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Predictive Value of Follicular Stimulating Hormone on Luteinizing Hormone Ratio for Ovarian Response to Simple Ovulation Induction in Patients with Polycystic Ovarian Syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is considered the most frequent ovulatory disorder. PCOS often has a problem in (GnRH) release, with increase in the pituitary secretion of (LH) hormone and high LH/FSH ratio.

Objective: The current study aimed at detecting the predictive level of LH/FSH ratio for the ovarian response, pregnancy and miscarriage rates in PCOS patients underwent mild ovarian stimulation.

Patients and methods: A prospective cohort study was conducted in Gynaecology and Obstetrics Department, Zagazig University Hospitals. The study included PCOS women aged from 20 to 37 years, with at least 1 year of infertility, and normal semen analysis. The exclusion criteria were pelvic surgery and/or pathology. Cycle day 2-5 Serum LH and FSH were measured. Transvaginal ultrasound was done on cycle day 2-3 to prove quiescent ovaries, letrozole (2.5-5mg) was started from day 2-3 for successive 5 days with/without HMG (75-150IU/d) then follicular tracking was done till 1-3 follicles reached ≥18 mm upon which ovulation trigger was given.

Results: A total 63 infertile women were included in the study. The mean age was 24.81 (SD 2.83) years, the mean BMI 30.65 (SD 6.58) Kg /m2. Basal FSH, LH level, and LH/FSH ratio ranged from 1.9-11.9 mIu/ml, 2.34-21 mIu/ml and 0.37-4.63, respectively. ROC curve analysis showed LH/FSH ratio to be non-useful predictor of ovarian response, occurrence of pregnancy or miscarriage in PCOS patients underwent simple ovarian induction, AUC (0.51, 0.64 and 0.69 respectively)**.**

Conclusion: LH/FSH ratio seems to have no role in prediction of stimulated cycle outcome.

Keywords: LH, FSH, LH/FSH ratio, PCOS, Diagnostic study, Zagazig University.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is believed to be the most common ovulatory disorder. PCOS has a large prevalence, may reach up to 5%-15% depending on different phenotype, ethnicity, & different criteria used for diagnosis [(1)]**.** Female with PCOS mostly has an abnormality in the GnRH release, with increase in the secretion of LH hormone and high LH/FSH level [(2)]**.**

In healthy ovulatory female, the ratio between both LH and FSH hormonal level appears to be from 1 to 2. However, in polycystic ovary women, the ratio level becomes reversed, and it might increase ≥2 [(3)]**.**

The response to ovulation induction therapy has rarely been explored concerning LH/FSH ratio. Furthermore, the algorithms available for predicting response to ovulation induction do not consider LH/FSH ratio [(4)]**.** The reverse ratio of LH/FSH may have a concealed negative influence on human reproduction but it is still a debatable issue [(5)]. The current study aimed to examine the predictive value of LH/FSH ratio for ovarian response, pregnancy, and miscarriage rates in PCOS patients underwent simple ovarian induction.

PATIENTS AND METHODS

A prospective cohort study was conducted in Gynaecology and Obstetrics Department, Zagazig University Hospitals, from August 2022 to February 2023. The study included PCOS women aged from 20 to 37 years.

Inclusion criteria were female aged from 20 to 37 years, women with at least 1 year of infertility, PCOS women diagnosed according to Rotterdam criteria [(6)]**,** and normal partner semen analysis according to WHO (2010).

Exclusion criteria were pelvic surgery, endometriosis, pelvic inflammatory disease, abnormal hysterosalpingography, male factors of infertility, uterine pathologies such as leiomyoma, adenomyosis, or polyp, and those with a previous history of ovarian drilling.

The sample size was calculated to be 60 infertile patients with PCOS; the sample was calculated using the Epi Info version 6 Program, at a confidence interval of 95% and power test of 80%.

History taking with complete general and local examinations was done. Blood sampling was withdrawn in the early follicular phase, between cycle day 2-5 Serum LH, FSH was measured and LH/FSH ratio was calculated.

Transvaginal sonography was done by the same observer on cycle day 2-3 to prove quiescent ovaries then ovarian stimulation using letrozole (2.5-5mg) (Femara®-NOVARTIS) starting from cycle day 2-3 for successive 5 days with/without HMG (75-150IU/d) then follicular tracking was done from day 10 of the cycle, until 1-3 maximumly dominant follicles reached ≥18 mm upon

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which ovulation trigger using 10.000 IU hCG (choriomon ®-IBSA) was given IM in single dose. Cycle cancellation was conducted if no ovarian response occurred till day 20 cycles or if more than 3 dominant follicles were noticed and when ultrasound picture suggested OHSS was noticed to avoid high order pregnancy and early and even late OHSS. Patients were informed to have coitus within 36 hrs from hCG injection then every other day for at least 4 times. Serum β-hCG was measured 2 weeks later and if the test was positive, (TVS) was done 14 days after that to confirm foetal heartbeats.

Our primary outcome was to measure the rate of ovulation and secondary outcome was to measure the clinical pregnancy rate (CPR) and the miscarriage rate.

Ethical Consideration: This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis: The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 25.0 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test/ Mann-Whiteny test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant. ROC curve was used to determine the role of serum LH/FSH ratio levels in prediction of ovarian response, clinical pregnancy and miscarriage rates. Reliability data was calculated (sensitivity, specificity, PPV, NPV and accuracy).

RESULTS

The age of the study population was 24.81 (SD 2.83) years (range 20–32 years), the BMI ranged from 19.6-57.9 Kg /m2 with a mean of 30.65 (SD 6.58) Kg/m2 **(Table 1)**.

Table (1): Demographic data and Body measurements of the studied women.

Variable	Mean±SD (n=63)
Age (year)	24.81±2.83
Height (cm)	159.21±7.75
Weight (kg)	77.52±16.76
BMI (kg/m2)	30.65±6.58

BMI: Body mass index, SD: Standard deviation

A total of 12 (19%) patients had a previous miscarriage and 27 (42.9%) patients had hirsutism. Concerning parity 42 (66.7%) were nullipara, 12 (19%) were primipara, and 9 (14.3%) were multiparous **(Table 2).** The irregular cycle was noticed in 82.5% of the cases, while 17.5% of them had regular flow.

Table (2): History distribution among the studied patients.

Variable		(N=63)	
		No	%
Parity:	0	42	66.7
	1	12	19
	2-3	9	14.3
Previous abortion:	-ve	51	81
	+ve	12	19
Hirsutism:	-ve	36	57.1
	+ve	27	42.9

The mean basal FSH was 6.15 (SD 1.99), while the median (IQR) level of LH and LH/FSH ratio were 7.9 (6.2-11.6) and 1.4 (0.85-1.82), respectively **(Table 3).**

Table (3): Hormonal profile of studied patients.

Variable	(N=63)
FSH:	6.15±1.99
LH: (mIu/ml) ***Median (IQR)***	7.9 (6.2-11.6)
LH/FSH ratio ***Median (IQR)***	1.4 (0.85-1.82)

FSH: follicle-stimulating hormone, LH: luteinizing hormone.

The ovarian response is observed in 88.9% of the patients **(Table 4).**

Table (4): Cycle response among the studied cases

Variable		(N=63)	
		No	%
Response:	No	7	11.1
	Yes	56	88.9
No follicle:	Mean ± SD	1.33 ± 0.33	
Clinical Pregnancy (N=56)	-ve	24	42.9
	+ve	32	57.1
Abortion among pregnant cases (N=32)	No	24	75
	Yes	8	25

SD: Standard deviation.

There was none statistically significant difference of LH/FSH ratio regarding ovarian response, occurrence of pregnancy or miscarriage rate **(Table 5).**

Table (5): Relation between LH/FSH ratio and cycle outcome among the studied cases.

Variable		N	LH/FSH			MW	P-value
			Median	IQR			
Response	-ve	7	1.31	1	1.94	0.09	0.93
	+ve	56	1.43	0.86	1.82		NS
Pregnancy	-ve	24	1.17	0.80	1.67	1.78	0.07
	+ve	32	1.6	0.98	2		NS
Abortion	-ve	24	1.77	1.4	2.05	1.57	0.12
	+ve	8	1.12	0.84	1.47		NS

SD: Standard deviation**;** MW: Mann Whitney test; NS: Non-significant (P>0.05).

The statistical analysis of the ability of LH/FSH ratio to predict ovarian response, clinical pregnancy and miscarriage rate in PCOS patients underwent simple ovarian induction therapy showed no statistically significant role; the AUC of each ROC curve was {(0.51, P=0.93) (0.64, P=0.07) and (0.69, p=0.12) respectively} **(Table 6).**

Table (6) predictive value of LH/FSH ratio on cycle outcomes.

Variable	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P value
Response	<1.54	0.51 (0.29-0.73)	53.6	42.9	88.2	10.3	52.4	0.93 (NS)
Pregnancy	<1.4	0.64 (0.50-0.79)	65.5	58.3	67.7	56	62.5	0.07 (NS)
Abortion	>1.77	0.69 (0.48-0.89)	75	50	33.3	85.7	56.3	0.12 (NS)

NS: Non-significant (P>0.05).

DISCUSSION

Polycystic ovary syndrome (PCOS) is considered one of the frequently occurring endocrinology problems affecting female in their age of reproduction. PCOS accounts for 5–10 per cent of worldwide women [(1)]**.** PCOS is accounting for > 80% of all patients diagnosed with anovulatory infertility [(7)]**.** Moreover, the infertility widespread in PCOS female is considered to be high, varies from 70 to 80% [(8)]. So, the PCOS females with an ovulatory problem receive multiple varieties of the ovulation induction.

LH/FSH ratio on their own is not adequate in the diagnosis of PCOS. Many endocrinological factors including LH/FSH ratio, LH level, AMH level, in addition to BMI and clinical characteristics may be helpful in PCOS diagnosis [(9)].

This is a cohort study that was prospectively took place in Gynaecology & Obstetrics Department, Zagazig University Hospitals to determine the ability of LH/FSH ratio to predict the ovarian response, clinical pregnancy, and miscarriage rate in PCOS patients underwent mild ovarian stimulation. We found that LH/FSH ratio showed non-statistically significant correlation with the ovarian response, clinical pregnancy, or miscarriage rate among pregnant cases. LH/FSH ratio also had non- statistically significant correlation with the number of follicles (r=0.19, P=0.17). Additionally, according to our results LH/FSH ratio failed to predict the outcome of stimulated cycle.

Studies discussing the impact of (LH/FSH) ratio in simple ovulation induction are a little bit deficient; IVF/ ICSI have the biggest share in research discussing this issue. As a developing country most patients have low income and requesting non-useful investigation will be a burden on their income upon this, we pointed out this research to discuss the value of routine basal LH, FSH sampling before starting simple induction in PCOS patients.

The studies done to evaluate the LH/FSH ratio showed confusing results; in a study done in Egypt by **Enien *et al*.** reported that the LH/FSH ratio was significantly in elevated in clomiphene citrate non-responders, this data was as the results by **Sachdeva *et al*.** noticed that LH/FSH ratio was significantly more in the CC resistant group than the CC sensitive groups (2.66±1.22 and 2.27±1.11, respectively, P=0.035), on the contrary of our study they depend in their results on CC response, not letrozole as we did [(10,11)].

In a multicentre study in China on 956 PCOS patients who underwent ovulation induction they found that high LH/FSH ratio in early cycle related to poor ovulatory response but higher clinical pregnancy and live birth. The elevated LH level may be related to follicular atresia or premature luteinization which adversely impact

the process of ovulation, especially the follicular growth and LH/FSH surge for ovulation induction [12].

On the other hand, elevated baseline LH/FSH had an elevated progesterone value which may support a perfect milieu for the embryo development [13], this makes pregnancy ended by a livebirth more liable to occur, and miscarriages are more difficult to happen [14]. Non-PCOS patients were not included in this study so LH/FSH ratio effect on fertility is still debatable [15].

LH/FSH ratio effect on IVF/ICSI had been discussed In a study done including 182 IVF cycles, they found that basal LH:FSH ratio ≥3, associated significantly with lower follicular number, oocytes and percentages of mature oocytes in PCOS patients treated with human menopausal gonadotropins only while PCOS patient treated with buserelin-long/HMG showed significantly higher level mature oocyte only when LH: FSH Ratio <3 [16]. However, **Singh *et al.*** found that high LH and LH/FSH ratio on the 2nd or 3rd day of the cycle did not adversely affect the result of the GnRH antagonist protocol-treated ART cycles in PCOS women. And decreasing the LH levels before treatment may be not advised [17].

The bright side of this study is that it was a prospective study done on a different type of population with different racial factors, genetics, nutritional culture, and BMI levels which may explain the conflict of our results with others. The most prominent limitation is that we depend on a small sample size and future research on larger scale is recommended.

CONCLUSION

LH/FSH ratio seems to be a poor predictor of ovarian response, pregnancy rate or miscarriage rate in PCOS patients underwent mild ovarian stimulation. However future studies on large numbers are still needed.

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REFERENCES

1. **Bozdag G, Mumusoglu S, Zengin D *et al*. (2016):** The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Human Reproduction, 31(12):2841-55.
2. **Tanbo T, Mellembakken J *et al.* (2018):** Ovulation induction in polycystic ovary syndrome. Acta Obstetric Gynecology Scandinavica, 97(10):1162-7.
3. **Mitrašinović-Brulić M, Buljan M, Suljević D (2021):** Association of LH/FSH ratio with menstrual cycle regularity and clinical features of patients with polycystic ovary syndrome. Middle East Fertility Society Journal, 26(1):40.
4. **Meun C, Oostingh E *et al*. (2022):** The influence of ethnicity on outcomes of ovulation induction with clomifene citrate in women with PCOS. Reproductive Biomedicine Online, 44(5):874-80.
5. **Mendoza C (2002):** Follicular fluid markers of oocyte developmental potential. Human Reproduction, 17(4):1017-22.
6. **Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004):** Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility Sterility, 81(1):19-25.
7. **Balen A, Morley L, Misso M *et al.* (2016):** The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Human Reproduction Update, 22(6):687-708.
8. **Ellakwa H, Sanad Z, Hamza H *et al*. (2016):** Predictors of patient responses to ovulation induction with clomiphene citrate in patients with polycystic ovary syndrome experiencing infertility. International Journal of Gynecology & Obstetrics, 133(1):59-63.
9. **Le M, Le V, Le D *et al*. (2019):** Exploration of the role of anti-Mullerian hormone and LH/FSH ratio in diagnosis of polycystic ovary syndrome. Clincal Endocrinology, 90(4):579-85.
10. **Enien W, Barghash N, Ali F (2004):** Clinical, ultrasonographic and endocrine predictors of ovarian response to clomiphene citrate in normogonadotropic anovulatory infertility. Middle East Fertility Society Journal, 9(3):242-50.
11. **Sachdeva G, Gainder S, Suri V *et al.* (2019):** Comparison of clinical, metabolic, hormonal, and ultrasound parameters among the clomiphene citrate-resistant and clomiphene citrate-sensitive polycystic ovary syndrome women. Journal of Human Reproductive Science, 12(3):216.
12. **Willis D, Watson H, Mason H *et al*. (1998):** Premature Response to Luteinizing Hormone of Granulosa Cells from Anovulatory Women with Polycystic Ovary Syndrome: Relevance to Mechanism of Anovulation. The Journal of Clinical Endocrinology & Metabolism, 83(11):3984-91.
13. **Escobar-Morreale H (2018):** Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nature Reviews Endocrinology, 14(5):270-84.
14. **Siristatidis C, Maheshwari A *et al*. (2018):** In vitro maturation in sub fertile women with polycystic ovarian syndrome undergoing assisted reproduction. doi:10.1002/14651858.CD006606.pub4
15. **Xia Q, Xie L, Wu Q *et al*. (2023):** Elevated baseline LH/FSH ratio is associated with poor ovulatory response but better clinical pregnancy and live birth in Chinese women with PCOS after ovulation induction. Heliyon, 9(1):e13024.
16. **Tarlatzis B, Grimbizis G, Pournaropoulos F *et al.* (1995):** The prognostic value of basal luteinizing hormone: follicle-stimulating hormone ratio in the treatment of patients with polycystic ovarian syndrome by assisted reproduction techniques. Human Reproduction, 10(10):2545-9.
17. **Singh N, Mishra N, Dogra Y (2021):** Do basal luteinizing hormone and luteinizing hormone/follicle-stimulating hormone ratio have significance in prognosticating the outcome of In vitro fertilization cycles in polycystic ovary syndrome? Journal of Human Reproductive Science, 14(1):21.