Original Article

Age-Specific Distribution of Serum Anti-Mullerian Hormone and Antral Follicle Count in Indian Infertile Women

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Abstract

Background: Ovarian reserve declines with age. However, there are considerable ethnic differences in the decline of ovarian reserve between individuals. **Aim:** This study aimed to make age-specific percentile charts of anti-Mullerian hormone (AMH) and antral follicle count (AFC) in Indian infertile women and to find the proportion of young women with low ovarian reserve. **Setting and Design:** This was a retrospective data analysis of AMH and AFC of 5525 infertile women from August 2015 to December 2018. **Materials and Methods:** Infertile women aged 20–44 years, with body mass index 18–32 kg/m^2 and having both ovaries were included in the study. Women with pituitary/adrenal disorders, malignancy, total AFC >40, tuberculosis, endometriosis, autoimmune disorders, smoking, chemotherapy, radiotherapy and recent ovarian surgery were excluded from the study. **Statistical Analysis:** Comparison between groups was done by Chi-square test. **Results:** About 14.5% of women <35 years and 50.5% of women >35 years had low AMH values (<1.1 ng/ml). In addition, 5.6% of women <35 years and 23.6% of women >35 years had a low AFC of ≤5. In this study, 55.7% of women who had low AMH and 50.7% who had low AFC were <35 years of age. The median AMH values were 4.23 ng/mL in 20–25 years' age group, 3.48 ng/mL in women aged 26–30 years, 2.43 ng/mL in women aged 31–35 years, 1.28 ng/mL in women aged 36–40 years and0.52 ng/mL in 40–44 years' age group. The median AFCs were 20, 18, 14, 10 and 6 for each of the age groups, respectively. **Conclusion:** This study suggests that approximately more than half of the infertile women who were tested to have low ovarian reserve were <35 years of age.

Keywords: *Anti-Mullerian hormone, antral follicle count, artificial reproductive technology, ovarian reserve*

Introduction

Serum anti-Mullerian hormone (AMH) and antral follicle count (AFC) are currently the most utilised ovarian reserve markers for predicting treatment response in Assisted reproductive technology (ART) cycles. AMH and AFC help to form individualised treatment plans and facilitate clinicians to predict the probability of ART success.[1] Measuring AMH and AFC can help in counselling infertile couples who wish to postpone childbearing.[2] Ovarian aging relates to the decline in the quality and quantity of the ovarian follicle pool with increasing age. Ovarian aging manifests as decreasing spontaneous fecundity and low fertility treatment success with advancing age.

There is considerable variation in ovarian aging between individuals and wide distribution of AMH and

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AFC results reported with each age.[3] This is largely due to the varying initial oocyte numbers at birth and varying pace of follicular recruitment/apoptosis between individuals.[4,5] Studies indicate that young women with low-age ovarian reserve markers may experience a decline in fertility causing a shift towards premature ovarian failure or early menopause.[6]

Furthermore, the literature reports that there are ethnic differences in ovarian aging. Studies show that Caucasian women have higher ovarian reserve markers and higher live birth rates in ART cycles compared with women from Asia, Africa and Middle East.[7-9] This may be due to genetics, nutritional factors, environmental exposure and developmental factors. The observation of young infertile women with a low ovarian reserve in ART clinics may or may not be due to an over-representation of young women with an early reduction of ovarian reserve.

This study aims to investigate the proportion of young infertile women with a low ovarian reserve and to make age-specific percentile charts of AMH and AFC amongst Indian infertile women. The results may provide reliable information with respect to a woman's ovarian reserve within a given age category and guides to counsel the prognosis related to fertility.

Materials and Methods

This is a retrospective cross-sectional study from August 2015 to December 2018. The hospital records of 5525 infertile women with primary or secondary infertility between the ages of 20 and 44 years with a body mass index (BMI) of 18–32 kg/m^2 and having both ovaries in ultrasound were included in the analysis after informed consent. This study was approved by Gunasheela Institutional Ethics Committee (IEC/0010/2019, dated 13.09.2019).

Women diagnosed with pituitary or adrenal disorders or any cancer or autoimmune disorders, endometriosis or tuberculosis were not included in the study. Women who had an AFC ≥20 per ovary[10] and/or had a history of smoking or gonadotoxic therapies such as chemotherapy and/or radiotherapy and women who had undergone recent ovarian surgery within the past 3 months were also excluded. Treatment informed consent was obtained for all the women included in this study. The consent form clearly outlined that data acquired from patients can be used for research purposes at a later date while maintaining complete anonymity of patient details.

Data collection was done using convenience sampling. *Post hoc* analysis was done and found to be statistically significant ($P < 0.05$). This may be due to larger sample size. Each woman was represented only once in the study. AFCs were classified as ≤5 (low), 6–14 (normal) and ≥15 (high). Serum AMH values are categorised as ≤1.1 ng/ml (low), 1.2 to3.4 ng/ml (normal) and ≥3.5 ng/ml (high).[11-13]

Analysis of serum AMH on day 2 or day 3 of menstrual cycle was determined in venous blood at a single laboratory with an ultrasensitive enzyme-linked immunosorbent assay (ELISA) in a concentration of ng/ml (Beckman-Coulter, Access2 gen II).[14] The assay range for AMH was 0.16–20 ng/mL, operative sensitivity was 0.08 ng/mL and the inter-analysis and intra-analysis degree of difference was 5.6% and 5.4%, respectively.[14] The analysis of serum samples was conducted on the same day in the same laboratory by a single operator.

AFC was measured in both ovaries on day 2 or day 3 of the menstrual cycle by real-time two-dimensional ultrasound using Voluson E8 (GE Healthcare) with a transvaginal transducer probe frequency of 8 MHz. Measurement of AFC included counting identifiable follicles with a mean diameter ranging from 2 to 10 mm[1].

Statistical analysis

R software version 3.22 (GNU GPL v2, free software foundation, Boston, Massachusetts, US) was used to analyse data. Descriptive analyses for the continuous variables and frequencies and percentages for the categorical variables were used to compare outcomes. Groups were formally compared using a Chi-square test (or Fisher's exact test).

Results

The median age of women in the sample (n = 5525) was 31.5 years of age ranging between 20–44 years. Tables 1 and 2 show that the percentage of women with low AMH and AFC increases as they become older. We report that older women (40–44 years) were eight times more likely to present with a poor ovarian reserve compared to younger women (20–24 years) (73% vs. 8.7%, P = 0.01) [Table 1 and Figure 1a]. Furthermore, women who were <25 years had a higher AFC compared to woman aged more than 40 years (71% vs. 12.7%, P = 0.01) [Table 2 and Figure 1b]. Amongst women aged <35 years (n = 4500), 14.5% presented with low AMH (<1.1 ng/ml) compared to 50.5% of women >35 years (n = 1025) (P = 0.01). A similar trend was also observed with low AFC counts (≤5) for women aged <35 years compared to women aged >35 years (5.6% vs. 23.6%, P = 0.01) [Table 3]. Interestingly, 21.2% (n = 1170) of the 5525 women screened had an AMH level ≤1.1 ng/ml and amongst the 1170 women, 55.7% (n = 652/1170) Were <35 [Table 4] years of age (P = 0.01). Moreover, of the 493 women who presented with AFC ≤5, 50.7% (n = 250/493) were <35 years of age (P = 0.01).

Table 1: Percentage of women with low, normal and good anti-Mullerian hormone in various age groups

AMH (ng/mL)	Age (years)					Total
	20-24	25-29	30-34	35-39	40-44	
≤1.1	8.6% (59)	9.6% (185)	21.5% (408)	45.5% (380)	73.0% (138)	21.2% (1170)
1.2-3.4	32.4% (220)	40.6% (780)	43.9% (835)	40.2% (336)	23.8% (45)	40.1% (2216)
≥3.5	58.9% (400)	49.7% (955)	34.6% (658)	14.4% (120)	3.2% (6)	38.7% (2139)
Total	679	1920	1901	836	189	5525

AMH=Anti-Mullerian hormone

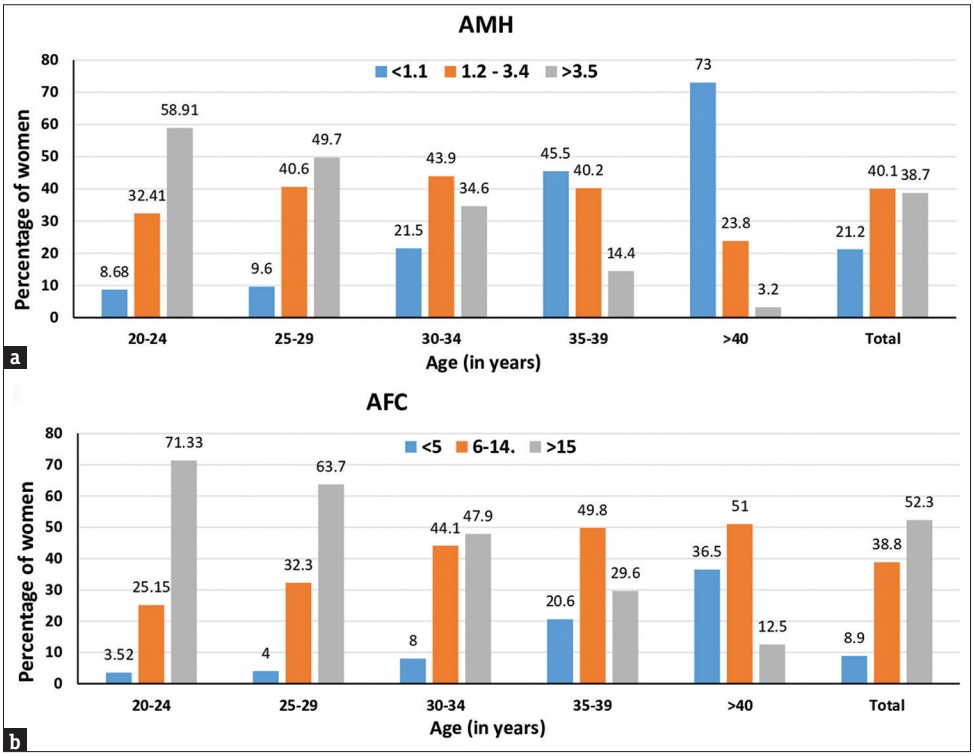

Figure 1: (a) Graphical representation of percentage of women with low, normal and good anti-Mullerian hormone in various age groups. (b) Graphical representation of percentage of women with low, normal and good antral follicle count in various age groups

Table 5 provides the median and range of AMH and AFC values between 3rd and 97th percentiles stratified by age groups for all women in the sample (n = 5525). We report that the 10th centile of AMH was 1.34 ng/ml in the 20–24 years' age group, 1.12 ng/ml in 25–29 years age group, 0.63 ng/ml in 30–34 years age group, 0.2 ng/ml in 35–39 years' age group and 0.04 ng/ml in 40–44 years age group. The 10th centile of AFC was nine, eight, six, four and three, respectively (P = 0.01) [Figure 2]. Figures 3a and b represent a wide variation of AFC levels with age, indicating a weak correlation detected between AFC and age (r = −0.2). Figure 4a and b also revealed a broad distribution of AMH levels with age (r = −0.2). This suggests that the correlation of AFC and AMH with the age of women was markedly weaker. The correlation of AMH and AFC with age is weaker in both younger (<35 years) and older women (>35 years). Figure 5a shows there was a moderate correlation between AFC and AMH in women with low ovarian reserve (r = 0.42) compared to those women who presented with a normal (r = 0.3) or high ovarian reserve (r = 0.2).

Discussion

Poor ovarian reserve is reported commonly in women in their late thirties but can also affect younger women. This is the result of a progressive depletion of the primordial follicular pool due to apoptosis. There is variation in the proportion of non-growing follicular pool (NGFP) as high as 100 fold between women of the same age and even in those with normal ovarian reserve. However, it is unclear whether this is due to a difference in the size of the initial follicular pool or due to the differences in the rate of depletion. Available data suggest that NGFPs at different ages may have variable ovarian responses to changes in hormone levels associated with age.[15]

The reduction in ovarian follicles occurs in two phases – a slow decline from birth until 38 years

Table 2: Percentage of women with low, normal and good antral follicle count in various age groups

AFC (2-10 mm)	Age (years)					Total
	20-24	25-29	30-34	35-39	40-44	
≤5	3.5% (24)	4.0% (76)	7.9% (150)	20.7% (173)	37.0% (70)	8.9% (493)
6-14	25.1% (170)	32.2% (619)	44.2% (840)	49.6% (415)	50.3% (95)	38.8% (2139)
≥15	71.4% (485)	63.8% (1225)	47.9% (911)	29.7% (248)	12.7% (24)	52.3% (2893)
Total	679	1920	1901	836	189	5525

AFC=Antral follicle count

Table 3: Percentage of women with low, normal and good ovarian reserve in <35 years and >35 years age groups

Parameters (years)	Poor ovarian reserve (%)	Normal ovarian reserve (%)	Good ovarian reserve (%)
<35 (AMH) *n*=4500	14.5	40.8	44.7
>35 (AMH) *n*=1025	50.5	37.2	12.3
<35 (AFC) *n*=4500	5.6	36.2	58.2
>35 (AFC) *n*=1025	23.6	50.0	26.4

AMH=Anti-Mullerian hormone, AFC=Antral follicle count

Table 4: Percentage of women <35 years and >35 years of age amongst all with low ovarian reserve

Parameters (years)	AMH <1.1 (*n*=1170) (%)	AFC <5 (*n*=493) (%)
<35	55.7	50.7
>35	44.3	49.3

AMH=Anti-Mullerian hormone, AFC=Antral follicle count

of age and a rapid decrease after 38 years. Current evidence does not agree with this concept and proposes that the reduction in the follicular pool is due to ongoing apoptosis occurring continuously in women of reproductive age group. Multiple theories explaining the mechanisms of ovarian aging have been described over the years, which include age-related changes in chromosome exchange and gene expression, programmed cell death and apoptosis, reactive oxygen species and mitochondrial DNA damage and telomere shortening. Furthermore, genetics, pathological conditions such as endometriosis, environmental exposures, hypothalamic–pituitary–adrenal changes and utero-ovarian changes may contribute to the reduction of a follicular pool.[16] Poor ovarian reserve often goes undetected in a small subset of women <35 years of age. The onset of ovarian insufficiency pre-dates menopause by an average of 10 years.[17,18]

There is a linear decrease in AMH over age after reaching a maximum in the mid-twenties, indicating that AMH exactly mirrors the decrease in the follicular pool with time, and thus, it is one of the preferable ovarian markers.[19,20] This study revealed that 14.5% of women <35 years of age and 50.5% of women more than 35 years of age presented with low AMH values (<1.1 ng/ml). Serum AMH and AFC levels can predict neither live birth nor infertility or the time it would take to achieve pregnancy (Practice Committee of the American Society for Reproductive Medicine, 2015). AMH and AFC are predictive of ovarian response in ART cycles and indirectly predict ART success rates and therefore can predict a woman's total fertility potential. Women having low age-specific AMH and AFC are at a high risk of premature and rapid loss of fecundity, early premature ovarian insufficiency and early menopause.[21]

Women who decide to delay their motherhood should receive information, guidance and counselling about age-related fertility decline to plan reproduction, as well as to better understand alternative options of preserving fertility by social gamete or embryo freezing.[22] Most research and practice guidelines do not support the use of ovarian reserve testing as a screening tool. This is because ovarian reserve testing does not reveal immediate spontaneous conception potential and informing the patient about their low ovarian reserve result may heighten their levels of anxiety. Furthermore, there is good evidence that the number of false-positive test results may potentially increase when screening tests for ovarian reserve are offered in low-risk populations.[23] However, long-term risks of premature menopause or sterility have not been considered in these studies.[24]

The literature reports that Caucasian women have 25% higher AMH values compared to African and Hispanic woman of similar age.[25,26] The ovarian age of Indian women has been reported to be 6 years older than Spanish women of similar chronological age.[27] Furthermore, it has been reported that the decrease in AMH is more prominent in Chinese women compared to Caucasian women reflecting a 28% and 80% decrease in AMH value at age 35 and 40, respectively.[28] These ethnic variations may be associated with genetics, diet and environmental influences.[27] One of the limitations of using AMH as an ovarian marker is the apparent unavailability of age-specific levels in various ethnic groups.

This study provides a better understanding of AMH and AFC levels amongst infertile women in a reproductive

clinical setting. Serum AMH and AFC below the 10th percentile for the age indicates poor/low ovarian reserve. In this study, the 10th centile of AMH was 1.34 ng/ml in women <25 years of age and 0.04 ng/ml in women aged more than 40 years of age. The 10th centile of AFC was nine and three, respectively, for these two age groups. Moreover, guidelines recommend repeating AMH and AFC tests after 2 months for confirmation and follow-up testing of AMH and AFC after 12 months to assess the changes in AMH and AFC levels.[19]

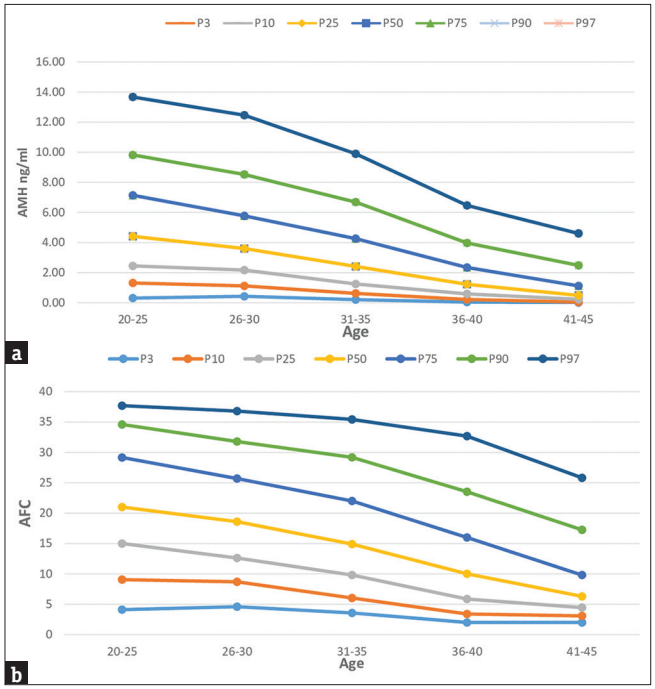

Figure 2: (a) Graphical representation of age-specific anti-Mullerian hormone percentile values. (b) Graphical representation of age-specific antral follicle count percentile values

Age-specific percentile charts can assist clinicians to better understand the age-related normative values for AMH and AFC to individualise fertility treatment plans. It is recommended to offer AFC and AMH testing in women above 30 years of age who ask for their fertility status, in conjunction with pre and post-test counselling. The literature recommends voluntary ovarian reserve testing in younger women <30 years of age with risk factors for poor ovarian reserve such as endometriosis, prior ovarian surgery, chemotherapy, radiation therapy, smoking and autoimmune disorders.[21]

A study on 202 infertile women younger than 35 years reported the association between serum AMH level, conception rate and time to conception after timed sexual activity. The spontaneous conception rate after trying naturally was similar in women with normal and low AMH (<2.5 ng/mL in women <31 years and <2.0 ng/mL in women 32–34 years). It has been observed that women with very low AMH (<1.19 ng/mL in women <31 years and <0.6 ng/mL in women 32–34 years) took longer to conceive than women with normal AMH.[29]

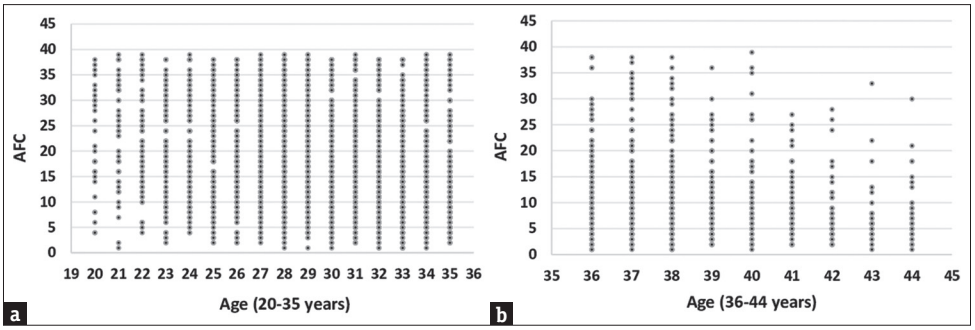

Figure 3: Correlation between antral follicle count and age (20–35 years) with correlation coefficient of 0.21. (b) Correlation between antral follicle count and age (36–44 years) with correlation coefficient of −0.23

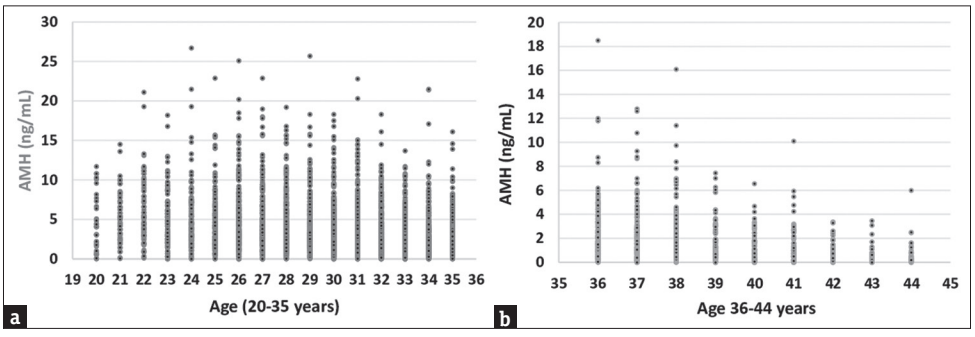

Figure 4: Correlation between antral follicle count and age (20–35 years) with correlation coefficient of 0.23. (b) Correlation between antral follicle count and age (36–44 years) with correlation coefficient of −0.25

Table 5: Age-specific distribution of anti-Mullerian hormone and antral follicle count

	Age group (years)									
	20-24		25-29		30-34		35-39		40-44	
	AMH	AFC	AMH	AFC	AMH	AFC	AMH	AFC	AMH	AFC
10th centile	1.34	9	1.12	8	0.63	6	0.2	4	0.04	3
25th centile	2.47	14	2.1	12	1.25	10	0.59	6	0.25	5
50th centile	4.23	20	3.48	18	2.43	14	1.28	11	0.52	6
75th centile	6.72	39	5.72	26	4.33	22	2.53	16	1.22	10
90th centile	9.77	34	8.21	32	6.88	30	4.2	24	2.62	18

AMH=Anti-Mullerian hormone, AFC=Antral follicle count

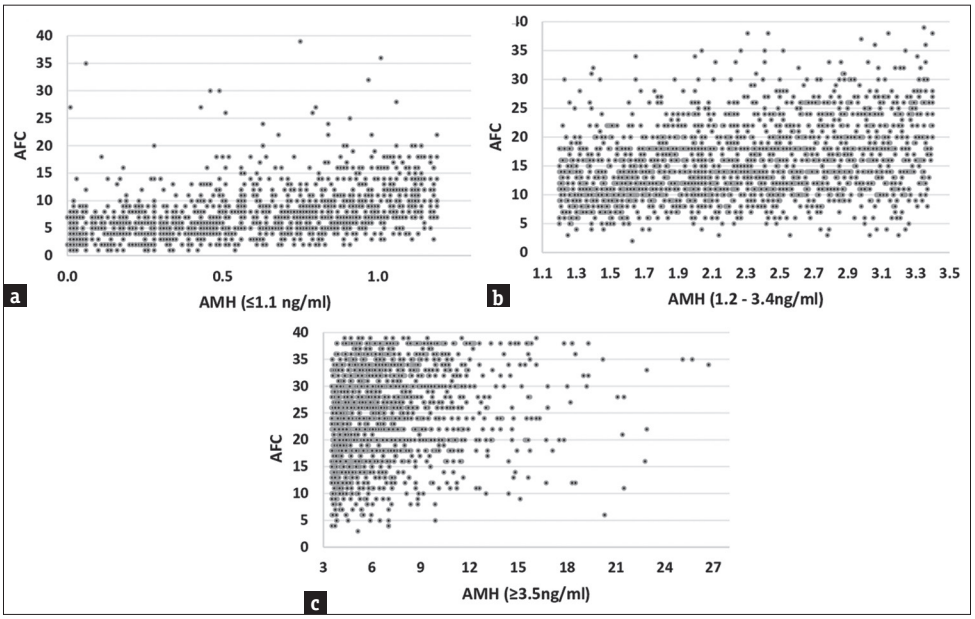

Figure 5: Correlation between antral follicle count and anti-Mullerian Hormone (≤1.1 ng/ml) in poor ovarian reserve with correction coefficient of 0.42. (b) Correlation between antral follicle count and anti-Mullerian hormone (≤1.2–3.4 ng/ml) in normal ovarian reserve with correction coefficient of 0.348. (c) Correlation between antral follicle count and anti-Mullerian hormone (≤3.5 ng/ml) in normal ovarian reserve with correction coefficient of 0.21

Furthermore, Shebl *et al*.[30] reported on the age-related distribution of AMH values amongst 2741 healthy women of reproductive age. The author showed an extensive variation in AMH across all age groups, even younger women, might have a poor ovarian reserve.

This study revealed that there was a wide distribution of AFC and AMH with age and hence a weak correlation of both markers with age [Figure 3 and 4]. A moderate correlation between AFCs and AMH was observed in women with low ovarian reserve compared to women with high and normal ovarian reserve [Figure 5].

There are huge inter-individual discrepancies in the reduction of ovarian reserve markers with increasing age. However, fertility outcomes are independent of AFC and AMH values.[31] Ovarian reserve markers do not predict live birth. While they predict ovarian response in IVF cycles, they do not predict the outcome of ART.[32,33] Another study compared the AMH and AFC levels of 382 infertile women aged 20–39 years, with 350 fertile women revealed that the age-related reduction in both markers (AMH and AFC) was similar in both cohorts of women.[31] This suggests that young women with a low ovarian reserve are often not over-represented in ART clinics.

Furthermore, this study showed that 14.5% of young infertile women may be at risk for poor response in ART cycles due to unexpected low ovarian reserve before the age of 35 years. Moreover, one of the parameters for poor response to ART treatment includes an AMH level <1.1 ng/ml and an AFC of <5.[34] Interestingly, in this study, 55.7% of women with an AMH <1.1 ng/ml and 50.9% of women with AFC <5 were <35 years of age.

Advantages

Serum AMH can be measured on any day of menstrual cycle because of minimal differences in values between and within menstrual cycles and it is independent of laboratory technician skills.[35,36] The increased accuracy

and automation of AMH assays has reinforced the value of serum AMH levels in the prediction of ovarian response in ART cycles and age of menopause.

The advantages of this study include a large number of infertile women of reproductive age group from a single center, the use of a single laboratory and the use of same the immunoassay tool, reducing potential laboratory disparities. Age-specific centile charts help in counselling Indian infertile women regarding their reproductive lifespan and aid women not to delay planning treatment or pregnancy if they are in the lower centiles (below the 10th centiles) for their age group.

Limitations

The limitations around this study include inter- and intra-observer variations in AFC measurements as different operators were involved in conducting ultrasounds on infertile women. A good correlation was found between the AMH Gen II ELISA and Elecsys Cobas AMH methods, but the Elecsys Cobas method achieved optimal performance throughout the measuring range, whereas the AMH Gen II only achieved optimal performance in the high end of the measuring range.[37] There is an inter-cycle variability measuring AFC[38,39] and also AFC levels may be over-calculated because of measuring atretic follicles.[40] In most ART clinics worldwide, the sources of ultrasound variability include pressure, interposition of the bowel and machine settings used to maximise the contrast, operator skill and technique.[41] Proper adjustment of the machine settings and pattern recognition is critical for an accurate count. Other limitations of the study include the cross-sectional nature of the data analysis and the small sample of infertile women who were not followed over a period. It is well known that serum AMH and AFC values are widely variable in infertile conditions. As this study did not include a comparative fertile group of women, our observations could not be generalised to the general fertile population. Age-specific percentiles may have limited value in routine clinical practice.

The internal and external elements that regulate AMH expression need to be studied further for the correct interpretation of AMH values. An international consensus on assay independent AMH values is required.[42] However, evidence for its use as a screening tool in healthy fertile women is insufficient. Further studies are required to have a global consensus regarding the screening of ovarian reserve in healthy fertile women.[43] Future studies about age-specific reference values and AMH–age models considering BMI, smoking, endometriosis, polycystic ovary syndrome and fertility status are required.

Conclusion

Outcomes from this study may aid in understanding the age-dependent distribution of ovarian reserve markers in Indian infertile women. Further larger trials with healthy fertile and infertile women are required to explore these results. The relatively high proportion of young women with low ovarian reserve in the study may be due to factors other than age such as genetics or environmental endocrine disruptors, which may require further studies to understand their role and effect. However, age-specific AMH and AFC values may provide information beneficial for infertile couples and reproductive clinicians, to plan pregnancy and fertility treatment.

Data availability statement

The data analysed are available with the corresponding author.

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Nil.

Conflicts of interest

Devika Gunasheela is a member of the national advisory board of the Journal of Human Reproductive Sciences. She has had no role in the review process of the manuscript or editorial decisions.

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