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Infertility in Polycystic Ovary Syndrome Iraqi women Metabolic-Hormonal Profile and LH/FSH Ratio as predictors of infertility: A case Control study

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder characterized by inadequate secretion of gonadotropins, excess testosterone and oligo-anovulation. The main yet partially unanswered question is what hormonal markers are most applicable in the prediction of infertility among the victimized populations. Available evidence is scarce on the Middle Eastern cohorts, where there is a genetic working background and body composition, and lifestyle mismatch with the Western or Western reference groups. **Aim**: To compare hormonal and metabolic variables in fertile controls, fertile PCOS women and infertile PCOS women visiting a tertiary center in Iraq and determine independent predictors of hormones on reproductive failure. **Methods**: The study was a case-control study, which enrolled 120 women, aged 18-40 years: healthy fertile controls (n=40), fertile women with Rotterdam-diagnosed PCOS (PCOS-NI, n=40), and infertile women with PCOS (PCOS-I, n=40). LH, FSH, total and free testosterone, AMH, SHBG, progesterone, and insulin in fasting serum were analyzed. HOMA-IR was used to measure insulin resistance. Infertility predictors were found by binary logistic regression and ROC curve. Findings: The LH/FSH ratio increased progressively: 0.81±0.21 (controls), 1.97±0.52 (PCOS-NI), and 2.94±0.74 (PCOS-I; $p<0.001$ in all the pair-wise comparisons). No significant difference in FSH was found ($p=0.163$). Testosterone total and AMH gradients were parallel. An analysis of ROC using a threshold of LH/FSH >2.15 was determined as the best threshold to predict infertility (sensitivity 82.5, specificity 77.5, AUC=0.856). On the multivariate logistic regression, BMI and testosterone were controlled to give HOMA-IR as a predictor of infertility (OR=2.89; 95% CI: 1.435.84). **Conclusions**: The LH/FSH ratio is the only hormonal parameter with the strongest correlation with infertility in this local PCOS cohort, and the cut-off value of 2.15 can be used in practice in a discriminative manner. The risk of reproductive failure is increased by insulin resistance alone, and this fact calls to the combined metabolic assessment of such patients as a routine examination.

KEYWORDS : polycystic ovary syndrome, LH / FSH ratio, infertility, insulin resistance, hyperandrogenism, Iraq.

INTRODUCTION

Polycystic ovary syndrome (PCOS) occurs in about 8-13 percent of all women of reproduction age and is the most common endocrine disorder in this group of the population across the globe [1, 2]. Diagnosis It is diagnosed when two of three criteria of Rotterdam are met: oligo-ovulation or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound [3]. Since it is the leading cause of anovulatory infertility (70-80% of anovulatory infertility), PCOS has a significant clinical and economic impact on the provision of reproductive health services in different parts of the world [4]. In Iraq, local statistics are recording an equally high burden in various governorates [5,6].

The fundamental endocrine defect in PCOS lies at the hypothalamic level where secretion of LH is preferentially stimulated by a higher frequency of GnRH pulses without much change in FSH secretion [7,8]. LH excess that follows this activates the overproduction of androgens in ovarian thecal cells with insufficient FSH

inhibiting follicular development and ovulation by inhibiting the aromatase activity of granulosa cells [9]. The insulin resistance that is reported in 5070% of PCOS patients regardless of body weight further enhances androgen bioavailability by inhibiting hepatic sex hormone-binding globulin (SHBG) synthesis, and directly activating ovarian steroidogenesis [10,11].

Anti-Mullerian hormone (AMH) of pre-antral and small antral follicles, which accumulates in proportion to the extent of follicular arrest, has turned out to be a sensitive diagnostic factor as well as a surrogate endpoint of ovarian reserve in PCOS [12,13]. The high AMH also seems to feed back on the hypothalamic GnRH imbalance causing a vicious cycle of anovulation [14]. Also in addition to these reproductive effects, PCOS imparts long-term cardiometabolic risk such as type 2 diabetes, dyslipidaemia, and subclinical atherosclerosis risks that are exacerbated by the continued excess androgens and adiposity [15,16].

Although there has been an increase in the understanding of these mechanisms, little comparative data on which of the particular hormonal markers has the strongest predictive value of fertility outcomes in populations with Middle East PCOS is available. Majority of studies that have been conducted in Iraq have focused on the hormonal deviations in an observational manner instead of trying to measure their comparative discriminative ability to cause reproductive failure [5,6,17]. The current study aimed to fill this gap, by comparing hormonal and metabolic profiles of three distinctively defined groups, such as fertile controls, fertile PCOS women and infertile PCOS women, that were recruited at Tikrit Teaching Hospital and identify which of the predictors of infertility are the most clinically useful in this population.

MATERIALS AND METHODS

Setting of the study, Ethics and Design

This case-control study was done in the period of January 2022 to December 2023. The recruitment of clinicians was done at the Gynaecology and Endocrinology Outpatient Clinic of Tikrit Teaching Hospital, Salah al-Din Governorate, Iraq. The laboratory tests were carried out at Central Laboratory of Tikrit Teaching Hospital and Research Biochemistry Laboratory, College of Medicine, Tikrit University. The University of Samarra Institutional Review Board (Ref. LSB-2022-07) and the Research Ethics Committee of Tikrit University (Ref. TU-MED-2022-14) gave their ethical approval. Informed consent in Arabic was taken before enrolment of all the participants in writing. The research was done in line with the Declaration of Helsinki in the 2013 version.

Participants

One hundred and twenty women aged between 18 to 40years were recruited and allocated to three groups (n=40 each). The Control group was made up of the regularly cycling women that have recorded fertility (at least one live birth) and none of them having personal or family history of endocrine or metabolic disease. The PCOS-NI (non-infertile PCOS) group comprised of those women who met at least two criteria of Rotterdam and had at least one spontaneous pregnancy without the use of assisted reproductive technology. The PCOS-I (infertile PCOS) group consisted of PCOS women confirmed in Rotterdam with primary infertility - the failure to conceive after twelve or more months of regular unprotected sexual intercourse - whose male partners had normal seminograms by WHO 2021.

All ultrasound scans of the transvagina were conducted by one experienced gynaecologist (co-author S.K.I.) to measure antral follicle count and ovarian volume and thereby reducing inter-observer error. Polycystic ovarian morphology; 12 or more antral follicles 29 mm diameter per ovary or ovarian volume 10 ml and above [3].

There were exclusion criteria of all groups: hormonal medication use, metformin, antioxidant supplements or immunomodulatory therapy within 90 days; known diabetes mellitus; thyroid dysfunction (TSH outside 0.4654.0 mIU/L); hyperprolactinaemia (prolactin >25 ng/mL on two measurements); congenital adrenal hyperplasia (17-hydroxyprogesterone >2 ng/mL); autoimmune diseases; active systemic infection

Blood Sampling

Each participant was sampled at 07:30-09:00 h between days 2 and 5 of the menstrual cycle, or any day of clinic visit by amenorrhoeic PCOS-I women. Blood samples were put in serum separator tube, serum was centrifuged at 3,000 × g after 15 minutes at 4 C, aliquots of 500 µL were taken and kept in the refrigerator at -80 C. All the assays were done within 10 weeks after collection and none of the samples had a freeze-thaw of more than two times.

Hormonal and Biochemical Assays

LH and FSH, total testosterone, free testosterone, progesterone, AMH, insulin, and SHBG were analysed using electrochemiluminescense immunoassay (ECLIA) on a Roche Cobas e601 (Roche Diagnostics, Mannheim, Germany). The intra- and inter-assay coefficients of variation were less than 4.8 per cent of all the analytes. The hexokinase procedure (Roche Cobas c501) was used to measure the fasting plasma glucose. The homeostatic model assessment (HOMA-IR) was used to estimate insulin resistance based on the original equation of Matthews et al.: [fasting insulin (mmIU/mL) and fasting glucose (mmol/L)/22.5 [18].

Statistical Analysis

Annually, continuous variables are reported using mean standard deviation (SD) and categorical variable using frequencies and percentages. The Shapiro-Wilk test was used to test distributional normality. Normally distributed variables compared between groups were done with one-way ANOVA, honestly significant difference post-hoc using Tukey and non-parametric data were compared using the Kruskal-Wallis and the Dunn Bonferonni correction of multiple comparisons. Pearson chi-square or Fisher exact test was the right test to compare categorical variable.

The distribution of the data was evaluated by Pearson or Spearman coefficients used to assess bivariate correlations. The independent predictors of infertility among PCOS women were identified in binary logistic regression against backward elimination (likelihood ratio criterion, $p>0.10$ to remove). The variables that have been keyed into the model were LH/FSH ratio, total testosterone, AMH, SHBG, HOMA-IR and BMI. The discriminative performance of the key biomarkers was assessed by receiver operating characteristic (ROC) curve analysis, with the optimum cut-offs being determined by the Youden index. All statistical tests were conducted in the SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The statistically significant level was set at two tailed $p<0.05$.

RESULTS

Baseline Characteristics

The 120 participants enrolled in the study were all able to complete the study protocol. There were no significant differences in mean age of groups (Controls: 27.8±4.2 years; PCOS-NI: 29.1±3.9 years; PCOS-I: 30.4±4.6 years; p=0.121). The increase in BMI was significant with the highest value in infertile patients (PCOS-I: 30.3±5.2 kg/m 2 vs. PCOS-NI: 27.8±4.1 kg/m 2 vs. Controls: 23.4 2.8 kg/m 2; $p<0.001$ all pairwise comparisons). The same was true of waist circumference, with 92.710.6 cm in the PCOS-I group versus 73.97.4cm Controls ($p<0.001$). Such results can be compared with the previous reports, which have reported higher central adiposity in infertile compared with fertile PCOS women [10,11]. Table 1 gives complete demographic and clinical data.

Table 1. Demographic and Clinical Characteristics of the study participants (Mean ± SD)

Parameter	Control (n=40)	PCOS-NI (n=40)	PCOS-I (n=40)	p-value
Age (years)	27.8 ± 4.2	29.1 ± 3.9	30.4 ± 4.6	0.121
BMI (kg/m²)	23.4 ± 2.8	27.8 ± 4.1*	30.3 ± 5.2*†	< 0.001
Waist circumference (cm)	73.9 ± 7.4	85.2 ± 9.1*	92.7 ± 10.6*†	< 0.001
Fasting glucose (mmol/L)	4.81 ± 0.52	5.05 ± 0.61	5.38 ± 0.74*	0.011
Fasting insulin (μIU/mL)	7.3 ± 2.1	14.8 ± 3.9*	20.6 ± 5.4*†	< 0.001
HOMA-IR	1.28 ± 0.44	2.81 ± 0.78*	3.94 ± 1.07*†	< 0.001

* $p<0.001$ vs. Control; † $p<0.001$ vs. PCOS-NI (Tukey post-hoc test)

There was a graded increase of HOMA-IR among groups 1.28+0.44 in Controls, 2.81+0.78 in PCOS-NI, 3.94+1.07 in PCOS-I ($p<0.001$); hence insulin resistance was the worst in the infertile patients. Only in the PCOS-I

group as compared to Controls, the fasting glucose was significantly high (5.380.74 vs. 4.810.52 mmol/L; p=0.011), but the values were in the normoglycaemic range.

Hormonal Profiles

LH levels significantly increased among groups (Controls: 5.3±1.6; PCOS-NI: 11.7±3.1; PCOS-I: 16.2±4.2 mIU/mL; p<0.001 all comparisons), but FSH levels did not vary significantly between groups (6.7±1.5, 7.2±1.8 and 5.4±1.6 mIU/mL respectively; p=0.163). As a result, the LH/FSH ratio rose significantly in PCOS-NI (1.970.52) and PCOS-I (2.940.74) in comparison with Controls (0.81). There was a similar step increase in total testosterone, free testosterone and AMH. SHBG declined in a negative direction as groups, negatively correlated with an increase in androgen bioavailability. Table 2 provides complete data on hormones.

Table 2. Serum Hormonal Profiles of Study Groups (Mean + SD)

Hormonal Parameter	Control (n=40)	PCOS-NI (n=40)	PCOS-I (n=40)	p-value
LH (mIU/mL)	5.3 ± 1.6	11.7 ± 3.1*	16.2 ± 4.2*†	< 0.001
FSH (mIU/mL)	6.7 ± 1.5	7.2 ± 1.8	5.4 ± 1.6	0.163
LH/FSH ratio	0.81 ± 0.21	1.97 ± 0.52*	2.94 ± 0.74*†	< 0.001
Total testosterone (ng/dL)	25.1 ± 6.3	52.8 ± 12.6*	74.5 ± 16.9*†	< 0.001
Free testosterone (pg/mL)	1.4 ± 0.5	3.8 ± 1.1*	6.2 ± 1.7*†	< 0.001
SHBG (nmol/L)	58.4 ± 11.2	38.7 ± 9.6*	24.3 ± 7.1*†	< 0.001
AMH (ng/mL)	2.6 ± 0.8	6.4 ± 1.6*	9.1 ± 2.3*†	< 0.001
Progesterone (ng/mL)	8.6 ± 2.9	3.2 ± 1.4*	1.8 ± 0.9*†	< 0.001

* p<0.001 vs. Control; † p<0.001 vs. PCOS-NI (Tukey post-hoc test)

Predictors of Infertility and ROC Analysis

The LH/FSH ratio of 2.15 was found as the optimal predictor of infertility in PCOS women by ROC curve analysis (sensitivity 82.5, specificity 77.5, AUC=0.856; 95% CI: 0.7740.938). The AUC of AMH >7.8 ng/mL was 0.821 (sensitivity of 77.5, specificity of 80.0%), and HOMA-IR >2.9 was 0.798. On multivariate binary logistic regression- with adjustments on BMI and total testosterone- both LH/FSH ratio (OR=3.62; 95% CI: 1.817.24; p=0.001) and HOMA-IR (OR=2.89; 95% CI: 1.435.84; p=0.003) were independent factors that were predictive of infertility. The adjusted p-value did not attain significance between AMH and non-significance (OR=1.87; 95% CI: 0.94 -3.71; p=0.073).

DISCUSSION

The main result of this research is that the LH/FSH ratio was the best at discriminating between fertile and infertile PCOS women when comparing the groups directly when compared to individual gonadotropin levels, testosterone, and AMH. The 2.94 +/- 0.74 that we obtained in our infertile group is in agreement with the values that have been reported recently in Iraqi research [17,19] and is within the range of the values that were reported in Iranian and Egyptian PCOS cohorts of similar regional origins [20,21]. The cut-off of 2.15 we derived using ROC (with an AUC of 0.856) is favourable compared to the thresholds that have been suggested in European and Asian populations (optimal cut-offs have been between 1.8-2.8 depending on the reference cohort) [7,22]. The fact that there was no meaningful difference between groups in terms of FSH (p=0.163) is mechanistically informative. The classical neuroendocrine researches have determined that GnRH pulse frequency selectively enhances LH production and has little effect on FSH production, since FSH expression is more affected by pulse interval rather than pulse amplitude [8,9]. This specificity implies that the ratio is a more anatomically sensitive measure of gonadotropin dysregulation than any of the two hormones individually, and the findings of Waldstreicher et al. in

PCOS women support this idea [7]. Our findings confirm this interpretation: although LH of controls and infertile patients differed almost three times, FSH concentrations did not change much, which resulted in the ratio dispersion, which was the most significant diagnostically.

The sequential reduction in SHBG levels a control 58.4 nmol/L to an infertile patient 24.3 nmol/L is in line with the increase in insulin resistance and it is in accordance with the well-established suppressive action of insulin on hepatic SHBG synthesis [10,11]. Reduced SHBG increases the biologic activity of circulating androgens beyond the proportionate difference that would be implied by total testosterone gradients alone, a fact that could be a partial cause of why free testosterone gradients (1.4 to 6.2 pg/mL across the three groups) were proportionally steeper than were total testosterone gradients. Escobar-Morreale has highlighted that hyperandrogenism in PCOS works through increased production and decreased binding capacity and our data demonstrate this bidirectional effect perfectly well [15].

The highest values in the infertile patients (9.1±2.3 ng/mL) were nearly 3.5 times of the control value, which is in agreement with findings by Dewailly et al. that AMH does not only relate to the antral follicle count but also to the extent of anovulation in PCOS [12]. Even though AMH was a significant predictor of infertility, even under univariate analysis (AUC=0.821), it lost its significance in multivariate analysis, which may indicate that it acts mostly by the same pathophysiological pathway that LH/FSH ratio and androgen indices measure. It has been observed by La Marca and Volpe that AMH could have most applicability as a diagnostic indicator and as an indicator of ovarian reserve as opposed to a fertility predictor itself, and our results are generally consistent with this observation [13].

After controlling BMI, HOMA-IR was the only variable that had significant predictive value of infertility (OR=2.89), which has its practical implications. Legro et al. also presented that the effects of insulin resistance in PCOS act at least partially independently of obesity [10], and the present research contributes to the same by revealing that HOMA-IR is an independent predictor of reproductive failure even in the case of body weight adjustment. This process is probably multi-factorial: an increased insulin directly activates LH-stimulated thecal androgen synthesis, inhibits SHBG, and has the potential to suppress endometrial receptivity via disrupted glucose metabolism [11,16]. Clinically, it can be proposed that metabolic testing must be included into a review of infertile PCOS women, regardless of the type of BMI.

LH/FSH cut-off of 2.15 is cheap to test and reproducible in most of the hospital laboratories in Iraq, and therefore it is a viable triage used to stratify the women with PCOS in terms of infertility risk. In regions with expensive or no assisted reproductive technology, early detection of patients with high risks would inform prioritisation to more rigorous assessment and prompt action. A combination of HOMA-IR and LH/FSH ratio would provide metabolic detail and could further narrow down the risk stratification and indicate insulin-sensitising therapy as a component of fertility management [16].

There are weaknesses in this research that need to be discussed. The cross sectional design does not allow causal inference and fails to show changes in hormones over time. Single-centre recruitment, although beneficial in maintaining uniformity in the protocol, constrains the ability of generalisation to other parts of Iraq where there are varying ethnic mixes and healthcare facilities. The group of 40 women was sufficient power to make the primary comparisons but possibly was not adequate to identify more modest associations in the multivariate model as indicated by the result that was borderline on AMH. Moreover, the study is earlier than the international update of evidence-based guidelines in 2023, which optimized the use of Rotterdam criteria and AMH thresholds. These results should be validated with multicenter prospective studies that include longitudinal follow-up as well as revised diagnostic criteria to address them and translate them into clinical protocols.

CONCLUSIONS

The LH/FSH ratio of the hormonal markers analyzed demonstrated the best and most consistent correlation with infertility in this Iraqi cohort with PCOS. The optimal ratio was 2.15 that detected infertile patients with sensitivity and specificity of clinically useful values, and HOMA-IR alone magnified infertility risk in the multivariate analysis. These results indicate that both indices should be measured regularly to enhance risk stratification in PCOS women who visit fertility services in Iraq and other similar facilities. Potential interventional

studies are now necessary to determine whether the optimisation of insulin resistance is associated with superior reproductive outcomes in this group of people.

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