Age Related Antral Follicle Count Nomogram for Egyptian Women

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Declarations of interest:

The authors declare that they have no competing interests.

Abstract

Objectives : To investigate relation between antral follicle count (AFC) and chronological age to determine normal values for AFC in women with regular menstrual cycles.

Study design : A Cross-sectional study was conducted on 575 women aged from 18–48 years with regular menstrual bleeding at EL-Shatby Maternity University Hospital to assess the AFC, scanning was performed in the early follicular phase. the results were compared with previous nomogram.

Results: 575 normal menstruating females were categorized into 5 groups according to their ages and TVUS was done in the early follicular phase to detect the AFC. There's significant linear decline in mean AFC along different age groups in normal menstruating women with significant decline after age 38 years, There's a negative linear relationship between age and AFC in all studied centiles in normal menstruating women.

Conclusion: the first step in providing patients with scientifically based counselling is the creation of a nomogram of AFC values for assisted reproductive technologies and also for the natural conception chance and pregnancy outcome.

Key words: Antral follicle count; Nomogram; Ultrasonography.

INTRODUCTION

The ovarian reserve (OR) can be defined as the number and quality of the remaining follicles and oocytes in both the ovaries at a given age.[(1)]Decrease in the follicles number under a threshold level results in irregular cycles and eventually menopause therefore decrease in their quality leads to poor reproductive outcome.

Folliculogensis starts in early fetal life reaching a maximum number of 6 to 7 million at 20 weeks, concurrently with the process of atresia. At time of birth, the number of follicles that are available range from 1 to 2 million. After puberty, a number of follicles was selected, one of them grows to be the dominant follicle and rest become degenerated and undergo apoptosis. The atrophied follicles cannot regenerate again. Due to the gradual depletion of primordial follicles number, the antral follicular count (AFC) decreases and the accelerated decrease in numbers after remaining of less than 25,000 primordial follicles.[2, 3]

After the age of 31 years the female fecundity declines and accelerated after the 37 years , and by age of 41 years leading to sterility [4] The degree of decrease differs considerably between females of the same age.

An indirect indicator of a woman's remaining follicular pool is provided by ovarian reserve tests(ORT) [5] .An ideal tests should be easy to conduct and repeatable, an optimal ORT should enable the distinction between women who have a normal ovarian response and those who do not.[6]

ORTs are divided in to clinical by Age, Menstrual cycle characteristics. Biochemical: including FSH, E2, Inhibin B, AMH. And Ultra sonographic: by AFC, Ovarian volume and Ovarian blood flow. Or Dynamic using Clomiphene citrate challenge test or Gonadotropin agonist stimulation test or Exogenous FSH ovarian response test.

Ovarian antral follicles can be identified and counted using transvaginal ultrasound. [7, 8]

Since the availability of a test to evaluate the true ovarian reserve is not present, AFC is accepted as a good representive marker. [9, 10]AFC is regularly assessed in women of reproductive age, for different reasons as in infertility and work-up of assisted reproduction technique. [11] In prediction of the risk of menopause.[12, 13] to detect the suspicion of ovulatory dysfunction as a consequent of hyperandrogenism anovulation[14, 15] and in other specific clinical situations.[7, 16]

It is a non-invasive easy technique [17] that could be used as a marker for the ovarian reserve of each ovary distinctly.[14]

AFC and AMH evidently have the same accuracy in providing information as regards OR and in prediction of ovarian stimulation response.[14, 18-22] AMH assessment has restrictions because of the lack of international standardization [18, 21] and high-priced costs; A consistent automated test together with standardization should improve the assay's ability to predict ovarian response.[22]

One of the prominent advantage of AFC over AMH is that, the observer can evaluate many other significant aspects of the ovaries, like their position and the presence ovarian lesions as chocolate cysts or other lesions, and assessing the functional ovarian reserve by AFC, further more gaining important information as regards the fallopian tubes and the uterus. Combining both of AMH and AFC enhance the prediction of excessive ovarian stimulation response , but no prediction to poor ovarian response.[20]

AFC can be done any time in the menstrual cycle. Nevertheless, investigator should put in mind that in early follicular phase counting of follicles is more easier, and decreases the possibility of the presence of a corpus luteum or ovarian cysts, which might conceal some antral follicles.[7, 18]

AFC can predict both poor and exaggerated ovarian response [20, 23] and therefore, it is useful to categorize optimal gonadotropin dosage. [11, 23-25] AFC $< 5–7$ is related to small number of oocytes retrieved[26, 27] and decreased pregnancy rate.[28] A total AFC ≥ 20 is associated with high ovarian response and increase the risk of (OHSS). [18, 29-31]

AFC may help in prediction of menopausal age, AFC ≤ 4 being associated with high risk of menopause within 7 years (35%) when compared to other women with AFC > 4 (13%). [12, 13].

AIM OF THE WORK

To investigate the relationship between AFC and chronological age to establish normal values for AFC in women that have regular menstrual cycles.

PATIENTS

The study involved females that attend the outpatient clinic of El Shatby Maternity University Hospital for preconception counseling, contraception counseling, gynecological checkup or for infertility evaluation. Five hundred (575) women were selected with eligibility criteria: having regular menstrual cycle (length 25-35 days) with <5 days' difference between cycles, female age range from 18 -48 years, and presence of both ovaries .and all the antral follicles of 2–10 mm in diameter were included.

Females were excluded if age <18 years or >48years, had a history of taking hormones in the past six months, history of chocolate cyst cystectomy or detection of a current one or any ovarian surgery, history of pelvic inflammatory disease (PID), history of chronic systemic disease, metabolic or immunological disease, patients with poor ultrasound visualization of the ovaries, presence of at least one functional ovarian cyst >25mm.Women (n) will be categorized into 5 groups based on age:

i. 18-28 years **(n = 120)**

ii. 29-33 years **(n = 138)**

iii. 34-38 years **(n = 104)**

iv. 39-43 years **(n=113)**

v. 44-48 years **(n = 100)**.

METHODS

Cross-sectional study was conducted, informed consent from all women were taken, all patients have attended the clinic in their follicular phase of the menstrual cycle between day 2 and 4 to avoid the effect of intra-cycle variation, trans-vaginal sonography using MINDRAY DP-2200 ultrasound machine was done using two dimensional imaging with transvaginal transducer with a minimum frequency 7 MHz, to detect AFC in order to present AFC nomogram for general population for every age group in normal menstruating women, also to compare our data with previous studies in Normal women (La Marca et al)[32]

By using a systematic process for antral follicles counting:[31]

First Identify the ovary by Exploring the dimensions in two planes by performing a scout sweep and decide on the direction of the sweep to measure the size of follicles and count them, then measuring the largest follicle in two dimensions. If the largest follicle is less than 10 mm in diameter start to count from the outer ovarian margin of the sweep to the opposite margin and consider every round or oval transonic structure within the ovarian margins to be a follicle repeating the procedure with the other ovary and finally combine the number of follicles in each ovary to obtain the AFC.

If the largest follicle is greater than 10 mm in diameter a further detection of the size range of the follicles by measuring each sequentially smaller follicle, in turn, until a follicle with a diameter of less than 10 mm is found then performing a total count as described before regardless of follicle diameter finally, subtract the number of follicles of greater than 10 mm from the total follicle count.

STATISTICAL METHODS

Data were fed to the computer and analyzed using IBM SPSS software package version 21.0. (Armonk, NY: IBM Corp) The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using mean and standard deviation. Significance of the obtained results was judged at the 5% level. The used tests were Student t-test, Pearson coefficient and Bland Altman plot

For agreement with other study Bland Altman plot was used and one sample t test (between the difference and zero) (if significant then there is fixed bias).

The Bland Altman statistical method was used to measure the limits of agreement between our study and previous studies. The difference between the two studies per centile was calculated and plotted against the mean of the two studies per centiles separately. Then the limits of agreement were calculated as d ±2 SD where 'd' is the mean of the difference between the two studies and 'SD' is the standard deviation of the difference [(33)].

RESULTS

There's significant linear decline in mean AFC along different age groups in normal menstruating women with significant decline after age 38 years as shown in Table (1), There's a negative linear relationship between age and AFC in all studied centiles in normal menstruating women. and on detecting values of 5th, 25th, 50th, 75th and 95th centiles as a function of age in normal menstruating women as shown in Table (2) and represented in figure (1)

On using Bland altman's plotting between our study and la marca study[(32)], there was positively correlated (there's an agreement) to the other study, which means that centiles in both studies decline by the same interval per year. As shown in Table (3) and figure (2).

DISCUSSION

This study was to investigate the relationship between AFC and age on a large general population. Most of studies have investigated AFC in patients with known fertility or infertile patients.

On planning this study, we scheduled to include number of healthy women aged between 18- 48 years with regular menstrual cycle (length 25-35 days) with less than five days difference between cycles and with the presence of both ovaries, These women have attended the clinic for ultrasound examination for estimation of Antral follicular count using transvaginal sonography.

The results of our study have confirmed that there is an age related decrease in AFC. With (R^2 =0.32 for normal women), which mean 32% from change in AFC is related to age. Like previous studies there was numerous discrepancy in AFC in different age groups, and age alone have explained the decrease in AFC.

As regard normal menstruating women, the study revealed that the median of AFC was 0.4 follicle per year which was similar to La Marca et al[(32)] who have found that there was age related decline in AFC with median decline also 0.4 follicle per year.

In our study we found that there was significant negative linear relationship between age and AFC along different age groups in normal menstruating women, these findings was similar to La marca et al [(32)]who also reported a negative linear relationship between age and AFC in normal women.

In contrast Almog et al[(34)] have reported a biphasic linear correlation reflecting two different rates of antral follicle count loss by age for most percentiles in normal healthy women, This difference might be related to the features of the study population.

However, the highest rate of follicle loss was between age of 18 and 30. These results confirm previous reports of age related decrease in AFC among normal women.

Regarding the impact of aging on AFC, the literature contains scant and unclear evidence. Scheffer et al [(17)] described a biphasic pattern of AFC reduction as it decreased by 4.8% per year before the age of 37 years, then declined to11.7% after this threshold .The same dataset had a 2 second analysis and a model with linear decline in AFC till the age of 43 years followed by an exponential decrease with asymptote at zero was used to explain the data. The conventional linear model provided the most accurate match to the AFC in all other studies investigating the correlation between age and AFC. We also aimed to establish the normal values for AFC in normally menstruating women using IBM SPSS statistics program version 21. we estimated centiles for AFC all over the female reproductive period in normal healthy women for the first time, a nomogram reporting normal and interquartile values for AFC, age by age, throughout the reproductive period has been provided.

By subjective comparison between our data and La Marca et.al. 's data, it was observed that our centiles are slightly higher than LaMarca 's et al [32]centiles which may be due to racial or ethnic variety of different population.

Bland Altman's plot [33] is a statistical analysis, based on the quantification of the agreement between two quantitative measurements by studying the mean difference and constructing degree of agreement.

We have used it to study the degree of agreement between our study and la Marca in normal menstruating women, by calculating [1] correlation coefficient(r) which when positively significant (<0.001) means the two groups correlated to each other and [2] Mean difference between both groups which is represented as fixed bias which is present due to different studied population number or different characteristics.

When the centiles of our study and other study La Marca et al[32]were plotted according to Bland Altman plotting in normal menstruating women, there was found that all points were situated at the mean ± 1.96 which explain that our study was positively correlated(there's an agreement) to the other study, which means that centiles in both studies decline by the same interval per year.

CONCLUSIONS

AFC is the most common measured variable that is connected to ovarian function. However, because there were no normal data up to this point, the interpretation of the measurement was mostly dependent on the operator's unique experience. Therefore, the first step in providing patients with scientifically based counselling is the creation of a nomogram of AFC values, to give a clear idea regarding their potential fertility for assisted reproductive technologies as well as for spontaneous conception and the outcome of pregnancy, particularly in the event of ovarian disease such as endometriomas, which are more likely to be linked to decreased AFC.

Conflict of interest

There is no conflict of interest.

Table (1): The descriptive value for AFC that are stratified according to female age

Female age	N	AFC Mean ± SD.
18 – 28	120	15.77 ± 3.83
29 – 33	138	14.34 ± 3.61
34 – 38	104	13.17 ± 4.45
39 – 43	113	9.43 ± 3.80
44 – 48	100	4.08 ± 1.92

SD: **Standard deviation**

Table (2) Values of 5th, 25th, 50th, 75th and 95th centiles as a function of age in normal menstruating women

Our data

Age (years)	5th	25th	50th	75th	95th
18	10	14.75	15.5	18.5	20
19	10	14.5	17.5	20.25	22
20	15	17	18	19.75	21
21	7	12.75	15.5	20	22
22	12	14.5	16.5	18.5	20
23	14	16	18	20	20
24	12	15.5	17	17	17
25	5	7.5	13.5	18.5	22
26	11	12	17	20	22
27	7	13	15	17	22
28	7	8.5	14.5	18	18
29	10	14.5	16	17.5	20.5
30	7	13	15	17	23
31	6.05	12	15	16	20.95
32	7	13	14.5	15	20.9
33	6.15	8.75	12.5	15	22.1
34	6.2	10	14	18	22
35	6.05	8.75	13.5	16.5	21.95
36	5	9.5	15	15.5	20
37	5	9	13	15	18.7
38	7	7	13	13	19
39	5	11.5	12	14.5	16
40	3.2	7	8	11	14.8
41	5	6.25	8.5	11.75	19.8
42	3.15	4.75	7.5	9.25	20.25
43	5	6	7	10	11
44	3.1	5	6	7	9
45	2	3.5	4	5	7.7
46	1.05	2	4	5	6
47	1	2	3	4	5
48	1	2	2.5	3.25	5.85

LaMarca et al data

Age (y)	5th	25th	50th	75th	95th
16	6.2	11.6	16.6	22.6	33.2
17	6.0	11.4	16.2	22.1	32.4
18	5.9	11.1	15.8	21.5	31.6
19	5.7	10.8	15.4	21.0	30.8
20	5.6	10.5	15.0	20.5	30.0
21	5.4	10.2	14.6	19.9	29.2
22	5.3	10.0	14.2	19.4	28.4
23	5.1	9.7	13.8	18.8	27.6
24	5.0	9.4	13.4	18.3	26.8
25	4.8	9.1	13.0	17.7	26.0
26	4.7	8.8	12.6	17.2	25.2
27	4.6	8.6	12.2	16.6	24.4
28	4.4	8.3	11.8	16.1	23.6
29	4.3	8.0	11.4	15.5	22.8
30	4.1	7.7	11.0	15.0	22.0
31	4.0	7.4	10.6	14.4	21.2
32	3.8	7.1	10.2	13.9	20.4
33	3.7	6.9	9.8	13.4	19.6
34	3.5	6.6	9.4	12.8	18.8
35	3.4	6.3	9.0	12.3	18.0
36	3.2	6.0	8.6	11.7	17.2
37	3.1	5.7	8.2	11.2	16.4
38	2.9	5.5	7.7	10.6	15.6
39	2.8	5.2	7.3	10.1	14.8
40	2.6	4.9	6.9	9.5	14.0
41	2.5	4.6	6.5	9.0	13.2
42	2.3	4.3	6.1	8.4	12.4
43	2.2	4.1	5.7	7.9	11.6
44	2.0	3.8	5.3	7.3	10.8
45	1.9	3.5	4.9	6.8	10.0
46	1.7	3.2	4.5	6.3	9.2
47	1.6	2.9	4.1	5.7	8.4
48	1.4	2.7	3.7	5.2	7.6
49	1.3	2.4	3.3	4.6	6.8

Table (3): Comparison between our study and La Marca study using Bland altman's plotting

Centile	Age (years)	Our study	Other study	T	P
5th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	1.0 – 15.0 6.61 ± 3.68 6.15 **↑2.95 ± 2.60** 0.863*(<0.001*)	1.40 – 5.90 3.66 ± 1.35 3.70	6.310*	<0.001*
25th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	2.0 – 17.0 9.73 ± 4.43 9.50 **↑2.86 ± 2.45** 0.891*(<0.001*)	2.70 – 11.10 6.87 ± 2.55 6.90	6.507*	<0.001*
50th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	2.50 – 18.0 12.32 ± 4.75 14.0 **↑2.56 ± 2.11** 0.906*(<0.001*)	3.70 – 15.80 9.76 ± 3.68 9.80	6.763*	<0.001*
75th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	3.25 – 20.25 14.41 ± 5.17 16.0 **↑1.06 ± 2.09** 0.916*(<0.001*)	5.20 – 21.50 13.35 ± 4.96 13.40	2.811*	0.009*
95th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	5.0 – 23.0 17.76 ± 5.54 20.0 **↓1.84 ± 4.94** 0.735*(<0.001*)	7.60 – 31.60 19.60 ± 7.27 19.60	2.076*	0.047*

t: Paired t-test for comparing between the two techniques (if significant there is a difference)
r: Pearson coefficient
*: Statistically significant at $p \leq 0.05$

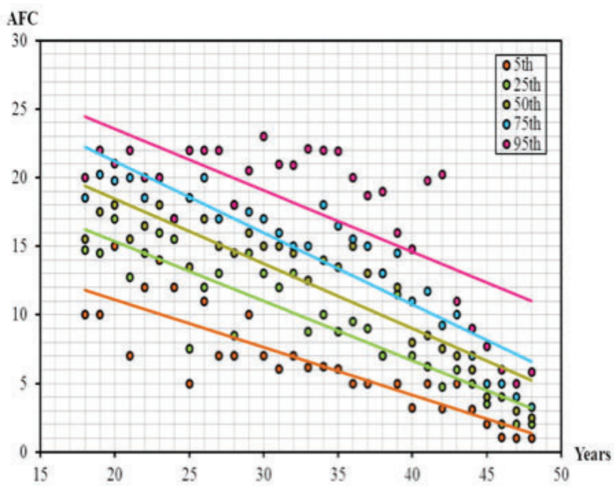

Figure (1): Values of 5th, 25th, 50th, 75th and 95th centiles as a function of age in normal menstruating women which proved that there's a negative linear relationship between age and AFC.

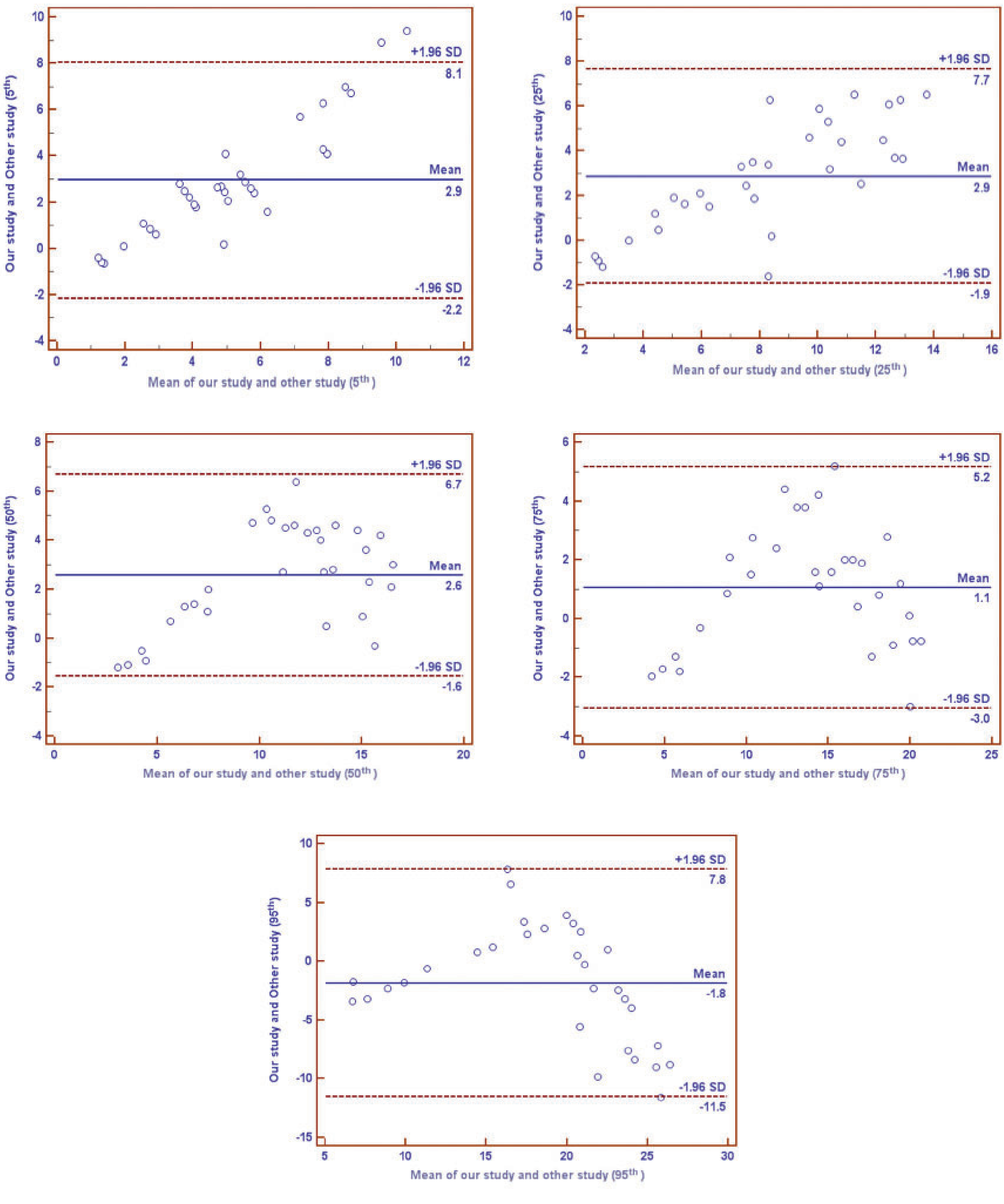

Figure (2): Comparison between our study and La Marca study concerning (5th 25th 50th,75th ,95th).

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