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Maternal age at birth and daughter's fecundability

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STUDY QUESTION: Do daughters of older mothers have lower fecundability?

SUMMARY ANSWER: In this cohort study of North American pregnancy planners, there was virtually no association between maternal age ≥35 years and daughters' fecundability.

WHAT IS KNOWN ALREADY: Despite suggestive evidence that daughters of older mothers may have lower fertility, only three retrospective studies have examined the association between maternal age and daughter's fecundability.

STUDY DESIGN, SIZE, DURATION: Prospective cohort study of 6689 pregnancy planners enrolled between March 2016 and January 2020.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Pregnancy Study Online (PRESTO) is an ongoing pre-conception cohort study of pregnancy planners (age, 21-45 years) from the USA and Canada. We estimated fecundability ratios (FR) for maternal age at the participant's birth using multivariable proportional probabilities regression models.

MAIN RESULTS AND THE ROLE OF CHANCE: Daughters of mothers ≥30 years were less likely to have previous pregnancies (or pregnancy attempts) or risk factors for infertility, although they were more likely to report that their mother had experienced problems conceiving. The proportion of participants with prior unplanned pregnancies, a birth before age 21, ≥3 cycles of attempt at study entry or no follow-up was greater among daughters of mothers <25 years. Compared with maternal age 25–29 years, FRs (95% CI) for maternal age <20, 20–24, 30–34, and ≥35 were 0.72 (0.61, 0.84), 0.92 (0.85, 1.00), 1.08 (1.00, 1.17), and 1.00 (0.89, 1.12), respectively.

LIMITATIONS, REASONS FOR CAUTION: Although the examined covariates did not meaningfully affect the associations, we had limited information on the participants' mother. Differences by maternal age in reproductive history, infertility risk factors and loss to follow-up suggest that selection bias may partly explain our results.

WIDER IMPLICATIONS OF THE FINDINGS: Our finding that maternal age 35 years or older was not associated with daughter's fecundability is reassuring, considering the trend towards delayed childbirth. However, having been born to a young mother may be a marker of low fecundability among pregnancy planners.

STUDY FUNDING/COMPETING INTEREST(S): PRESTO was funded by NICHD Grants (R21-HD072326 and R01-HD086742) and has received in-kind donations from Swiss Precision Diagnostics, FertilityFriend.com, Kindara.com, and Sandstone Diagnostics. Dr Wise is a fibroid consultant for AbbVie, Inc.

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Key words: fecundability / maternal age / time to pregnancy / fertility / developmental factors

Introduction

Average age at first birth has increased in most high-income countries (Mills *et al.*, 2011; Schmidt *et al.*, 2012; Mathews and Hamilton, 2016; Daniluk and Koert, 2017; Ely and Hamilton, 2018; OECD, 2019). The correlation of age at first birth between parents and their children (Steenhof and Liefbroer, 2008; Rijken and Liefbroer, 2009; Murphy, 2013; Kim, 2014, Kolk, 2014) has been attributed to continuity in socioeconomic status and transmission of parental values (Kolk, 2014). Yet, maternal age at conception may also have a biological influence on offspring reproductive health. The size of the primordial follicle pool is an important determinant of ovarian life span (Depmann *et al.*, 2015), making foetal life a potentially critical period for establishing reproductive potential (Evans *et al.*, 2012; Aiken *et al.*, 2013; Nelson *et al.*, 2013; Depmann *et al.*, 2015).

Mitochondria, which are maternal in origin and play an important role in reproduction, can be damaged by age-related oxidative stress (May-Panloup *et al.*, 2016; Demain *et al.*, 2017; Mihalas *et al.*, 2017), making it plausible that conception at older ages would lead to transmission of dysfunctional mitochondria (Rebolledo-Jaramillo *et al.*, 2014; May-Panloup *et al.*, 2016; Mihalas *et al.*, 2017). Additionally, two reports (Markunas *et al.*, 2016; Moore *et al.*, 2019) suggested that daughters of older mothers had altered methylation patterns that persisted to adulthood, including in a gene (LIM homeobox 8 (LHX8)) hypothesized to play an important role in female fertility (Moore *et al.*, 2019).

Studies of non-contracepting populations have reported lower fertility, including a higher rate of childlessness (Smits *et al.*, 2002), among daughters of older mothers (Smits *et al.*, 2002; Gillespie *et al.*, 2013). Among women born between 1930 and 1964, daughters of mothers aged ≥30 years had a 25–30% higher probability of lifetime childlessness. Although some women may have chosen to not have children, the association was highly consistent across strata of birth cohort and education (Basso *et al.*, 2018).

Three studies have examined daughters' time to pregnancy (TTP) as a function of maternal age. Of these, only a historical study of women born in Quebec in the late 19th century suggested that maternal age >30 years was associated with a longer interval from marriage to first birth, compared with 24–30 years. This study also reported a weak association with maternal age <21 years, similar to a recent survey of US women recruited online (Reynolds *et al.*, 2020), in which daughters of mothers <20 years had lower fecundability. The third study, of British pregnancy planners with at least one birth (Joffe and Barnes, 2000), examined only crude categories of maternal age (≥30 vs <30 years) and reported no association. However, the two latter studies were prone to recall bias, as they relied on self-reports of TTPs that could have occurred several years earlier.

In this article, we examined the association between mother's age at birth and daughter's fecundability in a large prospective cohort of North American women trying to conceive.

Materials and methods

Study population

The study population included female participants of Pregnancy Study Online (PRESTO), an ongoing prospective preconception cohort study of women in the USA and Canada that began in 2013. Eligible women were aged 21–45 years, not currently using contraception, and planning a pregnancy (Wise *et al.*, 2015). Enrolment and data collection occurred primarily through the study website (http://presto.bu.edu). After completing an online consent form, answering several screening questions, and providing a valid email address, potential participants were invited to complete an extensive baseline questionnaire, followed by shorter follow-up questionnaires every 2 months, for up to 12 months or until conception. Women with a plausible date of last menstrual period (LMP) who lived in the USA or Canada were eligible if they had tried to conceive for ≤6 menstrual cycles at study entry and had the opportunity to complete at least one follow-up questionnaire (9301 out of 12 644, as of June 2020). For this analysis, we further restricted the study population to women who had not been adopted and had enrolled after the 1st week of March 2016, when the question on mother's age at the participant's birth (referred to as 'maternal age' going forward) was introduced ($n = 6732$). Finally, we excluded women with missing values for maternal age ($n = 39$) and other key variables (gravidity: $n = 2$; prior infertility: $n = 1$; birth order: $n = 1$).

Ethics approval

The PRESTO protocol was approved by the IRB of Boston University Medical Campus. This analysis was additionally approved by the IRB of the McGill University Health Center.

Exposure, outcome and covariates

Maternal age, reported in years, was categorized as <20, 20–24, 25–29, 30–34, and ≥35 years. At baseline, women reported their LMP, menstrual cycle characteristics and duration of pregnancy attempt. The questionnaires asked about usual or most recent cycle length (for women with regular cycles not on hormonal contraception and for those who had stopped hormonal contraception, respectively). At each follow-up questionnaire, participants reported their LMP and whether they had conceived since the last questionnaire. We estimated TTP based on discrete menstrual cycles at risk, calculated as: cycles of attempt at study entry + [(LMP from most recent follow-up questionnaire—date of baseline questionnaire completion)/usual cycle length] +1 (Willis *et al.*, 2019). Women contributed cycles from enrolment until conception, initiation of fertility treatment, cessation of pregnancy attempt, withdrawal, loss-to-follow-up, or 12 cycles, whichever came first.

As potential confounders for the main analyses, we considered the factors that could have been causes (direct or indirect) of both the age at which the mother gave birth to the participant and the latter's fecundability. We left out variables that were not determinants—or that may have been a consequence—of maternal age at birth (e.g. participant's age at baseline, which could not have influenced the mother's age, and parents' education, which may be a determinant or a consequence of timing of childbirth). Thus, our *base model* included the participant's race/ethnicity (loosely based on: https://nces.ed.gov/programs/edge/Census/RaceInfo.asp), and birth order, plus two maternal variables reported by the daughter: cigarette smoking while pregnant with the participant, and difficulties conceiving (based on the question 'Did your mother have difficulties getting pregnant with you or any siblings?').

Statistical analysis

The analytic sample comprised 6689 women. We generated 20 imputation sets, with missing values imputed using the fully conditional specification approach, which allows for specification of the multivariate model for each incomplete variable (Van Buuren, 2007). Participants with no follow-up (i.e. the 20.1% who did not fill out any questionnaire after baseline) were assigned one cycle with conception imputed as yes/no. All estimates were based on the imputed data sets. 'Don't know' answers to the two questions about the mother were treated as missing and thus imputed.

After tabulating the distribution of baseline characteristics by maternal age, we examined the extent to which the difference in six correlates of fecundability persisted after accounting for the base covariates, plus parental education (defined as the highest education achieved by the mother or father). We estimated prevalence ratios (PR) for the following endpoints: (i) BMI $\geq$30 kg/m^2 (calculated based on self-reported weight and height), (ii) daily smoking, (iii) having had $\geq$1 unplanned pregnancy, (iv) history of sexually transmitted infection (STI: chlamydia, genital herpes, genital warts, or bacterial vaginosis), (v) prior diagnosis of gynaecologic disorders (polycystic ovary syndrome, endometriosis, or pelvic inflammatory disease), and (vi) prior fertility problems (defined as having had a past TTP $>$ 1 year or having consulted a physician for difficulties conceiving) among participants with a prior pregnancy attempt. PRs were estimated using log-binomial regression for outcomes (ii), (iv), and (v), and Poisson regression with robust standard errors for outcomes (i), (iii), and (vi), because log-binomial models failed to converge (Cummings, 2009).

We estimated the crude cumulative probability of conception in the study population using the life table approach (Cox, 1972), both among women with at least one cycle of follow-up and in the imputed data sets (averaging over the 20 imputations and using Rubin's rules to calculate the pooled standard error (Rubin, 2004)).

The fecundability ratio (FR) represents the ratio of the average per-cycle probability of conception for a given exposure level relative to the reference category (an FR $<$ 1 denotes lower fecundability). We estimated FRs using proportional probability regression models, with menstrual cycles of attempt time as the unit of analyses (Weinberg and Wilcox, 2008). Cycles were numbered from the beginning of the attempt (e.g. the first observed cycle for a woman who had tried for three cycles before enrolment was numbered '4') and included as an indicator variable. Unlike the life table approach, in which all women are included in the denominator from the first cycle, regardless of when they entered the study, the proportional probabilities model accounts for left truncation and for the declining probability of conception over time.

After examining the association between maternal age and daughter's fecundability in the full sample, we restricted the analysis to participants who had tried for $\leq$2 cycles before enrolment, to reduce the proportion of women with delayed entry. To try and limit the proportion of participants with unobserved cycles at risk, we further restricted to those who reported using effective birth control [i.e. hormonal contraception or intrauterine device (IUD) (Trussell *et al.*, 2018)], after excluding 1.5% of couples who reported previous sterilization in either member. To check whether the results differed among participants with no knowledge of their fecundability, we repeated the above analyses among nulligravid women who stated that they had not previously tried to conceive (34.5% of the analytic sample and 71.2% of nulligravida).

In sensitivity analyses, we examined whether the FRs changed appreciably when we added to the base model risk factors from childhood and adolescence (steps 1 and 2 below), as well as more proximal determinants of fecundability that differed by maternal age at birth (including some that may have been a consequence of maternal age). The variables listed below were progressively added at each step (except in model 4):

(1) Base model + highest parental education, and participant's birth weight $<$6 lbs ($\sim$2.7 kg)
(2) + participant's BMI at age 17 years and age at menarche
(3) + prior diagnoses of gynaecologic disorders (polycystic ovary syndrome (PCOS) pelvic inflammatory disease (PID), or endometriosis) and STI (chlamydia, genital herpes, genital warts, or bacterial vaginosis)
(4) + daily smoking and BMI at baseline (*after removing BMI at age 17* years)
(5) + reversed sterilization in either member of the couple and any recent hormonal contraception (both categorized as yes/no), as the former was associated with lower fecundability and the latter lowers probability of conception for the first 2–3 months after stopping (Mikkelsen *et al.*, 2013)
(6) + participant's age at baseline (categorized as in Table I)

Next, we stratified the full analytic sample, first by participant's age at baseline ($<$30 vs $\geq$30 years), to assess whether the association varied by daughter's age, and then by birth order (firstborn vs $\geq$2), as parents who had their first child at a later age may themselves have had lower fecundability.

Finally, we carried out the main analyses among women without missing data ('complete case' analysis), adjusting only for race/ethnicity and birth order (due to the high proportion of 'don't know' answers in the variables concerning the mother).

Multiple imputations were carried out with SAS (Cary, NC, USA); all other analyses with STATA 16 (College Station, TX, USA).

Results

The distribution of several of the baseline characteristics differed substantially across strata of maternal age. The proportion of participants with Non-Hispanic White race/ethnicity, college-educated parents, BMI ($<$30 kg/m^2), and with a mother who had experienced problems conceiving increased with increasing maternal age. Daughters of mothers $<$20 years were more likely to be daily smokers and to have been prenatally exposed to maternal smoking (Table I).

Table II summarizes baseline reproductive history and other correlates of fertility. Daughters of mothers 30 years or older were more likely to be nulligravid and to report no prior pregnancy attempt. Daughters of mothers younger than 25 years, particularly those born when the mother was $<$20 years, had more unplanned pregnancies and were more likely to have given birth before age 21. They were also more likely to have experienced fertility problems (i.e. they had a prior TTP $>$1 year or had consulted a physician for help with conceiving) and to have been diagnosed with an STI or a gynaecologic

Table I Baseline characteristics of 6689 participants in Pregnancy Study Online (PRESTO), by maternal age.

Characteristic	Mother's age at the participant's birth (maternal age), years									
	<20		20–24		25–29		30–34		≥35	
	n = 488		n = 1685		n = 2273		n = 1667		n = 576	
	n	%	n	%	n	%	n	%	n	%
Participant's age (years)										
20–24	62	12.7	182	10.8	158	7.0	112	6.7	40	6.9
25–29	201	41.2	721	42.8	927	40.8	645	38.7	242	42.0
30–34	149	30.5	530	31.5	903	39.7	713	42.8	227	39.4
≥35	76	15.6	252	15.0	285	12.5	197	11.8	67	11.6
Race/ethnicity[a]										
Non-Hispanic White	347	71.1	1381	82.0	1940	85.4	1459	87.5	486	84.4
Hispanic, any race	53	10.9	143	8.5	125	5.5	84	5.0	35	6.1
Non-Hispanic Black	54	11.1	57	3.4	59	2.6	40	2.4	19	3.3
Other race or ethnicity	34	7.0	103	6.1	147	6.5	83	5.0	34	5.9
Highest education of parents[a]										
≤High School	203	41.6	403	23.9	347	15.3	186	112	74	12.9
Some college (incl vocational)	164	33.6	608	36.1	649	28.6	366	22.0	101	17.5
College	79	16.2	402	23.8	688	30.3	518	31.1	196	34.0
Graduate School	35	7.2	262	15.6	584	25.7	591	35.5	204	35.4
Birth order of participant										
First	412	84.4	1118	66.4	1243	54.7	580	34.8	159	27.6
Second or later	76	15.6	567	33.6	1030	45.3	1087	65.2	417	72.4
Participant's birth weight <6 lb (~2.7 kg)	61	12.5	187	11.1	205	9.0	143	8.6	54	9.4
Missing	25	5.1	84	5.0	121	5.3	89	5.4	29	5.0
Age at menarche (years)[a]										
8–11	158	32.4	466	27.7	556	24.5	388	23.3	153	26.6
12–14	286	58.6	1062	63.0	1534	67.5	1134	68.0	362	62.8
≥15	43	8.8	148	8.8	176	7.7	139	8.3	57	9.9
Mean height (SD)	164.2	(7.1)	164.7	(7.1)	165.4	(6.9)	165.8	(7.2)	166.1	(7.3)
BMI at age 17 years (kg/m^2)[a,b]										
<25	305	62.5	1148	68.1	1645	72.4	1266	75.9	419	72.7
25–29	92	18.9	328	19.5	369	16.2	272	16.3	91	15.8
≥30	86	17.6	201	11.9	247	10.9	125	7.5	66	11.5
BMI at study entry (kg/m^2)[a]										
<25	138	28.3	599	35.6	1001	44.0	824	49.4	271	47.0
25–29	104	21.3	406	24.1	552	24.3	423	25.4	153	26.6
30–34	99	20.3	305	18.1	297	13.1	184	11.0	66	11.5
≥35	147	30.1	374	22.2	419	18.4	236	14.2	86	14.9
Daily smoking	73	15.0	166	9.9	114	5.0	78	4.7	22	3.8
Mother had difficulties conceiving	38	7.8	182	10.8	366	16.1	344	20.6	146	25.4
Don't know/Missing	72	14.8	221	13.1	346	15.2	286	17.2	103	17.9
Mother smoked while pregnant with participant	121	24.8	274	16.3	267	11.8	159	9.5	66	11.5
Don't know/Missing	113	23.2	201	11.9	193	8.5	105	6.3	44	7.6

[a]Percent may not add to 100% due to missing values. Variables with missing values <1% were: race/ethnicity (n = 6), highest education of the mother or father (n = 29), age at menarche (n = 27), height (n = 3), BMI at age 17 (n=29), BMI at baseline (n = 5).
[b]BMI at age 17 was calculated based on recalled weight at 17 years and current height.

Table II Participants' reproductive factors at baseline, by maternal age.

Factor	Mother's age at the participant's birth (maternal age), years									
	<20 n = 488		20–24 n = 1685		25–29 n = 2273		30–34 n = 1667		≥35 n = 576	
	n	%	n	%	n	%	n	%	n	%
Reported no prior pregnancy attempt	95	19.5	475	28.2	817	35.9	682	40.9	240	41.7
Gravidity at baseline										
Never pregnant	158	32.4	686	40.7	1161	51.1	919	55.1	321	55.7
1 pregnancy	115	23.6	455	27.0	591	26.0	414	24.8	131	22.7
≥2 pregnancies	215	44.1	544	32.3	521	22.9	334	20.0	124	21.5
Had ≥1 prior unplanned pregnancy[a]	257	52.3	666	39.5	613	27.0	409	24.5	155	26.9
n unplanned pregnancies (mean, SD)	1.14	1.59	0.71	1.19	0.42	0.87	0.38	0.87	0.44	0.95
Had ≥1 prior birth	249	51.0	678	40.2	709	31.2	475	28.5	166	28.8
Gave birth before 21 years[b]	111	22.8	208	12.3	114	5.0	80	4.8	39	6.8
Prior TTP > 1 yr. or sought help to conceive										
Among all	129	26.4	340	20.2	340	15.0	214	12.8	86	14.9
Among women with a prior attempt	129	36.2	340	32.0	340	28.7	214	27.2	86	31.2
PCOS, endometriosis, or PID[c]	82	16.8	263	15.6	283	12.5	163	9.8	74	12.9
Sexually transmitted infection (STI)[d]	168	34.4	445	26.4	545	24.0	395	23.7	137	23.8
Recent and past use of hormonal contraception/IUD[e]	290	59.4	999	58.3	1310	57.6	956	57.4	336	58.3
Prior male or female sterilization	17	3.5	33	2.0	24	1.1	18	1.1	8	1.4
Tried for ≤2 cycles at entry	272	55.7	1049	62.3	1537	67.6	1157	69.4	412	71.5
No follow-up questionnaires	170	34.8	395	23.4	387	17.0	289	17.3	102	17.7

Abbreviations: TTP, time-to-pregnancy; PCOS, polycystic ovary syndrome; PID, pelvic inflammatory disease; STI, sexually transmitted infections; IUD, intrauterine device.
[a]Information on prior pregnancies was asked for up to 10 pregnancies (9 women had >10 pregnancies). In total, 3444 women reported 7233 pregnancies. Among the 7210 for which information was asked, 40 (0.6%) had missing pregnancy outcome and 3551 ended in birth (including 74 stillbirths).
[b]Participant's age at a prior birth was missing for 54 years. Among babies born to mothers younger than 21 years, eight were stillborn.
[c]Prior diagnosis of polycystic ovary syndrome (PCOS), endometriosis, or pelvic inflammatory disease (PID).
[d]Prior diagnosis of chlamydia, genital herpes, genital warts, or bacterial vaginosis.
[e]Excludes prior male or female sterilization. Includes couples who *also* reported less effective contraception.

disorder. Young maternal age was associated with entering the study after ≥3 cycles of trying and, especially, with not answering any follow-up questionnaire.

After accounting for the base covariates, plus parental education, women born to mothers <25 years had a higher prevalence of obesity, smoking, gynaecologic disorders, and prior fertility problems, compared with daughters of mothers ≥25 years (Fig. 1).

The cumulative conception rate over 12 cycles in the study population was 0.71 (95% CI: 0.70, 0.72) among women with at least one cycle of follow-up and 0.69 (95% CI: 0.68, 0.71) when averaged over all imputed data sets. As shown in Fig. 2, cumulative conception rates were substantially lower for participants born to mothers younger than 20 years and, to a lesser degree, for daughters of mothers 20–24 years. The estimates based on the average over the imputed data sets were lower than those restricted to women with some follow-up, reflecting the fact that, compared with the latter, women with no follow-up were more likely to be daily smokers (40.8 vs 18.6%), to have a BMI of > 30 kg/m^2 (27.9 vs 16.2%), and to have experienced prior fertility problems (34.8 vs 17.2%).

We saw similar results for fecundability (Fig. 3): compared with maternal age 25–29 years, maternal age ≥35 years was not associated with longer TTP. However, women born to mothers <20 years had the lowest fecundability in most models, followed by daughters of mothers 20–24 years. Among women with no prior pregnancy attempt, the association was attenuated for maternal age <20 years but not for maternal age 20–25 years; however, in this subset, confidence intervals were wide.

Overall, our estimates were minimally sensitive to the selected confounders (Supplementary Table SI). When we included additional risk factors, particularly proximal ones, such as smoking and BMI, the FR for maternal age <20 years was slightly attenuated (Table III).

Results were not appreciably different in analyses stratified by participant's age at entry (Supplementary Table SII) or birth order (Supplementary Table SIII), nor when we restricted the analyses to participants with at least one follow-up questionnaire (complete case analysis, Supplementary Table SIV). Supplementary Fig. S1 shows the cycle-specific mean predicted probabilities of conception based on the complete case models, stratified by maternal age.

Discussion

In this contemporary cohort of female pregnancy planners from all 50 US states and 10 Canadian provinces, we saw no evidence that having

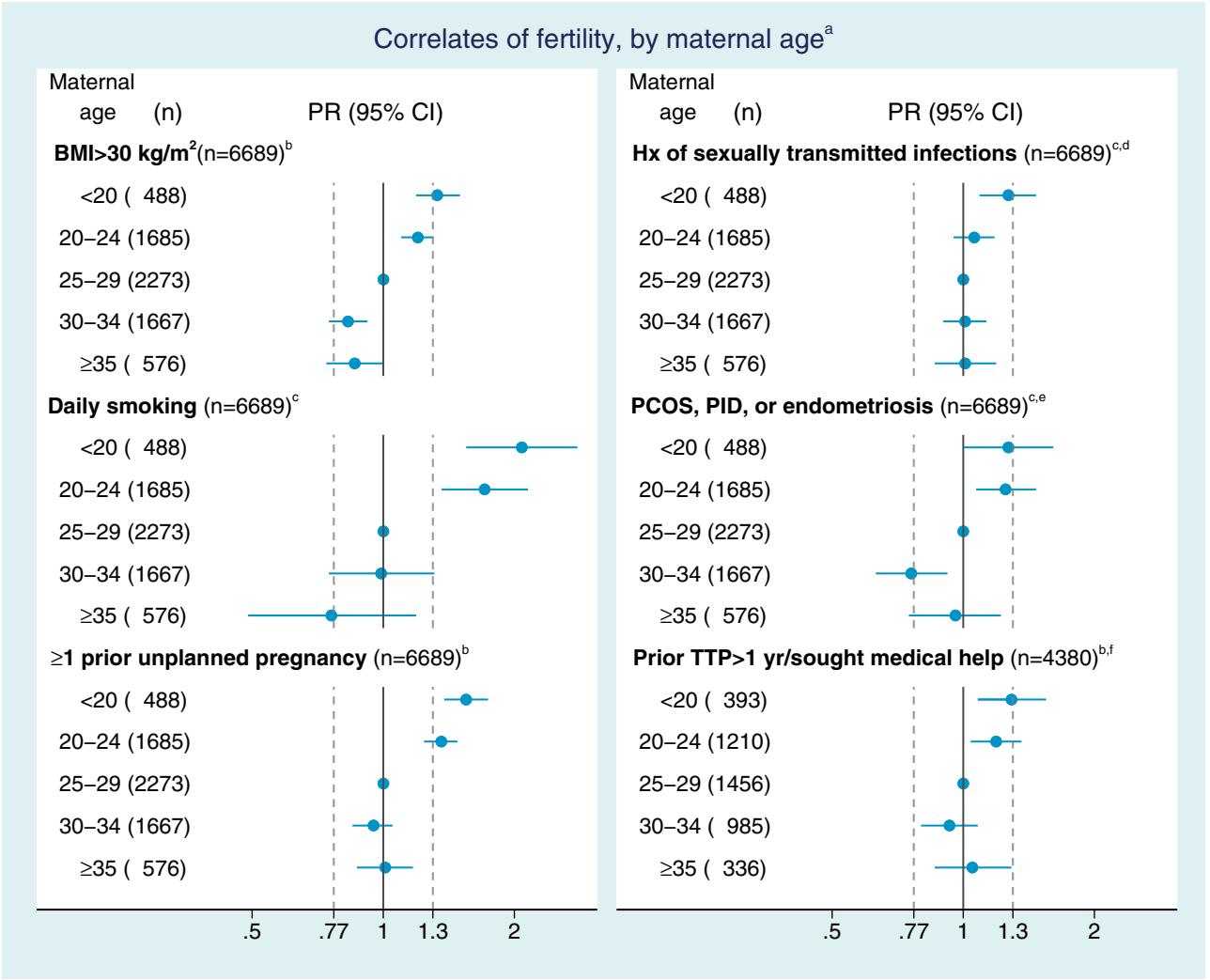

Figure 1. Association between maternal age (years) and six correlates of fecundability in daughters.[a] Vertical lines at 0.77 and 1.3 are provided to aid visualization. PR, prevalence ratio. [a]Adjusted for participant's race/ethnicity, birth order, highest educational level achieved by the mother or father, whether the mother had difficulties conceiving, and whether the mother smoked while pregnant with the participant. [b]Poisson regression with robust standard errors. [c]Log-binomial regression. [d]History (Hx) of sexually transmitted infection was defined as having had a diagnosis of chlamydia, genital herpes, genital warts, or bacterial vaginosis. [e]Prior diagnosis of polycystic ovary syndrome (PCOS), endometriosis, or pelvic inflammatory disease (PID). [f]Defined as having had a prior time to pregnancy>1 year or having sought medical help to conceive. Women who reported never having tried to conceive are excluded from this analysis.

been born to a mother ≥35 years was associated with fecundability. However, young maternal age, particularly maternal age younger than 20 years, was associated with lower fecundability.

Although some studies have reported that daughters of older mothers have fewer children (Smits *et al.*, 2002; Gillespie *et al.*, 2013), a higher probability of childlessness (Smits *et al.*, 2002; Basso *et al.*, 2018), and a higher frequency of menstrual irregularity (Smits *et al.*, 1997), these outcomes are relatively poor proxies of fecundability. The evidence for an adverse effect of older maternal age on fecundability is limited. In a recent online survey (Reynolds *et al.*, 2020) of 2854 women (recruited mainly through www.researchmatch.org) who recalled the TTPs of their previous (planned) pregnancies, maternal age ≥35 years was not associated with fecundability. In a study of British men and women born in 1958 (Joffe and Barnes, 2000), fecundability was similar in daughters of mothers ≥30 and <30 years. However, besides considering only crude categories of maternal age, this study was based on couples recalling the TTP leading to the birth of their first child, which had to have occurred by the time participants were 33 years old (and may not have been the most recent pregnancy). Only in a study of 2204 women born between 1860 and 1870 in Quebec (Canada), when effective contraception was not available, was there a suggestion of lower fecundability among daughters of older mothers. The odds ratios (OR) of monthly conception failure (the inverse of fecundability) for maternal ages 31–39 and 40–55 years

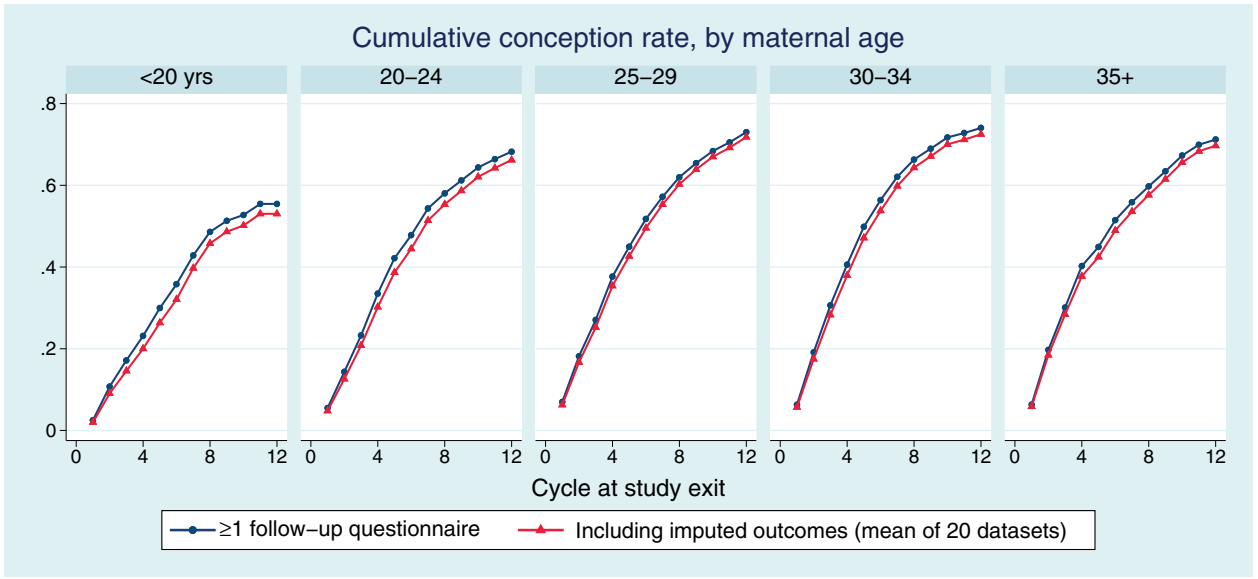

Figure 2. Life table estimates of cumulative probabilities of conception, by maternal age. Red shows estimates based on imputed data sets, blue shows estimates restricted to data from women with at least one follow-up questionnaire.

were, respectively, 1.10 (95 CI: 0.95, 1.26) and 1.11 (95 CI: 0.91, 1.35), compared with maternal age 24–30 years. However, two of the above studies suggested that daughters of younger mothers may have lower fecundability. In the study of 19th century Quebec women, daughters of mothers 14–20 years had a slightly higher risk of monthly conception failure, measured from the date of marriage [OR 1.08 (95% CI: 0.89, 1.30)], compared with daughters of women 24–30 years (Smits *et al.*, 1999). In the online survey (Reynolds *et al.*, 2020), the fecundability OR associated with maternal age <20 years was 0.84 (95% CI: 0.72, 0.99), compared with maternal age 20–24 years. Unlike the above, our study had a prospective design, resulting in a more accurate measurement of TTP and the ability to rely on covariates collected before conception.

Animal studies provide some evidence of the potential influence of maternal age on offspring reproductive function. In two species of birds, female offspring of older mothers had fewer chicks throughout their lifetime, despite having a similar lifespan (Bouwhuis *et al.*, 2015; Schroeder *et al.*, 2015). Conversely, in Angus heifers, having a younger mother was associated with having fewer primordial follicles (Tenley *et al.*, 2019). In an analysis of 228 229 fertility records of UK dairy cows (Banos *et al.*, 2007), first-born heifers born to younger dams had slightly earlier first service (the interval from birth to insemination) but required 7% more inseminations than those born to older dams. However, among second-born heifers, younger dam's age was associated with earlier first service and fewer inseminations. The authors hypothesized that the need for more inseminations in first-born calves of younger dams may have been due to competition between the foetus and a still growing mother (Banos *et al.*, 2007).

In humans, early-life exposure to an adverse nutritional environment, including maternal obesity, can result in impaired reproductive health (Jazwiec and Sloboda, 2019); teenage mothers are more likely to be disadvantaged (Meade *et al.*, 2008; Kahn and Anderson, 1992) and to have smaller infants (Scholl and Hediger, 1993; Kaplanoglu *et al.*, 2015), potentially resulting in daughters having smaller ovaries and higher levels of follicle stimulating hormone (Ibáñez *et al.*, 2000; Petraitiene *et al.*, 2020). These factors may partly explain the lower fecundability among daughters of younger mothers, although our estimates for daughters of mothers < 20 years were virtually unchanged in models including surrogate measures of early-life nutrition and adversity (birth weight <6lbs parental education, participant's age at menarche, and BMI at 17 years) and only slightly attenuated when we further added well-established determinants of fecundability. While parental education may be both a determinant of childbearing age and a consequence of having had a child at a young age, the other factors, particularly the more proximal ones, are not actual confounders of the association between maternal age and fecundability. Still, as these factors differed substantially by maternal age, we included them in sensitivity analyses to indirectly address confounding not accounted for by the base covariates. Although the estimates were relatively stable, we cannot rule out that residual confounding (or interactions) may partly explain the increased risk among daughters of young mothers. Likewise, the better socioeconomic and health conditions of daughters of older mothers may have obscured a modest biologic effect of older maternal age. Our aim was to assess a possible etiologic effect of maternal age on daughter's fecundability; however, lack of knowledge of the possible causal pathways and limited information about the participant's mother constrained our ability to address the complex confounding underlying this association.

Selection bias, specifically, 'planning bias' (Baird and Wilcox, 1985; Baird *et al.*, 1994; Weinberg *et al.*, 1994), may also partly explain the association with young maternal age. If daughters of younger mothers are more likely to have children at a young age (Meade *et al.*, 2008;

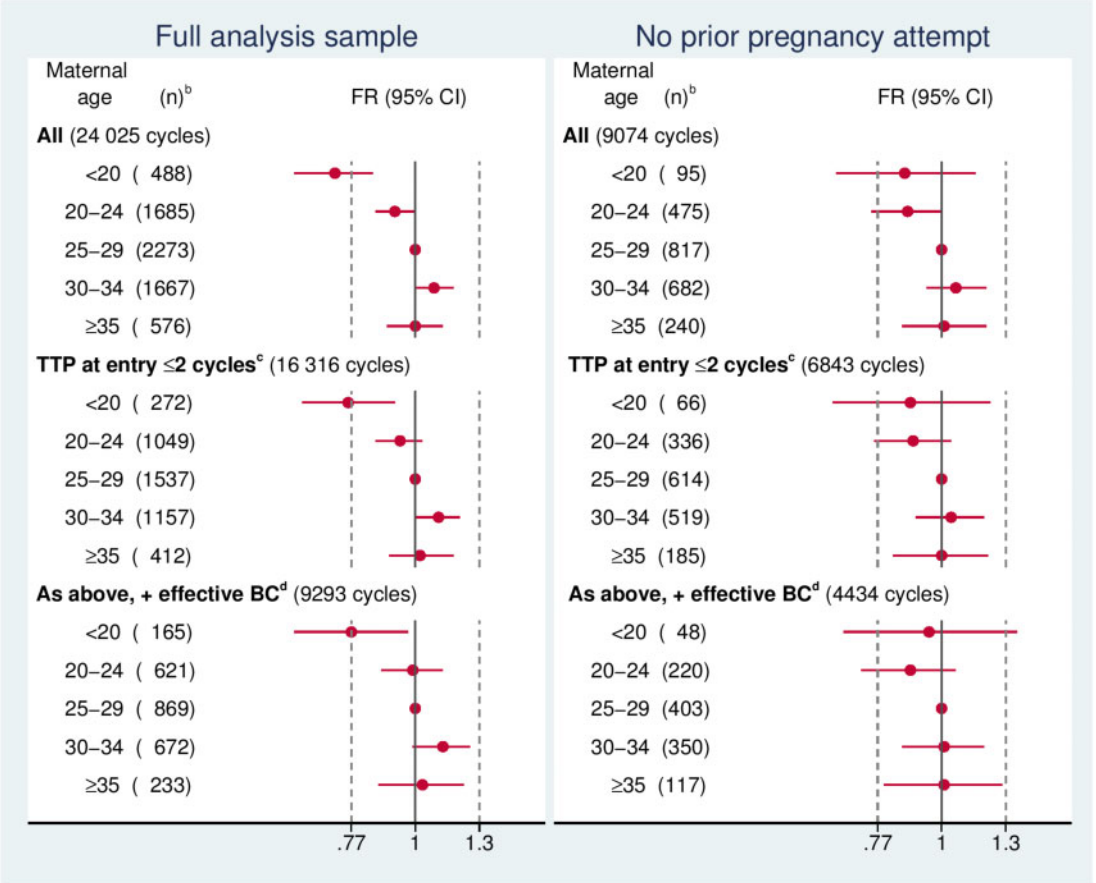

Figure 3. Association between maternal age and fecundability in daughters: full sample and participants who reported no prior pregnancy attempt.[a] Vertical lines at 0.77 and 1.3 are provided to aid visualization. FR, Fecundability ratio. [a]Proportional probabilities models, with cycles as the units of analysis. All models were adjusted for participant's race/ethnicity, birth order, whether the mother had difficulties conceiving, and whether she smoked while pregnant with the participant. [b]Number of women in each category. [c]Analysis restricted to women with ≤2 cycles of trying at study entry. [d]Analysis further restricted to women who reported using effective birth control (BC), which comprised any type of hormonal contraception and IUD. This category includes couples who reported additionally using a less effective contraceptive method but excludes those in which either member had previously undergone sterilization.

Kahn and Anderson, 1992, Lehti *et al.*, 2012), higher fecundability may result in a greater proportion having the desired number of children without planning. Unplanned (or mistimed) pregnancies are disproportionately more frequent among low-income women; however, high-income women are more likely to terminate unplanned pregnancies (Reeves and Venator, 2015). In this study, daughters of mothers aged <20 years were more likely to have given birth before age 21 and to have had prior unplanned pregnancies (thus, they presumably also had more cycles at risk that did not end in conception). Besides coming from families with lower educational level, daughters of mothers <20 years had a higher prevalence of risk factors for infertility, a slightly longer pregnancy attempt time at study entry, and were substantially more likely to have no follow-up. Thus, it is possible that, among pregnancy planners, daughters of younger mothers may be more selected for low fecundability than daughters of older mothers. Our observation that the association between younger maternal age and low fecundability was attenuated in analyses restricted to nulligravid participants who reported no prior pregnancy attempt is consistent with some degree of planning bias.

Conclusion

In conclusion, in this study of pregnancy planners, daughters of older mothers did not have lower fecundability, a reassuring finding considering the trend towards delayed childbearing in industrialized nations. However, having been born to a young mother may be a marker of reduced fecundability among female pregnancy planners.

Table III FRs of maternal age.

	All		No prior pregnancy attempt	
Maternal age (years)	**FR**	**95% CI**	**FR**	**95% CI**
0. Base model[a]				
<20	0.72	0.61, 0.84	0.86	0.65, 1.15
20–24	0.92	0.85, 1.00	0.87	0.75, 1.00
25–29	1.00	Reference	1.00	Reference
30–34	1.08	1.00, 1.17	1.06	0.94, 1.20
≥35	1.00	0.89, 1.12	1.01	0.85, 1.20
1. + Highest education parents, participant's birth weight < 6 lb				
<20	0.73	0.62, 0.86	0.87	0.65, 1.16
20–24	0.94	0.86, 1.02	0.86	0.74, 0.99
25–29	1.00	Reference	1.00	Reference
30–34	1.07	0.99, 1.16	1.05	0.93, 1.19
≥35	0.99	0.88, 1.11	1.01	0.84, 1.20
2. + Participant's age at menarche, BMI at 17 years				
<20	0.75	0.64, 0.88	0.87	0.65, 1.16
20–24	0.94	0.87, 1.02	0.86	0.93, 1.19
25–29	1.00	Reference	1.00	Reference
30–34	1.06	0.98, 1.15	1.05	0.93, 1.19
≥35	0.99	0.88, 1.12	1.01	0.84, 1.20
3. + Prior diagnosis of gynaecologic disorders, sexually transmitted infections				
<20	0.76	0.65, 0.89	0.89	0.67, 1.19
20–24	0.96	0.88, 1.04	0.87	0.76, 1.01
25–29	1.00	Reference	1.00	Reference
30–34	1.06	0.98, 1.14	1.06	0.94, 1.20
≥35	0.99	0.88, 1.11	1.01	0.85, 1.20
4. + Smoking, BMI at baseline (*minus BMI at 17* years)				
<20	0.79	0.67, 0.92	0.91	0.68, 1.21
20–24	0.97	0.89, 1.05	0.88	0.76, 1.02
25–29	1.00	Reference	1.00	Reference
30–34	1.05	0.97, 1.13	1.04	0.92, 1.17
≥35	0.97	0.86, 1.09	0.98	0.82, 1.17
5. + Recent hormonal contraception, prior sterilization				
<20	0.80	0.68, 0.94	0.90	0.68, 1.21
20–24	0.97	0.90, 1.06	0.87	0.76, 1.01
25–29	1.00	Reference	1.00	Reference
30–34	1.05	0.97, 1.14	1.04	0.92, 1.17
≥35	0.98	0.87, 1.10	0.98	0.82, 1.17
6. + Participant's age at baseline[b]				
<20	0.79	0.67, 0.93	0.91	0.68, 1.21
20–24	0.97	0.90, 1.06	0.86	0.75, 0.99
25–29	1.00	Reference	1.00	Reference
30–34	1.05	0.97, 1.14	1.04	0.92, 1.18
≥35	0.97	0.86, 1.09	0.97	0.81, 1.16

Main analysis and models including additional covariates.
FR, fecundability ratio.
[a]Includes birth order, participant's race/ethnicity, mother experienced difficulties conceiving, mother smoked while pregnant with the participant.
[b]Participant's age was categorized as in Table I.

Supplementary data

Supplementary data are available at *Human Reproduction* online

Data availability

The data on which this article is based cannot be shared publicly for confidentiality reasons.

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Authors' roles

L.A.W., E.E.H., E.M.M. and K.J.R. designed the parent study; O.B. developed the hypothesis, performed the literature review, carried out the statistical analysis, and took the lead in drafting the manuscript; S.K.W. contributed to data quality control and analyses. All authors contributed to the interpretation of results and the writing of the manuscript.

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Conflict of interest

PRESTO has received in-kind donations from Swiss Precision Diagnostics, FertilityFriend.com, Kindara.com and Sandstone Diagnostics. Dr Wise is a fibroid consultant for AbbVie, Inc.

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