INVITED COMMENTARY

Birth defects in diabetic pregnancies: where do we go from here?

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Major congenital malformations affecting predominantly the central nervous system, heart and great vessels, kidneys and skeleton occur in 8–12% of pregnancies complicated by type I or type II diabetes in the absence of special preconceptional diabetes care. As morbidity and mortality from other complications of diabetic pregnancies have been reduced by careful maternal blood glucose regulation during the second and third trimesters, malformations have become the major cause of perinatal mortality and an important cause of perinatal morbidity associated with maternal diabetes. A review of human embryology indicates that the developmental disturbances that cause the malformations occur very early in pregnancy, probably during the first six weeks of development. Because ethical considerations preclude the study of human embryos during this period, animal models have been developed to study the biochemical mechanisms by which maternal diabetes causes embryonic malformations. One of the most useful techniques was developed by New and colleagues in the 1970s and involves the removal of embryos from normal rodent mothers near the beginning of neural tube closure and the subsequent culture of the embryos in test serum in vitro for 24–48 h, the period of neural tube development and closure. When the test serum is derived from normal animals, embryonic development in vitro is virtually identical to development in vivo. By contrast, when the test serum is derived from animals that have been made diabetic, embryos from several rat and mouse strains exhibit a high rate of gross developmental anomalies.

This model of “post-implantation” embryogenesis, so named because the embryos are removed from their mothers soon after they have implanted in the uterus, has proved very useful for identifying possible teratogens and teratogenic mechanisms related to maternal diabetes. Regarding potential teratogens, metabolic fuels such as glucose, β-hydroxybutyrate and the amino acid analog alpha-keto-isocaproic acid can induce malformations when added to normal serum in high concentrations prior to embryo culture. Low-molecular-weight serum fractions containing somatomedin inhibitory activity have also been shown to be teratogenic in rodent embryo culture. These factors are synergistic in their embryotoxic effects (1, 2), a finding that has suggested a multifactorial etiology for diabetic malformations. The study by Wentzel and Eriksson in this issue of European Journal of Endocrinology and a publication by our group (3) provide experimental proof that factors other than glucose and ketones contribute to malformations in rodent models of diabetes. Both studies showed that diabetic serum retains a significant portion of its teratogenic activity after circulating glucose and ketone concentrations are normalized in serum donors with exogenous insulin. Thus, diabetic teratogenesis must be viewed as resulting from factors that are more complex than hyperglycemia alone, although the data of Wentzel and Eriksson and many other investigators indicate that high glucose concentrations contribute to embryonic malformations induced by diabetes.

Studies of the biochemical mechanisms by which diabetes could disrupt embryogenesis have generally focused on individual teratogens added to normal serum in vitro prior to embryo culture. Such studies have revealed at least three basic abnormalities that can be induced by components of diabetic serum. First, studies by several groups using rat and mouse models of neural tube closure have revealed that high concentrations of glucose simultaneously induce neural tube defects and deplete myo-inositol in post-implantation embryos through competitive blockade of myo-inositol uptake. The resulting neural tube defects can be prevented in part or in whole by supplementation of myo-inositol or “downstream” components of the phospholipase A2-arachidonic acid cascade, including arachidonic acid and prostaglandin E2. These findings indicate that myo-inositol depletion causes a reduction in arachidonic acid and prostaglandins, which in turn mediate glucose-induced neural tube closure defects in these rodent models (4). Second, studies by Eriksson and Borg (2) in a rat strain that manifests an excess of skeletal defects and resorbed embryos in the presence of maternal diabetes in vivo have provided strong evidence that free oxygen radicals are involved in diabetes-related malformations and early pregnancy losses. In this strain, provision of oxygen radical scavengers reduces the frequency of malformations that would otherwise occur when embryos are exposed to high concentrations of glucose and other oxidative fuels in vitro during the period of neural tube closure. These findings provide a potential application to human pregnancy, because several vitamins have antioxidant properties that could be useful for reducing radical toxicity. Finally, several studies have linked maternal diabetes to disruptions of DNA synthesis and structure.
Sadler’s group (5) have shown that high concentrations of \( \beta \)-hydroxybutyrate induce neural tube anomalies in mouse embryos at least in part by inhibiting the pentose phosphate pathway that normally provides ribose molecules for nucleic acid synthesis. Provision of ribose molecules to bypass the blockade restores rates of DNA synthesis to normal and reduces rates of neural tube defects in vitro. Exposure to maternal diabetes in vivo has also been linked to DNA mutations in reporter genes such as lac-I in transgenic mice, although it is not known whether analogous mutations occur in functional genes related to normal embryogenesis. It is important to note that animal data not cited above indicate that the occurrence of malformations is determined not only by the metabolic environment but also by the genetic susceptibility of the embryos, raising the possibility that the biochemical mechanisms underlying diabetic teratogenesis may differ among animal strains and species and between laboratory animals and humans.

How does all this information about potential mediators and mechanisms of diabetic teratogenesis help clinicians to reduce the frequency of malformations in human diabetic pregnancies? At the present time, none of the basic mechanistic information cited above has reached the stage of clinical testing or applicability. However, results from earlier animal studies and from recent clinical trials provide clinicians with a powerful tool to reduce or eliminate excess congenital malformations in diabetic pregnancies: good glycemic control. Without indicating which potential mediators and mechanisms might be involved, at least five clinical studies have revealed that enrolment in a program of preconceptional diabetes care designed to lower maternal blood glucose concentrations toward normal is associated with a reduction in, or elimination of, the excess malformation rates in infants. While a patient selection bias may have resulted in exceptionally good results in the studies that demonstrated a complete elimination of excess malformations, there can be little doubt that careful preconceptional diabetes management can reduce the risk of major malformations in offspring. Two important questions remain to be answered regarding the optimal implementation of preconceptional diabetes care strategies: “How strict should glycemic control be?” and “How do we get diabetic women to achieve that control?”.

Some clues regarding the answer to the first question can be gleaned from existing data on the relationship between glycemic control and malformation rates. Information from studies in which first-trimester glucose and glycohemoglobin concentrations have been related to malformation and spontaneous abortion rates in “all comers” to clinics in the USA and Europe (6–8) indicate that glucose and glycohemoglobin concentrations slightly above the normal range (e.g. fasting plasma glucose concentrations up to 6.7 mmol/l and glycohemoglobin concentrations up to four standard deviations above the mean for non-diabetic individuals) are associated with malformation rates that are either no greater than rates in the general population or no greater than rates in diabetic women with lower glycohemoglobin concentrations. Prospective data from women participating in preconception programs (9) also indicate very low malformation and spontaneous abortion rates when plasma glucose concentrations are normal or slightly above normal (e.g. <9.4 mmol/l for the mean of a fasting and three postprandial capillary glucose measurements daily). The desired range of glycemia in preconception studies has been achieved by setting rather stringent glycemic goals (e.g. capillary glucose concentrations <5.5 mmol/l fasting and <7.8 mmol/l 2 h after meals), realizing that not all patients will achieve the goals but that most will be within the “acceptable” range defined above (9).

The answer to the question about patient compliance with prevention strategies is somewhat more problematic. While the concept of preconception clinics for diabetic women is simple and sound, the application of the concept to clinical practice requires extensive education of diabetic women and primary care physicians together with effective family planning. Data from several Western countries indicate that a lack of pregnancy planning is the major reason why diabetic women do not participate in preconception programs even though many patients are aware of the risks involved in not participating. Gregory and Tatersall (10) have presented convincing evidence that another strategy, i.e. provision of improved care to all diabetic patients, can lower population-based rates of diabetic malformations as much as preconception clinics. This latter strategy appears to have reduced diabetes-related malformation rates by \( \sim 50\% \) in Sweden, Denmark and parts of the UK in the last decade. The optimal strategy for a region or country will depend on the types of resources that are available for diabetes care: a combination of the two strategies may prove to be the ideal course.

Where do we go from here? Certainly, results from European and American studies indicating that good glycemic control is beneficial for all patients with type I (and probably type II) diabetes dictate that attainment of better glycemic control in all diabetic patients should be an important target for any country’s health care resources. Specific targeting of young diabetic women for education about the risks of congenital malformations and the importance of effective family planning and preconception care should be emphasized as well. However, given the realities of human behavior, it seems unrealistic to expect that these two approaches will completely eliminate the excess of birth defects in diabetic pregnancies. Therefore, pending a cure for diabetes itself, it is important that we continue to support basic research to identify biochemical mechanisms that cause diabetic malformations in animals, to develop safe and effective interventions that can reverse
those mechanisms in the laboratory and, most importantly, to begin testing such interventions in humans. If safe and effective interventions can be identified, then they can be offered to all young women with diabetes, along with recommendations that they plan their pregnancies and maintain good glycemic control from the preconception period onward.

References