SM Journal of Gynecology and Obstetrics ISSN: 2573-6744

Research Article

Does ethnicity affect ovarian reserve? A retrospective study of Anti-Mullerian hormone levels in Leicester UK

Kanishka Gogna MBChB[1], Ayisha A. Ashmore MPH MBBS[1], Alex S. Harrison PhD MSc BSc[3], Neelam Potdar MD MSc FRCOG[1,2]

[1]University Hospitals of Leicester NHS Trust, Leicester, UK

[2]Department of Health Sciences, University of Leicester, Leicester, UK

[3]Department of Health Sciences, University of York, York, UK

Abstract

Objective: This study wished to ascertain whether women undergoing fertility treatment had varying AMH levels based on their ethnic group. Our second objective was to assess the relationship between ethnicity, age and whether further fertility treatment was undertaken.

Methods: Single centre retrospective observational study. Data were collected from women who presented to Leicester Fertility Clinic with primary subfertility between 2017 and 2019. Age, ethnicity, fertility outcomes and AMH results (pmol/L) were obtained from the electronic records. Data were also collected on women's polycystic ovary syndrome (PCOS) status, follicle stimulation hormone levels (FSH) and antral follicle count (AFC). Univariate analysis compared AMH with age and ethnicity, respectively and further logistic regression modelling was performed. Further statistical testing was used to determine with there were differences in fertility treatment between different ethnic and age groups.

Results: A total of 1249 women included in the study. Chi^2 testing demonstrated a statistically significant difference in AMH levels between ethnic groups (p= 0.052). Further logistic regression modelling found that being an Asian ethnicity was not a significant predictor of reduced AMH level (p=0.90) independent of PCOS status, FSH and age. There was also a statistically significant difference between ethnic groups in women who had fertility treatment in the age 40-42 years (p=0.037).

Conclusion: This study shows that ethnicity does not predict lower AMH levels directly. However, larger sample size studies are required to assess the rate of change in AMH in women based on age and whether certain ethnic groups seek fertility treatment at a later age.

Keywords: AMH; Infertility; Ovarian reserve

Introduction

Anti-Mullerian hormone (AMH) has been used as a reliable marker of ovarian reserve in the investigation and treatment of fertility patients for many years [1]. Recently studies have begun to evaluate the reasons behind the differences in AMH in populations and whether these differences could account for varying success in assisted reproductive techniques (ART). Genetic factors as well as obesity, BMI, smoking have all been considered to have an impact on AMH [2]. However the most prominent factor associated with declining AMH is increasing age [3,4]. In fact Loy et al. reported a 0.38ng/mL reduction in AMH per 1 year of increasing age in a study of Chinese women in Singapore [4]. The findings in the evidence base are mixed in determining the relationship between ethnicity and AMH. Another paper demonstrated no statistical variation in AMH levels between different ethnic groups in the UK [5]. However, other studies conducted in the USA have shown differences in AMH levels between ethnic groups with a potentially independent effect [6,7].

Submitted: 29 November 2022 | **Accepted:** 28 December 2021 | **Published:** 31 December 2021

***Corresponding author:** Kanishka Gogna, Kensington Building, Leicester Royal Infirmary, Infirmary Square, Leicester, LE1 5WW, Tel: 07805499329

Citation: Gogna K, Ashmore AA, Harrison AS, Potdar N (2021) Does ethnicity affect ovarian reserve? A retrospective study of Anti-Mullerian hormone levels in Leicester UK. SM J Gynecol Obstet 8: 8.

Materials and Methods

The study utilised single centre retrospective observational approach based at Leicester Royal Infirmary and Fertility Centre, UK. Data were collected from patients who had been referred from primary care to infertility clinic after 12 months of trying to conceive without contraception. Women included in the study were also required to meet the criteria for NHS funding. This involved having no previous children, age 23-43 years, having a BMI <30kg/m^2 and being a non-smoker. Women included in this study were referred between January 2017 and December 2019. A total of 1249 women were included who had their AMH level measured. All blood samples were sent to one single laboratory, and we used an AMH cut-off value of 5.5pmol/L and above for providing ART (as per NICE guidance).

Data for the patients' ethnicity was gathered from hospital demographic records and self-identification. Data for serum AMH and follicular phase FSH were collected from electronic laboratory records. Age, antral follicle count (AFC), fertility treatments and outcomes were collected using electronic hospital records.

Ethnicity was classified into 4 subgroups which were defined as White, Asian, Black and Other/Mixed simplified from the Office of National Statistics classification of ethnicity.

Statistical Analysis

Statistical analyses were performed using SPSS 26. Continuous variables were checked for normality of distribution, those with normal distribution were presented as Mean +/- SD and those with non-normal distribution as Median and interquartile range (IQR). Serum AMH was the primary outcome variable. It was assessed as a continuous variable and for ease of analysis categorised into 2 subgroups of <5.5 pmol/L and 5.5pmol/L and above.

Initially bivariate descriptive analysis was performed to test for differences between age and AMH as well as ethnicity and AMH. Univariate linear regression was then performed to demonstrate the relationship between age and AMH. Logistic regression was performed to determine whether there was an association between ethnicity and AMH independent of age.

Secondly, Chi^2 analysis investigated whether there was a difference in between in age or ethnicity in women who underwent fertility treatment.

Results

A total of 1249 women were included in this study (see figure 1). The mean age at the time of AMH collection was 32.5 years. The mean AMH level was 20.77pmol/L. 55.7% of women were White, 37.9% were Asian, 3.6% were Black and 2.8% were Mixed or Other ethnicity (see table 1 and figure 2).

Multiple linear regression demonstrated that age was a significant predictor for AMH (Beta = -1.03, p = 0.00). The overall model fit was R^2 =0.91 (see figure 3). FSH was also a significant predictor of AMH (Beta= -0.50, p=0.00). This means that with increasing age or FSH the AMH reduces (see table 3 and figure 4). R^2 for this model was 0.11.

We also investigated whether AFC was able to predict AMH results. Only 468 women had their AFC recorded and an independent samples t-test was performed to check for differences in the populations with and without the AFC result. We found that there was a statistically significant difference in age (mean difference= -0.60, p=0.20) and FSH (mean difference = 1.13, p= 0.00) between the population with AFC recorded and the population without AFC recorded. However, these differences were small and clinically not relevant. Further linear regression analysis was performed which found that AFC was a significant predictor of AMH (see figure 5). It demonstrated that with every unit increase in AFC, the AMH increased by 1.2 units (Beta 1.21, p=0.00). However, when AFC was added to the model, age and FSH as predictors of AMH became statistically insignificant (see table 4).

A Chi^2 test was performed which showed that there was not a statistically significant difference in AMH between the ethnic groups when stratified by age (p=0.052) (see table 5).

Logistic regression analysis was performed where the AMH variable was coded as 0 if the AMH was considered normal (>5.5pmol/L and above) and 1 if the AMH was low (<5.5 pmol/L). The Hosmer and Lemeshow Test was not statistically significant (p=0.556). The model found that being an Asian ethnicity was not a significant predictor of AMH level (p=0.90) (see table 6). In fact, having an Asian ethnicity compared to a White ethnicity could not reliably predict whether one's AMH was normal or low.

The model confirmed that a woman older than 35 years were more likely to have an AMH less than 5.5pmol/L (see table 6). It also confirmed that women with a higher FSH would be four times more likely to have a low AMH. The model found that PCOS was not a reliable indicator for predicting low AMH.

We compared fertility outcome to women's AMH results and whether this was affected by age or ethnicity. As many patients did not have any fertility treatment, our population size was significantly reduced. As such, we performed an independent samples t test which showed that there was no difference in age between the two populations (p=0.86). However, a significant significance was found between the two populations studied with regards to their AMH levels (p=0.02). Chi^2 was also performed and this revealed that there were no significant differences in ethnicities between the populations (p=0.11).

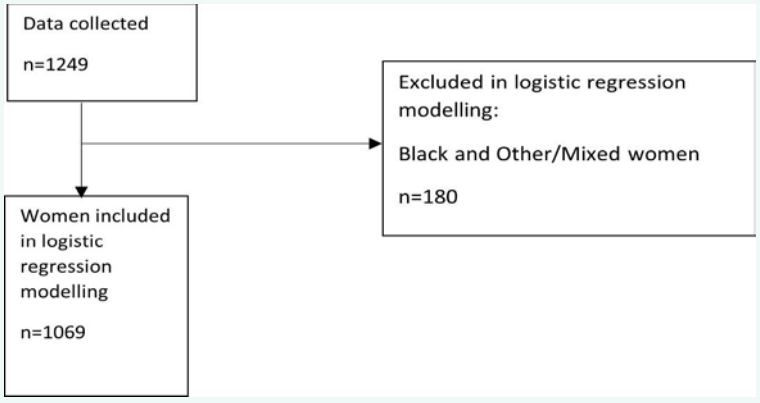

Figure 1 Consort flow diagram of women included in study.

Table 1: Demographics and Anti-Mullerian Hormone Levels (pmol/L).

	Count	%	Age		Anti-Mullerian Hormone (pmol/L)			
			Mean	SD	Mean	SD	95% Confidence Interval	
							Lower Bound	Upper Bound
White	697	55.7	32.30	5.10	19.78	15.65	18.61	20.94
Asian	475	37.9	32.83	4.89	21.65	18.5	19.98	23.32
Black	45	3.6	33.73	4.83	22.62	23.16	15.66	29.57
Mixed and Other	32	2.8	31.09	5.01	26.96	25.25	17.86	36.07
Total	1249	100	32.5	5.02	20.7	17.4	19.81	21.74

Table 2: Showing the demographics of the population and the split of those with <5.5 and 5.5 and above AMH (pmol/L).

		AMH				Total	Chi² P value
		<5.5		5.5+			
		Count	%	Count	%	Count	
Age (years)	**<35**	64	8.3%	705	91.7%	769	<0.001
	35-37	45	22.8%	152	77.2%	197	
	38-39	24	25.5%	70	74.5%	94	
	40-42	47	42.0%	65	58.0%	112	
Fertility Treatment	**No**	141	25.3%	416	74.7%	557	<0.001
	Yes	39	6.3%	576	93.7%	615	
Polycystic Ovary Syndrome	**No**	175	15.5%	955	84.5%	1130	0.527
	Yes	5	11.9%	37	88.1%	42	
Ethnicity	**White**	107	15.4%	590	84.6%	697	0.994 (For White and Asian only)
	Asian	73	15.4%	402	84.6%	475	
	Black	8	17.8%	37	82.2%	45	
	Other and Mixed	2	6.3%	30	93.8%	32	

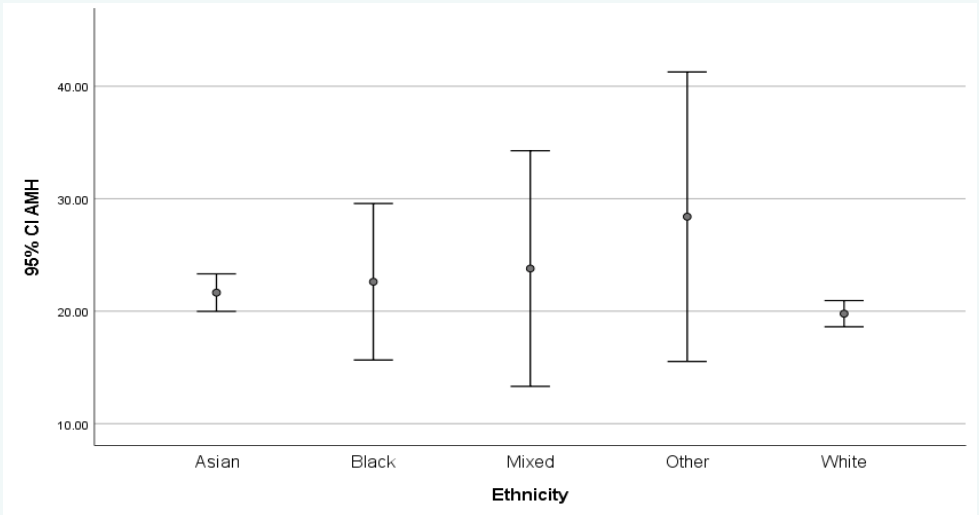

Figure 2 Boxplot showing Mean AMH by Ethnicity with 95% CI.

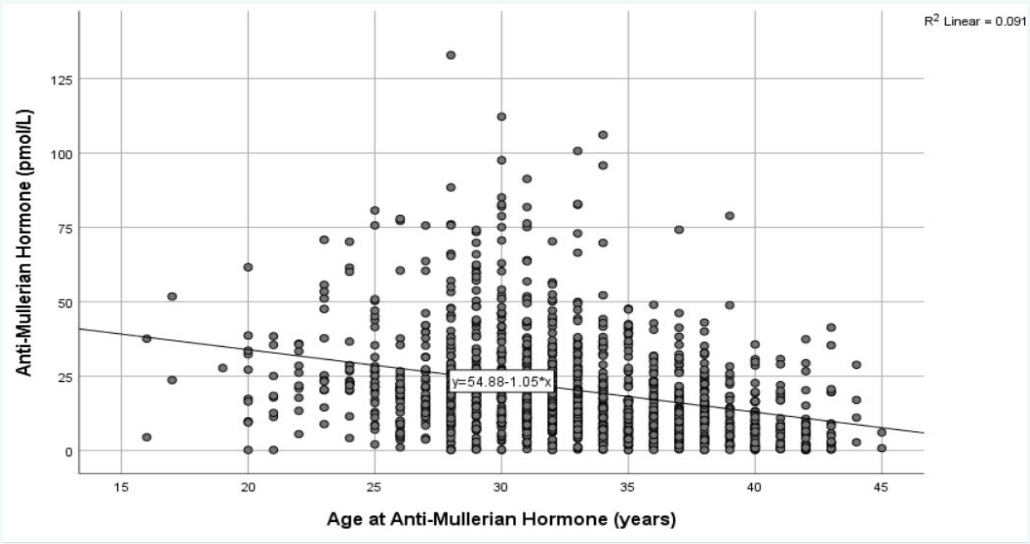

Figure 3 Relationships between Anti-Mullerian Hormone and Age.

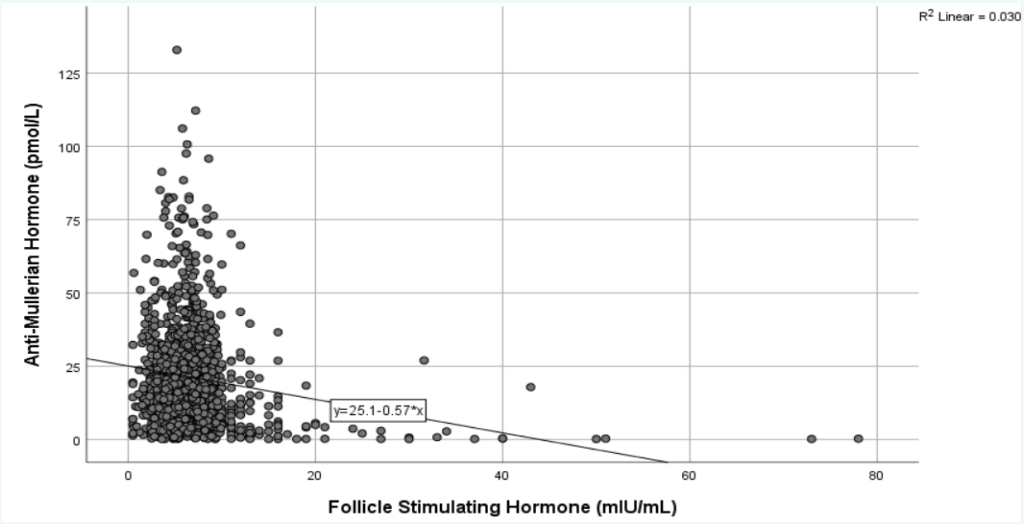

Figure 4 Relationships between Anti-Mullerian Hormone and Follicle Stimulating Hormone.

We then compared whether there was a difference in ethnicity per age group between women who underwent fertility treatment and those women who did not. When comparing all ethnic groups, there was a statistically significant difference between women who had fertility treatment in the age 40-42 years bracket (p=0.037). However, due to low number of women who were from a Black or Other and Mixed group we compared whether there was a difference between White women and Asian women. We found there was a statistically significant difference between White and Asian women undergoing fertility treatment in age 35-37 years (p=0.05) and 40-42 years (p=0.01). We noticed that in the 35-37 years age, more Asian women received fertility treatment but this effect was reversed in the 40-42 years age group.

Discussion

Main Findings

This study has showed no direct association between ethnicity and AMH. However, a higher proportion of Asian women had been diagnosed with PCOS than White, Black, Other or Mixed women. After controlling for confounding factors of age, PCOS, FSH, the differences in AMH levels between the ethnic groups were not found to be significant. Increasing age was directly correlated with a lower AMH.

Strengths and limitations

The study population comprised of women selected from fertility clinic with similar characteristics. They were all selected

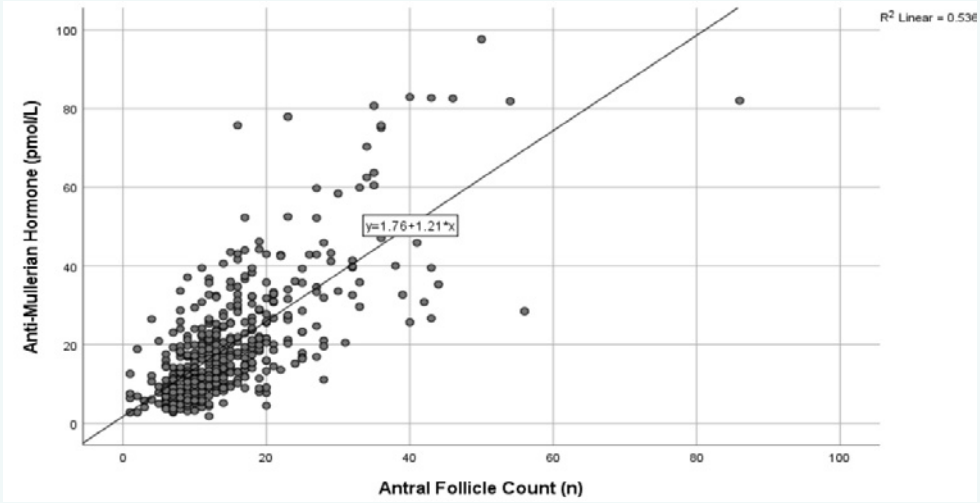

Figure 5 Relationships between Anti-Mullerian Hormone and Antral Follicle Count.

Table 3: Logistic Regression of Age and Follicle Stimulating Hormone as predictors for Anti-Mullerian Hormone.

			95% Confidence Interval	
	Odds Ratio	**P-value**	**Lower Bound**	**Upper Bound**
Age at Anti-Mullerian Hormone (years)	-1.03	0.00	-1.22	-0.83
Follicle Stimulating Hormone (mIU/mL)	-0.50	0.00	-0.68	-0.32

Table 4: Logistic Regression of Age, Follicle Stimulating Hormone and Antral Follicle Count as predictors for Anti-Mullerian Hormone.

			95% Confidence Interval	
	Odd Ratio	**P-value**	**Lower Bound**	**Upper Bound**
Age at Anti-Mullerian Hormone (years)	-0.08	0.49	-0.31	0.15
Follicle Stimulating Hormone (mIU/mL)	-0.10	0.59	-0.46	0.26
Antral Follicle Count (n)	1.21	0.00	1.09	1.32

from a local British population with high ethnic diversity; Leicester has 28% Asian population which is one the largest proportions in the UK. In our study, 44% of the women included were from an ethnic minority background and this is a major strength of our study. Our Asian sub-group alone accounted for 38% of our sample. Therefore, our findings within this group are particularly representative of the general and local population. Conversely, a limitation of our study is that we had small numbers of Black, Other and Mixed ethnic minority women. Consequently, our study is likely to have been underpowered to demonstrate associations and differences within these groups. All patients were selected from the fertility clinic with primary subfertility, a BMI of less than 30kg/m^2 and were non-smokers. This meant that we could attribute our findings to specific differences in a relatively homogenous population. However, this does make our results less generalisable to the wider population of subfertile women. Another strength of our study was that the AMH samples were all sent to the validated and accredited lab leading to consistent results which were comparable.

Another limitation of our study which could lead to selection bias is the retrospective design. However, we included all women who matched strict selection criteria which was predetermined to reduce this risk. Lastly, we were not able to control for all factors that may affect fertility. PCOS may have been underdiagnosed and this could significantly affect our results. We also did not have a complete dataset for AFC and our preliminary analysis showed that AFC significantly affected AMH results.

Interpretation

The literature demonstrates conflicting evidence in relation to the association between ethnicity and AMH levels. Many studies have been performed in the USA and in Europe but there are a limited number of studies in the UK population. Bhide et al. reported similar findings of no statistically significant differences

Table 5: Chi² analysis of ethnicity and Anti-Mullerian Hormone stratified by age.

				AMH (pmol/L)						P value for Chi²
				<5.5			5.5 and above			
				Count	Row %	Column %	Count	Row %	Column %	
Age (years)	<35	Ethnicity	White	46	9.8%	66.7%	422	90.2%	56.0%	0.143
			Asian	18	6.0%	26.1%	283	94.0%	37.6%	
			Black	4	14.3%	5.8%	24	85.7%	3.2%	
			Other and Mixed	1	4.0%	1.4%	24	96.0%	3.2%	
	35-37		White	22	20.0%	46.8%	88	80.0%	55.0%	0.944
			Asian	23	26.4%	48.9%	64	73.6%	40.0%	
			Black	1	16.7%	2.1%	5	83.3%	3.1%	
			Other and Mixed	1	25.0%	2.1%	3	75.0%	1.9%	
	38-39		White	13	22.4%	50.0%	45	77.6%	60.8%	0.624
			Asian	11	30.6%	42.3%	25	69.4%	33.8%	
			Black	2	33.3%	7.7%	4	66.7%	5.4%	
			Other and Mixed	0	0.0%	0.0%	0	0.0%	0.0%	
	40-42		White	26	42.6%	54.2%	35	57.4%	48.6%	0.386
			Asian	21	41.2%	43.8%	30	58.8%	41.7%	
			Black	1	20.0%	2.1%	4	80.0%	5.6%	
			Other and Mixed	0	0.0%	0.0%	3	100.0%	4.2%	
	Total		White	107	15.4%	56.3%	590	84.6%	55.7%	0.524
			Asian	73	15.4%	38.4%	402	84.6%	38.0%	
			Black	8	17.8%	4.2%	37	82.2%	3.5%	
			Other and Mixed	2	6.3%	1.1%	30	93.8%	2.8%	

Table 6: Logistic regression model predicting AMH 5.5pmol/L and below.

	P value	Odds Ratio	95% C.I.for Odds Ratio	
			Lower	Upper
Age Variable (Base <35 years)	<0.001			
Age 35-37 years	<0.001	3.520	2.231	5.552
Age 38-39 years	<0.001	3.120	1.708	5.702
Age 40-42 years	<0.001	7.459	4.547	12.238
FSH (8.9 mIU/mL and above)	<0.001	4.388	2.978	6.467
PCOS (Yes)	0.815	0.884	0.316	2.477
Ethnicity (Asian)	0.900	1.024	0.706	1.485
Constant	<0.001	0.061		
n = 1,069, Percentage Correctly Predicted 85.4%, Nagelkerke R2 = 0.215, Hosmer Lemeshow p value =0.556				

in serum AMH between different ethnic groups. Their sample population was derived from a tertiary referral centre with a diverse British population and comparisons may be drawn with our own study population. Another reason for differences between findings in the UK and other international studies may be the influence of environmental factors which we have not accounted for in our study. For instance, low vitamin D has been associated with lower AMH levels [8] and has been postulated to lead to poorer fertility outcomes in women living on the Arabian Peninsula [9]. This may be relevant in our study as Asian women from certain religious backgrounds are more likely to have less skin exposure to sunlight and therefore are often vitamin D deficient. Genetic factors have also been well studied as potential contributors to differences in ovarian reserve and these factors may have differing prevalence between our population and those of other studies [2].

PCOS is another factor which has been heavily implicated in fertility outcomes and is associated with higher AMH levels [10,11]. Our study had a small number of women with a diagnosis of PCOS (3.7%) which, in comparison to the UK population of 8-13%, is low [12]. In fact, Mani et al. report that Leicestershire has one of the lowest rates of PCOS due to underreporting [12]. Consequently, many women may have had a higher AMH result which would not be truly reflective of their actual ovarian reserve. This would result in inadequate adjustment during our logistic regression modelling and thus may account for the non-statistically significant findings following modelling as compared to the Chi^2 test.

In our study, only half the women included had ART and this significantly reduced our sample size. When testing for differences between the treated (ART) and non-treated populations, we noticed there was a statistically significant difference in their AMH level. One reason for this may be that women with very low AMH levels may not have been eligible for NHS funded ART and therefore did not undergo treatment. However, this would be a very small proportion of women and would not fully explain this difference; but it is an interesting finding which warrants further evaluation. Furthermore, we also noticed that larger proportions of Asian women sought fertility treatment in the 35-37 years age group whilst in the 40-42 years age group, there was a higher proportion of White women. Access and utilisation of fertility treatment between ethnic groups may have on future fertility outcomes of women between ethnicities [13]. Black women in North America have been reported to experience significantly longer durations of infertility prior to seeking care compared to White women [13,14]. A number of reasons exist for these differences have been postulated and include funding, access, level of education and awareness [14-17]. Fertility awareness in particular has been reported to differ between ethnicities with women with lower fertility awareness waiting longer before seeking medical help [16,17]. One study evaluating fertility awareness in Indian women identified that less than half of the women studied understood the need for assisted fertility treatment and donor oocytes in advanced ages [18]. This may be somewhat reflected in our study results if Asian women in older age groups were not presenting for fertility treatment.

Suggestions for future research

We would recommend further research using a prospective study design with a larger sample size. We would suggest studying differences in AMH between the subfertile population which present to fertility clinics and the fertile population in order to draw more generalisable comparisons. We would also suggest a study to investigate the rate of decline in AMH, particularly after the age of 35 years between ethnic groups. Lastly, we would also recommend a study to assess the awareness of fertility problems within minority ethnic populations as one study reported a longer period to presentation to fertility clinics by Asian women [19].

Conclusion

In conclusion, our study found that ethnicity does not predict lower AMH. However, age was found to be a significant factor in AMH decline with women of higher ages having a lower AMH. We also found that in women between 40 and 42 years old, there were differences between different ethnic groups on whether they sought fertility treatment. We therefore recommend that women should be counselled to seek fertility advice and treatment at an earlier stage if they are experiencing subfertility.

Conflicts of interest/Competing interests

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

Consent for publication

All named contributors' consent for publication.

Availability of data and material

The authors confirm that the data supporting the findings of this study are available within the article.

Code availability

Further data set available on request

Authors' contributions

KG and AAA collected, analysed and interpreted data gathered and wrote the manuscript. ASH analysed and interpreted the data and reviewed the manuscript. NP conceived the idea for the study. NP and KG reviewed the final manuscript. All authors read and approved the final manuscript. All authors listed have contributed towards the article and have read and approved the final version.

References

1. Broer SL, Broekmans FJM, Laven JSE, Fauser BCJM. Anti-Müllerian hormone: ovarian reserve testing and its potential clinical implications. *Hum Reprod Update*. 2014;20(5):688-701. doi:10.1093/humupd/dmu020

2. Tal R, Seifer DB. Potential mechanisms for racial and ethnic differences in antimüllerian hormone and ovarian reserve. *Int J Endocrinol*. 2013;2013:818912. doi:10.1155/2013/818912

3. de Kat AC, van der Schouw YT, Eijkemans MJC, et al. Back to the basics of ovarian aging: a population-based study on longitudinal anti-Müllerian hormone decline. *BMC Med*. 2016;14. doi:10.1186/s12916-016-0699-y

4. Loy SL, Cheung YB, Fortier MV, et al. Age-related nomograms for antral follicle count and anti-Mullerian hormone for subfertile Chinese women in Singapore. *PLoS ONE*. 2017;12(12):e0189830. doi:10.1371/journal.pone.0189830

5. Bhide P, Gudi A, Shah A, Homburg R. Serum anti-Mullerian hormone levels across different ethnic groups: a cross-sectional study. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2015;122(12):1625-1629. doi:10.1111/1471-0528.13103

6. Iglesias C, Banker M, Mahajan N, Herrero L, Meseguer M, Garcia-Velasco JA. Ethnicity as a determinant of ovarian reserve: differences in ovarian aging between Spanish and Indian women. *Fertility and*

Sterility. 2014;102(1):244-249. doi:10.1016/j.fertnstert.2014.03.050

7. Nelson SM, Aijun S, Ling Q, et al. Ethnic discordance in serum anti-Müllerian hormone in healthy women: a population study from China and Europe. *Reproductive BioMedicine Online*. 2020;40(3):461-467. doi:10.1016/j.rbmo.2019.11.013

8. Merhi ZO, Seifer DB, Weedon J, et al. Circulating Vitamin D Correlates with Serum Anti-Mullerian Hormone Levels in Late Reproductive-Aged Women: Women's Interagency HIV Study. *Fertil Steril*. 2012;98(1):228-234. doi:10.1016/j.fertnstert.2012.03.029

9. Tabbalat AM, Pereira N, Klauck D, Melhem C, Elias RT, Rosenwaks Z. Arabian Peninsula ethnicity is associated with lower ovarian reserve and ovarian response in women undergoing fresh ICSI cycles. *J Assist Reprod Genet*. 2018;35(2):331-337. doi:10.1007/s10815-017-1071-7

10. Laven JSE, Mulders AGMGJ, Visser JA, Themmen AP, De Jong FH, Fauser BCJM. Anti-Müllerian hormone serum concentrations in normoovulatory and anovulatory women of reproductive age. *J Clin Endocrinol Metab*. 2004;89(1):318-323. doi:10.1210/jc.2003-030932

11. Pigny P, Merlen E, Robert Y, et al. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. *J Clin Endocrinol Metab*. 2003;88(12):5957-5962. doi:10.1210/jc.2003-030727

12. Mani H, Liarakos AL, Levy MJ. Health in the UK. *The Lancet*. 2019;394(10201):828. doi:10.1016/S0140-6736(19)31242-5

13. Tierney K. Is there evidence of weathering among women seeking fertility treatments?: Evidence and insights. *Social Science & Medicine*. 2020;247:112816. doi:10.1016/j.socscimed.2020.112816

14. Jain T. Socioeconomic and racial disparities among infertility patients seeking care. *Fertility and Sterility*. 2006;85(4):876-881. doi:10.1016/j.fertnstert.2005.07.1338

15. Dieke AC, Zhang Y, Kissin DM, Barfield WD, Boulet SL. Disparities in Assisted Reproductive Technology Utilization by Race and Ethnicity, United States, 2014: A Commentary. *Journal of Women's Health*. 2017;26(6):605-608. doi:10.1089/jwh.2017.6467

16. Pedro J, Brandão T, Schmidt L, Costa ME, Martins MV. What do people know about fertility? A systematic review on fertility awareness and its associated factors. *Ups J Med Sci*. 2018;123(2):71-81. doi:10.1080/03009734.2018.1480186

17. Swift BE, Liu KE. The Effect of Age, Ethnicity, and Level of Education on Fertility Awareness and Duration of Infertility. *Journal of Obstetrics and Gynaecology Canada*. 2014;36(11):990-996. doi:10.1016/S1701-2163(15)30412-6

18. Mahey R, Gupta M, Kandpal S, et al. Fertility awareness and knowledge among Indian women attending an infertility clinic: a cross-sectional study. *BMC Womens Health*. 2018;18(1):177. doi:10.1186/s12905-018-0669-y

19. Lamb JD, Huddleston HG, Purcell KJ, et al. Asian ethnicity is associated with decreased pregnancy rates following intrauterine insemination. *Reprod Biomed Online*. 2009;19(2):252-256. doi:10.1016/s1472-6483(10)60081-8.