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Prospective study of time to pregnancy and adverse birth outcomes

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Objective: To investigate the association between time to pregnancy (TTP) and adverse birth outcomes.
Design: Prospective cohort study.
Setting: Not applicable.
Patient(s): A total of 3,521 singletons born to women aged 18-40 years at cohort entry.
Intervention(s): None.
Main Outcome Measure(s): Selected birth outcomes, including preterm birth (PTB, <37 weeks' gestation), low birth weight (<2,500 g), small for gestational age, large for gestational age, and placental disorders, ascertained from the Danish Medical Birth Registry and Danish National Registry of Patients. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using log-binomial regression, with adjustment for potential confounders and fertility treatment.
Result(s): Multivariable RRs for PTB in relation to TTP of 3–5, 6–11, and ≥12 vs. <3 cycles were 1.59 (95% CI 0.94–2.69), 0.85 (95% CI 0.48–1.50), and 1.57 (95% CI 0.93–2.65). The association was slightly stronger for spontaneous PTB (TTP ≥12 vs. <3 cycles: RR 1.69, 95% CI 0.84–3.42) than for medically indicated PTB (RR 1.39, 95% CI 0.62–3.12). Longer TTPs (≥12 cycles) were associated with increased risks of low birth weight (RR 1.80, 95% CI 0.97–3.35), cesarean delivery (RR 1.64, 95% CI 1.27–2.12), placental disorders (RR 2.21, 95% CI 1.07–4.56), ischemic placental disease (RR 1.56, 95% CI 0.99–2.44), pre-eclampsia (RR 1.45, 95% CI 0.79–2.65), and postpartum hemorrhage (RR 1.58, CI 1.14–2.19), and decreased risks of macrosomia (≥4,500 g; RR 0.63, 95% CI 0.35–1.13) and large for gestational age (RR 0.76, 95% CI 0.58–1.00). Longer TTP showed little association with small for gestational age.
Conclusion(s): In a prospective cohort study of Danish pregnancy planners, delayed conception was a marker for adverse birth outcomes, after accounting for fertility treatment. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Fertility, preterm birth, low birth weight, prospective study, cohort study

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Studies have documented that infants conceived using assisted reproductive technology (ART) have an increased risk of adverse obstetric and perinatal outcomes (1, 2). In addition, couples conceiving spontaneously after a long time to pregnancy (TTP) have been shown to have an increased risk of adverse birth outcomes, independent of fertility treatment or multiple gestation (3–9). In a recent systematic review and meta-analysis (4), infertility (TTP >12 months) was associated with an approximately 30% increased risk of preterm birth (PTB) and low birth weight (LBW) relative to TTP ≤12 months. Furthermore, infertility or longer TTP was associated with an increased risk of pre-eclampsia in three studies (10–12). However, no study has used a prospective measure of TTP, and most studies have relied on the conventional definition of infertility (>12 months attempting to conceive without success) (5–10, 12–14). Ascertaining the effect of subfertility

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on adverse birth outcomes, independent of ART, could help identify high-risk women who might benefit from greater obstetric surveillance.

We used data from a prospective cohort study of Danish pregnancy planners to examine the relation between TTP and selected birth outcomes. In the study, participants reported their TTP prospectively (i.e., before the occurrence of pregnancy). Selected adverse birth outcomes were ascertained from the Danish population health registries. We further assessed the extent to which the use of fertility medications explained the associations of interest.

MATERIALS AND METHODS

Study Population

The Snart-Gravid Study is an Internet-based prospective cohort study of pregnancy planners in Denmark. The study methodology has been described in detail elsewhere (15–17). Briefly, recruitment was initiated in June 2007 by advertising on a health-related website (www.netdoktor.dk) and by implementing a coordinated media strategy involving radio, print media, online news sites, and television. Enrollment and primary data collection were carried out using self-administered online questionnaires.

Before enrollment, participants read a consent form and completed an online screening questionnaire to confirm eligibility. Eligible women were aged 18–40 years, residents of Denmark, in a stable relationship with a male partner, and not using any fertility treatments. Participants provided a valid e-mail address and their Civil Personal Registration (CPR) number, a unique 10-digit personal identification number assigned to each resident by the Central Office of Civil Registration (18). The study was approved by the Danish Data Protection Board and the Institutional Review Board at Boston University.

The baseline questionnaire collected information on demographics; reproductive and medical history; and lifestyle and behavioral factors. Follow-up questionnaires, completed by participants every 2 months, evaluated changes in selected exposures and outcomes. Participants were contacted every 2 months for 12 months or until clinically recognized conception. Those who conceived were asked to complete one questionnaire during early pregnancy to assess changes in exposures, after which active follow-up ceased. After 54 months of recruitment, 5,046 eligible women were enrolled in the cohort. Cohort retention after 12 months of follow-up was approximately 82% (17).

Assessment of TTP

On each follow-up questionnaire, women reported the date of their last menstrual period (LMP), whether they were currently pregnant, and whether they had experienced any other pregnancies since the date of their last questionnaire, including miscarriage, induced abortion, or ectopic pregnancy. Time to pregnancy, in cycles, was calculated as months of attempt time at study entry plus months of attempt time after enrollment in the study until the date of LMP, divided by menstrual cycle length (as reported on baseline and follow-up questionnaires). The date of LMP for the index pregnancy was calculated as the due date in the birth registry minus 280 days.

Assessment of Covariates

Data on age, weight, height, parity, smoking history, current alcohol consumption, last method of contraception, physical activity, frequency of intercourse, and history of infertility (defined as having tried for ≥ 12 months to conceive without success before the index pregnancy attempt), hypertension, and diabetes were self-reported on the baseline questionnaire. We estimated total metabolic equivalents of reported physical activity per week by summing the metabolic equivalents from moderate exercise (hours per week multiplied by 3.5) and vigorous exercise (hours per week multiplied by 7.0) (19). We calculated body mass index (BMI) as weight (kilograms)/height (meters)^2. Self-reported height and weight among women who delivered infants conceived during our study showed excellent agreement with health provider–based measures in the Danish Medical Birth Registry (20).

Data on pregnancy loss before 22 weeks' gestation were obtained from two sources: [1] the Snart-Gravid follow-up questionnaire, and [2] the Danish National Registry of Patients, using International Classification of Diseases, 10th revision (ICD-10) codes DO03 for spontaneous abortion and DO04 for therapeutic abortion. Data on fertility treatment use were obtained from the Danish National Database of Reimbursed Prescriptions and the Danish National Registry of Patients. These data were supplemented with data from the follow-up questionnaires, on which women reported the initiation of fertility treatment, and with data from the early pregnancy questionnaire, on which women reported the use of fertility treatment to conceive the index pregnancy. Additional data on pre-existing hypertension complicating pregnancy were obtained from the Danish Medical Birth Registry and the Danish National Registry of Patients (ICD-10 codes: O10, O100-O109).

Assessment of Adverse Birth Outcomes

To obtain complete information on pregnancy outcomes from Snart-Gravid participants, we matched each woman's CPR number to her records in the Danish National Birth Registry and Danish National Registry of Patients. The Danish National Registry of Patients provides information on all hospital inpatient and outpatient encounters, and the Danish National Birth Registry provides information on all live and still births. From these registries we abstracted data on birth weight, gestational age, infant sex, cesarean section, preeclampsia (including eclampsia and HELLP syndrome [characterized by hemolysis (H), elevated liver enzymes (EL), and low platelet count (LP)]), gestational hypertension, gestational diabetes, placenta previa, placental abruption, placental accreta, placental insufficiency, malformations of the placenta; retained or adherent placenta, cotyledons, or membranes; placental transfusion syndrome; intrauterine growth restriction; and infant Apgar scores. Postpartum hemorrhage was defined as blood loss of ≥ 500 mL. Ischemic placental disease (IPD) included intrauterine growth