Original Article

The Impact of High Circulating Anti-Müllerian Hormone on Endometrial Thickness and Outcome of Assisted Reproductive Technology in Women with Polycystic Ovarian Syndrome: A Cohort Study

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Abstract

Background: Elevated circulating anti-Müllerian hormone (AMH) in women with the polycystic ovarian syndrome (PCOS) has been found to have a detrimental effect on endometrial function. This may adversely affect the outcome of *in vitro* fertilisation (IVF) in PCOS women. **Aims:** To investigate the impact of high serum AMH concentrations on endometrial thickness (ET) and the outcome of IVF in women with PCOS. **Settings and Design:** This retrospective cohort study included all PCOS women who underwent fresh IVF\intracytoplasmic sperm injection cycles between January 2016 and December 2021 in one major IVF centre. **Materials and Methods:** PCOS diagnosis was based on Rotterdam criteria, and participants were identified from centre database. All women received antagonist protocol. Primary outcomes were trigger-day ET and live birth rate (LBR). Circulating AMH was correlated with ET and ovarian response. **Statistical Analysis Used:** AMH levels were compared between women with and without live birth. ET and LBRs were compared between women with AMH <7.0 ng/ml versus those with AMH ≥7.0 ng/ml. **Results:** The study included 102 PCOS women, of which six were excluded due to poor response (n = 4), hyperresponse (n = 1) or fertilisation failure (n = 1). Of the remaining 96 women, 42 (43.8%) achieved a live birth. There was no statistically significant (P > 0.05) correlation between AMH and ET. Mean ± standard deviation AMH concentration was not significantly (P > 0.05) different between women with live birth (6.5 ± 3.4 ng/ml) and those without (6.5 ± 2.4 ng/ml). High AMH positively correlated with the number of oocytes retrieved, metaphase II oocytes and embryos (P = 0.003, 0.006 and 0.006, respectively). There was no statistically significant (P > 0.05) difference in ET or LBR between women with AMH <7.0 ng/ml (n = 72; ET, 10.7 ± 1.8 mm; LBR, 45.8% [33/72] versus those with AMH ≥7.0 ng/ml (n = 24; ET, 10.8 ± 1.7 mm; LBR, 37.5% [9/24]). **Conclusions:** High circulating AMH in PCOS women does not seem to negatively affect ET or LBRs during assisted reproductive technology.

Keywords: *Anti-Müllerian hormone, assisted reproduction, endometrial thickness, polycystic ovarian syndrome*

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Introduction

Anti-Müllerian hormone (AMH) is a member of the transforming growth factor (TGF)-beta, which is exclusively produced by the small antral follicles. Polycystic ovarian syndrome (PCOS) is characterised by a two-to-three-fold increase in serum AMH concentration.[1] Circulating AMH is widely accepted as a reliable marker for ovarian reserve, which can predict response to controlled ovarian stimulation (COS) and is currently used globally in clinical practice to predict *in vitro*-fertilisation (IVF) outcomes.[2,3] However, the predictive accuracy of AMH in women undergoing IVF remains uncertain with conflicting literature data. A major factor contributing to the variation between studies is the heterogeneity in patient populations included in various studies. It is, therefore, necessary to study predictive value of serum AMH in different populations.

High circulating AMH, which is a characteristic of PCOS, has been shown to adversely affect reproductive outcomes in PCOS women receiving ovulation induction with clomiphene citrate, laparoscopic ovarian drilling and follicle-stimulating hormone (FSH).[4-6] A possible contributing factor to this adverse reproductive effect of PCOS-related high AMH is its negative impact on endometrial function.[7] Several studies have reported that AMH and its receptor AMHRII are expressed in the endometrial stromal and epithelial cells.[8-10] Increased AMH concentrations in cultured endometrial tissue have been shown to decrease cell viability and promote apoptosis.[10] Similar findings were also reported in cultured endometriosis tissue.[11] Another possible mechanism behind the suggested negative impact of high AMH levels on reproductive outcomes has been based mainly on its inhibiting effect on FSH-dependent dominant follicle selection, which could adversely affect ovarian responsiveness to COS during IVF.[12] Furthermore, AMH inhibits the FSH-directed intrafollicular aromatase activity with subsequent elevation of intra-follicular androgens, which could further compromise folliculogenesis.[13-15] Based on the above, it is possible to hypothesise that elevated serum AMH levels seen in PCOS women could adversely affect endometrial receptivity and folliculogenesis during COS, which in turn could compromise assisted reproductive technology (ART) outcomes.

To date, there are only a few studies that have investigated the impact of high serum AMH levels on IVF\intracytoplasmic sperm injection (ICSI) outcomes with conflicting results.[16-22] While three studies[16-18] reported a negative impact, two[19,20] reported a positive impact and two[21,22] reported no impact of high circulating AMH on IVF outcome including pregnancy, and live birth rates (LBRs). In one study, high AMH positively correlated with ovarian response but was not predictive of pregnancy or live birth outcomes.[20] Furthermore, the impact of high circulating AMH on endometrial development and receptivity in women with PCOS undergoing IVF/ICSI remains to be investigated.

To address this important gap of knowledge, we designed this cohort study to investigate the possible effects of high serum AMH levels on the endometrium, ovarian response and the outcome of IVF/ICSI in PCOS women.

Materials and Methods

This cohort study was approved by the Institutional Review Board (IRB) at (Assiut Faculty of Medicine) Faculty of Medicine (IRB approval number: 17300702, date: 2nd January, 2022). The study adhered to the principles of the Helsinki Declaration (2013). Informed consent was obtained from participants for the use of anonymised data for research and educational purpose.

Study participants

This retrospective cohort study included all women with PCOS (aged 18–40 years) who underwent fresh IVF\ICSI cycles between January 2016 and December 2021 at (Women Health Hospital IVF Centre) IVF Centre, (Assuit University), (Egypt). Diagnosis of PCOS was made according to Rotterdam consensus criteria when at least two of the following three criteria existed: oligo-/anovulation, clinical and/or biochemical hyperandrogenaemia and/or sonographic appearance of polycystic ovaries.[23] PCOS diagnosis was established after the exclusion of other endocrine conditions, including hyperprolactinaemia, thyroid disease, Cushing's syndrome, congenital adrenal hyperplasia, or androgen-secreting tumours. Cases with possible endometrial pathology detected by ultrasound scan or previously treated surgically were excluded. In addition, women who underwent frozen cycles or preimplantation genetic testing were excluded from the study.

The primary outcome measures were trigger-day endometrial thickness (ET) and live LBR. Secondary outcomes included the number of retrieved oocytes, the number of metaphase II (MII) oocytes, fertilisation rate and number of embryos transferred. AMH concentration was measured for all women before starting COS.

Controlled ovarian stimulation and embryo transfer

All women utilised the same GnRH antagonist protocol. We used a combination of recombinant FSH (Gonal-F, follitropin alfa, Merck Sereno, Modugno (Bari), Italy) and HMG (Menopur, Ferring, Kiel, Germany). Starting

dose was estimated according to the women's age and antral follicle count. Afterwards, the daily dose was adjusted by tracking follicular growth and oestradiol levels. When at least 2–3 follicles reached 17 mm, ovulation trigger was achieved by subcutaneously recombinant human chorionic gonadotropin (rhCG, Ovitrelle, Merck Sereno, Modugno (Bari), Italy) 250 µg. For those who were at high risk of ovarian hyperstimulation syndrome, one dose of triptorelin acetate 0.2 mg (Decapeptyl, Ferring, Kiel, Germany) was injected. Ovum pickup was performed after 34–36 h using transvaginal ultrasound-guided needle aspiration.

ICSI was performed in all cases regardless of the cause of infertility. The quality of embryos was evaluated based on the Society for ART embryo grading system.[12] The day of transfer (3 or 5) and the number of embryos transferred were determined according to the number and quality of available embryos and at the discretion of the physician and patient.

All women received progesterone for luteal phase support. Two weeks following embryo transfer, serum B-hCG was measured. Pregnancy was confirmed by positive, B-hCG test and the presence of intrauterine gestational sac on ultrasound examination.

Anti-Müllerian hormone assay kit

Serum AMH concentration was measured using VIDAS automated AMH assay. This automated test was performed with VIDAS instruments (Enzyme Linked Fluorescent Assay). The reported limits for detection ranged from 0.02 to 9.00 ng/mL. Women were divided into two groups according to kit reference (normal/moderately elevated AMH, markedly elevated).

Sample size and power calculation

In this retrospective cohort study, we aimed to include all consecutive PCOS women who underwent IVF during the study period. Power calculation was carried out to calculate the sample size required to detect a clinically significant difference in ET of 1.5 mm between women with normal versus high AMH serum levels. Approximately, one-third of PCOS women have markedly elevated circulating AMH.[4] We estimated a sample size of 63 (21 with high AMH and 42 with normal AMH) to have a statistical power of 90% to detect the clinically significant difference in ET between the two groups with a 5% significance level.

Statistical analysis

Statistics were conducted using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA, version 22) for Windows, version 22. We used mean ± standard deviation (SD) for normally distributed continuous data and median (Interquartile, interquartile range) for skewed continuous variables. Correlation between AMH levels and outcome variables was carried out using the Spearman's correlation test. Participants were divided into two groups according to serum AMH levels, including normal/moderately elevated (<7.0 ng/ml) and markedly elevated AMH (≥7.0 ng/ml). Numerical data were compared between the two groups using parametric or non-parametric tests depending on the type of data distribution. Categorical data were compared using the Chi-square test. Multivariate linear and logistic regression analysis models were performed to adjust for the effect of various confounders on numerical and categorical outcomes, respectively.

Results

Baseline characteristics

A total of 102 women with anovulatory PCOS who have undergone IVF/ICSI were identified as eligible for the study. Baseline characteristics of included women are summarised in Table 1. Their mean ± SD age and body mass index (BMI) were 27.3 ± 4.6 years and 28.9 ± 4.3 kg/m^2, respectively. The mean ± SD serum AMH level was 6.4 ± 2.8 ng/ml

In vitro fertilisation cycle characteristics and outcomes

The cycle was cancelled in six participants due to poor response in four women, hyper-response in one

Table 1: Baseline characteristics of 102 women with anovulatory polycystic ovarian syndrome undergoing *in-vitro* fertilisation

Characteristic	(*n*=102)
Age (years)	27.25±4.63
BMI (kg/m^2)	28.87±4.29
Duration of infertility (years)	6.22±3.37
Other causes of infertility	
Tubal factor	6 (5.9)
Male factor	43 (42.1)
None	53 (52.0)
Previous reproductive surgery	
No	61 (59.8)
LOD	32 (31.4)
Tubal disconnection	6 (5.9)
Ovarian cystectomy	3 (3.9)
FSH (IU/L)	5.06±1.40
LH (IU/L)	7.22±4.88
AMH (ng/mL)	6.46±2.83
TSH (IU/L)	1.77±0.72
Prolactin (MIU/L)	14.16±8.49

Data are presented as mean±SD; *n* (%). AMH=Anti-Müllerian hormone, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, LOD=Laparoscopic ovarian drilling, SD=Standard deviation, TSH=Thyroid-stimulating hormone, BMI=Body mass index, IQR=Interquartile range

patient and fertilisation failure in another patient. Of the remaining 96 women who had embryo transfer, 42 achieved a live birth (43.75%). The mean ± SD trigger-day ET was 10.8 ± 1.8 mm.

Effect of anti-Müllerian hormone on study outcomes

There was no statistically significant correlation between circulating AMH and trigger-day ET (*r*, −0.058; *P* = 0.563). Serum AMH concentrations did not differ between women who had a live birth (*n* = 42; mean ± SD 6.5 3.4) and those who did not (*n* = 54; mean ± SD 6.5 ± 2.4) (*P* = 0.754). However, there were positive correlations between serum AMH concentrations and the number of oocytes retrieved (*P* = 0.003), number of MII oocytes (*P* = 0.006) and number of fertilised embryos (*P* = 0.006) [Table 2].

When grouping women according to the level of serum AMH, average/moderately elevated (AMH <7.0 ng/ml, *n* = 72) versus markedly elevated (AMH ≥7.0 ng/ml, *n* = 24), neither ET (10.7 ± 1.8 mm vs. 10.8 ± 1.7 mm, respectively) nor LBR (45.8% versus 37.5%%, respectively) differed between the two groups [Table 3].

Multivariate linear regression analysis was conducted to adjust for confounders' effect on ET. The model included AFC, total gonadotropins dose, duration of ovarian stimulation, number of retrieved oocytes and peak E2 and AMH levels. No significant association was revealed between AMH and ET (B coefficient 0.165, 95% confidence interval [CI]-0.567–0.927, *P* = 0.616). Likewise, a multivariate binary logistic regression was used to account for the confounders' effect on LBR. The model included age, AMH, BMI, number of retrieved oocytes, grade of the transferred embryos and ET. The results showed no statistically significant association between AMH or ET with LBR (adjusted Odds ratio [aOR] 1.042, 95% CI 0.833–1.231, *P* = 0.625: aOR 1.115, 95% CI 0.787–1.581, *P* = 0.541, respectively).

Effect of day of embryo transfer on live birth rate

Further subgroup analysis according to the day of embryo transfer revealed no statistically significant (*P* = 0.429) difference in LBR between women having an embryo transfer on day 3 (27/67, 40.3%), day 4 (8/18, 44.4%) and day 5 (7/11, 63.6%).

Effect of laparoscopic ovarian drilling

Of the 96 participants included in this study, 29 had undergone laparoscopic ovarian drilling (LOD) before their IVF. The mean serum AMH concentrations did not significantly (*P* < 0.05) differ between women who had undergone LOD (6.75 ± 2.92 ng\ml) versus those (*n* = 67) who had not (6.33 ± 2.80 ng\ml). Similarly, LBRs did not significantly (*P* > 0.05) differ between both groups (48.3% versus 41.8%, respectively) [Table 4].

Discussion

The current cohort investigated the impact of increasing serum AMH concentrations on endometrial development and reproductive outcome in 102 PCOS women undergoing IVF/ICSI. The study showed no correlation between high AMH levels and trigger-day ET. High circulating AMH had no impact on ET or LBR. However, AMH level positively correlated with ovarian response to COH in terms of the number of oocytes retrieved, mature oocytes and embryos available for transfer. Our study sample size (*n* = 96) had >90% power to detect a difference of 1.5 mm in ET between women with normal AMH (*n* = 72; ET = 10.7 ± 0.8) and women with high AMH (*n* = 24).

The positive correlation between AMH level and the degree of ovarian response shown in our data is in agreement with previous studies that suggested AMH as an accurate predictor for the degree of ovarian responsiveness to COH.[20-22] A recent study conducted by Tal *et al*. did not find any significant effect for AMH on the number of retrieved oocytes, peak E_2 or fertilisation rate in a subgroup of women (*n* = 184) assumed to have PCOS being in the high percentiles (>75th %) of AMH

Table 2: Correlation between serum Anti-Müllerian hormone and study outcomes

	AMH	
	r	*P*
The endometrial thickness on the day of the trigger	−0.058	0.563
Number of oocytes retrieved	0.292	0.003
Number of MII oocytes	0.276	0.006
Number of embryos fertilised	0.274	0.006

AMH=Anti-Müllerian hormone, MII=Metaphase II

Table 3: Endometrial thickness and full-term pregnancy according to Anti-Müllerian hormone level

	AMH level (ng/mL)		*P*
	<7.0 (*n*=72)	≥7.0 (*n*=24)	
Trigger-day ET (mm)	10.7±1.8	10.8±1.7	0.298
Live birth rate	33 (45.8)	9 (37.5)	0.845

Data are presented as mean±SD; *n* (%). AMH=Anti-Müllerian hormone, ET=Endometrial thickness, SD=Standard deviation

Table 4: Effect of laparoscopic ovarian drilling on serum Anti-Müllerian hormone and live birth

	LOD (*n*=29)	No LOD (*n*=67)	*P*
AMH (ng/mL)	6.75±2.92	6.33±2.80	0.552
Live birth rate	14 (48.3)	28 (41.8)	0.556

Data are presented as mean±SD; *n* (%). LOD=Laparoscopic ovarian drilling, AMH=Anti-Müllerian hormone

level.[19] Nevertheless, the precise analysis of their data reveals a significantly lower total gonadotropins dose in the above 75th percentiles subgroup. Thus, this reduction in gonadotropin dose consumed during COH can be an indirect indicator for a better ovarian response in the high AMH group.

A prospective study of 164 PCOS women undergoing IVF by Xi *et al*. revealed that day 3 circulating AMH positively correlates with ovarian response to COH, which is consistent with our study. However, in disagreement with our findings, they found high AMH levels to be associated with a lower implantation rate with a trend towards lower pregnancy rates. The authors proposed that the observed decrease of implantation and pregnancy rates may be due to the remarkably increased luteinising hormone (LH) concentrations, which positively correlate with the high AMH levels. They explained that high LH could suppress FSH function, promote premature luteinisation and follicular atresia and adversely affect endometrial development.[12] This can lead to impairment of the oocyte/embryo quality and endometrial receptivity deterioration.

A recent retrospective cohort study assessed the impact of high AMH on LBRs and other reproductive outcomes in 184 PCOS women who underwent their first fresh IVF/ICSI cycle.[17] The study divided participants into three groups according to the <25th (low), 25–75th (average) or >75th (high) percentiles of serum AMH concentrations. The low serum AMH group was older than the other two groups and required more gonadotropins dose during stimulation. In contrast to our findings, high AMH had no impact on oocytes retrieved but was associated with lower live LBRs compared to average and low AMH, even after adjusting for age, BMI, number of embryos transferred, and the transfer day.[17] The reason for this discrepancy is not clear but could be related to the differences in PCOS populations and in stimulation protocols. For instance, our cohort was younger (age, 27.2 ± 4.6 years) with a higher BMI (28.8 ± 4.3 kg/m^2) than their cohort (age, 33.9 ± 0.8 years; BMI, 26.5 ± 5.7 kg/m^2).

Another prospective study of 60 PCOS women who underwent 80 cycles with long protocol showed a positive predictability for AMH on ovarian response and reproductive outcomes such as fertilisation, implantation and pregnancy rates.[22] Similarly, another retrospective study reinforced these results and elucidated that women with AMH ≥10 ng/mL experienced better pregnancy rates despite having comparable age and number of transferred embryos with the group of AMH 5–10 ng/mL. Furthermore, AMH showed a positive relation with levels of LH, dehydroepiandrosterone sulphate and total testosterone.[21] However, on examining the data of Kaya *et al*.,[22] a considerable, yet statistically non-significant, age difference can be found between different AMH subgroups.

Interestingly, other studies have gone further to examine the effect of AMH on IVF outcomes in different PCOS phenotypes, yet no consensus was established.[24,25] Notably, PCOS phenotype was found to be an independent predictor for pregnancy[25] and live births[24] with the lowest outcomes in the hyperandrogenic category, particularly when accompanied by chronic anovulation.[25]

The effect of AMH on endometrial receptivity has been a matter of concern. The presence of AMH and its receptors in the endometrium proposes that AMH can act on the endometrium via autocrine, paracrine and endocrine manners.[8] Moreover, the AMH signalling pathway was found intact during both proliferative and secretory phases of the menstrual cycle.[9,26] Signorile *et al*. proposed that the high AMH concentration could affect endometrial homeostasis through pro-apoptotic effects when using the endometriosis model.[11] In addition, excess AMH was linked to the Akt (protein kinase B), nuclear factor-kB pathways[27] and TGF-beta family type I receptors.[28]

In contrast to the above, the current study investigated ET as a predictor for endometrial receptivity and did not find any significant effect of excess AMH and ET. It is possible that the high estradiol levels in COH could prevent the putative negative effect of high AMH on the endometrium. In agreement with our results, a previous systematic review and meta-analysis, including 11 studies, demonstrated a weak predictive value for the AMH for implantation and clinical pregnancy in women undergoing IVF/ICSI, particularly those with high ovarian reserve.[19]

Interestingly, a normal endometrial expression of aVb3, a critical integrin for embryo attachment, was found in polycystic ovarian morphology (PCOM without hyperandrogenism). Yet, there was a lack of osteopontin, which is the main ligand for aVb3.[29]

Unfortunately, data on endometrial grading were not available in our study. Nevertheless, the lack of any adverse effect of markedly elevated AMH on the LBR provides indirect evidence that rising AMH levels did not compromise endometrial receptivity. However, further studies are required to investigate the potential impact of high AMH with the investigation of a surrogate marker for endometrial receptivity.

One of the limitations of this study is its retrospective design, which could introduce an element of bias.

Furthermore, the lack of any data on implantation and androgen levels did not allow us to investigate the relevance of these parameters to the study outcomes. Nevertheless, the study included all consecutive women in our well maintained and accurate database. Furthermore, the use of antagonist protocol in all our participants and the inclusion of a considerably good sample size could strengthen our study. Moreover, we reported data on LBRs, which is considered the gold standard outcome for any fertility study.

Conclusions

Our data did not support the hypothesis that high serum AMH levels could be detrimental to endometrial development or the success of IVF/ICSI. The study reinforces the positive predictability of AMH for ovarian response in PCOS women undergoing IVF/ICSI. PCOS women with markedly elevated circulating AMH could be reassured that the success of IVF and their chance of having a live birth are not compromised.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Raw data is available upon request.

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