Fertility problems and risk of gestational diabetes mellitus: a nationwide cohort study

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Objective: To determine whether women with a history of fertility problems have a higher risk of gestational diabetes mellitus (GDM) than women without a history of fertility problems after adjustment for maternal factors.
Design: Nationwide population-based cohort study.
Setting: Not applicable.
Patient(s): All live and stillbirths during 2004–2010 among women with fertility problems (n = 49,616) and women without fertility problems (n = 323,061) were identified by linkage between the Danish Medical Birth Registry and the Danish Infertility Cohort. Information on GDM was obtained from the Danish National Patient Registry.
Intervention(s): None.
Main Outcome Measure(s): Odds ratios and 95% confidence intervals for the association between fertility problems and risk of GDM after adjustment for potentially confounding factors, including maternal age, prepregnancy BMI, parity, parental history of diabetes, level of education, and smoking during pregnancy.
Result(s): In total, 7,433 (2%) pregnant women received a diagnosis of GDM. Multivariate analysis showed that pregnant women with a history of fertility problems had a statistically significantly higher risk of GDM than pregnant women without fertility problems. In stratified analyses, the association between fertility problems and risk of GDM attenuated with increasing age and was more pronounced among primiparous women and women with polycystic ovary syndrome.
Conclusion(s): Our findings suggest that pregnant women with a history of fertility problems are at increased risk of GDM. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Cohort study, Denmark, fertility problems, gestational diabetes mellitus, infertility

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Gestational diabetes mellitus (GDM), defined as glucose intolerance beginning or first recognized during pregnancy, is one the most common pregnancy complications, affecting 2%–6% of all pregnancies in Europe (1). GDM may have severe adverse outcomes for both mother and child during pregnancy, at childbirth and later in life, including increased risks for preeclampsia, perinatal morbidity, type 2 diabetes, and cardiovascular disease (2–4). The risk factors for GDM include advanced maternal age at pregnancy, prepregnancy overweight or obesity, polycystic ovary syndrome (PCOS), high parity, family history of diabetes, smoking during pregnancy, and multiple gestations (5–9). Increasing trends sin the prevalence of GDM have been reported in several Western countries and have mainly been attributed to delayed maternal age at pregnancy and increasing rates of obesity (10, 11). Current evidence suggests that early detection and

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treatment of GDM improve the outcome of pregnancy and the health of the affected women and their offspring (12, 13). Because most women with GDM have no symptoms, a screening program is required to detect the condition. In Denmark and several other European countries, women who present with an increased risk of GDM undergo screening. Hence, identification of GDM risk factors is essential to identify pregnancies at high risk for the condition.

The number of women experiencing fertility problems, defined as 12 months attempting to achieve a pregnancy without conception, is increasing, and worldwide it is estimated that 5%–15% of all women aged 20–44 years suffer from fertility problems (14). In Denmark, ~9% of the birth cohort in 2014 was conceived after treatment for fertility problems (15), which is the highest proportion in Europe (16). Alongside the expanding advances in assisted reproduction, the implications of this in relation to the obstetrical outcomes of pregnancy are being widely discussed. A growing number of epidemiologic studies have addressed the potential association between fertility problems, fertility treatment, and risk of GDM (17–28); most found an increased risk (17–20, 22, 26–29), although a few showed no marked association (21, 23–25). Several of these studies have been limited by methodologic shortcomings, including lack of information on important confounding or effect modifying factors, such as prepregnancy body mass index (BMI) and PCOS.

To gain further insight into the association between fertility problems and risk of GDM, we conducted a nationwide cohort study of all pregnant women who gave birth to a singleton in Denmark during 2004–2010. Using information from the Danish Infertility Cohort, one of the largest cohorts of subfertile women to date, we compared the risk of GDM among women with fertility problems with that of women in the Danish background population without fertility problems and adjusted for a number of potentially confounding factors. A further aim of the study was to assess whether the association between fertility problems and risk of GDM differed according to risk factors for GDM, including maternal age, prepregnancy BMI, and PCOS.

MATERIALS AND METHODS

Study Population

Since 1973, virtually all births in Denmark have been recorded in the Danish Medical Birth Registry (30). The information recorded includes birth and maternal characteristics, including maternal smoking status and prepregnancy BMI, the latter having been recorded only since 2004. In order to obtain virtually complete information on prepregnancy BMI and other important risk factors, we extracted data for all women with at least one singleton live or stillbirth in Denmark from January 1, 2004 to December 31, 2010.

Each resident of Denmark is assigned a unique personal identification number (PIN) at birth, which is registered in the Civil Registration System; it includes date of birth, sex, and parent-child links. The PIN is used in all Danish health registries and permits accurate linkage of information among them. With the use of the PIN, we linked the cohort of women who gave birth during 2004–2010 to other Danish registries, including the National Patient Registry, the Danish Infertility Cohort, the National Diabetes Registry, and the Population Education Registry, to obtain information on GDM, fertility status, and maternal factors.

For the present analyses, we excluded pregnancies of <22 or >44 completed weeks of gestation (n = 258), pregnancies for which there was no information on gestational age (n = 3,280), and pregnancies for which information on important potential confounders was missing, including prepregnancy BMI (n = 28,461), smoking during pregnancy (n = 9,514), and level of education (n = 19,546). In addition, we excluded the pregnancies of women with pregestational diabetes (n = 4,963), who are considered to have diabetes in pregnancy and by definition are not included in the diagnosis of GDM (31). Women with pregestational diabetes were identified in the Danish National Patient Registry (International Classification of Diseases, 10th Revision [ICD-10]) codes E10–E14 and O24, excluding O24.4) and in the Danish National Diabetes Registry, which includes information on type 1 or type 2 diabetes diagnosed outside pregnancy and is considered to be >90% complete (32). In total, 372,677 singleton pregnancies resulting in a live or stillbirth among 279,852 individual women were included for analysis. Excluded pregnancies were not significantly different from those included regarding the prevalence of fertility problems and other key covariates in the study.

Identification of GDM

Women with a diagnosis of GDM were identified by linkage to the Danish National Patient Registry in the period 2004–2010 by means of the ICD-10 code O24.4. For the present study, we included GDM diagnoses from both hospitalizations and outpatient visits. Cases of GDM diagnosed at any time during pregnancy were included; the total number of pregnancies complicated by GDM was 7,433 (2.0%).

Identification of Fertility Status

To determine fertility status, we linked the study population to the Danish Infertility Cohort. This cohort, which has been described previously in more detail (33), was established in 1997 and initially consisted of 54,362 women ever referred to public Danish hospitals or private fertility clinics from 1963 to 1998 because of fertility problems. According to the Danish clinical guidelines, women are evaluated for fertility problems after failure to become pregnant after ≥12 months of unprotected sexual intercourse (34). Women in the Danish Infertility Cohort were identified either from medical records or local computerized systems directly at public gynecologic hospital departments or private fertility clinics in Denmark, or through the Danish National Patient Registry, by means of ICD-8 code 628 and ICD-10 code DN97. Subsequently, we updated the Danish Infertility Cohort by including women with a diagnosis of infertility recorded in the Danish National Patient Registry during 1999–2012, women recorded in the Danish In Vitro Fertilization Registry in the period 1994–2011, and women who claimed