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# Age Related Serum Antimullerian Hormone Concentrations among Infertile Versus Fertile Women

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author CBC designed the study and wrote the protocol. Authors CG and AP collected all data. Author CG performed the statistical analysis, and wrote the first draft of the manuscript. Authors MB and CBC did the literature search and also wrote part of the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aims:** Antimullerian hormone (AMH) has been accepted as a marker for the size of the ovarian follicle pool. To interrupt the results of this investigation, age-specific concentrations are needed. The purpose of this study is to compare antimullerian hormone (AMH) concentrations among infertile women ages 22 to 32 years experiencing regular menses with oocytes donors of the same age.
**Study Design:** Cohort study.
**Place and Duration of Study:** South Florida Institute for Reproductive Medicine, Miami, Florida and Reproductive Medicine Institute, Evanston, IL. Samples drawn between June 2008

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and June 2012.
**Methodology:** 400 infertile women and 102 oocyte donors aged 22-32 years with a history of regular menses and who were undergoing in vitro fertilization procedures for treatment of infertility had blood drawn for determination of AMH concentrations. Serum AMH was measured by enzyme-linked immunosorbent assay using an AMH ELISA kit (Beckman Coulter, Chaska, MN, USA).
**Results:** When the mean +2 standard deviations of the serum AMH concentrations among infertile women with regular menses were compared with age-specific oocyte donors, a significant decrease among infertile women was noted at all age groups.
**Conclusion:** A significant proportion of infertile women have lower than average ovarian reserve, suggesting that serum AMH values reflect follicular supply somewhat independent of age.

*Keywords: Antimullerian hormone; AMH; infertility; oocyte donor.*

## 1. INTRODUCTION

Antimullerian hormone (AMH) is a homodimeric disulfide-linked glycoprotein member of the transforming growth factor-beta superfamily with a molecular weight of 140kDa [1]. In contrast to other members of the superfamily, AMH is expressed only on the gonads. In females, AMH is secreted by granulosa cells of growing follicles measuring 4-6mm in diameter [2] or follicles that have undergone recruitment from the primordial follicle pool but have not as yet been selected for dominance. The main physiologic role of AMH appears to be limitation of transition from primordial into growing follicles [3] as well as to diminish the responsiveness of growing follicles to follicle stimulating hormone (FSH) [4]. By decreasing sensitivity to FSH, AMH limits the number of follicles that develop to the pre-ovulatory stage [3]. The ovary-specific expression pattern in granulosa cells of growing non-selected follicles makes AMH an ideal marker for the size of the ovarian follicle pool. Since AMH is secreted by the ovary into the circulation with little variation throughout, it has emerged as a marker of ovarian reserve and response to gonadotropin stimulation permitting the identification of both poor and hyper-response to gonadotropin administration [5-8]. As a result, serum AMH testing in women is often obtained during the initial clinical evaluation at fertility centers. To interpret the results of this test, age-specific concentrations are needed. While age specific values for circulating AMH concentrations have been reported for both regularly menstruating women [9] and infertile [10] populations, comparisons have not been made. The present study compares results of AMH concentrations among infertile women with age specific values in fertile women serving as oocyte donors.

## 2. MATERIALS AND METHODS

### 2.1 Patients

A total of 400 women, aged 22-32 years, who were undergoing in vitro fertilization (IVF) procedures for the treatment of infertility had blood drawn for determination of AMH concentration. All women had a history of regular menses occurring every 28 to 30 days. Women with a diagnosis of polycystic ovarian disease were excluded from the study [11].

One hundred two (102) women aged 22-32 years participating as oocyte donors for *in vitro* fertilization (IVF) and embryo transfer programs served as age-matched fertile controls.

This study was approved by the Institutional Review Board and all women had blood drawn for serum AMH concentrations after informed consent were obtained.

### 2.2 AMH Assay

Blood was drawn in a tiger or red topped tube and allowed to clot. The sample was then centrifuged within 2 hours of collection at 3500 rpm for 15 minutes. The serum was removed and immediately frozen at -20 degrees C until assayed. Serum AMH was measured by enzyme-linked immunosorbent assay using an AMH ELISA kit (Beckman Coulter, Chaska, MN, USA). AMH values are presented as ng/ml (conversion factor to pmol/l=ng/ml x 7.143). The detection limit of the assay is 0.14 ng/ml; intra- and inter-assay coefficients of variation were 12.3% and 14.2%, respectively.

### 2.3 Statistical Analysis

Age-specific serum AMH concentrations among infertile women were compared with oocyte donors using the Welch's unpaired t tests. A

probability (P) value of <0.05 was considered significant.

## 3. RESULTS AND DISCUSSION

Of the 400 infertile women included in the study, 277 had a single diagnosis and 123 had multiple diagnoses for the cause of infertility. The single diagnoses included: low ovarian reserve (n=42), male factor (n=126), tubal (n=53), endometriosis (n=30) and unexplained (n=26). Among the multiple diagnoses were: male + low ovarian reserve (n=72), male + tubal (n=25), male + endometriosis (n=18) and low ovarian reserve +tubal (n=8).

The mean ± 2 standard deviations (ng/ml) of the age- specific AMH concentrations among infertile women with regular menses and oocyte donors are shown in Fig. 1 (data presented at the 2014 Pacific Coast Reproductive Society, Indian Hills, California, USA, March 19-23, 2014). A significant difference (P<0.05) was noted at all age groups.

Our data provide age-specific concentrations of serum AMH among infertile women who were menstruating regularly compared with oocyte donors. Since serum AMH concentrations vary with age (Fig. 1) [5,12-14], age –specific values are more accurate in predicting ovarian reserve than the normal values reported in the AMH assay kit. When AMH values from regularly menstruating women experiencing infertility were compared with those from the literature who were not infertile [9], a significant difference was noted for each age group. While the mean values of serum AMH were significantly lower among women experiencing infertility compared with those who were not, a wide range of overlapping values was noted making an absolute cut off value for normal values for that age impossible. Nonetheless, the significant difference in mean values between the two groups sheds light on the pathophysiology of unexplained infertility. A significant proportion of infertile women have lower than average reserve of ovarian follicles irrespective of the diagnosis of cause of her infertility, suggesting that serum AMH values reflect follicular supply somewhat independent of age. The age-specific AMH values provided by the present study are lower than those previously reported by a larger study of 17,120 randomly selected serum specimens sent to a single reference laboratory from U.S. fertility centers located in 37 different states between 2007 and 2010 [10]. In that report, age-specific values were not stratified based on menstrual history or diagnosis. Thus patients with a diagnosis of polycystic ovarian disease were included in the age-specific reference values. Since patients with polycystic ovarian disease have been reported as having increased serum AMH concentrations in previous studies [12] and confirmed in an age-specific manner in the current study, the differences in results can be explained.

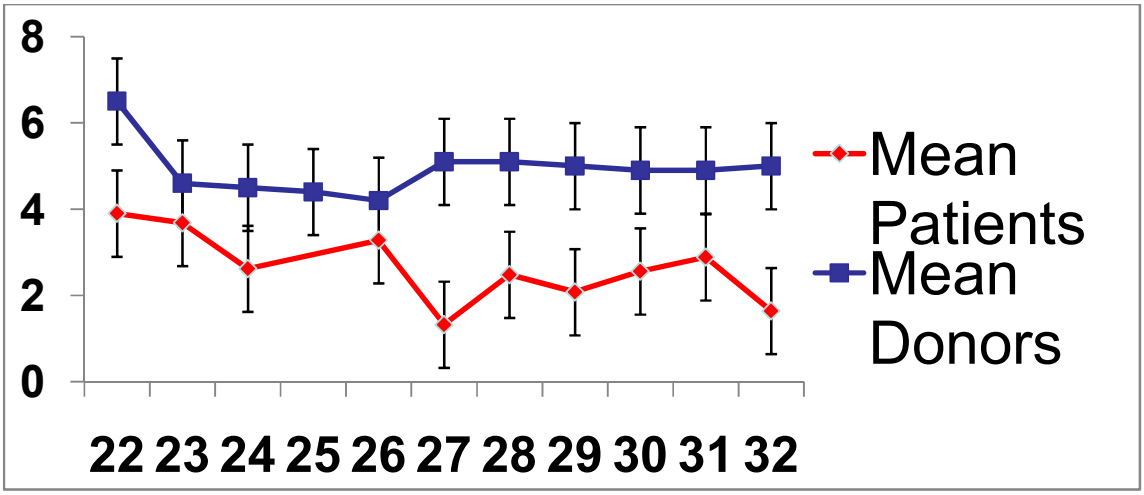


**Fig. 1. Mean ±2 SD serum AMH concentrations (ng/ml) among 400 infertile women and 102 oocyte donors**

In addition to being a marker for a diminishing ovarian follicle pool, serum AMH can also serve as a marker for an enlarged follicle pool such as seen in polycystic ovarian disease. Although the mechanisms leading to polycystic ovarian disease are still poorly understood, the common denominator is a disturbance in the selection of the dominant follicle resulting in oligo-anovulation. The defect in selection results in an accumulation of small antral follicles, which contribute significantly to the production of AMH. High serum AMH concentrations are associated with ovarian hyper-response and hyperstimulation syndrome [8,13,14]. Thus, serum AMH concentration is a good marker for the extremes of ovarian 4reserve and age-specific values can be used to determine ovarian stimulation strategies [13,14].

Knowledge of age-specific AMH serum concentrations will help the clinician in indentifying risk factors contributing to the cause of infertility and aid in determination of strategies for treatment of infertility including dosage of FSH for ovarian stimulation. It is hoped that in the future age-specific serum AMH levels will serve as one component among others to evaluate a woman's reproductive potential early in life so that prophylactic measures can be taken before a problem declares itself.

## 4. CONCLUSION

A significant proportion of infertile women have lower than average ovarian reserve, suggesting that serum AMH values reflect follicular supply somewhat independent of age.

## ETHICAL APPROVAL

This study was approved by the Institutional Review Board of the Fertility and Cryogenic Laboratory # 002-11. All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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