INVITED COMMENTARY

Sulphonylureas and pregnancy

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Gestational diabetes usually develops after the 24th week of pregnancy because of the counter-insulin effects of placental hormones such as human placental lactogen, oestrogen and cortisol. It can be well controlled in most cases by diet alone. However, when diet does not achieve good glycaemic control, insulin treatment is recommended to manage diabetes until delivery after which the gestational diabetes disappears. Immediately after delivery, transient hypoglycaemia, resolving in a few hours of life, may occur in those newborns whose mothers were chronically hyperglycaemic. The pathogenesis of this transient hypoglycaemia is attributed to high fetal levels of insulin produced by the pancreatic β -cell in response to prolonged exposure to maternal hyperglycaemia. Insulin treatment during gestational diabetes does not exaggerate the risk of severe and prolonged hypoglycaemia after delivery because maternal insulin does not cross the placenta. Sulphonylureas do, however. Indeed, these drugs easily cross the placenta (1) and exert profound stimulatory effects on fetal β -cells with the consequence of potentiating the hyperplastic effect of maternal hyperglycaemia on β -cells and enhancing the release of high levels of blood insulin. The effect of sulphonylureas on neonatal β -cells can last from many hours up to several days after delivery, exposing babies to a high risk of severe and prolonged hypoglycaemia.

The case reported by Christensen *et al.* (2) is that of a baby born prematurely at 34 weeks as the result of intrauterine asphyxia. Its mother's diabetes was ascertained at 11 weeks of pregnancy. She was put on tolbutamide from the 24th week of pregnancy until delivery. The baby developed severe hypoglycaemia (plasma glucose ranging from 0.8 to 1.3 mmol/l) without convulsions after delivery and during the first hours of life, accompanied by hyperinsulinaemia and a high level of serum tolbutamide. The baby required infusion of large amounts of glucose for three days and administration of octreotide for nine days to stabilize blood glucose. No episode of hypoglycaemia occurred subsequently. At the age of three months the baby's psychomotor development was apparently normal. In this case, intrauterine asphyxia might have aggravated hypoglycaemia at birth.

Although tolbutamide is known to have a quite short half-life (4 to 7 h) (3) compared either with other

sulphonylureas, such as chlorpropamide (24 to 48 h), or with the second-generation agents which have short half-lives (1.5 to 5 h) but more powerful hypoglycaemic effects evident up to 24 h, tolbutamide can induce severe and prolonged hypoglycaemia in the newborn to the same extent that other sulphonylureas can. The key point in understanding the physiopathologic basis of sulphonylurea-induced post-birth hypoglycaemia is the β -cell hyperplasia development which results from a continuing administration of sulphonylureas during pregnancy. In fact, when sulphonylureas are administered day after day, all of them induce hyperplasia of β -cells. As a consequence, islets hyperplasia keeps releasing insulin post delivery. In contrast, acute administration of tolbutamide to diabetic mothers in one study (1) increased serum tolbutamide concentrations in the neonates but did not cause hypoglycaemia.

Prolonged and severe hypoglycaemia following administration of sulphonylureas (chlorpropamide, acetohexamide) has been described in older reports as well (4, 5). In many cases, prolonged infusion of glucose, administration of glucocorticoids, and also exchange transfusion was carried out to correct hypoglycaemia. Surprisingly, no neurological complications following resolution of severe hypoglycaemia were reported. Apparently, newborns can have blood glucose as low as 0.8 mmol/l soon after birth without exhibiting symptoms and it is not known whether they suffer any cerebral damage or dysfunction at all. Oxidative metabolism of free fatty acids might sustain newborn brain metabolism during prolonged hypoglycaemia by supplying ketone bodies. Indeed, ketone bodies cross the blood–brain barrier and act as an alternative fuel, although to a lesser degree than glucose, for brain metabolism in the newborns.

Because of the increased risk of newborn hypoglycaemia, sulphonylureas, including tolbutamide, should never be prescribed to pregnant women with gestational, or type 2, diabetes mellitus. Insulin is readily available for use whenever glycaemic control needs improvement.

Because this risk is well known and a safe alternative exists, prescription of sulphonylureas raises serious legal and ethical questions. Newborn hypoglycaemia following use of sulphonylureas is iatrogenic. The drug

manufacturer itself in its package insert information warns against the use of sulphonylureas during pregnancy. If the drug is used despite the warning, it advises withdrawal in the two weeks of pregnancy before delivery. But such a precaution is of little use in the case of unpredicted premature birth. In fact, classic textbooks clearly indicate that sulphonylureas are contraindicated in pregnancy (3, 6).

It is far safer for the newborn and more prudent for the physicians to prescribe insulin, never sulphonylureas, in cases of gestational diabetes.

References

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Received 26 January 1998

Accepted 2 February 1998