Review Articles

Is Gestational Diabetes a Clinical Entity?

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Summary. Gestational diabetes is a clinical entity associated with a significant incidence in diabetes in the later life of the mother and increase in fetal and neonatal morbidity. Lack of agreement on diagnostic criteria and the methodology of glucose tolerance testing has led to inconsistency in the results of

published studies. It is recommended that all women should be screened for carbohydrate intolerance in pregnancy.

Key words: Gestational diabetes, malformations, perinatal mortality, morbidity, macrosomia, incipient diabetes.

No-one would dispute the fact that pre-existing diabetes is of considerable clinical importance in pregnancy. The increase in insulin requirement with advancing pregnancy, difficulty in achieving good diabetic control, and the greater risk of stillbirth and neonatal death are just a few of the problems for mothers with this condition. But can the same be said for gestational diabetes? Undoubtedly there are two widely differing points of view. On the one hand, many regard gestational diabetes as a temporary and usually mild disturbance of metabolism that does not justify the anxiety evoked in the mother by being labelled a diabetic, while on the other hand, there are those who advocate universal screening of all pregnant women to detect any abnormality of carbohydrate tolerance. Obstetricians usually subscribe to the latter view, tending to adopt an interventionist delivery policy in the belief that the fetus of mothers with this condition are at risk of dying in utero. Both views have a certain validity but the literature on the subject is conflicting and needs to be reviewed if anything like a rational approach to the management of the condition is to evolve.

Certain questions about gestational diabetes need to be answered: [1] Exactly what do we mean by gestational diabetes? [2] Once this has been established, what is the incidence? [3] Can the condition be shown to have an adverse effect on the baby in the short and long term? [4] Is there an increased risk of permanent diabetes in the long term and if so, is there any way of diminishing this risk?

Definition of Gestational Diabetes

The literature is crowded with studies which defy comparison with each other because of the different interpretations of what is meant by the term gestational diabetes. A recent symposium on gestational diabetes in 1979, jointly sponsored by the American College of Obstetricians and Gynaecologists and the National Institutes of Health, clearly demonstrated major drawbacks inherent in the lack of comparable studies. Some would insist that for a diagnosis of gestational diabetes to be made, not only must the condition be first detected in pregnancy but that carbohydrate tolerance must return to normal after pregnancy [1], yet most studies have not included systematic testing in the postnatal period in their protocol. An alternative approach is the classification introduced by White [2] in 1965 with diabetic mothers grouped according to the severity and duration of the disease. This has enabled a relationship to be demonstrated between the class into which the mother falls and fetal and neonatal outcome [3]. The majority of gestational diabetic patients fall into Class A (chemical diabetes treated with diet and/or oral hypoglycaemic agents). However, confusion has arisen in the application of the White classification as knowledge about the effect of mild diabetes on the baby has increased. For example, it is now becoming increasingly common usage for Class A to be subdivided into fasting normoglycae-

mia (A) and fasting hyperglycaemia (A1) because of the different prognosis in the two groups [4, 5]. Pedersen [3] and his group have used an alternative modification by limiting Class A to women treated with diet alone and transferring those treated with insulin to Class B [3] with the result that Class A contains the milder gestational diabetic mothers and it is not possible to be certain of the outcome of those who developed a more severe form of diabetes in pregnancy. A possible solution would be to subdivide diet-treated mothers into groups A and A1 depending on their level of fasting glycaemia and to create a separate group of Class AB for women who are found to be carbohydrate intolerant in pregnancy and are treated with insulin. The issue is complicated by the need to agree on criteria for starting insulin treatment so that, for the time being, it is probably best for all workers to define their terminology with regard to the level of fasting plasma glucose, the treatment used and the duration of pregnancy when insulin was started.

Glucose Tolerance Testing

Variations in methodology and the interpretation of glucose tolerance tests have always been a source of misunderstanding amongst clinicians. In pregnancy it represents a potentially serious source of error, because of the clinical action that is often initiated after an abnormal glucose tolerance test. O'Sullivan and his co-workers [6, 7] have done a great deal to standardise the glucose tolerance test and to relate the results to the outcome of the pregnancy. They have established carefully derived limits of carbohydrate tolerance based on a 100 g oral glucose tolerance test. The test is abnormal if two or more blood glucose levels meet or exceed the following limits: fasting: 6.1 mmol/l; 1 h: 9.4 mmol/l; 2 h: 6.7 mmol/l and 3 h: 6.1 mmol/l. Unfortunately the fact that the 100-g test tends to be confined mainly to the USA, whilst in Europe the 50-g test is more popular, has meant that O'Sullivan's work, which could have resulted in acceptable standardisation, has received only limited acceptance in Europe. Comparability of data has been further reduced by differing practice, such as the use of the intravenous rather than the oral route of glucose administration, the use of whole blood glucose determination in some centres and plasma glucose in others and a whole galaxy of methodology for glucose assay.

Despite the difficulty of persuading clinicians to change long established practice, there is a strong case for standardising the methodology and interpretation of the oral glucose tolerance test in pregnancy. The considerable body of knowledge about the long term prognosis for the mother and the outcome for the baby of the diabetic that has accumulated from the studies of O'Sullivan and his group is a strong argument for using his methodology as recommended by the Symposium on Gestational Diabetes [8] rather than adopting the compromise solution of a 75-g test. Certainly, without a

measure of agreement on this matter, screening for gestational diabetes and the subsequent management of the mothers affected will remain unresolved.

Incidence

There are no reliable figures on the incidence of gestational diabetes. This is partly due to the problems of methodological variation and lack of standardisation already referred to, but also to such influences as ethnic origin. For example, the incidence of Type 2 (non-insulin dependent) diabetes amongst the Pima Indians in the USA is 19 times the national figure [9]. O'Sullivan [6], studying a mixed Caucasoid and American negro population from Boston, USA, reported an incidence of gestational diabetes of 2.5% amongst 752 pregnant women. Merkatz et al. [10], using a 75-g glucose load rather than the 100-g load of O'Sullivan, administered mainly between 20–32 weeks of pregnancy and using a modified form of O'Sullivan's criteria, found an incidence of 3.3% among 1352 whites and of 2.9% among 855 blacks living in Cleveland, USA, the difference being statistically significant. A figure for the overall incidence of gestational diabetes in an obstetric population subjected to universal screening seems to vary between 1.6% [11], 2.5% when a full oral glucose tolerance test was performed on all subjects [12] and a top figure of 3.0% [10]. This gives a ratio of gestational to established diabetic mothers of about 4:1 which is in marked contrast to the reversed ratio of 1:3 reported by C. Lowy and R. W. Beard at the 1981 Meeting of the Diabetic Pregnancy Study Group, Liege (unpublished data) from the interim results of the UK National Enquiry into Diabetic Pregnancy. These figures are evidence for the relatively haphazard attempts to detect gestational diabetes which are prevalent in most maternity units in the UK, and could be interpreted as indicating the need for a generally agreed policy on screening for this condition.

Congenital Malformations

It is only in recent years that it has become generally accepted that congenital malformations in the offspring of insulin-dependent diabetic patients are about two to three times more common than among those of non-diabetic mothers [13–15]. It is less certain that there is an increased risk for the offspring of women with gestational diabetes.

Recently Miller et al. [16] published evidence confirming an earlier suggestion by Leslie et al. [17] that the incidence of malformations was higher amongst mothers with established diabetes in whom an abnormally high haemoglobin A_{1c} value had been detected in early pregnancy. However, there was considerable overlap between individual values of women bearing normal and abnormal infants suggesting that the blood glucose con-

centration was not the only determinant of whether the fetus would be malformed or not. The survey of 2041 diabetic pregnancies in Copenhagen [18] and the UK National Enquiry into Diabetic Pregnancy (unpublished observations) supports the concept that the more severe the diabetes the higher the incidence of fetal anomalies. In the Copenhagen series [18], the incidence of anomalies among the White Class A diabetic patients treated with diet alone was 4.1%, significantly higher than the 2.6% incidence for the control group. Unfortunately it is difficult to interpret this study because of the relative lack of comparability between the diabetic group (1976–78) and the control group (1959–61). However, it should be remembered that, for the reasons previously mentioned, Pedersen was studying the less severe gestational diabetic patients and that the true incidence of congenital malformations is likely to have been higher if the gestational diabetic patients transferred to Class B had been included. Other investigators found no evidence of an increase amongst Class A mothers in their series [19, 20]. The carefully documented study of Pima Indians is no help in this respect, for although most complications of pregnancy were increased even with a mild abnormality of maternal carbohydrate tolerance, there was no clear association between the incidence of congenital malformations at the end of the pregnancy and the severity of the diabetes [18].

Animal studies have shown that congenital malformations can be induced by hyperglycaemia at the time of organogenesis [21, 22]. More specifically Baker et al. [23] have shown in diabetic rats that fetal lumbo-sacral defects only arise if the mother is hyperglycaemic at the time of organogenesis. Normoglycaemia achieved by insulin treatment at this critical time appears to prevent this lesion which is specific for diabetes. If this effect occurs in the human female, then the determinant of whether or not the fetus of a mother with gestational diabetes is malformed or not will be the gestational age when hyperglycaemia appears, and may explain the reported low small incidence of malformations amongst gestational diabetic patients.

At present it does not seem possible from the available evidence to say whether there is increased risk of congenital malformations among gestational diabetic patients. It may be that reliance on whether a visible or symptomatically evident malformation is present or not in the first few days will be shown eventually to be too crude an index of the effect of abnormal metabolism at the time of fetal organogenesis. Certainly the results of Yssing's study [24] of 740 children of diabetic patients, in which 36% were shown to have some form of cerebral dysfunction, are a reminder that it would be unwise to be complacent about the results of studies showing apparent lack of effect of gestational diabetes on early fetal development. From available evidence it seems likely that the concept of a 'metabolic teratogen' induced by diabetes, as proposed by Freinkel [5] is viable and that normalisation of hyperglycaemia amongst the few gesta-

tional diabetic mothers who are picked up in early pregnancy is a desirable objective.

Perinatal Mortality and Morbidity

For obstetricians it is of paramount importance to know whether or not gestational diabetes increases the risk of perinatal mortality or morbidity, but the literature is filled with conflicting results on the association which Gabbe has reviewed [25]. Much of the confusion arises from four major sources: (1) The criteria employed for diagnosing gestational diabetes. For example, O'Sullivan showed that by using his current, stricter criteria for abnormal glucose tolerance [12], a prevalence rate considerably lower than that previously reported [6] would have been obtained. (2) All the more recent studies have reported a perinatal mortality amongst gestational diabetic patients which is not significantly different from a non-diabetic population [1, 26, 27]. This is likely to be due, firstly, to the fact that nearly all the mothers in these studies had some form of treatment to normalise their blood glucose in addition to close antenatal supervision. Inevitably such treatment will diminish the perinatal risk. Secondly, no distinction is made between the mild cases of carbohydrate intolerance who compose the majority of mothers with gestational diabetes and the insulin-requiring mother with a high fasting glucose for whom the risk of perinatal mortality is higher. (3) Perinatal mortality has been falling steadily throughout the Western world and this must have been reflected by an improved prognosis for the baby of the mother with gestational diabetes. (4) The quality of obstetric management is an important determinant of perinatal mortality which is independent of the effect of diabetes. This is well illustrated by Gabbe et al. who reported that babies of Class A diabetic mothers delivered electively at 37 weeks gestational age had a perinatal mortality more than three times that of an equivalent group of babies whose mothers had been allowed to go into spontaneous labour, the difference being due to the disappearance of hyaline membrane disease in the latter group [28].

There is general agreement that perinatal mortality amongst diabetic mothers is closely related to the severity of the condition, whether this is judged by the White classification [3] or by the severity of hyperglycaemia of the mother [9, 29]. In established diabetic patients, congenital malformations and 'metabolic' death, usually associated with fetal macrosomia, are the major cause of fetal wastage, while malformations and hyaline membrane disease are chiefly responsible for death amongst the newborn. When one looks at the data on gestational diabetes, the association of the condition with a raised perinatal mortality is less convincing. In order to exclude the possibility that treatment of gestational diabetic patients is reducing the risk of perinatal death to normal levels, it is necessary to look at the few studies in which the condition was untreated in pregnancy either because

it was unrecognised or was purposely not treated. H.W. Sutherland and P. Fisher performed an intravenous glucose test after delivery on 97 women who had had an unexplained antenatal or intrapartum stillbirth and found that 26% of the tests were abnormal (unpublished observations). Gabbe et al. found amongst 196 Class A diabetic mothers that 13% had a history of previous stillbirth [28]. Likewise, Merkatz et al. [10] noted that among 124 multiparous women with gestational diabetes who had a total of 288 pregnancies, the perinatal mortality was 9.7% (18 stillbirths and 10 neonatal deaths). In other words, in previous pregnancies when diabetes was unsuspected, possibly because it was less severe, perinatal mortality is at least five times higher than among normal mothers.

Jarrett has correctly commented that other associated factors, such as age and obesity, need to be excluded before it can be assumed that diabetes was the cause of the raised perinatal mortality [30]. A prospective survey of the outcome of pregnancy complicated by untreated gestational diabetes was reported by O'Sullivan et al. [31]. Identical routine antenatal and intrapartum care was provided for 187 gestational diabetic and 259 control mothers. The perinatal mortality was 6.4% among the diabetic patients compared with 1.5% in the control group. Further analysis revealed that 'age was found to have a disproportionately adverse effect, enhanced slightly by obesity . . .'. The significance of this observation is underlined by the fact that approximately 75% of gestational diabetic mothers were aged 25 years or more [31, 32]. Evidence of gestational diabetes being associated with an increased perinatal mortality is provided by Muck and Christ [33], quoted by Pedersen [3] who showed that treatment of gestational diabetes resulted in a fall from 5.4% to 1.9%. A similar result was reported in a later study by O'Sullivan [34] on the effects of treatment of gestational diabetes.

If the baby of a mother with gestational diabetes has an increased chance of dying, then it is reasonable to assume that there is also a greater risk of morbidity although little data are available on this point. Gabbe et al. [28] confirmed the well known tendency to macrosomia amongst babies of Class A diabetic mothers; observing that 20% of them weighed more than 4 kg compared with 9% of the babies of non-diabetic mothers. They also noted that of 49 macrosomic babies delivered vaginally, five sustained significant birth trauma. Macrosomia is a well-recognised cause of morbidity but there is also an increase in complications such as respiratory distress, hypoglycaemia and hyperbilirubinaemia [32]. The overall figure of 25% of babies of Class A diabetic mothers having some form of perinatal morbidity seems high [25], but may well be correct although it is not possible to assess the significance of this figure because no comparable statistics for babies of non-diabetic mothers were presented. O'Sullivan [34] showed that insulin treatment significantly reduced the birthweight of the babies of mothers with gestational diabetes which may also have

contributed to the lowered perinatal mortality in this group. This is an important observation because it suggests that treatment may well be effective by 'normalising' the environment for the developing fetus, thereby reducing other causes of neonatal morbidity. However, more work needs to be done on this subject before a definite statement can be made.

Long-Term Significance of Gestational Diabetes

The possibility that pregnancy unmasks incipient diabetes which only becomes clinically evident in later life has always been an intriguing question that has never been satisfactorily answered. O'Sullivan and Mahan have reported on 615 gestational diabetic mothers who have been followed up annually for at least 16 years [35]. The cumulative incidence of diabetes using the United States Public Health Service criteria was approximately 60%, of whom 16% had more severe or decompensated diabetes. These are alarming figures if they can be confirmed, supporting the concept that pregnancy unmasks an incipient diabetic state. Mestman has shown that 40% of gestational diabetic women have an abnormal oral glucose tolerance test after pregnancy [32]. Follow-up of the gestational diabetic mothers amongst the Pima Indians 4-8 years after the pregnancy, when diabetes was first detected, reveals an incidence of subsequent diabetes ranging from 4% to 45%, depending on the severity of the carbohydrate intolerance during the pregnancy [9].

One may well ask whether the future diabetic woman will benefit from an early diagnosis in pregnancy. The possibility that some form of treatment may protect the B cells of the mother from damage resulting from the increased insulin demand of pregnancy has been suggested and investigated by O'Sullivan and Mahan [35]. They observed that insulin treatment of women with gestational diabetes only seemed to benefit those who had a large baby, resulting in a significantly lower incidence of decompensated diabetes 16 years later. These results are difficult to explain but may well be an illustration of the heterogeneity of diabetes. Nevertheless, the possibility of long-term preventative benefits from insulin therapy in even a small number of mothers with gestational diabetes is an interesting possibility that deserves further investigation.

Conclusion

On balance there is sufficient evidence to view gestational diabetes as a clinical entity, particularly with regard to fetal development and survival. This is not surprising when one considers the serious fetal and neonatal complications associated with pregnancy in mothers with established diabetes. Normal fetal development is so dependent on the maintenance of homeostatic environment for the fetus of the mother that even a relatively

small change in maternal metabolism is likely to have an adverse effect. A good example of the effect of the metabolic disturbance in untreated gestational diabetes is demonstrated when these babies tend to be heavier than normal, which may well be due to the growth-promoting effect of fetal hyperinsulinism [36, 37]. While it may be argued that this is a relatively unimportant effect, the possibility that premature triggering of the fetal pancreas may be damaging to fetal pancreatic B cells leading to insulin deficiency in later life remains a strong possibility [38].

The weight of evidence points quite clearly to the fact that maternal hyperglycaemia affects fetal development adversely. In early pregnancy this may result in malformations, while in later pregnancy which is particularly relevant to the mother with gestational diabetes, perinatal mortality rises in direct proportion to the severity of the maternal hyperglycaemia [29]. The demonstration that normoglycaemia achieved by home monitoring in pregnant diabetic mothers eliminates most of the adverse effects of diabetes on the fetus and newborn is further evidence in favour of treating even minor deviation of diurnal blood glucose from normal [39]. Jarrett [30] has criticised haphazard screening for gestational diabetes on the grounds that it has no demonstrable benefit. We would argue that there is a good case for routine screening of all pregnant women. The glucose load described by O'Sullivan [6] for universal screening not only detects more gestational diabetes than confining glucose tolerance testing to potential diabetes but is also more cost-effective [40].

Finally we are concerned by the recommendation of the World Health Authority Expert Authority that diagnostic criteria for diabetes should be the same in all adults, pregnant or not [30]. This appears to reject all the evidence that even a minor disturbance of carbohydrate tolerance conveys some increased risk to the fetus and may well be a useful predictor of subsequent established diabetes in the mother. It is our view that there is a strong argument for retaining the more liberal diagnostic criteria recommended by O'Sullivan [12] for the pregnant woman.

References

1. Hadden DR (1980) Screening for abnormalities of carbohydrate metabolism in pregnancy 1966-77. The Belfast experience. *Diabetes Care* 3: 440-446
2. White P (1965) Pregnancy and diabetes. Medical aspects. *Med Clin North Am* 49: 1015-1024
3. Pedersen J (1977) The pregnant diabetic and her newborn. Munksgaard, Copenhagen
4. Gibbons JM, Nagle MP (1980) Assessing fetal health when the mother is diabetic. *Contemp Obstet Gynecol* 15: 115-124
5. Freinkel N (1980) Of pregnancy and progeny. *Diabetes* 29: 1023-1035
6. O'Sullivan JB (1979) Gestational diabetes: factors influencing the rates of subsequent diabetes. In: Sutherland HW, Stowers JM (eds) *Carbohydrate metabolism in pregnancy and the newborn* 1978. Springer Verlag, Berlin, pp 425-435
7. O'Sullivan JB, Mahan CM (1964) Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 13: 278-285
8. Proceedings of Symposium on Gestational Diabetes (1980) Summary and Recommendations. *Diabetes Care* 3: 499-501
9. Pettit DJ, Knowler WC, Baird R, Bennett PH (1980) Gestational diabetes: infant and maternal complications of pregnancy in relation to third trimester glucose tolerance in Pima Indians. *Diabetes Care* 3: 458-464
10. Merkatz IR, Duchon MA, Yamashita TS, Houser HB (1980) A pilot community based screening programme for gestational diabetes. *Diabetes Care* 3: 453-457
11. Gillmer MDG, Oakley NW, Beard RW, Nithyananthan R, Cawston M (1980) Screening for diabetes during pregnancy. *Br J Obstet Gynaecol* 87: 377-382
12. O'Sullivan JB (1980) Establishing criteria for gestational diabetes. *Diabetes Care* 3: 437-439
13. Kučera J (1971) Rate and type of congenital anomalies among offspring of diabetic women. *J Reprod Med* 7: 73-82
14. Naeye RL (1965) Infants of diabetic mothers - a quantitative morphological study. *Pediatrics* 35: 980-985
15. Pedersen LM, Tygstrup I, Pedersen J (1964) Congenital malformations in newborn infants of diabetic women. *Lancet* 1: 1124-1126
16. Miller E, Hare JW, Cloherty JP, Dunn PJ, Gleason RE, Soeldner JE, Kitzmiller JL (1981) Elevated maternal HbA_{1c} in early pregnancy and major congenital anomalies in infants of diabetic mothers. *New Eng J Med* 304: 1331-1333
17. Leslie RDG, Pyke DA, John PN, White PM (1978) Haemoglobin A₁ in diabetic pregnancy. *Lancet* 2: 958-959
18. Pedersen LM (1980) Pregnancy and diabetes. A survey. *Acta Endocrinol* 94: (Suppl 238): 13-19
19. Malins JM (1979) Fetal anomalies related to carbohydrate metabolism - the epidemiological approach. In: Sutherland HW, Stowers JM (eds) *Carbohydrate metabolism in pregnancy and the newborn* 1978. Springer-Verlag, Berlin, pp 229-246
20. Haukkamaa M, Nilsson CG, Luukkaainen J (1980) Screening, management and outcome of pregnancy in diabetic mothers. *Obstet Gynecol* 55: 596-602
21. Deuchar EM (1979) Culture in vitro as a means of analysing the effect of maternal diabetes on embryonic development in rats. In: Elliott K, O'Connor M (eds) *Pregnancy, metabolism, diabetes and the fetus*. CIBA Foundation Symposium No. 63 (new series). Excerpta Medica, Amsterdam, Oxford, New York pp 181-197
22. Eriksson U (1981) Diabetes in pregnancy. A study of complications in the offspring of the rat. MD Thesis, Acta Universitatis Upsalien-sis, Uppsala, Sweden
23. Baker L, Egler JM, Klein SH, Goldman AS (1981) Meticulous control of diabetes during organogenesis prevents congenital lumbosacral defects in rats. *Diabetes* 30: 955-959
24. Yssing M (1975) Long-term prognosis of children born to diabetic mothers when pregnant. In: Camerini-Davalas RA, Cole HS (eds) *Early diabetes in early life*, Academic Press, New York, pp 575-586
25. Gabbe SG (1977) Congenital malformations in infants of diabetic mothers. *Obstet and Gynecol Surv* 32: 125-132
26. Roversi GD, Gargiulo M, Nicolini U, Pecretti E, Marini A, Barbarini V, Peneff P (1979) A new approach to the treatment of pregnant diabetic women. 479 cases (1963-1975). *Am J Obstet Gynecol* 135: 567-576
27. Gyves MT, Schulman PK, Merkatz IM (1980) Results of individualised intervention in gestational diabetes. *Diabetes Care* 3: 495-496
28. Gabbe SG, Mestman JH, Freeman RK, Anderson GV, Lowensohn RI (1977) Management and outcome of class A diabetic mellitus. *Am J Obstet Gynecol* 127: 465-469
29. Karlsson K, Kjellmer I (1972) The outcome of diabetic pregnancies in relation to the mothers blood sugar level. *Am J Obstet Gynecol* 112: 213-217
30. Jarrett R (1981) Reflections on gestational diabetes. *Lancet* 2: 1220-1222
31. O'Sullivan JB, Charles D, Mahan CM, Dandrow RV (1973) Gestational diabetes and perinatal mortality rate. *Am J Obstet Gynecol* 116: 901-904

32. Mestman JH (1980) Outcome of diabetes screening in pregnancy and perinatal morbidity in infants of mothers with mild impairment in glucose tolerance. *Diabetes Care* 3: 477–482
33. Muck BR, Christ F (1973) Pathologische Glukosetoleranz bei Schwangeren. Eine Untersuchung des geburtshilflichen Kollektivs der Erlanger Universitäts-Frauenklinik 1971. *Arch Gynaekol* 215: 95–109
34. O'Sullivan JB (1975) Insulin treatment for gestational diabetes. In: Camerini-Davalos RA, Cole HS (eds). *Early diabetes in early life*. Academic Press, New York, pp 447–453
35. O'Sullivan JB, Mahan CM (1980) Insulin treatment and high risk groups. *Diabetes Care* 3: 482–485
36. Isles TE, Dickson M, Farquahar JN (1968) Glucose tolerance and plasma insulin in newborn infants of normal and diabetic mothers. *Pediat Res* 2: 198–208
37. Molsted-Pedersen L (1972) Aspects of carbohydrate metabolism in newborn infants of diabetic mothers – intravenous glucose tolerance tests. *Acta Endocrinol* 69: 174–188
38. Hulquist GT, Olding L (1975) Pancreatic islet fibrosis in young infants of diabetic mothers. *Lancet* 2: 1015–1016
39. Jovanovic L, Druzin M, Peterson CM (1981) Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. *Am J Med* 71: 921–927
40. Hoet JJ, Beard RW (1979) Clinical perspectives in the care of the pregnant diabetic patient. In: Elliott K, O'Conner M (eds). *Pregnancy, metabolism, diabetes and the fetus*. CIBA Foundation Symposium No 63 (new series). Excerpta Medica, Amsterdam, Oxford, New York, pp 283–300

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