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## Type 1 Diabetes and Autism: Is there a link?

Response to Harjutsalo and Tuomilehto

**W**e thank Harjutsalo and Tuomilehto (1) for their most informative comments. There can be no doubt that they have thoroughly investigated the potential association between type 1 diabetes and autism spectrum disorder (ASD) in a large population-based cohort of Finnish children and failed to find any suggestion of an association. Why might their data differ from ours?

Based on clinical experiences, we reported what had appeared to be a higher-than-expected prevalence of ASD in our clinic-based cohort of children with type 1 diabetes (2). Our report was submitted in the hope of stimulating further evaluation and discussion about possible links between these two common disorders of childhood. As discussed in our report, it is possible that our patient population is biased in that it is derived from a large tertiary care center rather than being population based as in the case of the Finnish analysis. Thus, our patient population may be more likely to suffer other serious chronic conditions in addition to type 1 diabetes than would a group receiving therapy in a more community-based diabetes program.

However, it is possible that the Finnish data mask the possible association between ASD and type 1 diabetes for one or more reasons. First, it is possible that ASD remains relatively underdiagnosed in their diabetic population. Second, it is more likely that there are significant differences between the two cohorts that make comparison difficult. For example, there are reports that suggest that the rising incidence of childhood type 1 diabetes is associated with reduced contributions of high-risk HLA haplotypes (3). These data suggest that, in a country with a very high incidence of type 1 diabetes such as Finland, the relative contribution of genetic susceptibility to the expression of the disorder is therefore diminished. If the relationship between ASD and type 1

diabetes is on the basis of shared genetic influences, then any possible relationship may be diluted out by the heavier contribution of environmental factors in high compared to medium or lower incidence countries.

The contribution of Harjutsalo and Tuomilehto is greatly appreciated in helping to facilitate a definitive answer to the question of disease association between type 1 diabetes and ASD. There may be other investigators willing to share their experiences on this issues.

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## Metformin in Pregnancy

Its time has not yet come

*The American Diabetes Association (ADA) responds to letters concerning published articles in Diabetes Care. It does not respond to letters concerning presentations at the ADA Annual Scientific Sessions or reports of such presentations. The ADA held an entire conference on the treatment of gestational diabetes in November 2005, in which the use of metformin was discussed.*

**O**n 12 June 2005, the ADA's newsletter from the 65th Annual Scientific Sessions, the *Bayside Tribune* (1), ran a piece entitled "Metformin Shown to be Safe and Effective in Pregnancy". The article erroneously stated that speakers at a symposium answered "with a resounding 'Yes'" to the question of whether met-

formin is safe and effective for diabetes in pregnancy. We are concerned with that message.

A symposium entitled "Metformin in Pregnancy—Is it Safe? Does it Work?" discussed metformin in pregnancy. Dr. Clifford Bailey reviewed cellular mechanisms of metformin in nonpregnant patients (2) and suggested applications in pregnancy. Professor Gerald Briggs discussed how to determine the teratogenic risk of drugs and suggested that metformin use in the first trimester may be low risk based on animal and human data. Dr. Charles Glueck presented data on the use of metformin with diet throughout three trimesters in patients with polycystic ovary syndrome (PCOS) (3,4). His data showed a decreased risk of first-trimester spontaneous abortions compared with previous pregnancies in the same women not on metformin. Compared with community control subjects, Dr. Glueck's study subjects had a decreased risk of gestational diabetes, decreased maternal weight gain, and decreased insulin resistance. There was no increase in infant birth weight compared with gestational age- and sex-matched norms from the Centers for Disease Control and Prevention. Dr. Glueck attributed the slight increase in prematurity to a higher BMI in the PCOS patients compared with community control subjects. Neonatal outcomes were good, with normal growth and development up to 4 years in exposed offspring. Dr. Rowan presented retrospective data on the use of metformin in women with type 2 diabetes during pregnancy. Although the results were reassuring, she emphasized caution until randomized data are available. She presented an outline of an Australasian randomized trial, comparing insulin with metformin in women with gestational diabetes. This study will be called Metformin in Gestational Diabetes (MiG) and the follow up of offspring (MiG:TOFU). It will finish recruiting during 2006.

Metabolic effects of metformin include enhanced hepatic insulin sensitivity and reduced hepatic glucose output (2). Metformin might reduce insulin resistance in pregnancy, decrease maternal weight gain, reduce maternal glucose levels and fetal hyperinsulinemia, and, as a consequence, reduce neonatal adiposity and birth trauma. Long-term sequelae of neonatal adiposity, including childhood obesity and diabetes, might be diminished with metformin.

Adverse effects of metformin in non-pregnant individuals include nausea, diarrhea, and the rare complication of lactic acidosis (2). This complication is reduced by careful patient selection. Metformin crosses the human placenta (5). Cord levels may exceed maternal levels (6) and could affect fetal cellular function and embryonic development, as insulin is an important fetal growth hormone. Metformin could be detrimental in conditions associated with decreased placental perfusion and fetal growth restriction, when the fetus may rely on development of peripheral insulin resistance to enhance survival.

Preliminary data suggest that metformin may be safe, but there is minimal evidence suggesting efficacy. Results of randomized clinical trials are necessary before the questions of safety or efficacy are answered. In PCOS, there is a randomized trial underway, comparing metformin with placebo through pregnancy. In women with gestational diabetes, MiG: TOFU will address neonatal and childhood outcomes.

It is premature for the ADA to claim that metformin has been shown to be safe and effective in pregnancy (1). The article in the *Bayside Tribune* misrepresented the speakers' message of caution. This newsletter was distributed to many of the 18,000 meeting attendees. The article's prominent position (on the first page) in-

sured broad readership, misinforming many providers.

In our opinion, women with diabetes who present in the first trimester of pregnancy and are taking metformin should change to insulin therapy. There may be specific circumstances when metformin is continued or started during pregnancy, but this decision should be made with a woman giving informed consent after discussing the limitations of current data. Metformin's time has not yet come.

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**Acknowledgments**—We acknowledge Drs. Clifford Bailey and Charles Glueck for their advice and comments on this letter.

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