

A Mosaic of Risk Factors for Female Infertility in Pakistan

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Abstract

Background: To identify different risk factors for female infertility including hormonal imbalance (FSH, LH and Prolactin)

Methods: Infertile women were enrolled in this prospective study. A questionnaire was designed to collect information regarding socio-demographic and clinical characteristics of the study participants. Serum FSH, LH and Prolactin levels were estimated between 1-5 days of post menstrual period. Independent sample t- test, Spearman correlation and multivariate logistic regression were performed to find the association of different risk factors with female infertility.

Results: Highest percentage (57.7%) of infertile females was in the age bracket of 26 to 35 years. The prevalence of primary infertility was 60.4% . Mean levels of LH and prolactin were significantly higher in women with primary infertility compared to those with secondary infertility. No significant difference was observed in the mean level of FSH . A significant positive correlation was found between infertility and age , marital history and infertility duration. On multivariate logistic regression analysis women with secondary infertility were more likely to be hypertensive(OR=2.126,95%CI:1.020-4.474, p-value0.044), using contraceptive OR=5.876, 95% CI: 2.491-13.86, p-value .001),have hyperprolactinemia (OR=1.289,95%CI:0.960-1.996,p-value0.001) and have marital history of more than 16 years OR=12.166,95%CI:5.048-29.322, p-value0.001).

Conclusion:Highest prevalence of infertility was seen in the age group of 26-35 years. Advanced age, hypertension, hyperprolactinemia, use of contraceptive and marital history of more than 16 years are significantly associated with female infertility

Key Words: Infertility, Hypertension, Hyperprolactinemia, Luteinizing hormone, Follicle-stimulating hormone.

Introduction

Infertility is multi-factorial problem that affects millions of females globally. Implications of hormonal imbalance and other risk factors in female infertility are an interesting area that requires to be explored in the recent times. Infertility is a global health concern affecting millions of women. It is defined as failure to achieve a clinical pregnancy after 12 month or more of regular unprotected sexual intercourse. ¹⁻³ Infertility can be classified as either primary or secondary. In the primary infertility, a couple has never been able to conceive. Secondary infertility is the case where there is a difficulty in conceiving after already having conceived.⁴ Globally, 50-80 millions of women are currently affected by this pathology and 25% of the couples in developing nations are affected by infertility.^{5,6} Infertility rates varies among countries ranging from 5 to 8% in developed countries and from 5.8% to 44.2% in developing countries.⁷ There is unequivocal evidence that infertility is a major health issue in Asian countries. ⁸ Prevalence of infertility in Pakistan is estimated to be 22% inclusive of 4% primary and 18% secondary infertility, ultimately affecting one in every five married couples.⁹

Numerous genetic, physiological, environmental and acquired factors have been linked with infertility, including being 35 years old or more, a history of pelvic inflammatory disease, hormonal imbalance, galactorrhea, obesity, surgical history, hypertension, T.B, diabetes, thyroid disorders and life style practices.¹⁰ Ovulation is the primary requirement for conception. Obesity contributes to an-ovulation and menstrual irregularities, culminating in reduced conception rates.¹¹ Polycystic ovary Syndrome (POS), a hormonal disorder described by hyperandrogenism is another important factor for anovulation.^{12,13} Prevalance of PCOS is estimated to be 4-25% among Lower ovarian reserves leads to reduced fertility at younger ages in Asian women. ¹⁴ The key hormones for female infertility workup includes follicle stimulating hormone (FSH), luteinizing

hormone(LH), prolactin (PRL) and thyroid stimulating hormones(TSH). An excess or deficiency of any of these hormone can cause anovulation and infertility. In hypothyroidism, elevated concentration of TSH and PRL can affect synthesis and secretion of the sex hormones and cause infertility.¹⁵ In hypopituitarism, raised LH and FSH levels may lead to amenorrhea and infertility in women. Further, elevated prolactin levels suppress FSH and LH serving as "nature's contraceptive."¹⁶

Patients and Methods

All the subjects were enrolled during August, 2018 to January 2019 at Benazir Bhutto Hospital, Rawalpindi. A total of 508 samples were included in this study. Women with diagnosed primary and secondary infertility, in the age bracket of 26-45 year, and having marital history of at least one year were included. Serum FSH, LH and Prolactin levels were estimated between the 1-5 days of post menstrual period by Chemiluminescence Immunoassay (CLIA). The data was tested for normality by Shapiro-Wilk test. Continuous variables were presented as mean ± Standard Deviation while categorical variables were expressed as frequency (percentages). Mean levels of hormones were compared with Mann-Whitney U test. Spearman's correlation and binary logistic regression analysis were used to determine the correlation between infertility, hormonal imbalance and other risk factors. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Mean age of the women enrolled in this study was 28.7 ± 5.5 years. Majority (88.2%) of the participants belonged to rural areas and 11.8% (n=60) were from urban areas (Table 1).

Table 1: Sociodemographic characteristics of the infertile women.

Characteristic	Groups	Frequency (n= 508)	Percentage (%)
Age (years)	16-25	153	30.1
	26-35	293	57.7
	36-45	62	12.2
Residence	Rural	448	88.2
	urban	60	11.8
Economic level	Adequate	151	29.7
	Adequate to some extent	310	61
	Inadequate	47	9.3
Occupational status	Housewife	450	88.6
	Employer	58	11.4

Table 2: Educational status

Educational level	Percentage
Illiterate	21.1
Read and write	18.7
Primary	18.5
Secondary	26.6
Intermediate	10.6
Higher studies	4.5

Table 3: Clinical characteristics of the infertile women.

Characteristics	Groups	Frequency (n=508)	Percentage (%)
Duration of infertility	1-3	163	32.1
	4-6	167	32.9
	7-9	133	26.2
	>10	45	8.9
Age at menarche	≤13	293	57.7
	≥14	215	42.3
Obesity	Normal	250	49.2
	Overweight	258	50.8
PCOs	Present	80	15.7
	Absent	428	84.3
Hypertension	hypertensive	40	7.9
	Normal	468	92.1
Diabetes	Present	15	3.0
	Absent	493	97.0
T.B	Present	20	3.9
	Absent	488	96.1
Thyroid disorder	Enlarged	29	5.7
	Normal	479	94.3
Galactorrhea	Present	23	4.3
	Absent	485	95.5
Hirsutism	Present	145	28.5
	Absent	363	71.5
Surgical history	Present	122	24
	Absent	368	76
Menstrual Cycles	Regular	369	72.6
	Irregular	139	27.4

Highest percentage (26.6%) of the females had attained secondary education (Table 2). Majority (60.4%) of the females had primary infertility. Highest percentage (65%) of the females had marital history of up to six years, 57.7% of the females were ≤13 years of age at menarche, 28.5% had hirsutism, 27.4% had irregular menstrual cycle, 19.2% had hyperprolactinemia, 19.1% (n= 97) had acne, 15.7% (n= 80) had PCOS, 7.9% (n= 40) were hypertensive, 5.7% (n= 29) had enlarged thyroid, 4.3% (n= 23) of the females had galactorrhea (Table 3). A significant positive correlation was found between infertility and age (r = 0.110, p-value 0.013), marital history (r = 0.340, p-value 0.0001) and Infertility duration (r = 0.137, p-value 0.002).

Table 4: Surgical history

Surgical history	Percentage
Laparotomy	8.2
Laparoscopy	5.7
Appendectomy	4.8
Thyroidectomy	2.5
Salpingectomy	1.8
Myomectomy	1
No Surgical History	76%

Twenty four percent women gave history of a surgical procedure (Table 4) FSH levels were significantly correlated with age($r = 0.095$, p - value 0.05) and PCOS($r = 0.162$, p - value 0.001). Mean levels of LH (7.58 ± 6.37 vs 6.03 ± 4.46 , p - value .0001) and prolactin (19.2 ± 14.8 vs 16.0 ± 10.8 p - value 0.005) were significantly higher in women with primary infertility compared to those with secondary infertility respectively. No significant difference was observed in the mean level of FSH(p -value=0.629) (Table 5&6;Figure 1&2). Multivariate logistic regression analysis revealed women with secondary infertility were more likely to be hypertensive (OR=2.126,95%CI:1.020-4.474, p -value0.044). They were six times more likely using contraceptive (OR=5.876, 95% CI: 2.491-13.86, p -value .001) compared to primary infertile women, had hyperprolactenemia (OR=1.289,95%CI:0.960-1.996, p -value0.001) and have marital history of more than 16 years OR=12.166,95%CI:5.048-29.322, p -value0.001) (Figure 1&2).

Table 5: Biochemical infertility risk markers in primary and secondary Infertility

measurement	n= 508	primary infertility n = 309	secondary infertility n= 199	p- value
FSH IU/ml	6.2 ± 3.6	6.31 ± 3.81	6.15 ± 3.51	0.629
LH IU/ml	6.9 ± 5.7	7.58 ± 6.37	6.03 ± 4.46	0.001**
PRL ng/ml	17.9 ± 13.5	19.2 ± 14.8	16.0 ± 10.8	0.005*

Table 6: Correlation of FSH,LH and Prolactin with other risk factors for infertility

Characteristic	FSH (r)	p value	LH (r)	p- value	Prolactin (r)	p-value
Age	$r = 0.095$	<0.05*	$r = 0.16$	<0.001*	$r = -0.001$	>0.05
PCOS	$r = 0.162$	<0.001**	$r = 0.051$	>0.05	$r = 0.000$	>0.05
Menstrual Cycles	$r = 0.124$	<0.001**	$r = 0.094$	<0.05 *	$r = -0.027$	>0.05
Galactorrhea	$r = 0.04$	>0.05	$r = 0.11$	<0.05 *	$r = -0.01$	<0.05

Table 7: Correlation of infertility with other risk factors

Variables	r value	p value
Age	0.110	0.013*
Obesity	- 0.017	0.708
Hypertension	0.088	0.04*
Diabetes	0.069	0.123
Galactorrhea	- 0.058	0.192
Hirrusitism	0.043	0.335
Thyroid disorder	-0.093	0.360
PCOS	0.059	0.184
Contraception	0.230	<0.001**
FSH	-0.011	0.798
LH	0.104	0.019*
Prolactin	0.110	0.013*
T.B	-0.003	0.939
Surgical history	0.136	0.002*
Menstural Cycles	0.183	<0.001*
Menarche	-0.023	0.598
Marital history	0.340	<0.001**
Infertility duration	0.137	0.002*

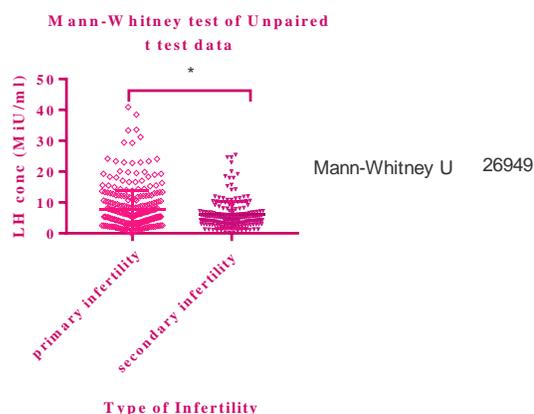


Figure 1:LH levels in primary and secondary infertile women.

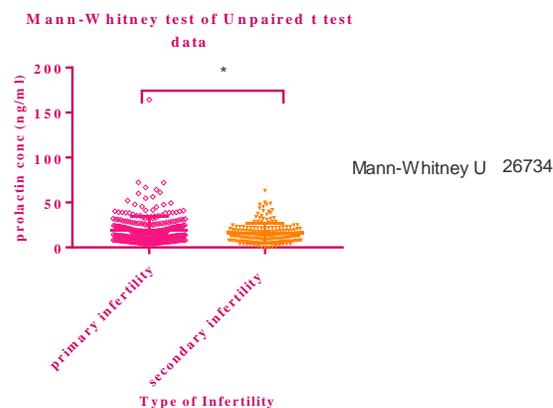


Figure 2:Prolactin levels in primary and secondary infertile women

Table 8:Multivariate logistic regression analysis

Risk factors	OR	95%CI		p-value
		Lower	Upper	
Age (16 years vs 45 years)	2.094	0.953	2.209	0.706
Obesity(overweight vs normal)	0.760	0.485	1.19	0.23
Hirusitism (yes vs no)	1.005	0.588	1.715	0.987
Galactorrhoea (yes vs no)	1.598	0.606	4.182	0.345
Thyroid (enlarged vs normal)	0.438	0.157	1.22	1.114
Infertility duration (1 year vs >16)	0.652	0.359	1.199	0.037*
Pcos (yes vs no)	0.862	0.475	1.566	0.627
Diabetes (yes vs no)	0.315	0.078	1.272	0.331
Contraception (yes vs no)	5.876	2.491	13.86	<0.0001**
FSH (1.5 vs 40 microU/ml)	0.993	0.936	1.055	0.827
LH (1.0 vs 41 microU/ml)	0.957	0.919	0.996	0.031*
PRL (2.5 vs 25.1 ng/ml)	1.289	0.96	1.996	0.001*
T.B (yes vs no)	1.461	0.536	3.988	0.485
B.P(hypertensive vs ormal)	2.126	1.02	4.474	0.044*
Surgical history(yes vs no)	1.191	0.733	1.936	0.481
Menstrual Cycle(regular vs irregular)	0.957	0.511	1.491	0.618
Menarche (≤ 13 vs ≥ 14)	0.967	0.62	1.478	0.844
Marital history (1 year vs >16 yr.)	12.16	5.048	29.32	<0.0001**

Discussion

In current study 60.4% of the females had primary infertility and 39.6% had secondary infertility. Our results are in line with others studies.^{17,18} To the contrary Sami et al observed higher prevalence of secondary infertility in Pakistan, and Mascarenhas et al (2011) observed higher prevalence of secondary infertility compared to secondary infertility in Asian countries.^{4,19} It is suggested that secondary infertile females may opt to seek consultation less frequently because they already had kids.

In present study most affected age group was 26-35 years. Similar findings were reported by Adamson et al where mean age of infertile women was found to be 25.9 years and Shumaila et al where most affected age group was 25-35 years.^{17,20} Our results are in contrast to a Canadian study where most affected age group was 35-44 years old.²¹ It can be ascribed to early marriages in Muslim countries. In women 35 years and above the risk of impaired fertility increases via secondary amenorrhoea,PCOs and endometriosis.²³

In present study a significant positive correlation was observed between FSH level and age, FSH level and PCOS in the infertile women. This is supported with similar study that indicated the significant increase levels of FSH with age, this results in disturbances in the ovarian functions which are directly correlated with infertility.²⁴ Hyperprolactinemia is a prevalent complication in reproductive dysfunction affecting about 1/3 of infertile women.^{25,26} It is suggested that hyperprolactinemia, at the ovarian level interferes with the action of the gonadotrophin and impairs gonadal steroid secretion, which in turn alters positive feedback effects at the hypothalamic and pituitary levels leading to lack of gonadotrophin cyclicity and infertility.²⁷ Prolactin may inhibit the follicular estradiol synthesis culminating in infertility.²⁸ A significantly higher levels of serum LH was found in primary infertile women compared to secondary infertile group. LH is responsible for ovulation and luteinisation and stimulate ovarian theca cells to produce androstenedione.²⁹

In current study women with secondary infertility were more likely to be hypertensive . Chronic hypertension is associated with poor ova quality. Pathological contributors to infertility like PCOs and endometriosis may foster hypertension through associated metabolic changes e.g obesity , insulin resistance, enhanced estrogen synthesis and hyperactive sympathetic nerve.^{30,31} Use of oral contraceptive alters the hormonal milieu along with causing a temporary rise in blood pressure.³² Most commonly used medications for treatment of female infertility such as estradiol, leuprolide letrozole are reported to induce hypertension with a prevalence rate of 3-7% , 8% and 5-8% respectively.³³⁻³⁷ An inverse relationship between fertility and use of contraceptives has been documented from many countries.^{38,,39,40,41,42}

Conclusion

Highest prevalence of infertility was seen in the age group of 26-35 years. Advanced age, hypertension, hyperprolactinemia, use of contraceptive and marital history of more than 16 years are significantly associated with female infertility

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