Preterm Birth—A Risk Factor for Type 2 Diabetes?

The Helsinki Birth Cohort Study

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OBJECTIVE — The association between low birth weight and type 2 diabetes is well established. We studied whether preterm birth carries a similar risk.

RESEARCH DESIGN AND METHODS — The Helsinki Birth Cohort includes 13,345 men and women born between 1934 and 1944. Of them, 12,813 had adequate data on length of gestation, which we linked with data on special reimbursement for diabetes medication.

RESULTS — Of the subjects, 5.1% had received special reimbursement after age 40. In subjects born before 35 weeks of gestation, the odds ratio for diabetes was 1.68 (95% CI 1.06–2.65) compared with that in those born at term. After adjustment for birth weight relative to length of gestation, the odds ratio was 1.59 (1.00–2.52).

CONCLUSIONS — Preterm birth before 35 weeks of gestation is associated with an increased risk of type 2 diabetes in adult life. The risk is independent of that associated with slow fetal growth.

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Low birth weight is a risk factor for type 2 diabetes (1,2). It can be a consequence of slow fetal growth, short gestation, or both. Although the link between type 2 diabetes and slow fetal growth is well established, the link between it and preterm birth has been much less studied (1). Most, although not all (3), of the few existing studies support increasing rates of diabetes in people born preterm, but they have limitations: two focus on severe prematurity (4,5), one is limited to diagnoses in a hospital discharge register (6), and one is based on self-report (7). We assessed whether the rates of type 2 diabetes, according to special medication reimbursement, differ according to gestational age at birth.

RESEARCH DESIGN AND METHODS

— The Helsinki Birth Cohort (8,9) includes 13,345 men and women born in Helsinki between 1934 and 1944. We calculated length of gestation based on the mother's last menstrual period, which was available from birth records for 13,094 subjects. Studies suggest that an exclusion of improbable gestational ages is sufficient to make misclassification of term birth to preterm birth unlikely (10). Accordingly, we excluded 244 subjects (1.9%) whose gestational age was over 44 weeks and 37 subjects (0.3%) born before 37 weeks with birth weight over 2 SDs relative to the length of gestation. Thus, 12,813 subjects (96.0%) had adequate data for length of gestation. Birth weight adjusted for gestational age was calculated, separately for both sexes, as the standardized residual of the regression (birth weight = $\alpha + \beta \times$ gestational age + residual). Using the national identification number, we linked these data with data of special medication reimbursement, available until the end of 2002. In Finland, special reimbursement is granted on the basis of a physician at National Social Insurance Institution confirming each diagnosis of diabetes (11,12). Six hundred and fifty-two people had received reimbursement after 40 years of age. In addition, 82 subjects had received reimbursement before age 40 years. As in previous studies (12), we excluded these subjects because the register does not distinguish between type 1 and type 2 diabetes. This left us with 12,731 subjects.

Data were analyzed by χ^2 test, Student *t* test, and multiple logistic regression. All regression models included sex and year of birth. Because preliminary analyses suggested a nonlinear relationship between gestational age and risk of diabetes (*P* for quadratic trend = 0.009), we illustrate this relationship by presenting gestational age in categories. The study was accepted by the ethics committee. Data were linked with permission from the Ministry of Social and Health Affairs.

RESULTS

— Clinical characteristics are shown in supplementary Table 1 in the online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc10-0912/DC1. More men (6.5%) than women (3.6%) had diabetes. Because there was no interaction between the effects of sex and gestational age ($P = 0.3$), we present the results pooled for both sexes. Subjects with diabetes had a lower birth weight. For each SD unit decrease in birth weight, adjusted for the length of gestation, the odds ratio

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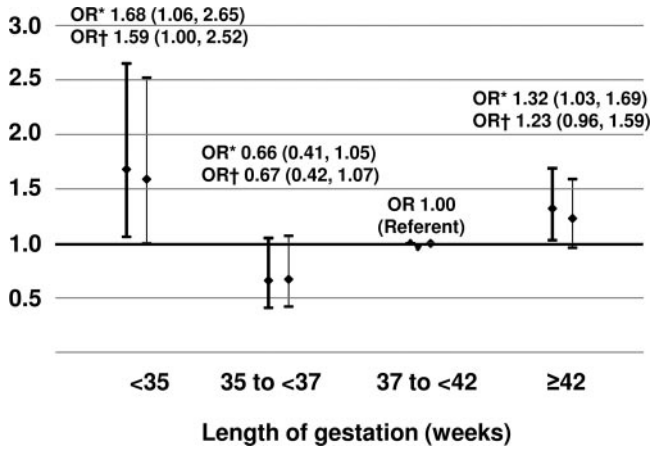

Figure 1—*OR (95% CI) for diabetes according to gestational age at birth. *Adjusted for sex and year of birth (thick bars). †Adjusted for sex, year of birth, whether firstborn, socioeconomic status in childhood, and birth weight relative to length of gestation (thin bars).*

(OR) for diabetes was 1.20 (95% CI 1.11–1.30). There was no quadratic relationship between birth weight SD score and diabetes and no interaction between the effects of preterm birth and birth weight SD score ($P \geq 0.5$).

The OR for diabetes in subjects born before 35 completed weeks of gestation was 1.69 compared with that in subjects born at term. When further adjusted for childhood socioeconomic status, whether firstborn, and birth weight SD score, it was 1.59 (Fig. 1); with further adjustment for maternal BMI in late pregnancy, it was 1.72 (95% CI 1.03–1.69). The odds of diabetes were also increased in subjects born after 42 weeks of gestation, which attenuated to nonsignificance after adjustment for birth weight SD score.

CONCLUSIONS — Our main finding was that preterm birth before 35 weeks of gestation is associated with an increased risk of type 2 diabetes in adult life. The risk is independent of that associated with slow fetal growth. We also found evidence for a moderately increased risk in people born postterm, which remains to be confirmed.

We have previously discussed the limitations of the Helsinki Birth Cohort Study (8,9). Although the diagnosis of diabetes was confirmed by a physician at the National Social Insurance Institution (11), this group was limited to subjects who use medication for diabetes.

Two previous studies reported an increased risk of type 2 diabetes in middle-aged or older people born preterm. These studies and our study each assess a different subset of people who develop diabetes. A study in the Aberdeen 1950–1956 cohort assessed diabetes by self-report at age 46–50 years (7) and was thus limited to early-onset cases. In a Swedish cohort born between 1925 and 1949, diabetes was assessed from Hospital Discharge Register for 1987 to 2006 (6), which may be biased toward cases with complications requiring hospitalization. Our study was based on medication reimbursement and thus also includes nonhospitalized cases. That the findings are consistent in these studies is a strong argument for an increased risk of diabetes conferred by preterm birth.

Several putative mechanisms could underlie an association between preterm birth and type 2 diabetes. Studies in children (5) and young adults (4) born preterm at very low birth weight (<1,500 g) show increased indexes of impaired glucose regulation from an early age onwards. The study in children used intravenous glucose tolerance test and suggested that this is attributable to low insulin sensitivity. This finding was, however, not confirmed in a study in young adults, which also included term small-for-gestational-age subjects and was focused on a lesser degree of prematurity (3). Impaired glucose regulation can be in part contributed to by the lower amount of muscle mass (4) and lower rates of physical activity (13). These may originate from the immediate postnatal period in preterm infants, which corresponds to late gestation in infants born at term, but is characterized by highly different environmental conditions than those in utero. Among infants born at term, this period is important in determining the risk of type 2 diabetes (2,12).

In conclusion, our results reinforce previous suggestions that preterm birth is a risk factor for type 2 diabetes later in life.

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