

# Anti-Mullerian Hormone Levels in Indian Women Seeking Infertility Treatment: Are Indian Women Facing Early Ovarian Senescence?

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ABSTRACT

**Background:** Antimullerian hormone (AMH) is a key marker of ovarian reserve and predictor of response to fertility treatment. **Aim:** To understand the prevalence of low ovarian reserve in Indian women seeking infertility treatment, compare their AMH with age-matched fertile Indian controls and understand ethnic differences with Caucasian women. **Setting and Design:** Retrospective observational study done as collaboration between our *in vitro* fertilization centre and a laboratory with Pan-India presence. **Materials and Methods:** Women aged 20–44 years were selected as Group A (seeking infertility treatment  $n = 54,473$ ), Group B (conceived naturally in the past;  $n = 283$ ) and Group C (data of Caucasian women;  $n = 718$ ). Serum AMH levels were measured and descriptive analysis done. **Statistical Analysis:** Descriptive statistics and Chi-square test. **Results:** In Group A, 28.7%, 48.7% and 70.6% of women aged <30 years, 30–34 years and 35–39 years had serum AMH levels  $\leq 2$  ng/mL and the proportions were higher than Group B. The rate at which median AMH decreased was 1.1–2 times faster in Group B as compared to Group C. The decrease in median AMH across age groups in Group A was similar to Group B. **Conclusions:** Indian women in their late twenties and early thirties visiting fertility centers showed a worrisome trend of low AMH. Our study can be used as a reference for those women considering postponing pregnancy. It may be time to look at intangible cultural factors linked to social habits, ethnicity, diet, genetic predispositions, and environmental factors like endocrine disrupting chemicals contributing to premature ovarian senescence.

**KEYWORDS:** Anti-Mullerian hormone, infertility, ovarian reserve, young Indian women

## INTRODUCTION

Antimullerian hormone (AMH) is a glycoprotein hormone produced by the granulosa cells of the preantral and small antral follicles<sup>[1]</sup> and is considered a surrogate marker for ovarian reserve. AMH levels reach a peak at 20–25 years of age<sup>[2]</sup> and gradually decline until they become undetectable in the menopausal and postmenopausal periods.<sup>[3]</sup> Declining AMH levels indicate declining ovarian reserves and ovarian senescence.

AMH is used for evaluation of infertility to guide the clinician in making appropriate decisions regarding

management of women seeking conception.<sup>[3]</sup> In recent years, prediction of future reproductive potential has become vital because of the trend in delayed childbearing due to various social, cultural and economic factors. AMH can be a useful tool for the clinician in counseling women seeking to delay conception regarding fertility potential and preservation.<sup>[4]</sup> As opposed to other

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markers of ovarian reserve, AMH levels do not exhibit significant variability over the menstrual cycle or even between different menstrual cycles.<sup>[5,6]</sup> Automated assays are robust and demonstrate superior prediction of ovarian reserve over alternative laboratory markers.<sup>[7,8]</sup>

Ethnicity has been shown to affect age-related declines in AMH levels and ovarian function over time. Very few studies have assessed the prevalence of low ovarian reserve and possible subfertility in Indian women and the comparison of the age-specific AMH values to other ethnic groups. It is important that decisions regarding fertility and childbearing are taken by a woman in an informed manner. The clinician therefore needs to be aware of the factors to be considered besides the clinical factors and age while counseling and be aware of the racial/ethnic differences in the counseled group.

This large study was conducted to understand the prevalence of low ovarian reserve in Indian women seeking infertility treatment, to compare their AMH with age-matched fertile Indian controls and to understand ethnic differences in AMH values with Caucasian women.

### MATERIALS AND METHODS

This study included retrospective data from women aged 20–44 years seeking infertility treatment and those who had undergone assessment of serum AMH (Group A; *n* = 54,473). The data was retrieved from the database of a large referral laboratory for all women for a period of 3 years from May 2017 to April 2020 and represents data from across India. Apparently healthy women aged 20–44 years who had history of natural conception and no history of infertility visiting the pediatric outpatient department with their wards in the period from March 2020 to February 2021 were included into the study and AMH testing was conducted (Control group; Group B; *n* = 283). These women had no known history of a significant illness including gynecological illnesses like polycystic ovarian syndrome and endometriosis, previous pelvic surgery, genetic diseases, use of contraceptives, smoking and had regular menstrual cycles. Data of apparently healthy Caucasian women aged 20–44 years and not taking contraceptives (Group C; *n* = 718) was also included.<sup>[9]</sup> The Data of Group C was obtained from the pack insert of Elecsys® AMH kit.<sup>[9]</sup>

Serum was stored at - 20°C and tested for serum AMH levels within a period of 5 days using the fully automated Elecsys® AMH assay based on the electrochemiluminescence assay (Roche Diagnostics GmbH, Mannheim, Germany). The testing for Groups A and B was carried out on the Cobas e 601 system.

### Statistical analysis

Data of Group A was collected for a predetermined time period of 3 years. In Group B, data was collected over the study period to obtain at least 10 samples in each age group. The proportion of women in Group A with AMH ≤2 ng/mL and AMH ≤1 ng/mL was calculated.<sup>[5,6]</sup> The distribution of AMH levels was compared between Group A and B using Chi square analysis. The median AMH and the percent reduction across successive age groups was compared between Groups A, B and C. Descriptive statistics and Chi-square test were used for statistical analysis.

The study was conducted in accordance with the principles of Declaration of Helsinki and Institutional Ethics committee approval (EC/1091/2021) was obtained. The Institutional Ethic committee has permitted publication of the retrospective data in Group A. Written informed consent was obtained for subjects of Group B.

### RESULTS

Groups A, B and C consisted of 54473, 283 and 718 women, respectively. The mean age of the women was 31.4 years in Group A and 32.2 years in Group B. The distribution of women from Group A and B across AMH values in different age groups is summarized in Table 1 and the distribution of women with low AMH is represented in Figure 1. In Group A, 28.7% of those below 30 years had AMH levels of 2 ng/mL or below and 11.7% had AMH of 1 ng/mL or lower. In the same group, 48.7% of women between the ages of 30–34 had AMH of 2 ng/mL or lower and 23.3% had AMH below 1 ng/mL. This showed that there was a rise in percentage of women having AMH below 2 ng/mL as their age increased.

The percent of women aged <30 years having AMH levels ≤2 ng/mL or ≤1 ng/mL was numerically higher

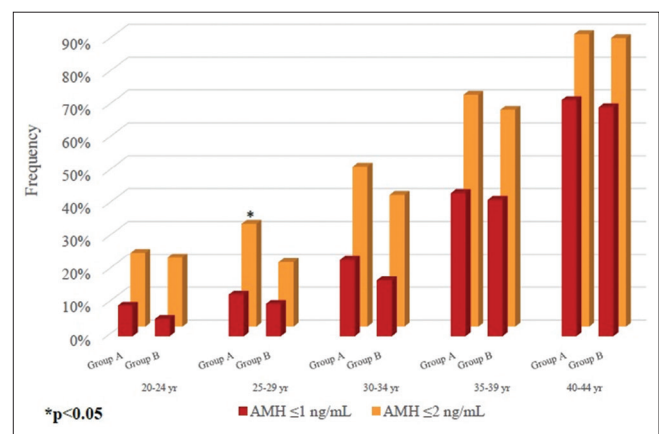


Figure 1: Distribution of Antimullerian hormone values (ng/mL) in Group A and Group B by age groups

in Group A as compared to Group B (28.7% vs. 20% for AMH ≤2 ng/mL [ $P = 0.086$ ]; 11.7% vs. 8.8% for AMH ≤1 ng/mL [ $P = 0.411$ ]). Similar results were obtained in the age group 30–34 years (48.7% vs. 40.2% for AMH ≤2 ng/mL [ $P = 0.066$ ]; 23.3% vs. 17.1% for AMH ≤1 ng/mL [ $P = 0.116$ ]).

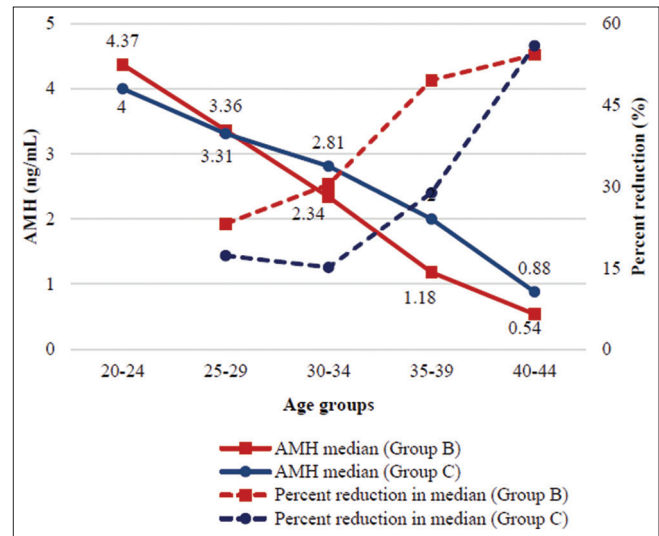
The distribution of median AMH values and the percent fall in AMH across successive age groups in Groups B and C is shown in Figure 2. The median AMH values up to 29 years were similar in both groups. The median AMH value in any age group was lower in Group B as compared to Group C from the age of 30 years. The AMH values were lower in successively increasing age groups in both Group B and Group C. However, the decrease in AMH (median) values between successive age groups was greater in Group B as compared to Group C. The rate at which median AMH decreased between successive age groups was 1.1–2 times higher in Group B. Group B showed a sharp decrease in the median AMH values from age 30–34 years to 35–39 years. The trend of decrease in median AMH values across age groups in Group A was similar to Group B [Table 2].

**DISCUSSION**

This large Pan-India study based on the laboratory data

of more than 50,000 women seeking infertility treatment offers some insights into the trend of declining AMH levels in Indian women, particularly among the younger age groups. It also demonstrates a faster rate of decline in AMH levels with age in healthy Indian women as compared to healthy Caucasian women.

In our study, the proportion of Indian women with low AMH was numerically higher in the group seeking



**Figure 2:** Differences in median Antimullerian hormone in successive age groups in Group B and Group C

**Table 1: Distribution of serum antimullerian hormone levels in Group A and Group B**

Age groups (years)	Group	Sample size (n)	Frequency distribution by AMH level (ng/mL) categories (%)											
			0-0.55	0.56-1.00	Up to 1	1.01-1.55	1.56-2.00	2.01-2	Up to 2	2.01-2.55	2.56-3.00	2.01-3	3.01-4	>4
20-24	Group A	6276	6.6	2.7	9.3	7.4	5.7	13.1	22.4	6.7	5.4	12.0	10.6	54.9
	Group B	19	0.0	5.3	5.3	15.8	0.0	15.8	21.1	0.0	15.8	15.8	10.5	52.6
25-29	Group A	14,866	7.9	4.9	12.7	10.9	7.7	18.6	31.3	8.2	5.7	13.9	11.0	43.7
	Group B	61	3.3	6.6	9.8	6.6	3.3	9.8	19.7	11.5	13.1	24.6	13.1	42.6
30-34	Group A	16,582	14.4	8.8	23.3	16.5	9.0	25.5	48.7	8.5	5.9	14.4	9.7	27.2
	Group B	117	9.4	7.7	17.1	14.5	8.5	23.1	40.2	15.4	8.5	23.9	15.4	20.5
35-39	Group A	12,004	31.0	12.6	43.6	19.2	7.8	27.0	70.6	6.8	4.2	11.0	6.4	12.0
	Group B	53	20.8	20.8	41.5	22.6	1.9	24.5	66.0	11.3	9.4	20.8	1.9	11.3
40-44	Group A	4745	57.8	14.1	71.9	13.2	4.0	17.2	89.1	3.6	1.8	5.4	2.4	3.2
	Group B	33	57.6	12.1	69.7	12.1	6.1	18.2	87.9	3.0	0.0	3.0	6.1	3.0

AMH=Antimullerian hormone

**Table 2: Differences in median antimullerian hormone in successive age groups in Group A, Group B and Group C**

Age groups (years)	Group A		Group B		Group C	
	Median AMH (ng/mL)	Reduction in median AMH in successive age groups (%)	Median AMH (ng/mL)	Reduction in median AMH in successive age groups (%)	Median AMH <sup>[10]</sup> (ng/mL)	Reduction in median AMH in successive age groups (%)
20-24	4.52	-	4.37	-	4	-
25-29	3.42	24.3	3.36	23.1	3.31	17.3
30-34	2.08	39.2	2.34	30.4	2.81	15.1
35-39	1.1	47.1	1.18	49.6	2	28.8
40-44	0.42	61.8	0.54	54.2	0.88	55.9

AMH=Antimullerian hormone

infertility treatment than group B who conceived naturally in the past though the difference did not reach statistical significance. The sample size of Group B was low in certain age brackets, which might have reduced the possibility of getting a statistical difference between the age groups. However, a trend is seen. Also, the fact to be noted is that amongst young women seeking infertility treatment, almost one-third of women (28.7%) below 30 years had low AMH levels (2 ng/mL or below) and this proportion rises to about half (48.7%) in women aged 30–34 years and further rises to approximately three-fourths (70.6%) in women aged 35–39 years. Alarming, even in women aged 20–24 years, this proportion was about one-fourth (22.4%). Only one-third of the women (37.7%) 30 years or older and one-fourth (24.2%) 35 years or older in group A had optimal AMH levels ( $>2$  ng/mL).

The increasing use of Assisted Reproductive Technology has unmasked the existence of poor ovarian reserve. It is believed that approximately 10% of women undergoing *in vitro* fertilization (IVF) will show poor response to gonadotropin stimulation.<sup>[10-12]</sup> However, the incidence may be much higher in the infertile population as many may never undergo a complete evaluation or IVF. The low/poor AMH levels in younger age groups are alarming and need further investigations. The average age of women seeking infertility treatment in the study was around 31–32 years. This indicates that ovarian senescence might have set in a significant proportion of women even before they seek counseling. It is important to note that we did not know the cause of infertility in the women whose AMH was analyzed in the central laboratory, since it was a pan-India study where the only relevant history noted while analyzing the samples was that of infertility. This suggests that there are a high proportion of women who have a decrease in ovarian reserve which may be a stand-alone cause of infertility or an additional contributing factor to the couple's infertility.

Shebl *et al.* showed that even in a presumably healthy cohort of women attending a reproductive center for male factor infertility, there was a wide range of serum AMH levels in younger women with many being suboptimal.<sup>[13]</sup> It is well known that low AMH is a predictor of low oocyte yield with inconsistent evidence of its association with oocyte quality.<sup>[3]</sup> Our observations are important as there is no study from India currently, portraying this picture.

A similar retrospective study by Naasan *et al.* conducted in an Irish subfertile population showed that only 8.1% had 'optimal fertility' as per the predefined lab reference ranges.<sup>[14]</sup> By age 32, over 50% of women had AMH

levels categorized as "low fertility" (AMH  $\leq 19.5$  pmol/L or 2.73 ng/mL), increasing to 75% by age 39. Though the proportion of women with low fertility/AMH appears similar to our study, the cut-off used in this study (2.73 ng/mL) is higher than our study (2 ng/mL). Hence, the proportion of women falling in the low fertility/AMH category would be lower in the Naasan *et al.* study than stated here, if our cut offs were used. Consequently, the actual proportion of women with low AMH would be lower than that observed in our study for Indian women (approximately 49% at age 30–34 years and 71% at 35–39 years).

As expected, we found that AMH decreased as age advanced. Many other studies have reported an inverse correlation between age and AMH levels.<sup>[15-18]</sup> Interestingly, the decrease in median AMH with age observed in Groups A and B was faster as compared to Group C. This indicates that Indian women, whether seeking infertility treatment or with history of natural conception, experience a faster decline in AMH as compared to their healthy Caucasian counterparts. This trend was observed starting at a young age and continues consistently throughout the studied age groups. A study by Iglesias *et al.* has shown that Indian women aged 6 years earlier than their Spanish counterparts depending on their observation of markers of ovarian reserve such as AMH in infertile women undergoing controlled ovarian stimulation.<sup>[19]</sup> In a study by Raeissi *et al.*, though a falling trend in AMH levels with age was noted in both the infertile and healthy control groups, the decline was more pronounced in the infertile group.<sup>[20]</sup> In our study, though we found a higher proportion of women with low AMH in the group seeking infertility treatment as compared to the Indian healthy control group, the degree to which AMH decreased between successive age groups in both the groups was similar.

Some variables may occur as implicit parameters and are difficult to identify, such as intangible cultural factors linked to social habits, ethnicity, diet, and genetic predispositions that account for some females ageing slowly with a better quality of life than others. Sohal and Weindruch (1996) in their study showed that the amount of calorie intake, type of food consumed, lifestyle (smoking, drugs, various exposure to toxins, physical activities) influence oxidative damage which is a key contributor to senescence and may also be relevant to ovarian ageing.<sup>[21]</sup>

Exposure to endocrine disrupting chemicals (EDCs) such as phthalates, bisphenol and parabens which are present in pesticides, plasticizers, and textiles, among others, has been associated with diminished reproductive potential including an effect on egg quality and viability.<sup>[22-28]</sup>

Environmental agents, especially EDCs could interfere with the ovary by disrupting the function of the key reproductive hormones.<sup>[23,29]</sup>

Plastic consumption in India started in 1957. These plastics contain EDCs like bisphenol and phthalates.<sup>[22]</sup> Dichlorodiphenyltrichloroethane (DDT) was used in India as an insecticide earlier, but its use in agriculture has been banned.<sup>[22]</sup> Speculation points towards the ubiquitous role of plastics containing EDCs that entered the Indian environment half a century ago and the rampant use of DDT in India from 1957 till 1989. This corresponds to the exposure time when these women were *in utero*. Hence their mother's fertility and even the parental gametes could have been affected.<sup>[22]</sup>

The major strength of this study is the large sample size of infertile women including women across the country and reproductive age ranges. The study used an automated AMH assay with low variability and high precision. We acknowledge the several limitations of our study. As it is a retrospective observational study and no clinical data was available for the subjects, the infertile group could not be characterized as to the cause, type (primary/secondary) and duration of infertility, definitive diagnosis of infertility, comorbidities, medical and surgical treatments, smoking history and body mass index. AMH levels are influenced by multiple factors e.g., women with polycystic ovarian syndrome tend to have higher AMH levels, while ovarian suppression with oral contraceptives or GnRH agonists lowers the AMH levels.<sup>[30]</sup> AMH levels also vary according to race and ethnicity, ovarian surgery, current smoking status, Vitamin D levels and certain chromosomal abnormalities like Turner syndrome and fragile-X syndrome.<sup>[30]</sup> These factors could confound the AMH values and could have strengthened or weakened the hypothesis. In addition, the sample size was not calculated based on power calculations and the sizes of Groups A, B and C differ considerably.

The findings from our study have strong implications for fertility counseling. Many women seek fertility counseling with a view to postpone pregnancy or marriage. Our study suggests that even for young women, assessment of ovarian reserve with AMH is an essential part of counseling. Also, women should be counseled not only on their present AMH value but also about its sharp decline with age.

## CONCLUSION

Our study concludes that a large proportion of women seeking infertility treatment had low ovarian reserve as shown by their serum AMH levels. There is a more rapid decrease in serum AMH with age in Indian women of

reproductive age group compared to healthy Caucasian women. Young Indian women in their late twenties and early thirties visiting fertility centers Pan-India showed a worrisome trend of low AMH. The findings of our study can be used as a reference for Indian women seeking fertility counseling with a view to postpone pregnancy or even for young women seeking oocyte preservation. It may be time to look at intangible cultural factors linked to social habits, ethnicity, diet, genetic predispositions, and environmental factors like EDCs contributing to premature ovarian senescence in young Indian women.

## Data availability statement

The data set used in the current study is available from the corresponding author on reasonable request.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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