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COMMENTARY

Congenital anomalies in diabetic pregnancy: an important confirmation

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Abbreviations
NorCAS Northern congenital abnormality survey
NorDIP Northern diabetes in pregnancy survey

> *The study of things caused must precede the study of the causes of things*
> J.H. Biggart [1]

The birth of a baby with a severe congenital anomaly is a family tragedy. Feelings are often suppressed, and this is perhaps even more likely if there has been a therapeutic termination. Much obstetric effort is now focused on prevention of these tragedies, but with regard to diabetes the underlying suspicion is that excess glucose is the teratogen, and that if the mother's blood glucose level had been entirely normal in the very early days of the conception the developmental anomaly would have been less likely to occur. Not totally prevented, just reduced to the background risk in the non-diabetic population. So it is the responsibility of the diabetes care team, as much as the mother herself, to try and achieve this perhaps unattainable goal—a totally normal maternal blood glucose level at a time when she will not know for sure whether she is pregnant or not.

I remember a baby born with a badly twisted foot—a subset or 'sequence' of the caudal dysplasia syndrome that we all learnt about as a diabetes-related congenital fetal anomaly. After much orthopaedic effort the foot eventually had to be amputated. The young man must now be in his mid-30s, but his mother will still have her sense of guilt—the record of the pregnancy and the evidence of the early hyperglycaemia were all in her hospital record, and there was even a photograph of the twisted foot, until she could no longer stand the questions and well-meant interest from the next junior doctor who happened to open her chart, and she defaulted from the diabetic clinic for some time. Removing the offending part of the record to a separate folder helped, but the guilt should not have been hers, but ours, for not having a better system of diabetes management, or a better sort of insulin, or even being able to prevent her diabetes altogether.

The paper in this issue of *Diabetologia* by Bell et al. is important [2]. It is the first time that epidemiologists with particular knowledge of congenital fetal anomalies, and of diabetes management before and during pregnancy, have come together to observe—albeit retrospectively—all of the actual outcomes of pregnancy in a defined region. The authors, from the Institute of Health and Society in Newcastle upon Tyne, with its related Northern Congenital Abnormality Survey (NorCAS) and Northern Diabetes in Pregnancy Survey (NorDIP) are the first combined group to have properly tackled this observational task.

Although many of the problems associated with pregnancy in a diabetic woman have been recognised since the very first reported case, by Heinrich Bennewitz at the Charité Hospital, Berlin, in 1824 [3, 4], and might have been thought to have been overcome by the use of insulin following the first successful diabetic pregnancy managed with insulin by George Graham at St Bartholomew's Hospital, London, 100 years later [5], it is perhaps strange that the increased risk of fetal congenital anomalies was not

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suspected until much later. A report by the UK Medical Research Council in 1955 carefully documented a number of congenital anomalies in several centres during a randomised clinical trial [6], but as the report was focused on disproving the alleged benefit of oestrogen therapy in diabetic pregnancy, this perhaps more important observation was overlooked. The larger series from the Rigshospitalet in Copenhagen in 1964, by Lars Mølsted-Pedersen and coworkers [7], established the problem. A number of experimental models of hyperglycaemic pregnancy in rats by Ulf Eriksson in Uppsala, Sweden, subsequently established the teratogenic role of excess glucose in the very early stages of gestation, and threw some light on possible aetiological mechanisms [8]. Norbert Freinkel's stimulating Banting Lecture on 'fuel-mediated teratogenesis' led to much research on this aspect of diabetic pregnancy [9].

It was, however, the prospective randomised clinical trials of folic acid supplementation in non-diabetic pregnancy that have provided the evidence base for current guidelines on nutritional supplementation in diabetic pregnancy. The worthy aim of the St Vincent Declaration of a pregnancy outcome for a diabetic woman not different from that of a non-diabetic mother [10] has still not in general been achieved, and the persistence of fetal congenital anomalies, associated with undoubted early pregnancy hyperglycaemia, is one of the main reasons for this ongoing problem. The UK Confidential Enquiry on Maternal and Child Health (CEMACH) report on diabetes and pregnancy [11] confirmed the practical difficulty in achieving normoglycaemia in very early pregnancy—effective universal prepregnancy counselling may be an impossible goal.

Nevertheless, there has always been a degree of doubt concerning the actual relationship between maternal hyperglycaemia and congenital anomalies. These same anomalies all occur in non-diabetic pregnancies. A distinguished paediatrician from Cincinnati, Harold Kalter, who had a background in teratology, was brave enough to challenge the long-accepted belief in a detailed monograph [12] suggesting that errors might have arisen from misclassification of anomalies and from overenthusiastic reporting of uncontrolled series of diabetic pregnancies. Previous cohort studies have included only cases diagnosed antenatally, or apparent shortly after birth, which is a major methodological limitation. This paper from Newcastle upon Tyne is a final answer to Dr Kalter, and sets the record straight in a large population-based epidemiological study.

The north of England has a population of around three million, and there are about 30,000 pregnancies per year. Specific results for all of these pregnancies are presented for the years 1996–2008, including all births after 20 weeks' gestation and terminations following prenatal diagnosis of a fetal anomaly. We might ask 'Has this sort of analysis or audit not been done before?' The answer is no, not at this degree of sophistication. The unique juxtaposition of regionally funded surveys to record the outcomes of all pregnancies in diabetic women, and separately to record and classify all congenital anomalies in the region (NorDIP and NorCAS) has resulted in an answer to Dr Kalter's question. With some appropriate statistical analyses, including bootstrapping and locally weighted scatter plot smoothing (LOWESS) graphics, the answer is very clear.

In the 12 year period there were 401,149 singleton live births, spontaneous fetal losses and terminations. Of these, 1,677 occurred in mothers who had type 1 or type 2 diabetes (those with 'gestational diabetes' or 'hyperglycaemia in pregnancy' were excluded, wisely in view of ongoing differences in definition). Using the very detailed European Surveillance of Congenital Anomalies (EUROCAT) classification, the risk of any major congenital anomaly, excluding chromosomal anomalies, in the diabetic pregnancies was nearly four times that in the non-diabetic background population. In regard to early pregnancy glycaemia, for each 1% increase in HbA_{1c} above 6.3% (or rise of 11 mmol/mol above 45 mmol/mol), the odds of a pregnancy being affected by a congenital anomaly increased by 30%. Overall, one in 13 (7.7%) singleton deliveries to women with pre-existing diabetes was affected, and the relative risk of an anomaly was nearly four times that in the general population. These data are visually presented in a graph that will certainly become a major educational demonstration for diabetic mothers-to-be, as well as all of their advisors.

As in all studies there are some imponderables. Why should maternal diabetic nephropathy (not fully defined) also be a risk factor? Not so long ago, severe nephropathy was considered one of the few absolute contraindications to pregnancy in a diabetic woman, because of the risk to the woman herself. Could ACE inhibitors be at fault? Is maternal obesity a separate risk or is it compounded in type 2 diabetes? These points are discussed and possible explanations offered. Those of us who have been along this road for many years will be grateful to the collaborative teams in Newcastle upon Tyne for producing this definitive epidemiological assessment of an important diabetes-related pregnancy problem. The clinical cause of the problem is already clear. Now that any lingering doubt is removed about the additive effect of maternal hyperglycaemia superimposed on a background population risk, we can all try to facilitate normoglycaemia in very early gestation.

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Duality of interest The author declares that there is no duality of interest associated with this manuscript.

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