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The association between miscarriage and fecundability: the Norwegian Mother, Father and Child Cohort Study

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STUDY QUESTION: Is fecundability associated with miscarriage history and future miscarriage risk?

SUMMARY ANSWER: Prior miscarriage was associated with lower fecundability, and participants with a history of subfertility (time-to-pregnancy (TTP) ≥12 months) were at a higher risk of subsequent miscarriage.

WHAT IS KNOWN ALREADY: Although miscarriage and low fecundability share common risk factors, prior studies have reported both lower and higher fecundability after miscarriage.

STUDY DESIGN, SIZE, DURATION: In this study, we examined two related associations: one, between miscarriage history and subsequent fecundability and, two, between fecundability and miscarriage risk in the subsequent pregnancy. The study is based on the Norwegian Mother, Father and Child Cohort Study (MoBa). In addition, the outcome of the pregnancy after the MoBa index pregnancy was obtained by linking information from three national health registries: the Medical Birth Registry of Norway, the Norwegian Patient Registry and the general practice database.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We examined the association between number of prior miscarriages and fecundability in 48 537 naturally conceived, planned pregnancies in participants with at least one prior pregnancy. We estimated fecundability ratios (FRs) and 95% CIs using proportional probability regression. We further estimated the relative risk (RR) of miscarriage in the subsequent pregnancy as a function of TTP in the MoBa index pregnancy for 7889 pregnancies using log-binomial regression. Multivariable analyses adjusted for maternal age, pre-pregnancy maternal BMI, smoking status, cycle regularity, income level and highest completed or ongoing education.

MAIN RESULTS AND THE ROLE OF CHANCE: Fecundability decreased as the number of prior miscarriages increased. The adjusted FRs among women with one, two and three or more prior miscarriages were 0.83 (95% CI: 0.80–0.85), 0.79 (95% CI: 0.74–0.83) and 0.74 (95% CI: 0.67–0.82), respectively, compared with women with no prior miscarriages. Compared to women with a TTP of <3 months, the adjusted RR of miscarriage in the subsequent pregnancy was 1.16 (0.99–1.35) with TTP of 3–6 months, 1.18 (0.93–1.49) with TTP of 7–11 months and 1.43 (1.13–1.81) with TTP of 12 or more months.

LIMITATIONS, REASONS FOR CAUTION: Information on TTP and prior miscarriages was obtained retrospectively, and TTP was self-reported. MoBa is a pregnancy cohort, and findings may not be generalizable to all women. We were unable to examine the effect of changing partners between pregnancies, as well as other paternal factors such as seminal parameters. We also did not know what proportion of our participants had changed partners between their prior pregnancies and the index pregnancy. Furthermore, it is likely that many early miscarriages are not recognized.

WIDER IMPLICATIONS OF THE FINDINGS: The association between miscarriage and fecundability may reflect a contribution of occult pregnancy losses to TTP, as well as shared underlying causes for reduced fecundability and miscarriage.

STUDY FUNDING/COMPETING INTEREST(S): The study was funded by the Research Council of Norway through its Medical Student Research Program funding scheme (project number 271555/F20), its Centres of Excellence funding scheme (project number 262700) and through the project 'Women's fertility – an essential component of health and well-being' (project number 320656). M.C.M. has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement number 947684). A.J.W. is supported by the Intramural Program of the National Institute of Environmental Health Sciences at the National Institutes of Health, USA. The authors report no competing interests.

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Key words: miscarriage / fecundability / time-to-pregnancy / subfertility / Norwegian Mother, Father and Child Cohort Study / Medical Birth Registry of Norway

Introduction

Miscarriage, defined as the spontaneous loss of an embryo or fetus before the 22nd week of gestation, occurs in 12–14% of recognized pregnancies, with a significant recurrence risk (Magnus *et al.*, 2019). Fecundability can be defined as the probability of conceiving in a given menstrual cycle and is often estimated using time-to-pregnancy (TTP), which is the number of cycles taken to conceive while having regular, unprotected intercourse (Sozou and Hartshorne, 2012).

How these two indicators of fertility are related is not yet fully clear. Miscarriage and low fecundability share common risk factors, such as advanced maternal age, smoking, alcohol use and obesity (Agenor and Bhattacharya, 2015). Miscarriage has been found to be associated with both higher and lower fecundability, and few studies have explored how fecundability may be related to risk of miscarriage in subsequent pregnancies.

Several studies have found that long TTPs are associated with higher miscarriage risk in that pregnancy (Rachootin and Olsen, 1982; Strobino *et al.*, 1986; Schaumburg and Boldsen, 1992; Joffe and Li, 1994; Gray and Wu, 2000; Axmon and Hagmar, 2005). However, in studies limited to patients with recurrent pregnancy loss, defined as either two or more or three or more consecutive miscarriages, pregnancies that ended in miscarriage had shorter TTPs (Salker *et al.*, 2010; Orlando and Coulam, 2014; Bhandari *et al.*, 2016; Ticconi *et al.*, 2020).

Few studies have investigated the association between fecundability and miscarriage across different pregnancies. This association is important because it relates to risk factors and mechanisms involving the long-term fertility of women and couples, rather than only factors related to a specific pregnancy.

With regard to the association between miscarriage history and subsequent fecundability, two prior studies reported longer TTP in the pregnancy following a miscarriage (Hassan and Killick, 2005; Sapra *et al.*, 2014). However, they considered only the first pregnancy following a miscarriage, and included no participants with more than one prior miscarriage. In contrast, one study of subclinical pregnancy loss found that such loss before the sixth gestational week was associated with higher odds of conceiving in the subsequent cycle (Wang *et al.*, 2003). Studies of patients with recurrent pregnancy loss have suggested that a higher number of preceding miscarriages was associated with lower subsequent cumulative pregnancy rates (Kling *et al.*, 2016) and chance of achieving a live birth (Lund *et al.*, 2012). A recent study not restricted to such patients grouped participants according to number of prior miscarriages, but the small number of participants with more than one miscarriage (N = 23) yielded inconclusive results (Wildenschild *et al.*, 2019).

With regard to the association between fecundability and future risk of miscarriage, a study of 148 healthy volunteers found that participants with a history of fertility problems had a higher risk of early pregnancy loss (Hakim *et al.*, 1995).

These heterogeneous results from different populations are difficult to assess. The nature of the association between fecundability and miscarriage therefore remains unclear. The objective of the current study was to clarify the relation by examining the association of fecundability with both miscarriage history and future miscarriage risk within a large population-based cohort.

Materials and methods

Study population

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus *et al.*, 2016). Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114 500 children, 95 200 mothers and 75 200 fathers. The current study is based on version 12 of the quality-assured data files released for research in January 2019. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The study was approved by the Regional Committee of Medical and Health Research Ethics of South/East Norway (ref. 2014/404).

This study consisted of two parts with different designs. The first treated prior miscarriage as an exposure, investigating how miscarriage history before the MoBa pregnancy was associated with fecundability. The other treated fecundability as the exposure, investigating how TTP in the MoBa pregnancy was associated with risk of miscarriage in the next pregnancy.

We excluded unplanned pregnancies and pregnancies conceived with assisted reproduction. For the analysis of miscarriage history and fecundability, we also excluded pregnancies in primigravid women, as these participants had never been at risk of experiencing the outcome of interest. To avoid oversampling of highly fertile women, who are

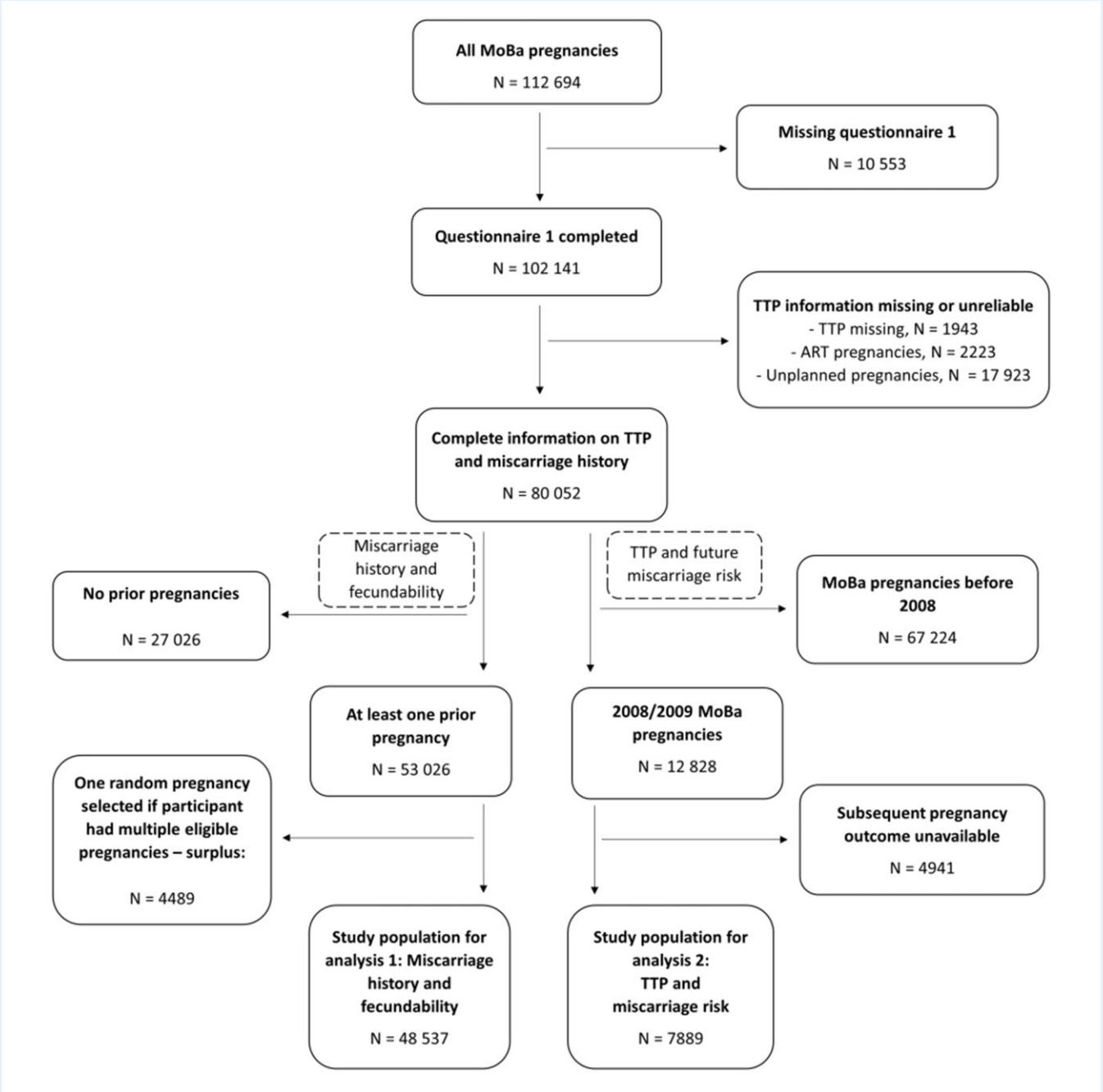

Figure 1. Illustration of inclusion criteria for the two analytic designs. MoBa, Norwegian Mother, Father and Child Cohort Study; TTP, time-to-pregnancy.

more likely to have participated in MoBa with more than one pregnancy, we selected one random pregnancy for the inclusion if a participant had multiple eligible pregnancies, leaving us with 48 537 pregnancies for this analysis (Fig. 1). The included MoBa pregnancy is referred to as the index pregnancy.

As the Norwegian Patient Registry only started recording information on an individual level in 2008, we had to restrict our analysis of TTP and future miscarriage risk to participants who had their index pregnancy in 2008 and later, to make sure that we were able to identify their next pregnancy (Fig. 1). This analysis included a total of 7889 participants with available information on the outcome of the subsequent pregnancy. All participants in this analysis had live birth as the outcome of their MoBa index pregnancy.

Miscarriage history at recruitment

In the questionnaire administered at the time of recruitment, around 18 gestational weeks, participants were asked to provide information

for up to 10 prior pregnancies. Participants reported the year the pregnancy started, pregnancy outcome (live birth, fetal death, induced abortion and ectopic pregnancy) and the gestational week of fetal death if applicable. Fetal deaths occurring between week 6 and week 22 were defined as miscarriage. Pregnancies are not usually confirmed before week 5–6, and miscarriages occurring very early are likely to be interpreted as a regular or late menstruation in most women. To mitigate the impact of differential reporting of early miscarriage among participants with unfavorable reproductive histories, we excluded miscarriages reported to have occurred in or before week 5. This means that participants who only reported miscarriages occurring in or before week 5 were in the reference group. We also explored using a threshold of 8 weeks.

TTP of index pregnancy

At recruitment, participants were asked whether the pregnancy was planned. If the pregnancy was planned, participants were asked to report the trying time in months. The response options were '<1 month', '1–2 months' and '3 months or more'. If women responded '3 months or more', they were further asked to provide the exact number of months. Participants also reported their average cycle length: we set TTP to be 1, 2 and 3 months for the three first categories, respectively, and used the exact number of months if reported. We subsequently corrected the TTP for the woman's reported average cycle length where information on cycle length was available (94.1%), and left TTP unchanged in remaining participants.

A total of 2.6% of participants had included a prior pregnancy within their TTP—most often a miscarriage. They were identified by having a pregnancy outcome after the calculated beginning of their reported TTP. We had information only on the year that the prior pregnancies began, not the date. Therefore, for both analytic designs, the TTP of these participants was corrected by subtracting the length of the pregnancy/pregnancies within their TTP (or if pregnancy length was unavailable, 8 weeks) and then dividing the remaining TTP by two, three and four, respectively, for one, two and three pregnancies included in TTP.

For the analysis of TTP and future miscarriage risk, we categorized TTP as <3, 3–6, 7–11 and ≥12 cycles (subfertility).

Outcome of subsequent pregnancy

We obtained information on the outcome of the first recorded pregnancy after the MoBa index pregnancy by linking information from three national health registries: the Medical Birth Registry of Norway, the Norwegian Patient Registry and the general practice database. The birth registry includes mandatory reported information on pregnancies ending in gestational week 12 or later (live births, stillbirths, late miscarriages and late induced abortions). We used the patient registry and the general practice database to obtain information on pregnancies ending before 12 completed gestational weeks, including miscarriages and induced abortions. We have previously described the identification of these pregnancies, the administrative codes used, and the data-cleaning procedures (Magnus *et al.*, 2021). The outcome of interest was miscarriage, and the reference group consisted of all other pregnancies (induced abortions, live births and stillbirths).

Covariates

The models for both designs were adjusted for pre-pregnancy maternal BMI (<18.5/18.5–24.9/25–29.9/≥30 kg/m^2), smoking status (non-smoker/quit smoking early in the current pregnancy/current smoker), cycle regularity in the last year before conception (regular/irregular), income level (<200 000 Norwegian Krone (NOK)/200 000–399 999 NOK/≥400 000 NOK) and highest completed or ongoing education (less than high school/high school/up to 4 years of college/more than 4 years of college). Data on all these covariates were collected at the time of recruitment of the index pregnancy (the association of the covariates with the exposures and outcomes of the two designs are illustrated in directed acyclic graphs in Supplementary Figs S1 and S2). In addition, the analysis of miscarriage history and subsequent fecundability was adjusted for maternal age at the time when the couple started trying to conceive as a linear and squared term. The analysis of TTP and future miscarriage risk was adjusted for maternal age at the delivery of the subsequent pregnancy as a linear and squared term and gravidity at the time of the index pregnancy. We estimated models both with and without number of prior miscarriages as a covariate.

Statistical analyses

All statistical analyses were carried out in Stata version 16 (StataCorp, TX, USA).

Miscarriage history and fecundability

We calculated fecundability ratios (FRs) for participants with one, two and three or more prior miscarriages, using participants with no prior miscarriages as a reference group. We used proportional probability regression with cycles as the unit of analysis and cycle number included as an indicator variable, censoring at six cycles. We censored at six cycles to reduce the bias that would result from longer TTPs that may erroneously include one or more prior miscarriages. Multivariable analyses were adjusted for the covariates described under 'Covariates'. We imputed missing information on covariates by conducting multiple imputation using chained equations, imputing a total of 10 datasets.

We conducted a number of sensitivity analyses to check the robustness of our findings. We explored the effect of adjusting for age at the time of beginning of trying to conceive rather than at the time of conception by excluding participants with TTPs >12 months, as the two time points were further apart in these participants. Another sensitivity analysis excluded participants who chose the alternative '3 months or more' for TTP but reported no further information on the exact TTP, as their TTPs may have been less precise. In two additional sensitivity analyses, we accounted for participants with prior pregnancies in their TTP, first by excluding all identified participants with a pregnancy within TTP (whose TTPs were corrected in the main analysis), and second, by excluding participants who reported to have started trying to conceive between January and June. Participants who conceived in the first half of the year were less likely to be identified as having a pregnancy within their TTP, given that such pregnancies would be more likely to fall within the same year as the start of TTP. We also carried out a sensitivity analysis including non-planners. Their TTPs were set to 1 as they are assumed to be a relatively fecund group. Another sensitivity analysis excluded all participants who reported a TTP of 1, as it is likely that any non-planner who reported a TTP

would have reported a TTP of 1. In addition, we explored adjustment for self-reported underlying chronic conditions, including endocrine conditions (diabetes mellitus type 1 and 2, hyperthyroidism and hypothyroidism), autoimmune conditions (celiac disease, systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis) and gynecological conditions (endometriosis and ovarian cysts). We also explored the effect of paternal age by including this as a covariate in the model. However, it should be noted that we only had access to paternal age in whole years and hence had to use paternal age at conception and not at the beginning of trying to conceive. We also do not know what proportion of our participants had changed partners between their prior pregnancies and the index pregnancy. Finally, we explored the effect of the recency of the latest miscarriage. However, these categories were quite crude, as we only knew the year and not the date of the prior miscarriages.

TTP and future miscarriage risk

We calculated the relative risk (RR) of miscarriage according to TTP category using log-binomial regression. For this analysis, we also imputed missing information on covariates using chained equations, imputing a total of 10 datasets. To test for a linear trend across the TTP categories, we included the TTP variable as a continuous covariate in the regression model.

To evaluate the role of prior pregnancies within TTP, we carried out sensitivity analyses excluding participants with completed pregnancies within TTP and including only participants whose TTP started between July and December, as described above. We also carried out a sensitivity analysis including paternal age at the time of conception of the index pregnancy in the model, as described earlier. In two additional sensitivity analyses, we excluded participants whose subsequent pregnancy ended in induced abortion (as we cannot know whether those pregnancies would have ended in miscarriage had they progressed further) and participants where the number of years between delivery of the MoBa index pregnancy and delivery of the subsequent pregnancy exceeded 5 years (to ensure that differences in age at the time of outcome and exposure were not biasing our estimates).

Results

Miscarriage history and fecundability

The analysis of miscarriage history and fecundability included 48 537 participants (Fig. 1). A total of 10 400 (21%) participants had one prior miscarriage, 2106 (4.3%) had two prior miscarriages, while 671 (1.4%) had three or more prior miscarriages. Participants with a history of prior miscarriage were older and more likely to have a parity of 0 at recruitment (Table I).

As shown in Table II, the adjusted FR in the imputed analysis was 0.83 (95% CI: 0.80–0.85) after one miscarriage, 0.79 (95% CI: 0.74–0.83) after two miscarriages and 0.74 (95% CI: 0.67–0.82) after three or more miscarriages, as compared to participants without a history of miscarriage. Adjustment for covariates had only a very slight attenuating effect. Results were somewhat attenuated in the complete case (non-imputed) analysis (Supplementary Table SI), as well as when including only prior miscarriages reported to have occurred in week 8 to week 22. In both cases, the dose–response pattern was retained. The results of the main analysis using different truncation points are shown in Supplementary Table SII.

The association was relatively consistent across sensitivity analyses, as shown in Fig. 2. All sensitivity analyses showed a similar dose–response pattern between the number of prior miscarriages and fecundability. The only exception was the sensitivity analysis excluding participants whose TTP had been corrected because they had one or more pregnancies within the reported TTP, where the dose–response was not observed, with adjusted FRs of 0.89 (95% CI: 0.87–0.92) after one miscarriage, 0.89 (95% CI: 0.84–0.94) after two miscarriages, and 0.85 (95% CI: 0.76–0.95) after three or more miscarriages. Results stratified by the recency of the latest miscarriage are reported in Supplementary Table SIII.

TTP and future miscarriage risk

The analysis of TTP and future miscarriage risk included 7889 participants (Fig. 1). In total, 4354 (55%) participants conceived within the first two cycles, 2210 (28%) between 3 and 6 cycles, 708 (9.0%) between 7 and 11 cycles and 617 (7.8%) after 12 cycles or longer (Table III). With regard to the outcomes of the subsequent pregnancies, 6400 (81%) ended in a live birth, 25 (0.3%) ended in a stillbirth, 1032 (13%) ended in a miscarriage, while 432 (5.5%) ended in an induced abortion. Participants with TTP $\geq$3 cycles were not older when they started trying to conceive the MoBa index pregnancy, but they were slightly older at delivery of the pregnancy after the MoBa index pregnancy. They were also less likely to have a college education of more than 4 years, more likely to be overweight or obese, and more likely to be primigravid and have a parity of 0 at the time of the MoBa index pregnancy (Table III). A comparison of the participants in the two study designs is shown in Supplementary Table SIV.

As shown in Table IV, the RR of miscarriage in the subsequent pregnancy when not adjusting for miscarriage history was 1.16 (95% CI: 0.99–1.35) for participants with a TTP 3–6 cycles in the index pregnancy, 1.18 (95% CI: 0.93–1.49) for participants with a TTP of 7–11 cycles, and 1.43 (95% CI: 1.13–1.81) for participants with TTP $\geq$12 cycles, when compared with participants with TTP <3 cycles. There was evidence of an overall linear trend in the association between TTP and future risk of miscarriage ($P = 0.002$). Estimates were only slightly attenuated after adjusting for covariates and were virtually unchanged when additionally adjusting for miscarriage history (Table IV).

All four sensitivity analyses also yielded significant overall linear trends, and point estimates were similar to those of the main analysis. Results are reported in Supplementary Table SV.

Discussion

A higher number of prior miscarriages was associated with lower fecundability and, conversely, a history of subfertility was associated with a higher risk of miscarriage. These associations, in both directions, support an overall association between reduced fecundability and miscarriage. Our results are consistent with those of several prior studies demonstrating lower fecundability after miscarriage (Hassan and Killick, 2005; Sapra *et al.*, 2014; Wildenschild *et al.*, 2019), and report for the

Table I Characteristics of study participants in analysis of miscarriage history and fecundability, by number of prior miscarriages.

Characteristics	No prior miscarriages	1 prior miscarriage	2 prior miscarriages	≥3 prior miscarriages
Participants, N (%)	35 360 (72.9)	10 400 (21.4)	2106 (4.3)	671 (1.4)
Complete cases, N (%)	32 329 (91.4)	9549 (91.8)	1920 (91.2)	614 (91.5)
Mean age (years) at beginning of conception attempts	30.6	30.7	32.0	32.9
Missing, N (%)	333 (0.9)	107 (1.0)	33 (1.6)	10 (1.5)
Education, N (%)				
Less than high school	2169 (6.1)	560 (5.4)	133 (6.3)	53 (7.9)
High school	9848 (27.9)	2783 (26.8)	584 (27.7)	218 (32.5)
College, up to 4 years	14 636 (41.4)	4299 (41.3)	846 (40.2)	250 (37.3)
College, more than 4 years	8551 (24.2)	2722 (26.2)	531 (25.2)	148 (22.1)
Missing	156 (0.4)	36 (0.4)	12 (0.6)	2 (0.3)
Maternal income, N (%)				
<200 000 NOK	9634 (27.3)	2599 (25.0)	548 (26.0)	175 (26.1)
200 000–399 999 NOK	20 496 (58.0)	6052 (58.2)	1225 (58.2)	395 (58.7)
≥400 000 NOK	3896 (11.0)	1400 (13.5)	254 (12.1)	79 (11.8)
Missing	1334 (3.8)	349 (3.4)	79 (3.8)	23 (3.4)
Smoking, N (%)				
Non-smoker	25 160 (71.2)	7454 (71.7)	1525 (72.4)	482 (71.8)
Quit smoking early in the current pregnancy	6723 (19.0)	1971 (19.0)	392 (18.6)	113 (16.8)
Current smoker	2907 (8.2)	800 (7.7)	157 (7.5)	64 (9.5)
Missing	57 (1.6)	175 (1.7)	32 (1.5)	12 (1.8)
Maternal pre-pregnancy BMI, N (%)				
<18.5 kg/m^2 (underweight)	943 (2.7)	247 (2.4)	51 (2.4)	16 (2.4)
18.5–24.9 (normal weight)	22 249 (62.9)	6502 (62.5)	1273 (60.5)	403 (60.1)
25–29.9 (overweight)	7982 (22.6)	2398 (23.1)	496 (23.6)	180 (26.8)
≥30 (obese)	3388 (9.6)	1036 (10.0)	242 (11.5)	57 (8.5)
Missing	798 (2.3)	217 (2.1)	33 (2.1)	15 (2.2)
Cycle regularity in the last year before conception, N (%)				
Regular	26 225 (74.2)	7724 (74.3)	1553 (73.7)	494 (73.6)
Irregular	8994 (25.4)	2638 (25.4)	548 (26.0)	174 (25.9)
Missing	141 (0.4)	38 (0.4)	5 (0.2)	3 (0.5)
Parity, N (%)				
0	3926 (11.1)	3464 (33.3)	550 (26.1)	137 (20.4)
1	22 908 (64.8)	4585 (44.1)	933 (44.3)	283 (42.2)
2	7309 (20.7)	1941 (18.7)	493 (23.4)	191 (28.5)
≥3	1217 (3.4)	411 (4.0)	130 (6.2)	80 (8.9)
Gravidity, N (%)				
1	22 909 (64.8)	2925 (28.1)	–	–
2	9419 (26.6)	4296 (41.3)	459 (21.8)	–
≥3	3401 (8.6)	3179 (30.6)	1647 (78.2)	671 (100)

NOK, Norwegian Krone.

first time a dose–response pattern for one, two and three or more miscarriages.

Important strengths of this study include the large sample size and the possibility of investigating both aspects of the study question within the same cohort. The availability of detailed information on lifestyle characteristics and predisposing conditions is another advantage of the MoBa cohort.

A limitation of this study is that TTP was self-reported. Although prior studies have found that TTPs shorter than 12 months are generally well recalled when retrospectively reported during pregnancy

Table II Association between number of prior miscarriages and fecundability.

Number of prior miscarriages	N			Unadjusted fecundability ratio (95% CI)	Adjusted[2] fecundability ratio (95% CI)
	Participants (total = 48 537[1])	Cycles at risk (total = 179 018)	Number of conceptions within 6 cycles (total = 45 351)		
0	35 360	125 712	33 139	Reference	Reference
1	10 400	41 435	9671	0.83 (0.80–0.85)	0.83 (0.80–0.85)
2	2106	8868	1927	0.77 (0.73–0.81)	0.79 (0.74–0.83)
≥3	671	3003	614	0.71 (0.64–0.78)	0.74 (0.67–0.82)

[1]Multiple imputation carried out to include 3846 participants with missing covariate information.
[2]Adjusted for maternal age at start of conception attempts as a linear and squared term, highest completed or ongoing maternal education, maternal income, maternal smoking during pregnancy, maternal pre-pregnancy BMI, and cycle regularity in the last year before conception.

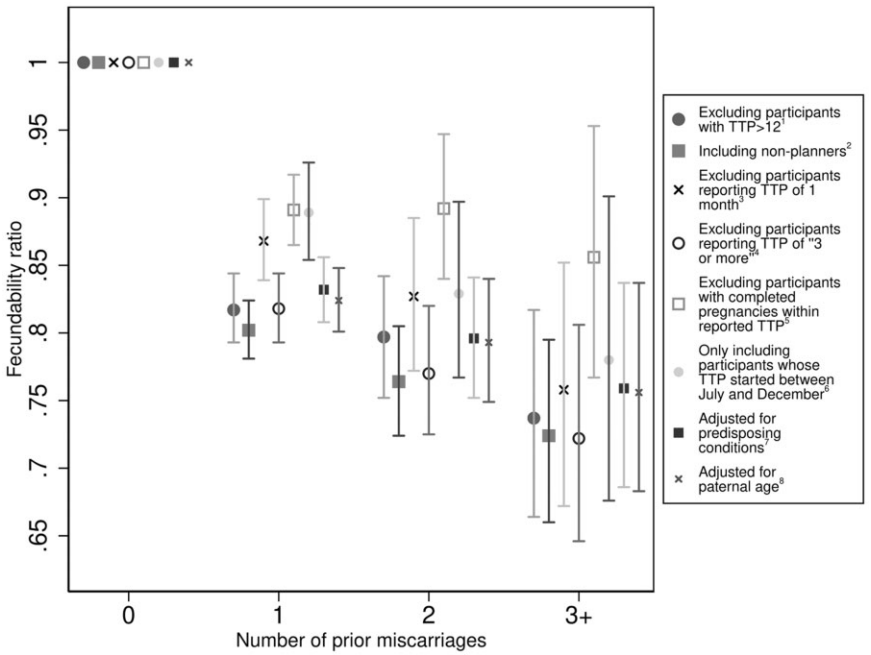

Figure 2. Association between number of prior miscarriages and fecundability: results of sensitivity analyses. [1]N = 3186 participants with TTP >12 excluded. [2]N = 9259 otherwise eligible participants with unplanned pregnancies included, setting their TTP to 1. [3]N = 11 502 participants with a self-reported TTP of 1 excluded, as there may be non-planners who reported a TTP in this group. [4]N = 4963 reporting «3 or more», but not their exact TTP, excluded. [5]N = 1306 participants reporting one or more completed pregnancies within their estimated TTP excluded. [6]N = 23 283 participants whose reported TTP started between January and June excluded, as they may have had unidentified pregnancies within their TTP due to only the year of the prior pregnancies being reported. [7]Adjusted for pre-pregnancy endocrine conditions (diabetes mellitus type 1 and 2, hyperthyroidism and hypothyroidism), autoimmune conditions (celiac disease, systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis) and gynecological conditions (endometriosis and ovarian cysts). [8]Adjusted for paternal age at the time of conception of the MoBa index pregnancy as a linear and squared term.

(Radin *et al.*, 2015), the longer TTPs included in our analyses may be affected by recall bias. Self-reported TTP is also prone to digit preference and inclusion of prior pregnancies within reported TTP. The inclusion of prior pregnancies within TTP was addressed both by correcting TTPs and by censoring at 6 months. Censoring at 6 months also mitigates some of the issues of digit preference, as 6 and 12 months were preferentially reported (over, e.g. 5 or 11). A related limitation is the likely higher ascertainment of early miscarriage among

Table III Characteristics of study participants in analysis of TTP and future miscarriage risk, by TTP category.

Characteristics	<3 cycles	3–6 cycles	7–11 cycles	≥12 cycles
Participants, N (%)	4354 (55.2)	2210 (28.0)	708 (9.0)	617 (7.8)
Complete cases, N (%)	4181 (96.0)	2096 (94.8)	685 (96.8)	592 (96.0)
Mean age (years) at delivery of subsequent pregnancy	32.1	32.4	32.6	33.1
Mean age (years) at beginning of conception attempts	28.7	28.9	28.7	28.6
Education, N (%)				
Less than high school	100 (2.3)	76 (3.4)	22 (3.1)	18 (2.9)
High school	708 (16.3)	414 (18.7)	147 (20.8)	144 (23.3)
College, up to 4 years	1839 (42.2)	929 (42.1)	285 (40.3)	261 (42.3)
College, more than 4 years	1684 (38.7)	779 (35.3)	251 (35.5)	192 (31.1)
Missing	23 (0.5)	12 (0.5)	3 (0.4)	2 (0.3)
Maternal income, N (%)				
<200 000 NOK	862 (19.8)	360 (16.3)	114 (16.1)	89 (14.4)
200 000–399 999 NOK	2467 (56.7)	1346 (60.9)	410 (57.9)	376 (60.9)
≥400 000 NOK	940 (21.6)	456 (20.6)	168 (23.7)	140 (22.7)
Missing	85 (2.0)	48 (2.2)	16 (2.3)	12 (1.9)
Smoking, N (%)				
Non-smoker	3375 (77.5)	1665 (75.3)	552 (78.0)	429 (69.5)
Quit smoking early in the current pregnancy	823 (18.9)	452 (20.5)	126 (17.8)	158 (25.6)
Current smoker	141 (3.2)	80 (3.6)	28 (4.0)	25 (4.1)
Missing	15 (0.3)	13 (0.6)	2 (0.3)	5 (0.8)
Maternal pre-pregnancy BMI, N (%)				
<18.5 kg/m^2 (underweight)	132 (3.0)	72/3.3)	18 (2.5)	21 (3.4)
18.5–24.9 (normal weight)	3122 (71.7)	149 (67.5)	468 (66.1)	375 (60.8)
25–29.9 (overweight)	778 (17.9)	436 (19.7)	138 (19.5)	134 (21.7)
≥30 (obese)	269 (6.2)	168 (7.6)	78 (11.2)	81 (13.1)
Missing	53 (1.2)	43 (2.0)	6 (0.9)	6 (1.0)
Cycle regularity in the last year before conception, N (%)				
Regular	3416 (78.5)	1610 (72.9)	461 (65.1)	419 (67.9)
Irregular	923 (21.2)	590 (26.7)	244 (34.5)	198 (32.1)
Missing	15 (0.3)	10 (0.5)	3 (0.4)	0 (0.0)
Parity, N (%)				
Primiparous	2955 (67.9)	1577 (71.4)	541 (76.4)	500 (80.0)
1	1172 (26.9)	536 (24.3)	135 (19.1)	95 (15.4)
2	183 (4.2)	81 (3.7)	30 (4.3)	15 (2.4)
≥3	44 (1.0)	16 (0.7)	2 (0.3)	7 (1.1)
Gravidity, N (%)				
0	2291 (52.6)	1162 (52.6)	421 (59.5)	403 (65.3)
1	1319 (30.3)	665 (30.1)	181 (25.6)	144 (23.3)
2	483 (11.1)	263 (11.9)	74 (10.5)	42 (6.8)
≥3	261 (6.0)	120 (5.43)	32 (4.5)	28 (4.5)
Number of prior miscarriages, N (%)				
0	3767 (86.5)	1802 (81.5)	585 (82.6)	539 (87.4)
1	478 (11.0)	334 (15.1)	103 (14.6)	59 (9.6)
2	81 (1.9)	61 (2.8)	14 (2.0)	16 (2.6)
≥3	28 (0.6)	13 (0.6)	6 (0.9)	3 (0.5)

NOK, Norwegian Krone; TTP, time-to-pregnancy.

Table IV Association between TTP in MoBa index pregnancy and miscarriage risk in subsequent pregnancy.

TTP category (cycles)	N (total = 7889[1])	N miscarriage in next pregnancy (total = 1032)	Unadjusted RR (95% CI)	Adjusted[2] relative risk (95% CI), not adjusting for miscarriage history	Adjusted[3] relative risk (95% CI), adjusting for miscarriage history
<3	4354	519	Reference	Reference	Reference
3–6	2210	307	1.19 (1.02–1.39)	1.16 (0.99–1.35)	1.15 (0.98–1.34)
7–11	708	100	1.22 (0.97–1.53)	1.18 (0.93–1.49)	1.17 (0.92–1.48)
≥12	617	106	1.53 (1.22–1.93)	1.43 (1.13–1.81)	1.41 (1.11–1.78)
***P* for trend**			<0.001	0.002	0.003

MoBa, Norwegian Mother, Father and Child Cohort Study; RR, relative risk; TTP, time-to-pregnancy.
[1]Multiple imputation carried out in order to include 305 participants with missing covariate information.
[2]Adjusted for maternal age at delivery of the subsequent pregnancy as a linear and squared term, highest completed or ongoing maternal education, maternal income, maternal smoking during pregnancy, maternal pre-pregnancy BMI, gravidity and cycle regularity in the last year before conception.
[3]Adjusted for maternal age at delivery of the subsequent pregnancy as a linear and squared term, highest completed or ongoing maternal education, maternal income, maternal smoking during pregnancy, maternal pre-pregnancy BMI, gravidity, and number of prior miscarriages.

participants with unfavorable reproductive histories, although a substantial proportion of this bias should be corrected by not counting miscarriages reported to have occurred before week 6. The lack of information on last use of contraception is another limitation of the study.

Confounders were only measured at the time of the index pregnancy. As such, in the analysis of miscarriage history and subsequent fecundability, the effects of confounders on the exposure are indirect, via the association between measurements at different time points (illustrated with a directed acyclic graph in Supplementary Fig. S1). Our ability to adjust for paternal factors was also limited. The addition of paternal age at the time of conception of the index pregnancy as a covariate did not have a pronounced effect in either of the analyses, but we were unable to examine the effect of changing partners between pregnancies, as well as other paternal factors such as seminal parameters.

It is also important to note that MoBa is a pregnancy cohort, and only participants whose pregnancy lasted to the time of recruitment (around the 18th gestational week) were included. Because the cohort does not include sterile women or women who are unable to carry a pregnancy this far, our findings may not be generalizable to all women.

Our results were consistent across various sensitivity analyses. The only notable exception was the lack of a pronounced dose–response pattern when we restricted the analysis to participants with no pregnancy within the reported TTP. However, such an attenuation was expected, as 7.8% of participants with miscarriage and 9.8% of participants with subfertility were excluded.

The association between fecundity and miscarriage may reflect a contribution of occult pregnancy loss to prolonged TTP. Miscarriage rates are high around the gestational weeks in which pregnancy is typically confirmed (Wilcox *et al.*, 1999), and, for this reason, it is likely that many early miscarriages are not recognized. Given the established high recurrence risk of miscarriage, some participants may recognize only a proportion of their miscarriages, with the unrecognized miscarriages instead contributing to perceived prolonged TTP.

Another potential explanation for the association is that there are underlying shared risk factors for both reduced fecundability and miscarriage. One of our sensitivity analyses adjusted for several conditions that could have represented such common biological mechanisms, including diabetes mellitus type 1 and 2, hyper- and hypothyroidism, celiac disease, systemic lupus erythematosus and rheumatoid arthritis (Khizroeva *et al.*, 2019), as well as multiple sclerosis (Houtchens *et al.*, 2020) and endometriosis (Buck Louis *et al.*, 2016; Zullo *et al.*, 2017). In addition, the adjustments for BMI and ovarian cysts taken together represent at least a partial adjustment for polycystic ovary syndrome, which is a risk factor for both miscarriage and reduced fecundability (Corbett and Morin-Papunen, 2013). Although the prevalence of these conditions in our cohort is likely underestimated, the apparent robustness of the estimates against our adjustment points to an association that is unlikely to be fully explained by predisposing conditions.

There is a multitude of potential shared causal mechanisms that we could not account for in our model. Some are known predictors of subfertility and pregnancy loss, such as diminished ovarian reserve (Bukman and Heineman, 2001; Bunnewell *et al.*, 2020), which is only partially accounted for by the adjustment for maternal age. Another possibility lies in the decidual immune system, which plays a major role in acceptance and adequate development of the blastocyst, and which could therefore possibly be involved both in early developmental failure and rejection of the blastocyst altogether (Ehsani *et al.*, 2019). Intriguing findings in this area include changes in the Th1/Th2 ratio during pregnancy and abnormal ratios of inflammatory to anti-inflammatory cytokines (Ozkan *et al.*, 2014), as well as higher-than-normal levels of Th17 cells (Ozkan *et al.*, 2014; Saifi *et al.*, 2014).

Although we do not fully understand the underlying biological mechanisms, our results suggest an intimate connection between miscarriage and fecundability. Our results suggest that women with a history of several miscarriages may benefit from earlier intervention with ART, as they may be at increased risk of subfertility.

Conclusion

Women with a prior miscarriage have reduced fecundability, with a further reduction for each additional prior miscarriage. There is also an

association between longer TTP in a prior pregnancy and miscarriage risk in the subsequent pregnancy, in particular among those with a history of subfertility. The findings highlight an opportunity to uncover as yet unrecognized biological mechanisms underlying these two indicators of fertility.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data used for this article are available by application to the Norwegian Mother, Father and Child Cohort study (mobaadm@fhi.no) and by application to www.helsedata.no. An ethical approval is required for application.

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Authors' roles

M.C.M. and S.E.H. conceived the idea for the study. L.A.A. performed statistical analyses and wrote the first draft, supervised by M.C.M., S.E.H. and Ø.N. O.B. and A.J.W. contributed to interpretation and discussion of the analyses and findings. All authors took part in revision of the manuscript.

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Conflict of interest

The authors report no conflicts of interest.

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