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Short report

Association of anti-mullerian hormone and free androgen index level on response to clomiphene citrate in PCOS infertile women

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the leading cause of anovulatory infertility. Clomiphene citrate, insulin-sensitizing drugs, aromatase inhibitors, gonadotropins, or laparoscopic ovarian drilling are various methods used for ovulation induction in women with PCOS. PCOS women with high levels of anti-mullerian hormone (AMH) and free androgen index (FAI) do not respond well to ovulation induction. This prospective observational study explores the relationship between FAI and AMH levels on ovarian response to clomiphene citrate in infertile women with PCOS.

Methods: This prospective observational study included 40 infertile with PCOS who underwent ovulation induction with clomiphene citrate with dose ranging from 50 to 150 mg. Participants were classified into four phenotypes by NIH(National Institute of Health) consensus panel criteria. The clinical and endocrine parameters of participants who were sensitive to clomiphene were compared to those who were resistant.

Results: The most common phenotype was A, with all three features of PCOS: hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. There was no significant difference in clinical and endocrine parameters among the different phenotypes of PCOS except AMH and FAI values. The mean FAI was 9.39 ± 1.11 and AMH 7.26 ± 0.48 (ng/ml) in clomiphene resistant and 5.31 ± 1.93 and 3.69 ± 1.84 (ng/ml) respectively in clomiphene-sensitive women. Women with FAI > 7.5 and AMH >7 ng/ml might be resistant to clomiphene.

Conclusion: FAI and AMH values were significantly higher in women resistant to clomiphene induction. AMH and FAI may help women with PCOS to tailor their ovulation induction protocol.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine condition in women of reproductive age, with a incidence rate of 5%–10%,[1] and is the major cause of anovulatory infertility.[2] Conventional treatment is ovulation induction with clomiphene citrate.[3] Other ovulation induction interventions include insulin-sensitizing drugs, aromatase inhibitors, gonadotropins, and laparoscopic ovarian drilling.[4–6] Anti-mullerian hormone (AMH) inhibits follicle-stimulating hormone(FSH)-dependent follicle selection and aromatase expression, resulting in increased androgen levels. Because clomiphene stimulates ovulation by increasing FSH levels, AMH and androgen levels can interfere with its response. Calculated free testosterone, calculated bioavailable testosterone or free androgen index (FAI) could be used to assess biochemical hyperandrogenism in PCOS. Previous studies have indicated that high AMH and FAI levels are associated with poor response to ovulation induction in PCOS women. The cut-off value of AMH for response to ovulation induction varies from 1.2 ng/ml to 7.7 ng/ml.[7]

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Hyperandrogenaemia is also associated with poor response to ovulation induction.[8] This prospective study explores the relationship between FAI and AMH level on ovarian responsiveness to clomiphene citrate in infertile women with PCOS.

1.1. Methods

After institutional research and ethical committee clearance, a prospective observational study was conducted. The sample size was determined to be 40 (n Master version 2.0) based on the sensitivity of AMH to predict successful ovulation as 97.2%[8] with 5% absolute precision and 95% confidence interval. The population studied were patients who came to our gynecology department for infertility treatment. The inclusion criteria were women with primary infertility due to PCOS in the age group of 19–35 years with patent fallopian tube and a normal uterine cavity, as determined by hysterosalpingogram or sonosalpingography and male partner with normal semen analysis according to WHO 2010 guidelines criteria.[9] Ovulatory dysfunction was diagnosed when menstrual cycles were < 21 or > 35 days or < 8 cycles per year or > 90 days for anyone cycle. FAI >5 was considered biochemical hyperandrogenism. Hirsutism was defined as a modified Ferriman- Galleway score of more than 6. Clinical diagnosis of acanthosis nigricans (AN) was made by noting dark velvety patches on the posterior neck/axilla. Polycystic ovarian morphology (PCOM) was diagnosed with transvaginal ultrasound when there were >20 follicles per ovary or ovarian volume ≥ 10 ml ensuring no corpora lutea, cysts, or dominant follicles.[10] The National Institutes of Health (NIH) evidence-based methodology workshop of PCOS 2012 recommended that specific phenotypes should be reported explicitly in all research.[11] Clinical/biochemical hyperandrogenism (HA), ovulatory dysfunction (OD), and PCOM are features of PCOS. Phenotype A has all three features HA, OD, and PCOM; phenotype B has HA and OD; Phenotype C has HA and PCOM; Phenotype D has OD and PCOM.

Body mass index (BMI) and waist: hip ratio was categorized using WHO cut-off points for the Asian population.[12] On day 2 of a spontaneous menstrual cycle or after a withdrawal bleed, 5 ml of blood was drawn to measure AMH, total testosterone, serum sex hormone-binding globulin (SHBG), follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), and prolactin. Plasma was separated within 2 h of venipuncture, stored in aliquots at – 70 °C until thawed, and analyzed in batches. On the same morning, all the participants underwent transvaginal ultrasound (6 MHz transducer (Siemens –Acuson X300, Model: KT-LM150XD, USA) 0 to note the number of early antral follicles measuring 2–6 mm in diameter. Serum total testosterone and SHBG were determined using SIEMENS ADVIA CENTAUR-CP immunoassay. The free androgen index was determined as the ratio of total testosterone divided by SHBG and multiplied by 100.

On day 2 of a spontaneous menstrual cycle or after a withdrawal bleeding, participants received an incremental dose of clomiphene citrate ranging from 50 mg to 150 mg for five days. Follicular tracking was started on day 9 using transvaginal ultrasound and continued until the rupture of the dominant follicle. The clomiphene dose at which the ovulation occurred and endometrial thickness (ET) were documented. Women who ovulated with clomiphene were referred to as clomiphene-sensitive. Women who failed to ovulate with 150 mg of clomiphene were referred to as clomiphene-resistant.

1.2. Statistical analysis

Data was entered into a Microsoft Excel datasheet and analyzed using SPSS 22 software. Categorical variables were represented in the form of frequencies and percentages. The normal distribution of continuous variables was determined using a Q-Q plot. Continuous variables were expressed using mean and standard deviation. Continuous and categorical variables were compared using Pearson's Chi-square and unpaired *t*-test.

2. Results

The recruitment process of patients is represented in Fig. 1. Sixty-five consecutive patients with PCOS seeking infertility treatment were enrolled in the study; twenty participants were excluded for failing to meet the inclusion criteria, and five patients were lost to follow-up.

The baseline characteristics of the research population are given in Table 1. In our study, the most common phenotype of PCOS is A (42.5%), and the least common phenotype is B (10%). In the study, 55%, 27.5%, and 17.5% were in the age groups <25 years, 26–30 years, and >30 years, respectively. Most participants (57.5%) were married for 3–5 years. Twenty-two percent had been married for less than two years, 17.5% for 6–10 years, and 2.5% for more than ten years. According to the WHO categorization of BMI, 37.5%, 27.5%, 22.5%, and 12.5% were normal, overweight, obese, and extremely obese, respectively. The mean BMI in our study was 24.5 ± 3.45, and the waist: hip ratio was 0.88 ± 0.07. Women in our study group had central obesity, a marker of metabolic abnormality which is independent of BMI. AN, another marker of metabolic abnormality, was present in 82.5% of study subjects. Fifty-five percent of women responded to clomiphene citrate, of which 45% responded to 50 mg, 45% to 100 mg, and 10% to 150 mg. In 15% of study subjects, hirsutism was present, and acne in 57.5%. There was no significant difference in clinical and endocrine parameters among the different phenotypes of PCOS except AMH and FAI values. Serum AMH and FAI values are significantly higher in phenotype A.

There was no major difference in mean age, duration of infertility, presence of clinical hyperandrogenism, BMI, TSH, prolactin, FSH, and LH in participants sensitive and resistant to clomiphene citrate. The levels of AMH and FAI were significantly higher in clomiphene-resistant participants. Endometrial thickness was also significantly less in women who did not ovulate with clomiphene (Table 2).

The clomiphene citrate dose to induce ovulation increases with an increase in mean AMH and FAI level (Table 3). The level of AMH and FAI in women who responded to clomiphene was in the range of 1.5- 7.0 ng/ml and 2.2- 7.5 respectively. Women in our study group with FAI > 7.5 and AMH level >7 ng/ml might be resistant to clomiphene.

Fig. 2 represents the R-value of 0.8503 with a strong positive correlation between FAI and AMH. The FAI level increases with increasing AMH value.

3. Discussion

In our study, 55% of women with PCOS ovulated with clomiphene citrate, while 45% were resistant. The most common phenotype in our study is phenotype A(52.5%) followed by phenotype C(25%). Five women (12.5%) had phenotype D, and four (10%) had phenotype B. The prevalence of phenotype is similar to a study done in Jordan where the prevalence of phenotypes A, B, C, and D in infertile women were 50.3%, 14.5%, 29.6%, and 5.7%, respectively.[13] The most prevalent phenotype in clinical cohorts is A, though this could change if participants from the

Fig. 1. Flowchart of the recruitment process of the patients.

Table 1
Baseline characteristics of all participants n(%)/(mean ± SD).

Variable	Phenotype A (HA + OD + PCOM)	Phenotype B (HA + OD)	Phenotype C (HA + PCOM)	Phenotype D (OD + PCOM)	*P*-value
No.participants (%)	21 (52.5)	4 (10)	10 (25)	5 (12.5)	
Age (years)	24.6 ± 3.6	29.5 ± 1.7	25.6 ± 3.4	25.4 ± 4.0	0.91
Duration of infertility (years)	3.8 ± 2.6	6.3 ± 2.0	3.1 ± 1.4	5.4 ± 3.9	0.13
BMI	24.5 ± 3.3	29 ± 1.8	22.6 ± 3.2	24 ± 2.0	0.12
Waist: hip ratio	0.88 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.85
FAI	8.4 ± 2.0	6 ± 1.0	7 ± 2.0	3 ± 0.8	0.01*
AMH(ng/ml)	6.2 ± 1.7	3.9 ± 2.0	5.5 ± 2.5	2.4 ± 0.5	0.02*
FSH (mIU/ml)	5.9 ± 1.8	4 ± 1.5	7.2 ± 3.2	4.9 ± 1.7	0.08
LH (mIU/ml)	7.3 ± 2.5	6.2 ± 1.3	6.8 ± 3.0	8.5 ± 3.5	0.59
TSH (mIU/ml)	2.7 ± 0.6	1.9 ± 1.0	2.4 ± 0.7	2.5 ± 0.2	0.14
Prolactin (ng/ml)	10 ± 3.3	12 ± 4.6	9.4 ± 4.4	9.18 ± 3.2	0.65
ET (mm)	5 ± 2.3	6.5 ± 1.5	5.7 ± 2.0	7.4 ± 0.5	0.11
Women with acne (%)	12 (57)	0	6 (60)	5 (100)	0.03*
Women with hirsutism (%)	3 (14)	1 (25)	1 (10)	1 (20)	0.01*
Women with AN (%)	17 (81)	4 (100)	8 (80)	4 (80)	0.82
Women ovulated (%)	9 (43)	3 (75)	5 (50)	5 (100)	0.11

*P-value significant.
AN: acanthosis nigricans, BMI: body mass index, FAI: free androgen index, AMH: anti-mullerian hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone, ET: endometrial thickness.

Table 2
Comparison of clinical and endocrine variables between clomiphene-sensitive and clomiphene-resistant participants(mean ± SD)n(%).

Variables	Clomiphene citrate		*P* value
	Sensitive N = 22	Resistant N = 18	
Age	25.8 ± 1.7	25.1 ± 1.5	0.16
Duration of infertility (months)	46.4 ± 29.3	52 ± 34.8	0.58
AN	20 (91)	13 (72)	0.06
Acne	12 (54.5)	11 (61)	0.29
Hirsutism	2 (9)	4 (2)	0.53
BMI	24.8 ± 3.4	24 ± 0.3	0.42
FAI	5.4 ± 1.9	9.3 ± 1.11	<0.001*
AMH (ng/ml)	3.7 ± 1.8	7.26 ± 0.5	<0.001*
FSH (mIU/ml)	8.8 ± 3.7	7.7 ± 3.4	0.360
LH (mIU/ml)	7.6 ± 2.5	6.7 ± 2.8	0.332
Prolactin (ng/ml)	9.5 ± 3.9	10.5 ± 3.6	0.383
TSH (mIU/ml)	2.4 ± 0.8	2.6 ± 0.5	0.198
ET (mm)	7.5 ± 0.5	3.5 ± 0.9	<0.0001*

*P- value significant.
AN: acanthosis nigricans, BMI: body mass index, FAI: free androgen index, AMH: anti-mullerian hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone, ET: endometrial thickness.

population were screened.[14] In our investigation, there was no significant difference in FSH and LH levels between phenotypes, with greater FAI values in phenotype A, which contrasts with another study in which women with type A PCOS had higher levels of FSH and LH but no difference in FAI.[13] In phenotype A, the AMH value was >6 ng/ml, but in other studies, AMH was >10 ng/ml.[15,16]

In our study, more than 50% of women who presented with infertility were <25 years. Our study found no significant relationship between age and ovulation success, consistent with an Egyptian study that demonstrated no statistically significant relationship between age and clomiphene sensitivity. The range of age of the study population is similar to ours, between 19 and 35 years.[17] Many studies have established that the success rate for infertility treatment diminishes with age. Even in the general population, the fertility rate decreases with age, but the period at which the decline starts differs with countries. In Denmark, the peak fecundability rate appears to decline from age 28 onwards in nulliparous women while from 30 years on in parous women.[18] In North America, the highest crude possibility rate of pregnancy was among women aged 25–27. There is also a linear decline in fertility rate with age which appears to be strong among nulliparous women. The Faddy/Gosden model describes two phases of linear decline with a sudden acceleration at 37 years, which is now modified into a single exponential decline.[19]

Acanthosis Nigricans (AN) is a velvety, mossy, hyperpigmented skin disorder and a reliable PCOS-cutaneous marker. AN appears to be more of a sign of insulin resistance. In our study, 82.5% of women had AN, but

Table 3
FAI & AMH comparison with respect to the different doses of clomiphene among clomiphene-sensitive participants.

Clomiphene citrate		FAI	AMH(ng/ml)	*P*-value
Clomiphene-sensitive	50 mg	3.8 ± 1.2	2.2 ± 0.5	<0.001*
	100 mg	6.3 ± 0.8	4.7 ± 1.5	
	150 mg	8.9 ± 1.6	6.1 ± 1.6	

*P- value significant.

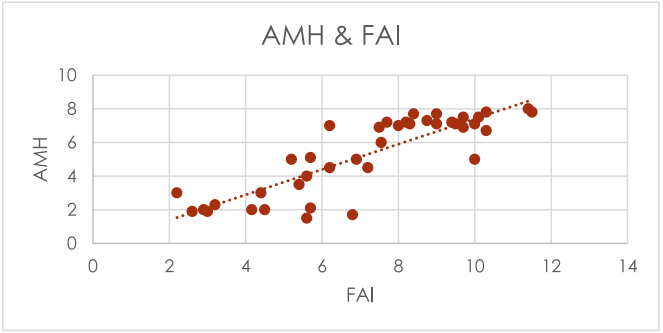

Fig. 2. Pearson correlation between FAI and AMH.

there is no association with clomiphene responsiveness. In a cross-sectional study, AN was present in 56% of women with PCOS in the age group of 15–35.[20]

In our study, the duration of infertility, when divided into groups of less than two years or more than two years, did not have a significant predictive value for successful ovulation induction. Other studies have established that the duration of infertility alone doesn't predict ovulation.[17] Even in women with unexplained infertility treated either with clomiphene or gonadotropin, the duration of infertility did not have a significant effect on the responders.[21]

Women with PCOS are 35%–80% overweight and 20%–69% obese, with the percentage varying by ethnicity,[4] which is consistent with our findings. The odds ratio of resistance to clomiphene was 0.2 (95%CI 0.05–1.04) for overweight women and 1(95%CI 0.2–4.6) for obese women compared to women with normal BMI. In our study, BMI did not differ significantly between those who ovulated and were resistant to clomiphene citrate, in contrast to a Japanese study.[22] In China, where the effect of BMI on controlled ovarian hyperstimulation was studied, though women in the obese category required an increased dose of gonadotropins, there was no major difference in the number of oocytes retrieved.[23]

The mean waist: hip ratio in our participants is 0.88 ± 0.07, which is comparable to a hospital-based study done in women with PCOS-related infertility which had a waist: hip ratio of 0.88 ± 0.04,[24] indicating central obesity is more prevalent in PCOS-infertile women. Women with PCOS have greater truncal abdominal fat distribution independent of BMI in Asian women, similar to our study.[25] Central obesity with associated insulin resistance results in abnormalities during folliculogenesis and follicular growth.

Hyperandrogenism was found in 85.6% of PCOS women aged 16–45 years,[26] similar to our study, which found biochemical hyperandrogenism in 73%. The mechanisms which may contribute to hyperandrogenism include pituitary LH hypersecretion, relative FSH insufficiency, and high levels of insulin and AMH.[27] Forty percent of women with high FAI had clomiphene resistance which is similar to a study where serum testosterone and androstenedione levels were higher in clomiphene citrate non-responders.[28] FAI had high specificity, and androstenedione, high sensitivity to differentiate PCOS from controls.[29] FAI is the most significant predictor of ovarian response.[30] Ovarian hyperandrogenism by inhibiting proliferation and maturation of granulosa cells, increasing 5α-reductase activity, and inhibiting aromatase activity arrests folliculogenesis in PCOS women.[27] Women in our study group with FAI > 7.5, were resistant to clomiphene.

AMH levels ranging from 2.8 ng/ml to 8.4 ng/ml have been proposed with varying sensitivities and specificities to diagnose PCOS.[31,32] A meta-analysis showed a cut-off level for serum AMH for diagnosis of PCOS at 4.7 ng/ml with a sensitivity of 79.4%, specificity of 82.8%, and an AUC of 0.87.[33] Women resistant to clomiphene had an AMH level >7 ng/ml in our study, comparable to a cross-sectional study in which women with poor ovarian response had an AMH >6.3 ng/ml[34] The mean values of AMH for different doses of clomiphene citrate were similar to a study conducted in the Derby fertility unit.[8] AMH counteracts the action of FSH, thereby leading to failure of follicle development. By contrast, when AMH was measured using two different assays, there was no significant predictive value for induction with 50 mg clomiphene which may be due to the mean BMI being normal in the study group and the lack of precision of measurement of AMH.[35]

A randomized control trial compared clomiphene citrate, metformin, and a combination of both as first-line ovulation induction in PCOS women.[36] The ovulation rate in the clomiphene group was 56.2%, which is comparable to the ovulation rate in our research of 55%. In contrast to prospective observational research in which clomiphene resistance was more common in phenotype A, our investigation found no significant connection between different PCOS phenotypes and clomiphene sensitivity.[24] In another prospective observational study in southern India, there was no difference in response to an escalating dose of letrozole with different PCOS phenotypes.[37]

Our study shows a strong positive correlation between AMH and FAI. The positive correlation between testosterone and AMH was reported in previous studies.[38,39] Elevated AMH downregulates aromatase gene expression, inhibiting the conversion of androgens to oestradiol.[40] Androgen, in turn, stimulates follicule stimulating hormone receptor (FSHR) expression, promoting follicular growth and possibly increasing AMH production.[41] AMH is not only a marker for excessive follicle number and hyperandrogenism.[42]

Our study's drawback was the small sample size, which limited the generalizability of the findings. The study's strength is that it gives a detailed comparison of PCOS phenotypes in infertile women.

4. Conclusion

FAI and AMH were significantly higher in clomiphene-resistant women. AMH and FAI determination in PCOS women may help tailor their ovulation induction protocols. Women with AMH >7 ng/ml and FAI >7.5 may be started on gonadotropins for ovulation induction directly instead of trying oral ovulation induction agents.

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None.

Author contributions

J.k.W is responsible for protocol preparation, collection of data, and analysis. M.J is responsible for protocol preparation, data collection, analysis, interpretation of data, and organization. G.K.P is responsible for data processing and literary input. R.S is responsible for data processing and literary input.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethics approval

The study proposal has been reviewed and approved by the institutional ethics committee of Sri Manakula Vinayagar Medical College and Hospital, Puducherry.

Consent to participate (from patients)

The patients gave informed consent and the patient anonymity preserved.

Consent for publication (all authors)

All authors consent for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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