HHS Public Access

Author manuscript

Menopause. Author manuscript; available in PMC 2022 December 06.

Published in final edited form as:

Menopause. ; 29(2): 225–230. doi:10.1097/GME.0000000000001905.

Association of Oral Contraceptives and Tubal Ligation with Anti-Müllerian Hormone

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Abstract

Objective: Oral contraceptives and tubal ligation are commonly used methods of contraception that may impact ovarian function. Few studies have examined the association of these factors with anti-Müllerian hormone (AMH), a marker of ovarian aging.

Methods: We examined the association of oral contraceptive use and tubal ligation with AMH in the Nurses' Health Study II prospective cohort among a subset of 1,420 premenopausal participants who provided a blood sample in 1996–1999. History of oral contraceptive use and tubal ligation were reported in 1989 and updated every two years until blood collection. We utilized generalized linear models to assess whether mean AMH levels varied by duration of and age at first use of oral contraceptives and history, age, and type of tubal ligation.

Results: In multivariable models adjusted for smoking, reproductive events, and other lifestyle factors, we observed a significant, inverse association between duration of oral contraceptive use and mean AMH levels (*P* for trend=.036). Compared to women without a tubal ligation, AMH

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levels were significantly lower when the procedure included a clip, ring, or band (1.04 ng/ml vs. 1.72 ng/ml, $p<.01$). AMH levels were not associated with age at first use of oral contraceptives or age at tubal ligation.

Conclusions: Our analysis found an association between duration of oral contraceptive use and certain types of tubal ligation with mean AMH levels. Further research is warranted to confirm the long-term association of these widely used contraceptive methods with AMH.

Keywords

anti-Müllerian hormone; epidemiology; oral contraceptives; ovarian aging; reproductive factors; tubal ligation

INTRODUCTION

Natural menopause occurs after 12 consecutive months of amenorrhea and occurs at an average age of 52 years in Western populations.[1] Early menopause occurs between the ages of 40 to 45 years and is experienced by approximately 5% of women whereas menopause prior to the age of 40 years is considered premature and occurs in roughly 2% of women.[1] Current research suggests that women who experience menopause prior to the age of 45 have a higher risk of cardiovascular disease, cognitive decline, osteoporosis, and premature mortality.[2,3]

Presently, 65% of American women of reproductive age (15 to 49 years) use some form of contraception, with oral contraceptives (OCs; 25.3%) and tubal ligation (TL; 21.8%) the most common.[4] OCs prevent pregnancy by manipulating hormone levels, which may inhibit ovarian follicle growth, prevent ovulation, and modify the rate of follicular atresia.[5,6] Thus, it is plausible that OC use could slow the rate of decline in the ovarian follicle pool.[7,8] Tubal ligation may cause a disruption in the ovarian vascular blood supply which may lead to diminished levels of sex steroid hormones produced by the ovaries.[9] Alternatively, particular methods of TL may cause damage to the surrounding neural tissues and ovary.[10,11] As such, it has been hypothesized that the procedure may have negative impacts on ovarian function and reserve.

Anti-Müllerian hormone (AMH) is produced in granulosa cells of developing ovarian follicles.[12] In premenopausal women, AMH is released in measurable serum levels that have been shown to be correlated with the number of developing follicles.[12] Recently, AMH has become an established marker for the timing of menopause[12,13] and was found to be strongly associated with risk of early menopause.[14] Yet, the association of reproductive and lifestyle factors with AMH levels remains unclear.[15] Short-term use of OC's is thought to have a decreasing, yet reversible, effect on AMH levels;[16–19] however, some studies have observed no impact of current OC use on AMH levels.[20–22] Much less is understood about the AMH levels of long-term OC users[17,18,23,24] and women who have had a tubal ligation procedure.[25–27] We therefore assessed the association of OC use and TL with AMH in the Nurses' Health Study II (NHSII) population-based cohort.

METHODS

Study population

The NHSII is a prospective cohort study established in June 1989 when 116,429 female registered nurses aged 25 to 42 years responded to a baseline questionnaire. Cohort members have completed questionnaires every two years to identify new diagnoses of disease and update information on health-related behaviors.[28] From 1996 to 1999, cohort members who were not previously diagnosed with cancer were invited to provide self-collected blood samples. The methods for the NHSII blood cohort have been previously documented in detail.[29] Briefly, over 29,000 participants provided blood samples, of which ~23,000 were premenopausal. Upon receipt, samples were centrifuged, separated into blood components, and archived at −130°C or colder in continuously monitored liquid nitrogen freezers. For the present analysis, we included 642 premenopausal women who were controls in a nested case-control study of early menopause[14] and 800 additional premenopausal women selected for a separate analysis of change in AMH and menopause timing. Participants included in the present analysis experienced menopause at age 45 or later.

Laboratory assays

Current evidence suggests that intra- and inter-cycle variation in AMH is relatively low in healthy, ovulating women[30,31] thus, AMH levels were measured in a single luteal phase or untimed blood sample. Assays were conducted in 2015 and 2018 at Children's Hospital, Boston, MA by an ultra-sensitive ELISA assay from ANSH Laboratories (picoAMH; Webster, TX), using a quantitative sandwich enzyme immunoassay technique. The day-to-day variabilities of the assay at concentrations of 0.023, 0.087 and 0.373 ng/ml were 5.8%, 3.2% and 4.3%, respectively. The coefficient of variation (CV) from samples from a blinded plasma pool assayed alongside NHSII analytic samples were 8.6% for the nested case-control samples and 17.4% for the additional 800 samples.

Assessment of oral contraceptive use and tubal ligation

At baseline, participants self-reported each OC brand they used for two months or more and for 10 months or more for each year of age from 13 to 42 years. From 1991 through blood collection, biennial questionnaires asked participants to indicate the duration of oral contraceptive use during the past two years, with the following response categories: 1 month or less, 2–4, 5–9, 10–14, 15–19, or 20–24 months. Tubal ligation was assessed every two years through blood collection by asking participants if they currently used TL as a form of contraception. In 1993, participants reporting a history of TL were asked to indicate age at TL as follows: <25, 25–29, 30–34, 35–39, 40–44, 45+. After 1993, age at TL was derived from age at the biennial questionnaire. In 1997, participants were asked to report the type of their TL procedure as follows: Cautery/Coagulation, Ligation, Clip/ring/band, Other/don't know.

Covariates

At the time of blood collection, participants provided information on current weight, exogenous hormone use, alcohol use, and smoking status. Information on demographic and

other factors was obtained from the biennial questionnaires. Age at menarche, race/ethnicity, and height were reported in 1989. Body mass index was calculated using height reported at baseline and weight reported at blood collection. Age, pregnancy history, number of cigarettes smoked per day, and infertility due to ovulatory disorder were assessed every two years. Cumulative breastfeeding was measured in 1993 and 1997 among all cohort members, and one subsequent measurement was ascertained for women reporting pregnancies after 1997. For all time varying covariates, we used data measured closest in time to each individual's date of blood collection.

Statistical analysis

Participant characteristics were examined according to measures of OC duration at blood collection using age-adjusted generalized linear models. We evaluated associations of OC use and AMH by modeling cumulative duration of OC use at the time of blood collection and age at first OC use. For the association of TL and AMH we examined history of TL, age at TL, and type of TL procedure.

To control for potential confounding, we created two multivariable models: model 1, adjusted for age (squared), sample type (control from nested case-control study of early menopause, from additional sample of premenopausal women), and blood collection factors (fasting status, season of blood collection, and luteal day); and model 2, additionally adjusted for age at menarche (≤11, 12, 13, 14, ≥15 years), smoking status (current, not current), smoking pack years (continuous), alcohol intake (0, <1, 1, >1 drink/day), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), parity (0, 1, 2, 3+), cumulative total breastfeeding (0-<1, 1–12, 13–24, >24 months, breastfeeding data missing), and infertility because of ovulatory disorder (no, yes). Models were mutually adjusted for OC duration (1–23, 24–47, 48–71, 72–95, 96–119, ≥120 months) and TL (no, yes) as appropriate.

We limited analyses of OC use, TL and AMH levels to women not using exogenous hormones within six months of blood collection (n=1,420), as current hormone use may temporarily decrease AMH.[32,33] For our OC models, we further limited to participants with complete data on duration of OC use (n=1,398) and for our TL models, we included participants with reported history of whether a TL procedure had been performed (n=1,419). We used general linear models to compare means of log transformed AMH levels by OC use and TL characteristics, and then back transformed estimates for interpretability. Linear trends were assessed by modeling category medians for duration of OC use, age at first OC use, and age at TL. We also assessed statistical differences between each exposure category and the referent category of either no OC use or no TL depending on the model. All statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Participant characteristics by categories of OC duration for 1,420 premenopausal participants aged 32 to 49 at the time of blood collection are shown in Table 1. At blood collection, participants who had the longest duration of OC use had the highest levels of smoking pack-years, the lowest mean parity, the lowest mean cumulative duration of total

breastfeeding, and were youngest at first use of OCs (mean [SE] age 18.7 [0.29]). Nineteen percent of participants (n=276) had a self-reported TL procedure (Table 2).

Results of AMH analysis are shown in Table 2. In fully adjusted models evaluating duration of OC use, geometric mean AMH levels demonstrated a significant dose-response relationship (*P* for trend = .036). We did not observe trends in AMH levels by age at first OC use or age at TL nor were AMH levels different by overall occurrence of TL. However, women who reported that their TL procedure included the use of a clip, ring, or band had significantly lower AMH levels compared to women who never had a TL procedure (1.05 vs. 1.72 ng/ml, p<.01). Results from sensitivity analyses that excluded women with infertility due to ovulatory disorder and women with AMH levels above the threshold established by Iliodromiti et al.[34] for polycystic ovary syndrome (PCOS) screening were nearly identical (results not shown).

DISCUSSION

To our knowledge, this is the largest study to date examining the association of both OC use and TL with AMH levels among premenopausal women. We observed a significant, inverse association between duration of OC use and mean AMH levels. Furthermore, women whose fallopian tubes were blocked by a clip, ring, or band had significantly lower AMH levels compared to women who never had a TL. We did not find associations of age at first OC use or age at TL with mean AMH levels.

Among studies that examined long-term duration of OC use and AMH serum levels, results have been mixed. In a large population-based cohort, Dolleman et al. observed a significant negative relation of AMH with OC use, with levels −8.8 percentiles lower among women who used OCs for >20 years compared to women who used OC's for <1 year.[17] In a cross-sectional analysis of more than 700 healthy women from Denmark, Bentzen et al. observed the suggestion of an inverse linear association of duration of OCs and AMH levels, but the trend was not significant.[35] More recent studies found no significant effect of duration of OC use on AMH levels.[18,23,24]

We recently examined the association of OC use and risk of early menopause in the full NHSII cohort[36] and, although we observed a significant trend of increasing risk associated with longer duration of OC use in our age-adjusted models (*p* for trend=0.003), results were substantially attenuated and non-significant in our fully adjusted models (*p* for trend=0.71). In our AMH analysis, the pattern of attenuation was similar to our early menopause analysis, although our final AMH model remained significant.

Similar to our findings, a recent examination among 1,643 African American women in the Study of the Environment, Lifestyle and Fibroids (SELF) found that age at first use of hormonal contraceptives was not associated with AMH levels.[18] Although our examination of age of first use of OCs did not demonstrate a significant trend, AMH levels for women who began using OCs in their thirties were notably lower than women who began using OCs at an earlier age. We hypothesize that these lower AMH values may be due to confounding

by indication, as women who initiate the use of OCs in their later reproductive years may do so for the management of perimenopausal menstrual irregularities.[37]

Two previous studies that examined AMH levels 3 months[25] and 12 months[26] after the TL procedure, did not observe differences between their pre- and post- operative AMH levels (p=0.079 and p=0.23, respectively).[25] In our study, AMH levels were significantly lower for women with TL involving the blocking of the fallopian tube with a clip, ring, or band compared to women who never had the procedure; however, we caution the interpretation of these results as only 32 women (11%) reported this type of TL procedure and type was unknown for one-third of women who reported a history of TL. A previous study comparing postoperative AMH levels by type of tubal ligation suggested that TL by electrocoagulation may have an adverse effect on ovarian reserve, but not mechanical clips.[27]

Our study has several limitations. While much of our OC use data was collected prospectively, information on use during the early reproductive years was collected retrospectively at baseline, which could lead to some misclassification. However, the accuracy of retrospectively reported OC use and duration has been previously validated in the NHSII cohort.[38] Among a randomly selected sample of 215 participants OC data collected via the baseline questionnaire was compared to data collected during a subsequent, detailed interview. Agreement for a history of ever having used OCs was high (exact agreement 99%), reported durations of use were equivalent (Spearman correlation=0.94, p=0.0001), and medical records confirmed a high proportion of the formulations and doses reported (71% to 80%). Although we had complete history of TL for all but one of our participants and prior validation studies have suggested that women have good recall of history of TL,[39,40] misclassification is possible. Age at tubal ligation was reported in 5-year categories or derived from the biennial questionnaires; as such, we were unable to analyze the exact length of lapsed time from the procedure to AMH blood collection. However, 37% of our participants who had a TL reported the history at baseline meaning that the procedure was performed at least 7 to 10 years prior to the assessment of AMH. Furthermore, potential misclassification of TL procedure type is also a limitation as well as not knowing if women had their TL procedure at the time of a cesarean delivery, during the postpartum period, or at another time which may possibly contribute to the impact on ovarian reserve.[41] Serum samples used in our study were stored anywhere from 16 to 22 years prior to being assayed; however, long-term stability of AMH has been observed when very cold storage temperatures are used and freeze/thaw cycles are avoided,[42] which is true of blood stored in the NHSII Biorepository.[28] Additionally, the overall CV of 17.4% for our second assay was modestly higher than we would expect, yet, any misclassification resulting from lab error would be non-differential with respect to OC and TL and would not contribute to the observed association. Lastly, our population is fairly homogenous with respect to race and ethnicity and examination of AMH levels by race/ethnicity has shown variability in AMH levels among women of different racial and ethnic backgrounds.[43–45] While we would not expect the use of OCs or having a TL procedure to influence AMH levels differently by race or ethnicity, further examination in more diverse populations is important.

CONCLUSION

In this large, population-based study that included over 1,400 premenopausal women we observed a significant, inverseassociation of duration of OC use and AMH levels and significantly lower levels of AMH for women who had a TL procedure that involved the use of a clip, ring, or band. Further research is warranted to confirm the long-term association of these widely used contraceptive methods with AMH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding:

The study was sponsored by UO1CA176726 and R01HD078517 from the National Institutes of Health and Department of Health and Human Services. The work was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Financial Disclosures/Conflicts of Interest:

Lynette Leidy Sievert is supported by an NSF grant. The other authors have nothing to disclose.

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Table 1.

Age-adjusted Characteristics of 1,420 Participants by Oral Contraceptive Duration at Blood Collection, Nurses' Health Study II, 1996–1999

Characteristic[b]	Never (n=277)	[a]OC use 1–23 mo (n=275)	OC use 24–71 mo (n=462)	OC use 72–119 mo (n=238)	OC use ≥120 mo (n=146)	*P* Value
Age, y[c]	39.1 (2.7)	39.4 (2.8)	38.9 (3.0)	39.2 (3.2)	39.4 (2.8)	<0.001
Non-Hispanic white, %	95.3	96.8	96.7	96.7	97.3	0.79
Body mass index	25.2 (.29)	24.7 (.30)	24.5 (.23)	24.9 (.32)	24.2 (.41)	0.30
Alcohol >1 drink/day, %	2.9	1.7	2.5	3.7	4.7	0.52
Current smoker, %	2.5	7.6	6.5	10.9	9.5	<0.01
Smoking, pack-years[d]	8.4 (1.00)	7.8 (.86)	10.0 (.65)	9.9 (.79)	12.1 (.95)	<0.05
Age at menarche, y	12.5 (.08)	12.6 (.08)	12.5 (.07)	12.4 (.09)	12.6 (.12)	0.25
Age at first OC use, y	N/A	21.8 (.21)	20.9 (.16)	19.4 (.23)	18.7 (.29)	<0.001
Infertility due to ovulatory disorder, %	6.1	4.0	10.0	5.0	6.8	<0.05
Parity	1.8 (.07)	2.1 (.07)	1.9 (.05)	1.8 (.08)	1.4 (.10)	<0.001
Breastfeeding, mo[e]	22.6 (.98)	21.2 (.90)	18.9 (.71)	13.2 (.96)	10.7 (1.32)	<0.001
Tubal ligation, %	14.2	21.8	20.5	29.7	20.2	<0.001

Abbreviation: OC, oral contraceptive.

[a]Women with missing duration of OC use at blood collection (n=22) are not shown.

[b]Values are age-adjusted means (SE) unless otherwise indicated.

[c]Values are expressed as unadjusted means (SD).

[d]Among past or current smokers.

[e]Among parous women.

Table 2.

Oral Contraceptive Use and Tubal Ligation History at the Time of Blood Collection and Geometric Mean AMH (ng/ml) Levels, Nurses' Health Study II

		Model 1[a]	Model 2[b]
	N[c]	AMH GM (95% CI)	AMH GM (95% CI)
Duration of oral contraceptive use, mo[d]			
Never (referent)	277	1.90 (1.69–2.16)	1.88 (1.65–2.14)
1–23	275	1.84 (1.62–2.08)	1.79 (1.57–2.04)
24–47	279	1.72 (1.51–1.94)	1.70 (1.51–1.94)
48–71	183	1.62 (1.39–1.90)	1.59 (1.37–1.86)
72–95	148	1.50 (1.26–1.79)[f]	1.56 (1.31–1.84)
96–119	90	1.50 (1.19–1.86)	1.56 (1.25–1.94)
120+	146	1.51 (1.26–1.79)[f]	1.60 (1.34–1.90)
P Value for Trend		.002	.036
Age at first oral contraceptive use, mo[d,e]			
Never (referent)	277	1.90 (1.69–2.16)	1.75 (1.51–2.04)
13–17	183	1.57 (1.35–1.84)	1.74 (1.48–2.06)
18–19	336	1.67 (1.50–1.88)	1.77 (1.57–2.00)
20–21	243	1.60 (1.39–1.84)	1.60 (1.39–1.84)
22–23	162	1.79 (1.51–2.10)	1.77 (1.51–2.10)
24–29	155	1.69 (1.42–2.00)	1.60 (1.35–1.90)
30–34	25	1.45 (0.95–2.21)	1.37 (0.90–2.08)
≥35	7	1.57 (0.71–3.50)	1.21 (0.51–2.86)
Age, unspecified	10	1.59 (0.82–3.10)	1.57 (0.80–3.04)
P Value for Trend		.83	.09
Tubal ligation[e]			
No (referent)	1123	1.72 (1.62–1.84)	1.72 (1.62–1.83)
Yes	296	1.64 (1.45–1.84)	1.64 (1.44–1.84)

		Model 1[a]	Model 2[b]
	N[c]	AMH GM (95% CI)	AMH GM (95% CI)
Age at tubal ligation[e]			
No (referent)	1123	1.74 (1.62–1.84)	1.72 (1.62–1.83)
<25	7	2.34 (1.06–5.22)	2.44 (1.10–5.43)
25–29	60	1.60 (1.22–2.10)	1.59 (1.20–2.08)
30–34	129	1.62 (1.35–1.94)	1.60 (1.33–1.94)
35–39	77	1.65 (1.30–2.10)	1.69 (1.33–2.14)
≥40	16	1.34 (0.79–2.28)	1.34 (0.79–2.28)
Age, unspecified	7	2.14 (0.96–4.72)	1.90 (0.86–4.23)
P Value for Trend		.72	.91
Type of tubal ligation[e]			
No (referent)	1123	1.74 (1.62–1.84)	1.72 (1.62–1.83)
Cautery/Coagulation	66	2.00 (1.54–2.59)	2.08 (1.60–2.72)
Ligation	103	1.69 (1.37–2.08)	1.65 (1.34–2.04)
Clip/ring/band	32	1.05 (0.73–1.54)[f]	1.04 (0.72–1.51)[g]
Other/don't know	95	1.59 (1.29–1.98)	1.59 (1.27–1.98)

Abbreviation: AMH, anti-Müllerian hormone; GM, geometric mean; ng/ml, nanograms per milliliter; OC, oral contraceptives; TL, tubal ligation.

[a] Adjusted for age (squared), fasting status, season of blood collection, luteal day, paired sample (no, yes).

[b] Additionally adjusted for age at menarche (≤11, 12, 13, 14, ≥15 years), smoking (current, not current), smoking pack years (continuous), alcohol (0, <1, 1, >1 drink/day), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), parity (0, 1, 2, 3+), total breastfeeding (0-<1, 1–12, 13–24, >24 months, breastfeeding data missing), and infertility because of ovulatory disorder (no, yes).

[c] Due to missing exposure data 1,398 participants are included in the OC models and 1,419 participants included in the TL models.

[d] Model 2 additionally adjusted for tubal ligation (no, yes).

[e] Model 2 additionally adjusted for OC duration (category medians).

[f] p<0.05

[g] p<0.01