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A prospective study of time-to-pregnancy and adverse birth outcomes

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Abstract

Objective—To investigate the association between time-to-pregnancy (TTP) and adverse birth outcomes.

Design—Prospective cohort study.

Setting—Internet-based observational study of Danish pregnancy planners (2007-2012).

Patient(s)—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 (LBW, <2500 g), small-for-gestational age (SGA), large-for-gestational age (LGA), and placental disorders— ascertained from the Danish Medical Birth Registry and Danish National Registry of Patients. Risk ratios (RR) and 95% confidence intervals (CI) were estimated using log-binomial regression, with adjustment for potential confounders and fertility treatment.

Results—Multivariable RRs for PTB in relation to TTP of 3-5, 6-11, and ≥12 versus <3 cycles were: 1.59 (CI: 0.94, 2.69), 0.85 (CI: 0.48, 1.50), and 1.57 (CI: 0.93, 2.65). The association was slightly stronger for spontaneous PTB (TTP ≥12 versus <3 cycles: RR=1.69, CI: 0.84, 3.42) than medically-indicated PTB (RR=1.39, 95%: 0.62, 3.12). Longer TTPs (≥12 cycles) were associated

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with increased risks of LBW (RR=1.80, CI: 0.97, 3.35), caesarean delivery (RR=1.64, CI: 1.27, 2.12), placental disorders (RR=2.21, CI: 1.07, 4.56), ischemic placental disease (RR=1.56, CI: 0.99, 2.44), preeclampsia (RR=1.45, CI: 0.79, 2.65), and postpartum hemorrhage (RR=1.58, CI: 1.14, 2.19), and decreased risks of macrosomia (≥4,500g; RR=0.63, CI: 0.35, 1.13) and LGA (RR=0.76, CI: 0.58, 1.00). Longer TTP showed little association with SGA.

Conclusion—In a prospective cohort study of Danish pregnancy planners, delayed conception was a marker for adverse birth outcomes, after accounting for fertility treatment.

MeSH words

fertility; preterm birth; low birth weight; prospective study; cohort study

Introduction

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 preeclampsia 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 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.

Subjects 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 healthrelated 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 time-to-pregnancy

On each follow-up questionnaire, women reported the date of their last menstrual period, 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. TTP, in cycles, was calculated as months of attempt time at study entry + months of attempt time post-enrollment in the study until date of last menstrual period, divided by menstrual cycle length (as reported on baseline and follow-up questionnaires). The date of last menstrual period 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 or more months to conceive without success prior to 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/week multiplied by 3.5) and vigorous exercise (hours/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 of gestation were obtained from two sources: 1) the Snart-Gravid follow-up questionnaire, and 2) the Danish National Registry of Patients, using 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 in 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, caesarean section, preeclampsia (including eclampsia and HELLP syndrome), 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 restriction, placental abruption, and preeclampsia (21, 22). A list of ICD-10 codes used to identify selected birth outcomes is shown in Table 1.

Medically-indicated PTB was defined as a birth <37 weeks of gestation with either i) labor that was induced medically or ii) delivery by c-section prior to onset of labor. Spontaneous PTB was defined as a birth <37 weeks of gestation due to premature preterm rupture of membranes (PPROM) or the initiation of labor for no known reason. This PTB subtype was identified by codes for PPROM (ICD-10 codes O42.0 and O42.2) and the absence of any codes indicating surgery or medical induction of labor in the Danish Medical Birth Registry. LBW was defined as <2,500g and macrosomia was defined as ≥4,500g. Small-for-gestational-age (SGA: lowest 10% of birth weight by gestational age) and largefor-gestational-age (LGA: highest 10% of birth weight by gestational age) were classified based on ultrasonically-estimated fetal weights from a Scandinavian population.(23)

Exclusions

Of the 5,046 women enrolled in the Snart-Gravid Study between June 2007 and August 2011, we excluded women with an invalid CPR number (N=8), women who either reported a pregnancy loss on the follow-up questionnaire (N=347) or were found in the Abortion Patient Registry (N=88), women who were assumed to have had an intervening pregnancy loss based on the lack of agreement between LMP dates on the questionnaire and the registry (N=375), women who had multiple gestations recorded in the registry (N=126 twins, N=1 triplets), women whose LMP date was within 44 weeks of December 31, 2012 (N=11), and women who completed follow-up without a recognized conception and who did not have a study-related birth in the Medical Birth Registry through December 31, 2012 (N=569), leaving 3,521 women for the present analysis.

We did not place any restrictions on attempt time at study entry in our primary analyses, but we performed sensitivity analyses in which we restricted the cohort to those who had been trying for <3 cycles at entry (see Data Analysis).

Data analysis

We examined the association between prospectively-reported TTP classified into 4 categories (<3 (referent), 3-5, 6-11, ≥12 cycles) and selected birth outcomes. We used logbinomial regression models to estimate unadjusted and multivariable-adjusted risk ratios (RR) and 95% confidence intervals (CI) for the association between TTP and the outcomes of interest, controlling for potential confounders. We controlled for putative risk factors for each outcome that could plausibly be related to longer TTP, including maternal age at infant birth, paternal age at infant birth, maternal education, maternal pre-pregnancy BMI, maternal smoking, and parity before the index birth. In additional models, we further controlled for use of fertility medications because some research has indicated that the association between delayed TTP and adverse birth outcomes such as PTB is explained by fertility treatment use (1, 2), and because an infertility work-up is not recommended in Denmark until after couples have attempted pregnancy for at least 1 year (24). We considered additional variables as potential confounders, including cycle regularity, uterine fibroids, male birth, and preexisting high blood pressure or type 2 diabetes, but they did not change the effect estimates by more than 5%.

We repeated the analyses after excluding women with preexisting medical conditions, including hypertension and diabetes, in an attempt to rule out confounding by these variables. Finally, to address the concern that some women entered the study after having tried to conceive for several months, which might allow for larger error in the reporting of TTP (25), we repeated the analysis among women who had been trying to conceive <3 months at study entry. We used multiple imputation to impute missing data on exposures, outcomes, and covariates (PROC MI and PROC MIANALYZE in SAS) (26). Missingness was <5% for all variables in the present analysis. It was not necessary to account for clustering of births within women because the study included only one birth per participant. SAS version 9.2 was used for all analyses (27).

Results

TTP for the index birth was positively associated with female age, BMI, regular smoking at baseline, smoking during pregnancy, fertility treatment use, infertility history, and attempt time at study entry, and inversely associated with cycle regularity, gravidity, parity, and higher education (Table 2). There was little evidence of an association between TTP and pre-existing high blood pressure or type 2 diabetes. TTP at the index birth was not materially associated with the probability of male birth. After restricting to non-users of fertility treatment with fewer than <3 cycles of attempt time at study entry, the age-standardized probabilities of male birth for TTPs of <3, 3-5, 6-11, and ≥12 were 49.8%, 51.5%, 47.9%, and 52.2%, respectively. Median attempt time at study entry was 2 cycles (interquartile range: 1-6 cycles; range: 0-87 cycles).

Our data indicated a non-monotonic positive association between TTP and the risk of PTB (Table 3). The association was attenuated after adjustment for potential confounders. The fully-adjusted RRs for PTB in relation to TTP of 3-5, 6-11, and ≥12 versus <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

RRs for TTP (≥12 versus <3 cycles) in relation to spontaneous and medically-indicated PTB were 1.69 (95% CI: 0.84, 3.42) and 1.39 (95% CI: 0.62, 3.12), respectively. There was only a weak association between fertility treatment and PTB risk (RR=1.05, 95% CI: 0.72, 1.54), which explains why control for fertility treatment had little effect on the association between TTP and PTB. When we further controlled for ischemic placental disease (IPD), which accounts for up to 50% of medically-indicated PTB (21), the RR for TTP (≥12 versus <3 cycles) and medicallyindicated PTB was 1.05 (95% CI: 0.48, 2.31). The overall association between TTP (≥12 versus <3 cycles) and PTB became stronger when we used a more stringent definition of PTB (<36 weeks' gestation: IRR=2.25, 95% CI: 1.09, 4.65; <35 weeks' gestation: IRR=4.20, 95% CI: 1.48, 11.9).

Longer TTP was positively associated with both intrauterine growth restriction and LBW, but there was little evidence of an association with SGA. The crude positive association between TTP and SGA (TTP ≥12 versus <3 cycles: RR=1.49) weakened markedly after control for potential confounders, including fertility treatment (TTP ≥12 versus <3 cycles: RR=1.00). In contrast, TTP (≥12 versus <3 cycles) was inversely associated with LGA before (RR=0.72, 95% CI: 0.56, 0.93) and after control for covariates including fertility treatment (RR=0.76, 95% CI: 0.58, 1.00). Fertility treatment itself was strongly associated with SGA (RR=1.53, 95% CI: 1.14, 2.05) but not LGA (RR=1.06, 95% CI: 0.82, 1.38). Results for macrosomia were consistent with those for LGA.

Longer TTP was associated with a doubling in the risk of placental disorders for all categories of TTP above the referent: RRs for the three longest TTP categories relative to the shortest were: 2.12, 2.10, and 2.21 (Table 3). Maternal characteristics and fertility treatment explained some, but not all, of the excess risk. Positive associations were observed between TTP and each of the placental disorders, though associations were imprecise and not all outcomes demonstrated monotonic associations with TTP (Supplemental Table 1). The strongest associations were observed for TTP (≥12 versus <3 cycles) in relation to placental abruption (RR=2.62, 95% CI: 0.58, 11.8) and morbidly retained placenta, membranes, or cotyledons (RR=2.72, 95% CI: 0.88, 8.35). The positive association between TTP and placental disorders was relatively uniform across strata of age and parity (Supplemental Table 2). TTP was positively associated with IPD (RR=1.56, 95% CI: 0.99, 2.44; Table 3), and the association was stronger among parous women (RR=3.08, 95% CI: 1.04, 9.13) and women aged ≥30 (RR=2.81, 95% CI: 1.22, 6.50) women (Supplemental Table 2) relative to nulliparous and younger.

Longer TTP was associated with an increased risk of gestational diabetes and caesarean delivery in a dose-dependent fashion (Table 3), and TTP≥12 cycles was associated with a 45% increased risk of preeclampsia (95% CI: 0.79, 2.65) and a 58% increased risk of postpartum hemorrhage (95% CI: 1.14, 2.19). There was little evidence of an association of TTP with polyhydramnios, oligohydramnios, gestational hypertension, or infant Apgar scores <9 at 5 minutes (data not shown).

Results restricted to women with fewer than 3 cycles of attempt time at study entry were similar to those found among all women, with the exception that associations were slightly stronger for TTP in relation to IPD and medically-indicated PTB, and weaker for

spontaneous PTB (Table 4). Because cycle irregularity may influence the estimate of both TTP and gestational age (7), we repeated our analysis among the 2,662 women who reported regular cycles at baseline (data not shown). In this subgroup of women, results for PTB, intrauterine growth restriction, SGA, placental disorders, IPD, and caesarean section were somewhat stronger, whereas results for LGA were nearly identical to the original results. Using months of attempt time instead of menstrual cycles of attempt time as the time metric made little difference in the effect estimates (data not shown).

Discussion

Studies have consistently documented a positive association between assisted reproductive technologies (ART) and risk of adverse birth outcomes (1, 2). Subsequent studies have suggested that infertility itself, independent of ART, is also associated with adverse birth outcomes (3-9). In a 2012 systematic review and meta-analysis of 17 studies (4), the pooled adjusted odds ratios for infertility (TTP≥12 vs. <12 months) in relation to PTB and SGA were 1.31 (95% CI: 1.21, 1.42) and 1.17 (95% CI: 1.03, 1.33), respectively. Results from the present study, which take into account maternal characteristics and the use of fertility treatment, agree with previous studies showing positive associations of TTP with PTB (1, 4), LBW (4), placental disorders (1), caesarean section (1, 4), and preeclampsia (1, 10-12), but not with those showing an increased risk of SGA (4). Moreover, contrary to expectation, control for fertility treatment in addition to other measured covariates made little difference in the effect estimates for TTP and the birth outcomes studied, with the exception of SGA.

To our knowledge, there are no previous studies of TTP in relation to subtypes of PTB. The disaggregation of subtypes can help distinguish between the different etiologies of PTB (28-31). Although the same processes that lead a clinician to intervene tend to result in spontaneous PTB if there is no intervention, previous research indicates that medically-indicated PTB is associated with greater intensity of medical care (28, 31). Our analysis indicated that the positive association between longer TTP and PTB overall was not wholly explained by medically-indicated PTB.

The observed positive dose-response relation between TTP and caesarean section could be explained by the tendency of women with longer TTPs to receive greater obstetric surveillance, to be identified as in need of medical intervention, and to accept medical intervention when offered, than women with shorter TTPs. However, this phenomenon did not appear to explain the association between TTP and PTB because spontaneous PTB also showed an elevated risk.

Although our study showed evidence of a positive association of TTP with both intrauterine growth restriction and LBW, there was little association between TTP and SGA, consistent with other studies showing longer TTP to be either weakly (1, 4) or not associated (13) with SGA. Longer TTP was inversely associated with risk of LGA. These associations could be explained by greater obstetrical surveillance and early medical intervention among women with longer TTPs. For example, if a woman whose fetus is measured to be large is being more closely monitored due to her subfertility or infertility, it is more likely that the obstetrician will recommend interventions for reducing LGA. Likewise, a woman whose

fetus is determined to be at risk for SGA might be delivered earlier to reduce SGA risk (possibly leading to PTB and LBW).

The observed positive association between TTP and placental disorders was evident after control for maternal age and fertility treatment use, which are well-established independent risk factors for placental disorders (32). These findings were relatively uniform across maternal age and parity status. Uterine or tubal pathologies may have confounded the association between delayed TTP and disorders in placentation (33), but we could not assess this possibility directly. The association between longer TTP and postpartum hemorrhage may also reflect an underlying association with placental disorders, given that about 10% of postpartum hemorrhage is due to retained placenta or abnormal placental implantation (the most common cause being uterine atony, 80%) (34).

In line with our positive findings for placental disorders, we found a positive association between TTP and IPD, a syndrome that includes preeclampsia, intrauterine growth restriction, and placental abruption (21, 22). These three obstetrical conditions have been hypothesized to represent distinct clinical manifestations of the same underlying disease process at varying gestational ages (21). Ananth postulated that IPD results from inadequate placental attachment or premature placental detachment (21). Risk factors for IPD include abnormal extracellular matrix remodeling, thrombosis and coagulation defects, inflammation, infection, and angiogenesis (21). Studies have indicated greater overlap in IPD conditions among preterm than term births, and IPD is implicated in greater than 50% of all medically-indicated PTB (21). We found that control for IPD markedly attenuated the association between TTP and medicallyindicated PTB. Thus, our data indicate that delayed TTP may be a marker for heightened risk of abnormal placentation.

The present study is the first to use a prospective measure of TTP to evaluate risk of adverse birth outcomes. Results were similar with and without the introduction of left truncation (i.e., attempt time at study entry <3 vs. ≥3). Our use of the full spectrum of TTP instead of a dichotomous variable for clinical infertility (≥12 months of trying without success) is an additional strength. With these data, we were able to evaluate dose-response relations and also assess the extent to which findings would be obscured when using a dichotomous measure. Unlike previous registry-based studies, our study incorporated data from self-administered questionnaires, which permitted adjustment for a wide range of potential confounders, including maternal and paternal characteristics.

As with all registry data, there are challenges in the sensitivity of data capture and the accuracy of diagnostic coding. Selected registry variables have been validated against medical chart review, showing a range of sensitivities: placenta previa (sensitivity=53%) (35), hypertensive disorders (sensitivity=54%) (35), placental abruption (sensitivity=66%) (35), polyhydramnios (sensitivity=71%) (35), and uterine rupture (sensitivity=84%) (36). Our classification of spontaneous PTB was likely to have high specificity but poor sensitivity because this PTB subtype was identified by codes for PPROM and the absence of any codes indicating surgery or medical induction of labor in the Danish Medical Birth Registry. It is plausible that PTB could start spontaneously and then require subsequent medical intervention. Thus, a subset of women classified as having had a medically-

indicated PTB actually may have had a spontaneous PTB. If we assume that TTP is not truly associated with spontaneous PTB and a non-negligible fraction of spontaneous PTB was misclassified as medically-indicated, then we would expect the results for medically-indicated PTB to be biased towards the null. Finally, because our study is restricted to pregnancy planners, the results may not be generalizable to women with unplanned pregnancies. Differential recognition of pregnancy is unlikely to be a concern in our study because 96% of women reported having used home pregnancy tests to document their pregnancy (37).

We cannot rule out unmeasured confounding as an explanation of our findings. If an unmeasured confounder caused couples to experience difficulties conceiving and also compromised the pregnancy, our associations would be biased. For instance, exposure to stress, pelvic infections, and environmental contaminants may contribute to subfertility and pregnancy complications, including disorders of placentation (38, 39), but we did not have data on these variables.

In this study that combined data from population health registries and self-administered questionnaires, we found positive associations of prospectively-measured TTP with PTB (both subtypes), intrauterine growth restriction, LBW, placental disorders, IPD, gestational diabetes, caesarean section, preeclampsia, and postpartum hemorrhage, but little evidence of an association with SGA. TTP was inversely associated with LGA. Our observation that spontaneous PTB was equally, if not more strongly, associated with TTP than medicallyindicated PTB implies that greater obstetric surveillance or medical preferences for early intervention do not fully explain the positive association between TTP and PTB. Indeed, infertility may result from a range of underlying pathologies and some of the mechanisms leading to infertility may play a role in the etiology of adverse birth outcomes (3, 4, 7, 40-42). This implies that the observed associations may not be causal. Nevertheless, delayed TTP may serve as a useful clinical marker for identifying women at increased risk for several adverse birth outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Danish ICD-10 codes identified to define selected birth outcomes

Outcome	Danish ICD-10 codes	N[a]
Placental disorders		134
Placenta previa	O440, O441, O443, O449	19
Placental abruption	O452, O453,O458, O459	17
Placental insufficiency	O365A	72
Placenta accreta	O722B, O730A, O730A1	3
Placenta increta	O730A2	0
Placenta percreta	O722H, O730A3	0
Malformation of placenta[b]	O431, O431A-O431E	1
Placental transfusion syndrome	O430, O430A	4
Morbidly retained, trapped or adherent placenta, cotyledons, or membranes	O722C, O722F, O722H, O730, O731	22
Polyhdramnios	O409	21
Oligohydramnos	O410	53
Uterine rupture	O710A, O710B, O711A, O711AA, O711B	1
Postpartum hemorrhage	O720, O721, O722, O723	429
Intrauterine growth restriction, all causes	O365, O365A-O365F	102
Gestational hypertension	O139	88
Gestational diabetes	O244	118
Preeclampsia (including eclampsia and HELLP syndrome)	O140, O141, O142, O149, O150, O151, O152, O159	142
Caesarean section (singleton births)		738
Elective (planned) c-section	O820	233
Emergency c-section before labor	O821A	120
Emergency c-section during labor, previously planned	O821B	60
Emergency c-section during labor due to complications	O821C	325
Preterm birth		
Spontaneous: preterm premature rupture of membranes	O420, O422	50
Spontaneous: early labor for no known reason	O800, O821B, or O821C; GA<37 weeks	70
Medically-indicated preterm birth (induced or c-section)	O820, O821A, or O838A; GA<37 weeks	65
Small-for-gestational-age birth	<10% birth weight for GA(23)	278
Large-for-gestational-age birth	>10% birth weight for GA(23)	466

[a] N=number of women out of 3,529 participants in analysis. GA=gestational age.

[b] Marginata placenta, vasa previa, circumvallate placenta, or placenta partita.

Table 2

Baseline characteristics of 3,521 Snart-Gravid participants according to time-to-pregnancy

	Time-to-pregnancy at index conception (cycles)			
Characteristic [a]	**<3**	**3-5**	**6-11**	**≥12**
Number of women	504	851	942	1,224
Age, years (mean)	29.2	29.0	29.4	30.7
Male partner's age, years (mean)	31.2	30.7	30.9	30.3
BMI, kg/m^2 (mean)	23.4	24.0	24.1	24.8
Regular cycles (%)	78.1	79.4	72.8	73.8
Gravid (%)	54.0	50.4	46.9	36.2
Parous (%)	46.6	38.1	32.5	21.6
Current regular smoker at baseline (%)	7.8	9.8	11.7	17.2
≥5 pack-years of ever smoking (%)	15.1	15.4	16.9	18.8
Smoked during pregnancy (%)	4.4	5.5	5.7	8.7
Higher education >4 years (%)	28.3	27.4	22.1	18.0
High blood pressure (%)	8.9	9.0	8.1	9.3
Type 2 diabetes (%)	1.9	1.4	1.7	1.1
Uterine fibroids (%)	2.0	2.6	2.5	1.8
Infertility history reported at baseline (%)	4.1	6.8	10.3	28.9
Use of fertility drugs for index pregnancy (%)	1.3	1.6	10.7	32.5
Male birth	49.9	52.1	49.8	52.3
Attempt time at study entry, cycles (mean)	0.6	1.5	3.4	8.4

[a] All characteristics (except age) are age-standardized to cohort at baseline. Restricted to first imputed data set.

Table 3

Time-to-pregnancy and selected adverse birth outcomes, Snart-Gravid Study, 2007-2012.

	Time to pregnancy (cycles)			
	<3 (N=504)	**3-5 (N=851)**	**6-11 (N=942)**	**≥12 (N=1,224)**
Preterm birth (<37 weeks)				
N (%) with outcome	18 (3.6)	51 (6.0)	32 (3.4)	84 (6.9)
Unadjusted RR (95% CI)	1.00 (ref.)	1.68 (0.99, 2.84)	0.95 (0.54, 1.68)	1.92 (1.17, 3.16)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.59 (0.94, 2.69)	0.86 (0.48, 1.52)	1.63 (0.98, 2.71)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.59 (0.94, 2.69)	0.85 (0.48, 1.50)	1.57 (0.93, 2.65)
Spontaneous preterm birth				
N (%) with outcome	10 (2.0)	36 (4.2)	22 (2.3)	52 (4.3)
Unadjusted RR (95% CI)	1.00 (ref.)	2.13 (1.07, 4.26)	1.18 (0.56, 2.46)	2.14 (1.10, 4.18)
Adjusted RR (95% CI)[a]	1.00 (ref.)	2.05 (1.03, 4.08)	1.06 (0.51, 2.21)	1.86 (0.94, 3.68)
Adjusted RR (95% CI)[b]	1.00 (ref.)	2.05 (1.03, 4.07)	1.03 (0.49, 2.16)	1.69 (0.84, 3.42)
Medically-indicated preterm birth				
N (%) with outcome	8 (1.6)	15 (1.8)	10 (1.1)	32 (2.6)
Unadjusted RR (95% CI)	1.00 (ref.)	1.11 (0.47, 2.60)	0.67 (0.26, 1.68)	1.65 (0.76, 3.55)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.01 (0.43, 2.34)	0.59 (0.23, 1.53)	1.32 (0.61, 2.88)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.01 (0.43, 2.35)	0.60 (0.23, 1.56)	1.39 (0.62, 3.12)
Preterm birth (<36 weeks)				
N (%) with outcome	9 (1.8)	26 (3.1)	27 (2.9)	56 (4.6)
Unadjusted RR (95% CI)	1.00 (ref.)	1.71 (0.81, 3.62)	1.61 (0.76, 3.39)	2.56 (1.28, 5.14)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.67 (0.79, 3.53)	1.48 (0.70, 3.12)	2.19 (1.08, 4.46)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.67 (0.79, 3.54)	1.49 (0.70, 3.15)	2.25 (1.09, 4.65)
Preterm birth (<35 weeks)				
N (%) with outcome	4 (0.8)	17 (2.0)	18 (1.9)	46 (3.8)
Unadjusted RR (95% CI)	1.00 (ref.)	2.52 (0.85, 7.44)	2.41 (0.82, 7.08)	4.74 (1.71, 13.1)
Adjusted RR (95% CI)[a]	1.00 (ref.)	2.46 (0.83, 7.27)	2.17 (0.74, 6.39)	4.00 (1.42, 11.2)
Adjusted RR (95% CI)[b]	1.00 (ref.)	2.51 (0.85, 7.42)	2.27 (0.77, 6.68)	4.20 (1.48, 11.9)
Intrauterine growth restriction				
N (%) with outcome	10 (2.0)	26 (3.1)	33 (3.5)	33 (2.7)
Unadjusted RR (95% CI)	1.00 (ref.)	1.54 (0.75, 3.17)	1.77 (0.88, 3.55)	1.36 (0.67, 2.73)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.56 (0.76, 3.18)	1.76 (0.86, 3.60)	1.32 (0.64, 2.72)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.56 (0.76, 3.21)	1.83 (0.91, 3.70)	1.52 (0.73, 3.16)
Low birth weight (<2,500g)				
N (%) with outcome	12 (2.4)	29 (3.4)	33 (3.5)	65 (5.3)
Unadjusted RR (95% CI)	1.00 (ref.)	1.43 (0.74, 2.78)	1.47 (0.77, 2.82)	2.23 (1.22, 4.09)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.43 (0.75, 2.74)	1.39 (0.73, 2.68)	1.99 (1.08, 3.65)

	Time to pregnancy (cycles)			
	<3 (N=504)	**3-5 (N=851)**	**6-11 (N=942)**	**≥12 (N=1,224)**
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.43 (0.75, 2.74)	1.36 (0.70, 2.62)	1.80 (0.97, 3.35)
Small-for-gestational-age birth				
N (%) with outcome	31 (6.1)	62 (7.3)	73 (7.8)	112 (9.2)
Unadjusted RR (95% CI)	1.00 (ref.)	1.18 (0.78, 1.80)	1.26 (0.84, 1.89)	1.49 (1.01, 2.18)
Adjusted RR (95% CI)a	1.00 (ref.)	1.11 (0.73, 1.67)	1.13 (0.76, 1.70)	1.17 (0.79, 1.74)
Adjusted RR (95% CI)b	1.00 (ref.)	1.10 (0.73, 1.67)	1.07 (0.72, 1.63)	1.00 (0.66, 1.51)
Large-for-gestational-age birth				
N (%) with outcome	79 (15.7)	117 (13.8)	132 (14.0)	138 (11.3)
Unadjusted RR (95% CI)	1.00 (ref.)	0.88 (0.67, 1.14)	0.89 (0.69, 1.16)	0.72 (0.56, 0.93)
Adjusted RR (95% CI)[a]	1.00 (ref.)	0.90 (0.69, 1.16)	0.92 (0.71, 1.18)	0.78 (0.60, 1.01)
Adjusted RR (95% CI)[b]	1.00 (ref.)	0.90 (0.69, 1.16)	0.91 (0.71, 1.18)	0.76 (0.58, 1.00)
Macrosomia (≥4,500g)				
N (%) with outcome	20 (4.0)	25 (2.9)	27 (2.9)	30 (2.4)
Unadjusted RR (95% CI)	1.00 (ref.)	0.74 (0.42, 1.32)	0.72 (0.41, 1.27)	0.62 (0.35, 1.08)
Adjusted RR (95% CI)[a]	1.00 (ref.)	0.75 (0.42, 1.33)	0.74 (0.42, 1.31)	0.64 (0.36, 1.15)
Adjusted RR (95% CI)[b]	1.00 (ref.)	0.75 (0.43, 1.33)	0.74 (0.41, 1.31)	0.63 (0.35, 1.13)
Placental disorders				
N (%) with outcome	9 (1.8)	32 (3.8)	37 (3.9)	56 (4.6)
Unadjusted RR (95% CI)	1.00 (ref.)	2.11 (1.01, 4.38)	2.20 (1.07, 4.52)	2.56 (1.28, 5.14)
Adjusted RR (95% CI)[a]	1.00 (ref.)	2.12 (1.02, 4.40)	2.14 (1.04, 4.40)	2.38 (1.18, 4.81)
Adjusted RR (95% CI)[b]	1.00 (ref.)	2.12 (1.02, 4.39)	2.10 (1.02, 4.32)	2.21 (1.07, 4.56)
Ischemic Placental Disease				
N (%) with outcome	25 (5.0)	60 (7.0)	63 (6.7)	99 (8.1)
Unadjusted RR (95% CI)	1.00 (ref.)	1.42 (0.90, 2.24)	1.35 (0.86, 2.12)	1.63 (1.06, 2.50)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.34 (0.85, 2.11)	1.24 (0.79, 1.95)	1.41 (0.91, 2.19)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.34 (0.85, 2.11)	1.27 (0.81, 2.00)	1.56 (0.99, 2.44)
Gestational diabetes				
N (%) with outcome	11 (2.2)	21 (2.5)	30 (3.2)	56 (4.6)
Unadjusted RR (95% CI)	1.00 (ref.)	1.13 (0.55, 2.33)	1.46 (0.74, 2.89)	2.10 (1.11, 3.97)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.03 (0.50, 2.10)	1.20 (0.61, 2.37)	1.48 (0.77, 2.84)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.03 (0.50, 2.10)	1.22 (0.62, 2.40)	1.56 (0.81, 3.01)
Preeclampsia				
N (%) with outcome	14 (2.8)	36 (4.2)	32 (3.4)	60 (4.9)
Unadjusted RR (95% CI)	1.00 (ref.)	1.52 (0.83, 2.80)	1.22 (0.66, 2.27)	1.76 (1.00, 3.12)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.35 (0.73, 2.49)	1.03 (0.56, 1.91)	1.34 (0.74, 2.41)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.35 (0.73, 2.49)	1.05 (0.57, 1.95)	1.45 (0.79, 2.65)
Caesarean section				

	Time to pregnancy (cycles)			
	<3 (N=504)	**3-5 (N=851)**	**6-11 (N=942)**	**≥12 (N=1,224)**
N (%) with outcome	67 (13.3)	161 (18.9)	199 (21.1)	311 (25.4)
Unadjusted RR (95% CI)	1.00 (ref.)	1.42 (1.09, 1.85)	1.59 (1.23, 2.05)	1.91 (1.50, 2.44)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.36 (1.05, 1.77)	1.48 (1.15, 1.91)	1.63 (1.27, 2.09)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.36 (1.05, 1.77)	1.48 (1.15, 1.91)	1.64 (1.27, 2.12)
Postpartum hemorrhage				
N (%) with outcome	44 (8.7)	94 (11.0)	90 (9.6)	201 (16.4)
Unadjusted RR (95% CI)	1.00 (ref.)	1.27 (0.90, 1.78)	1.09 (0.78, 1.54)	1.88 (1.38, 2.56)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.21 (0.86, 1.69)	1.02 (0.73, 1.44)	1.70 (1.24, 2.33)
Adjusted RR (95% CI)[b]	1.00 (ref.)	1.20 (0.86, 1.69)	1.00 (0.71, 1.41)	1.58 (1.14, 2.19)

RR = risk ratio, CI = confidence interval.

[a] Adjusted for maternal age, paternal age, maternal smoking, BMI, education, and parity.

[b] Adjusted for all factors in footnote a plus fertility medication use.

Table 4

TTP and adverse birth outcomes among women with attempt time <3 cycles at entry, Snart-Gravid Study, 2007-2012.

	Time to pregnancy (cycles)			
	<3 (N=504)	**3-5 (N=693)**	**6-11 (N=439)**	**≥12 (N=343)**
Preterm birth (<37 weeks)				
N (%) with outcome	18 (3.6)	39 (5.6)	17 (3.9)	19 (5.5)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.54 (0.90, 2.65)	1.02 (0.53, 1.96)	1.54 (0.79, 3.01)
Spontaneous preterm birth				
N (%) with outcome	10 (2.0)	29 (4.2)	10 (2.3)	11 (3.2)
Adjusted RR (95% CI)[a]	1.00 (ref.)	2.11 (1.05, 4.26)	1.03 (0.44, 2.43)	1.38 (0.56, 3.39)
Medically-indicated preterm birth				
N (%) with outcome	8 (1.6)	10 (1.4)	7 (1.6)	8 (2.3)
Adjusted RR (95% CI)[a]	1.00 (ref.)	0.84 (0.35, 2.05)	0.97 (0.35, 2.69)	1.61 (0.56, 4.61)
Preterm birth (<36 weeks)				
N (%) with outcome	9 (1.8)	18 (2.6)	13 (3.0)	11 (3.2)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.45 (0.66, 3.21)	1.66 (0.72, 3.85)	1.86 (0.77, 4.47)
Preterm birth (<35 weeks)				
N (%) with outcome	4 (0.8)	13 (1.9)	10 (2.3)	9 (2.6)
Adjusted RR (95% CI)[a]	1.00 (ref.)	2.38 (0.78, 7.26)	2.87 (0.90, 9.07)	3.31 (1.02, 10.7)
Intrauterine growth restriction				
N (%) with outcome	10 (2.0)	21 (3.0)	15 (3.4)	12 (3.5)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.46 (0.69, 3.07)	1.58 (0.71, 3.49)	1.54 (0.71, 3.57)
Low birth weight (<2,500 g)				
N (%) with outcome	12 (2.4)	24 (3.5)	14 (3.2)	15 (4.4)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.53 (0.80, 2.94)	1.32 (0.62, 2.81)	1.75 (0.82, 3.73)
Small-for-gestational-age birth				
N (%) with outcome	31 (6.1)	51 (7.4)	32 (7.3)	22 (6.4)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.12 (0.72, 1.72)	1.07 (0.67, 1.73)	0.86 (0.50, 1.47)
Large-for-gestational-age birth				
N (%) with outcome	79 (15.7)	93 (13.4)	63 (14.3)	38 (11.0)
Adjusted RR (95% CI)[a]	1.00 (ref.)	0.91 (0.70, 1.20)	1.03 (0.76, 1.39)	0.75 (0.51, 1.10)
Macrosomia (≥4,500 g)				
N (%) with outcome	20 (4.0)	18 (2.6)	17 (3.9)	10 (2.9)
Adjusted RR (95% CI)[a]	1.00 (ref.)	0.70 (0.37, 1.31)	1.06 (0.56, 2.03)	0.83 (0.37, 1.87)
Placental disorders				
N (%) with outcome	9 (1.8)	23 (3.3)	19 (4.3)	15 (4.4)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.85 (0.87,3.94)	2.27 (1.04, 4.95)	1.97 (0.81, 4.83)
Ischemic placental disease				

	Time to pregnancy (cycles)			
	<3 (N=504)	**3-5 (N=693)**	**6-11 (N=439)**	**≥12 (N=343)**
N (%) with outcome	25 (5.0)	46 (6.6)	25 (5.7)	29 (8.5)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.27 (0.80, 2.04)	1.09 (0.64, 1.89)	1.87 (1.09, 3.22)
Gestational diabetes				
N (%) with outcome	11 (2.2)	15 (2.2)	12 (2.7)	16 (4.7)
Adjusted RR (95% CI)[a]	1.00 (ref.)	0.94 (0.44, 2.02)	1.08 (0.49, 2.39)	1.45 (0.69, 3.08)
Preeclampsia				
N (%) with outcome	14 (2.8)	28 (4.0)	13 (3.0)	16 (4.7)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.36 (0.71, 2.58)	0.92 (0.43, 1.96)	1.36 (0.66, 2.77)
Postpartum hemorrhage				
N (%) with outcome	44 (8.7)	77 (11.1)	52 (11.9)	67 (19.5)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.21 (0.85, 1.72)	1.25 (0.85, 1.85)	1.96 (1.33, 2.89)
Caesarean section				
N (%) with outcome	67 (13.3)	129 (18.6)	88 (20.0)	92 (26.8)
Adjusted RR (95% CI)[a]	1.00 (ref.)	1.31 (1.00, 1.72)	1.37 (1.02, 1.83)	1.57 (1.15, 2.14)

RR = risk ratio, CI = confidence interval.

[a]Adjusted for maternal age, paternal age, pack-years of smoking, BMI, education, parity, and fertility medication use.