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Age related normogram for antral follicle count in general population and comparison with previous studies

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ABSTRACT

Objective: To construct antral follicle count (AFC) nomogram of general population for every age and to compare our data with previous studies to assess whether available AFC nomograms present any geographical inconsistency.
Study design: A prospective cross-sectional study was conducted to document AFC nomogram among women in 20–50 years with regular menstrual bleeding. Patients admitted with hirsutism, menstrual irregularity, diagnosis of current/history of endometrioma and hormonal drug use within the last 6 months were excluded. For the final analysis, a total of 381 eligible women were recruited in which all scanning was performed in the early follicular phase. The 25th, 50th and 75th percentiles were compared with previous nomogram.
Results: The mean decrease of AFC in each year was 0.41. Among the age groups, there were no statistical significance between 20–24, 25–29 and 30–34, whereas decline in AFC was obvious after 35 years and beyond. The figures comparing our data and previous studies depicted similar steady decline at 25th, 50th and 75th percentiles.
Conclusion: The current age related nomogram presented a steady decline in AFC that became significant after 35 years in otherwise healthy women with regular menstrual bleeding. Those percentiles might be used as a reference guide to point out the current status of ovarian reserve for a given woman. Additionally, producing nomogram might enforce using percentiles instead of constant thresholds to define various medical conditions such as polycystic ovarian morphology or diminished ovarian reserve. However, longitudinal data with larger sample size are still needed for the validation of those percentiles.

Introduction

Ovarian reserve tests have crucial role in the management of assisted reproduction technologies regarding with the prediction of poor [1] or excessive ovarian response [2], tailoring the controlled ovarian hyperstimulation protocol [3,4] and gonadotropin dosing [5,6] to retrieve the optimal number of oocyte. They have been also utilized in the definition of polycystic ovary syndrome (PCOS), even though the ideal thresholds and the type of marker that should be taken into account are not clear [7,8]. Additionally, expected age of natural menopause can be individually predicted by ovarian reserve tests, in spite of a wide confidence interval [9,10]. Eventually, ovarian reserve “screening” for general population has been recently argued under the ethical dilemmas in order to permit reproductive life planning for all women [11].

Among the ovarian reserve tests, either anti-Müllerian hormone (AMH) or antral follicle count (AFC) are established surrogates in reflecting the primordial follicle pool within the ovaries [12]. Whereas AMH presents less individual intra- and inter-cycle variation than AFC [13], the latter might be less expensive as a direct quantitative marker of ovarian reserve [14] and excludes the current confusion related with (pre)analytic variations with AMH [15]. Although it is still not clear whether the decline in AFC has a biphasic [16] or a linear pattern [17,18], a negative correlation with chronologic age has been recently established. Nevertheless, the two largest cross-sectional studies that investigate general population from Italy [17] and infertile cohort from Canada [19] reported normal and interquartile values for AFC, age by age, throughout the reproductive period. Those efforts might be highly important for assigning age-based individual thresholds rather than extrapolating a certain cut-off values that are expected to fit to all women. However both of those

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studies are single center based studies and there is paucity of data whether they are valid for worldwide use.

In the current study, our primary objective was to present the AFC nomogram of general population for every age. Secondly, by comparing our data with previous studies, we aimed to assess whether available AFC nomograms present any geographical inconsistency [17,19].

Material and methods

Study population

This cross-sectional study was conducted in the Department of Obstetrics and Gynecology, School of Medicine, Hacettepe University between November—2013 and March—2014. In the outpatient clinic, among all patients that had been requested for examination with ultrasonography (n = 2085), women that are suitable for the inclusion criteria were recruited for the study. In that context, all patients had been questioned for the following inclusion criterion: (1) female age 20–50, (2) regular menstrual bleeding between 21 to 35 days, (3) being during the menstrual period of D1 to D12 and (4) optimal visualization of both ovaries. The exclusion criteria were (1) admission to outpatient clinic due to hirsutism or menstrual irregularity, (2) any hormonal drug or oral contraceptive pill use within the last 6 months, (3) history of endometrioma cystectomy or detection of current endometrioma at the time of ultrasonography, (4) being unsuitable for transvaginal probe application due to virginity and (5) pregnancy. The status of fertility was not a criterion while deciding to include or exclude. Approval from institutional review board was obtained.

Ultrasonography

All ultrasound examinations were performed by one of the two physicians (P.C. or D.Z.) using the 5–9 MHz endocavitary probe with Voluson 730 (GE Healthcare, Istanbul, Turkey). The operator started to count the follicles from outer margin of the ovary through out to the opposite site while sweeping. Every round–oval structure within those margins between 2 to10 mm were considered an antral follicle, as recommended [14]. The sum of both counts produced the final AFC.

The interobserver reliability was analyzed with another cluster of 30 ovaries prospectively. The first observer examined ovaries with ultrasonography and noted antral follicle count in each side. Second observer was blind to the first observer's findings and performed another examination with the same setting to count number of antral follicles per ovary.

Statistical analysis

The LMS method was preferred to produce the smoothed centile curves of antral follicle count by age (LMS program, version 3.1.1, Medical Research Council, London). This method summarizes percentiles at each age based on age-specific Box-Cox power transformations that are used to normalize data. L (Lambda; skewness), M (Mu; median), S (Sigma; coefficient of variation) values depend on age. The final percentile curves are produced by three smooth curves representing L, M and S. For each set of percentile curves, the initial smoothing methods were applied to 10th, 25th, 50th, 75th and 90th percentiles.

For the comparison of AFC across the age groups, statistical analyses were performed by SPSS v21.0 (IBM SPSS Inc., Chicago, IL). Descriptive statistics were given by mean ± standard deviation (SD) and median (minimum–maximum). Age groups were compared by Kruskal Wallis test and significance was set to a p value of 0.05. The relationship between female age and AFC was determined by linear regression analysis. Interobserver reliability was assessed by intraclass correlation coefficient.

The study was approved by Ethical Board of Hacettepe University.

Results

Of the 2805 women that had been examined with ultrasonography during the study period, 381 were appropriate for the final evaluation according to inclusion and exclusion criterion. The mean female age was 34.6 ± 7.6 years. Of the 381 women, the mean ± SD and median (minimum–maximum) AFC that had been stratified according to the female age were given in Table 1. In Table 2, the 10th, 25th, 50th, 75th and 90th percentiles of AFC were given for each age. The intraclass correlation coefficient of the two operators of ultrasonography was 0.957 (95% CI: 0.910–0.979).

The steady decline in AFC was also depicted in Fig. 1. The mean decrease of AFC in each year was 0.41. Among the age groups, there were no statistical significance between 20–24, 25–29 and 30–34, whereas decline in AFC was obvious after 35 years (Fig. 2).

Table 1
The descriptive values for antral follicle count that are stratified according to the female age.

Female age (y)	n	Mean ± SD	Median (minimum–maximum)
20–24	32	14.8 ± 5.2	15.5 (6–26)
25–29	79	14.6 ± 5.9	13 (5–30)
30–34	87	11.8 ± 5.1	11 (3–29)
35–39	74	10.1 ± 4.7	9.5 (3–29)
40–44	73	7.6 ± 4.8	7 (2–26)
45–49	36	6.0 ± 4.0	4.5 (2–19)
Total	381	10.9 ± 5.8	10 (2–30)

SD: Standard deviation.

Table 2
The percentiles of antral follicle count according to each age.

Female age (y)	n	10th	25th	50th	75th	90th
20	4	10.5	13.2	17.0	21.7	26.8
21	9	10.0	12.6	16.3	20.9	26.0
22	3	9.5	12.1	15.6	20.2	25.3
23	9	9.0	11.5	15.0	19.5	24.5
24	7	8.6	11.0	14.4	18.8	23.8
25	18	8.2	10.5	13.8	18.1	23.1
26	17	7.8	10.1	13.3	17.5	22.4
27	20	7.4	9.6	12.8	16.9	21.8
28	15	7.1	9.2	12.3	16.3	21.2
29	9	6.7	8.8	11.8	15.8	20.6
30	17	6.4	8.4	11.3	15.3	20.0
31	19	6.1	8.0	10.8	14.7	19.5
32	21	5.8	7.6	10.4	14.2	19.0
33	18	5.5	7.3	10.0	13.8	18.5
34	12	5.2	7.0	9.6	13.3	18.0
35	14	5.0	6.7	9.2	12.9	17.5
36	15	4.7	6.4	8.8	12.5	17.1
37	17	4.5	6.1	8.5	12.0	16.7
38	18	4.3	5.8	8.2	11.7	16.3
39	10	4.1	5.5	7.8	11.3	15.9
40	17	3.9	5.3	7.5	10.9	15.5
41	11	3.7	5.0	7.2	10.6	15.2
42	20	3.5	4.8	6.9	10.2	14.8
43	18	3.3	4.6	6.7	9.9	14.5
44	7	3.2	4.4	6.4	9.6	14.2
45	12	3.0	4.2	6.1	9.3	14.0
46	6	2.9	4.0	5.9	9.0	13.7
47	7	2.7	3.8	5.7	8.7	13.5
48	5	2.6	3.6	5.4	8.5	13.2
49	6	2.5	3.5	5.2	8.2	13.0
50	2	2.3	3.3	5.0	8.0	12.8