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A lower AFC is Associated with Infertility

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Abstract

Study Objective—To determine whether infertile women have lower antral follicle counts (AFC) than age-matched normal women

Design—Case- control

Setting—Academic center

Patients—881 infertile women and 771 women from the community

Interventions—Antral follicle count and basal hormone measurements

Main outcome measure(s)—Median AFCs and FSH levels were compared between the 2 groups within 5 year age strata, using the median test. A subanalysis was performed by identifying women in the control group with a history of attempting conception without success (Subfertile Group) and with a spontaneous conception in less than 12 months resulting in a live birth (Fertile Group). Age-specific AFC percentiles were calculated and compared within strata determined by age at the time of attempted conception

Results—AFCs were significantly lower in infertile women than in controls across age groups up to 40 years of age ($P < 0.001$). Average FSH levels were significantly higher in the younger age infertile group vs. the community ($P < 0.005$). AFC percentiles differ significantly between fertile and subfertile women within the community up until 40 years of age ($P < 0.02$)

Conclusion—Decreased AFC in infertile women suggests that factors affecting the size of the remaining follicle pool in younger women also affect oocyte quality and the likelihood of conception

Keywords

Antral follicle count; Decreased ovarian reserve; DOR; unexplained infertility; subfertile; FSH

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INTRODUCTION

With chronological aging, both oocyte quantity and quality, and hence reproductive potential, decline. It has been proposed that the intervals between reproductive events (decline in fertility, end of reproduction and menopause) are fixed, with the variable being the age at menopause [1]. This hypothesis would imply that quantity and “quality” decline in parallel[2,3], and may explain the considerable variation in the reproductive potential among women of the same chronological age[4]

Various non-invasive markers have emerged to assess “ovarian reserve”. These markers include FSH, E2, inhibin B, and AMH, and antral follicle count (AFC) [5]. Most studies of ovarian reserve have focused on the infertile population where predictors of ovarian reserve correlate with ovarian response to exogenous stimulation and pregnancy outcomes [6–8]. However, some investigators suggest ovarian reserve reflects primarily quantity and not the quality of remaining oocytes. In support, several studies have suggested that ovarian reserve testing is poorly predictive of achieving pregnancy or miscarriage in those that undergo assisted reproductive techniques [8–10]. In contrast, others suggest high FSH, as a marker of low ovarian reserve, is associated with a longer time to spontaneous pregnancy regardless of age, increase in miscarriage and earlier age of menopause [11]. Further, a recent study noted trisomic pregnancies were more common in women near menopause, with low oocyte recovery, and a prior history of ovarian surgery independent of age [12].

The limited data on ovarian aging in the general population have focused on whether ovarian reserve markers are associated with aneuploid pregnancies. While earlier studies suggested elevated FSH was associated with trisomies, a prospective study that followed 129 women in the general population failed to find an association between FSH and pregnancy outcome [13–16]. Consistent with these findings, Kline et al found no difference in levels of FSH, inhibin B, or AFC between women who had trisomic spontaneous abortions (n=54) compared with those with chromosomally normal(n=21) abortions or live births[17]. No studies to date have evaluated the association between ovarian reserve and fertility in the general population.

In light of this ongoing controversy and limited available data, we evaluated the relationship between ovarian reserve, as assessed by AFC and infertility in 2 populations. In the first, women presenting to the infertility clinic with unexplained infertility were compared to a sampling frame of women from the general community. In the second, subfertile women from the community, (defined as those with a history of attempting conception without success for at least 12 months) were compared to fertile women from the community (defined as those who experienced a spontaneous conception within 12 months resulting in a live birth).

MATERIALS AND METHODS

Study Populations

For the primary analysis, infertile subjects consisted of women that initially presented for consultation between 2004–2008 at the University of California San Francisco Center for Reproductive Health that were preparing for *in vitro fertilization*. The inclusion criteria for the infertile group included: i) age 25–45 years; ii).regular ovulatory menstrual cycles between 22 and 35 days, and iii) no endocrinopathies, and iv) with a diagnosis of unexplained infertility. Women with surgically diagnosed endometriosis, ovarian failure, tubal factor, isolated male factor, anovulation, or use of an oocyte donor or gestational surrogate were excluded. Institutional review board approval was obtained from both Kaiser Permanente and University of California, San Francisco.

The control group for the primary analysis (Community group) was comprised of ovulatory women with regular menstrual cycles between 22 and 35 days in length, aged 25–45 years, and enrolled in the OVA (Ovarian Aging) study. The OVA study is an ongoing, multi-ethnic, community-based study of genetic and environmental factors that contribute to ovarian aging([18]) Women with oligo- or anovulation, surgically diagnosed endometriosis, ovarian failure, or a history of uterine or ovarian surgery were excluded. Study subjects could not have used any hormonal medications in the 3 months prior to enrollment. OVA participants completed a comprehensive self-administered questionnaire, which included pregnancy and attempted conception history.

For the secondary analysis, two subgroups were defined from the Community group: 1) Subfertile group: women who had a history of attempting conception without success for at least a year, and 2) Fertile group: women with a history of spontaneous conception in within 12 months, resulting in a live birth.

AFC measurement

Antral follicle count was obtained from transvaginal ultrasound at initial consultation in infertile women, and between days 2 and 4 of the menstrual cycle for controls. Utilizing a Shimadzu SDU-450XL machine, with a variable 4–8 mHz vaginal probe, all echo-free structures in the ovaries with a mean diameter (of two dimensions) of 2–10 mm were counted as antral follicles[19]. Larger structures were considered cysts. All examinations on OVA participants were performed by one of two examiners (MIC, MPR); ultrasounds, for the subfertile women, were performed by reproductive endocrinologists in the UCSF practice (including MIC and MPR). Prior to initiation of this study, ultrasounds were performed on 50 infertile women by both examiners; correlation between repeated measurements was 0.92.

Assays

In the OVA women, serum FSH was drawn on the day of ultrasound, and assayed in the CLASS Laboratory at the University of Michigan, using a standardized 2-site chemiluminescence immunoassays. Assay sensitivity was 0.07 IU/L; intra-assay coefficient of variation was 1.9–2.1% and interassay, 5.2–6.8%. In the infertile women, FSH assays were performed in multiple local clinical laboratories on menstrual cycle day 2 or 3.

Analysis

Median age, AFC, FSH, estradiol, number of pregnancies, and pregnancy history were tabulated and compared between the Subfertile and Community group. Continuous variables were analyzed using the Mann-Whitney test. Categorical variables were analyzed using Chi-Square tests. Median AFCs were compared between the subfertile and community groups in each 5-year age stratum.

For the secondary analysis, AFC percentiles for each year of age were defined based on the entire Community group. Median age-specific AFC percentiles were then compared between those with Subfertile and Fertile women in the Community group. Women were then stratified based on the age at time of attempted conception, and median age-specific AFC percentiles were compared between the Fertile and Subfertile groups using the nonparametric median test. All analyses were performed using SAS version 9.0. Tests were declared statistically significant for a two-sided p-value <0.05.

RESULTS

The study population consisted of 881 infertile women and 771 women from the community based control group. The median age, AFC, basal FSH and estradiol, and number of pregnancies for each group are shown in Table 1. The median age was lower and number of pregnancies higher in the women that came from the community. The median AFC was lower, and FSH was significantly higher in the infertile women.

Pregnancy outcomes for the Infertile and Community groups are shown in Table 2. The proportion of women with a history of a live birth was significantly higher in the community compared to the infertile women (53% vs 8.2%; $P < 0.0001$). Ectopic pregnancies were more common in the Infertile group than in the Community (3.7% vs. 1.6%; $P = 0.0075$) while there no difference in spontaneous abortions.

The AFCs in the Infertile women were compared to women from the community, and are shown in Table 3. In this analysis we evaluated the median AFC for each age group. The infertile women have significantly lower AFC for each age group, except those women between 41–45 years of age. The difference in median AFC between groups was 4 for women between 25–30 and 31–35 years of age, and 3 for women between 36–40 years of age.

The median basal FSH concentrations for infertile women compared to the community women are shown in Supplemental Table 1. The FSH levels are significantly higher in infertile women that are 31–35 years of age, and show a tendency to be higher in women that are 25–30 years of age. There were no differences in FSH concentrations in women that are 36–40 or 41–45 years of age.

Within the Community group, there were 295 women with live births, spontaneously conceived in 12 months or less (fertile community) and 60 with infertility of 1 year or more (subfertile community). The age-specific AFC percentiles of women that experienced infertility compared to women that had proven fertility within the community are shown in Table 4, separated by age at the time of attempted conception. Across all ages, the mean AFC percentile for age was 49.9 in women with live births, and 36.4 in women with subfertility ($p = 0.001$).

DISCUSSION

There is an assumption that ovarian reserve may reflect not only decreased quantity, but also decreased fecundity. This study tested the hypothesis that ovarian reserve, as measured by AFC, in infertile women was different from that in a community-based population. In this analysis we found a significantly lower median AFC in women who are infertile. Furthermore, we showed within the community-based group, AFC is significantly lower in women who had experienced difficulties conceiving.

AFC is considered one of the most reliable non-invasive methods for determining ovarian reserve. This conclusion is based on AFC correlating well with the number of non-growing follicles noted in histological sections and following a parallel pattern of decline with age to that observed histologically [20–22]. In addition, AFC has been correlated with the occurrence of the menopausal transition, response to ovarian stimulation and possibly pregnancy outcomes [23–27]. In our study, we show that AFC is lower in women who are infertile over a wide range of ages.

Since menopause ensues when oocyte depletion is almost complete (postulated to be with approximately 1000 remaining oocytes), lowered AFC would be expected to predict an

earlier menopause[28]. And, consistent with teVelde's model of reproductive aging, lowered reproductive potential would be associated with both lowered AFC and earlier menopause[4]. Kok et al.(2003) studied a large study population (n= 2393) that had never used birth control and found the age at onset of menopause was significantly associated with reproductive potential[11]: for every 5 year increase in the age of onset of menopause, there was a decrease in the probability of consulting with a fertility specialist (OR=0.82; 95%CI 0.71,95), of being nulliparous (OR=0.78; 95%CI 0.64,96) and of requiring more than 5 years to achieve a second livebirth (OR=0.73; 95%CI 0.61,0.89).

While it has been demonstrated that the earlier age at onset of menopause is associated with diminished reproductive potential, clinical usefulness is limited unless we have a prospective marker for menopause. This has led to considerable interest over the last decade in identifying non-invasive (indirect) markers of ovarian age that may predict both menopause and the likelihood for successful pregnancy. Few studies, however, have evaluated whether ovarian reserve tests predict spontaneous pregnancy. Earlier studies in subfertile women suggested high FSH, as a marker of low ovarian reserve, was associated with a decline in pregnancy rate in subfertile patients and longer time to spontaneous pregnancy regardless of age [29,30] More recently, Haadsma et al (2008) addressed this question in an ovulatory, subfertile population, and found an inverted U-shape best described the relationship between pregnancy likelihood and both AFC and FSH. However, excluding those with low FSH and/or high AFC eliminated any significance of ovarian reserve testing for predicting conception. Additionally, as above, this was a cohort of subfertile patients who were only allowed to continue with expectant management if their chances for conception were thought to be > 30%. (31) Thus only those considered to have the best fertility prognosis continued expectant management for a prolonged period. To identify if poor ovarian reserve was predictive of spontaneous pregnancy, they performed a sub- analysis of those women with an FSH>10 and found no association. In our study, rather than modeling within a group already known to be subfertile, we compared women with unexplained infertility to women in the community. We observed a significant decrease in AFC in the infertile women, up to age 40. FSH differences between the groups were variable which may be expected since FSH is considered a late marker of ovarian aging and varies from month-to-month [31–34].

The association of age with diminishing reproductive capacity is well known. The etiology is often attributed solely to aneuploidy[35–37]. The mechanisms that are thought to promote meiotic nondisjunction are multifactorial and are thought to accumulate over time. Therefore they are considered most dependent upon chronological age. However, it has also been proposed that aneuploidy can independently be attributed to falling oocyte number resulting from poorer quality oocytes remaining in the ovary after euploid oocytes have been selected for ovulation[2,38]. This would imply aneuploidy is negatively associated with the quantity of oocytes remaining in the ovary. This hypothesis is supported by studies that have shown decreased AFC in women with spontaneous abortions following IVF compared with those with live births, and increased FSH among those with miscarriages and aneuploid conceptions[14,15,27,39]. Interestingly, this finding has been observed when decreased follicular reserves resulted from both genetic and iatrogenic (ovarian surgery) causes, and was independent of age [12,40,41]. However, as discussed above, this conclusion has not been supported by all studies[10,17,42]. These inconsistencies may be explained by differences in study populations and study design. In addition many of these studies lack sufficient power to assure no difference. It is also possible that loss of oocyte developmental competence results from *different* mechanisms when associated with advanced ovarian aging or iatrogenic loss rather than expected chronologic aging.

The major limitation of our study is its cross-sectional nature, as we cannot establish that lower AFC actually results in infertility. In addition, while lower AFCs are seen among infertile women at the time of presentation, it is uncertain whether this results from a smaller initial oocyte pool or an accelerated rate of loss. If an increased rate of loss is responsible, it is necessary to know the timing of onset of this loss to improve predictive ability for women. Longitudinal studies of AFC in both fertile and infertile women will be necessary to determine the predictive value of AFC for future fertility. Threshold values that predict a very low likelihood of spontaneous conception may be identified and thus the nonspecific term “diminished ovarian reserve,” currently overused in the infertility literature, could gain clinical relevance among the general population.

Although age is considered to be the most predictive variable for pregnancy success, there is considerable variation in the onset of reproductive compromise for any individual woman. We are not yet able to predict who will have difficulty conceiving. In this study, we show AFC is decreased in women who are infertile and those with subfertility. Thus AFC appears to have an independent association with reproductive potential and may account for at least part of the considerable variation that exists between women for any given age. Decreased AFC *may*, in fact, be a marker of both oocyte quantity and quality. If our results are replicated in longitudinal studies, age-specific AFC percentile may represent a powerful tool helping women assess their future fertility potential.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics for the infertile and community group of women

	* Infertile (n=881)		* Community (n=771)		p-value
	Median	Range	Median	Range	
Age at TVUS years	37.0	20.0	35.4	20.5	<0.0001
AFC	10.0	39.0	14.0	58.0	<0.0001
Estradiol	38.0	413.0	39.5	620.7	0.9397
FSH	6.9	29.9	6.4	38.4	0.0018
Number of Pregnancies	0.9	1.27	1.71	2.19	<0.0001

* The infertile group are patients that have presented to UCSF Center for Reproductive Health with a diagnosis of unexplained infertility. The community group is sample frame of the general population.

Table 2
Past pregnancy outcomes for the infertile compared to the community group of women

	* Infertile (n=881)		* Community (n=771)		p-value
	N	%	N	%	
Spontaneous abortion	186	21.7	156	20.2	0.4598
Pregnancy termination	180	21.5	332	43.0	< 0.0001
Ectopic pregnancy	31	3.7	12	1.6	0.0075
Live birth	67	8.2	409	53.0	< 0.0001

* The infertile group are patients that have presented to UCSF Center for Reproductive Health with a diagnosis of unexplained infertility. The community group is sample frame of the general population

Table 3

The AFC for the infertile compared to the community group of women stratified by age

Age group	* Infertile (AFC)			* Community (AFC)			Z	p-value
	N	Median	Range	N	Median	Range		
25-30	45	16	4-40	175	20	4-58	-3.68	0.0002
31-35	267	11	1-30	215	15	5-48	5.64	<0.0001
36-40	373	9	1-32	217	12	0-52	3.83	0.0001
41-45	196	7.5	1-21	163	7	1-33	-0.64	0.5203

* The infertile group are patients that have presented to UCSF Center for Reproductive Health with a diagnosis of unexplained infertility. The community group is sample frame of the general population

Table 4

AFC percentiles estimates for women that failed to conceive (subfertile) compared to those that spontaneously conceived within 12 months(fertile) within the community group of subjects, stratified by age.

Age at attempted conception	N	Percent infertile	* Median AFC Percentile ** (Subfertile)	* Median AFC Percentile ** (Fertile)	P-value
≤20	35	19%	56	56	0.97
21–30	171	15%	25	50	0.02
31–40	141	18%	25	44.5	0.03
>40	5	40%	33.5	50	0.37

* Median AFC percentile based on the entire OVA population as an estimate of AFC at the time of attempted conception.

** The subfertile group is defined as those women with a history of attempting conception without success within the community group, and the fertile group is defined as those women who experienced a spontaneous conception in under 12 months, resulting in a live birth within the community group