormality would falsely reduce the true incidence of fetal abnormalities.

There is good evidence from the epidemiological approach that the offspring of diabetic fathers do not carry a greater risk of congenital abnormalities [61]. Combined with the similar evidence that there is no increased risk during a pregnancy occurring in a woman before the onset of diabetes, this eliminates the possibility that the problem is simply a consequence of genetic determinants linked to diabetes-related genes.

There is now a considerable amount of experimental data which supports the clinical evidence of an association between maternal diabetes and fetal malformations. This has been fully reviewed [62, 63], and allows some further exploration of the mechanisms involved. The fear that some earlier techniques, where diabetes was induced in experimental mice or rats by alloxan or streptozotocin, would be confounded by a possible teratogenic effect of the drug given during the pregnancy has been removed by the demonstration that the effect is still seen when streptozotocin is given at least 2 weeks

before conception. Further, malformations were virtually eliminated by insulin administration to the severely diabetic animals [64].

When insulin administration was interrupted in early gestation, skeletal malformations became more prevalent, and the effect was not seen if insulin was withdrawn after day 8 of the 21-day rat gestation [65]. In animal work, as in human experience, it is always difficult to completely exclude the effect of heredity, and the Uppsala have recognised that, when their strain of Sprague-Dawley rats was temporarily outbred with Hannover rats, their usually steady rate of 15–20% severe skeletal abnormalities in the offspring of diabetic mothers dropped to zero, in spite of equally severe maternal hyperglycaemia [63].

In vitro rodent embryo culture systems have also been developed, using either serum from diabetic animals or media with excess added glucose [66, 67]. These studies have confirmed that severe malformations can be caused merely by increasing the glucose concentration of the culture medium [68, 69]. The chick egg is also malformation-sensitive to glucose and several other sugars during early incubation [70]. Insulin-induced hypoglycaemia may also produce malformations in the chick embryo, and this effect has been shown in early embryogenesis in the rabbit [62]. The lethal effects of D-mannose in the honeybee have been known for over 50 years, and Freinkel et al. [71] have shown in culture of nine and a half day rat embryos that D-mannose will cause the growth retardation and faulty neural tube closure associated with inhibition of glycolysis. This model shows the metabolic vulnerability during early organogenesis and may explain the teratogenesis of other seemingly unrelated agents, such as trace element aberations, at the same stage.

Given the epidemiological and experimental evidence, there is little doubt that the main therapeutic thrust in the prevention of congenital fetal abnormalities in human diabetic pregnancy must centre on achieving normal maternal plasma glucose during the very early stages of embryogenesis. Whether other metabolites are also deranged and need separate attention is not proven, but it would seem wise not to be deficient in trace elements nor to be exposed to other possible teratogens. The introduction of measures of glycosylation of haemoglobin or other proteins has allowed retrospective study of mean plasma glucose levels at the crucial stage. Several groups have shown that increased glycosylated haemoglobin, when measured during the first trimester, is associated with an increased risk of fetal abnormality [72, 73]. The converse, that a normal level of plasma glucose and of glycosylated haemoglobin throughout early pregnancy will abolish the risk of congenital abnormality, is more difficult to prove [21]. Other factors such as better nutrition, improved social circumstances, and recognition of the risks of smoking and of alcohol must play a part. Skyler [26] states dogmatically that the advent of patient self-monitoring of plasma glucose has made the desired metabolic normality feasible and practical, but Tattersall and his colleagues [24], during 7 years experience of home monitoring in diabetic pregnancy, were unable to prevent the occurrence of three serious congenital abnormalities in 58 pregnancies. They recognised that completely normal mean blood glucose levels were not achieved in any trimester or at any time of the day, but the mean haemoglobin A, did fall into their normal range (5.5–8.5%) in the second and third trimesters.

Gestational diabetes

The first case of temporary diabetes in pregnancy to be recorded was probably that of Bennewitz, reported in the Edinburgh Medical Journal in 1828, but originally published in Berlin in 1823–25. A stout young woman, aged 22, in her fifth pregnancy, produced a premature stillborn child weighing 12 lbs (5.5 kg). There was good evidence from careful urinalysis during pregnancy of large amounts of saccharine matter in the urine, which disappeared postpartum. Diabetes occurred in her fourth, fifth and sixth pregnancies, but disappeared after each. This case is recorded among 15 pregnancies with diabetes collected by Matthews Duncan [74], and is one of only five of those mothers who survived the pregnancy. At the meeting of the Obstetrical Society of London in 1882 there was disagreement amongst the participants about the prevalence of puerperal diabetes, about the significance of screening all mothers for glycosuria, and whether any special rules of treatment could be laid down. Over 100 years later, there is still disagreement on these points. In the past five years there have been three international meetings specifically directed to gestational diabetes [75–77], and the subject has been fully discussed on many other occasions. It is the opinion of the present reviewer that the difficulty in reaching a simple agreed position on definition, diagnosis and screening arises from two distinct aspects of the subject. Firstly, there may very well be a difference in the disorder between different populations with different genetic, nutritional and environmental backgrounds in different countries, and there have been no useful comparisons between such populations using standard criteria [58]. Secondly, there is a legitimate difference in outlook between the obstetrician who tends to adopt an interventionist policy in the belief that the fetuses of mothers with this condition are at risk of dying in utero [78], and the epidemiologist who reflects that the condition might almost be abolished if the diagnostic criteria were reset at a slightly higher level [79].

Given such an apparently muddy and intractable field, there is a tendency to look for consistent and well-founded stepping stones. The series of reports by O'Sullivan [80], who used a well-defined simple 50 g glucose loading test during pregnancy followed by another more formal 100 g glucose tolerance test when the first

test was judged abnormal, now extend over 20 years. The O'Sullivan criteria, based on an unselected population of 752 South Boston mothers attending the Boston City Hospital over a 4-month period in 1961, produced 2% defined as gestational diabetes. These criteria, applied to a different group of South Boston mothers selected between 1954 and 1960 by a multiple clinical and post-glucose load screening procedure, produced the group of 615 mothers on which the O'Sullivan study is founded. These gestational diabetic mothers had a perinatal loss rate of 4–5%, which was greater than the 2% perinatal mortality of a control population of mothers with normal glucose tolerance. Insulin treatment of half of the gestational diabetic mothers did not reduce the perinatal mortality, but did significantly reduce the number of large babies. These figures are recalled, as this aspect of the Boston study is of interest to the obstetrician and must be compared to the more recent evidence from several centres - Copenhagen [81], Aberdeen [82], Belfast [83], London [84] and others that there is not an increased perinatal mortality with simple recognition of the condition, and if dietary advice is offered without intensive antenatal or intrapartum supervision. The South Boston population 30 years ago may not be epidemiologically different from present-day similar populations in other U.S. cities, and the O'Sullivan data may well still be applicable to them. The current European experience appears to be better, although there is no doubt that perinatal mortality reflects general obstetrical care and improvement in all parts of the world.

There is some academic vested interest in exactly which criteria are adopted to define abnormal carbohydrate metabolism in pregnancy. From the short term point of view of the pregnant mother and her baby, it would seem that good antenatal care must exclude the possibility of gestational diabetes; the risk of this condition, however, apart from a degree of fetal macrosomia, is low. Various authorities have tried to reconcile the different standards proposed [58, 85]. The European viewpoint is probably more in favour of the 75 g oral glucose tolerance test, and co-operative studies in progress should produce an unselected baseline from which to define the appropriate (95th centile?) cut-off points for this test in pregnancy.

The main strength of the O'Sullivan study relates not to its obstetrical use, but to the predictive value for subsequent diabetes in the mother. As an epidemiological observation this is beyond the immediate scope of a discussion of diabetes in pregnancy, and its value will have to be measured against that of screening populations for carbohydrate intolerance as a risk factor for mortality or morbidity from ischaemic heart disease or other causes. It must be observed that plasma glucose is a relatively low risk factor in this situation, but to be at the extreme upper end of any biological distribution is probably not to be recommended.

The population of 917 unselected mothers studied in Aberdeen in 1980 [82] forms what is undoubtedly the most careful prospective study of carbohydrate intolerance in pregnancy. Unfortunately, the 25 g intravenous glucose tolerance test was used, which has certain advantages of interpretation and procedure but has not been adopted elsewhere. From this statistically powerful study, there is an undoubted relation between maternal glucose tolerance and baby size, and also with the risk of congenital abnormality. However, the authors felt that the relationships were too weak to justify the routine screening of all pregnant women by this method. For the biologically unusual Pima Indian tribe [86], there is also good statistical evidence that mothers not previously known to have diabetes, diagnosed by the 75 g oral glucose tolerance test in pregnancy, had a higher rate of perinatal mortality and macrosomia but not of congenital malformation.

The practical problem of how to screen unselected pregnant women for possible gestational diabetes remains unresolved. Glycosuria and other clinical criteria are inaccurate. A full glucose tolerance test, by whatever protocol, is tedious and expensive if carried out on all mothers, and the returns are uncertain. The question now turns on whether an untimed plasma or capillary glucose value at antenatal visits [17], or a value adjusted for the last known meal [87], or, alternatively, a routine 50 g glucose load with a single blood glucose one hour later [80], will be effective in directing a small subgroup of mothers to have a full oral glucose tolerance test. European experience points towards one of the former random tests for hyperglycaemia. In the United States, preference remains for a true screening test of carbohydrate intolerance which necessitates a glucose load. The matter was fully debated at the second Chicago workshop-conference [77], of which the carefully considered summary and recommendations represents the present "state of the art".

To return to the historical viewpoint, there is still no doubt that acute diabetes mellitus can present itself during pregnancy, and that it will require insulin treatment. This situation is different from the more common occurrence of glucose intolerance which may be managed by control of excess energy intake. Whether these two conditions represent Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes mellitus will require further study. The challenge remains to use the experiment of nature in producing the stress of pregnancy on carbohydrate metabolism as a means of preventing the expression of diabetes as a disease in later life.

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