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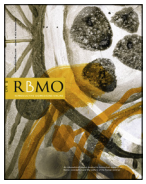

ARTICLE

Ethnic discordance in serum anti-Müllerian hormone in European and Indian healthy women and Indian infertile women

BIOGRAPHY

Piotr Gromski started his career as a data scientist with a PhD at the University of Manchester followed by postdoctoral training at the University of Strathclyde and Glasgow. He is now part of a wider multidisciplinary group at the University of Glasgow leading a team using large population datasets to improve clinical outcomes.

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KEY MESSAGE

AMH is substantially lower in healthy Indian women at all ages than their European counterparts. Infertile Indian women have variable differences in AMH from their healthy Indian controls, with the extent and direction of differences primarily reflecting the underlying cause of infertility.

ABSTRACT

Research question: Does anti-Müllerian hormone (AMH) differ between healthy European and Indian women, and are potential ethnic differences modified by infertility diagnosis?

Design: Cross-sectional analysis of three prospectively recruited cohorts (n = 2758); healthy European women (n = 758), healthy community cohort from Kolhapur, India (n = 400) and infertility cohort from Kolhapur, India (n = 1600). AMH was determined by assay. Ethnicity, age and cause of infertility were modelled using additive quantile regression models.

Results: Healthy Indian women had lower AMH than their healthy European counterparts (population estimates 20.0% lower [95% CI 7.2–36.5]), with increasing discordance with increasing age; at 25 years AMH was 11.9% lower (95% CI 9.4–14.1), increasing to 40.0% lower (95% CI 0–64.6) by age 45. Comparison of healthy and infertile Indian women revealed differences that were related to cause of infertility. Women whose male partner had severe oligoasthenoteratozoospermia (n = 95) had similar AMH to controls; women with polycystic ovary syndrome (n = 220) had higher AMH, especially in those <30 years, and in women with a principal diagnosis of unexplained infertility (n = 757) AMH was lower (median difference 22.6% lower; 95% CI 9.1–37.7) than controls.

Conclusions: AMH is substantially lower in healthy Indian women at all ages than their European counterparts. Infertile Indian women have variable differences in AMH from healthy Indian controls, with the extent and direction of differences primarily reflecting the underlying cause of infertility. Recognition of ethnic and cause-specific differences are critical to ensure accurate contextualizing of results and clinical outcomes for patients.

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KEYWORDS
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INTRODUCTION

The age of natural menopause has significant implications for a woman's reproductive lifespan as well as her long-term health. Earlier age at menopause has been associated with an increased risk of cardiovascular disease (*Honigberg et al., 2019*; *Maas et al., 2021*; *Zhu et al., 2019*), bone loss (*Kanis et al., 2019*) and overall mortality (*van der Schouw et al., 1996*). Studies assessing the determinants of age at natural menopause suggest that, in addition to a wide range of genetic, reproductive, lifestyle, and early life and social/environmental factors, the timing differs between race/ethnic groups (*Mishra et al., 2019*). Compared to White women, studies show menopausal onset is earlier in African-American (*Bromberger et al., 1997*), Latina (*Henderson et al., 2008*), Chinese (*Wang et al., 2018*) and Indian (*Prasad et al., 2021*) women, and later in Japanese women (*Henderson et al., 2008*).

Racial or ethnic differences in the age of natural menopause suggest that trajectories of reproductive ageing over the life course may differ between women of different racial or ethnic backgrounds. In adult women, anti-Müllerian hormone (AMH) has emerged as a surrogate marker of the functional ovarian reserve (*Dewailly et al., 2014*); with correlations with the primordial follicle pool (*Kelsey et al., 2012*), inverse relation to chronological age (*Kelsey et al., 2011*), prediction of ovarian response in assisted reproductive technologies (*Iliodromiti et al., 2015*), and prospective relation to menopausal timing (*Anderson and Nelson, 2020*; *Finkelstein et al., 2020*) all supporting its role as an estimate of reproductive ageing. Compared with age at natural menopause, studies assessing ethnic differences in AMH have been more limited and smaller, but in general follow similar patterns, with lower AMH values observed in African-American, Latina and Chinese women (*Kotlyar and Seifer, 2021*). Despite an average age of natural menopause of 46.6 years in Indian women (*Prasad et al., 2021*), as compared with 50 to 51 years in European or US women (*Kato et al., 1998*), the data on Indian/South Asian women has been inconsistent. A single-centre study of UK fertility patients suggested equivalence (*Bhide et al., 2015*), while a comparison of fertility patients between clinics in Spain and India reported lower AMH in the Indian women (*Iglesias et al., 2014*). There is now recognition that the pathological mix of infertility clinic populations may adversely impact on multi-ethnic comparisons, as biomarkers like antral follicle count and AMH are higher in women with polycystic ovary syndrome (PCOS) (*Dewailly et al., 2014*; *Iliodromiti et al., 2013*), and lower in women with unexplained infertility (*Iliodromiti et al., 2016*).

The present study used three prospective cohorts (n = 2758); two were community-based cohorts of healthy women with regular cycles from India (n = 400) and Europe (n = 758), with no history of infertility or other factors that may impact on AMH, to examine the cross-sectional association between Indian race/ethnicity and AMH. The third cohort was prospectively recruited Indian women with a diagnosis of infertility (n = 1600), to determine whether estimates of AMH differed between women with a history of infertility and healthy Indian women.

MATERIALS AND METHODS

Study design and participants

Three distinct population cohorts were prospectively recruited: (i) healthy European women living in the Netherlands, Belgium, Germany, France and Turkey; (ii) healthy Indian women living in the community of Kolhapur, India and (iii) Indian women presenting to a fertility clinic in Kolhapur, India.

Healthy participants in both Europe and India were recruited from the community, with the European women initially recruited to a multicentre study to evaluate the analytical performance of the Elecsys® AMH assay (Roche Diagnostics, Basel, Switzerland) and to facilitate determination of a reference range (*Anckaert et al., 2016*). Indian controls were recruited from community adverts and were resident within 50 km of Kolhapur city. All Indian women (cases and controls) were recruited between January 2016 and July 2020. All participants in Europe and India had a regular menstrual cycle (length 21–35 days) and were aged between 20 and 45 years of age. Women with a body mass index (BMI) exceeding 30 kg/m^2 and/or receiving hormone replacement therapy or using hormonal contraceptives in the preceding 3 months were excluded from the study. Furthermore, women with infertility, gonadal disorder/dysfunction, diagnosed endometriosis, pelvic surgery, and known previous or current endocrine or metabolic disorders were excluded. Early follicular serum samples were collected on day 2–5 for all participants. Infertile women presenting to Shreyas Hospital and Sushrut Assisted Conception Clinic, Kolhapur, India were recruited as a separate cohort at their first visit. All patients underwent blood collection at day 2 to 4 of their cycle in ovulatory women, with anovulatory women sampled at the time of their antral follicle count, which was performed in accordance with consensus statements (*Broekmans et al., 2010*).

All investigation and sample collection sites followed the International Conference on Harmonisation Guideline for Good Clinical Practice E6 and conducted the study in accordance with the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong and Edinburgh). Ethics committee approval of the respective institutions was obtained. Specifically, ethical approval for the European cohort is on file at Roche Switzerland and was obtained from the following institutions: UZ Brussels, Free University of Brussels (VUB), Belgium; Duzen Laboratories, Ankara, Turkey; Laboratoire Eylau, Paris, France; Limbach Laboratory, Heidelberg and MVZ Wagnerstibbe für Laboratoriumsmedizin and Pathologie GmbH, Hannover, Germany. Ethical approval for the Indian cohort was initially obtained from the Shreyas Hospital, India on 16 January 2016 (reference: ECR/1448/Shreyas/Inst/MH) and amended in 2020 to include the European cohort and approved by Shreyas Hospital, India on 21 February 2020 (reference: ECR/962/nst/MH/2017/RR-20).

Sample measurement

Serum aliquots (3 ml) for each participant were stored at −80°C. AMH was measured on first thaw of stored samples using the Elecsys AMH automated method on a clinically validated platform (cobas e 411, e 601 and E170, Roche Diagnostics) (*Anckaert et al., 2016*). The assay was calibrated and quality controlled using the manufacturer's reagents. All AMH samples from the European and Indian population were measured in the respective laboratories (Ambika

Pathology Laboratory and Laboratory of Hormonology and Tumour Markers, Universitair Ziekenhuis Brussel) using the same AMH assay. Across the range of 0.24 ng/ml (1.71 pmol/l) to 19.17 ng/ml (136 pmol/l) the within-run imprecision was 0.7 to 3.4%, the repeatability coefficient of variation ranged from 1.3 to 1.7% and the intermediate coefficients of variation ranged from 2.1% to 4.5%. The repeatability and intermediate imprecision were investigated using two levels of quality control material (Elecsys PreciControl AMH 1 and 2 assay, Roche Diagnostics) sent to the sites in frozen aliquots, with paired comparison of performance across the two sites. The limit of quantitation (LoQ) was 0.03 ng/ml.

Statistical analysis

AMH was compared between the three studied groups (European control, Indian control and Indian infertile) using general additive models incorporating quantile regression. The distribution of AMH concentration in each investigated group followed a right skewed distribution, reflecting that a few women have high values while the majority of women have lower values, with some closer to zero. The median and interquartile range (IQR) of the untransformed data are presented in the descriptive data and log-transformed AMH data were modelled using generalized additive models (GAM) incorporating quantile regression allowing for non-linear relationships with predictor variables, with the quantile set at 0.5. These values were then back-transformed and are interpreted as the ratio of geometric means (GM/GMR). Graphs displayed are in original units and values were derived by back-transforming from the log scale.

Age and ethnicity were included in each of the models, and the Indian control group was used as the reference group. Prediction for six different ages from all backgrounds were selected to numerically display the differences between groups. Model fit was assessed via standard methods (e.g. graphical plots) using the predict function in R. This included checking that the relationship between the observed and predicted values was linear, checking if there was constant variance between the predicted values and the residuals, and confirming that the residuals were normally distributed.

Three additional sensitivity analyses were conducted to further evaluate potential differences/similarities between healthy and infertile Indian women. The first was comparison of women where their partner had severe oligoasthenozoospermia as defined by a total motile sperm count of <4.99 million to healthy controls, as if male factor was the dominant factor these women should have similar values to healthy women. Secondly, women with PCOS as defined by the Rotterdam consensus (*Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004*) were excluded, as PCOS is known to be associated with increased AMH concentrations and PCOS may be over-represented in the Indian infertile population, particularly in young women. Lastly, women where unexplained infertility was the primary diagnosis were compared, as it has previously been shown that diminished ovarian reserve may be over-represented in infertile women compared with healthy women (*Iliodromiti et al., 2016*). All statistical analyses were performed using R version 4.0.3, 2020 for Windows (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 2758 subjects met the inclusion criteria and participated in the study; 758 healthy European women, 400 healthy Indian women and 1600 Indian women with a diagnosis of infertility (FIGURE 1). Compared to European women (median age 32 years, interquartile range [IQR] 26–39), both Indian healthy women

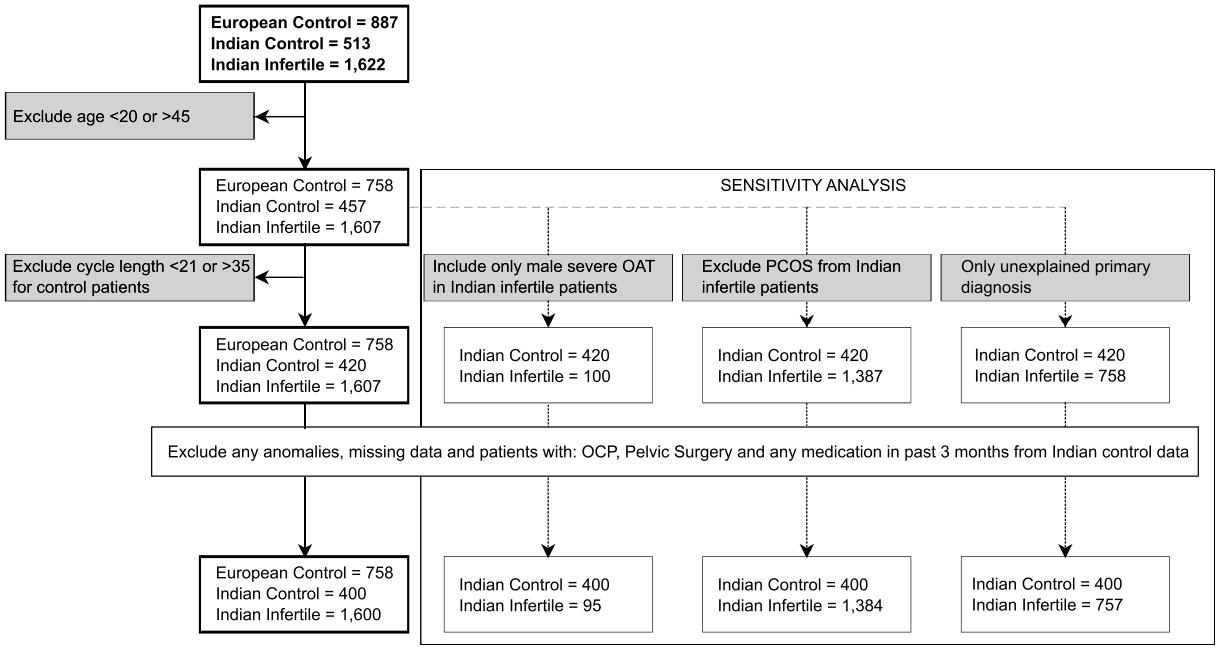

FIGURE 1 Definition of cohort for analysis. Left-hand flow shows data arrangement for AMH comparison between the three groups using general additive models incorporating quantile regression. The right-hand side shows the three different sensitivity analyses and their respective approaches for data omission. AMH = anti-Müllerian hormone; OAT = oligoasthenoteratozoospermia; OCP = oral contraceptive pill; PCOS = polycystic ovary syndrome.

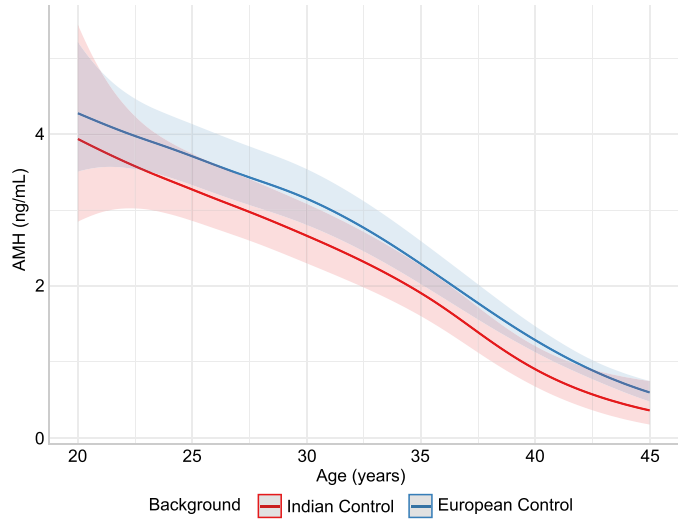

FIGURE 2 Comparison of AMH in Indian healthy women (n = 400) and European healthy women (n = 758). Geometric median with 95% confidence interval (CI) by background ethnic group. Model is established on a smooth additive quantile regression model on age with background and an interaction between age and ethnicity. AMH = anti-Müllerian hormone.

(29.2 years, IQR 25.0–34.5) and Indian women with infertility (30.4 years, IQR 27.3–33.8) were slightly younger (P < 0.001) (Supplementary Table 1). For each age strata, the observed median AMH concentrations in Indian healthy women were lower compared to their European counterparts and in Indian women with infertility they were also generally lower than healthy European women (Supplementary Table 1).

In the additive quantile regression models, there was strong evidence that the healthy Indian women had an estimated 20.0% (95% CI 7.2–36.5) lower AMH at all ages than their healthy European counterparts (FIGURE 2). To further illustrate the impact of Indian ethnicity on AMH, the predicted values for women aged 20, 25, 30, 35, 40 and 45 are shown in TABLE 1. Overall lower AMH concentrations were found in the Indian healthy population compared to the European population: at age 20 AMH was 7.9% (95% CI 4.4–18.8) lower, age 25 AMH was 11.9% (95% CI 9.4–14.1) lower, age 30 AMH was 15.6% (95% CI 12.7–18.1) lower; at age 35 AMH was 16.6% (95% CI 12.4–20.8) lower; at age 40 AMH was 30.2% (95% CI 17.7–40.7) lower; at age 45 AMH was 40.0% (95% CI 0–64.6) lower (TABLE 1).

In comparing the 1600 Indian women with infertility to their 400 healthy Indian controls, AMH concentrations were dynamic and divergent across the age range (FIGURE 3A). Specifically, they were increased in infertile women below 30 years, then from age 30 to 40 years there was a crossover, with infertile women having lower AMH than their healthy controls, before having broadly similar AMH concentrations from age 40 years (FIGURE 3A). To explore these age differences further, three sensitivity analyses were carried out (FIGURES 3B to 3D). The first was to examine only women whose male partner had severe oligoasthenoteratozoospermia (n = 95) compared to healthy Indian women. In this analysis the age effects were attenuated, with no overall significant differences between the two groups (P = 0.62) (FIGURE 3B). The second sensitivity analysis was to exclude women with PCOS (n = 220); in this analysis infertile women (n = 1384) at all ages had an estimated 14% (95% CI 3.7–23.3) lower AMH concentration than their healthy Indian counterparts (FIGURE 3C). There was also no crossover in younger infertile women, as observed in FIGURE 3A, consistent with PCOS dominating in this age group. Lastly, the 757 Indian women with a principal diagnosis of unexplained infertility were assessed, and again values were generally lower (median difference 22.6% lower, 95% CI 9.1–37.7) than their healthy Indian counterparts (FIGURE 3D), with attenuation of the age-related differences from age 38 years. For all analyses of Indian infertile women, graphical comparison with Indian and European healthy controls are provided in Supplementary Figures S1 to S4, with any observed differences with healthy Indian women exaggerated relative to the European healthy controls.

TABLE 1 PREDICTED AMH FROM QUANTILE REGRESSION MODEL AND ASSOCIATED 95% CI FOR AGE RELATIVE TO ETHNIC BACKGROUND

Age	European	Indian control	Indian infertile
20	4.28 (3.51–5.22)	3.94 (2.85–5.45)	4.56 (3.41–6.11)
25	3.71 (3.33–4.14)	3.27 (2.86–3.75)	3.65 (3.32–4.02)
30	3.15 (2.81–3.54)	2.66 (2.30–3.09)	2.67 (2.49–2.87)
35	2.29 (2.02–2.59)	1.91 (1.60–2.27)	1.60 (1.46–1.75)
40	1.29 (1.13–1.47)	0.90 (0.67–1.21)	0.87 (0.74–1.03)
45	0.60 (0.48–0.75)	0.36 (0.17–0.75)	0.48 (0.31–0.74)

Prediction for six different ages from all backgrounds were selected to numerically display the differences between groups.

AMH concentrations reported as ng/ml.

AMH = anti-Müllerian hormone; CI = confidence interval.

DISCUSSION

Using three prospectively recruited cohorts, this study demonstrates that healthy Indian women have significantly lower AMH concentrations at all ages than their European counterparts. Secondly, it shows that in Indian women with a diagnosis of infertility there may be age-related differences, but the degree and direction of these differences are primarily dependent on the underlying cause of infertility. Specifically, in women where the principal cause of infertility was male factor and attributable to their partner due to severe oligoasthenoteratozoospermia, AMH concentrations were similar to healthy Indian women. In contrast, the observed higher values of AMH in infertile women below 30 years is primarily driven by an increased prevalence of PCOS, while in women with unexplained infertility, AMH values are lower than healthy controls, with increasing divergence with increasing maternal age. This study

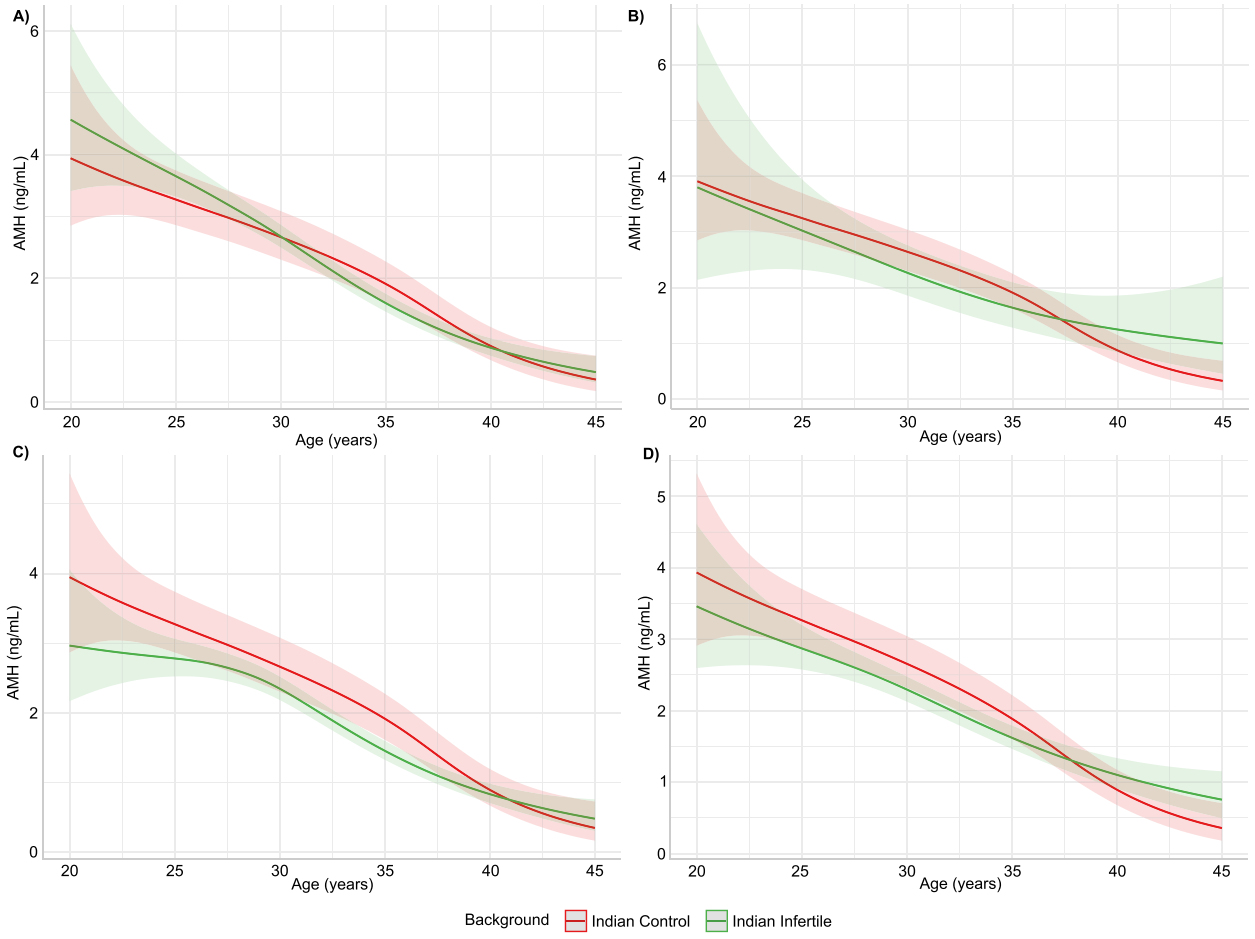

FIGURE 3 Comparison of AMH in Indian healthy controls and Indian women with infertility. (A) Indian healthy control (n = 400) *versus* Indian women with infertility (n = 1600). (B) Indian healthy control (n = 400) *versus* Indian women whose male partner had severe oligoasthenoteratozoospermia (n = 95). (C) Indian healthy control (n = 400) *versus* Indian women with infertility but not PCOS (n = 1384). (D) Indian healthy control (n = 400) *versus* Indian women with unexplained infertility (n = 757). Geometric median with 95% confidence interval (CI) calculated using smooth additive quantile regression model on age with background and an interaction between age and ethnicity. AMH = anti-Müllerian hormone; PCOS = polycystic ovary syndrome.

highlights the importance of undertaking studies of racial and ethnic backgrounds in healthy populations, rather than samples of convenience from infertility clinics, and confirms that in women with unexplained infertility there is an over-representation of diminished ovarian reserve.

Racial differences in AMH have previously been reported for both infertile and fertile populations (*Kotlyar and Seifer, 2021*), with in general lower age-specific values reported for African-American/Black, Hispanic and East Asian populations as compared to European women (*Armstrong and Plowden, 2012*; *Bleil et al., 2014*; *Seifer et al., 2009*). Across all ethnicities the age-related decline from early adulthood through to approximately age 50 and the menopause has been consistently observed (*Kelsey et al., 2011*; *Seifer et al., 2011*). However, subtle differences in age-specific ranges have been reported, with analyses of healthy Chinese women living in Beijing demonstrating typically higher AMH values up to age 25 years as compared to European women, and then AMH concentrations tended to be lower than Caucasian women after age 25, with increasing divergence with increasing age (*Nelson et al., 2020*). In contrast, Indian healthy women exhibited consistently lower AMH concentrations, potentially reflecting ethnic differences or altered cohort composition at earlier ages, as the healthy Indian women were extensively screened for PCOS.

Previous comparative analyses of AMH concentrations in South Asian populations compared with Europeans has been limited, with a recent systematic review only identifying a single-centre study from a UK fertility clinic assessing five different ethnicities including 214 women from the Indian subcontinent. The authors reported that despite initially higher AMH concentrations seen in South Asian patients compared to 384 European women, this difference disappeared in their multivariable analysis (*Bhide et al., 2015*). This study was limited by selection bias as all women were attending an infertility clinic, approximately 10% of all women had previous ovarian surgery, PCOS rates varied from 9 to 26% depending on ethnicity and up to 23.9% were smokers, all of which are key confounders and known to substantially impact AMH concentrations (*Bhide et al., 2015*). Comparative analyses of other biomarkers of ovarian reserve, like antral follicle count, have similarly been limited, however, the current findings of lower AMH in Indian women are consistent with previous analyses of 236 infertile Indian women living in Delhi and Ahmedabad

and 236 infertile Spanish women living in Madrid, where despite the Spanish women being 6 years older, antral follicle counts and day 3 FSH concentrations were similar and in multivariate analyses Indian ethnicity was associated with a lower AMH (*Iglesias et al., 2014*).

Age at natural menopause appears to vary across different regions, countries and ethnic groups (*Thomas et al., 2001*), with Indian women experiencing the menopause several years earlier than European or Australian women. This may be due to genetic variation (*Murabito et al., 2005*), but may also reflect differences in socioeconomic position (SEP) and environmental, lifestyle, reproductive or early childhood factors, which may manifest through epigenetic modification (*Li et al., 2021*). Lower AMH concentrations during adult life have consistently been shown to be associated with increased risk of earlier menopause (*Depmann et al., 2016*; *Nelson and Anderson, 2021*). That this study observed a lower AMH for each age strata of Indian women would be consistent with the known associations of lower AMH, lower primordial follicle pool size and earlier age at natural menopause (*Depmann et al., 2015*). Estimates from meta-analyses for education and occupation level both demonstrate a dose–response for later age at natural menopause, with increasing education or occupation level associated with increasing age at natural menopause. SEP and overall measures of health have also been positively associated with AMH concentrations (*Bleil et al., 2018*; *Vanni et al., 2022*). The mechanisms underlying the dose–response association between higher SEP and later menopause and higher AMH concentrations are largely unknown, but higher education and occupation levels but may be partially explained by lifestyle factors such as smoking and diet, which are known to adversely impact on AMH concentrations (*Freour et al., 2008*), or through potential epigenetic modification of ovarian ageing pathways (*Li et al., 2021*). A UK birth cohort study, predominantly in White women, also found that lower childhood, but not adulthood, social class was associated with earlier age at natural menopause (*Hardy and Kuh, 2005*). Adverse childhood experiences may include household crowding, father's occupation, no hot water supply in the house, shared bedroom and no car access (*Mishra et al., 2009*). Similarly early nutrition may impact, as a study of women from New Guinea where the median age of menopause in a population who had suffered severe and prolonged malnourishment, and who were consequently of short height and low weight, was estimated to be 4 years earlier than women in the same region with better nourishment (*Scagy, 1993*). Collectively many of these factors may be over-represented in the healthy Indian cohort.

In the comparison of AMH between healthy Indian women and Indian women with infertility, distinct age patterns were observed. That young infertile women with PCOS had higher AMH concentrations and effectively pulled up the median value of the young women with infertility is not surprising. PCOS has consistently been associated with higher AMH concentrations (*Iliodromiti et al., 2013*), reflecting both the increased antral follicle load characteristic of PCOS and their increased granulosa cell secretion of AMH (*Teede et al., 2019*). In women with a diagnosis of infertility that was directly attributable to their partner having severe oligoasthenoteratozoospermia, AMH concentrations were similar to healthy controls across all age strata. In contrast, in women with unexplained infertility, AMH concentrations were lower than healthy controls in women below 37 years, with the confidence intervals becoming wider, reflecting the fewer participants beyond age 37. The current study, and others, have previously reported a similar excessive-age-related decline in the functional ovarian reserve biomarker, AFC, in women with unexplained infertility (*Iliodromiti et al., 2016*; *Rosen et al., 2011*). Whether this is mainly a result of over-representation of women with low ovarian reserve among infertile patients, or this indicates an additional accelerated ovarian ageing above and beyond any ethnic differences and thereby even earlier menopause in women with infertility is unclear. Despite recognition of the ethnic differences in AMH, the predictive capacity of AMH with respect to egg oocyte yield is unchanged, with recent data from Japan and China showing that the underlying correlations of AMH with FSH dose and anticipated ovarian response are similar in European, Japanese and Asian women (*Ishihara and Arce, 2021*; *Nyboe Andersen et al., 2017*; *Qiao et al., 2021*).

The major strengths of the current study are that healthy Indian and European women were prospectively recruited and sampled in a standardized manner from the community, with a detailed medical history taken to ensure no factors were present that may contribute to a depleted ovarian reserve, but it must be acknowledged that healthy women were not known to have proven fertility. The large sample size enabled accurate representation of AMH across the reproductive lifespan, with reduced risk of incorrect model fitting due to inadequate data points. The use of additive models incorporating quantile regression ensured flexibility of the underlying relationships as it is distribution agnostic, robust to outliers and avoids overfitting. It is acknowledged that the cross-sectional nature of the AMH data limits the potential for longitudinal extrapolation of the reference ranges, and fitting to external populations would provide additional validity. In India healthy women and infertile women attended the clinics at the same time, and similar assay methodology was used, minimizing the possibility of measurement bias. Unfortunately, contemporaneous European healthy and infertile women were not available. In addition, similar protocols in data collection and AMH assessment were applied across all the participating reproductive centres within Europe, further reducing between-centre variation. It is acknowledged that AMH was measured in two different laboratories, but the use of the same AMH assay on automated platforms, which were confirmed to show equivalence though common quality control material between the two laboratories, gives further confidence in the comparability of the results. Additional confounders such as BMI could have contributed to the differences observed between European and Indian women. However, BMI and other baseline data were not available for individual European women and the study was specifically limited to non-obese participants to minimize the risk of a negative effect of adiposity on AMH (*Moslehi et al., 2018*). Lastly, although the Indian populations were recruited from Maharashtra, Goa and Karnataka, this population and the associated AMH reference values are similar to national laboratory data, suggesting that the findings are generalizable to women living on the Indian subcontinent (*Palgamkar et al., 2021*).

It is concluded that AMH declines with advancing age in both European and Indian healthy women, but AMH

is substantially lower in healthy Indian women at all ages, consistent with their known earlier age at natural menopause. Infertile Indian women have variable differences in AMH compared to healthy Indian controls, with the extent and direction of differences primarily reflecting the underlying cause of infertility. Recognition of ethnicity and cause-specific differences are critical to ensure accurate contextualizing of results and clinical outcomes for patients.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2022.06.023.

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