HHS Public Access

Author manuscript

Fertil Steril. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Fertil Steril. 2016 June ; 105(6): 1584–1588.e1. doi:10.1016/j.fertnstert.2016.02.028.

The Impact of Female Age and Nulligravidity on Fecundity in an Older Reproductive Age Cohort

Anne Z. Steiner, MD, MPH[1] and **Anne Marie Z. Jukic, PhD**[2]

[1]Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, NC

[2]Yale School of Public Health, New Haven, CT

Abstract

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

Design—Prospective, time-to-pregnancy cohort study

Setting—Community-based cohort

Patient(s)—Women, between 30 and 44 years of age, attempting to conceive for three or fewer months, and no known history of infertility, polycystic ovarian syndrome, or endometriosis

Intervention—None

Main Outcome Measure (s)—Fecundability and incidence of infertility

Result—Compared to women ages 30–31, fecundability was reduced by 14% in women 34–35 years of age (Fecundability Ratio (FR) 0.86, 95% 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 (FR 0.70, 95% CI: 0.48–1.01), 53% in women 40–41 (FR 0.47, 95% CI 0.28–0.78) and 59% in women 42–44 (FR 0.39, 95% CI 0.16–0.93). Fecundability did not differ between women ages 30–31 and women ages 32–33 years. In general, fecundability and cumulative probability of pregnancy was lower for women, who had never had a prior pregnancy.

Conclusions—Women experience a significant reduction in fecundity and increase in the probability of infertility in their late thirties. At any age over 30, women who have never conceived before have a lower probability of achieving a pregnancy.

Keywords

Reproductive aging; infertility; fecundability

Corresponding Author: Anne Z. Steiner, MD, MPH, Department of Obstetrics and Gynecology, University of North Carolina, CB#7570, Old Clinic Building, Chapel Hill, NC 27599, Fax: 919-966-5214, ; Email: asteiner@med.unc.edu

INTRODUCTION

Over the 20th Century women had increasing access to graduate and professional schools, careers, and contraceptive methods ([1]). This has led to a delay in age at marriage in age at first birth. In fact, the average age at first birth rose 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 following assisted reproductive technology by female age are readily available. There is a suggestion that pregnancy rates start to decline in the early thirties; however, pregnancy rates for women 30–34 years of age are similar to women less than 30 years of age. This may be due to the fact that pregnancy rates appear to "peak" in the late twenties to early thirties. An almost linear downward trend is observed after age 35. ([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 non-contracepting 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 having adequate representation of women over the age of 35 are even more limited. A recent study by Rothman et al. sampled 2,820 women in Denmark, who were attempting to conceive, of which 208 were between the ages of 35 and 40 ([7]). They found that 72% of women between the ages of 35 and 40 compared to 87% of women between the ages of 30 and 34 conceived within 12 cycles of pregnancy attempt. Women over 40 were not included and more refined estimates for women between 35 and 40 were not provided.

To study female age-related declines in fertility, one must assure 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 before, 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, which enrolls women, who are trying to conceive naturally, between the ages of 30 and 44 years of age. Women were recruited through informational mass emails, introductory letters, web and radio advertising and instructed to contact study personnel via email 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 or less. Women are excluded if they reported a history of infertility, polycystic

ovarian syndrome, endometriosis, a partner with infertility, or are currently breastfeeding. IRB approval was obtained for this research.

After enrollment and consent, women complete 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 are provided with home pregnancy tests and standardized instructions on their use. Women complete daily diaries for the first 4 months of enrollment and then monthly diaries thereafter. Women are withdrawn if they initiate fertility treatment, stop trying to conceive, or self-withdraw. Enrollment for TTC 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 over 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 subgroups: no prior pregnancy and prior pregnancy. Prior pregnancy was based on a subjects report to the question “Have you ever been pregnant before” in the enrollment questionnaire. The proportional hazards assumption was tested prior to analysis using Schoenfeld residuals, and no significant was violation noted (p=−.30). All analyses were completed using Stata 14.0

RESULTS

A total of 960 women provided 3593 cycles for analysis. 17% of subjects either withdrew, were censored for fertility medication use, or were lost to follow up. The likelihood of such an event increased with age (p=0.01) and cycle of attempt (p=0.001). The cohort is described in Supplemental Table 1. In summary, 79% of subjects were between the ages of 30 and 35, 16% between 36 and 39, and 5% 40 or older. Most women were non-Hispanic Caucasian, well-educated, and of normal weight. Half the cohort had conceived previously and 36% had a prior live birth. Most women enrolled in their first cycle of attempt (median cycle 1, interquartile range 1–2). Average fecundability in the cohort was 17.5%. Sixty-five percent of the cohort conceived in the first 6 cycles of attempt and 78% by 12 cycles of attempt. In the cohort, as female age increased, the probability of being white decreased, body mass index increased, male partner age increased, and probability of having previously been pregnant increased (Table 1).

Time-to-pregnancy was longer for older women (Figure 1). The median time to pregnancy was 3 months for women under 38, four months for women 38–39 years of age, 8 months for women 40–41 years of age and longer than 12 months for women 42 and over.

Fecundability and cumulative probability of pregnancy by female age for the entire cohort is presented in Table 2. Women 34–35 years of age had a 14% reduction in fecundability (Fecundability Ratio (FR) 0.86 , 95% CI: 0.68–1.08), women 36–37 years a 19% (FR 0.81,95% CI: 0.60–1.08), women 38–39 a 30% reduction (FR 0.70, 95% CI: 0.48–1.01), women 40–41 a 53% reduction (FR 0.47, 95% CI 0.28–0.78) and women 42–44 a 59% reduction (FR 0.39, 95% CI 0.16–0.93) in fecundability compared to women ages 30–31. Fecundability was similar for women ages 32–33 compared with ages 30–31 (FR 1.06, 95%CI: 0.87–1.29). There was no interaction between age and BMI, and adjustment for BMI did not substantially change these estimates.

In general, fecundability and cumulative probability of pregnancy was lower for women, who had never conceived before (Table 3). The pattern of the decline; however, differed by whether they had previously been pregnant. Women, who had previously been pregnant, had a less steep decline in fecundability across age groups compared to women, who had not previously been pregnant. Differences in pregnancy rates between groups were small at younger ages (30–31) and greatest at older ages. Women over the age of 40, who had never conceived, were half as likely to conceive in 12 cycles as their counterparts with proven prior fertility.

DISCUSSION

In our cohort, fecundity declined for women in their late thirties and early forties. Among women with proven prior fertility, the probability of infertility increased from 10% to 20% after age 35 and to 45% in the early forties. Women, who had never conceived before, were at a greater risk of infertility at all ages. Among these women, the decline in fertility began at a younger age.

It should be noted that we present the incidence of infertility, and not the prevalence. Prevalence, as measured in cross-sectional studies, will always be higher, as once a woman is diagnosed with infertility, she will always be considered infertile. Infertile women can be treated to help them conceive, but in general, the infertility is not reversed. We feel that incidence of infertility is more meaningful to an individual woman.

There are few prospective time-to-pregnancy studies that have data on women in their thirties and fourties. In a cohort of German women, Gnoth et al found that 88% of women between the ages of 31–34 (N=82) conceived in 12 cycles of attempt and 73% of women 35–44 years of age (N=10) ([6]). Rothman et al. using a cohort from Denmark also found an 87% pregnancy rate among women 30–34 years of age (N=791) and a 72% pregnancy rate in women 35–40 years of age (N=208) ([7]). Thus there is relative consistency across cohorts.

The lower fecundity among women, who have never conceived before, is not surprising. The fact that the difference between gravid and nulligravid women is not stable, but diverges across age categories is interesting. It is likely due to the fact that even among women who use contraception regularly, unplanned pregnancies occur. Thus, as women age, if they do not experience an unplanned pregnancy, it may suggest lower underlying fecundity. Women may also intermittently attempt to conceive in their lifetime. Women, who may have

attempted to conceive for a month or two in the past and never became pregnant, are inherently less fertile than women that conceived.

This study has some weaknesses. First, while the cohort was designed to only include women of “older reproductive age”, few women enrolled in the cohort were in their forties. Second, for those women, who previously conceived, we could not differentiate those trying to conceive with a new partner from those trying to conceive with their partner from their prior pregnancy. In general, the cohort is white and highly educated; however, this likely reflects the population planning pregnancies at older ages. According to national statistics, sixty-nine percent of pregnancies in black women are unplanned ([9]), and the average age at first delivery for black women is 3.6 years younger than white women ([10]). However, this cohort has a number of strengths in that it enrolled women early in their attempts to conceive. Women were queried multiple ways to determine when they started attempting to conceive, and women were followed using standardized and free pregnancy testing.

The topic of female age-related declines in fertility is commonly discussed in the media. There has been debate as to “when” fertility starts to decline and “when” there is a steep drop off. These data may serve as a resource for women, researchers, physicians, and the media. Current guidelines encourage women over 35 years of age to seek reproductive evaluation and necessary treatment after 6 months of attempting to conceive ([11]). These data suggest that perhaps the age at which women seek fertility evaluation after 6 months of attempt should differ by prior pregnancy history. Women, who are in their thirties and have previously conceived, may be able to wait longer before seeking infertility evaluation and treatment, assuming they have no risk factors for infertility.

When using these data to advise women, it will be important for clinicians to clarify that these data do not necessarily reflect live birth rates. Miscarriage rates increase with age. Therefore, age-associated decrease in live birth rates may be due to both the decline in pregnancy rates and the increase in miscarriage rates with aging. In conclusion, women experience a significant reduction in fecundity and increase in the probability of infertility in their late thirties. At any age over 30, women who have never conceived before have a lower probability of achieving a pregnancy compared to women with prior fertility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (R21 HD060229 and R01 HD067683)

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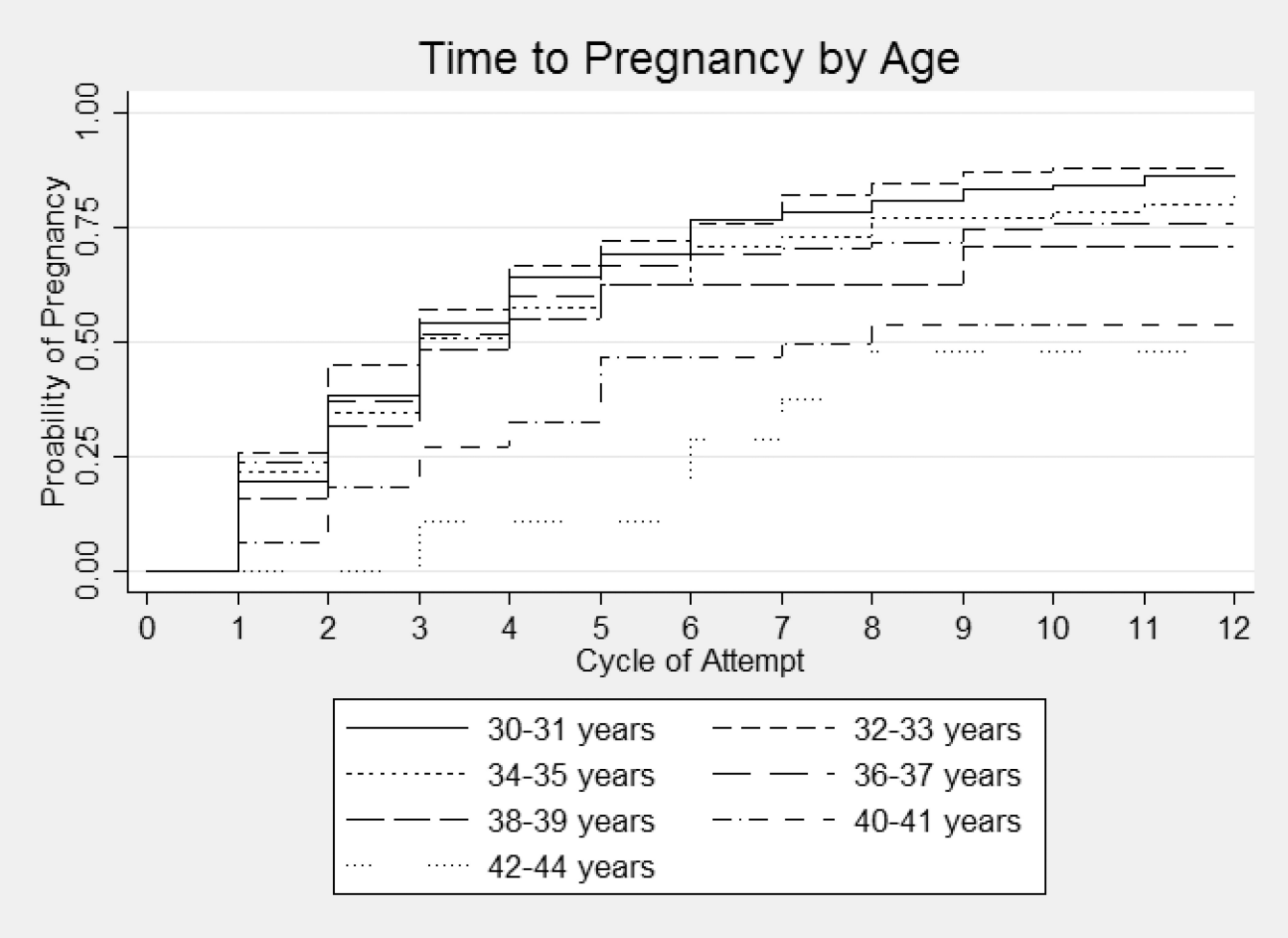

Figure 1.
Kaplan Meier curves for cumulative probability of pregnancy across cycles of pregnancy attempt by age group

Table 1

Description and comparison of female age groups based on baseline characteristics

Characteristic	Female Age (years)			
	30–34	35–39	40–44	P-value*
Race				0.07
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%)	
Caucasian	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%)	0.29
Attempt cycle at enrollment	1.8 (±1.1)	1.8 (±1.3)	2.2 (1.4)	0.05
Nulligravid	369 (55%)	81 (35%)	10 (20%)	<0.001
Parous	210 (31%)	112 (48%)	27 (53%)	<0.001
History of one or more therapeutic abortions	66 (10%)	34 (15%)	18 (35%)	<0.001
History of ectopic pregnancy	7 (1%)	4 (2%)	2 (4%)	0.32
History of miscarriage	114 (17%)	66 (28%)	16 (31%)	<0.001
Education level				0.03
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 Post-graduate degree	159 (24%)	66 (28%)	12 (24%)	
Current marijuana use	29 (4%)	7 (3%)	0	0.24
Partner age (years)	33 (±4.2)	37 (±5.6)	42 (±5.2)	<0.001
Regular menstrual cycles (yes)	571 (84%)	206 (88%)	46 (90%)	0.50
Smoking history				0.15
Never	524 (77%)	173 (74%)	34 (27%)	
Current	12 (2%)	1 (<1%)	1 (2%)	
Past	140 (21%)	59 (25%)	16 (31%)	
Body Mass Index				0.006
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%)	

*Chi square or t-test, where appropriate

Table 2

Fecundability and cumulative pregnancy rates for the cohort as calculated from survival analysis. Data presented as percentage with 95% Confidence Interval.

			Fecundability		Cumulative Pregnancy Rate	
Age	**Subjects**	**Cycles at risk***	**First cycle**	**Average**	**6 cycles**	**12 cycles**
30–31	353	1261	19.7% (15.9–25.9)	19.5% (17.3–22.2)	77% (72–81)	87% (82–91)
32–33	247	826	26.0% (19.2–34.7)	20.9% (18.0–24.3)	76% (70–81)	88% (83–92)
34–35	153	629	22.0% (14.4–32.6)	16.2% (13.4–19.7)	71% (63–78)	82% (74–88)
36–37	95	380	23.9% (14.0–39.0)	14.5% (11.1–18.9)	69% (59–79)	76% (66–85)
38–39	61	234	16.1% (7.1–34.5)	13.2% (9.3–18.8)	62% (49–76)	71% (56–84)
40–41	37	187	6.2% (0.9–36.8)	8.6% (5.2–14.0)	47% (31–66)	54% (37–72)
42–44	14	76	0	6.6% (2.7–15.8)	29% (10–65)	48% (24–80)

*Number of cycles of attempt observed for all subjects in the given age group.

Table 3

Fecundability and cumulative pregnancy rates by history of prior pregnancy as calculated from survival analysis. Data presented as percentage with 95% confidence interval.

Nulligravid						
			Fecundability		**Cumulative Pregnancy Rate**	
Age	**Subjects**	**Cycles at risk***	**First cycle**	**Average**	**6 cycles**	**12 cycles**
30–31	212	796	17.2% (11.5–25.4)	17.3% (14.7–20.5)	74% (67–80)	83% (77–89)
32–33	119	420	29.3% (19.4–42.8)	18.8% (15.1–23.5)	73% (64–81)	85% (77–92)
34–35	71	345	13.2% (5.7–28.8)	11.3% (8.3–15.5)	56% (44–69)	66% (54–77)
36–37	34	142	16.7% (4.5–51.8)	12% (7.4–19.3)	58% (39–78)	73% (53–89)
38–39	14	76	0	5.2% (2.0–14.0)	35% (15–68)	35% (16–68)
40–41	6	34	0	2.9% (0.4–20.9)	0	25% (4–87)
42–44	4	31	0	3.2% (0.5–22.9)	0	33% (5–95)
History of Prior Pregnancy						
			Fecundability		**Cumulative Pregnancy Rate**	
Age	**Subjects**	**Cycles at risk***	**First cycle**	**Average**	**6 cycles**	**12 cycles**
30–31	141	465	23.0% (15.5–33.3)	23.4% (19.4–28.2)	81% (74–87)	92% (85–96)
32–33	128	406	23.1% (14.6-35.3)	23.2% (18.9–28.3)	79% (71–86)	90% (83–95)
34–35	82	284	29.6% (18.4–45.4)	22.2% (17.4–28.4)	83% (74–90)	93% (84–98)
36–37	61	238	26.5% (14.8–44.7)	16% (11.6–21.9)	75% (62–85)	78% (66–88)
38–39	47	158	21.7% (9.7–44.6)	17.1% (11.7–24.9)	71% (57–85)	81% (65–93)
40–41	31	153	7.7% (1.1–43.4)	9.8% (5.9–16.3)	52% (35–72)	56% (39–75)
42–44	10	45	0	8.9% (3.3–23.7)	43% (16–83)	54% (25–88)

*Number of cycles of attempt observed for all subjects in the given age group.