Received: 14 August 2020 | Revised: 25 April 2021 | Accepted: 10 July 2021

DOI: 10.1002/nop2.1011

RESEARCH ARTICLE

NursingOpen Open Access WILEY

Correlations among anti-Müllerian hormone levels, body mass index and lipid profile in reproductive-aged women: The Korea Nurses' Health Study

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Funding information
The KNHS received financial support to conduct research from the KCDC at the Korea National Institute of Health. This research was supported by a grant (2016ER630500, 2016ER630501) or research from the KCDC

Abstract

Aim: This study aimed to evaluate the correlations among anti-Müllerian hormone levels, body mass index and lipid profile in female nurses of reproductive age.

Design: This is a descriptive cross-sectional study that used data from the Korea Nurses' Health Study, based on Nurses' Health Study 3 in the United States.

Methods: Participants included 448 female nurses of reproductive age. They provided details about their work experience, shift work, body mass index and history of polycystic ovary syndrome. Serum anti-Müllerian hormone levels and lipid profile were measured using blood samples. Statistical analysis included quantile regression analysis using STATA 13.0. Data were collected between November 2016 and March 2017 from Module 5 of the Korean Nurses' Health Study.

Results: Approximately 12% of the participants were underweight, and roughly one-tenth were either overweight or obese. Although linear regression showed no relationship between anti-Müllerian hormone levels and body mass index, quantile regression showed that body mass index, total cholesterol levels and low-density lipoprotein levels were negatively correlated with anti-Müllerian hormone levels at the lower tails of the dependent variable. Meanwhile, high-density lipoprotein levels were positively correlated with anti-Müllerian hormone at the higher percentiles of anti-Müllerian hormone levels.

Conclusion: These findings suggest the possibility that changes in the lipid profile may influence anti-Müllerian hormone levels in women with diminished ovarian function, rather than obesity itself.

KEYWORDS

anti-Müllerian hormone, body mass index, lipids, the Korea Nurses' Health Study

Clinical trial information: Clinical Research Information Service KCT0001011.

1 | INTRODUCTION

Increased age at first marriage due to social participation by women has become a major cause of infertility, and approximately 8%–12% of women worldwide struggle with infertility (Barut et al., 2016). Infertility is associated with ovarian reserve, which refers to the reproductive potential of a woman considering the quantity and quality of her ovarian follicles (Gleicher et al., 2011). As ovarian reserve cannot be fully determined by chronological age alone, various biochemical markers and imaging-based diagnostic tests are being used (Broekmans et al., 2006).

Recently, South Korea has been known as the country with the world's lowest fertility rate. The country's fertility rate decreased by 0.98 children per women in 2018 compared to 1.24 children in 2015. Consequently, the Korean government has implemented policies to resolve the low fertility rate. As a part of the effort, the authority provides financial support for infertility treatment. According to Statistics Korea, the prevalence of infertility in married women aged 15–49 years was 12.1% in 2015–2018. During the same period, 63.8% of women and men received infertility services from healthcare professionals (Statistics Korea, 2019). Women comprise over 95% of the nursing workforce in Korea, the majority of which are of reproductive age (Korea Institute for Health & Social Affairs, 2018). Therefore, nurses would be a valuable population for a female cohort because of their high interest in health, knowledge about medical conditions and the presence of a registration system (Kim et al., 2017).

Anti-Müllerian hormone (AMH) is recognized as a marker with the most outstanding sensitivity and specificity for ovarian reserve because it undergoes changes during early age and has less fluctuations according to the menstrual cycle than do conventional ovarian reserve markers such as follicle-stimulating hormone (FSH), oestradiol (E2) and inhibin B (Rustamov et al., 2014). AMH levels are influenced by various factors, including environmental factors such as obesity (Bernardi et al., 2017), oral contraceptive use (Dólleman et al., 2013), menstrual irregularity (Dólleman et al., 2013), smoking (White et al., 2016), vitamin D deficiency (Dastorani et al., 2018) and socio-economic status (Barut et al., 2016), as well as some genetic factors (Shahrokhi et al., 2018; Tal & Seifer, 2013).

With the association between obesity and female reproductive health receiving much attention recently, various studies have been conducted to explore the association between AMH and body mass index (BMI). However, such studies have reported conflicting results, with some reporting a negative correlation between AMH and BMI (Bernardi et al., 2017; Moy et al., 2015; Steiner et al., 2010), whereas others reporting no statistically significant associations (Albu & Albu, 2019; Dólleman et al., 2013; Steiner et al., 2017). Moreover, several previous studies regarding AMH had mostly focused on infertility patients and did not include biochemical markers such as lipid profile, making it difficult to comprehensively identify variability in hormone levels due to fat accumulation.

Therefore, this study aimed to investigate the factors affecting AMH levels in female nurses of reproductive age and to specifically identify the correlations among AMH levels, BMI and lipid profile. This study's results may suggest future directions for the improvement of nurses' reproductive health and their occupational environment.

2 | BACKGROUND

Since its first discovery during the early 1990s, AMH has been used as a major indicator for women's reproductive potential as it can account for the number of remaining ovarian follicles. AMH is produced by the ovarian granulosa cells at around 36 weeks of gestational age and reaches peak levels at around 25 years of age. The level of secretion continues to decrease with age and is no longer detectable at menopause (Dólleman et al., 2013; Kelsey et al., 2011).

Clinically, AMH is widely used for predicting oocyte yield during in vitro fertilization (IVF). Particularly in cases with very low levels of AMH (<1 ng/ml), a more aggressive protocol is recommended for ovarian stimulation, while having a high oocyte yield has been reported to increase the likelihood of conception and normal childbirth (Iwase et al., 2015; Santoro, 2017; Yoo et al., 2011). As AMH decreases rapidly over approximately 5 years prior to menopause, it is also used as a predictor of premature ovarian failure and onset of menopause (Santoro, 2017).

Obesity can cause negative reproductive health outcomes including anovulation, infertility, miscarriage and adverse pregnancy (Talmor & Dunphy, 2015). Compared with non-obese women, obese women have a higher incidence of menstrual disorders and anovulation and have a poorer oocyte yield and quality during IVF. Moreover, obese women have a lower success rate for natural conception and conception with assisted reproductive technology and a higher risk of miscarriage and birth defects (Dağ & Dilbaz, 2015; Pandey et al., 2010). It has been reported that obese women exhibit alterations in their ovarian follicular environment, which causes a negative impact on AMH production (Bernardi et al., 2017). However, the underlying physiological mechanism has not been clearly identified, while conflicting study results on the association between AMH levels and BMI have been reported. On the other hand, previous studies on ovarian function and cardiovascular disease have shown that women with diminished ovarian function have higher total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), C-reactive protein (CRP), fasting glucose and homeostatic model assessment for insulin resistance (HOMA-IR) and lower high-density lipoprotein (HDL) level than women with normal ovarian function (Tehrani et al., 2014; Verit et al., 2016, 2017), suggesting a possible association between AMH and changes in the endocrine environment, including the lipid profile. Despite the strong association between obesity and lipid profile, however, very few studies have comprehensively identified the associations among AMH levels, BMI and lipid profile. Studies on healthy reproductive-aged women with a low obesity rate are even more rare. Accordingly, this study analysed data from the Korea Nurses' Health Study (KNHS) to explore the correlations among AMH levels, BMI and lipid profile in female

nurses of reproductive age and find a basis for enhancing the reproductive health of women of childbearing age. This study aimed to answer the following research questions: (a) What are the factors affecting AMH levels in Korean nurses of reproductive age? (b) Are there correlations among AMH levels, BMI and lipid profile?

2.1 | Design

This is a descriptive cross-sectional study that analysed data from the KNHS, which is a prospective cohort study of female nurses of reproductive age.

2.2 | Methods

2.2.1 | Setting and participants

The KNHS is the first large-scale cohort study in Korea, based on the Nurses' Health Study 3 (NHS3) in the United States (Kim et al., 2017). The KNHS is funded by the Korea Centers for Disease Control and Prevention (KCDC) of the Korea National Institute of Health (KNIH). It began as a web-based questionnaire survey in 2013 with 20,613 participants, and follow-up online surveys have been conducted at every 6–8-month intervals. The inclusion criteria for the surveys were female Registered Nurses aged 20–45 years, who were actively working in a hospital for more than one year in South Korea at the time of the baseline survey (module 1). Female Registered Nurses who were not working at a hospital due to being on temporary or sick leave or having resigned from work were also allowed to participate as long as they had experience working in a hospital in the past year. Blood samples were collected from 2,000 participants from November 2016–March 2017 in module 5. Sampling for AMH was based on population parameters, and simple random sampling was employed. To calculate the sample size, G* power (Faul et al., 2007) was used; a needed sample size of 157 participants was determined after applying a medium effect size of 0.15, power of 0.80, significance level of 5% and 20 predictors.

2.2.2 | Measures

The KNHS surveys comprised 112 items in 11 categories, which included demographic characteristics, anthropometric measures, health screening, illness, family history, health behaviour, lifestyle and diet, reproductive health, pregnancy, mood and subjective health perception, employment, and occupational exposure. Multidisciplinary experts in the research team translated and back-translated the fifth survey of NHS3. Expert opinions of a multidisciplinary advisory board were used to test the reliability of the edited questionnaires. The advisory board consisted of experts from the fields of epidemiology, statistics, nutrition, public health and nursing. The questionnaire items were mostly consistent with those in the NHS3, while some items were modified to be more suitable for Korea. For example, questions related to shift work were modified because the shift work patterns in Korea differ from those in the United States. In Korea, hospitals do not implement 12-hr shifts or fixed duties. Overall values of Cronbach's alpha of entire module 5 ranged from .74–.92.

Among the data extracted from KNHS, this study analysed demographic characteristics (age, educational level, work experience and rotational shift work), BMI (based on self-reported values), diagnosis of polycystic ovary syndrome (PCOS) and haematological parameters (AMH, TC, HDL, LDL and TG).

2.2.3 | Data collection procedure

Among the 11,620 nurses who participated in module 5 of the KNHS between November 2016–March 2017, this study randomly selected and analysed a total of 448 nurses who did not have any missing data for major research variables and blood test results, including AMH levels. Module 5 used in this study did not include any questions regarding the diagnosis of PCOS; thus, the diagnosis status was verified through ID matching based on module 3, which included such questions.

2.2.4 | Assays

Blood samples were collected on a random day of the menstrual cycle. AMH was measured in serum obtained after centrifugation and aliquoted, frozen at −20°C on the same day of collection and stored for batch analysis. All samples were analysed under the same conditions on the same day.

A commercial enzyme-linked immunosorbent assay kit (AMH Gen II ELISA Kit; Beckman-Coulter) was used to perform an enzymatically amplified two-site immunoassay for detecting AMH, according to the manufacturer's instructions. For this assay, the inter-assay imprecision with coefficient of variation was reported as <11.9% at levels >2.2 ng/ml. The inter- and intra-assay imprecision were reported as 11.4% and 17.3%, respectively (Wheeler, 2013), and the limit of detection was 0.08 ng/ml.

For the Elecsys® AMH automated assay, the intra- and inter-assay coefficients of variation were reported as 0.5%–1.4% and 0.7%–1.9%, respectively, and the limit of detection was 0.08 ng/ml.

2.3 | Analysis

Data were analysed using STATA 13.0 in the following manner. Due to the characteristic of AMH levels being skewed to the right instead of showing a normal distribution, haematological parameters, including AMH levels, were analysed by medians and quartiles. Differences in AMH levels according to general characteristics, including BMI category (underweight, normal, overweight or obese), were analysed

by non-parametric methods (Wilcoxon rank-sum test and Kruskal–Wallis rank test), while correlations between AMH levels, BMI (kg/m^2) and lipid profile were analysed by quantile regression analysis.

Although a multiple linear regression is useful for examining the average influence of independent variables on changes in the dependent variables, it has its statistical limitations for a dependent variable with non-normal distribution (Wyka et al., 2017), such as AMH in this study. Accordingly, quantile regression was used to overcome such limitations by analysing correlations with independent variables at all points on the dependent variable distribution. In other words, quantile regression demonstrates various possibilities with outliers, in regions that deviate from the mean, allowing for understanding relationships between variables outside of the mean. Lê Cook and Manning (2013) emphasized the unique advantages of quantile regression in relation to assessing medical services. They also stated that the group with the highest medical resource utilization and medical expenditure is not the average group and that identifying information about such group is difficult with linear regression, and even if results are derived, there is a high likelihood of such relationships being over- or underestimated. Accordingly, this study considered the non-normal distribution of AMH levels and used quantile regression to analyse the correlations between AMH levels, BMI and lipid profile at different percentiles of AMH levels.

2.4 | Ethics

The KNHS was approved by the Institutional Review Board (IRB) of Ewha Womans University (IRB No. 117-4). Informed consent was obtained via online forms from all participants who voluntarily agreed to participate prior to initiation of the online or mobile survey, and their anonymity and confidentiality were guaranteed in compliance with the Declaration of Helsinki.

3 | RESULTS

3.1 | Differences in AMH levels according to general characteristics

The differences in AMH levels according to the general characteristics of participants are shown in Table 1. Among the 448 participants, the age group of 25–29 years had the greatest proportion of participants (N = 180, 40.2%), and as suggested in previous studies, AMH levels tended to decrease with age ($p \leq .001$). Moreover, AMH levels showed significant correlations with educational level ($p = .021$) and work experience ($p \leq .001$). Rotational shift work accounted for 80.4% of all work types, and AMH levels were higher among shift workers than among non-shift workers ($p \leq .001$).

TABLE 1 Associations between general characteristics and anti-Müllerian hormone (N = 448)

Characteristics		*N* (%)	Median (IQR)	*p*
Age (years)	≤24	6 (1.3)	3.645 (3.215–4.502)	<.001
	25–29	180 (40.2)	4.605 (2.860–6.485)	
	30–34	152 (33.9)	3.680 (2.270–5.428)	
	35–39	96 (21.5)	2.580 (1.435–4.195)	
	≥40	14 (3.1)	1.045 (0.633–2.978)	
Education	3-year college	97 (21.7)	3.640 (2.130–5.540)	.021
	4-year college	302 (67.4)	3.990 (2.320–5.630)	
	Master's degree or higher	49 (10.9)	2.840 (1.408–4.525)	
Work experience (years)	Less than 3	7 (1.6)	5.240 (3.193–7.210)	<.001
	≥3, less than 5	102 (22.8)	4.685 (3.328–6.933)	
	≥5, less than 10	190 (42.4)	4.020 (2.252–5.633)	
	≥10	149 (33.3)	2.860 (1.540–4.255)	
Shift work in preceding year	Yes	360 (80.4)	4.030 (2.380–5.660)	<.001
	No	88 (19.6)	2.850 (1.498–4.480)	
Night shift in preceding year (N = 360)	Yes	325 (90.3)	4.110 (2.520–5.770)	.003
	No	35 (9.7)	3.120 (1.190–4.560)	
Body mass index (kg/m^2)	<18.5 (underweight)	52 (11.6)	3.600 (2.163–5.245)	.559
	18.5–22.9 (normal)	299 (66.7)	3.860 (2.380–5.530)	
	23–24.9 (overweight)	50 (11.2)	3.345 (1.596–5.470)	
	≥25 (obese)	47 (10.5)	3.640 (2.010–5.240)	
PCOS	Yes	29 (6.5)	5.770 (3.635–10.085)	<.001
	No	419 (93.5)	3.640 (2.130–5.300)	

Abbreviations: IQR, interquartile range; PCOS, polycystic ovary syndrome.

Moreover, among rotational shift workers, 90.3% responded that they worked night shifts, and those who worked night shifts showed higher AMH levels than those who did not ($p = .003$). Such results may be due to the fact that the percentage of non-shift workers and those who work during weekdays is higher among relatively older age groups in Korea (Kim & Jo, 2013; Son & Ham, 2018). BMI was classified as underweight (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2) and obese (≥25 kg/m^2), according to the 2000 World Health Organization (WHO) Asia-Pacific classification.

3.2 | Lipid profile

The study population was divided into those diagnosed with PCOS ($N = 29$, 6.5%) and those who were not diagnosed with PCOS ($N = 419$). The sample included 419 women who were not diagnosed with PCOS but reported various health histories (1 cervical cancer, 9 endometriosis, 4 oophorectomy, 9 oral contraceptive use and 5 other contraceptive hormone therapies).

The results of analysing the lipid profiles of both groups are shown in Table 2. No statistically significant differences in the lipid profile were observed according to the diagnosis of PCOS.

3.3 | Correlations among AMH levels, BMI and lipid profile

Table 3 shows the results of analysing the correlations among AMH levels, BMI and lipid profile by each independent variable using quantile and linear regression analyses. Because patients diagnosed with PCOS are at risk of disturbance of serum lipids, they were excluded, and only data from 419 participants without PCOS were analysed.

Age showed negative correlations with all except the 3rd percentile of AMH levels, while BMI showed a negative correlation with the 20th percentile ($\beta = -.087$, $p = .04$) of AMH levels. TC levels were found to have an influence at the 10th ($\beta = -.008$, $p = .03$) and 20th percentiles ($\beta = -.008$, $p = .04$) of AMH levels, while LDL showed a negative correlation with the 20th percentile ($\beta = -.009$, $p = .03$) of AMH levels. Meanwhile, HDL showed positive correlations with the 50th ($\beta = .02$, $p = .04$), 90th ($\beta = .095$, $p < .01$) and 97th percentiles ($\beta = .200$, $p < .01$) of AMH levels. TG showed no statistically significant correlations with AMH levels at all percentiles. In the linear regression analysis, only age ($\beta = -.216$, $p < .001$) and HDL levels ($\beta = .024$, $p = .02$) showed significant correlations with AMH levels.

4 | DISCUSSION

This study on healthy reproductive-aged nurses showed that AMH levels had negative correlations with BMI, TC and LDL levels at the 10–20th percentiles of AMH levels and positive correlations with HDL levels at the 50th, 90th and 97th percentiles of AMH levels. Such findings partially support the negative correlation between AMH levels and BMI in women with diminished ovarian function and suggest the possibility that changes in the lipid profile influenced the AMH levels, rather than obesity itself. A previous study of infertile women also showed similar results on the correlation between AMH levels and BMI (Buyuk et al., 2011). In that study, 290 infertile women were divided into groups with normal ovarian function ($N = 138$) and diminished ovarian function ($N = 152$) based on serum FSH levels. In the group with diminished ovarian function, AMH levels were lower by 33% in women who were overweight or obese (BMI ≥25 kg/m^2) than in normal-weight women. In the group with normal ovarian function, however, no statistically significant association was found between AMH levels and BMI. Among the study participants, 109 women actually underwent a controlled ovarian hyperstimulation cycle during IVF, of which 58 women with diminished ovarian function showed a negative correlation between BMI and oocyte yield, whereas women with normal ovarian function showed no correlation between both variables (Buyuk et al., 2011).

Our findings provide more detail than some previous studies which reported a negative correlation between AMH levels and BMI. A cohort study of 1,654 community-dwelling African American women aged 23–35 years showed that AMH levels were lower by 23.7% in obese women (BMI ≥30 kg/m^2) than in normal-weight and underweight women (BMI <25 kg/m^2) and that not only current BMI but also BMI and maximum weight at age of 18 years were also negatively correlated with AMH levels (Bernardi et al., 2017). Similarly, a study by Steiner et al. (2010) examined the effects of oral contraceptives on AMH levels in women aged 18–35 years who had regular menstruation and found that AMH levels were lower by 34% in obese women than in non-obese women. Contrarily, a cohort study conducted in the Netherlands examined 2,320 premenopausal women and found no significant differences in AMH levels according to BMI or waist circumference (Dólleman et al., 2013). Moreover, a study of 2,204 Romanian infertile women showed no statistically significant correlation between BMI and AMH levels, and the age-based subgroup analysis in that study showed that AMH levels increased with higher BMI in women aged ≤35 years (Albu & Albu, 2019).

Regarding the general characteristics of the study population, our sample's mean age of 31.3 years was similar to mean of 28.7 and 29 years as reported by Bernardi et al. (2017) and Steiner et al. (2010), respectively. However, other studies have examined AMH with older participants, for example mean 38 years (Buyuk et al., 2011), 37.3 years (Dólleman et al., 2013) and 34.6 years (Albu & Albu, 2019). Because AMH levels continuously decrease with age, changes in hormone levels according to the risk factors for obesity may be higher in groups with relatively young age.

With regard to subject inclusion and exclusion criteria, the study by Bernardi et al. (2017) excluded patients who had received treatment for cancer or autoimmune diseases, while the study by Dólleman et al. (2013) excluded patients who were undergoing hormone therapy or had a history of ovarian surgery. The study by Albu and Albu (2019) excluded patients who had a history of PCOS, ovarian failure, endometriosis, ovarian surgery or oral contraceptive use. Conversely, as this study included 419 women who were not

TABLE 2 Median values for lipid profile ($N = 448$)

Variables	PCOS ($N = 29$) Median (IQR)	Non-PCOS ($N = 419$) Median (IQR)	*p*	Normal range[a]
TC (mg/dl)	175 (158.5–214)	176 (159–194)	.561	125–200
HDL (mg/dl)	59 (52.5–71)	66 (57–75)	.050	≥50 (women)
LDL (mg/dl)	107 (91–131)	100 (86–118)	.093	<100
TG (mg/dl)	73 (62–112)	69 (56–89)	.186	<150

Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; PCOS, polycystic ovary syndrome; TC, total cholesterol; TG, triglyceride.
[a]Guidelines from U.S. National Heart, Lung, and Blood Institute (2019).

diagnosed with PCOS but had various reproductive health histories, there may be some differences in health-related characteristics between this study and previous studies. However, a strength of this study was that participants were relatively healthy women, belonging to the same occupational group, and as such had more homogeneous traits than participants of other studies.

As there are conflicting results on the association between AMH levels and BMI in previous studies, BMI values of the patients needed to be carefully reviewed. The study population in this study had a relatively low mean BMI of 21.4 kg/m^2, whereas the study by Bernardi et al. (2017) showed a very high median BMI of 32.4 kg/m^2 and the study by Steiner et al. (2010) showed mean BMI values of 37.3 and 21.9 kg/m^2 among obese and normal-weight women, respectively. Meanwhile, the study by Buyuk et al. (2011) showed mean BMI values of 27.3 and 25.3 kg/m^2 among women with normal ovarian function and those with diminished ovarian function, respectively, while studies by Dólleman et al. (2013) and Albu and Albu (2019) showed mean BMI values of 24.3 and 22.4 kg/m^2, respectively. Moreover, the study by Bernardi et al. (2017) also found a negative correlation between current BMI and AMH levels, but when multiple regression analysis was performed according to the BMI categories, a statistically significant correlation was found only in the extremely obese group (BMI ≥45 kg/m^2). Based on these findings, it appears that lipid disturbance above a certain level has an influence on AMH level, but because 89.5% of the study population in this study had a relatively healthy BMI (<25 kg/m^2), the correlation between obesity and AMH levels requires cautious interpretation.

To determine the association between obesity and AMH levels, it is necessary to understand the mechanism by which obesity influences the ovarian follicular microenvironment (Bernardi et al., 2017), but despite significant effort, such mechanism has yet to be clearly identified. One possible mechanism presented to date is increased aromatase activity and oestrogen-to-androgen ratio in obese women interfering with the production of AMH (Steiner et al., 2010). In relation to this, adiponectin has been reported to inhibit ovarian aromatase activity (Ledoux et al., 2006), and obese women are known to secrete relatively less adiponectin than normal-weight women (Parida et al., 2019). Other studies also claimed that insulin resistance in obese women influences ovarian granulosa cells to induce changes in AMH levels (Park et al., 2010). Furthermore, it is suspected that AMH is metabolized, stored and eliminated differently between obese and normal-weight women (Tal & Seifer, 2013). In other words, obesity may cause changes in the ovarian follicular environment; thus, follow-up studies are needed to confirm whether such effect is due to the number or physiology of follicles or dysfunction of granulosa cells (Bernardi et al., 2017).

This study also showed that AMH levels were negatively correlated with TC and LDL levels at the lower percentiles of AMH levels and positively correlated with HDL levels at the higher percentiles of AMH levels. These results indicate the possibility that changes in the lipid profile may have a greater influence on AMH levels in women with diminished ovarian function than obesity itself. There are ongoing studies on the relationship between diminished ovarian function and risk of cardiovascular disease. Menopause due to ovarian ageing increases the risk of cardiovascular disease, and changes in lipid profiles are often observed before and after menopause. It has been found that such changes are more closely associated with the onset of menopause, rather than the chronological age (Mathews et al., 2009). A study by Verit et al. (2016) equally divided 180 infertile women into groups with diminished ovarian function and normal ovarian function to examine the association between ovarian function and risk of cardiovascular disease. The results showed no statistically significant difference in BMI or waist circumference between the groups, but the group with diminished ovarian function had a higher HOMA-IR, CRP, TG and LDL levels and lower HDL levels than the group with normal ovarian function, based on which the AMH level was suggested as a potential marker for risk of cardiovascular disease. Moreover, a study by Tehrani et al. (2014) tracked the risk of cardiovascular disease according to ovarian function over 12 years in 1,015 healthy premenopausal women who had no history of endocrine disease or gynaecological surgery. The results showed that the group with AMH levels belonging to the 1st quartile had a higher margin of increase in TC, fasting glucose and systolic and diastolic blood pressure than the group belonging to the 4th quartile. Similar findings are reported in a study comparing 65 healthy women and 65 women with unexplained infertility; while no differences in BMI, FSH, luteinizing hormone and E2 levels were found, the infertile group showed higher TC, TG, LDL and CRP and lower HDL levels than their healthy counterparts (Verit et al., 2017).

As described, the possible mechanism for the association between diminished ovarian function and risk of cardiovascular disease involves specific factors that can cause atherosclerosis or cardiovascular disease and inhibit ovarian vascularization, whereby ovarian failure and premature ovarian ageing are caused by reduced oxygen

TABLE 3 Quantile regression on the influencing factors of anti-Müllerian hormone ($N = 419$)

Variables	LR	3%	10%	20%	30%	40%	50%	60%	70%	80%	90%	97%
	Coefficient (*p*)											
Age	−.216** (<.001)	−.04 (.14)	−.116** (<.001)	−.128** (<.001)	−.151** (<.001)	−.177** (<.001)	−.198** (<.001)	−.211** (<.001)	−.19** (<.001)	−.226** (<.001)	−.325** (<.001)	−.648** (<.001)
BMI	−.038 (.42)	.12 (.66)	−.039 (.21)	−.087* (.04)	−.075 (.13)	−.082 (.14)	−.034 (.57)	−.009 (.88)	−.019 (.74)	.020 (.71)	−.037 (.71)	−.222 (.38)
TC	.001 (.84)	−.007 (.10)	−.008* (.03)	−.008* (.04)	−.008 (.08)	−.008 (.13)	−.004 (.48)	−.003 (.55)	.000 (.98)	.001 (.85)	.022 (.19)	.46 (.26)
HDL	.024* (.02)	.005 (.56)	−.011 (.22)	.004 (.59)	.007 (.50)	.009 (.50)	.02* (.04)	.009 (.30)	.017 (.12)	.027 (.10)	.095** (<.01)	.200** (<.01)
LDL	−.003 (.58)	−.005 (.20)	−.007 (.15)	−.009* (.03)	−.009 (.09)	−.007 (.20)	−.011 (.13)	−.005 (.50)	−.003 (.55)	−.006 (.48)	.005 (.79)	.014 (.74)
TG	−.002 (.59)	−.001 (.70)	−.004 (.17)	−.000 (.89)	−.000 (.82)	−.002 (.50)	−.003 (.41)	−.001 (.65)	−.002 (.57)	.001 (.80)	.000 (.97)	−.003 (.87)

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LR, linear regression; TC, total cholesterol; TG, triglyceride.
*p value < .05 and **p value < .01.

supply. Another mechanism suggested is that changes in the endocrine environment cause diminished ovarian function, which in turn causes an increased risk of cardiovascular disease. It is also thought that somatic ageing occurs relatively faster in women with diminished ovarian function, which causes an increased risk of cardiovascular disease, including changes in the lipid profile (Verit et al., 2016). In particular, HDL levels and age influenced the AMH levels in this study. HDL is known to prevent cardiovascular disease by reducing oxidation, vascular inflammation and thrombosis and improving endothelial function (Barter, 2011). Therefore, lipid disturbance in reproductive-aged women may affect the ovarian vessels, resulting in diminished ovarian function. Future studies are warranted to identify the effects of changes in lipid metabolism on the synthesis, storage and secretion of AMH.

Recently, there has been growing interest in racial and ethnic disparity in AMH levels. A study by Bleil et al. (2014) in community-dwelling women aged 25–45 years in the United States found that AMH levels appeared to be highest among Caucasian women, followed by Chinese, African American and Latina women in descending order, and that every increase in BMI by 1 unit resulted in a 2.5% decrease in the AMH level. In a study of 350 reproductive-aged women aged 16–46 years, however, while no ethnic disparity in AMH levels was observed, Caucasian women showed a decrease in AMH levels with higher BMI ($\beta = .17$, $p = .01$), whereas African American, Hispanic and Asian women showed no statistically significant association between both variables (Moy et al., 2015). Moreover, a study of 865 infertile women categorized into Afro-Caribbean, South Asian, white European, Middle Eastern and South East Asian subgroups found that South East Asian women had higher AMH levels than white European and Afro-Caribbean women, but after adjusting for confounding factors such as age, BMI, smoking status and PCOS, no difference in AMH levels existed between the ethnic groups (Bhide et al., 2015). These conflicting results could be attributed to imbalance in the sample size for each ethnic group (Bhide et al., 2015; Moy et al., 2015) or differences in the general characteristics of subjects, including BMI and smoking status. This study provided data on relatively healthy, non-smoking Korean women of reproductive age, adding to the gap in the literature. Follow-up studies that explore differences in AMH levels among different ethnic groups will be beneficial, perhaps by pooling existing data from prior studies.

In this study, 6.5% were diagnosed with PCOS, which falls within its reported prevalence of 6%–10% (Bozdag et al., 2016). PCOS women showed significantly higher AMH levels than their healthy counterparts, related to androgens facilitating AMH production in the ovarian granulosa cells (Anderson & Lossl, 2008). A study by Lin et al. (2011) divided 290 women into three groups based on serum AMH levels and prospectively estimated the incidence of PCOS. The results showed that PCOS incidence increased by 21%, 37% and 80% in groups with low AMH (<4 ng/ml), moderate AMH (4–11 ng/ml) and high AMH levels (>11 ng/ml), respectively. Some researchers have noted that elevated AMH levels in women with no gynaecological disease suggest the possibility of potential diseases such as PCOS (Konishi et al., 2014). This study's finding appears to echo

prior associations between PCOS and elevated AMH, but caution is required as the diagnosis of PCOS was inferred from module 3 data, rather than at the time of AMH sampling (module 5 timepoint), which may have resulted in under-identification.

This study has a few limitations. As the mean age of the participants was 31.3 years, the number of women with diminished ovarian function may have been low. Consequently, the statistical power between the variables may have been lower. Moreover, the healthy worker effect, that is healthy individuals have a higher probability of getting hired and maintaining employment (Monson, 1986), may have contributed to the presence of healthy individuals with relatively low disease morbidity in this study population. As a result, the findings may be inconsistent with those of previous studies on infertile women. However, the strengths of this study are that the sample comprised a fairly large cohort of generally healthy, working Korean women of reproductive age. As nurses tend to have more accurate knowledge of medical conditions and an interest in health research, prospective cohort studies such as NHS have provided insights on risk factors for disease prevention and health promotion. In South Korea, nurses experience difficulties in pregnancy and giving birth due to the high workload (Korea Institute for Health & Social Affairs, 2018). Furthermore, as previous studies have indicated associations between night shift and infertility by several mechanisms (Fernandez et al., 2016), this study evaluated AMH as the primary marker for fertility in reproductive-aged nurses. Although correlations were relatively weak, the findings may provide evidence to help evaluate the reproductive health status and improve occupational environment for women of childbearing age.

As such, our findings provide information on non-Caucasian women and can be compared with those of prior studies on women with infertility or an underlying disease such as PCOS. As this cohort is ongoing, examination of future changes in BMI and lipid profile, with reference to AMH as a parameter, may also be possible.

5 | CONCLUSION

Using KNHS data, this study revealed that AMH levels were negatively correlated with BMI and TC and LDL levels at the lower percentiles of AMH levels and positively correlated with HDL levels at the higher percentiles of AMH levels. Such findings suggest the possibility that changes in the lipid profile may influence the AMH levels in women with diminished ovarian function, rather than obesity itself. Although this study has not identified any direct correlations among AMH, BMI and lipid profile, findings suggest that detailed analyses of association between AMH and different components of lipid profile may be beneficial. In-depth further studies will give better information regarding the mechanisms of change in AMH levels along with lipid disturbance.

ACKNOWLEDGEMENTS

We thank all the nurses who participated in the study.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

S.K. and H.L. contributed to the study design, data interpretation and writing of the manuscript. S.L. contributed to statistical analysis, data interpretation and writing of the manuscript. B.K. and H.J. contributed to data collection and discussion of the results. H.J., O.K. and K.-P.K. contributed to organize the survey and discussion of the results. All authors contributed to manuscript preparations and discussion and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The participants of the KNHS were selected from among those who were living in Korea and were between 20–45 years of age. Individual data were collected through the KNHS website. Data were collected anonymously and on a voluntary basis. However, data are not publicly accessible and freely available since the use and analysis of the pooled data and the publication of any research findings and study results out of it are restricted by contract with the KCDC.

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How to cite this article: Lim, S., Kim, S., Kim, O., Kim, B., Jung, H., Ko, K.-P., & Lee, H. (2021). Correlations among anti-Müllerian hormone levels, body mass index and lipid profile in reproductive-aged women: The Korea Nurses' Health Study. *Nursing Open*, 8, 2996–3005. https://doi.org/10.1002/nop2.1011