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Fecundability among Danish women with a history of miscarriage: a prospective cohort study

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ABSTRACT

Objective To examine the association between history of miscarriage and fecundability (the cycle-specific probability of conception).

Design Nationwide prospective cohort study using web-based questionnaires.

Setting Denmark, 2007–2012.

Participants 977 women attempting to conceive, not using fertility treatment, and with a reproductive history of only miscarriage or only live birth.

Exposure and outcome measures Information on previous pregnancy outcomes, including miscarriage, came from self-report or from relevant registries. Participants were followed for up to 12 months or until they reported a pregnancy, stopped trying to conceive or started fertility treatment, whichever came first. We used Kaplan-Meier methods to estimate cumulative probabilities of conception for women whose reproductive history included only miscarriage or only live birth. Using proportional probabilities regression modelling, we computed fecundability ratios (FR) with 95% CI comparing women with a history of only miscarriage with women with a history of only live birth.

Results After adjustment for potential confounders, the cumulative probabilities of conception within 12 cycles of follow-up were 85% (95% CI 81% to 89%) for women with a history of 1 miscarriage, 85% (95% CI 73% to 92%) for women with a history of ≥2 miscarriages and 88% (95% CI 87% to 89%) for women whose reproductive history included only live birth. Adjusted FRs were 0.87 (95% CI 0.71 to 1.07) and 0.65 (95% CI 0.36 to 1.17) for women with a history of 1 and ≥2 miscarriages, respectively.

Conclusions Our results indicate that women with a history of miscarriage may have slightly reduced fecundability compared with women with a history of only live birth. The reduction in fecundability was greater for women with repeated miscarriages, although the estimates were imprecise. Despite a potential delay in conception, women with previous miscarriage may have similar probability of pregnancy by 12 cycles of attempts to women with proven fertility.

Strengths and limitations of this study

- ► We supplemented women's self-reported data on previous miscarriage with registry-based data, improving the completeness of miscarriage ascertainment.
- ► Some necessary restrictions resulted in small subgroups and imprecision of some results, particularly for women with ≥2 miscarriages.
- ► We had no data on gestational length at the time of miscarriage and were not able to evaluate whether the effect on fecundability differed for early and later pregnancy losses.

BACKGROUND

Miscarriage, defined as a spontaneous loss of an embryo or a fetus, affects up to 20% of pregnancies.[1] Approximately 30% of biochemically detected conceptions, including early losses occurring before a pregnancy is clinically recognised, fail to survive.[2 3] Miscarriage is associated with an increased risk of obstetric and perinatal complications in the subsequent pregnancy, including repeated miscarriage,[4 5] threatened miscarriage, preterm birth and perinatal death,[6 7] and may also be associated with impaired fecundity. The probability of conception among women with previous miscarriage ranges from 60% to 80% within 12 months of pregnancy attempts,[8–12] in contrast to 83%–92% in the general population of women attempting to conceive.[13 14]

Relative to women who had a live birth, longer time to pregnancy (TTP) in the subsequent pregnancy attempt was reported among women with miscarriage in their most recent pregnancy.[15] This finding was based on retrospectively self-reported TTP, raising concerns about differential recall of TTP by previous pregnancy outcome. A prospective cohort study of pregnancy planners reported a subsequently longer TTP within 12 months of a pregnancy loss, but this was primarily limited to losses occurring early in gestation (median gestation at time of loss: 35 days).[16] Contrary to these results, another prospective cohort study of pregnancy planners reported that early pregnancy loss (pregnancy loss before 6 weeks after onset of the

last menstrual period (LMP)) in a preceding cycle was associated with increased odds of clinical pregnancy in a subsequent cycle.[3]

Given the lack of conclusive evidence, we examined the association between history of miscarriage and fecundability using prospectively collected data on TTP in a cohort of Danish women attempting to become pregnant.

SUBJECTS AND METHODS

Study population

Data for this study originated from a population-based prospective cohort study of Danish pregnancy planners ('Snart-Gravid'), initiated in 2007. The study has been described in detail elsewhere.[17] Eligible participants were Danish female residents, 18–40 years old at study enrolment, in a relationship with a male partner, attempting to conceive and not receiving fertility treatment. Study enrolment was accomplished using advertisement on a health-related Danish website, and in various Danish media.[17] Consenting participants completed a web-based baseline questionnaire and bimonthly follow-up questionnaires for up to 12 months after enrolment. At baseline, participants also provided their Civil Personal Registration (CPR) number, a unique 10-digit personal number assigned to Danish citizens at birth or immigration, enabling identification of persons in national health registries.[18] Participants were randomised to completion of either a short or a long version of the baseline questionnaire during the first 6 months of the study.[19] Subsequently, all new participants received the long version of the questionnaire. Study enrolment continued until 2011, and follow-up for all participants ended in 2012.

From among the 6033 potential participants for the study, we initially excluded 1824 women according to the criteria shown in figure 1. From the remaining 4209 women, we excluded women who were nulligravid, women with a history of only stillbirth, induced abortion or ectopic pregnancy and women with gravidity >1 with heterogeneous pregnancy outcomes (eg, both live births and miscarriages). The final study population comprised 977 women who had been pregnant at least once, with pregnancies ending only in at least one miscarriage (n=191) or only in at least one live birth (n=786). Women who had experienced only live birth served as the reference group; these women had no history of fetal loss (stillbirth, ectopic pregnancy or miscarriage) and had demonstrated their fertility by having had a live birth. Women who had experienced only miscarriage were considered as the exposed in order to obtain the cleanest comparison between exposed and unexposed women.

Some women did not complete the entire 12 months of observation and did not provide a reason for non-response; in all, 9 of 191 (4.7%) women with history of miscarriage and 57 of 786 (7.3%) women with history of live birth had only partial follow-up. Women with a history of miscarriage who had partial follow-up were more likely to have a body mass index (BMI) ≥30 kg/m^2 and a history of having attempted pregnancy for ≥12 months than women with previous miscarriage who had complete follow-up. There were no appreciable differences in other baseline characteristics. Women who had partial follow-up contributed cycles at risk to the analyses until the date of completion of their last follow-up questionnaire.

Assessment of miscarriage and other pregnancy outcomes

We obtained data on participants' history of miscarriage and other birth outcomes from the baseline questionnaire, and also from the Danish National Patient Registry (DNPR) (miscarriage, induced abortion and ectopic pregnancy), and the Danish Medical Birth Registry (DMBR) (stillbirth and live birth) by linkage with participants' CPR numbers. Pregnancy outcomes observed in a hospital setting are assigned a diagnosis code according to the International Classification of Diseases; the Eighth Revision (ICD-8) was in use through 1993, and the 10th Revision (ICD-10) thereafter.[20] Miscarriage was defined as the loss of an embryo or fetus before 22 gestational weeks.[21]

On the baseline questionnaire, participants reported previous pregnancies and the outcome of each pregnancy (live birth, stillbirth, miscarriage, induced abortion, ectopic pregnancy, or other), with dates. We combined self-reported and registry data on pregnancy outcomes to reconstruct women's reproductive histories. Cases of discordance between the two sources of data were solved as follows: if a woman did not report any pregnancy outcomes on the baseline questionnaire, but had a record of ≥1 miscarriage(s) in the DNPR, and no record of other types of pregnancy outcomes, she was considered to have had miscarriage(s) as her only pregnancy outcome. Similarly, if a woman reported miscarriage as her only type of pregnancy outcome at baseline, and had no records of miscarriage or of other types of pregnancy outcomes in the registries, she was considered to have had a history of miscarriage only. In cases of discrepancy between self-report and registry, the woman was considered to have had heterogeneous outcomes, unless her gravidity was 1, in which case the registry record was considered to represent the true outcome. Using this approach, miscarriages that did not lead to a hospital encounter were also included in the analyses. We identified women who had only given live birth by the same strategy. Online supplementary table 1 shows ICD-8 and ICD-10 diagnosis codes for the pregnancy outcomes.

Assessment of fecundability

We measured fecundability, that is, the cycle-specific probability of conception, using data on TTP, defined as the number of menstrual cycles at risk of pregnancy.[22] At study entry, participants reported the number of months of attempted pregnancy, the date of their LMP and usual cycle length. In the follow-up questionnaires, they reported the date of their LMP and whether they were currently pregnant or had had a pregnancy termination (miscarriage, induced abortion or ectopic pregnancy)

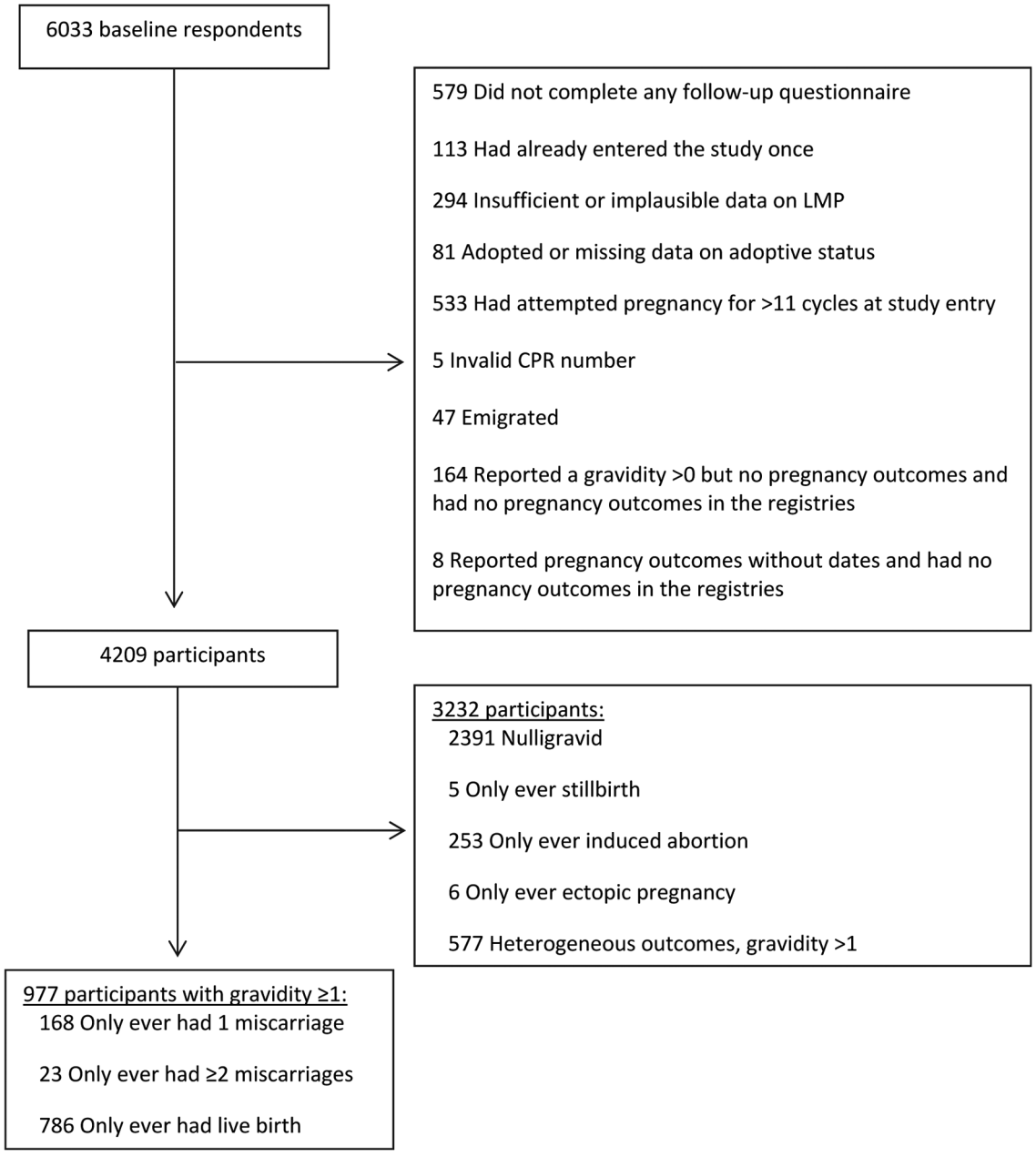

Figure 1 Study flow chart. CPR, Civil Personal Registration; LMP, last menstrual period.

since the previous follow-up. The event of interest in our study was pregnancy. Over 96% of the participants used a home pregnancy test to determine pregnancy.[23] TTP was estimated using the following formula: (days of pregnancy attempt at study entry/days of usual cycle length)+((LMP date from the most recent follow-up questionnaire – date of study entry)/days of usual cycle length)+1.[24] Participants contributed cycles at risk until report of pregnancy or until censoring by failing to respond to follow-up questionnaires, discontinuation of pregnancy attempts, initiation of fertility treatment or reaching the end of the 12-month observation period, whichever came first. To account for left truncation, that is, of women initiating their pregnancy attempts one or more cycles before study entry, we defined observed cycles at risk as those contributed after study entry.[24] The number of cycles of pregnancy attempts at study entry considered only the cycles following the most recent miscarriage or live birth.

Assessment of covariates

At baseline, participants reported their age, educational level, height and weight, menstrual cycle regularity, frequency of intercourse and history of fertility problems (history of attempting pregnancy ≥12 months, and history of consultation with a physician due to difficulty conceiving). We estimated participants' BMI as weight (kg) divided by height squared (m^2).

Familial predisposition to miscarriage has been associated with history of at least one miscarriage[25] and recurrent miscarriage (≥3 consecutive miscarriages[26]).[27 28] Considering a mother's history of miscarriage as an indicator of her own fertility, with a potential influence on the

fertility of her daughters, we hypothesised that the miscarriage-fecundability association may vary by maternal history of miscarriage. We also considered whether the participants' sisters had a history of miscarriage, as a proxy measure of familial characteristics. Data on miscarriage were only available since 1977 in the DNPR,[20] thus, for the participants' mothers, we supplemented with data on history of miscarriage from the DMBR. These data were reported by women at prenatal visits since 1978, thus including some of the miscarriages experienced by the participants' mothers before 1977.[29 30]

Data analysis

We first assessed the distribution of baseline characteristics for women with 1 miscarriage, ≥2 miscarriages or with live birth. We used the Kaplan-Meier method to estimate crude and adjusted cumulative probabilities of conception with 95% CI, allowing for left truncation and censoring.[31] We fitted a proportional probabilities regression model to estimate fecundability ratios (FR) and 95% CI, comparing fecundability among women with a history of miscarriage with that among women with a history of live birth.[32] An FR<1 indicates lower relative fecundability (longer TTP). We examined the effect of miscarriage in categories of 1 or ≥2 miscarriages, and repeated the analysis with a restriction to women with a gravidity of 1 at entry into the study. In another sensitivity analysis, we computed FRs with a restriction to women with ≤3 cycles of pregnancy attempts at study enrolment. To assess the effect of miscarriage recency on fecundability, we calculated FRs for women who had their miscarriage <1 year or ≥1 year before initiation of their current pregnancy attempts; this analysis was restricted to women with a gravidity of 1. In a subanalysis, we stratified the FR estimates by participants' mothers' or sisters' history of miscarriage (yes/no).

Based on published evidence[4 5 13 24 33–37] and on available data, we adjusted the FR estimates for age at first miscarriage or live birth (continuous), calendar year at first miscarriage or live birth (<2003; 2003–2007; >2007), higher education (none; <3 years; 3–4 years; >4 years), BMI (<18.5; 18.5–24.9; 25.0–29.9; ≥30.0 kg/m^2), history of pregnancy attempts ≥12 months (yes; no) and history of consultation with a physician due to difficulty conceiving (yes; no). At baseline, participants also reported levels of caffeine and alcohol consumption, smoking status and physical activity. These lifestyle factors may be associated with miscarriage[34 38 39] and with impaired fecundability,[36 40–43] thus qualifying as potential confounders. Even though these lifestyle exposures could have changed from the time of miscarriage to the time of attempting to conceive again, possibly as a result of the earlier miscarriage, we examined potential confounding by these factors. As we found that adjustment did not affect the estimates, we did not include these variables in the analyses presented here.

Analyses were conducted using Stata V.12.0 (StataCorp, College Station, TX, USA) and SAS V.9.2 (SAS Institute Inc., Cary, NC, USA).

Missing observations

For variables with missing values, the proportions of missing observations were below 2%, except for the variable on participant's history of consultation with a physician due to difficulty conceiving. For 26% of the participants, this information was not provided. This variable was not included in the short version of the baseline questionnaire, contributing to the high proportion of missing values. We estimated the missing covariate values using multiple imputation by chained equations, and included all variables considered in the analyses in the imputation procedure.[44]

Ethical approval

The 'Snart-Gravid' study was approved by the Danish Data Protection Agency (record number 2013-41-1922) and by the Institutional Review Board at Boston University. The Danish Data Protection Agency granted the permission to retrieve data from the DNPR and the DMBR. Participants provided informed consent before completing study questionnaires.

Patient and public involvement

There were no patients involved in any aspect of the design, recruitment or conduct of this study. Results of the study will be accessible to participants and the public through the study homepage.

RESULTS

Of 977 women in the study population at the start of follow-up, 786 women had a history of live birth only, and 191 women had a history of miscarriage only; 168 had had 1 miscarriage, and 23 women had ≥2 miscarriages. Table 1 shows the baseline characteristics of the women according to previous pregnancy outcome. Women with a history of miscarriage tended to be younger, more likely to have had their first pregnancy event after 2007, have no higher education, to have intercourse ≥4 times/week and more likely to have attempted to become pregnant for at least 4 cycles at study entry than women with live births. Among women with ≥2 miscarriages, there was a lower prevalence of irregular menstrual cycles, and an elevated prevalence of BMI≥30 kg/m^2, history of pregnancy attempts ≥12 months and having consulted a physician due to difficulty conceiving, as well as familial history of miscarriage.

Crude Kaplan-Meier estimates for the cumulative probability of conception within 6 and 12 cycles of pregnancy attempts were 69% (95% CI 62% to 75%) and 85% (95% CI 80% to 88%) for women with a history of 1 miscarriage, 46% (95% CI 21% to 63%) and 69% (95% CI 49% to 82%) for women with a history of ≥2 miscarriages, and 76% (95% CI 74% to 79%) and 89% (95% CI 87% to 90%) for women with previous live birth. The corresponding adjusted estimates were similar except for women with ≥2 miscarriages; the adjusted cumulative probabilities of conception were 71% (95% CI 52%

Table 1 Characteristics of 977 participants who experienced only miscarriage or only live birth

Characteristic	Only ever 1 miscarriage	Only ever ≥2 miscarriages	Only ever live birth
Women, n	168	23	786
Age at study entry, mean (SE), years	27.9 (0.3)	27.5 (0.9)	30.6 (0.1)
Age at first pregnancy event, mean (SE), years*	26.3 (0.3)	25.0 (1.0)	27.1 (0.1)
Calendar year of first pregnancy event, %*			
<2003	10.1	17.4	20.0
2003–2007	53.0	60.9	75.5
>2007	36.9	21.7	4.6
Higher education, %			
None	14.3	17.4	8.5
<3 years	33.9	30.4	30.7
3–4 years	31.6	30.4	38.4
>4 years	20.2	21.7	22.4
BMI, kg/m^2, %			
<18.5	1.8	4.4	3.4
18.5–24.9	67.9	39.1	58.5
25.0–29.9	17.9	26.1	23.2
≥30.0	12.5	30.4	14.9
Irregular menstrual cycles, %	24.4	13.0	22.4
Intercourse frequency ≥4 times/week, %	17.3	26.1	11.8
Number of cycles of attempted pregnancy at study entry, %			
0–1	34.5	30.4	55.6
2–3	28.0	17.4	20.6
4–6	26.2	21.7	12.7
7–11	11.3	30.4	11.1
History of pregnancy attempts ≥12 months, %	13.7	30.4	19.0
History of consultation with a physician due to difficulty conceiving, %	15.5	30.4	21.0
Miscarriage in mother or sister, %	26.8	30.4	22.0

*First pregnancy event: first miscarriage or first live birth.
BMI, body mass index.

to 82%) within 6 cycles and 85% (95% CI 73% to 92%) within 12 cycles. Figure 2 shows that the differences in the adjusted cumulative probabilities of conception associated with miscarriage were largest during the first 6 cycles of pregnancy attempts, gradually tapering off by 12 cycles.

Table 2 shows that the adjusted FRs were 0.87 (95% CI 0.71 to 1.07) for women with a history of 1 miscarriage, and 0.65 (95% CI 0.36 to 1.17) for women with a history of ≥2 miscarriages.

When we restricted to women with gravidity of 1 at entry into the study, the result for 1 miscarriage was similar (FR 0.85 (95% CI 0.69 to 1.05)). The adjusted FRs for women with a pregnancy attempt time of ≤3 cycles at study enrolment were 0.95 (95% CI 0.73 to 1.22) for women with a history of 1 miscarriage, and 0.55 (95% CI 0.22 to 1.38) for women with a history of ≥2 miscarriages. Among women with gravidity of 1, the adjusted FR for women who had their miscarriage <1 year before initiating their current pregnancy attempts was 0.86 (95% CI 0.68 to 1.08), and 0.82 (95% CI 0.52 to 1.29) for women with miscarriage ≥1 year before current attempts (table 3). The FRs did not vary appreciably by history of miscarriage among the mothers and sisters of the participants (results not shown).

DISCUSSION

We found that women with a previous miscarriage had a 13% decrease, and women with at least 2 previous miscarriages, a 35% decrease, in fecundability compared with women who had only a live birth. However, the estimates were imprecise and the CIs were consistent with a broad range of values, from strong effects to little or no association. The cumulative probability of conception was lower among women with miscarriage, but this difference

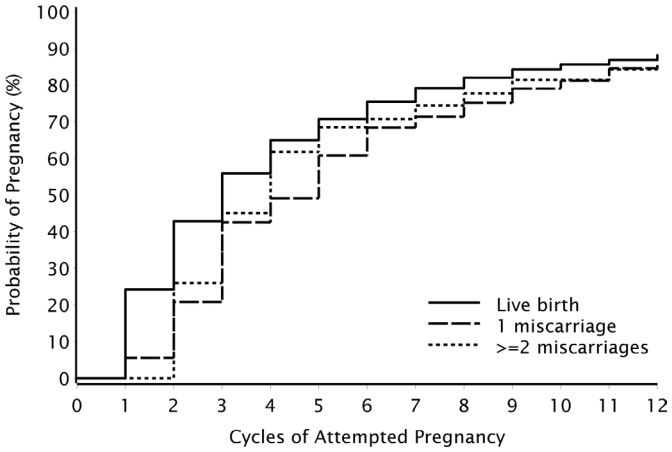

Figure 2 Adjusted cumulative probabilities of conception after miscarriage or live birth. Adjusted for age at first miscarriage or live birth, calendar year of first miscarriage or live birth, higher education, body mass index, history of pregnancy attempts ≥12 months and history of consultation with a physician due to difficulty conceiving. Adjusted cumulative probability of conception with 95% CI, 6 cycles: 1 miscarriage: 68% (62% to 74%); ≥2 miscarriages: 71% (52% to 82%); live birth: 75% (74% to 77%). Adjusted cumulative probability of conception with 95% CI, 12 cycles: 1 miscarriage: 85% (81% to 89%); ≥2 miscarriages: 85% (73% to 92%); live birth: 88% (87% to 89%).

gradually diminished and had disappeared by 12 cycles of pregnancy attempts.

One advantage of our study is that we were able to combine registry and self-reported data on previous pregnancy outcomes, improving the completeness of miscarriage ascertainment when compared with each data source alone. Prevalence of pregnancies ending in a miscarriage is 11%–16%, based on data from Danish national health registries, and 21% based on self-report.[1 33] Entry errors and incorrect assignment of diagnosis codes are potential sources of information bias when using data from registries. However, the positive predictive value of miscarriage diagnoses in the DNPR was 93%–100% in the period 1980–2008, regardless of the ICD classification used.[21] The proportion of self-reported miscarriages that cannot be identified in the DNPR has been estimated to be 30%.[1] On the other hand, recall of prior miscarriages may depend on duration of the pregnancy and time since the event, with losses occurring at an early gestation and several years ago less likely to be recalled.[45–47] Since we supplemented women's self-reports with registry-based data, the number of women with unidentified miscarriages is likely to be minor. Importantly, data on previous pregnancy outcomes were retrieved independently of outcome information, implying that differential misclassification is an unlikely explanation for our results. Further, as over 96% of participants in 'Snart-Gravid' confirmed their pregnancy using a home pregnancy test, it is plausible that recognition of pregnancy was unrelated to the woman's previous pregnancy outcome. If women with co-occurring previous miscarriages and impaired fecundability were more likely to enrol in our study, the FRs that we observed might overestimate the deleterious effect of previous miscarriage. Still, fecundability did not appear to be appreciably different among women with only up to three cycles of pregnancy attempts at study enrolment, suggesting that such a mechanism was not of substantial concern.

In a prospective study of women with ≥2 previous miscarriages who were attempting to conceive, Kaandorp *et al* reported crude 6 and 12-month cumulative incidences of conception to be 56% and 74%,[8] which was marginally higher than our respective estimates of 46% and 69%. This difference may be partly attributable to the fact that 13% of women in the study by Kaandorp *et al* conceived with fertility treatment. After adjustment for confounding, we found that the probability of conception within 12 cycles increased to 85% and was comparable with that for women with one previous miscarriage (85%), previous live birth (88%) and general populations of women attempting to conceive (83%–92%).[13 14] Wang *et al* observed that early pregnancy loss in a preceding cycle was associated with increased odds of clinical pregnancy in a subsequent cycle (OR 2.0 (95% CI 1.3 to 3.0)).[3] That study considered pregnancy losses occurring before 6 weeks post-LMP. In our study, we were not able to distinguish between early and later pregnancy losses, as we did not have data on gestational length at the time of miscarriage. Further, the study by Wang *et al* considered nulliparous women who were younger than women in our cohort (mean age 25 years vs 30 years), and excluded those with a history of pregnancy attempts ≥12 months, suggesting that they were reproductively healthier than women in our

Table 2 Fecundability ratio for women with one or more previous miscarriages, relative to those with only previous live birth

				Unadjusted model		Adjusted model*	
Pregnancy outcome	**Women, n**	**Cycles, n**	**Pregnancies, n**	**FR**	**95% CI**	**FR**	**95% CI**
Only miscarriage							
Total	191	727	121	0.87	0.73 to 1.04	0.85	0.70 to 1.03
1	168	632	111	0.91	0.76 to 1.09	0.87	0.71 to 1.07
≥2	23	95	10	0.60	0.33 to 1.07	0.65	0.36 to 1.17
Only live birth	786	2796	565	1	Reference	1	Reference

*Adjusted for age at first miscarriage or live birth, calendar year of first miscarriage or live birth, higher education, body mass index, history of pregnancy attempts ≥12 months and history of consultation with a physician due to difficulty conceiving.
FR, fecundability ratio.

Table 3 Fecundability ratio for women with previous miscarriage, relative to those with previous live birth, according to recency of miscarriage.* Gravidity=1.

Pregnancy outcome	Women, n	Cycles, n	Pregnancies, n	Unadjusted model		Adjusted model†	
				FR	95% CI	FR	95% CI
Miscarriage							
<1 year	136	509	93	0.91	0.74 to 1.11	0.86	0.68 to 1.08
≥1 year	32	123	18	0.72	0.47 to 1.11	0.82	0.52 to 1.29
Live birth	607	2105	442	1	Reference	1	Reference

*Number of years before initiation of current pregnancy attempts.
†Adjusted for age at first miscarriage or live birth, calendar year of first miscarriage or live birth, higher education, body mass index, history of pregnancy attempts ≥12 months and history of consultation with a physician due to difficulty conceiving.
FR, fecundability ratio.

study. Thus, those results are difficult to compare with our findings. In contrast, in a cross-sectional study of pregnant women, Hassan and Killick compared self-reported TTP before and after a miscarriage in the previous pregnancy with TTP before and after a previous live birth.[15] Women with a miscarriage in their previous pregnancy had longer TTP after miscarriage than before miscarriage (risk ratio 2.1 (95% CI 1.4 to 3.0)) and longer TTP than women with a previous live birth (OR 2.1 (95% CI 1.6 to 2.6)). The retrospective ascertainment of TTP in that study may have created a spurious association because of recall bias. Still, in a prospective study of women attempting to conceive, Sapra *et al* found that TTP after an early miscarriage (median gestation at pregnancy loss: 35 days (5%: 26 days, 95%: 81 days)) was longer than before miscarriage. Relative to the first attempt (before the miscarriage), fecundability was reduced in the second pregnancy attempt (fecundability OR (FOR) 0.42 (95% CI 0.28 to 0.65)), and in the third pregnancy attempt (FOR 0.56 (95% CI 0.11 to 2.79)).[16] Despite differences in the measurement of miscarriage and TTP across studies, our results corroborate these previous reports of a small delay in conception among women with miscarriage.

Impaired fertility after a miscarriage may be related to tubal damage from infection, or to intrauterine adhesions, which may occur as a consequence of, for example, infection or dilatation and curettage procedures, performed to manage miscarriage.[48] Although several studies have reported similar probabilities of conception after miscarriage irrespective of medical, surgical or expectant management,[10–12 49] a meta-analysis found the prevalence of intrauterine adhesions among women with previous miscarriage was 19%, with women having multiple miscarriages being more likely to have adhesions than women with a single miscarriage (OR 1.99 (95% CI 1.32 to 3.00)). This finding was mainly attributed to recurrent curettage procedures performed in the former group,[50] and might contribute to explain why women with ≥2 miscarriages had lower fecundability than women with one miscarriage. It is also possible that delayed resumption of ovulation contributed to our finding of lower fecundability after miscarriage.[51] We did not have data on gynaecologic complications associated with miscarriage or medical conditions with a potential influence on miscarriage and fecundability, which limited our ability to examine plausible biological mechanisms. Some studies suggest that women with infertility are more likely to experience miscarriage.[4 5 15 35] We controlled for pre-existing subfertility by adjusting for previous pregnancy attempts ≥12 months and having consulted a physician due to difficulty conceiving. This adjustment did not appreciably change our estimates. However, we cannot completely exclude the possibility that residual confounding by pre-existing subfertility contributed to our results.

CONCLUSIONS

Our results suggest a decreased fecundability among women with a history of miscarriage, most prominent among women with repeated miscarriages, although the estimates were imprecise. The delay in conception was most evident during the first cycles of pregnancy attempts. By 12 cycles, the probability of conception was similar to that of women with previous live birth, suggesting that although women with miscarriage may experience a lower average probability of conception, their fertility may be delayed rather than impaired.

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Contributors CW, VE, EMM and HTS developed the hypothesis and analytic plan. CW and AHR analysed the data. CW performed the literature review and took the lead on drafting the paper and AHR, VE, EEH, LAW, KJR, HTS and EMM contributed in revising the work. All authors gave their final approval of the manuscript and agree to be accountable for all aspects of the work.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Danish Data Protection Agency (record number 2013-41-1922); the Institutional Review Board at Boston University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data from the Snart-Gravid study are not yet publicly available, as this study and its extension Snart-Foraeldre are still in progress. Data

from the population-based registries (the DNPR and the DMBR) are only accessible by permission from The Danish Health Data Authority.

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