Association of Serum Müllerian-Inhibiting Hormone with the Gonadotrophins in Infertile Women

Naila Parveen[1], Dureshahwar Rehman[2], Naseer Baloch[3], Komal Masroor[4]

ABSTRACT

OBJECTIVE: To determine the relationship of serum Mullerian inhibiting hormone with gonadotrophins in infertile women.
STUDY DESIGN: A Cross-Sectional analytical study.
PLACE AND DURATION: The study was conducted in the Infertility Clinic of a tertiary care hospital in Karachi from 1st February 2012 to 20th January 2013.
METHODS: A total of fifty women with no history of any previous pregnancy i.e. primary infertility, between 18-33 years of age, patent fallopian tubes and normal semen analysis of their husbands were selected from the infertility clinic. Blood samples for basal follicle stimulating hormone, leutinizing hormone and Mullerian inhibiting hormone levels were assessed.
RESULTS: The mean serum level for follicle stimulating hormone was 8.82±1.402. Mean leutinizing hormone and Mullerian inhibiting hormone levels were found to be 7.51±3.23 mIU/ml and 1.32± 0.74ng/ml respectively. Statistical analysis revealed a strong negative and significant relationship between Mullerian inhibiting hormone and follicle stimulating hormone, though leutinizing hormone had inverse but insignificant correlation with Mullerian inhibiting hormone.
CONCLUSION: Mullerian inhibiting hormone was negatively associated with the gonadotrophins in infertile women and significant inverse correlation was found between MIH with FSH compared to the insignificant negative association with the leutinizing hormone. Therefore, MIH can be considered as a surrogative marker in the assessment of ovarian reserve.
KEY WORDS: Mullerian Inhibiting Hormone, Luteinizing Hormone, Follicle Stimulating Hormone, Infertility, Gonadotrophins, Reserve

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INTRODUCTION

Infertility is a major global issue and needs to be resolved. The prevalence of infertility worldwide is approximately 10-15%[1]. Prevalence rate of fecundity in Pakistan is reported to be 21.9%[2]. Anecdotal evidence has suggested an increase in the psychological, social and economical burden on couples with infertility. Timely diagnosis and early therapeutic intervention might play a major role in the prevention of this negative impact on the fecund individuals[1,2]. Conventional tests predictive of infertility include the ovarian reserve tests,follicle-stimulating hormone, luteinizing hormone, inhibin B, and estradiol and antral follicle count by transvaginal scan. Another endocrine marker, the Mullerian inhibiting hormone/Anti-Mullerian hormone has emerged as a useful marker for assessing the ovarian reserve in infertile women. Ovarian reserve reflects the reproductive potential in women by the quantity of oocytes residing in the ovaries and day 3 follicle stimulating hormone levels are considered as a reliable marker in determining individuals ovarian reserve pool. FSH is a gonadotrophic hormone produced by the anterior pituitary gland and is regulated by the hypothlamo-hypophysial negative feedback mechanism due to which its levels keep on fluctuating throughout the menstrual cycle.[3, 4] FSH plays a vital role during the early follicular development by the activation of aromatase enzyme to convert androgen into estradiol. LH is involved in the later stages of follicular development by increasing the production of estradiol, enhancing the actions of FSH and causing maximum development of follicles. [5] Conversely, MIH is a hormone produced by the granulosa cells of the early follicles. Moreover, its serum levels represent the continuous non-cyclic growth of small follicles due to which it shows minimal fluctuation throughout the menstrual cycle. It also acts as a predictor of ovarian response in

1. Assistant Professor of Physiology, Liaquat National Medical College, Karachi
2. Lecturer of Anatomy, King Saud Bin Abdulaziz University, Riyadh, KSA
3. Associate Professor of Anatomy, Liaquat National Medical College, Karachi
4. 3rd Year student MBBS Dow University of Health Sciences Karachi, Pakistan

Correspondence to:
Dr. Naila Parveen
Assistant Professor of Physiology,
Liaquat National Medical College, Karachi
Email: m_naila72@yahoo.com

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assisted reproductive techniques. Recent research have indicated the clinical application of MIH in conditions like polycystic ovarian syndrome and premature ovarian failure.[6,7] Advantages of MIH when compared with the other conventional tests for the assessment of ovarian reserve include that it is found to be the earliest marker to decline with age, does not show any inter and intra-cyclic variability and it can be measured on any day irrespective of the menstrual cycle days[8]. Mullerian inhibiting hormone is secreted directly by the ovaries into the blood, its levels remain stable, therefore it is easily accessible and a reliable marker measured in the serum predicting the reproductive potential in a woman[9]. The major advantage of MIH when compared with FSH is that it does not show much variation throughout the menstrual cycle. However, FSH levels do not remain stable and highest levels are reported on the third day of the menstrual cycle.[10] Therefore, along with the routine tests of infertility markers, utilization of Mullerian inhibiting hormone has tremendously increased to assess the quantity of oocytes residing in the ovaries [11,12]. The rationale of this study is to evaluate the importance of Mullerian inhibiting hormone as a reliable marker for assessment of ovarian reserve in infertile women by finding its relationship with the conventional hormonal markers such as the follicle stimulating hormone and leutinizing hormone. The main objective of this study was to determine the association of Mullerian inhibiting hormone with the gonadotrophins in infertile women.

METHODOLOGY

This cross-sectional analytical study was conducted in the Infertility Clinic of a tertiary care hospital in Karachi from 1st February 2012 to 20th January 2013. After approval from the ethical review board of Institute of Basic Medical Sciences and informed written consent, 50 infertile females in their reproductive age group were selected by non-probability convenience sampling. The study participants comprised of primary infertile women of reproductive age group between 18-33 years. Female infertile women having any previous history of pregnancy or concealed fallopian tubes or any factor interfering with the male infertility were excluded from the study. Blood samples for the determination of MIH, FSH and LH levels were drawn on third day of the menstrual cycle from each participant and collected in gel tubes. The samples were then centrifuged and stored in aliquots at- 20^0 C. Human Elisa kit (CDN-E 1350) was used to determine the MIH levels irrespective of the menstrual cycle days. However, to determine the serum FSH and LH levels, blood samples were drawn on the third day of the menstrual cycle using chemiluminescent immunoassay. **Data Analysis:** A software version of SPSS 16 was used for statistical analysis and cutoff was set at $P<0.05$. Mean values of FSH, LH and MIH were analyzed through descriptive statistics. Pearson's correlation was used to find out the association of MIH with FSH and LH.

RESULTS

The study included infertile female population of fifty subjects with mean age of 25±3·012 years· Data analysis showed a mean value of third day folliculotropin (FSH) levels as 8.82±1·402 and mean leutotropin (LH) and MIH levels were found to be 7.51±3.23 mIU/ml and 1.32± 0.74ng/ml respectively (Table - I). However, the interrelation of MIH with FSH levels showed that with decreasing MIH levels, there was an increase in FSH levels significantly with correlation coefficient of -0.5, p=0.001and relationship of MIH with LH showed negative but insignificant correlation with p=0.08 as in (Table-II).

TABLE-I: Descriptive statistics of age, Mullerian Inhibiting Hormone, Follicle Stimulating Hormone and Leutinizing Hormone. (N=50)

Variables **N=50**	Age	Mullerian Inhibiting Hormone	Follicle Stimulating Hormone	Luteinizing Hormone
Mean± SD	25 ±3.012 years	1.32 ± 0.74 ng/ml	8.82±1.402 mIU/ml	7.51±3.23 mIU/ml

Table – II:-Pearson's r of Gonadotrophins with MIH. (N=50)

Mullerian Inhibiting Hormone N=50 Pearson's Correlation Coefficient		p-value
Follicle Stimulating Hormone	- 0.51	0.001
Leutinising Hormone	- 0.13	0.08

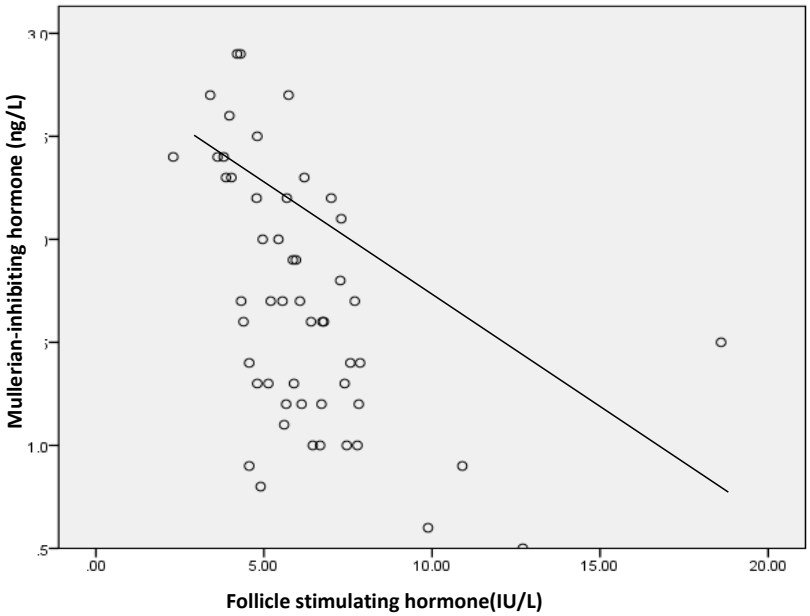

Figure - 1: Graph of scatter diagram demonstrating negative linear relationship between two variables

DISCUSSION

Mullerian inhibiting hormone has been depicted as a useful marker in the assessment of ovarian reserve in infertile patients besides the conventional screening tests including the day 3 FSH and LH levels, estradiol levels and early follicular count[13]. Association of Mullerian inhibiting hormone with FSH and LH was analyzed by Pearson correlation. In our study, negative inverse correlation was found between MIH and FSH (r= − 0.51) which was statistically significant. This finding was in agreement with a cohort study conducted by Singer et al 2009, who also observed negative association between MIH and FSH[11]. Dorotheam et al and Iverson et al also observed the same findings in their study with negative correlation coefficient as ($r = -0.38$, $p<0.05$)[14,15]. A study conducted by Barbakadze et al 2015 observed that MIH was negatively correlated with FSH (r=-0.48, p<0.0001) and Bala J et al also found significant inverse correlation between AMH and FSH concentration ($r = -0.488$, $P < 0.001$)[16]. Our results showed negative and insignificant relationship of MIH with LH. This was consistent with the findings of study conducted by Franchin et al who also observed statistically non-significant inverse correlation of MIH with LH (r= − 0.02, p>0.05)[17]. However, results of a study conducted by Homburg et al showed significant positive correlation of MIS and LH (r=0.321,P<0.01) in women with polycystic ovaries[18]. Descriptive statistics of our study showed mean MIH levels & FSH levels as 1.32 0.71 and 8.82±1.402 mIU/ml respectively. A similar study was conducted by Bala J et al in which 75 infertile women were selected with mean serum AMH and FSH as 1.18 ± 0.57 ng/ml and 9.09 ± 2.51 mIU/ml on day three of menstrual cycle respectively[19]. A study conducted in Egypt by Negm et al suggested that AMH is more reliable than basal FSH levels in predicting poor ovarian response to ovarian stimulation in assisted conception cycles and also found a significant negative correlation between serum AMH and serum FSH.[20] In a recent review conducted by Zehra et al, summarized the role of Mullerian inhibiting hormone compared to LH with much higher predictability of ovarian reserve in general and the response of ART than LH. Thus, in comparison to Mullerian inhibiting hormone, leutinizing hormone has a weak association with ovarian follicular pool and its response to ovarian stimulation.[21] Limitations include small sample size and cross-sectional design of the present study. More prospective studies on the importance of MIH should be conducted in our local population for its profound implications in the prediction of better fertility options in infertile women.

CONCLUSION

It is concluded that, Mullerian inhibiting hormone has shown negative association with the gonadotrophins in infertile women. However, a significant strong inverse correlation was found between MIH with FSH compared to the insignificant negative association with the leutinizing hormone. Thus, MIH can be used as a useful marker in the assessment of ovarian reserve in infertile women along with FSH.

CONTRIBUTION OF AUTHORS

Parveen N: Conceived idea, designed Research Methodology, Manuscript writing
Rehman D: Statistical analysis and data interpretation
Baloch N: Manuscript final reading and approval
Masroor K: Literature Review, Data collection

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