

Impact of female age and nulligravidity on fecundity in an older reproductive age cohort

Q3 Anne Z. Steiner, M.D., M.P.H.^a and Anne Marie Z. Jukic, Ph.D.^b

^a Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina; and ^b Yale School of Public Health, New Haven, Connecticut

Objective: To provide female age-related estimates of fecundity and incidence of infertility by history of prior pregnancy among women 30–44 years of age.

Design: Prospective, time-to-pregnancy cohort study.

Setting: Not applicable.

Patient(s): Women, between 30 and 44 years of age, attempting to conceive for ≤ 3 months, and no known history of infertility, polycystic ovarian syndrome (PCOS), or endometriosis.

Intervention(s): Not applicable.

Main Outcome Measure(s): Fecundability and incidence of infertility.

Result(s): Compared to women aged 30–31 years, fecundability was reduced by 14% in women 34–35 years of age (fecundability ratio [FR] 0.86, 95% confidence interval [CI] 0.68–1.08), 19% in women 36–37 years of age (FR 0.81, 95% CI 0.60–1.08, 30% in women 38–39 years of age (FR 0.70, 95% CI 0.48–1.01), 53% in women 40–41 years of age (FR 0.47, 95% CI 0.28–0.78), and 59% in women 42–44 years of age (FR 0.39, 95% CI 0.16–0.93). Fecundability did not differ between women aged 30–31 years and 32–33 years. In general, fecundability and cumulative probability of pregnancy was lower for women who had never had a prior pregnancy.

Conclusion(s): Women experience a significant reduction in fecundity and increase in the probability of infertility in their late thirties. At any age >30 years, women who have never conceived have a lower probability of achieving a pregnancy.

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Key Words: Reproductive aging, infertility, fecundability

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During the 20th and the 21st centuries women had increasing access to graduate and professional schools, careers, and contraceptive methods (1). This has led to a delay in age at marriage and in age at first birth. In fact, the average age at first birth increased from 22.7 years in 1980 to 27.2 in 2000 and 28.2 years in 2013 (2). Many women are choosing

to delay attempts to conceive to their thirties and forties. Women wish to know their probability of conceiving or having infertility at "older" ages. In addition, women choosing to delay now have the option and are choosing to freeze oocytes for fertility preservation for reproductive aging.

Data on success rates after assisted reproductive technology (ART) by

female age are readily available. There is a suggestion that pregnancy rates (PRs) start to decline in the early thirties; however, PRs for women 30–34 years of age are similar to women <30 years of age. This may be because PRs appear to "peak" in the late twenties to early thirties. An almost linear downward trend is observed after age 35 years (3). Data from therapeutic donation cycles also show an age-related decline in female fertility independent of male factor (4).

Cross-sectional data on natural marital fertility rates in noncontracepting populations such as the Hutterites are available (5). Prospective data in contemporary populations are available; however, the number of cohorts are relatively limited (6, 7). Cohorts

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Reprint requests: Anne Z. Steiner, M.D., M.P.H., Department of Obstetrics and Gynecology, University of North Carolina, CB#7570, Old Clinic Building, Chapel Hill, North Carolina 27599 (E-mail: asteiner@med.unc.edu).

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having adequate representation of women more than age 35 years are even more limited. A recent study by Rothman (7) sampled 2,820 women in Denmark, who were attempting to conceive, of which 208 were between the ages of 35 and 40 years. They found that 72% of women between the ages of 35 and 40 years compared with 87% of women between the ages of 30 and 34 years conceived within 12 cycles of pregnancy attempt. Women >40 years were not included and more refined estimates for women between ages 35 and 40 years were not provided.

To study female age-related declines in fertility, one must be assured that male factor or other causes of infertility do not contribute to the estimate. Women, who have previously conceived naturally, can be assumed to have patent fallopian tubes and partners with sufficient sperm. Thus, this population would be the purest to study age-related declines in fertility. However, women who have never conceived, are an inherently different population. Meaningful estimates of their fecundity at any given age are needed for counseling. Therefore, we sought to provide female age-related estimates of fecundity by history of prior pregnancy using a prospective, time-to-pregnancy cohort.

MATERIALS AND METHODS

Time to Conceive is a prospective, time-to-pregnancy cohort study that enrolls women who are trying to conceive naturally, between the ages of 30 and 44 years. Women were recruited through informational mass e-mails, introductory letters, web and radio advertising and instructed to contact study personnel by e-mail or telephone if interested. Women were screened for eligibility by telephone. Eligible women have been attempting to conceive, defined as having regular intercourse without doing anything to prevent pregnancy, for ≤ 3 months. Women are excluded if they reported a history of infertility, polycystic ovarian syndrome (PCOS), endometriosis, a partner with infertility, or are currently breastfeeding. Institutional Review Board approval was obtained for this research.

After enrollment and consent, women completed a questionnaire including demographics, reproductive history, contraceptive history, and habits. They are subsequently followed without intervention for up to 12 months or until pregnancy was detected. Women were provided with home pregnancy tests and standardized instructions on their use. Women completed daily diaries for the first 4 months of enrollment and then monthly diaries thereafter. Women withdrew if they initiate fertility treatment, stop trying to conceive, or self-withdraw. Enrollment for Time to Conceive began in April 2008 and concluded in August 2015. Women enrolled between April 2008 and April 2015 are included in this analysis.

Statistical Analysis

Pregnancy was defined as a positive pregnancy test. Cycle of attempt at enrollment was determined using data from the baseline questionnaire. Number of cycles-at-risk was determined using menses data from daily and monthly diaries; women who had not conceived were censored at 12 cycles.

Female age, when the subject began trying to conceive, was collapsed into 2-year intervals and modeled using indicator variables. Kaplan Meier curves were constructed. Subsequently discrete-time Cox-proportional hazard models (8) were constructed to predict fecundability in the first cycle of attempt, average fecundability during the cycles of attempt, probability of pregnancy by 6 cycles of attempt, probability of pregnancy by 12 cycles of attempt, and fecundability ratios. The analysis was then repeated within the

TABLE 1

Description and comparison of female age groups based on baseline characteristics.

Characteristic	Female age (y)			P value ^a
	30–34	35–39	40–44	
Race				.07
African American	58 (9)	32 (14)	8 (16)	
American Indian/ Alaskan	1 (<1)	1 (<1)	0	
Asian/Pacific Islander	37 (5)	20 (9)	4 (8)	
White	543 (80)	163 (70)	33 (64)	
Hispanic	14 (2)	8 (3)	3 (6)	
Other (mixed/ unknown)	23 (3)	9 (4)	3 (6)	
Current alcohol use	456 (67)	144 (62)	33 (65)	.29
Attempt cycle at enrollment	1.8 (± 1.1)	1.8 (± 1.3)	2.2 (1.4)	.05
Nulligravid	369 (55)	81 (35)	10 (20)	<.001
Parous	210 (31)	112 (48)	27 (53)	<.001
History of one or more therapeutic abortions	66 (10)	34 (15)	18 (35)	<.001
History of ectopic pregnancy	7 (1)	4 (2)	2 (4)	.32
History of miscarriage	114 (17)	66 (28)	16 (31)	<.001
Education level				.03
High school or less	7 (1)	0	2 (4)	
Some college	41 (6)	22 (9)	4 (8)	
College degree	130 (19)	46 (20)	15 (29)	
Some graduate or professional school	63 (9)	23 (10)	4 (8)	
Masters degree	276 (41)	76 (33)	14 (27)	
Advanced postgraduate degree	159 (24)	66 (28)	12 (24)	
Current marijuana use	29 (4)	7 (3)	0	.24
Partner age (y), mean ($\pm$ SD)	33 (4.2)	37 (5.6)	42 (5.2)	<.001
Regular menstrual cycles (yes)	571 (84)	206 (88)	46 (90)	.50
Smoking history				.15
Never	524 (77)	173 (74)	34 (27)	
Current	12 (2)	1 (<1)	1 (2)	
Past	140 (21)	59 (25)	16 (31)	
Body mass index				.006
Underweight	16 (2)	8 (3)	0	
Normal weight	444 (66)	125 (54)	32 (63)	
Overweight	134 (20)	51 (22)	8 (16)	
Obese	82 (12)	49 (21)	11 (21)	

Note: Values presented as n (%) unless stated otherwise.

^a χ^2 or -test, where appropriate.

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