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a case-control study from Copenhagen, Denmark

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Anti-müllerian hormone levels are reduced in women living with human immunodeficiency virus compared to control women: a case–control study from Copenhagen, Denmark

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Abstract

Objectives: Anti-müllerian hormone (AMH) is a marker of ovarian reserve. The purpose of this study was to compare AMH in women living with HIV with an age-matched control group of HIV-uninfected women, and to identify possible variables associated with decreasing AMH levels in women living with HIV.

Methods: AMH was measured in frozen EDTA samples from 84 white women living with HIV, aged 20 –40 years, with fully suppressed HIV RNA viral loads for at least 6 months and no hepatitis B or C virus co-infection. All women living with HIV were age-matched with HIV-uninfected control women.

Results: Eighty-four women living with HIV and 252 control women were included. Median age for the women living with HIV was 33.5 years (interquartile range [IQR] 30.6–35.3), and 33.2 years (IQR 30.6–35.5) for the control women. A significant difference (P=0.03) was found in the mean AMH levels for all age groups combined, which was 17.23 pmol/L (95% confidence interval [CI] 14.56–19.89) in the women living with HIV versus 21.65 pmol/L (95% CI 19.50–23.81) in the control women, although levels were within reference limits in both groups.

Only increasing age was significantly associated with decreasing AMH levels and not CD4 cell count, AIDS prior to inclusion, antiretroviral treatment/lack of treatment or antiretroviral treatment regimen.

Conclusions: Well-treated, white women living with HIV in Denmark, have reduced AMH levels compared with age-matched control HIV-uninfected women. The only variable associated with decreasing AMH levels in women living with HIV was increasing age.

Keywords: human immunodeficiency virus; women; anti-müllerian hormone

Introduction

Ovarian reserve can be assessed by measuring the dimeric glycoprotein anti-müllerian hormone (AMH), which is secreted by granulosa cells from birth to menopause [1]. AMH can be measured in blood and is used as a reliable marker of the female ovarian reserve [1–3].

Only a few studies have been conducted on AMH in women living with HIV, with diverging conclusions [4–9]. A French study from 2009 showed a reduction in age-adjusted AMH levels among fully suppressed women living with HIV [5]. In contrast, an American study from 2014 showed that in fully suppressed women living with HIV, AMH levels were higher than in HIV-uninfected control women, after adjustment for CD4 cell counts [6]. Another American study showed that AMH may be used for prediction of age at menopause in women living with HIV [10].

When interpreting the studies on AMH levels, it is also important to be aware that the earlier generation I assays have been criticised for lack of precision and low sensitivity [11,12]. Specifically, there have been concerns regarding complement interfering with the analysis [11]. We have therefore used the newly developed, fully automated Elecsys AMH assay (Roche, Rotkreuz, Switzerland) to analyse AMH levels in our study [12].

The objective of the present study was to estimate AMH using a fully automated precision assay in white women living with HIV, with fully suppressed HIV RNA, in comparison with a very well defined control group of age-matched, HIV-uninfected healthy women. Moreover, we wanted to identify possible variables associated with decreasing AMH levels in women living with HIV.

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Methods

Study population

Denmark, with a population of 5.6 million people, offers free access to healthcare, including antiretroviral treatment [13,14]. There are 1400 women living with HIV in Denmark, half of whom are immigrants, and mode of infection is predominantly through heterosexual exposure [15–17].

Women living with HIV were identified in the Danish HIV Cohort study (DHCS), which is an ongoing, nationwide, prospective, observational, multicentre, population-based cohort study of all individuals living with HIV seen at Danish departments of infectious diseases since 1 January 1995 [13].

Eligible participants were white women living with HIV, aged 20–40 years, with at least 6 months of fully suppressed viral load (<50 copies HIV RNA/mL), without hepatitis B or C virus co-infection, attending either the Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre or Copenhagen University Hospital, Rigshospitalet, and with available stored frozen EDTA plasma samples between December 1997 and September 2016.

Differences in AMH levels in women of different ethnicities have previously been reported, and because the control women were of European origin, consequently, only white women living with HIV were included in the study [9]. A flow chart of the inclusion process is shown in Figure 1.

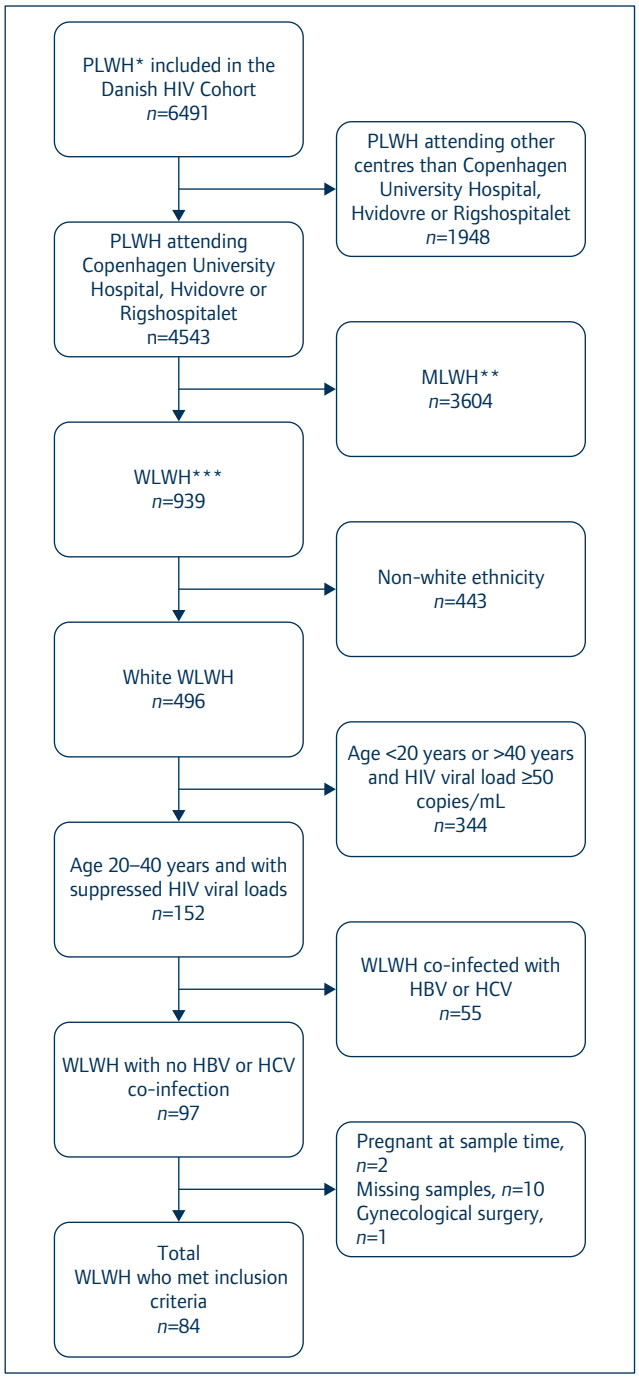

Figure 1. Flowchart illustrating inclusion process of 84 white, non-hepatitis B virus (HBV)-, non-hepatitis C virus (HCV)-infected, 20–40-year-old women living with HIV with HIV RNA ≤50copies/mL for minimum of 6 months. *PLWH: people living with HIV; **MLWH: men living with HIV; ***WLWH: women living with HIV

After eligible women living with HIV were found, their medical charts were reviewed in order to exclude women living with HIV who, at time of blood sampling, were pregnant, had gone through previous surgical procedures on the female reproductive organs, or had a diagnosis of gynaecological cancer. Information on CD4 cell counts, HIV RNA, place of birth, year of HIV diagnosis, mode of transmission, region of transmission, antiretroviral treatment and acquired immunodeficiency syndrome (AIDS) diagnoses was obtained from the DHCS. No information about BMI, menstrual history, fertility history or smoking habits was available.

Control women

Hospital white female employees, aged 20–40 years, were included at Copenhagen University Hospital, Rigshospitalet, from August 2008 to February 2010 (previously described [18]) for AMH measurement. Exclusion criteria were: pregnancy at time of the physical examination, use of hormonal contraception, amenorrhea or clinical hirsutism, previous ovarian surgery, presence of ovarian cysts or gynaecological cancer.

Pilot study participants

To compare serum to EDTA samples, 10 women living with HIV attending regular outpatient follow-up at the Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, were enrolled in a pilot study. In these women, AMH levels were measured in paired EDTA plasma and serum samples, to evaluate a possible difference in AMH levels. The manufacturer recommends using heparin plasma or serum as EDTA sampling has been shown to produce 10% higher results [19,20].

For the pilot study participants, written information was given and informed consent was achieved prior to blood sampling.

Anti-müllerian hormone assay

Blood samples from people living with HIV, who have consented to the use of their biological material for research, are stored in two biobanks: Copenhagen University Hospitals, Hvidovre and Rigshospitalet. Samples (EDTA plasma) of 0.5–1.5 mL are taken at regular outpatient clinic visits: once yearly at Copenhagen University Hospital, Hvidovre and twice yearly at Copenhagen University Hospital, Rigshospitalet. Samples are either immediately frozen at –20°C for the first few weeks, and subsequently stored at –80°C, or centrifuged and frozen at –80°C after 24–48 hours. Some samples may have been thawed and re-frozen. The samples included in this study have been stored between 4 and 19 years. No information concerning collection of blood samples in relation to the women's menstrual cycles was available, although this would not have changed the AMH level in the blood samples [1].

Frozen EDTA plasma samples were thawed and analysed (on 10 August 2016) at the Department of Clinical Biochemistry, Copenhagen University Hospital, Hvidovre, using the new Elecsys AMH assay according to the manufacturer's instructions [21].

During the autumn of 2015, frozen serum samples from the control women were analysed using the new Elecsys AMH assay at the Department of Clinical Biochemistry, Copenhagen University Hospital, Rigshospitalet.

Statistical analysis

Categorical variables were reported as absolute and relative frequencies. Continuous variables were summarised as median and interquartile ranges (IQR). Dependent group *t*-test was performed for the pilot study analysis, comparing AMH levels measured in paired serum and EDTA samples.

Women living with HIV were matched on age (+/– 3.5 years) with control women (1:3) using a SAS macro [22]. Comparison of AMH levels in women living with HIV and control women was performed with an unpaired *t*-test. Normal distribution was assessed by Q-Q plots.

A simple linear regression was performed to predict AMH levels based on independent variables, chosen *a priori*: age, CD4 cell count, prior AIDS diagnosis and antiretroviral treatment. A multiple linear regression model was used for all the variables.

Antiretroviral treatment was divided into three possible regimens: (1) Two nucleoside reverse transcriptase inhibitors (NRTIs) + one non-nucleoside reverse transcriptase inhibitor (NNRTI); (2) Two NRTIs + one protease inhibitor (PI); or (3) Other combinations.

SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for data analysis and *P*-values below 0.05 (two-sided) were considered statistically significant.

Ethical statement

The study was approved by the Danish National Ethical Committee (H-16021157, H-B-2007-129) and the Danish Data Protection Agency (2012-58-0004, 2008-41-1881).

Results

Pilot study

There was no statistically significant difference (95% confidence interval [CI] –0.27–0.64, *P*=0.38) between AMH levels in EDTA plasma and serum samples. The difference between EDTA and serum ranged from 0.1% (+0.02 pmol/L) to 6.8% (–1.35 pmol/L), with a median difference of 0.435 pmol/L. Based on these results, it was considered acceptable to compare data using EDTA versus serum samples for AMH measurements.

Demographic data

As seen in Table 1, a total of 84 white women living with HIV and 252 white control women between 20 and 40 years of age were included. The median age of the women living with HIV was 33.5 years (IQR 30.6–35.3) and the median age of the control women was 33.2 years (IQR 30.6–35.5). For the women living with HIV, median duration of HIV diagnosis was 6.6 years (IQR 3.3–10.9).

Among the 84 women living with HIV, 71 (85%) had CD4 cell counts above 350 cells/µL and 76 (91%) were on antiretroviral treatment (Table 1). All women had undetectable HIV RNA, and the eight (9%) allegedly not on antiretroviral treatment, were most likely on treatment, but this information was not recorded in the DHCS. The majority of the PI-based regimens (*n*=23/38; 61%) were based on boosted PIs.

For the majority of women living with HIV, mode of transmission was heterosexual (*n*=76; 91%), 68 (80%) indicated Europe as the most probable place of transmission, and 12 (14%) had prior AIDS-defining diagnoses (Table 1).

Table 1. Demographic data for 84 white, non-HBV, non-HCV, 20–40-year-old women living with HIV

Demographic data	WLWH (n=84) n (%)
Median age at inclusion (years, IQR)	33.5 (30.6–35.3)
Age groups (years)	
20–29	18 (21.4)
30–34	43 (51.2)
35–40	23 (27.4)
Median duration of HIV (years, IQR)	6.6 (3.3–10.9)
Region of transmission	
Denmark	51 (60.7)
Europe	17 (20.2)
Africa	4 (4.8)
Asia	2 (2.4)
Other	1 (1.2)
Missing	9 (10.7)
Mode of transmission	
Heterosexual	76 (90.5)
IDU	2 (2.4)
Blood transfusion	2 (2.4)
Missing	4 (4.7)
Latest CD4 count cells/µL	
<350	13 (15.5)
≥350	71 (84.5)
ART	
Yes	76 (90.5)
No	8 (9.5)
ART regimen	
Regimen 1 (2 NRTIs + 1 NNRTI)	21 (25.0)
Regimen 2 (2 NRTIs + PI)	38 (45.3)
Regimen 3 (other)	17 (20.2)
No ART	8 (9.5)
AIDS prior to inclusion	
Yes	12 (14.3)
No	72 (85.7)

AIDS: acquired immunodeficiency syndrome; ART: antiretroviral treatment; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; IDU: intravenous drug use; IQR: interquartile range; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

Anti-müllerian hormone levels

Table 2 shows the AMH levels in the women living with HIV and the control women. The median AMH level in the youngest age group (20–29 years) among women living with HIV was 23.0 pmol/L (95% CI 16.12–29.83) and 29.5 pmol/L (95% CI 24.10–34.83) among the control women (*p*=0.20). In the age group 30–34 years, the median AMH levels were 17.2 pmol/L (95% CI 13.47–21.09) and 21.0 pmol/L (95% CI 18.08–23.88), respectively (*P*=0.18). In the age group 35–40 years the median AMH levels were 12.6 pmol/L (95% CI 8.72–16.52) and 16.8 pmol/L (95% CI 13.24–20.37), respectively (*P*=0.21). When comparing all age groups collectively, there was a statistically significant difference in AMH level distribution between women living with HIV and control women, with median AMH levels of 17.23 pmol/L (95% CI 14.56–19.89) and 21.65 pmol/L (95% CI 19.50–23.81) (*P*=0.03), respectively.

Variables associated with AMH levels

Table 3 shows the *a priori* chosen variables tested for association with AMH levels in women living with HIV: age, CD4 cell count (cells/µL), AIDS diagnosis prior to inclusion and antiretroviral treatment, including types of antiretroviral treatment regimens. Age was the only variable, significantly associated with AMH levels, with a decrease in AMH level of 0.93 pmol/L per year increase in age (*P*=0.004, 95% CI –1.56––0.30), while none of the remaining variables wae statistically significantly associated with AMH levels (Table 3).

Discussion

To our knowledge, this is the first case–control study comparing AMH levels, measured with the new and improved Elecsys AMH assay, in white women living with HIV and with a very well-defined control group of HIV-uninfected women with no known fertility problems. We found a statistically significant difference in AMH levels between women living with HIV and age-matched HIV-uninfected women, when all age groups were analysed collectively.

Furthermore, of the tested variables, we only found age to be significantly associated with AMH levels.

Table 2. Mean AMH levels in 84 white, non-HBV, non-HCV, 20–40-year-old women living with HIV and 252 age-matched control women

Age group	Cases WLWH	Control women	*P*-value
20–29 years *n* (%)	18 (21.4%)	54 (21.4%)	
AMH pmol/L, mean (95% CI)	22.97 (16.12–29.83)	29.46 (24.10–34.83)	0.20
30–34 years *n* (%)	43 (51.2%)	129 (51.2%)	
AMH pmol/L, mean (95% CI)	17.28 (13.47–21.09)	20.98 (18.08–23.88)	0.183
35–40 years n (%)	23 (27.4%)	69 (27.4%)	
AMH pmol/L, mean (95% CI)	12.62 (8.72–16.52)	16.81 (13.24–20.37)	0.21
All age groups *n* (%)	84 (100%)	252 (100%)	
AMH pmol/L, mean (95% CI)	17.23 (14.56–19.89)	21.65 (19.50–23.81)	**0.03**

CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; WLWH: women living with HIV.

Table 3. Variables associated with anti-müllerian hormone in 84 white, non-HBV, non-HCV, 20–40-year-old women living with HIV. Simple linear regression analysis with the following variables: age, latest CD4 cell count, prior AIDS-defining diagnosis (reference: no prior AIDS diagnosis), antiretroviral treatment (reference: yes, receiving treatment), and antiretroviral treatment regimen (reference: Regimen 1)

Variables associated with AMH levels All age groups	Average change	95% CI	*P*-value
Age (years)	–0.93	–1.56––0.30	**0.004**
CD4 count (cells/μL)	0.01	–0.002–0.017	0.141
AIDS prior to inclusion	–1.85	–9.50–5.81	0.633
Antiretroviral treatment	4.39	–4.70–13.48	0.340
Antiretroviral regimens			
Regimen 1			
Regimen 2	1.80	–4.79–8.39	0.588
Regimen 3	–1.53	–9.43–6.38	0.702

AIDS: acquired immunodeficiency syndrome; AMH: anti-müllerian hormone; Average change: estimate of average change (β); HBV: hepatitis B virus; HCV: hepatitis C virus; IDU: injecting drug user; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; Regimen 1: 2 NRTIs + 1 NNRTI; Regimen 2: 2 NRTIs + PI; Regimen 3: other.

Demographic data

The present study population represents well-treated women living with HIV, living in Denmark, as all of the 84 participants had fully suppressed HIV RNA viral loads (≤50 copies/mL) and 91% were on antiretroviral treatment. The study population does differ from the general population of women living with HIV in Denmark in one important respect: all of the study participants were white, while approximately 45% of the total population of women living with HIV in Denmark originate from sub-Saharan Africa [16,23]. Some studies suggest that AMH varies with ethnicity [9,24,25]. An American study of 809 (628 HIV-infected, 181 HIV-uninfected) white, black and Hispanic women, with no known fertility issues, showed that AMH levels were significantly lower in women of black ethnicity, compared to women of white ethnicity [9]. That, as well as the HIV-uninfected women being white, was the basis for our decision to include only white women living with HIV.

AMH levels in women living with HIV and control women

When we compared all age groups, we found a statistically significant difference in mean AMH levels between women living with HIV and control women (*P*=0.03). Similar to our findings, Ohl *et al.* [5] showed a 23% reduction in AMH levels among 78 women living with HIV, with a mean age of 34 years (18–45), compared to expected, age-specific levels. Most of the women living with HIV studied had fully suppressed HIV viral loads and regular menstrual cycles [5]. The authors did not find any association between CD4 cell counts and AMH [5]. Also supporting our results, Scherzer *et al.* [6] found 16% lower AMH levels among 2621 women living with HIV (ages 19–80 years), although after adjusting for age, race, smoking, hormonal contraceptive use, amenorrhea, weight loss, current and nadir CD4 cell counts, nadir CD8 and T lymphocyte counts, AMH was higher than in 941 HIV-uninfected control women. The authors concluded that a good immune system was associated with a good ovarian reserve [6]. Of note, AMH measurements were conducted using the previous method (ELISA kit) [6].

Similar to the studies mentioned above, another study showed that 201 women living with HIV, requesting assisted reproductive technology, had significantly (*P*=0.001) lower levels of AMH, compared to 603 age- and cause of infertility-matched, HIV-uninfected women [26]. Increasing CD4 cell counts were associated with an increase in AMH levels. Also, it was recently shown that AMH can be used for predicting age at menopause in women living with HIV [10]. This may be an important factor when counselling fertility planning in women living with HIV, as it seems that AMH may be used as a 'reproductive lifespan' measurement.

The AMH values in both women living with HIV and control women were within reference limits, indicating that both groups have normal AMH values, although consistently lower in the women living with HIV group [27]. The clinical relevance of this may be questionable; however, as HIV infection has been associated with preterm onset of menopause, the reduced AMH values in this group of women living with HIV may have a significance in terms of ovarian reserve pool quantification and for the prediction of early onset of menopause [10].

Variables associated with AMH levels

As expected, we found that increasing age was associated with decreasing levels of AMH [1]. We did not find any significant association between AMH levels and the remaining variables, including CD4 cell counts. The association between AMH levels and fertility are uncertain, and it seems that AMH is an indeterminate predictor of pregnancy and live birth after IVF [28]. Only a few studies have reported on natural fertility and AMH, and it is unclear what clinical significance on fertility the reduced AMH levels in our study have, as no information on previous pregnancies was available [29–31]. We have previously shown that women living with HIV in Denmark conceive naturally, and national and international guidelines are leaning towards natural conception among women with fully suppressed viral loads [32,33]. It is possible that the fertility of women living with HIV has improved significantly since the introduction of effective antiretroviral treatment, but our study indicates that a significant difference in AMH levels between women living with HIV and HIV-uninfected women remains. Further studies should focus on clarifying whether this difference is clinically relevant.

The main strengths of this study were the two relatively homogenous populations, both in ethnicity and age. Another

strength was that all AMH analyses were performed with the new and improved Elecsys AMH assay, generating reliable results. Also, all women living with HIV had fully suppressed HIV RNA viral loads, and the vast majority had high CD4 cell counts, thus eliminating poor immune function as a possible confounder.

An important limitation to this study is that information on hormonal contraceptive use, which has previously been shown to reduce AMH levels, was not possible to obtain. However, our previous findings in the same population of women living with HIV show a general low usage [23,34]. In addition, no information on other factors that may influence AMH levels, such as BMI or smoking habits, were available.

Another limitation is the possibility of selection bias, as control women with symptoms of possible polycystic ovarian syndrome were excluded, but women living with HIV with similar symptoms were not. This may have resulted in higher AMH levels in control women, compared to women living with HIV.

Finally, it has previously been shown that freeze–thaw cycles and sample storage at –20°C or –80°C for up to 9 months have no impact on AMH levels, and our analyses showed no signs of sample degradation, despite freeze-time up to 19 years [20].

Our study shows that well-treated, white women living with HIV in Copenhagen, Denmark have significantly lower AMH levels than age-matched, HIV-uninfected control women. The clinical significance of this reduction in AMH levels remains unclear, and further studies are needed to establish the role of AMH in fertility assessments. However, as AMH may be used for predicting age at menopause in women living with HIV, our study may suggest that this group of women are at risk of entering menopause earlier than control women. This is important when health personnel provide counselling concerning menopausal symptoms and related co-morbidities.

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Declaration of interests

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