Infertility and age of menopause in a longitudinal cohort of women with primary infertility

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Abstract

Objectives: To analyze the association between primary infertility and infertility type with the age of natural menopause.

Methods: This is a retrospective cohort study reviewing a subset of women from the Mayo Primary Infertility Cohort (MPIC). The MPIC is a cohort of 1,001 women diagnosed with primary infertility and 1,001 age-matched referent women. In this study, we included all women at risk for natural menopause and further evaluated those who had reported natural menopause in the medical record. We compared the risk of natural menopause using Cox proportional hazard models with infertility status and infertility type as covariates. In those with documented menopause during the study period, the association between primary infertility and early and premature menopause was analyzed with χ^2 testing. We evaluated the association between age at natural menopause, primary infertility status, and infertility type in this group using linear regression.

Results: In all, 461 women with primary infertility, with 530 referent individuals, were at risk of natural menopause, and of these, 340 women with infertility and 346 referent women underwent documented natural menopause on review of medical records. Women with primary infertility had an increased risk of natural menopause (hazard ratio: 1.25, 95% CI: 1.06-1.46) and underwent menopause 1 year earlier than referent individuals ($\beta = -1.17$, 95% CI: −1.82 to −0.52) after adjustment for body mass index, tobacco use, race, menstrual cycle regularity, and previous contraception use. Women with primary infertility were more likely to undergo early menopause (age 40-45) than referent women (7.6% vs. 3.0%, $P = 0.01$). Compared with referent women, women with endometriosis underwent menopause 2.75 years earlier (95% CI: −4.38 to −1.13, $P = 0.0009$), and women with unexplained infertility underwent menopause 1.45 years earlier (95% CI: −2.26 to −0.64, $P = 0.0005$).

Conclusions: Women with primary infertility had an increased risk of early menopause and collectively underwent menopause 1 year earlier than women without a history of primary infertility.

Key Words: Infertility, Menopause, Natural menopause, Ovulatory dysfunction.

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Infertility is a common condition, affecting one in six people globally.[1] While not all individuals who meet criteria for infertility are evaluated or choose to pursue fertility treatment, this represents a large population of reproductive-aged individuals and has implications for not only family building but long-term health.[2,3] Individuals

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with infertility have been found to have higher rates of cancer and cardiovascular disease, with multiple proposed etiologies including genetic, hormonal, in utero, and lifestyle factors.[2]

Recently, several studies have investigated the link between infertility and both premature and early menopause. One large, pooled analysis using self-reported data showed a significant association between infertility and both premature and early menopause.[4] Another found that endometriosis-related infertility was associated with earlier onset of menopause.[5] This study excluded women with surgical menopause and stratified results by history of unilateral oophorectomy. Endometriosis was associated with the age of menopause regardless of unilateral oophorectomy history.[5] On the other hand, a retrospective cohort study of 12 IVF clinics did not find an increased risk of early menopause in individuals with a history of unexplained infertility.[6]

Early and premature menopause, such as infertility, is associated with long-term health consequences such as cardiovascular disease, osteoporosis, and neurocognitive disorders.[7,8] Premature and early menopause, defined as 12 months without menstrual bleeding before age 40 and 45, respectively, has been linked to several reproductive factors. Risks for premature and early menopause include tobacco use, low body mass index (BMI), nulliparity, and early menarche.[5,9-12] Conversely, increased parity and history of oral contraceptive use have been linked to later menopause.[13-15]

The correlation between infertility and premature or early menopause has been investigated with various conclusions. Given the long-term health implications of both infertility and early menopause, we aimed to further explore the association between a diagnosis of primary infertility and age of natural menopause in a historical population-based cohort of individuals who sought medical evaluation for infertility. We compared the age of menopause in women with a history of primary infertility and referent women. For women with a history of primary infertility, we additionally evaluated the association of infertility type and age of natural menopause, specifically evaluating the risk of early or premature menopause.

METHODS

Data collection

This is a retrospective cohort study using the Mayo Primary Infertility Cohort (MPIC). The MPIC was created using the Rochester Epidemiology Project, a medical records linkage system containing over 40 years of medical records for almost every resident of Olmsted County, Minnesota.[16,17] The MPIC cohort consists of 1,001 individuals with a diagnosis of primary infertility and 1,001 age-matched referent people.[18,19] A diagnosis of primary infertility, between January 1, 1980, and December 31, 1999, was identified by manual chart review. The date on which the participant received a diagnosis of primary infertility was used as the index date. Primary infertility was defined as an inability to conceive for 12 months in individuals < 35 years old and for 6 months in individuals ≥ 35 years old. Each woman was 1:1 age-matched to a randomly selected "referent" woman residing in Olmsted County on her index date who did not have a history of infertility or prior hysterectomy. For each woman with primary infertility, all women within 1 year of her age residing in Olmsted County on her index date were identified. One woman was selected as a control from this pool using a random number generator. This study was deemed exempt by our institutional IRB.

Basic demographic information, gynecologic and obstetric history, past medical history, level of education, tobacco use, and BMI were collected with manual chart review for individuals in the MCIP and referent cohorts. These data were collected as of the index date. Type of infertility, length of attempted conception, and any fertility treatment were collected for individuals in the MCIP cohort. Types of infertility included ovulatory dysfunction, male factor, tubal factor, uterine factor, or unexplained. For all but unexplained infertility, women could have more than one diagnosis. Ovulatory dysfunction included amenorrhea, polycystic ovarian syndrome, oligo-ovulation, diminished ovarian reserve, and hypothalamic hypogonadism. We also included women with a diagnosis of endometriosis, based on the inclusion of endometriosis in their medical history, as a subset of participants with infertility. We completed additional analyses excluding isolated male factor and tubal factor infertility to better assess underlying female physiology, which may be associated with both infertility and age of natural menopause.

Menopause was classified as surgical, natural, or unknown, and the date of menopause was collected by manual chart review completed between January 1 and December 31, 2020. All records between the index date and the time of data collection in 2020 were reviewed. The length of follow-up varied because the MPIC included women diagnosed with infertility between 1980 and 1999. No minimum follow-up was required. The date of surgical menopause was defined as the date of bilateral oophorectomy or the date of unilateral oophorectomy in individuals with prior unilateral oophorectomy. The date of natural menopause was defined as the month and year 12 months after the last reported menstrual period. A total of 340 women with primary infertility and 346 referent women underwent natural menopause in the study period. Age at menopause was classified as premature (< 40 y), early (40-44 y), normal (45-54 y), or late (≥ 55 y).

We excluded individuals from our analysis who had a history of surgical menopause and those with reported natural menopause, but at an unknown age. Although the MPIC identified age-matched referent individuals, this study does not present age-matched data, given potential exclusion for surgical or unknown age at natural menopause.

Statistical analysis

Baseline demographic variables were presented as mean and SD for continuous variables or count and percentage for categorical variables. These variables were compared between study groups using a two-sided *t* test, χ^2 test, or the Fisher exact test, as appropriate.

We first evaluated the risk of undergoing natural menopause during the study period in women with a history of primary infertility and referent women. Natural menopause was the primary event of interest, and absence of menopause by the end of follow-up was considered a censoring event. To limit the impact of informative censoring bias, two sets of analyses were performed.

The risk of undergoing natural menopause in the study period was assessed using Cox proportional hazard models fitted using infertility status or type of infertility as covariates. The second model, using the type of infertility, was fitted only for women who were diagnosed with primary infertility, and each infertility type was compared to the referent women. We completed analyses both including and excluding only male factor or tubal factor infertility to better assess the true effect of primary, female-focused, infertility. To account for multiple testing, the P value was corrected using the Bonferroni method, and a *P* value < 0.025 was considered significant. Each model was then adjusted for BMI, tobacco usage, race, menstrual cycle irregularity, and previous contraception use, as these factors were unbalanced in our participants and have previously been shown to impact age at menopause.[5,12,20,21] Kaplan-Meier analysis was used to evaluate the risk of menopause in primary infertility and referent women.

Women who did not have observed natural menopause in the study period were excluded. An analysis was performed on the subset of women who underwent menopause in the study period, as their age of menopause was known. The age of natural menopause was categorized into four groups: premature (< 40 y), early (40-44 y), normal (45-54 y), and late (≥ 55 y). To ensure that all participants were equally eligible for premature menopause, women with an index age > 40 years (n = 11) were excluded from this analysis. The association between primary infertility and each menopause group was analyzed with the χ^2 test. *P* values of < 0.05 were considered significant.

We evaluated the association between age at natural menopause and primary infertility status or infertility type using linear regression models. Again, we completed analyses including and excluding isolated male factor and tubal factor infertility. In the linear models, the continuous age of natural menopause was the dependent variable, and each infertility factor was the independent variable. The linear regression models were adjusted for BMI, tobacco use, race, menstrual cycle irregularity, and previous contraception use, and a *P* value < 0.025 was considered significant to account for multiple testing. The missing value in BMI was inputted by the median from participants' corresponding study group. The missing tobacco use was replaced by the status of "Never use." We assessed the linearity, normality, and outliers in the linear models using diagnostic plots generated with the "performance" R package (Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/MENO/B528). The homoscedasticity of the linear models was evaluated by both the Breusch-Pagan test and the Fligner-Killeen test. All *P* values were > 0.5, and there was no violation of the homoscedasticity assumption. Statistical software R version 4.2.2 was used for all analyses.

RESULTS

The original MPIC included 1,001 individuals with primary infertility and 1,001 age-matched referent individuals. This substudy included 461 individuals with primary infertility and 530 referent individuals from the MPIC. From the original MPIC, 698 individuals were excluded for unknown menopausal status, 141 for a history of surgical menopause, and 141 for unknown age at natural menopause. A total of 305 women did not undergo menopause within the study period. The subgroup analysis excluded these participants and included 340 people with primary infertility and 346 referent people who underwent natural menopause in the study period (Fig. 1).

Patients at risk for natural menopause

Demographic information for the study participants is shown in Table 1. Age at index date was similar between those with primary infertility and referent individuals (mean age 29.8 vs. 29.4 y, respectively; $P = 0.1615$). The groups differed by race, marital status, level of education, BMI, tobacco use, presence of regular menstrual cycles, and previous contraceptive use (Table 1). Compared with the reference group, women with a history of primary infertility were more likely to be White (*P* value < 0.0001), identify as not Hispanic or Latino (*P* value < 0.0001), be married (97.0% vs. 68.3%, *P* value < 0.0001), and have a higher education level (*P* value < 0.0001). They were more likely to have a lower BMI (*P* value $= 0.0210$), be a never smoker (*P* value < 0.0001), have irregular menstrual cycles (*P* value < 0.0001), and have used contraception in the past (*P* value $= 0.0042$) (Table 1).

We compared the risk of natural menopause between groups. Women with a history of primary infertility were more likely to undergo natural menopause than referent women during the study period (hazard ratio: 1.25, 95% CI: 1.06-1.46, $P = 0.006$) (Table 2 and Fig. 2). This analysis was adjusted for BMI, tobacco use, race, menstrual cycle regularity, and previous contraception use.

When compared with patients without infertility, the only infertility type significantly associated with the risk of natural menopause was unexplained infertility (hazard ratio: 1.56, 95% CI: 1.27-1.93, $P = < 0.0001$) (Table 2). Both the overall risk of natural menopause and the effect of infertility type remained unchanged when the analyses were run excluding those with only male factor or tubal factor infertility (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/MENO/B529).

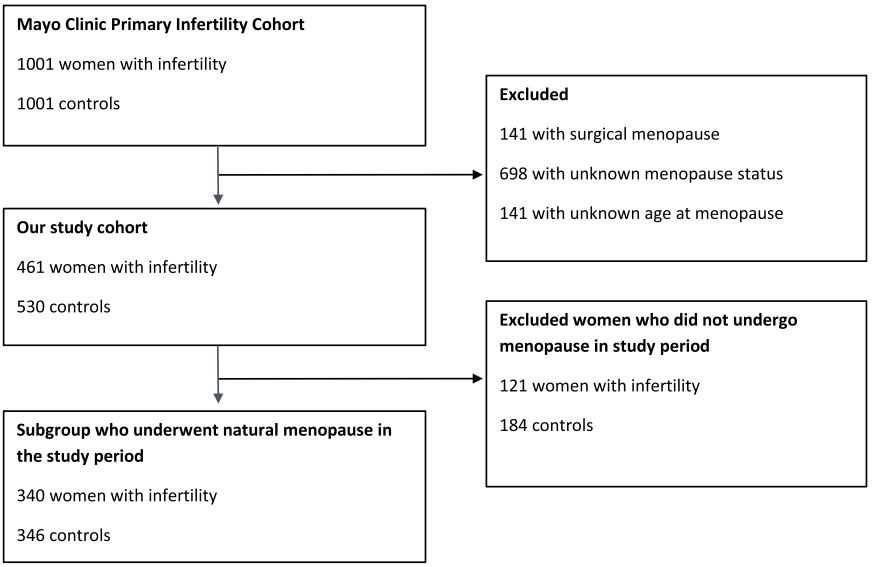

FIG. 1. Inclusion and exclusion criteria.

Patients who underwent natural menopause

Next, we performed subgroup analysis on the individuals who underwent natural menopause during the study period. Of the individuals who underwent natural menopause, baseline demographic characteristics were similarly unbalanced to those shown in Table 1. Compared with referent women, women with a history of primary infertility were significantly more likely to be White, identify as not Hispanic or Latino, be married, have a higher education level, have a lower BMI, be a never smoker, have irregular menstrual cycles, and have used contraception in the past (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/MENO/B529).

Individuals with a history of primary infertility were more likely to undergo early menopause than referent individuals (25/331 [7.6%] vs. 10/335 [3.0%], $P = 0.01$). There was no difference in the risk of premature menopause. Interestingly, referent women were more likely to undergo late menopause than women with primary infertility (58/335 17.3% vs. 39/331 11.8%) (Table 3).

Overall, for women who underwent menopause during the study period, those with a history of primary infertility underwent natural menopause 0.9 years earlier than referent individuals (95% CI: −1.53 to −0.28, $P = 0.005$). When adjusting for tobacco use, BMI, race, menstrual cycle regularity, and previous contraception use, this association remained statistically significant, and individuals with a history of primary infertility were found to undergo natural menopause 1.17 years earlier than referent individuals (95% CI: −1.82 to −0.52, $P = 0.0005$, Table 4).

We further evaluated the impact of infertility type on the age of natural menopause in women with a history of primary infertility. Women with endometriosis underwent menopause 2.75 years earlier than referent women (95% CI: −4.38 to −1.13, $P = 0.0009$), and women with unexplained infertility underwent menopause 1.45 years earlier than referent women (95% CI: −2.26 to −0.64, $P = 0.0005$) (Table 4). Again, these findings remained unchanged when we excluded isolated male factor or tubal factor infertility (Supplementary Table 3, Supplemental Digital Content 2, http://links.lww.com/MENO/B529).

DISCUSSION

We found that women with a history of primary infertility underwent natural menopause 1 year earlier than referent individuals, and more notably, those with a history of unexplained infertility or endometriosis had an increased risk of early menopause. Conversely, referent women were more likely to undergo late menopause than women with primary infertility. These findings may support accelerated ovarian aging or underlying endometriosis as a common etiology of primary infertility and early menopause, highlighting the potential long-term health risks of both.

Our findings are consistent with some prior studies. Several large population-based cohort studies using self-reported data have shown an association between subfertility or infertility and early menopause,[4,5,12] while only one study evaluated the risk of premature menopause.[4] Liang and colleagues found an association between infertility and both premature and early menopause. Our study confirms an association with risk of early menopause, but did not find an association with premature menopause. This difference may be explained by type II error, as the number of women with reported premature menopause in our study was low. Unlike prior studies, which relied on self-reported survey data, our study utilized medical records over a 20-year period,

TABLE 1. Characteristics of women in primary infertility and reference groups

	Reference (n = 530)	Primary infertility (n = 461)	*P*
Age at index date (y)			0.1615
Mean (SD)	29.4 (4.6)	29.8 (4.5)	
Median	28.6	29.1	
Range	(19-46.1)	(18.9-45.9)	
Race, n (%)			< 0.0001
White	415 (78.3)	413 (89.6)	
Black or African American	3 (0.6)	2 (0.4)	
Asian	7 (1.3)	8 (1.7)	
American Indian or Alaskan Native	3 (0.6)	0 (0.0)	
Other [a]	4 (0.8)	10 (2.2)	
Unknown	98 (18.5)	28 (6.1)	
Ethnicity, n (%)			< 0.0001
Not Hispanic or Latino	394 (74.3)	380 (82.4)	
Hispanic or Latino	5 (0.9)	17 (3.7)	
Unknown	131 (24.7)	64 (13.9)	
Marital status, n (%)			< 0.0001
Not documented	6 (1.1)	0 (0.0)	
Single	160 (30.2)	6 (1.3)	
Married or partnered	364 (68.7)	455 (98.7)	
Level of education, n (%)			< 0.0001
Less than high school	19 (3.6)	6 (1.3)	
High school graduate	101 (19.1)	67 (14.5)	
Some college	189 (35.7)	126 (27.3)	
College (4-y) graduate	128 (24.2)	166 (36.0)	
Beyond college (4-y)	62 (11.7)	76 (16.5)	
Not documented	31 (5.8)	20 (4.3)	
Body mass index (kg/m^2)			0.0210
Missing	8	4	
Mean (SD)	24.6 (5.9)	23.9 (5.5)	
Median	23.2	22.5	
Range	(15.4-64.5)	(15.3-57.3)	
BMI category, n (%)			0.0210
Missing	8 (1.5)	4 (0.9)	
Less than 18.5	13 (2.5)	28 (6.1)	
18.5-24.9	330 (62.3)	304 (65.9)	
25.0-29.9	107 (20.2)	75 (16.3)	
30.0-39.9	60 (11.3)	39 (8.5)	
40 or more	12 (2.3)	11 (2.4)	
Tobacco use, n (%)			< 0.0001
Missing	4	1	
Never use	334 (63.0)	352 (76.4)	
Former use	56 (10.6)	34 (7.4)	
Current use	136 (25.7)	74 (16.1)	
Regular menstrual cycles, n (%)			< 0.0001
Missing	17 (3.2)	0 (0.0)	
No	71 (13.4)	122 (26.5)	
Yes	442 (83.4)	339 (73.5)	
Previous contraceptive use, n (%)			0.0042
No	135 (25.5)	97 (21.0)	
Yes	381 (71.9)	362 (78.5)	
Unknown	14 (2.6)	2 (0.4)	
Type of contraceptive—each participant may have > 1 type, n (%)			
Combined (estrogen/progestin)	351 (66.2)	341 (74.0%)	0.0081
Progestin only	9 (1.7)	2 (0.4)	0.0581
IUD	12 (2.3)	4 (0.9)	0.0819
Implant	3 (0.6)	3 (0.7)	0.8638
Barrier	37 (7.0)	56 (12.1)	0.0054
Gynecologic surgery history, n (%)			
At least one of the following	58 (10.9)	38 (8.2)	0.1517
Cystectomy	11 (2.1)	9 (2.0)	0.8906
Unilateral oophorectomy	2 (0.4)	4 (0.9)	0.3210
Salpingectomy	15 (2.8)	5 (1.1)	0.0513
Dilation and curettage	32 (6.0)	14 (3.0)	0.0251
Myomectomy	0 (0.0)	4 (0.9)	0.0317
Endometriosis resection	5 (0.9)	13 (2.8)	0.0274
Prevalent conditions—each participant may have > 1[b]			

BMI, body mass index; COPD, chronic obstructive pulmonary disease; IUD, intrauterine device.

Data represent mean (SD) or number (percentage) unless otherwise specified.

Two-sample *t* test used for continuous variables.

χ^2 test or the Fisher exact test used for categorical variables as appropriate.

[a]Categories included as other race were unavailable to the authors.

[b]Prevalent conditions: no significant difference in depression, anxiety, substance abuse disorders, schizophrenia, hyperlipidemia, hypertension, diabetes, cardiac arrhythmias, arthritis, cancer, asthma, COPD, or chronic kidney disease between reference and primary infertility patients.

which may be less prone to recall bias than survey design, as menopause was still self-reported but at a time interval closer to the last menstrual period than can be captured by survey data. Conversely, a study by de Boer and colleagues found no difference in the age of natural menopause when evaluating individuals from 12 In Vitro Fertilization (IVF) and Insitutional Review Board (IRB) IVF clinics.[6] These differences are likely explained by the limited 5-year period of follow-up and by the inclusion of only women presenting for IVF and not more broadly those with infertility, as was included in our study.

Early menopause has been associated with multiple long-term health consequences, including increased risk of cardiovascular disease, osteoporosis, and neurocogni-

TABLE 2. Estimated hazard ratios for natural menopause

	Primary infertility status			
	N (%)	Hazard ratio	95% CI	*P*
Primary infertility	461 (46.5)	1.25	1.06-1.46	0.006[a]
Infertility types				
Ovulatory dysfunction	137 (20.5)	0.72	0.52-0.99	0.0446
Male factor	109 (17.1)	1.22	0.96-1.56	0.1104
Tubal factor	34 (6.0)	1.20	0.82-1.76	0.3471
Uterine factor	16 (2.9)	0.89	0.50-1.58	0.6966
Endometriosis	45 (7.8)	1.42	0.96-2.10	0.0822
Unexplained	180 (25.4)	1.56	1.27-1.93	< 0.0001

Adjusted for BMI, tobacco use, race, menstrual cycle regularity, and previous contraception use.

BMI, body mass index.

[a]To account for multiple comparisons, the significance level of 0.05 is corrected by the Bonferroni method. Therefore, a *P* value < 0.025 is considered statistically significant.

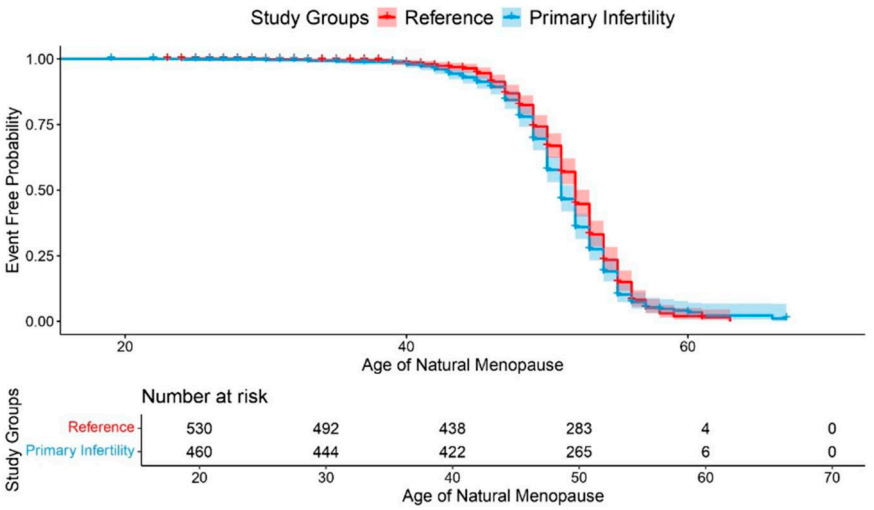

FIG. 2. Kaplan-Meier Curve comparing the menopause-free probability between primary infertility and reference women.

tive disorders.[7,8] Women who undergo early or premature menopause are often not aware of these health impacts or the recommendation for hormone therapy for those with premature menopause. Women with primary infertility may benefit from counseling that they are at risk of early menopause. This will allow them to monitor for early menopause and seek hormone therapy, if indicated.

Women with endometriosis and unexplained infertility underwent menopause earlier than referent women. No other infertility type was associated with earlier age at menopause or increased risk of menopause. Only unexplained infertility was associated with an increased risk of menopause during our study period. Multiple other studies have shown an association between endometriosis and earlier age of menopause.[5,22] It is unclear why endometriosis is associated with an earlier age of menopause, and the surgical and medical management of endometriosis have been proposed as possible contributing factors.[5] Unexplained infertility is a heterogenous category that, by definition, is poorly defined. However, this category may represent women with premature ovarian aging and represent a shared mechanism that underlies both the risk of infertility and early menopause.

Our study presents a longitudinal evaluation of the association between primary infertility and primary infertility type on the age of natural menopause. The length of follow-up, use of medical record data, and population-based analysis are unique strengths of our study. In addition, we included women presenting for evaluation and/or treatment of primary infertility, which presents a broader population and greater generalizability than prior studies that evaluated this outcome in women pursuing IVF.

Our findings add to the current literature and are not without limitations. Despite the use of medical record data, the age of menopause is impacted by recall bias, as by definition, it reflects a past event. Furthermore, many women from the original MPIC were excluded due to unknown menopausal status or unknown age at menopause. It is possible that women had undergone menopause without it being noted in their medical records. It is also possible that women moved from Olmsted County, and their records were unavailable. While we performed subgroup analysis on the women who underwent menopause in the study period to limit censoring bias, our

TABLE 3. Categorized age of natural menopause compared between the primary infertility and reference groups[a]

	Reference (n = 335)	Primary infertility (n = 331)	*P*
Premature (< 40)	6 (1.8)	5 (1.5)	0.01
Early (40-44)	10 (3.0)	25 (7.6)	
Normal (45-55)	261 (77.9)	262 (79.2)	
Late (≥ 55)	58 (17.3)	39 (11.8)	

Women aged over 40 at the index date were excluded from this analysis to ensure all women were equally eligible for premature menopause.

Data represent numbers (percentages) unless otherwise specified.

TABLE 4. Linear regression between primary infertility and age of natural menopause

	Primary infertility status		
	Coefficient	95% CI	*P*
Primary infertility	−1.17	−1.82 to −0.52	0.0005[a]
Infertility types vs. reference			
Ovulatory dysfunction	−0.18	−1.50 to 1.14	0.7930
Male factor	−0.77	−1.76 to 0.22	0.1285
Tubal factor	−0.67	−2.20 to 0.87	0.3937
Uterine factor	−0.13	−2.46 to 2.19	0.9116
Endometriosis	−2.75	−4.38 to −1.13	0.0009
Unexplained	−1.45	−2.26 to −0.64	0.0005

BMI, body mass index.

Adjusted for BMI, tobacco use, race, menstrual cycle regularity, and previous contraception use.

[a]To account for multiple comparisons, the significance level of 0.05 is corrected by the Bonferroni method. Therefore, a *P* value < 0.025 is considered statistically significant.

results could be biased by different follow-up for women with infertility compared with controls.

Furthermore, parity information past the index date is not available for this cohort, so full reproductive outcomes are unknown. It is possible that the referent women had never attempted pregnancy and thus did not receive a diagnosis of infertility. Although we used a population-based cohort, the geographic location of that cohort limits the inclusion of ethnic and racial diversity, which limits the generalizability of our findings. In general, our population has a higher proportion of White women, highly educated women, and women with normal BMI than the general population. While the original MPIC used age-matched controls, this substudy evaluating the age of menopause did not allow for continued age matching. It is possible that age at index date is a confounding factor in our results. Lastly, while our analysis adjusted for the known confounders BMI, tobacco use, race, menstrual cycle regularity, and previous contraception use,[5,12,20] other confounders may further influence our results.

CONCLUSIONS

We found that individuals with primary infertility, specifically those with unexplained infertility and a history of endometriosis, are at increased risk of early menopause and, overall, more likely to undergo menopause at a younger age, compared with referent individuals. Our results are both hypothesis-generating and impactful for patient care, as there may be a shared biological mechanism underlying primary infertility and early menopause. Given the systemic and long-term health effects of early menopause, women with a diagnosis of primary infertility may benefit from additional counseling and should be encouraged to pursue evaluation and treatment with new-onset secondary amenorrhea.

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