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ORIGINAL ARTICLE

REPRODUCTIVE HORMONE PROFILES OF WOMEN WITH INFERTILITY AND MENSTRUAL DISORDERS: A RETROSPECTIVE STUDY

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ABSTRACT

Background and Objectives: Hormonal disorders of the female reproductive system encompass a variety of problems resulting from dysfunction of the hypothalamic-pituitary-ovarian axis. Measurement of reproductive hormones play an important role in the management of females presenting with infertility and menstrual disorders. Current study aimed to determine the pattern of endocrinological disorders in females investigated for infertility and oligo/amenorrhea.

Methodology: Retrospective study carried out at National Health Research Complex (NHRC) and department of Obstetrics and Gynecology, Shaikh Zayed Hospital, Lahore. Females with infertility, oligomenorrhea and secondary amenorrhea who underwent hormonal assessment at NHRC immunoassay laboratory during the period of January 2010 to December 2012 were included in the study. Relevant information was extracted from the patient's medical-history files and NHRC immunoassay laboratory records. Hormone levels were determined using commercially available kits from Biocheck USA.

Results: Age of the study participants ranged between 14-40 years. Frequency of different conditions was; primary infertility (39.74%), secondary infertility (26.63%), oligomenorrhea (18.78%) and secondary amenorrhea (14.85%). Mean Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels were elevated in majority of females in hormonal imbalance subgroup of infertility and oligo/ amenorrhea however, some females had low LH and FSH levels. In females with infertility (primary/ secondary combined), Polycystic ovarian syndrome (PCOS) (38.18%) and hyperprolactinemia (30.9%) were the commonest disorders. In secondary amenorrhea, hyperprolactinemia (30.43%) was followed by premature ovarian failure (26.08%) whereas in oligomenorrhea, hirsutism (39.13%) and PCOS (34.78%) were more common.

Conclusion: This study shows the pattern of hormone profiles of females with infertility, oligomenorrhea and secondary amenorrhea and highlights the importance of role of pituitary gonadotrophins in management of infertility and menstrual disorders.

Keywords: Infertility, oligomenorrhea, secondary amenorrhea, reproductive hormones, hormonal imbalance.

INTRODUCTION

Fertility is given due attention in all societies. The inability to have children has traditionally been a source of pain, anxiety and shame, flagging the worse consequences to infertile couples.[1] Infertility is one of the main gynecological problems and is defined as failure to conceive after 1 year of normal, unprotected marital relations. It is classified as primary infertility if no previous pregnancy has occurred and secondary infertility if it occurred after one or more pregnancies.[2] Approximately 15 % of couples attempting their first pregnancy face primary infertility and another 10% face secondary infertility.[2,3]

Many causes of infertility have been established. Endocrinology studies on female infertility have brought to limelight problems of anovulatory cycle and hyperprolactinemia. Ovulation depends on a number of factors, including complex interactions among hormones secreted from the brain, the pituitary gland and the ovary after reproductive maturity.[1] During the menstrual cycle, the concentrations of hormones change dramatically resulting in ovulation and preparation of the uterus for implantation of the fertilized egg. If this highly orchestrated and tightly controlled sequence of events is interrupted, it may result into infertility or reduced fertility.[4] Measurement of peptide and steroid hormones in serum, play a key role in investigation and treatment of female reproductive problems.[5] Proper testing differs broadly according to the clinical picture, physical findings and results of other

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diagnostic procedures. Generally the most important hormones measured are LH, FSH, Prolactin and a variety of steroid hormones such as Estrogens, Progesterones and Androgens.

PATIENTS AND METHODS

This is a retrospective study, carried out from January 2013 to August 2013 at National Health Research Complex, Shaikh Zayed Hospital, Lahore, Pakistan. Females who were registered in Gynecology & Obstetrics department of Shaikh Zayed Hospital for infertility (either primary or secondary), oligomenorrhea and secondary amenorrhea and underwent hormonal assessment at NHRC immunoassay laboratory, from January 2010 to December 2012 were included in the study. Females with hypomenorrhea, polymenorrhea, primary amenorrhea and gestational amenorrhea were excluded from the study (due to very small number of patients in each group). After the approval of Ethical Review Board of Shaikh Zayed Medical Complex, demographic information including clinical presentation, age, hormone levels and diagnosis (including pelvic scans) were extracted from medical- history files of patients (available at record room of Gynae & Obs. department) and NHRC immunoassay laboratory data, and recorded on prescribed study proforma.

Primary infertility was considered when a patient has never been able to conceive a pregnancy in spite of unprotected marital relations, for a period of 1 year at least. Secondary infertility is failing to conceive, following a single previous pregnancy in presence of normal, unprotected marital relations. Oligomenorrhea was defined as irregular or infrequent menstrual periods with intervals of more than 6 weeks. Secondary amenorrhea was considered when menstruation has previously occurred but then stopped for a period of ≥ 6 consecutive months.

Venous blood samples (5 ml) were collected on 2nd day of cycle, for determination of reproductive hormone levels. Hormone levels were quantified in serum samples, using commercially available (enzyme immunoassay) kits from Biocheck USA. All assays were performed by a trained technician, according to manufacturer's instructions. Analysis of the assays was carried out on Anthox 2010 plate reader using softmax statistical package. For analytical accuracy of results all assays were performed with 6-7 standards and 3 quality control pools (Biorad USA) in each assay batch.

Data Analysis

Data was analyzed using statistical package for social sciences version 17.0. Hormone levels were reported as Mean ± Standard error of mean while Mann Whitney U test was used to test for differences in hormone levels between hormonal imbalance and no hormonal imbalance subgroups, value of $P \leq 0.05$ was considered as statistically significant.

RESULTS

During the retrospective study period, medical-history files of 257 females were available; out of those complete information, as per study proforma, was available for 229 females including clinical histories, hormone profiles and pelvic scans. Twenty eight females with incomplete clinical histories were excluded from the study. Age of study participants ranged between 14-40 years (Table 1). Out of 229 females, 101 (44.1%) presented with hormonal imbalance whereas 128 (55.9%) had no hormonal imbalance. Frequency of different gynecological conditions was primary infertility 91 (39.74%), secondary infertility 61 (26.63%), oligomenorrhea 43 (18.78%) and secondary amenorrhea 34 (14.85%) (Fig. 1).

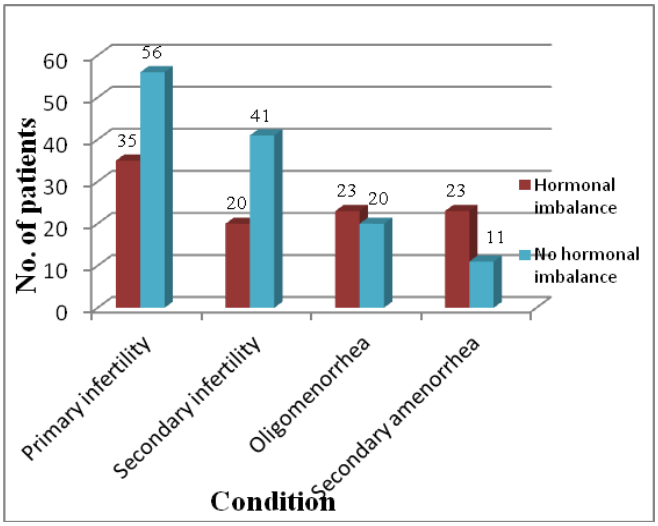

Fig. 1: *Distribution of patients with hormonal imbalance and no hormonal imbalance in different groups.*

Table 1: *Age distribution of study participants.*

Condition	*Age (Years)*	*No. of Cases*	*%age*
Primary infertility	18 – 24	24	26.37
	25 – 31	48	52.74
	32 – 36	19	20.87
Secondary infertility	19 – 24	10	16.4
	25 – 31	32	52.45
	32 – 38	19	31.14
Oligomenorrhea	14 – 23	23	53.48
	25 – 31	14	32.55
	32 – 40	06	13.95
Secondary amenorrhea	14 – 24	09	26.47
	25 – 31	17	50.0
	32 – 38	08	23.52

Table 2: *Level of LH, FSH and Prolactin in females with hormonal imbalance and no hormonal imbalance sub groups.*

Condition	*LH (mIU/ml)*	*P value*	*FSH (mIU/ml)*	*P value*	*Prolactin (mIU/L)*	*P value*
Primary Infertility Hormonal cause (n = 29) No hormonal cause (n = 56)	20.15 ± 4.3 7.6 ± 0.5	0.003	19.7 ± 5.5 5.5 ± 0.23	0.001	492 ± 44.1 334 ± 17.1	0.016
Secondary Infertility Hormonal cause (n = 17) No hormonal cause (n = 41)	16.8 ± 3.8 8.1 ± 0.64	0.047	11.3 ± 2.1 5.3 ± 0.28	0.004	464 ± 92.4 287 ± 20.7	0.011
Oligomenorrhea Hormonal cause (n = 19) No hormonal cause (n = 20)	16.9 ± 3.5 8.4 ± 0.82	0.041	18.9 ± 5.3 6.05 ± 0.59	0.003	619 ± 136 322 ± 26	0.004
Secondary Amenorrhea Hormonal cause (n = 19) No hormonal cause (n = 11)	25.63 ± 4.2 6.49 ± 0.77	0.012	21.5 ± 6.6 5.34 ± 0.64	0.022	703 ± 118.0 306 ± 27.0	0.001

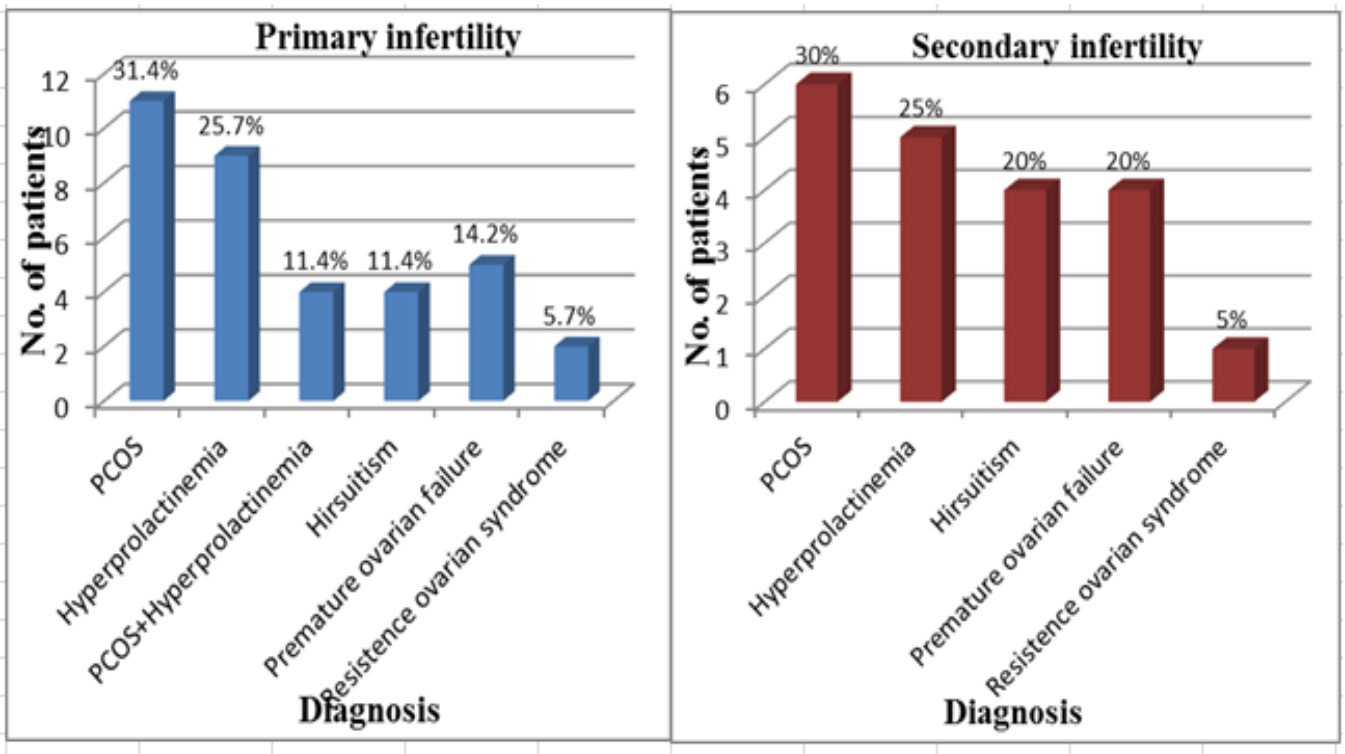

Fig. 2: *Frequency of different clinical conditions in females with primary and secondary infertility.*

LH and FSH levels were found to be elevated in majority of females with hormonal imbalance (Table 2). Elevation was more in females with secondary amenorrhea followed by primary infertility. Mean prolactin level was found to be the highest in females with secondary amenorrhea followed by females with oligomenorrhea (Table 2).

Major proportion of infertile females presented with PCOS and hyperprolactinemia; followed by premature ovarian failure, hirsuitism and resistance ovarian syndrome, respectively (Figure 2). Main presentations of females with oligomenorrhea were hirsutism and PCOS and of secondary amenorrhea were hyperprolactinemia and premature ovarian failure (Figure 3).

In case of primary infertility, LH level (1.63 ± 0.141

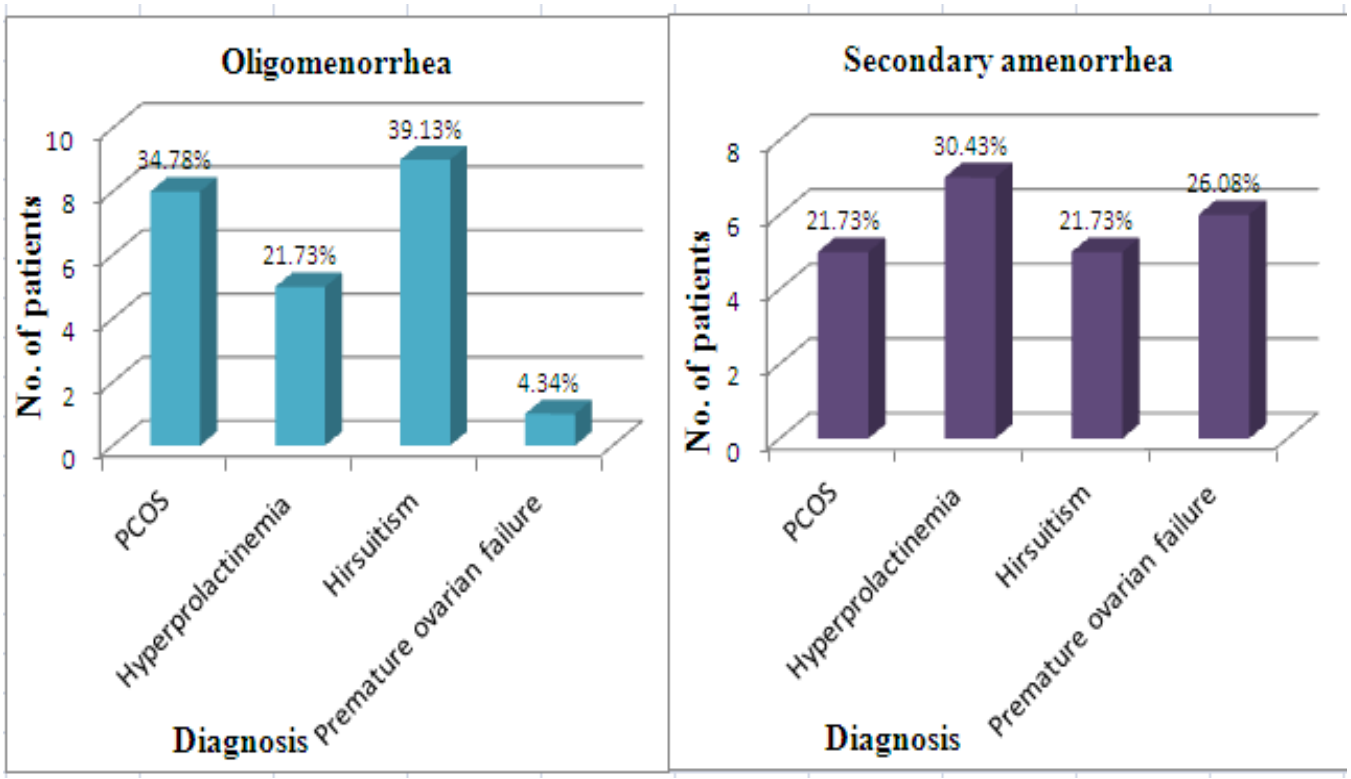

Fig. 3: *Frequency of different clinical conditions in females with oligomenorrhea and secondary amenorrhea.*

mIU/ml) of 2 females in the hormonal imbalance sub-group (n = 34) was lower than the normal cut off level (2 mIU/ml). Mean LH level of rest of females in this sub-group was significantly elevated (p = 0.0047) as compared to females with no hormonal imbalance sub-group. FSH level of 4 females was lower (0.857 ± 0.579 mIU/ml) than cut off level (2 mIU/ml) in hormonal imbalance sub-group. Remaining females had significantly elevated (p = 0.016) mean FSH level. Mean prolactin level was significantly elevated (p = 0.0017) in females with hormonal imbalance (Table 2).

Among females of secondary infertility, in hormonal imbalance subgroup, 2 females had low LH (1.6 ± 0.346 mIU/ml) and 3 had low FSH level (1.3 ± 0.529 mIU/ml) than cut off level, whereas remaining females of this subgroup had significantly elevated mean LH (p = 0.04) and mean FSH levels (p = 0.015) as compared to females in no hormonal imbalance subgroup. Mean prolactin level (464± mIU/ml) was also significantly elevated (p = 0.039) in females with hormonal imbalance (Table 2).

In females with oligomenorrhea, LH level (1.7 mIU/ml) of 1 female and FSH level (1.15 ± 0.265 mIU/ml) of 3 females were found lower than normal cut off levels whereas remaining females in this subgroup had significantly high mean LH (p = 0.0344), mean FSH (p = 0.018) and mean prolactin levels (p = 0.044) as compared to the females in no hormonal imbalance subgroup (Table 2).

Among females with secondary amenorrhea, four females in hormonal imbalance subgroup had low levels of FSH (1.4±0.36 mIU/ml) and one female among those 4, also had low LH level (1.7 ± mIU/ml) than the normal cut off. Remaining females in this subgroup had significantly high mean LH (p = 0.0002) and mean FSH levels (p = 0.027). In this subgroup mean prolactin level (703 ± mIU/ml) was significantly higher (p = 0.0034) as compared to the females in no hormonal imbalance group (Table 2).

DISCUSSION

Hormonal imbalance is one of the major causes of infertility and amenorrhea and results from dysfunction of hypothalamic-pituitary-gonadal axis, due to stress, environmental factors and diet (in case of hirsuitism). In the current study, 101 (44.1%) of the females showed evidence of hypothalamic-pituitary-gonadal axis dysfunction based on serum levels of LH, FSH and prolactin. A study carried out in Nigeria reported incidence of 58% hormonal imbalance in infertile females.[6] This variability could be due to different sets of studied population and geographical locations.

Results of the present study showed that majority of females with hormonal imbalance had increase in gonadotrophins concentrations (serum LH and FSH). These results are consistent with the studies done by Adegoke et al[7] and Braide et al.[1] Hyper secretion of LH is associated with menstrual cycle disturbances and

infertility. It is this endocrine feature that result in reduced conception rates and increased rate of miscarriages in both natural and assisted conception.[8] FSH levels are elevated in resistance ovarian syndrome and premature ovarian failure.[1] Moreover, in this study some females with hormonal imbalance also had low serum levels of LH and FSH, which is consistent with a Nigerian study conducted by Eniola et al.[9] This shows that both high and low levels of gonadotrophins can be the cause of female infertility and menstrual cycle irregularities.

In the present study frequency of PCOS in infertile women (primary and secondary combined) was found to be 38.18% while two studies done in Pakistan reported prevalence of PCOS as 40.9%[10] and 28%,[11] respectively. The frequency of hyperprolactinemia as the cause of female infertility was reported to be 28% by Eniola et al.[9] 25% by Mishra et al. [12], 19% by Onyenekwe et al.[6] and 18% by Kumkum et al.[13], however in the present study the frequency was found to be 30.9%. All subjects in this category had serum Prolactin level above 666 mIU/L (Normal range: 66-666 mIU/L).

In humans hyperprolactinemia is associated with a marked reduction in both the frequency and amplitude of LH pulses,[14] indirectly suggesting that both the brain and pituitary might be targets for prolactin.[1] The increase observed in prolactin may be the cause of low estrogen and progesterone concentration in the infertile females.[1] In vitro increase in prolactin level inhibits progesterone secretion in human porcine granulose cells.[15] A study demonstrated that high levels of prolactin, inhibit follicular steroidogenesis not only by interfering with aromatase activity but also by reducing the production by the theca of the androgen precursors necessary for oestrogen production.[1]

Oligomenorrhea can be a result of prolactinomas. It may also be caused by thyrotoxicosis, hormonal changes, PCOS and Graves disease. The main causes of oligomenorrhea in the present study were PCOS (34.78%) and hyperprolactinemia (21.73%). A study demonstrated that females with PCOS patients are more likely to present with oligomenorrhea (76%) as compared to amenorrhea (24%).[16]

The three most common causes of secondary amenorrhea seen in the current study were hyperprolactinemia (30.43%), premature ovarian failure (26.08%) and PCOS (21.73%). A study elsewhere has shown an approximate frequency of 14% hyperprolactinemia and 12% premature ovarian failure in secondary amenorrhea patients.[17] An Indian study reported premature ovarian failure is the aetiology in 10%–28% of the cases with primary amenorrhea and in 4%–18% of those with secondary amenorrhea.[18]

It is ***concluded*** that this study highlights the importance of role of pituitary gonadotrophins in management of infertility and oligo/amenorrhea. This study also shows that incidence of hormonal imbalance is on rise in women of reproductive age and is becoming a major cause of infertility and menstrual disorders.

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Author's Contributions:
SN: Design of study, data collection, data analysis, writing first draft of article, final approval from all authors. FG: Data analysis, review of draft article, final approval of article to be submitted. SM: Acquisition and interpretation of data, review of draft article, final approval of article to be submitted.

Conflict of Interest
All authors declare no conflict of interest

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Foot Line
Reproductive hormones in infertility/menstrual disorders.

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