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Serum Androstenedione Predicts Ovarian Response in Normal-BMI PCOS in Thi-Qar Province

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the leading cause of anovulatory infertility and a major source of variability in ovarian response during in vitro fertilization (IVF). Anti-Müllerian hormone (AMH) and antral follicle count (AFC) are the established pre-stimulation predictors but do not directly capture the androgenic biochemistry that defines PCOS.To assess basal serum A4 as a predictor of ovarian response operationalized as the follicular output rate (FORT), total oocytes retrieved, and excessive response (≥ 20 oocytes) among normal-BMI women with PCOS undergoing controlled ovarian stimulation (COS)A prospective single-center cohort study enrolled normal-BMI (18.5–24.9 kg/m²) women aged 20–38 years with PCOS by Rotterdam criteria, undergoing first-cycle gonadotropin-releasing hormone (GnRH) antagonist COS for IVF or intracytoplasmic sperm injection (ICSI). Basal day-2 to day-3 serum A4, AMH, AFC. Outcomes were FORT, total oocytes retrieved, mature (metaphase II) oocytes, and excessive response. Mean basal A4 was 3.8 ± 1.4 ng/mL. A4 correlated with FORT (Spearman $r = 0.59$, $p < 0.001$) and total oocytes retrieved ($r = 0.54$, $p < 0.001$). For prediction of excessive response, A4 achieved an area under the curve (AUC) of 0.84 (95% confidence interval [CI] 0.78–0.90), outperforming AMH (AUC 0.73, 0.65–0.81; DeLong $p = 0.02$). A combined A4 + AMH + AFC model reached AUC 0.89 (0.84–0.94; DeLong $p = 0.01$ versus AMH alone). In normal-BMI PCOS, basal serum A4 is an independent predictor of ovarian response and adds incremental discrimination beyond AMH and AFC for excessive response. A4 deserves consideration in pre-stimulation risk stratification.

INTRODUCTION

PCOS is the most common endocrinopathy of reproductive-aged women, with a global prevalence of 10–13% under contemporary diagnostic criteria [1],[2]. It is the leading cause of anovulatory infertility, and women with PCOS represent a substantial fraction of patients undergoing assisted reproductive technology (ART). Their ovarian response to COS is bimodal and difficult to predict: a large proportion hyper-respond yielding ≥ 20 oocytes and incurring elevated risk of ovarian hyperstimulation syndrome (OHSS) while a non-trivial minority unexpectedly under-respond despite high antral follicle counts and elevated AMH [3],[4].

AMH and AFC are the established pre-stimulation predictors of ovarian response and underpin most published nomograms, including the GnRH-antagonist-protocol model recently developed and validated in a 313-patient PCOS cohort by Xu and colleagues [5]. However, neither AMH nor AFC directly measures the androgenic biochemistry that is the defining feature of PCOS in the 2023 international guideline of Teede and colleagues [1]. A4 —IUPAC name androst-4-ene-3,17-dione is the principal androgen produced by ovarian theca cells under luteinizing hormone (LH) stimulation, the substrate from which granulosa-cell aromatase generates estradiol (E2), and a hormone whose serum concentration in PCOS correlates with theca-cell mass and follicular activity [6,7].

Three lines of evidence motivate the present study. First, Lebbi and colleagues showed in a prospective case–control study that the A4 response to recombinant FSH was a stronger predictor of selected follicle number in PCOS than the E2 response, with cycle-cancellation thresholds defined for excessive response [8]. Second, Lazzaroni-Tealdi and colleagues demonstrated that basal A4 in unselected ART cycles was a marker of ovarian response comparable to AMH and AFC and superior to FSH, and proposed an integrative G-index combining the three [9]. Third, FORT, defined as the ratio of preovulatory follicles to baseline AFC and originally described by Gallot and colleagues, captures the proportion of antral follicles that respond to exogenous FSH and adds qualitative information beyond simple AFC [10]–[12].

Two specific gaps justify the present work. First, body-mass index (BMI) confounds the relationship between PCOS, androgens, and ovarian response: obesity attenuates androgen elevation, alters gonadotropin pharmacokinetics, and worsens IVF outcomes [13],[14]. Most published cohorts include broad BMI ranges, making it difficult to isolate the androgenic signal. Restricting analysis to normal-BMI PCOS removes this confounder. Second, regional Iraqi data on basal androgen profiles and IVF outcomes in PCOS are essentially absent from the indexed literature, despite the high regional PCOS prevalence and the rapid expansion of ART services across Iraq.

This study had three objectives: to estimate the distribution of basal serum A4 in normal-BMI women with PCOS undergoing first-cycle COS at a tertiary center in Thi-Qar; to quantify associations between basal A4 and ovarian response, operationalized as FORT, total oocytes retrieved, and mature oocyte yield; and to evaluate the discriminative performance of A4 alone and in combination with AMH and AFC for prediction of excessive response.

MATERIAL

STUDY DESIGN AND SETTING

A prospective single-center observational cohort study was conducted at the gynecology and obstetrics department of Bint AlHuda teaching hospital, Nasiriyah, Thi-Qar, Iraq, from January 2023 through December 2024 (24 months). The study protocol was approved by the Research Ethics Committee of College of Medicine, University of Thi-Qar. All participants provided written informed consent before enrollment. The study followed the Declaration of Helsinki (2013 revision) and is reported in accordance with the STROBE statement for observational studies [15].

PARTICIPANTS AND ELIGIBILITY

Eligible women were aged 20–38 years, with normal BMI (18.5–24.9 kg/m²) measured at enrollment, and a diagnosis of PCOS by the 2003 Rotterdam criteria as reaffirmed in the 2023 international guideline (any two of: oligo-ovulation or anovulation; clinical or biochemical hyperandrogenism; polycystic ovarian morphology on transvaginal ultrasound, defined as ≥ 20 follicles per ovary or ovarian volume ≥ 10 mL) [1],[16]. Inclusion required first-cycle COS using a flexible GnRH antagonist protocol for IVF or ICSI for primary or secondary infertility. Exclusion criteria were: prior COS or IVF/ICSI cycle; underweight (BMI < 18.5) or overweight/obesity (BMI ≥ 25.0); endocrine disorder other than PCOS (hyperprolactinemia, untreated thyroid dysfunction, congenital adrenal hyperplasia, Cushing syndrome); ovarian surgery within the previous 12 months; severe endometriosis (rASRM stage III–IV); use of ovulation induction drugs, metformin, or hormonal contraception within the preceding 3 months; and pregnancy at screening. The participant flow is summarized in **Figure 1**.

STIMULATION PROTOCOL

All participants received a flexible GnRH-antagonist protocol. Recombinant follicle-stimulating hormone (rFSH; follitropin alfa) was started on cycle day 2–3 at an individualized dose of 150–225 IU/day determined by age, AMH, AFC, and clinician judgment. The GnRH antagonist (cetrorelix 0.25 mg/day subcutaneously) was started when the leading follicle reached 14 mm. Final oocyte maturation was triggered by recombinant human chorionic gonadotropin (rhCG; 250 µg) or, in cycles judged at high OHSS risk, by a GnRH agonist (triptorelin 0.2 mg) trigger. Transvaginal oocyte retrieval was performed 35–36 hours after trigger.

HORMONAL AND ULTRASOUND ASSESSMENT

Basal hormonal assays were performed on cycle day 2 or 3 immediately before stimulation start. Serum A4 was measured by competitive electrochemiluminescence immunoassay (Roche Cobas e601 platform) with intra-assay coefficient of variation (CV) < 8% and inter-assay CV < 10%, calibrated against the reference value range of 0.3–3.3 ng/mL for healthy adult women in the follicular phase. Serum AMH was measured by automated immunoassay (Roche Elecsys AMH Plus). Serum FSH, LH, E2, total testosterone, prolactin, and thyroid-stimulating hormone (TSH) were measured by automated chemiluminescent immunoassay. AFC was performed by transvaginal ultrasound at the same visit as the basal hormonal assay, by a single operator using a 7.5-MHz probe; antral follicles were defined as 2–9 mm in mean diameter, and AFC was the sum across both ovaries.

OUTCOMES

The primary outcomes were three measures of ovarian response: FORT, defined as the number of preovulatory follicles (≥ 16 mm) on the day of trigger × 100 / baseline AFC [10,11]; total number of oocytes retrieved; and number of mature (metaphase II) oocytes recovered after denudation. The secondary outcome was excessive response, defined as ≥ 20 oocytes retrieved, the threshold most commonly used in contemporary OHSS-risk literature [3],[17]. Cycle cancellation for poor response (defined as fewer than three follicles ≥ 12 mm after eight days of stimulation, or basal FSH > 10 IU/L on cycle day 2) was recorded as a secondary safety outcome.

SAMPLE SIZE AND STATISTICAL ANALYSIS

Sample size was determined for the primary correlation analysis: detecting a Spearman correlation of 0.30 between A4 and total oocytes retrieved with two-sided $\alpha = 0.05$ and 90% power required 113 evaluable participants; allowing for 20% non-completion, the recruitment target was 142 enrolled women. Continuous variables are summarized as mean ± standard deviation (SD) or median with interquartile range (IQR); categorical variables as counts and percentages. Univariable comparisons used the student t test or Mann–Whitney U test for continuous variables and the chi-squared or Fisher exact test for categorical variables. Spearman rank correlation was used for monotonic associations between basal hormones and outcomes. Multivariable linear regression assessed the independent association of A4 with FORT and total oocytes retrieved after adjustment for age, AMH, AFC, and basal LH/FSH ratio. Discriminative performance for excessive response was evaluated by the area under the receiver operating characteristic curve (AUC) with 95% CI calculated by the DeLong method [18]; AUCs were compared between predictors using DeLong's test. Calibration of the combined model was assessed by the Hosmer–Lemeshow goodness-of-fit test. Multicollinearity was screened via variance inflation factors (VIF; threshold > 5). Two-sided p-values < 0.05 were considered significant. Analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY) and R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria), with the pROC package used for ROC analysis.

RESULTS

COHORT ASSEMBLY AND BASELINE CHARACTERISTICS

Of 187 women assessed for eligibility during the 24-month enrollment window, 34 were excluded (22 not meeting inclusion criteria, 8 declined to participate, 4 other reasons), leaving 153 enrolled (see Figure 1). Five women dropped out before stimulation start for personal reasons, and two cycles were cancelled for predicted poor response (basal FSH > 10 IU/L). The final analytic cohort comprised 146 women who completed COS to oocyte retrieval. Baseline characteristics are summarized in Table 1. The mean age was 28.7 ± 4.6 years; mean BMI was 22.4 ± 1.6 kg/m² (by inclusion design); median modified Ferriman–Gallwey score was 9 (IQR 7–11); and 64.4% had primary infertility. The basal hormonal profile showed a typical normal-BMI PCOS pattern: median LH/FSH ratio 1.8 (IQR 1.4–2.4), median AMH 6.2 ng/mL (IQR 4.4–8.6), and median AFC 22 (IQR 18–28). Basal A4 followed an approximately normal distribution with mean 3.8 ± 1.4 ng/mL (range 1.2–7.8 ng/mL), with 38.4% of

participants exceeding the upper limit of the laboratory reference range (3.3 ng/mL).

OVARIAN RESPONSE OUTCOMES

Among the 146 evaluable cycles, the median total oocytes retrieved was 16 (IQR 12–22), and the median number of mature (metaphase II) oocytes was 13 (IQR 10–18). The median FORT was 67% (IQR 55–78). Excessive response (≥ 20 oocytes) occurred in 41 of 146 women (28.1%, 95% CI 21.0–35.9%). No participant developed severe early-onset OHSS; six women (4.1%) had moderate OHSS managed conservatively as outpatients Table 2.

UNIVARIABLE ASSOCIATIONS BETWEEN A4 AND OVARIAN RESPONSE

Basal serum A4 correlated positively with FORT (Spearman r = 0.59, 95% CI 0.47–0.69, $p < 0.001$) and with total oocytes retrieved (r = 0.54, 95% CI 0.41–0.65, $p < 0.001$) (see Figure 2). The correlation with mature oocyte number was of similar magnitude (r = 0.51, $p < 0.001$). High responders (≥ 20 oocytes) were clustered above an A4 threshold of approximately 4.0 ng/mL: of the 41 women with excessive response, 32 (78.0%) had basal A4 > 4.0 ng/mL, compared with 39 of 105 (37.1%) among women with non-excessive response ($\chi^2 = 19.3$, $p < 0.001$). Basal AMH and AFC also correlated with oocyte yield (r = 0.46 and r = 0.52 respectively, both $p < 0.001$), in keeping with the established literature [5],[9].

MULTIVARIABLE ANALYSIS

In multivariable linear regression with total oocytes retrieved as the dependent variable, basal A4 retained an independent positive association after adjustment for age, AMH, AFC, and LH/FSH ratio (standardized β = 0.31, 95% CI 0.18–0.44, $p < 0.001$). AMH (β = 0.21, p = 0.004) and AFC (β = 0.27, $p < 0.001$) also retained independent associations; age and LH/FSH ratio did not. The model explained 47% of the variance in oocyte yield (adjusted $R^2 = 0.47$). Variance inflation factors were all below 2.5, indicating no problematic multicollinearity. A parallel model with FORT as the dependent variable yielded similar results, with A4 retaining an independent positive association (standardized β = 0.34, 95% CI 0.20–0.48, $p < 0.001$).

DISCRIMINATIVE PERFORMANCE FOR EXCESSIVE RESPONSE

ROC analysis for prediction of excessive response (≥ 20 oocytes) is shown in **Figure 3** and **Table 3**. Basal A4 alone achieved AUC 0.84 (95% CI 0.78–0.90), outperforming AMH alone (AUC 0.73, 95% CI 0.65–0.81; DeLong p = 0.02). The combined model incorporating A4, AMH, and AFC achieved AUC 0.89 (95% CI 0.84–0.94), with significant incremental discrimination over AMH alone (DeLong p = 0.01). The optimal A4 cut-off by the Youden index was 4.0 ng/mL, yielding sensitivity 78.0% and specificity 75.2% for excessive response. The Hosmer–Lemeshow goodness-of-fit test for the combined model was non-significant ($\chi^2 = 5.9$, p = 0.66), supporting acceptable calibration.

DISCUSSION

In this prospective single-center cohort of 146 normal-BMI women with PCOS undergoing first-cycle GnRH-antagonist COS in southern Iraq, basal serum A4 emerged as an independent predictor of ovarian response. A4 correlated with FORT (r = 0.59) and oocyte yield (r = 0.54), retained independent significance after adjustment for AMH, AFC, age, and LH/FSH ratio, and discriminated excessive response (≥ 20 oocytes) with an AUC of 0.84 outperforming AMH alone (AUC 0.73) and adding significant incremental

discrimination to a combined A4 + AMH + AFC model (AUC 0.89). The 4.0 ng/mL Youden cut-off identified high responders with sensitivity and specificity around 75–78%.

These findings replicate and extend the earlier work of Lebbi and colleagues, who demonstrated that A4 response to rFSH is a stronger predictor of selected follicle number in PCOS than the E2 response and proposed cycle-cancellation thresholds for excessive response [8]. The present cohort confirms that the predictive value attaches not only to dynamic A4 changes during stimulation but also to basal A4 measured before stimulation start — a measurement that is more practical for clinical pre-stimulation counselling. Lazzaroni-Tealdi and colleagues' demonstration that basal A4 performs comparably to AMH and AFC and superior to FSH in unselected ART cycles is consistent with the present results [9]; the specific contribution here is that the predictive value persists, and may be amplified, when the cohort is restricted to normal-BMI PCOS, in which the obesity-mediated attenuation of androgen elevation is removed [13],[14].

Three findings deserve emphasis. First, in the present normal-BMI PCOS cohort, A4 outperformed AMH (AUC 0.84 versus 0.73) for excessive-response prediction. This reverses the more typical hierarchy seen in unselected ART populations, where AMH dominates [5],[9], and is mechanistically consistent: in normal-BMI PCOS, theca-cell hyperactivity is the proximate driver of excessive response, and A4 is the most direct serum reflection of theca-cell output [15],[16]. Second, the addition of A4 to AMH and AFC produced a combined model (AUC 0.89) with non-trivial incremental discrimination (ΔAUC 0.16 versus AMH alone, p = 0.01), supporting incorporation of A4 into pre-stimulation risk-stratification tools. Third, the excessive-response rate of 28.1% in this cohort is within the range reported for PCOS populations internationally [3],[17] and confirms that even with current GnRH-antagonist protocols and individualized dosing, hyper-response remains a substantial risk demanding better prediction.

Two clinical implications follow. First, in normal-BMI women with PCOS, basal A4 above approximately 4.0 ng/mL identifies a high-responder subgroup who may benefit from lower starting rFSH dose, GnRH-agonist trigger rather than rhCG, and elective freeze-all strategy, in line with current recommendations on OHSS prevention [18],[19]. Second, A4 measurement is technically straightforward, inexpensive, and available on the same automated immunoassay platforms that already perform AMH and androgen panels in PCOS workup; routine inclusion in pre-stimulation assessment is feasible without infrastructure expansion. Third, the integrative G-index proposed by Lazzaroni-Tealdi and colleagues (G = AMH × AFC / A4) [20]-[21] should be tested prospectively in normal-BMI PCOS, since the present data suggest that the relative weights may need recalibration when the cohort is restricted by BMI.

The present study contributes regional Iraqi data where indexed evidence is essentially absent, and applies a pre-specified analysis plan to a contemporary 24-month cohort. The restriction to normal-BMI PCOS, the use of a uniform GnRH-antagonist protocol, the standardized hormonal assays on a single automated platform, and the multivariable adjustment with both correlation and ROC analyses are methodological strengths. Concordance of the findings with the broader international literature supports external validity.

CONCLUSION

In normal-BMI women with PCOS undergoing first-cycle GnRH-antagonist controlled ovarian stimulation at a tertiary center in Thi-Qar, southern Iraq, basal serum androstenedione independently predicted ovarian response, with positive correlations with the follicular output rate and oocyte yield. For prediction of excessive response (≥ 20 oocytes), basal A4 outperformed AMH alone (AUC 0.84 versus 0.73) and added significant incremental discrimination to a combined model with AMH and AFC (AUC 0.89). The 4.0 ng/mL Youden cut-off identified high responders with sensitivity and specificity near 75–78%. These findings support inclusion of basal A4 in pre-stimulation risk stratification for normal-BMI PCOS and provide regional Iraqi data where indexed evidence has been lacking. Prospective external validation and randomized testing of A4-guided dosing strategies are the priority next steps.

CONFLICT OF INTEREST:

NON

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TABLES

Table 1. Baseline characteristics of the analytic cohort (n = 146)

Characteristic	Value
Age, mean ± SD (years)	28.7 ± 4.6
BMI, mean ± SD (kg/m²)	22.4 ± 1.6
Modified Ferriman–Gallwey score, median (IQR)	9 (7–11)
Primary infertility, n (%)	94 (64.4%)
Basal FSH, median (IQR) (IU/L)	5.6 (4.6–6.7)
Basal LH, median (IQR) (IU/L)	9.8 (7.4–13.1)
LH/FSH ratio, median (IQR)	1.8 (1.4–2.4)
Basal estradiol, median (IQR) (pg/mL)	42 (32–55)
Total testosterone, median (IQR) (ng/mL)	0.62 (0.48–0.78)
Basal A4, mean ± SD (ng/mL)	3.8 ± 1.4
A4 > 3.3 ng/mL (above reference range), n (%)	56 (38.4%)
AMH, median (IQR) (ng/mL)	6.2 (4.4–8.6)
AFC, median (IQR)	22 (18–28)
Starting rFSH dose, median (IQR) (IU/day)	175 (150–200)
Trigger: rhCG, n (%)	94 (64.4%)
Trigger: GnRH agonist, n (%)	52 (35.6%)

Table2 . Ovarian response outcomes (n = 146).

Outcome	Value
Total oocytes retrieved, median (IQR)	16 (12–22)
Mature (MII) oocytes, median (IQR)	13 (10–18)
FORT (%), median (IQR)	67 (55–78)
Excessive response (≥ 20 oocytes), n (%)	41 (28.1%)
Moderate OHSS, n (%)	6 (4.1%)
Severe OHSS, n (%)	0 (0.0%)
Cycle cancellation for poor response, n (%)	0 (0.0%)

Table3 . Discriminative performance for excessive response (≥ 20 oocytes)

Predictor	AUC (95% CI)	Optimal cut-off	Sens / Spec at cut-off
Basal A4 (ng/mL)	0.84 (0.78–0.90)	4.0	78.0% / 75.2%
AMH (ng/mL)	0.73 (0.65–0.81)	6.5	70.7% / 66.7%
AFC	0.78 (0.71–0.85)	23	75.6% / 71.4%
A4 + AMH + AFC (combined)	0.89 (0.84–0.94)	—	82.9% / 79.0%

FIGURES

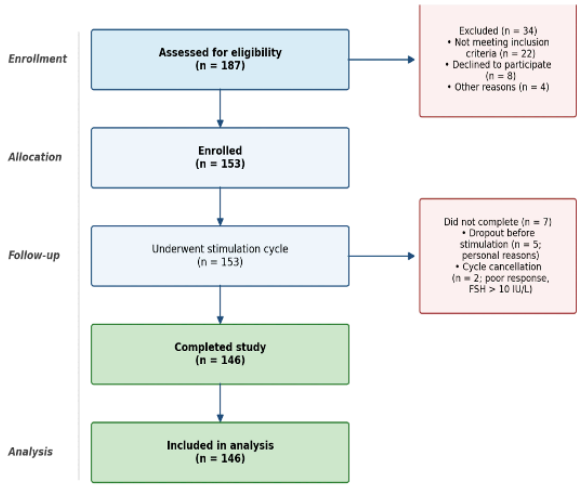

Figure 1. Participant flow diagram

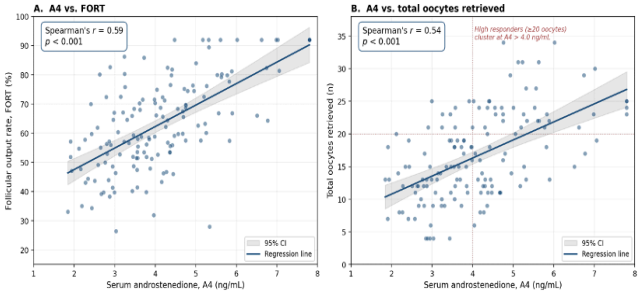

Figure 2. Scatter plots of basal serum A4 versus FORT and oocyte yield

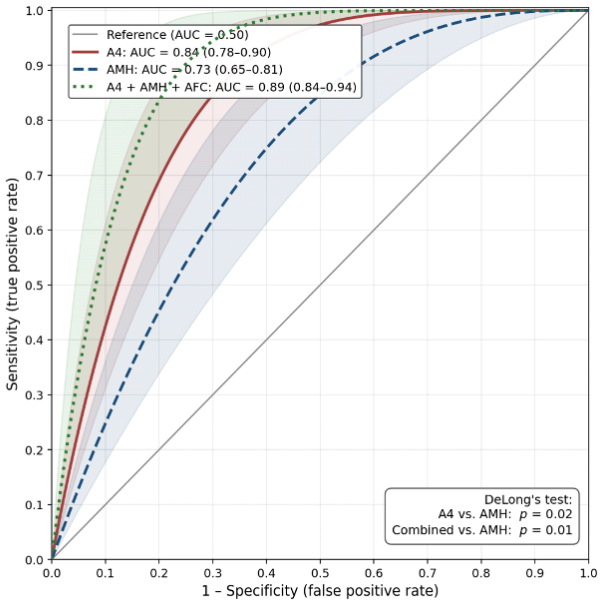

Figure 3. ROC curves for prediction of excessive response (≥ 20 oocytes)