Maternal diabetes mellitus and timing of pubertal development in daughters and sons: a nationwide cohort study

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Objective: To study the association between maternal diabetes and timing of pubertal development in daughters and sons.
Design: Prospective cohort study.
Setting: Not applicable.
Patient(s): A total of 15,822 mother-child pairs included in the Danish National Birth Cohort and the Puberty Cohort with prospectively collected, register-based and self-reported information on maternal diabetes and self-reported information on pubertal development.
Intervention(s): None.
Main Outcome Measure(s): Adjusted mean monthly difference in age at attaining pubertal milestones in children born of mothers with diabetes compared with children born of mothers without diabetes.
Result(s): A total of 502 children were born of mothers with diabetes during pregnancy. In daughters exposed to gestational diabetes mellitus, we observed advanced onset in all pubertal milestones. The associations were statistically significant with regard to pubic hair Tanner stage 2 (−4.8 months) (95% confidence interval [CI] −7.7, −2.0), pubic hair Tanner stage 3 (−2.2 months) (95 % CI −4.4, 0.0), pubic hair Tanner stage 5 (−6.0 months) (95% CI −10.8, −1.2), and menarche (−2.5 months) (95 % CI −4.9, 0.0). We observed no tendencies between maternal type 1 or type 2 diabetes mellitus and pubertal development in daughters. We observed no associations between maternal diabetes and pubertal development in sons.
Conclusion(s): Our findings suggest that gestational diabetes mellitus may accelerate the pubertal development in daughters. Our results did not support an association between type 1 or type 2 diabetes mellitus and daughters' pubertal development, as well as between any type of maternal diabetes and sons' pubertal development. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Puberty, Tanner stages, diabetes mellitus, gestational, prenatal exposure

The incidence and prevalence of type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM) have increased during the past 50 years (1–3). Concurrently, secular trends of declining age at pubertal onset have been observed since the 19th century, especially in girls, which most likely cannot be explained by genetics features alone (4–6). Causes of early onset of puberty are likely

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multifactorial and maternal diabetes might be a contributing factor to the observed decline.

Diabetes is a complex metabolic disorder mainly featuring hyperglycemia (7), and achieving optimal glycemic control can be challenging due to increased insulin resistance in pregnancy. The underlying pathophysiologies of T1DM and T2DM or GDM are vastly different. Whereas, T1DM is caused by an autoimmune destruction of insulin-producing pancreatic beta cells (2), T2DM and GDM are characterized by insulin resistance (8), and the relationship between obesity and T2DM or GDM is well-established (9). Gestational diabetes mellitus is diagnosed during pregnancy and is one of the greatest risk factors for T2DM later in life (10). Even when glucose levels are well controlled, pregnant women with diabetes have a higher risk of giving birth to a macrosomic child with increased adipose tissue (8, 11). As insulin cannot cross the placental barrier (12), hyperglycemia in pregnant women causes hyperglycemia in the fetuses due to transplacental transfer of glucose without concurrent transfer of maternal insulin (12) in both diabetic and nondiabetic women (13). Hyperglycemia subsequently stimulates the release of insulin by the fetal beta cells and causes fetal hyperinsulinemia (13). Furthermore, insulin stimulates hormonal secretion of the hypothalamus-pituitary-gonadal axis and the gonads (14, 15), and despite improvements in insulin therapy, patients with diabetes still experience reproductive challenges (15, 16). In utero, the fetal hyperinsulinemia might affect the regulation of fetal reproductive hormonal production and subsequently program the reproductive ability and pubertal development in daughters and sons.

Four published studies have indicated tendencies toward earlier pubertal development in daughters (17–19) and sons (19, 20) born of mothers with diabetes. However, none has investigated the association in both daughters and sons with prospective and extensive information on various pubertal milestones in a cohort of this size while taking type of diabetes into account. Thereby, despite these contributions, the question on whether maternal diabetes during pregnancy affects pubertal maturation in daughters and sons persists. We hypothesize that maternal diabetes is associated with earlier pubertal development in daughters and sons compared with children born of mothers without diabetes during pregnancy.

MATERIALS AND METHODS

Data Source and Study Population

This study was based on The Danish National Birth Cohort (DNBC), a nationwide birth cohort, which includes pregnant women and their children, enrolled during early pregnancy from 1997 to 2002 (21). Women were recruited at the first antenatal visit at their general practitioner between weeks 6 and 12 of gestation. A total of 101,042 pregnancies in 91,661 women were included (participation rate, 60%) (Fig. 1). Four computer-assisted telephone interviews were carried out at gestational weeks 17 and 32, as well as 6 and 18 months postpartum. Follow-up of the children was carried out at 7 and 11 years by web-based questionnaires (participation rate, 60 %). The 11-year questionnaire included information on pubertal development, which was used in combination with the questionnaires described later.

In 2012, the Puberty Cohort was established as a subcohort within the DNBC (Fig. 1). A total of 56,641 live-born singletons born between 2000 and 2003 were identified. To be eligible to participate, mothers had to have answered the first interview during pregnancy and not withdrawn their consent of participation before initiation of the Puberty Cohort in May 2012. Then, 27 sampling groups within 12 exposure subgroups of interest were constructed, including maternal diabetes, and combined with a randomly selected cohort sample of 8,000 children from the 56,641 eligible children. A total of 22,439 children were invited to participate in the Puberty Cohort. From the age of 11.5 years, the participants in the Puberty Cohort were asked biannually to provide information on their current stage of puberty, until they reached full sexual maturation (pubertal Tanner stage 5 in both pubic hair [sons and daughters] and breast development [daughters] or genital [sons]) (22, 23) or turned 18 years, whichever came first.

After combining the self-reported pubertal assessments from the 11-year follow-up in the DNBC and the longitudinal data collected in the Puberty Cohort, we had information on pubertal development on 15,822 children (8,125 daughters and 7,697 sons) from the Puberty Cohort. This corresponds to 71% of the invited 22,439 children.

The study was approved by the Committee of Biomedical Research Ethics in Denmark ((KF) 01-471/94) and by the steering committee of the DNBC (2012-04 and 2015-47), as well as registered by the Danish Data Protection Agency (2012-41-0379 and 2015-57-0002). The mothers provided written informed consent on behalf of themselves and their child when entering the DNBC during pregnancy. Participants can withdraw from the cohort at any time.

Assessment of Maternal Diabetes

Data on maternal diabetes during pregnancy, either pregestational (T1DM or T2DM) or GDM, was obtained through the Danish National Patient Registry (DNPR), which includes information on all hospital contacts in Denmark, including date of admission and discharge and the diagnoses classified according to the International Classification of Diseases (ICD). Therefore, we obtained information on maternal diagnoses of diabetes before or during pregnancy (ICD-8 (1977 to 1993): 249-250.09 and ICD-10 (1994 to 2012): E10-E14, O24-O24.9) (Supplemental Table 1, available online).

Through the two telephone interviews during pregnancy and the one telephone interview 6 months postpartum, the mothers also provided self-reported information on diabetes. In the first interview, they were asked “Do you have any severe diseases, e.g., diabetes?” In the second and third interview, they were asked whether they had diabetes at the current time (yes, no). If they had diabetes, they were further asked to indicate the type of diabetes (insulin-dependent, non-insulin-dependent, gestational, do not know). Among all mothers, information on maternal diabetes was missing