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Anti-Mullerian Hormone, a Marker of Ovarian Reserve, Is Protective Against Presence and Severity of NASH in Premenopausal Women

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Abstract

Background & Aims: Anti-müllerian hormone (AMH) is a marker of ovarian reserve with emerging data linking lower levels to some metabolic and inflammatory diseases in women. Whether AMH levels influence nonalcoholic fatty liver disease (NAFLD) is unknown.

Methods: Leveraging the NASH Clinical Research Network we determined the association of AMH levels within 6 months of liver biopsy with presence and severity of histologic measures of NAFLD in premenopausal women. Outcomes included presence of NASH, presence and severity of fibrosis, and NAFLD Activity Score (NAS) and its components. Logistic and ordinal logistic regression models were adjusted for age, race/ethnicity, HOMA-IR, body mass index, dyslipidemia, polycystic ovary syndrome (PCOS), estrogen-progestin use, and menstrual cyclicity.

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Results: Median cohort age was 35 years; 73% were white and 24% Hispanic. 33% had diabetes, 81% had obesity, and 95% had dyslipidemia. On biopsy 71% had NASH, 68% had any fibrosis, and 15% had advanced fibrosis. On adjusted analysis (n=205), higher AMH quartiles were inversely associated with NAFLD histology including prevalent NASH (AOR 0.64, 95% CI 0.41–1.00), NAS≥5 (AOR 0.52, 95% CI 0.35–0.77), Mallory's hyaline (AOR 0.54, 95% CI 0.35–0.82) and higher fibrosis stage (AOR 0.70, 95% CI 0.51–0.98). The protective effects of AMH were more pronounced among women without PCOS (n=164), including lower odds of NASH (AOR 0.53, 95% CI 0.32–0.90) and any NASH fibrosis (AOR 0.54, 95% CI 0.32–0.93).

Conclusions: AMH may reflect a unique biomarker of NASH in premenopausal women and findings suggest a novel link between reproductive aging and histologic severity of NAFLD in women.

Keywords

Nonalcoholic fatty liver disease (NAFLD); Sex hormones; Reproductive aging; Hepatic fibrosis; Polycystic Ovary Syndrome (PCOS)

Introduction

Nonalcoholic fatty liver disease (NAFLD) affects approximately 25% of the global population.[1] Remarkably, adolescents and young adults have experienced the most marked rise in NAFLD incidence, while women (specifically those over age 50 years) have a disproportionately higher risk of advanced NAFLD fibrosis.[2–4] Nonalcoholic steatohepatitis (NASH) is now the single most common indication for liver transplant in women,[5] and the most rapidly growing indication for liver transplant in young adults in the United States (U.S.).[6] Given lack of approved drug therapies and the heterogeneity of affected patients, there is an urgent need to identify unique biomarkers of NASH risk, particularly in young women.

Anti-müllerian hormone (AMH) is a marker of ovarian reserve that declines to undetectable levels with menopause. Independent of chronological aging, lower AMH levels in women are also associated with insulin resistance, obesity, cardiovascular disease, and clinical severity of some inflammatory diseases, such as multiple sclerosis.[7,8,9] As the ovaries are sensitive to global metabolic and inflammatory insults, lower AMH levels reflecting ovarian aging may be an early marker of systemic disease in young women.[9,10] Whether AMH influences or reflects more severe manifestations of NAFLD in women has not been studied.

Using the NASH Clinical Research Network (NASH CRN) database, we aimed to determine whether serum AMH levels, measured within 6 months of liver biopsy, are associated with histologic severity of NASH in premenopausal women, independent of chronologic aging or concurrent metabolic risk factors. If identified, AMH could serve as a unique biomarker of NASH risk in premenopausal populations, and support a novel link between ovarian health and NASH risk in young women.

Methods

Study Design and Patient Population:

Premenopausal women in the multicenter NASH CRN database (n = 205) were included. The NASH CRN encompasses the full spectrum of biopsy-confirmed NAFLD, from steatosis to NASH with advanced fibrosis.

Study predictor:

AMH levels were measured from banked serum within 6 months of liver biopsy. AMH was measured using an enzyme immunoassay from Ansh Labs (Webster, Tx, Cat # AL-105). The assay limit of detection was 0.023 ng/ml. Intra and inter-assay coefficient of variation were 5.1% and 8.5%, respectively. This measure was performed by the Assay Services at the Wisconsin National Primate Research Center. AMH was analyzed in quartiles to manage outliers.

Histologic Outcomes:

Liver biopsies were centrally assessed by a panel of NASH CRN pathologists for steatosis, fibrosis and NAFLD Activity Score (NAS) (a composite score of steatosis (0–3), lobular inflammation (0–3) and hepatocellular ballooning (0–2)).[11] Fibrosis stage ranged from 0–4 with advanced fibrosis defined as stage 3 or 4 disease. Using centralized NASH CRN pathology review, NASH was categorized as definite, possible/borderline, or absent. Our primary study outcomes were presence of NASH (defined as combination of borderline or definite NASH) and presence and severity of NASH fibrosis. We also evaluated the association of AMH with individual histologic features of NASH and NAS ≥5.

Cohort characteristics and covariates:

Demographic variables included age, race, and ethnicity. Metabolic risk factors were captured within 6 months of liver biopsy and included body mass index (BMI), waist circumference, fasting lipids (low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides), and homeostatic model assessment for insulin resistance (HOMA-IR). Dyslipidemia was defined as triglycerides ≥150mg/dL, HDL < 50mg/dL, and/or LDL ≥100mg/dL. Type 2 diabetes mellitus (DM2) and polycystic ovary syndrome (PCOS) were defined by self-report of ever having these diagnoses. PCOS was specifically captured as this condition is associated with presence and severity of NASH in pre-menopausal women,[12,13] but also marked by higher baseline AMH levels due to production from numerous “polycystic” ovarian follicles.[14] Abdominal adiposity was defined as waist circumference > 88cm. Use of any combined hormonal contraception (estrogen-progestin) within 12 months of liver biopsy was captured to account for potential protective effects of estrogen against hepatic fibrosis. As differences in menstrual cyclicity influence estrogen levels, menstrual cycles were captured by self-report of regular, irregular, rare, or no periods within 5 years of liver biopsy.

Statistical analysis:

Descriptive statistics were reported by Pearson chi-square, Fisher's exact or Kruskal-Wallis tests as appropriate. Logistic regression was used to assess the association between AMH quartiles and dichotomous NAFLD outcomes (histologic diagnosis of NASH, NAS≥5, presence of any steatosis (≥5%), severe steatosis (>66%), severe lobular inflammation (>2 grade, defined as >2–4 foci/20x optical field), any portal inflammation, any hepatocyte ballooning, severe hepatocyte ballooning, presence of Mallory's hyaline, any fibrosis (≥stage 1 versus none) and advanced fibrosis (stages 3–4 versus 0–2). Ordinal logistic regression was used to assess the association of AMH with fibrosis severity, ranging from stages 0 to 4. Regression models adjusted for demographic, metabolic, and reproductive factors selected a priori with established biologic relationships with AMH levels and/or NAFLD histology (age, race/ethnicity, HOMA-IR, BMI, dyslipidemia, PCOS, estrogen-progestin use, and menstrual cyclicity). Stratified analyses were also performed by PCOS status as inclusion of PCOS in the model was hypothesized to bias results towards the null given the association of PCOS with presence and severity of NASH as well as higher baseline AMH levels. A p value of ≤ 0.05 was considered statistical significance and analyses were performed with Stata MP 17 (StataCorp, College Station, Texas).

Results

Cohort Characteristics

A total of 205 premenopausal women met inclusion criteria (Table 1). The median age was 35 years (IQR 29.5–41.5); most reported white race (73.2%) and nearly a quarter were Hispanic (24.4%). Most women were obese (80.5%), had dyslipidemia (95.1%), and 33.2% had diabetes with median HOMA-IR score 4.6 (IQR 2.8–8.6). Median ALT level was 56U/L (IQR 38–97). On biopsy 70.7% had NASH (17.6% borderline and 53.2% definite), 49.8% had NAS≥5, and 68.3% had any fibrosis. Advanced fibrosis was present in 15.1%.

PCOS was present in 20% of the cohort (n=41). Compared to non-PCOS patients, those with PCOS were younger (median age 33 vs 35 years, p=0.05), had greater BMI (39.1 vs 35.9 kg/m^2, p=0.02), and waist circumference (114 vs 111 cm, p=0.04) (Supplemental Table 1). As expected, median AMH levels were higher with PCOS (5.41 vs 1.69 ng/mL, p<0.001). As a reference, AMH range in a multiracial/multiethnic population (n=947) of healthy, normal cycling reproductive-aged women found a mean AMH of 3.18 (SD 2.84).[15]

Figures 1a shows the proportion of patients with NASH, NAS >/=5 and any fibrosis by AMH quartiles in the overall cohort (n=205). These differences were more pronounced after excluding PCOS (Figure 1b), including presence of NASH (71.4% vs 48.5%, p=0.08), NAS≥5 (57.1% vs. 15.2%, p<0.01) and hepatic fibrosis (73.5% vs. 45.5%, p=0.03) in the lowest versus highest AMH quartiles.

On unadjusted analysis, higher AMH quartiles were inversely associated with NAS≥5 (AOR 0.70, 95% CI 0.55–0.90, p=0.006), more than mild portal inflammation (AOR 0.53, 95% CI 0.36–0.78, p=0.001), any ballooning (AOR 0.74, 95% CI 0.58–0.96, p=0.023), many ballooned hepatocytes (AOR 0.76, 95% CI 0.59–0.99, p=0.027), Mallory's hyaline (AOR

0.74, 95% CI 0.56–0.97, p=0.027) and higher fibrosis stage (AOR 0.72, 95% CI 0.58–0.91, p=0.006) (Table 2).

Findings were more pronounced on adjusted models including age, race/ethnicity, HOMA-IR, BMI, dyslipidemia, PCOS, combination estrogen-progestin use, and menstrual cyclicity (Table 2). The adjusted odds ratios (AORs) demonstrated an inverse association of higher AMH quartiles with NASH (AOR 0.64, 95% CI 0.41–1.00, p=0.051), NAS≥5 (AOR 0.52, 95% CI 0.35–0.77, p=0.001), more than mild portal inflammation (AOR 0.42, 95% CI 0.24–0.76, p=0.004), any ballooning (AOR 0.62, 95% CI 0.42–0.92, p=0.018), many ballooned hepatocytes (AOR 0.61, 95% CI 0.41–0.91, p=0.016), Mallory's hyaline (AOR 0.54, 95% CI 0.35–0.82, p=0.004) and higher fibrosis stage (AOR 0.70, 95% CI 0.51–0.98, p=0.037).

On stratified analyses excluding those with PCOS, we identified even stronger inverse associations between AMH levels and NASH histology including prevalent NASH (AOR 0.53, 95% CI 0.32–0.90, p=0.019), NAS≥5 (AOR 0.46, 95% CI 0.29–0.75, p=0.002), more than mild portal inflammation (AOR 0.40, 95% CI 0.21–0.78, p=0.007), any ballooning (AOR 0.61, 95% CI 0.39–0.96, p=0.031), many ballooned hepatocytes (AOR 0.51, 95% CI 0.32–0.83, p=0.006), Mallory's hyaline (AOR 0.53, 95% CI 0.32–0.88, p=0.013), higher fibrosis stage (AOR 0.59, 95% CI 0.40–0.88, p=0.009) as well as fibrosis ≥stage 1 (AOR 0.54, 95% CI 0.32–0.93, p=0.026) (Table 3). We did not identify an association of AMH with NASH histology in the subgroup of 41 women with PCOS (Supplemental Table 2).

Discussion

In this study of premenopausal women with biopsy-confirmed NAFLD we identified an independent inverse association of AMH levels with a range of histologic measures of NASH, including prevalent NASH, portal inflammation, hepatocyte ballooning, Mallory's hyaline, and fibrosis. Importantly, these findings were independent of chronologic aging and relevant metabolic and reproductive factors. As expected, findings were also more pronounced among premenopausal women without PCOS.

AMH is a glycoprotein that is produced by ovarian follicles, with gradual decline occurring through reproductive years and undetectable levels indicating transition to menopause. Ovarian follicles are the primary source of sex hormones in reproductive women, including estrogens and androgens. In reproductive women, AMH along with androgens, follicle stimulating hormone, and estradiol play essential roles in the development and maturation of ovarian follicles.[16] The relationships of these reproductive hormones in the context of liver disease are not fully understood and vary across patient populations and comorbidities. While estrogen levels also decline with ovarian aging, this may occur later, into the peri- and post-menopausal stages, after the initial decline of AMH.[9] Estradiol and other estrogens have been shown to protect against liver disease in women through various hepatic lipid metabolism signaling pathways[17] as well as by improving insulin sensitivity in adipose tissue.[18] Menopause, independent of chronologic aging, has been shown to increase NAFLD risk, and direct protective effects of estrogen against hepatic stellate cell activity have been demonstrated.[19–22] However, the relationship between AMH and NASH in our study is unlikely to be driven by loss of estrogens alone, as our cohort reflects a young

premenopausal population with a median age of 35 years, and with most (>80%) non-PCOS patients reporting presence of menstrual cycles.

Our findings most likely support the role of AMH as an early biomarker of chronic inflammation, opposed to direct involvement of AMH in the pathogenesis of NASH. Menopause and ovarian aging are associated with immune dysregulation, which contributes to chronic low-grade inflammation and increased risk of cardiovascular disease, diabetes, and other age-related illnesses.[23–26] Ovaries may be more sensitive to deleterious aging processes than non-reproductive tissues, as oocytes depend more heavily upon mitochondrial function than somatic cells.[27] Indeed, mitochondrial dysfunction has been implicated as a potential mechanism of ovarian aging and infertility.

Independent of chronologic age, prior studies have found associations between low AMH as a marker of reproductive aging in women and worsening cardiometabolic profiles.[28,29] A recent large prospective cohort study found lower age-specific AMH levels to increase the risk of type 2 diabetes in women.[30] Low AMH levels have also been associated with increased waist circumference, fasting insulin and HOMA-IR.[7] Proposed mechanisms linking lower AMH levels to metabolic conditions in women include suppressive activity of insulin and/or lipotoxic lipid species on AMH-producing granulosa cells, modulation of AMH production by adipokines such as leptin and adiponectin, and altered AMH metabolism and clearance in the setting of obesity.[31,32] Importantly, our study adjusted for BMI and insulin resistance, suggesting that the association of lower AMH levels with NAFLD severity was independent of these metabolic comorbidities.

NAFLD affects one third of the global population, with the greatest incident rise in adolescents and young adults. NASH is also a leading cause of cirrhosis in women.[1–5,33] Thus, there is a growing need for non-invasive markers that may identify young women at increased risk for clinically significant liver disease. The potential use of AMH as a marker of NASH risk in young women has several unique advantages, including its wide clinical availability and stability throughout the ovulatory cycle. As a marker of ovarian aging, AMH may also allow for early identification of young women at risk for NASH progression, cardiovascular disease and other age-related conditions, when prevention and intervention may be most beneficial. Future studies evaluating the predictive performance of AMH levels on the natural history of NAFLD in young women are needed.

Our study has notable strengths and limitations. Leveraging the multicenter NASH CRN cohort facilitated standardized pathologic review of liver biopsies along with comprehensive metabolic profiles. Our data included the full spectrum of NAFLD from simple steatosis to advanced NASH fibrosis across a diverse population. We also utilized the ultra-sensitive AMH enzyme-linked immunosorbent assay. However, our study was cross sectional in nature and could not establish causality of AMH with NASH histology. Those with the lowest AMH levels could also reflect a higher proportion of women in perimenopause, although we adjusted for both chronologic aging and menstrual cyclicity to account for this possibility. Moreover, point estimates remained consistent among women under 40 years of age (data not shown), thus findings are unlikely to be driven by perimenopausal participants. Importantly, our findings unlikely extrapolate to the 10% of premenopausal

women with PCOS, who naturally have higher AMH levels due to AMH production from numerous ovarian follicles, while also having higher risk for NASH due to more severe metabolic profiles and potential contributions of hyperandrogenism. [12,13,34,35] Larger studies within PCOS populations are needed to understand the role, if any, of AMH in their natural history of NAFLD. If validated in larger populations of non-PCOS patients, routine measurement of AMH in young women with NAFLD could help to identify those at higher risk of NASH and NASH fibrosis. Furthermore, applying a precision medicine lens to incorporate individual metabolic profiles has become a valuable strategy in light of the heterogeneity of NAFLD.[36] The addition of AMH levels to existing prediction tools may help to refine precision guided risk assessment and management in young women with NAFLD, including those at greatest risk for fibrosis progression. Validation studies including AMH in prediction models among young women would therefore be informative.

In summary, we identified a strong inverse association of AMH levels in premenopausal women with presence and severity of biopsy-confirmed NASH, independent of chronologic age, metabolic and reproductive-related risk factors. Our study supports a novel link between ovarian reserve and NAFLD severity, and the use of AMH as a potential early biomarker of NASH risk in young women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What you Need to Know

Background:

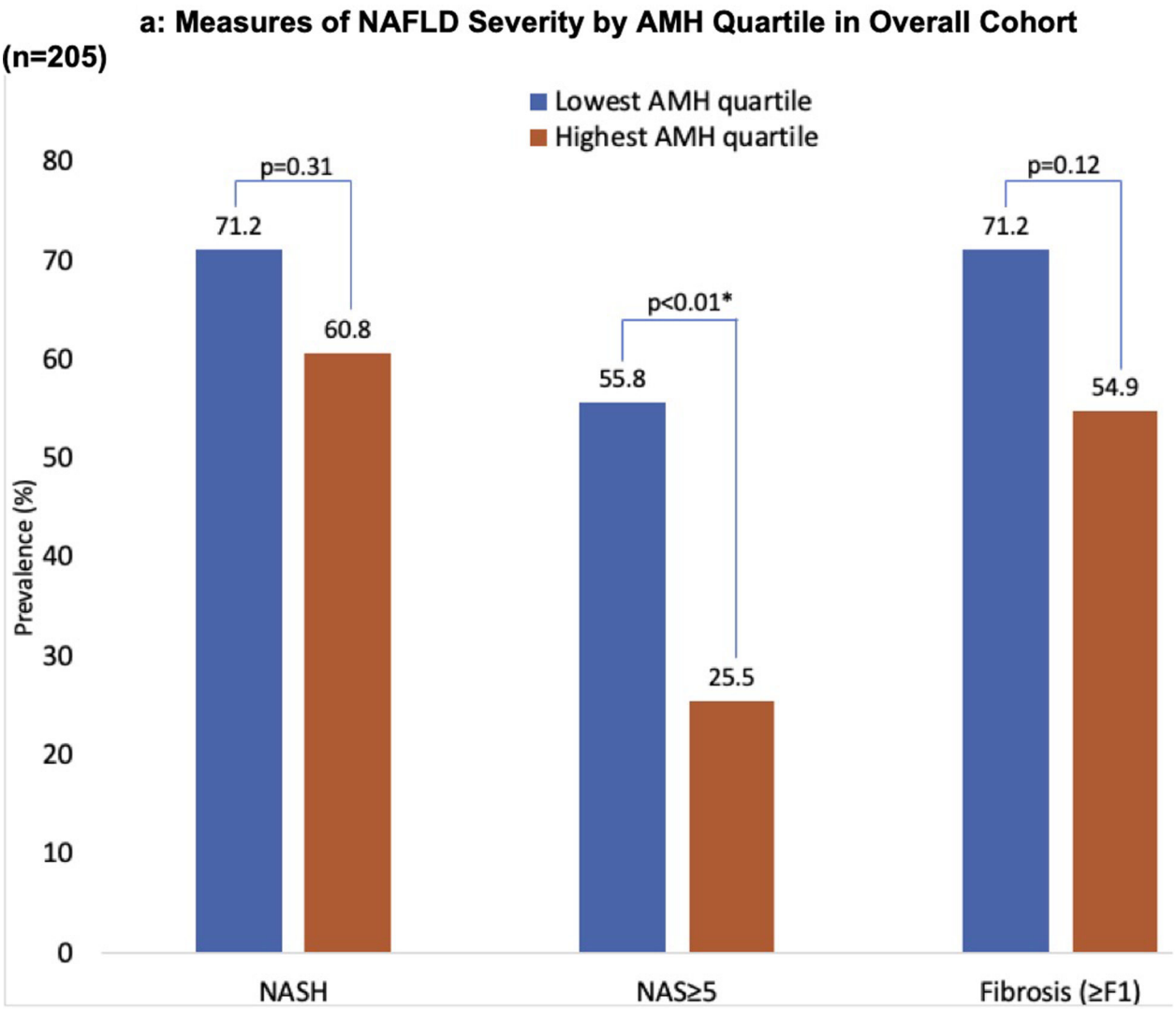
Anti-müllerian hormone (AMH) is a marker of reproductive aging with more recent data linking lower levels to some metabolic and inflammatory diseases in women. However, AMH has not been studied in relation to nonalcoholic fatty liver disease (NAFLD).

Findings:

In premenopausal women with NAFLD, lower AMH levels were independently associated with prevalent NASH and more severe NASH histology, including risk of hepatic fibrosis.

Implications for patient care:

AMH may reflect a unique biomarker of NASH risk in premenopausal women, and these findings support a novel link between ovarian aging and NAFLD severity.



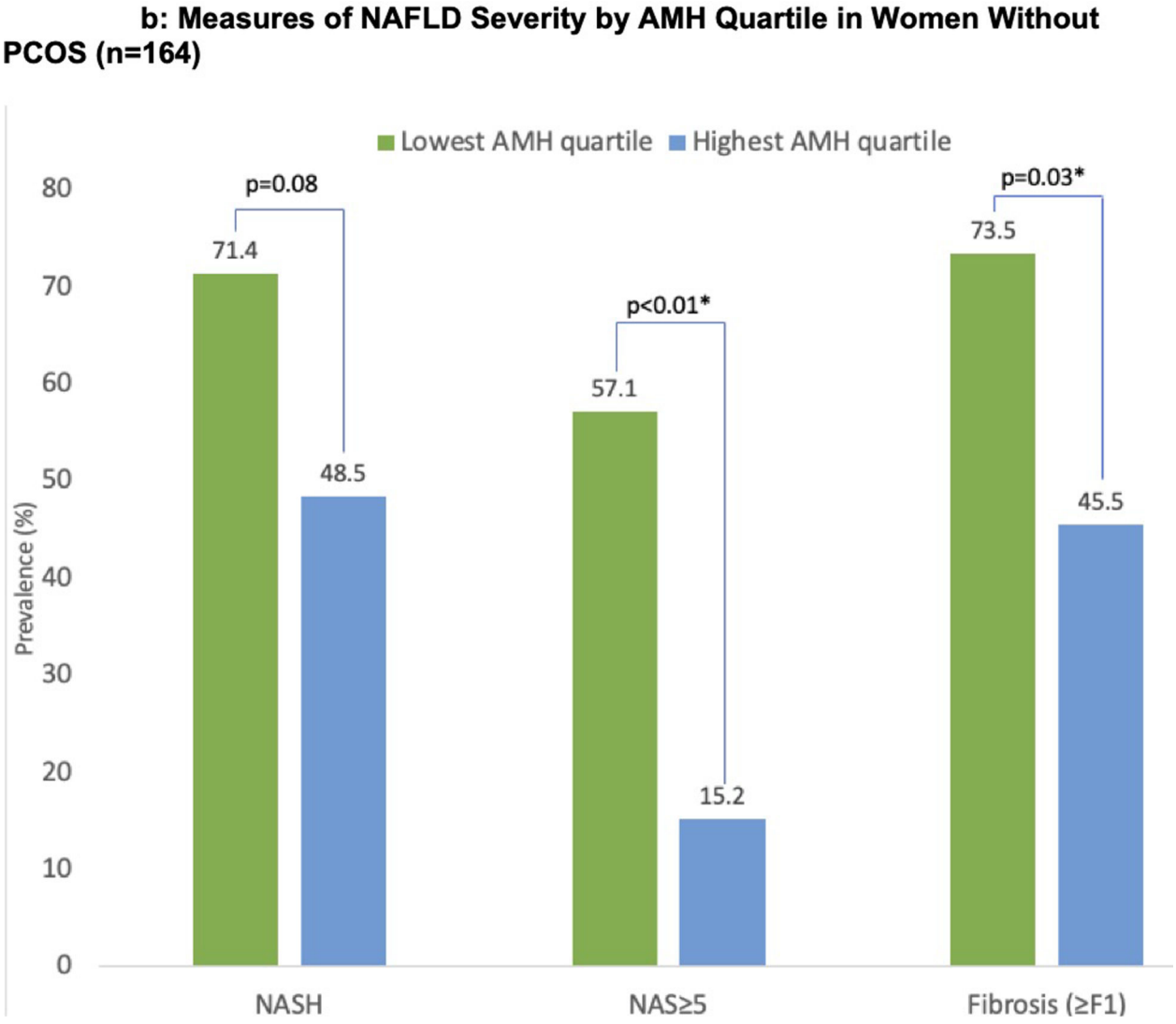


Figure 1.

Measures of NAFLD Severity by AMH Quartile in the Overall Cohort of Premenopausal Women with NAFLD, n=205 (Figure 1a, lowest AMH quartile in dark blue, highest AMH quartile orange) and Among Pre-Menopausal Women with NAFLD and Without PCOS, n=164 (Figure 1b lowest AMH quartile green, highest AMH quartile blue).

TABLE 1.

Cohort Characteristics Among Premenopausal Women with NAFLD (n=205)

Age (years), median (IQR)	35.3 (29.5–41.5)
Race n (%):	
White	150 (73.2)
Black	9 (4.4)
Asian	13 (6.3)
Native American	7 (3.4)
Pacific Islander	2 (1.0)
Mixed	5 (2.4)
Declined	19 (9.3)
Hispanic ethnicity, n (%)	50 (24.4)
Body mass index (BMI) (kg/m^2), median (IQR)	36.4 (31.8–41.1)
Obesity (BMI>30 kg/m^2) n(%)	166 (81.0)
Waist circumference (cm), median (IQR)	111.8 (98.8–120.4)
Waist circumference > 88 cm, n(%)	190 (92.7)
Total cholesterol (mg/dL), median (IQR)	190 (167–215)
HDL (mg/dL), median (IQR)	42 (35–50)
LDL (mg/dL), median (IQR)	116 (94–139)
Triglycerides (mg/dL), median (IQR)	146 (115–196)
Dyslipidemia *, n(%)	195 (95.1)
Type 2 diabetes, n(%)	68 (33.2)
HOMA-IR *, median (IQR)	4.6 (2.8–8.6)
PCOS, n(%)	41 (20.0)
ALT (U/L), median (IQR)	56 (38 – 97)
AMH (ng/mL), median (IQR)	2.30 (0.27–5.78)
Estrogen-progestin use, n(%)	45 (22.0)
Any NASH, n(%)	145 (70.7)
Borderline NASH, n(%)	36 (17.6)
Definite NASH, n(%)	109 (53.2)
NAS, median (IQR)	4 (3–6)

NAS ≥5, n(%)	102 (49.8)
Any fibrosis, n(%)	140 (68.3)
Advanced fibrosis (stage 3–4), n(%)	31 (15.1)

ALT, alanine transaminase; AMH, Anti-Müllerian hormone; BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of assessment of insulin resistance; IQR, interquartile range; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; PCOS, polycystic ovary syndrome.

* Dyslipidemia defined as HDL <50mg/dL, LDL ≥100mg/dL and/or triglycerides ≥150mg/dL; HOMA-IR defined as (glucose [mmol/L] × insulin[μ/mL]/22.5)

TABLE 2:

Association of AMH with NAFLD Histology Among Premenopausal Women (n=205)

	Univariate Analysis		Multivariate Analysis*	
Characteristic	**OR (95% CI)**	***P* value**	**AOR (95% CI)**	***P* value**
NASH (definite or borderline)	0.87 (0.66 – 1.14)	.309	0.64 (0.41 – 1.00)	.051
NAS≥5	**0.70 (0.55 – 0.90)**	**.006**	**0.52 (0.35 – 0.77)**	**.001**
Any steatosis (≥5%) **	0.99 (0.29 – 3.44)	.993	0.31 (0.01 – 8.06)	.479
Severe steatosis (>66%)	1.01 (0.78 – 1.32)	.895	0.89 (0.61 – 1.30)	.533
Severe lobular inflammation (>4 foci/200x)	0.88 (0.64 – 1.22)	.438	0.77 (0.47 – 1.26)	.296
Any portal inflammation	0.92 (0.65 – 1.30)	.628	1.01 (0.60 – 1.72)	.959
More than mild portal inflammation (>mild)	**0.53 (0.36 – 0.78)**	**.001**	**0.42 (0.24 – 0.76)**	**.004**
Any ballooning	**0.74 (0.58 – 0.96)**	**.023**	**0.62 (0.42 – 0.92)**	**.018**
Many/prominent ballooning	**0.76 (0.59 – 0.99)**	**.040**	**0.61 (0.41 – 0.91)**	**.016**
Mallory's hyaline	**0.74 (0.56 – 0.97)**	**.027**	**0.54 (0.35 – 0.82)**	**.004**
Any fibrosis (≥stage 1)	0.79 (0.61 – 1.03)	.084	0.67 (0.43 – 1.05)	.079
Advanced fibrosis (stage 3 or 4)	0.72 (0.51 – 1.03)	.077	0.75 (0.44 – 1.27)	.278
Higher fibrosis stage ***	**0.72 (0.58 – 0.91)**	**.006**	**0.70 (0.51 – 0.98)**	**.037**

* Logistic regression adjusted for age, race/ethnicity, HOMAIR, BMI, dyslipidemia, PCOS, estrogen-progestin use and menstrual cyclicity. From lowest (n= 52) to highest (n=51) AMH quartile.

** Race, dyslipidemia, combination estrogen-progestin use, rare and no periods within 5 years predict success perfectly, 110 observations not used

*** Fibrosis staged 0 (none), 1 (perisinusoidal or periportal), 2 (perisinusoidal and portal/periportal), 3 (bridging fibrosis) to 4 (Cirrhosis) analyzed via ordinal logistic regression using proportional odds assumption

TABLE 3:

Association of AMH with NAFLD Histology in Women without PCOS (n=164)

	Univariate Analysis		Multivariate Analysis*	
Characteristic	**OR (95% CI)**	***P* value**	**AOR (95% CI)**	***P* value**
NASH (definite or borderline)	0.76 (0.57 – 1.03)	.075	**0.53 (0.32 – 0.90)**	**.019**
NAS≥5	**0.62 (0.46 – 0.83)**	**.001**	**0.46 (0.29 – 0.75)**	**.002**
Any steatosis (≥5%)**	-		-	
Severe steatosis (>66%)	1.06 (0.79 – 1.42)	.701	0.92 (0.60 – 1.43)	.717
Severe lobular inflammation (>4 foci/200x)	0.76 (0.52 – 1.13)	.173	0.54 (0.28 – 1.04)	.066
Any portal inflammation	0.93 (0.63 – 1.37)	.719	1.06 (0.57 – 1.98)	.854
More than mild portal inflammation (>mild)	**0.51 (0.34 – 0.80)**	**.003**	**0.40 (0.21 – 0.78)**	**.007**
Any ballooning	**0.68 (0.51 – 0.91)**	**.010**	**0.61 (0.39 – 0.96)**	**.031**
Many/prominent ballooning	**0.69 (0.51 – 0.93)**	**.016**	**0.51 (0.32 – 0.83)**	**.006**
Mallory's hyaline	**0.70 (0.51 – 0.96)**	**.027**	**0.53 (0.32 – 0.88)**	**.013**
Any fibrosis (>stage 1)	**0.68 (0.50 – 0.92)**	**.012**	**0.54 (0.32 – 0.93)**	**.026**
Advanced fibrosis (stage 3 or 4)	**0.65 (0.42 – 0.99)**	**.046**	0.56 (0.28 – 1.09)	.086
Higher fibrosis stage*	**0.62 (0.47 – 0.81)**	**.000**	**0.59 (0.40 – 0.88)**	**.009**

*adjusted for age, race, ethnicity, HOMAIR, BMI, dyslipidemia, combination estrogen-progestin use, menstrual cyclicity

**AMH quartiles predicts success perfectly; therefore dropped from this model.

***Fibrosis staged 0 (none), 1 (perisinusoidal or periportal), 2 (perisinusoidal and portal/periportal), 3 (bridging fibrosis) to 4 (Cirrhosis) analyzed via ordinal logistic regression using proportional odds assumption