GYNECOLOGY

Age and fecundability in a North American preconception cohort study

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BACKGROUND: There is a well-documented decline in fertility treatment success with increasing female age; however, there are few preconception cohort studies that have examined female age and natural fertility. In addition, data on male age and fertility are inconsistent. Given the increasing number of couples who are attempting conception at older ages, a more detailed characterization of age-related fecundability in the general population is of great clinical utility.

OBJECTIVE: The purpose of this study was to examine the association between female and male age with fecundability.

STUDY DESIGN: We conducted a web-based preconception cohort study of pregnancy planners from the United States and Canada. Participants were enrolled between June 2013 and July 2017. Eligible participants were 21−45 years old (female) or ≥21 years old (male) and had not been using fertility treatments. Couples were followed until pregnancy or for up to 12 menstrual cycles. We analyzed data from 2962 couples who had been trying to conceive for ≤3 cycles at study entry and reported no history of infertility. We used life-table methods to estimate the unadjusted cumulative pregnancy proportion at 6 and 12 cycles by female and male age. We used proportional probabilities regression models to estimate fecundability ratios, the per-cycle probability of conception for each age category relative to the referent (21−24 years old), and 95% confidence intervals.

RESULTS: Among female patients, the unadjusted cumulative pregnancy proportion at 6 cycles of attempt time ranged from 62.0% (age, 28−30 years) to 27.6% (age, 40−45 years); the cumulative pregnancy proportion at 12 cycles of attempt time ranged from 79.3% (age, 25−27 years old) to 55.5% (age, 40−45 years old). Similar patterns were observed among male patients, although differences between age groups were smaller. After adjusting for potential confounders, we observed a nearly monotonic decline in fecundability with increasing female age, with the exception of 28−33 years, at which point fecundability was relatively stable. Fecundability ratios were 0.91 (95% confidence interval, 0.74−1.11) for ages 25−27, 0.88 (95% confidence interval, 0.72−1.08) for ages 28−30, 0.87 (95% confidence interval, 0.70−1.08) for ages 31−33, 0.82 (95% confidence interval, 0.64−1.05) for ages 34−36, 0.60 (95% confidence interval, 0.44−0.81) for ages 37−39, and 0.40 (95% confidence interval, 0.22−0.73) for ages 40−45, compared with the reference group (age, 21−24 years). The association was stronger among nulligravid women. Male age was not associated appreciably with fecundability after adjustment for female age, although the number of men >45 years old was small (n=37).

CONCLUSION: In this preconception cohort study of North American pregnancy planners, increasing female age was associated with an approximately linear decline in fecundability. Although we found little association between male age and fecundability, the small number of men in our study >45 years old limited our ability to draw conclusions on fecundability in older men.

Key words: age, fecundability, fertility, preconception cohort

Over the last several decades, couples in Western societies have been postponing conception gradually until older ages.[1] There are several hypothesized reasons for delayed childbearing[2] that include increased access to effective contraception,[3] higher female educational attainment,[4-6] increased female participation in the workforce,[7] cultural shifts that concern the ideal number of children,[8] improved gender equity,[9-12] economic uncertainty,[13,14] and the absence of family-friendly workplace policies.[15,16] Given the increasing number of couples who are attempting conception at older ages, a more detailed characterization of age-related fecundability in the general population is of great clinical utility.

There is a well-documented decline in fertility treatment success with increasing female age.[17,18] In addition, data from noncontracepting natural fertility populations have shown that marital fertility rates decline with increasing female age, with peak fecundability in the early to mid-twenties and a steady decline at older ages; in some populations, a more rapid decline was observed after age 30 years.[19-21]

Studies that examine the association between age and fecundability in infertile populations or populations of pregnant women are subject to selection bias[22] and misclassification.[23] Though limited in number, preconception cohort studies of women from the general population avoid these biases and support the hypothesis that a woman's fecundability begins to decline during her early thirties. In a Danish preconception cohort study, fecundability peaked at approximately age 30 years and then declined steadily at older ages. The age-related decline in fecundability was stronger among nulliparous women.[24] In a preconception cohort study of women in the United States who were 30−44 years old, fecundability began to decline at approximately age 34 years; this association was more marked among women who had never conceived.[25]

Studies also indicate that increasing male age, independent of female age, is associated with reduced fertility. Meta-analyses have shown age-related declines in semen quality that includes volume,

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motility, morphology, and DNA integrity.[26,27] However, prospective cohort studies that have examined male age and natural fertility[24,28] and success of assisted reproductive technologies[29-32] report conflicting results. In particular, in a preconception cohort from 7 European cities, among couples in which the female was 35 years old, the crude probability of conceiving within 12 cycles decreased from 82% if the male was 35 years old to 72% if the male was 40 years old.[28] However, in a Danish preconception cohort study, the crude probability of conceiving within 12 cycles did not vary substantially by male age (86%, 81%, and 86% among men 30–34, 35–39, and ≥40 years old, respectively), and men who were ≥40 years old had 0.95 times the fecundability of men 21–24 years old after adjustment for covariates.[24]

To better characterize the age-related decline in fecundability among couples who attempt to conceive naturally, we examined the association between female and male age and fecundability in a preconception cohort study of pregnancy planners from North America.

Material and Methods

Study design and population

Pregnancy Study Online (PRESTO) is an ongoing prospective cohort study of North American couples who are attempting conception.[33] Recruitment began in June 2013 with the use of primarily web-based methods. We used banner advertisements on social networking sites (ie, Facebook) that targeted women based on age, gender, and marital status. We also advertised on health-related websites, pregnancy-related websites, and parenting blogs. Eligible women were 21–45 years old, residents of the United States or Canada, who were in a stable relationship with a male partner and were attempting to conceive without the use of fertility treatments. Female participants could invite their male partner to participate if the partner was ≥21 years old (58% of participating women invited their male partners, and 51% of males invited chose to participate). Participation for both partners involved a baseline questionnaire on demographics, lifestyle and behavioral factors, and medical and reproductive histories. Women completed shorter bimonthly follow-up questionnaires for up to 12 months to ascertain pregnancies and update exposure information.

The study protocol was approved by the institutional review board at Boston University Medical Center. All participants provided informed consent online before initiating the study.

Exclusions

During the 50 months of recruitment, 5249 women completed the baseline questionnaire. We excluded couples in which the woman had implausible or missing last menstrual period (LMP) data (n=175) or was pregnant at study entry (n=46) and couples who had been attempting conception for >3 cycles at study entry (n=1856). We also excluded couples with a history of infertility (n=210), for a final analytic sample of 2962 couples.

Definition of study variables

On the female baseline questionnaire, women reported their date of birth and their partner's current age. On the male baseline questionnaire, men reported their date of birth. We calculated female and male ages at baseline from date of birth and date of female baseline questionnaire completion. When both partners participated in the study, we used information from the male questionnaire to measure male age. When only the female partner participated, we used information from the female questionnaire to measure male age. Agreement between female and male reports of age was high; among the 842 couples in which both partners contributed data, 810 couples (96.2%) reported male age identically; 30 couples (3.6%) reported ages discrepant by 1 year; 1 couple (0.1%) reported ages discrepant by 2 years, and 1 couple (0.1%) reported ages discrepant by 5 years.

We measured fecundability using data from the female baseline and follow-up questionnaires. We asked women with regular menstrual cycles about their typical cycle length. For women with irregular menstrual cycles, we estimated cycle length based on LMP dates at baseline and over the follow-up period. We estimated time-to-pregnancy in discrete menstrual cycles using the following formula: [(cycles of attempt at study entry)+[(LMP date from most recent follow-up questionnaire—date of baseline questionnaire)/cycle length]+1]. Only observed cycles at risk (those that occurred after study entry) were included in the analysis. Women who did not complete any follow-up visits (n=304) were assigned 1 cycle of observation; their outcome information was imputed.

We obtained additional information on female and male demographics and behaviors from the female baseline questionnaire. Women reported their race/ethnicity, education level, household income, menstrual cycle characteristics, weight, height, physical activity, pregnancy history, smoking history, current alcohol and caffeine intake, intercourse frequency, use of methods to improve chances of conception (ie, recording basal body temperature, monitoring cervical mucus, the use of an ovulation test kit, and other methods), and last method of contraception. Women also reported their male partner's weight, height, education level, and smoking status. Body mass index (BMI) for female and male patients was calculated as weight (kilograms) divided by height (square meters). Vigorous physical activity for women was calculated by summing the hours per week spent participating in each of the following activities: biking, jogging, swimming, racquetball, aerobics, and free weights.

Data analysis

All analyses were conducted with the use of SAS software (version 9.4; SAS Institute Inc, Cary, NC).[34] We applied life-table methods to estimate the cumulative pregnancy proportion at 6 and 12 cycles, overall and by age group. We measured effects of factors that affect fecundability with the fecundability ratio (FR), which is the average per-cycle probability of conception in exposed, compared with unexposed, women; a FR <1.00 indicates that exposure has an

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