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Association of Ovary-Sparing Hysterectomy With Ovarian Reserve

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Abstract

Objective—To evaluate the association of hysterectomy on ovarian function by comparing antimüllerian hormone, a marker of ovarian reserve, before and after hysterectomy.

Methods—The Prospective Research on Ovarian Function study prospectively followed 1) premenopausal women undergoing ovary-sparing hysterectomy for benign indications and 2) a referent cohort with similar age distributions and intact reproductive organs; they reported that women undergoing hysterectomy became menopausal 1.9 years earlier than referents. In a planned secondary analysis, baseline antimüllerian hormone levels and the absolute change and percent change in antimüllerian hormone levels between baseline and 1-year follow-up were compared between groups.

Results—Baseline median antimüllerian hormone levels were similar between the hysterectomy group (n=148) and the referent group (n=172). After 1 year, hysterectomy patients had a significantly greater median percent decrease (−40.7% vs −20.9%; $P<.001$), had a higher proportion with undetectable antimüllerian hormone (12.8% vs 4.7%; $P=.02$), and had on average 0.77 times the antimüllerian hormone level ($P=.001$) compared with referents. These differences were attenuated among white women, but remained significant among black women. Comparisons of women stratified by low or high ovarian reserve at baseline or among propensity score–matched cohorts showed similar findings; however, the absolute median change in antimüllerian hormone levels was similar between groups (−0.3 vs −0.2; $P=.31$).

Conclusion—Women undergoing hysterectomy had similar antimüllerian hormone levels at baseline and experienced a greater percent decrease in levels after 1 year compared with referents, suggesting that hysterectomy may lead to ovarian damage that is unrelated to baseline ovarian reserve.

Précis

Women with ovary-sparing hysterectomy have a greater percent decrease in antimüllerian hormone levels after 1 year compared with referent women, suggesting surgery-related ovarian damage.

Introduction

Prophylactic oophorectomy at the time of hysterectomy in low-risk women has negative health consequences, including increased risk of death, total cancer mortality, fatal and nonfatal cardiac disease, and neurologic disease (1–7). Although ovarian preservation is increasingly common, growing evidence suggests that women who undergo ovary-sparing hysterectomy nevertheless enter menopause at a younger age than referent women with intact reproductive organs (8–10).

The association of hysterectomy with ovarian reserve has important public health implications because hysterectomy is the second most common surgery performed on US women, with over 3 million procedures undertaken between 2000 and 2004 (11). Moreover, nationwide hysterectomy rates are highest among women aged 40 to 44 years, potentially making a large number of premenopausal women vulnerable to premature menopause and its adverse health consequences.

The Prospective Research on Ovarian Function (PROOF) cohort study demonstrated that despite ovarian preservation, women who underwent hysterectomy had increased risk of menopause (hazard ratio, 1.92; $P=.001$) compared with the referent group (10). If the increased risk of menopause was due to a deleterious effect of surgery on the ovaries, we hypothesized that women undergoing a hysterectomy would have lower antimüllerian hormone levels at follow-up compared with referent women with intact reproductive tracts.

Materials and Methods

This study was approved by the Institutional Review Boards of Mayo Clinic (Rochester, Minnesota) and Duke University School of Medicine (Durham, North Carolina). Serum samples from women prospectively enrolled in the PROOF Study from 2004 through 2007 were used to ascertain the association of hysterectomy with ovarian reserve. The PROOF was a large, prospective cohort study of racially diverse women who underwent ovary-sparing hysterectomy and referent women of similar age and race. Details of the PROOF cohort assembly have been previously described (12). In brief, at the time of enrollment, participants were from 30 to 47 years old, premenopausal, and without a history of cancer. An interviewer-administered questionnaire, blood samples, and anthropometric measurements were obtained at baseline and at yearly visits. The cohort was followed through 2009 (12).

In this planned secondary analysis, frozen sera from the PROOF cohort was used to further investigate the association between hysterectomy and menopause by comparing antimüllerian hormone levels, a marker of ovarian reserve (13–17), at baseline and 1 year after hysterectomy. Sera samples from women who had a baseline and a follow-up sample within 6 to 18 months were included in the antimüllerian hormone analyses reported herein.

Women in the hysterectomy group were included if they had both ovaries preserved at hysterectomy, proven fertility (ie, a history of at least 1 live birth), were nonsmokers, and were not using hormonal contraception at presentation. Women presenting to the gynecology and family medicine clinics within Duke University Health System were recruited to participate as referents through study brochures and ads. Referent women were included if they met all of the above criteria, had intact reproductive organs, and were not pregnant.

Sera samples were stored at -80°C . Antimüllerian hormone concentration was measured using the antimüllerian hormone Gen II enzyme-linked immunosorbent assay (Beckman Coulter, Inc). The interassay and intraassay coefficient of variation was $<5\%$ (range, $2\%–5\%$) at antimüllerian hormone levels of 3 and 12 ng/mL. All samples were tested with the same reagent lot and by using the antimüllerian hormone Gen II enzyme-linked immunosorbent assay–modified protocol provided by Beckman Coulter after the field safety notice (FSN 20434-3). The limit of detection for this assay was 0.1 ng/mL. This modified protocol includes the addition of 5 parts antimüllerian hormone Gen II assay buffer to the patient samples before addition of the microplate to eliminate complement interference. To minimize variability, sera were analyzed in batches with the same number of hysterectomy and referent samples, and each individual's sample was tested in duplicate and averaged.

Antimüllerian hormone levels were compared at baseline between groups to investigate whether changes in ovarian function were associated with symptoms requiring hysterectomy. If women presenting for hysterectomy had underlying ovarian dysfunction, we anticipated observing lower baseline antimüllerian hormone levels compared with referent women. In addition, we planned a priori to compare the percent change in antimüllerian hormone levels from baseline through 1 year for the hysterectomy and referent groups. Comparing percentage change (as opposed to absolute median value) was imperative because of the heterogeneity in antimüllerian hormone levels, even among women of similar age and menstrual cycle characteristics (18). However, analyses of the absolute change also are included for all comparisons. Lastly, analysis of covariance (ANCOVA) was included because it is best able to address the heterogeneity of antimüllerian hormone levels and answers the question “given 2 women with same baseline antimüllerian hormone level, how does their antimüllerian hormone level differ on average at follow-up?” We chose the 1-year sample to limit the influence of differing durations of follow-up.

Statistical analyses were performed using the SAS software package (version 9.4; SAS Institute Inc; Cary, NC, USA). All calculated P values were 2-sided, and P values less than .05 were considered statistically significant. Baseline characteristics were compared between the hysterectomy and referent groups using the 2-sample t test for age, the Wilcoxon rank sum test for body mass index (BMI), antimüllerian hormone, and ordinal variables, and the χ^2 test for nominal variables. The Wilcoxon rank sum test was also used to compare the following outcome measures between the 2 groups: follow-up antimüllerian hormone levels, the absolute change from baseline, and the percentage change from baseline. In addition, the effect of hysterectomy was also evaluated based on fitting an ANCOVA model. In the ANCOVA analysis, a constant of 0.08 was added to all antimüllerian hormone levels before applying the log base 2 transformation to deal with the skewed distribution of the levels and accommodate undetectable levels at follow-up; the transformed follow-up levels were then

compared between the hysterectomy and referent groups after adjusting for the transformed baseline levels. Because the ANCOVA model was fit using the transformed data, the appropriate antilog was applied to the parameter estimates and the resultant estimate of the effect of hysterectomy is interpreted as a ratio of the average follow-up antimüllerian hormone levels between the 2 groups.

Two subgroup analyses were performed to evaluate women with limited or robust antimüllerian hormone reserve at baseline. Low and high ovarian reserve was defined as antimüllerian hormone levels ≤ 1.2 ng/mL and >1.2 ng/mL, respectively, based on 2 standard deviations above the mean antimüllerian hormone value for women with the “aging” ovary profile as described by Sowers et al (18). Women with the “aging” profile may be at the cusp of or have just entered perimenopause because they had lower average levels of inhibin B and shorter menstrual cycles, despite having regular menses (18).

Because ovary-sparing hysterectomy was not randomly assigned in this cohort, standard analyses to adjust for baseline characteristics when comparing women undergoing hysterectomy vs the referent cohort may not adequately control for confounding and bias (19). Therefore, propensity score (PS) methodology was used to obtain a less biased estimate of the effect on hysterectomy on the outcomes of interest. A PS value was calculated for each woman by using a multivariable logistic regression model that was fit to estimate the conditional probability of having a hysterectomy, given a woman’s baseline covariates. Women with ovary-sparing hysterectomy were matched 1:1 on the logit of the PS values to women in the referent group using a greedy matching algorithm. Calipers of width equal to 0.2 SD of the logit of the PS value were used for matching. The balance produced by the PS values was assessed by examining the standardized difference of each baseline covariate, defined as the difference in means or proportions of that covariate between the 2 groups divided by a measure of the pooled SD of the covariate.

Results

Of the women enrolled in the PROOF cohort, 148 women in the hysterectomy group and 172 women in the referent group met inclusion criteria (Figure 1). Compared with the referent group, fewer women in the hysterectomy group were of Hispanic descent, and they had fewer years of education and a higher median BMI. At baseline, fewer women undergoing hysterectomy had regular menstrual cycle lengths (eg, 24–35 days between period onset) and more had undergone prior tubal ligation compared with the referent group (Table 1). Median baseline antimüllerian hormone levels were similar between groups, as was the proportion of patients with nondetectable antimüllerian hormone levels and aging or young ovary profiles. However, 7 women in the hysterectomy group (4.7%) and 23 women in the referent group (13.4%) had undetectable antimüllerian hormone levels at baseline, despite reporting regular menstrual cycles ($P=.008$) (Table 1). Similar findings were observed (data not shown) when we compared baseline characteristics of the subgroup of women younger than 40 years (ie, those less likely to be perimenopausal). These data suggest that women presenting for hysterectomy did not have underlying diminished ovarian reserve compared with similarly aged women in the referent group.

AMH levels were available for 117 women in the hysterectomy group and 129 referent women (all with both ovaries intact) at a median of 366 days (interquartile range [IQR], 350–391 days) and 365 days (IQR, 357–382 days) after the baseline assessment, respectively (Figure 1). We observed no difference in the absolute change in antimüllerian hormone levels at 1 year compared with baseline between the 2 groups (median, -0.3 vs -0.2 ; $P=.31$). Scatterplots of antimüllerian hormone levels showing the relationships between baseline and follow-up, absolute change, and percentage change showed that the percentage change had less dependence on the baseline antimüllerian hormone compared with the other measures of change (Figure 2) (20). Given this finding and our a priori plans, the remainder of the analysis focused on the percent change and ANCOVA analyses.

The median percent decrease in antimüllerian hormone levels was greater 1 year after hysterectomy (-40.7% vs -20.9% for referents; $P<.001$), and a greater proportion of women in the hysterectomy group had undetectable antimüllerian hormone levels (12.8% vs 4.7% ; $P=.02$). Similarly, women who underwent hysterectomy had on average 0.77 times the antimüllerian hormone level compared with the referent women (ANCOVA, $P=.001$). These differences were attenuated among white women but remained significant among black women (Table 2).

Among women with high ovarian reserve at baseline, the overall median percent change was not statistically different between the hysterectomy and referent groups (-34.4% vs -21.2% ; $P=.06$). No women in this subgroup had undetectable antimüllerian hormone at follow-up. However, women in the hysterectomy group with high ovarian reserve had on average 0.81 times the antimüllerian hormone level at 1 year compared with referent women (ANCOVA, $P=.03$). These differences were attenuated among white women but remained statistically significant for black women (Table 3). In the subgroup with low ovarian reserve at baseline (antimüllerian hormone levels <1.2 ng/mL), the overall median percent change in antimüllerian hormone levels was greater (median, -58.3% vs -19.1% ; $P=.003$), and more women from the hysterectomy group had undetectable antimüllerian hormone (24.6% vs 8.6% ; $P=.01$) (Table 3). Women who underwent ovary-sparing hysterectomy had on average 0.73 times the antimüllerian hormone level after 1 year compared with referent women (ANCOVA, $P=.01$). Similar findings were observed for black but not for white women in this subgroup (Table 3).

To reduce the effect of selection bias, we conducted an analysis of PS-matched women. A PS value was calculated for each woman by using a multivariable logistic regression model that was fit to estimate the conditional probability of having a hysterectomy, given the following 7 baseline covariates commonly accepted to influence age of menopause: age, BMI, baseline antimüllerian hormone level, race, and history of diabetes mellitus, autoimmune disease, and tubal ligation. The decrease in the total standardized difference for the 7 covariates in the full cohort compared with the matched cohort (1.68 to 0.42, respectively) showed a 75% reduction in bias due to measured covariates with PS-matching methodology. Consistent with the results of the primary analysis, among the PS-matched cohort, women undergoing hysterectomy had a significantly greater median percent change in antimüllerian hormone levels from baseline to 1 year when compared with the referent group (median change, -40.7% vs -21.4% ; $P=.02$). This difference was attenuated among

white women (median, -39.2% vs -27.6% ; $P=.40$) but persisted among black women (median, -48.9% vs -15.8% ; $P=.009$) (Table 4).. There was no difference in the proportion of women with undetectable antimüllerian hormone after 1 year (11.6% vs 6.3% ; $P=.20$). Women who underwent hysterectomy had 0.80 times the antimüllerian hormone levels at follow-up compared with referent women (ANCOVA, $P=.02$). These findings remained consistent among black but not white women (Table 4).

Among the hysterectomy cohort, a higher percentage of black women underwent non–minimally invasive hysterectomy (defined as total or supracervical hysterectomy) compared with white women (52.2% [35/67] vs 36.2% [17/47]; $P=.09$), but this difference was not statistically significant. Only 7 women had concomitant salpingectomy at the time of hysterectomy (left side, $n=3$; bilateral, $n=3$; side not specified, $n=1$). There was no difference in the percent change in antimüllerian hormone over time when minimally invasive hysterectomy (defined as vaginal, laparoscopic-assisted, or laparoscopic hysterectomy) was compared with non–minimally invasive hysterectomy (median, -38.3% vs -47.9% ; $P=.84$), when white and black women were compared (median, -38.5% vs -48.1% ; $P=.21$) and when the 2 modes of hysterectomy were compared separately among white women (median, -35.9% vs -40.0% ; $P=.78$) and black women (median, -40.5% vs -50.0% ; $P=.91$), suggesting that the racial differences observed above were not associated with the mode of hysterectomy.

Discussion

After prospectively comparing a racially diverse group of women, those undergoing ovary-sparing hysterectomy had a significantly greater percent decrease in antimüllerian hormone levels (-40.7% vs -20.9% ; $P<.001$) and were more likely to have nondetectable levels (12.8% vs 4.7% ; $P=.02$) at the 1-year follow-up compared with the referent group. This significant decrease in antimüllerian hormone was also observed with ANCOVA, in subgroups of women with low and high ovarian reserve at baseline, and among propensity score–matched women, but not after comparing median absolute change.

Moorman and Farquhar have shown that women who undergo ovary-sparing hysterectomy reach menopause on average 1.9 to 4 years earlier than referent women (9,10). This finding can be explained by at least 2 hypotheses (21–24): 1) hysterectomy disrupts ovarian blood flow or removes paracrine or endocrine signals from the uterus (or both), thereby hastening follicular depletion and leading to earlier menopause; 2) underlying diminished ovarian reserve in women presenting for hysterectomy causes symptoms (eg, menorrhagia, leiomyoma growth, etc) prompting hysterectomy. The present study argues against the latter hypothesis because we show that women presenting for hysterectomy had similar antimüllerian hormone levels as referent women at baseline. In addition, we observed a consistently greater percent decrease in antimüllerian hormone levels after hysterectomy compared with referent women. This finding may suggest a plausible mechanism for the association between earlier menopause after ovary-sparing hysterectomy: surgery causes, by a yet-unidentified mechanism, ovarian damage (and hence lower antimüllerian hormone levels at follow-up). In essence, after surgery, a woman’s ovarian age may be advanced to

that of a woman with a naturally diminished ovarian pool of similar, lower, antimüllerian hormone levels.

Others have reported no association of hysterectomy with antimüllerian hormone levels (21,25,26). However, these investigations had significant limitations, including homogeneous populations (primarily white or Korean) (21,25), small sample sizes (n=33, n=32, and n=20, respectively) (21,25,26), and lack of appropriate comparison groups (21,25).

Unexpectedly, we found that only black women had consistently significantly decreased percent change in antimüllerian hormone levels. This finding appeared to be unrelated to the mode of hysterectomy. A growing body of evidence suggests that reproductive function differs by race during a woman's reproductive life (27). Moreover, the prevalence of premature ovarian failure varies by race, suggesting that the ovarian senescence trajectory may not be the same for all races. In a multiethnic prospective study of changes in ovarian function, black race was a significant predictor of greater declines in antimüllerian hormone levels during a 6-year period (28). Another study showed that average antimüllerian hormone levels were 25% lower in blacks than whites after adjusting for age, BMI, and human immunodeficiency virus status (28). These data, in conjunction with our findings, suggest that black women may be more susceptible to the adverse effect of hysterectomy on ovarian reserve. Alternatively, the smaller number of white women in the cohort may have limited our statistical power to detect a consistent effect of hysterectomy in that group.

How then might hysterectomy lead to earlier onset or expedited depletion of the follicular pool? Animal studies have shown that hysterectomized rabbits have on average 50% fewer follicles 1 year after hysterectomy compared with controls (29). Surprisingly, if endometrial tissue is implanted in the abdominal wall during the hysterectomy, rabbits with endometrial implants had 40% more follicles compared with hysterectomized animals without an implant (29), suggesting a marked paracrine contribution of the endometrium to the rate of ovarian depletion. Alternatively, ischemic injury or changes in blood flow after transection of the utero-ovarian ligament (and the uterine artery contained therein) may expedite follicular depletion.

Our study is not without limitations. We studied only a subset of the original PROOF cohort, but this was because we wanted to remove known (eg, smoking) or possible confounders (eg, infertility, hormonal contraception) of menopause. The cohort design was prone to selection bias, but after PS-matching, we were able to eliminate 75% of the bias due to the measured covariates, and our findings remained consistent across analyses. Although we found no difference in the absolute change in antimüllerian hormone levels, we chose a priori to evaluate percent change. This decision was supported by the finding that percent change displayed less dependence on baseline antimüllerian hormone levels compared with absolute change. Moreover, given that the change in antimüllerian hormone levels over time is nonlinear (15), we observed that the absolute change of the log-transformed antimüllerian hormone values yielded similar findings to those obtained with percent change and ANCOVA (data not shown). In conclusion, women who underwent hysterectomy had a

greater decrease in antimüllerian hormone levels compared with referents. These findings suggest that ovarian damage was unrelated to baseline ovarian reserve.

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Abbreviations

ANCOVA	analysis of covariance
BMI	body mass index
FSH	follicle-stimulating hormone
IQR	interquartile range
PROOF	Prospective Research on Ovarian Function

References

1. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. *Obstet Gynecol*. 2005 Aug; 106(2):219–226. [PubMed: 16055568]
2. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology*. 2007 Sep 11; 69(11):1074–1083. Epub 2007 Aug 29. [PubMed: 17761551]
3. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. *Neurology*. 2008 Jan 15; 70(3):200–209. Epub 2007 Aug 29. [PubMed: 17761549]
4. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol*. 2006 Oct; 7(10):821–828. [PubMed: 17012044]
5. Shuster LT, Gostout BS, Grossardt BR, Rocca WA. Prophylactic oophorectomy in premenopausal women and long-term health. *Menopause Int*. 2008 Sep; 14(3):111–116. [PubMed: 18714076]
6. Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol*. 2009 May; 113(5):1027–1037. [PubMed: 19384117]
7. Keshavarz, H.; Hillis, H.; Kieke, BA.; Marchbanks, P. Hysterectomy Surveillance-United States, 1994–1999 [Internet]. Atlanta GA: Centers for Disease Control and Prevention; Updated 2002 Jul 2; Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5105a1.htm> [cited 2015 May 1]
8. Ahn EH, Bai SW, Song CH, Kim JY, Jeong KA, Kim SK, et al. Effect of hysterectomy on conserved ovarian function. *Yonsei Med J*. 2002 Feb; 43(1):53–58. [PubMed: 11854933]
9. Farquhar CM, Sadler L, Harvey SA, Stewart AW. The association of hysterectomy and menopause: a prospective cohort study. *BJOG*. 2005 Jul; 112(7):956–962. [PubMed: 15957999]
10. Moorman PG, Myers ER, Schildkraut JM, Iversen ES, Wang F, Warren N. Effect of hysterectomy with ovarian preservation on ovarian function. *Obstet Gynecol*. 2011 Dec; 118(6):1271–1279. [PubMed: 22067716]
11. Whiteman MK, Hillis SD, Jamieson DJ, Morrow B, Podgornik MN, Brett KM, et al. Inpatient hysterectomy surveillance in the United States, 2000–2004. *Am J Obstet Gynecol*. 2008 Jan; 198(1):34.e1–34.e7. Epub 2007 Nov 5. [PubMed: 17981254]

12. Moorman PG, Schildkraut JM, Myers ER, Wang F. Reported symptoms before and one year after hysterectomy in African American and white women. *J Womens Health (Larchmt)*. 2011 Jul; 20(7):1035–1042. Epub 2011 Jun 14. [PubMed: 21671769]
13. Burger HG, Hale GE, Dennerstein L, Robertson DM. Cycle and hormone changes during perimenopause: the key role of ovarian function. *Menopause*. 2008 Jul-Aug;(4 Pt 1):603–612. [PubMed: 18574431]
14. Vigier B, Picard JY, Tran D, Legeai L, Josso N. Production of anti-Müllerian hormone: another homology between Sertoli and granulosa cells. *Endocrinology*. 1984 Apr; 114(4):1315–1320. [PubMed: 6546716]
15. Sowers MR, Eyvazzadeh AD, McConnell D, Yosef M, Jannausch ML, Zhang D, et al. Anti-müllerian hormone and inhibin B in the definition of ovarian aging and the menopause transition. *J Clin Endocrinol Metab*. 2008 Sep; 93(9):3478–3483. Epub 2008 Jul 1. [PubMed: 18593767]
16. La Marca A, De Leo V, Giulini S, Orvieto R, Malmusi S, Giannella L, et al. Anti-Müllerian hormone in premenopausal women and after spontaneous or surgically induced menopause. *J Soc Gynecol Investig*. 2005 Oct; 12(7):545–548. Epub 2005 Jul 19.
17. van Disseldorp J, Faddy MJ, Themmen AP, de Jong FH, Peeters PH, van der Schouw YT, et al. Relationship of serum antimüllerian hormone concentration to age at menopause. *J Clin Endocrinol Metab*. 2008 Jun; 93(6):2129–2134. Epub 2008 Mar 11. [PubMed: 18334591]
18. Sowers M, McConnell D, Gast K, Zheng H, Nan B, McCarthy JD, et al. Anti-Müllerian hormone and inhibin B variability during normal menstrual cycles. *Fertil Steril*. 2010 Sep; 94(4):1482–1486. Epub 2009 Dec 6. [PubMed: 19969291]
19. D'Agostino RB Jr. Propensity scores in cardiovascular research. *Circulation*. 2007 May 1; 115(17):2340–2343. [PubMed: 17470708]
20. Kaiser L. Adjusting for baseline: change or percentage change? *Stat Med*. 1989 Oct; 8(10):1183–1190. [PubMed: 2682909]
21. Lee DY, Park HJ, Kim BG, Bae DS, Yoon BK, Choi D. Change in the ovarian environment after hysterectomy as assessed by ovarian arterial blood flow indices and serum anti-Müllerian hormone levels. *Eur J Obstet Gynecol Reprod Biol*. 2010 Jul; 151(1):82–85. Epub 2010 Mar 7. [PubMed: 20211514]
22. Petri Nahas EA, Pontes A, Nahas-Neto J, Borges VT, Dias R, Traiman P. Effect of total abdominal hysterectomy on ovarian blood supply in women of reproductive age. *J Ultrasound Med*. 2005 Feb; 24(2):169–174. [PubMed: 15661947]
23. Chalmers C. Does hysterectomy in a premenopausal woman affect ovarian function? *Med Hypotheses*. 1996 Jun; 46(6):573–575. [PubMed: 8803944]
24. Xiangying H, Lili H, Yifu S. The effect of hysterectomy on ovarian blood supply and endocrine function. *Climacteric*. 2006 Aug; 9(4):283–289. [PubMed: 16857658]
25. Hehenkamp WJ, Volkers NA, Broekmans FJ, de Jong FH, Themmen AP, Birnie E, et al. Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy. *Hum Reprod*. 2007 Jul; 22(7):1996–2005. [PubMed: 17582145]
26. Atabekoglu C, Taskin S, Kahraman K, Gemici A, Taskin EA, Ozmen B, et al. The effect of total abdominal hysterectomy on serum anti-Müllerian hormone levels: a pilot study. *Climacteric*. 2012 Aug; 15(4):393–397. Epub 2012 Jan 23. [PubMed: 22268398]
27. Seifer DB, Zackula R, Grainger DA. Society for Assisted Reproductive Technology Writing Group Report. Trends of racial disparities in assisted reproductive technology outcomes in black women compared with white women: Society for Assisted Reproductive Technology 1999 and 2000 vs. 2004–2006. *Fertil Steril*. 2010 Feb; 93(2):626–635. Epub 2009 Apr 14. [PubMed: 19368916]
28. Seifer DB, Golub ET, Lambert-Messerlian G, Benning L, Anastos K, Watts DH, et al. Variations in serum müllerian inhibiting substance between white, black, and Hispanic women. *Fertil Steril*. 2009 Nov; 92(5):1674–1678. Epub 2008 Oct 18. [PubMed: 18930217]
29. Sessums JV, Murphy DP. The influence of endometrium upon the rabbit ovary after hysterectomy. *Surg Gynecol Obstet*. 1933; 56:600–609.

Figure 1.

Flow diagram depicting selection of participants for the current investigation. *Women were excluded if they did not have at least one live birth. AMH, antimüllerian hormone; PROOF, Prospective Research on Ovarian Function; OCP, oral contraceptive pill; HT, hormone therapy.

Figure 2.

Scatterplots of the relationships between baseline antimüllerian hormone levels and either the follow-up level (A), absolute change (B), or percentage change (C).

Table 1

Baseline Characteristics

Characteristic	Hysterectomy Group (N=148)	Referent Group (N=172)	P Value ^a
Age at enrollment, mean±SD, y	40.9±4.3	41.6±4.0	.19
Race, No. (%)			.07
White	58 (39.2)	87 (50.6)	
Black	86 (58.1)	78 (45.3)	
Other	4 (2.7)	7 (4.1)	
Hispanic ethnicity, No. (%)	1 (0.7)	9 (5.2)	.02
Highest level of education, No. (%)			.008
Less than high school	4 (2.7)	4 (2.3)	
High school graduate	29 (19.6)	22 (12.8)	
Some college	62 (41.9)	59 (34.3)	
4-y college graduate	53 (35.8)	87 (50.6)	
BMI, median (IQR), kg/m ²	31.2 (26.7–36.4)	27.9 (24.1–34.6)	.004
Parity, No. (%)			.82
1	49 (33.1)	45 (26.2)	
2	52 (35.1)	81 (47.1)	
3	47 (31.8)	46 (26.7)	
Mean cycle length (d) in the past year, No. (%)			<.001
<24	30 (20.3)	14/171 (8.2)	
24–35	102 (68.9)	154/171 (90.1)	
Irregular, patient unable to estimate	16 (10.8)	3/171 (1.8)	
History of diabetes mellitus, No. (%)	6 (4.1)	13 (7.6)	.19
History of autoimmune disease, No. (%)	8 (5.4)	7 (4.1)	.57
History of tubal ligation, No. (%)	93 (62.8)	66 (38.4)	<.001
AMH at baseline, median (IQR), ng/mL	1.0 (0.3–2.1)	0.8 (0.3–2.5)	.47
Baseline AMH (ng/mL), No. (%)			.36
0	7 (4.7)	23 (13.4)	
<0.3 but detectable	19 (12.8)	16 (9.3)	
0.3–1.2	57 (38.5)	69 (40.1)	
1.3–2.2	32 (21.6)	16 (9.3)	
2.3	33 (22.3)	48 (27.9)	

Abbreviations: AMH, antimüllerian hormone; BMI, body mass index; IQR, interquartile range.

^aThe 2 groups were compared using the 2-sample *t* test for age; the Wilcoxon rank sum test for BMI, AMH, and all other ordinal variables; and the χ^2 test for nominal variables.

Table 2

Change in Antimüllerian Hormone Levels After 1 Year

Measure	Hysterectomy Group (n=117)	Referent Group (n=129)	P Value ^a
AMH at baseline, median (IQR), ng/mL	1.1 (0.4–2.2)	1.0 (0.5–2.8)	.46
AMH at 1-y follow-up, median (IQR), ng/mL	0.6 (0.2–1.7)	1.0 (0.3–2.3)	.04
Nondetectable AMH at 1-y follow-up, No. (%)	15 (12.8)	6 (4.7)	.02
Absolute change in AMH, median (IQR), ng/mL			
Overall (n=117; 129) ^{b,c}	−0.3 (−0.7 to −0.1)	−0.2 (−0.7 to 0)	.31
White (n=47; 64)	−0.2 (−0.6 to 0)	−0.2 (−0.6 to 0)	.59
Black (n=67; 60)	−0.3 (−0.9 to −0.1)	−0.2 (−0.8 to 0.1)	.23
Percent change in AMH, median (IQR), %			
Overall (n=117; 129) ^{b, c}	−40.7 (−70.5 to −4.0)	−20.9 (−44.4 to 0)	<.001
White (n=47; 64)	−38.5 (−66.7 to 0)	−23.1 (−47.7 to 0)	.13
Black (n=67; 60)	−48.1 (−76.0 to −11.1)	−16.0 (−42.6 to 1.6)	<.001
ANCOVA estimate of the effect of hysterectomy (95% CI)			
Overall (n=117; 129) ^{b,c}	0.77 (0.66–0.90) ^d		.001
White (n=47; 64)	0.85 (0.68–1.06)		.16
Black (n=67; 60)	0.71 (0.56–0.89)		.003

Abbreviations: AMH, antimüllerian hormone; ANCOVA, analysis of covariance; IQR, interquartile range.

^a Comparisons were evaluated using the Wilcoxon rank sum test for continuous variables and χ^2 test for nominal variables.^b Patient numbers are shown as follows: hysterectomy group; referent group.^c Separate results are not shown for other race: hysterectomy (n=3); referent group (n=5).^d After 1-year of follow-up the women in the hysterectomy group have on average 0.77 times the AMH level as compared to women in the referent group.

Table 3

Change in Antimüllerian Hormone Levels at 1 Year, Stratified by Baseline Ovarian Reserve

Measure	Hysterectomy Group	Referent Group	P Value ^a
High Baseline Ovarian Reserve (AMH >1.2 ng/mL)			
AMH at baseline, median (IQR), ng/mL	2.5 (1.7–3.8)	3.1 (2.0–4.4)	.05
AMH at 1-y follow-up, median (IQR), ng/mL	1.8 (0.9–3.4)	2.4 (1.8–3.9)	.02
Nondetectable AMH at 1-y follow-up, No. (%)	0	0	...
Absolute change in AMH, median (IQR), ng/mL			
Overall (n=56; 59) ^{b,c}	−0.8 (−1.3 to 0)	−0.7 (−1.0 to −0.1)	.44
White (n=25; 23)	−0.5 (−1.1 to −0.1)	−0.7 (−1.2 to −0.2)	.67
Black (n=29; 34)	−1.0 (−1.3 to −0.3)	−0.6 (−1.0 to 0.3)	.09
Percent change in AMH, median (IQR), %			
Overall (n=56; 59) ^{b,c}	−34.4 (−52.6, −2.0)	−21.2 (−33.3, −3.7)	.06
White (n=25; 23)	−33.3 (−46.2, −4.0)	−21.2 (−33.3, −4.9)	.52
Black (n=29; 34)	−38.1 (−62.5, −7.3)	−16.8 (−33.3, 3.2)	.02
ANCOVA estimate of the effect of hysterectomy (95% CI)			
Overall (n=56; 59) ^{b,c}	0.81 (0.67–0.98) ^d		.03
White (n=25; 23)	0.85 (0.61–1.18)		.32
Black (n=29; 34)	0.73 (0.58–0.94)		.01
Low Baseline Ovarian Reserve (AMH ≤1.2 ng/mL)			
AMH at baseline, median (IQR), ng/mL	0.4 (0.3–0.7)	0.6 (0.3–0.8)	.30
AMH at 1-y follow-up, median (IQR), ng/mL	0.2 (0.1–0.5)	0.3 (0.1–0.6)	.01
Nondetectable AMH at 1-y follow-up, No. (%)	15 (24.6)	6 (8.6)	.01
Absolute change in AMH, median (IQR), ng/mL			
Overall (n=61; 70) ^{b,c}	−0.2 (−0.3 to −0.1)	−0.1 (−0.3 to 0)	.15
White (n=22; 41)	−0.2 (−0.2 to 0)	−0.1 (−0.3 to 0)	.58
Black (n=38; 26)	−0.2 (−0.3 to −0.1)	−0.1 (−0.3 to 0)	.16
Percent change in AMH, median (IQR), %			
Overall (n=61; 70) ^{b,c}	−58.3 (−85.7 to −11.1)	−19.1 (−60.0 to 0)	.003
White (n=22; 41)	−52.3 (−85.7 to 0)	−25.0 (−57.1 to 0)	.09
Black (n=38; 26)	−59.2 (−100.0 to −14.3)	−7.1 (−66.7 to 0)	.02
ANCOVA estimate of the effect of hysterectomy (95% CI)			
Overall (n=61; 70) ^{b,c}	0.73 (0.57–0.92) ^e		.01
White (n=22; 41)	0.80 (0.58–1.12)		.19
Black (n=38; 26)	0.68 (0.46–1.01)		.05

Abbreviations: AMH, antimüllerian hormone; ANCOVA, analysis of covariance; IQR, interquartile range.

^aThe hysterectomy group with both ovaries intact and the referent group were compared using the Wilcoxon rank sum test for continuous variables and χ^2 test for nominal variables.^bPatient numbers are shown as follows: hysterectomy group; referent group.

^c Separate results are not shown for other race: hysterectomy group (high baseline ovarian reserve, n=2; low baseline ovarian reserve, n=1); referent group (high baseline ovarian reserve, n=2; low baseline ovarian reserve, n=3).

^d Among the women with high baseline ovarian reserve, after 1 year of follow-up, women in the hysterectomy group had on average 0.81 times the AMH level compared with women in the referent group.

^e Among the women with low baseline ovarian reserve, after 1 year of follow-up, women in the hysterectomy group had on average 0.73 times the AMH level compared with women in the referent group.

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Table 4

Change in Antimüllerian Hormone Levels at 1 Year for Propensity Score–Matched Women

Measure	Hysterectomy Group (n=95)	Referent Group (n=95)	P Value ^a
AMH at baseline, median (IQR), ng/mL	1.3 (0.4–2.4)	1.0 (0.5–2.9)	.73
AMH at 1-y follow-up, median (IQR), ng/mL	0.7 (0.2–1.8)	0.9 (0.3–2.3)	.17
Nondetectable AMH at 1-y follow-up, No. (%)	11 (11.6)	6 (6.3)	.20
Absolute change in AMH, median (IQR), ng/mL			
Overall (n=95; 95) ^{b,c}	−0.3 (−0.9 to 0)	−0.3 (−0.7 to 0)	.54
White (n=40; 40)	−0.2 (−0.6 to 0)	−0.4 (−0.7 to 0)	.97
Black (n=52; 50)	−0.3 (−1.0 to −0.1)	−0.2 (−0.8 to 0)	.20
Percent change in AMH, median (IQR), %			
Overall (n=95; 95) ^{b,c}	−40.7 (−70.0 to 0)	−21.4 (−50.0 to 0)	.02
White (n=40; 40)	−39.2 (−66.7 to 0)	−27.6 (−51.9 to 0)	.40
Black (n=52; 50)	−48.9 (−75.5 to −9.2)	−15.8 (−44.4 to 0)	.009
ANCOVA estimate of the effect of hysterectomy (95% CI)			
Overall (n=95; 95) ^{b,c}	0.80 (0.66–0.96) ^d		.02
White (n=40; 40)	0.90 (0.68–1.19)		.46
Black (n=52; 50)	0.70 (0.54–0.92)		.01

Abbreviations: AMH, antimüllerian hormone; ANCOVA, analysis of covariance; IQR, interquartile range.

^aThe hysterectomy group with both ovaries intact and the referent group were compared using the Wilcoxon rank sum test for continuous variables and χ^2 test for nominal variables.^bPatient numbers are shown as follows: hysterectomy; referent group.^cSeparate results are not shown for other race: hysterectomy (n=3); referent group (n=5).^dAfter 1 year of follow-up, women in the hysterectomy group had on average 0.80 times the AMH level compared with women in the referent group