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Community Medicine

STUDY OF THYROID PROFILE AND PROLACTIN IN INFERTILE WOMEN: A CASE CONTROL STUDY.

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ABSTRACT

Background: In Indian societies womanhood is defined through motherhood and infertile women usually carry the blame for the couple's inability to conceive. In many cases, the childless woman is made to feel inferior and may be abused or even tortured by the family. In India estimated infertility to be in the range of 4-6 %. Among all causes of female infertility, ovulatory dysfunction due to endocrinal abnormalities like, thyroid dysfunction and hyperprolactinemia are most common and most reversible (treatable) cause.

Method: Hospital based study of thyroid dysfunction and prolactin level in infertile women a case control study. Hundred consecutive infertile women from Infertility clinic of OBGY department was enrolled and equal number of fertile women of reproductive age group, controls were taken from OBGY OPD.

Result: Thyroid dysfunction (OR = 4.85, 95% CI = 2.39 - 9.81, P = 0.0001), Hyperprolactinemia (OR = 4.25, 95% CI = 1.82 - 9.92, P = 0.0004), Menstrual abnormalities (OR = 4.13, 95% CI = 2.12 - 8.02, P = 0.0001) were significantly associated with infertility. Difference between mean TSH values and mean prolactin level in cases and controls were found to be highly significant (p=0.0001).

Conclusion: Thyroid dysfunction, hyperprolactinemia and menstrual abnormalities were significantly higher in infertile women as compared to the fertile women. There was weak positive correlation between hypothyroidism and hyperprolactinemia in infertile women. Routine screening of infertile women will facilitate early diagnosis and treatment of these two disorders which will certainly help in restoring fertility in these women.

KEYWORDS : Infertility, Thyroid profile, Prolactin, Menstrual abnormalities.

INTRODUCTION:

Infertility is inability of a couple to achieve conception after 1 year of regular intercourse without contraception.[1] Approximately 85–90% of healthy young couples conceive within 1 year, most within 6 months.[2,3] Infertility can be either primary, when the female has never conceived or secondary, when there has been a previous documented pregnancy; either a live birth or even a failed pregnancy e.g. miscarriage or ectopic pregnancy.[1] In many cultures, womanhood is defined through motherhood and infertile women usually carry the blame for the couple's inability to conceive. Even when the man is having some problem, in many cases, the childless woman is made to feel inferior and may be abused or even tortured by the family.[4] In general, one in ten couples experiences primary or secondary Infertility. Alleviation of infertility therefore becomes a necessity on many levels and it has been declared a public health issue by the World Health Organization (WHO).[5]

Worldwide prevalence of infertility is estimated to range between 8-12% of the couples of reproductive age group.[6] Systemic analysis of 177 health surveys from 1990 onwards among women 20–44 years of age in all parts of world found 1.9% prevalence of primary infertility and 10.5% prevalence of secondary infertility i.e. this analysis estimates global infertility prevalence of 12.4%.[7] Data on prevalence of infertility in India is scarce, 2001 census of India[8] estimates infertility to be in the range of 4-6 %.

Among all causes of female infertility, ovulatory dysfunction due to endocrinal abnormalities is the most common and most reversible (treatable) cause. Endocrinal (Hormonal) abnormalities include PCOS (Polycystic ovarian syndrome), thyroid dysfunction, hyperprol actinemia etc. These abnormalities disturb the H-P-O (Hypothalamus Pituitary Axis) axis which is required for maintenance of normal reproductive physiology that includes ovulation, menstrual cycle, preparation of endometrium for implantation and fertility. Among these endocrinal abnormalities, thyroid dysfunction and hyperprola ctinemia are the major, easy to diagnose and easily treatable causes. Thyroid dysfunctions are associated with a variety of changes in female reproductive functions including delayed onset of puberty, menstrual disorders, anovulatory cycles, infertility and recurrent abortions even if pregnancy is achieved.[9, 10] Prolactin is a peptide hormone secreted by anterior pituitary and is primarily associated with lactation as it stimulates mammary glands to produce milk. Dopamine has inhibitory while TRH (TSH Releasing Hormone) has stimulatory effect on prolactin secretion. Prolactin levels are physiologically high during pregnancy and lactation and therefore act as a natural contraceptive during this period. High prolactin levels suppress the ovulatory cycle by inhibiting secretion of FSH (Follicle Stimulating Hormone) and GnRH (Gonadotropin Releasing Hormone).

Hypothyroidism causes high TRH which stimulates excessive prolactin secretion leading to suppression of ovulation and therefore infertility.[11] Hyperprolactinemia is usually associated with menstrual and ovulatory disorders like amenorrhoea, oligomenorrhoea, anovulation, short or inadequate luteal phase and galactarrohea.[12]

Considering thyroid dysfunction and hyperprolactinemia are common, important and treatable causes of infertility, this study to investigate above abnormalities in infertile women with comparison group, and to find any association between hypothyroidism and hyperprolactinemia in these infertile women.

MATERIAL AND METHODS:

STUDY DESIGN AND SETTING

The present case control study has been carried out in Indira Gandhi Government Medical College, Nagpur. All consecutive cases of infertility were enrolled from Infertility Clinic of Obstetrics and Gynaecology (OBGY) department and controls from OBGY OPD. Data was collected during the period of February 2013 to November 2014.

SELECTION OF STUDY SUBJECTS

All cases of primary and secondary infertility of more than one year duration, and staying with husband and not using any contraceptives were selected. Exclusion criteria for cases with mechanical factor like tubal block, pelvic adhesion compromising tubal mobility. Cases with male factor infertility, diagnosed cases of thyroid dysfunction and

hyperprolactinemia and receiving treatment were also excluded. Fertile women of reproductive age group (20 -45 years) willing to participate and apparently normal were selected as controls randomly. Women who are pregnant, lactating or using hormonal contraceptives were excluded as control from study.

Sample size

For sample size calculation was carried out by using the study done by Binita G et al[13] where prevalence of hyperprolactinemia in infertile women 41% and prevalence of hyperprolactinemia in fertile women15%, α- error 5% and power (1-β) = 90%. The sample size required in each group was 95. However 100 cases and 100 controls were recruited for the study.

METHODOLOGY

Ethical clearance from the Institutional Ethics Committee was obtained prior to the study. Written permission from Department of Obstetrics and Gynaecology of study institute were obtained. All details of study were explained to subjects and informed written consent was obtained. Study subjects information collected using predesigned and pretested proforma. Clinical examination was done and recorded. Height was measured to the nearest of 0.5 cm with bare foot and weight was measured in using a platform scale to the nearest of 100 gm. The scales were standardized to zero before each use.

Serum TSH, T3, T4 and Prolactin were estimated and washing of the wells were done on Robonik Readwell Touch ELISA plate analyser and washer. TSH was estimated with manual ELISA one step non-competitive immunoenzmatic sandwich assay. Total T3 and T4 were estimated with manual ELISA two step competitive immunoenzmatic sandwich assay. Prolactin was estimated with manual ELISA one step non-competitive immunoenzymometric sandwich assay.

STATISTICALANALYSIS

Continuous variables (Age, TSH, T3, T4 and Prolactin level) were presented as Mean ± SD. Categorical variables (Type of infertility, Thyroid status, Prolactin status, and menstrual pattern) were expressed in actual number and percentages. TSH, T3, T4 and Prolactin levels were compared between cases and controls by performing Wilcoxon Rank sum test for non-normally distributed data. Odds ratio and 95% confidence interval were calculated. Categorical variables were compared by performing chi-square test. Spearman's correlation coefficient was calculated to determine direction and magnitude of correlation between TSH and prolactin level in study subjects. P-value less than 0.05 was considered as statistically significant, Statistical software STATA version 10.0 was used for statistical analysis.

RESULTS:

The present case control study was carried out to study thyroid dysfunction and hyperprolactinemia in infertile women. Hundred consecutive cases of infertility from Infertility Clinic of Obstetrics and Gynaecology OPD, who fulfil the eligibility criteria and 100 fertile, apparently normal women as controls within reproductive age (20-45 years), were randomly selected as study subject. All study subjects were investigated for thyroid profile and prolactin level.

Out of 100 infertile cases 78 were primary infertile women and 22 were secondary infertile women. Mean duration of infertility was 3.51 ± 2.48 years. Majority of cases (70%) having duration of infertility from 1 to 3 years, 17% from 4 to 6 years, 10% from 7 to 10 years and 3% were from 11years and above.

TABLE 1. Charastastics of study subjects.

Charastastics	Cases (n=100)	Controls (n=100)
Age (Years)		
≤ 25	59	22
26-30	31	59
31-35	09	18
≥ 36	01	01
BMI (KG/M^2)		
< 18.5 (Underweight)	07	05
≥ 18.5 – 24.99(Normal Weight)	72	79
≥ 25- 29.99 (Overweight)	19	14
≥ 30 (Obese)	02	02

Table 1 shows the characteristics of study subjects. The mean age for cases was 25.60 ± 3.5 years with the range of 21-39 years, while the mean age for controls was about 28.02 ± 2.99 years with the range of 23-36 years. The difference between mean age of cases and controls was found to be statistically significant ($p < 0.0001$). Similarly the mean age in cases with primary infertility was 24.82 ± 2.84 years with the range of 21-35 years, while in cases with secondary infertility it was 28.36 ± 4.24 years with the range of 22-39 years and this difference was also significant ($p < 0.0001$). Mean BMI in cases was 23.13 ± 2.93 kg/m2 as compared to 22.40 ± 2.62 kg/m^2 in controls. This difference in BMI of cases and control was not statistically significant ($p = 0.0599$).

TABLE 2. Relationship of study subjects with different parameter.

Parameter	Cases (n=100)	Controls (n=100)	OR (95% CI)	X^2 Value	P Value
Thyroid status					
Thyroid dysfunction	42	13	4.85 (2.39 - 9.81)	21.09	0.0001
Euthyroid	58	87			
Prolactin status					
Hyperprolactinemic	27	08	4.25 (1.82 - 9.92)	12.50	0.0004
Normoprolactinemic	73	92			
Menstrual pattern					
Menstrual abnormalities	44	16	4.13 (2.12 - 8.02)	18.67	0.0001
Normal Menstruation	56	84			

Table 2 shows the relationship of study subject with different parameters. Association of thyroid dysfunction, hyperprolactinemia and menstrual abnormalities are highly significant with infertility. Among the 44 menstrual abnormalities, 21 were Oligomenorrhoea, 7 were menorrhagia, 5 each were of hypo-menorrhoea, dysmenorrhoea and polymenorrhoea and one of secondary amenorrhoea.

TABLE 3. Patterns of thyroid profile and prolactin level in study subjects.

(Mean ±SD)	Cases (n=100)	Control(n=100)	P value
Thyroid parameter			
TSH (μIU/ml)	4.96 ± 5.75 (0.1 – 32.59)	2.56 ± 2.88 (0.18 - 17.5)	0.0001
T 3 (ng/ml)	1.26 ± 0.72 (0.32 - 6.84)	1.17 ± 0.34 (0.4 - 2.1)	0.7918
T 4 (μg/dl)	8.37 ± 3.95 (0.67 - 36.85)	9.08 ± 2.5 (2.27 - 14.6)	0.2096
Prolactin level			
Prolactin (ng/ml)	16.39 ± 10.38 (3.12 - 67)	10.59 ± 8.77 (3.48 - 73)	0.0001

Figures in parenthesis are range

Table 3 shows the pattern of thyroid parameters and prolactin level in study subjects. Difference between mean TSH values in cases and controls were found to be highly significant (p=0.0001). When mean T3 and T4 values were compared between cases and controls the difference was not statistically significant. Difference between mean prolactin level of cases and controls were found to be highly significant (p=0.0001).

TABLE 4. Correlation between TSH and Prolactin level in study subject.

Study subjects	Spearman correlation coefficient (rho)	p-value
Cases	0.2497	0.0122
Controls	0.0879	0.3842

Table 4 shows correlation between TSH and prolactin level in study subject. There was positive weak correlation between TSH level and prolactin level in cases with rho-value 0.2497 (p=0.0122) and in controls no correlation between TSH level and prolactin level with rho-value 0.0879 (p=0.3842).

DISCUSSION:

In present case control study of thyroid profile and prolactin level in infertile women, majority of the cases 59% were less than or equal to 25 year age followed by 31% in 26-30 age groups. This finding correlates with a study done by Sharma B et al[14] and Shabab W et al[15].

The mean age in cases with primary infertility was 24.82 years while in cases with secondary infertility it was 28.36 years. The lower mean age in primary infertility as compared to secondary infertility was also observed by Sharma P et al[16] (27.52 years versus 29.00 years). In the present study maximum 78% cases were of primary infertility (PI) whereas 22% cases were of secondary infertility (SI). The finding is in accordance with Sharma P et al[16] who observed 76% cases of PI and 24% of SI. Sharma B et al[14] got similar findings with PI in 80% and SI in 20%. Jungare S et al[17] also observed more patients with PI (58%) than of SI (42%).

In the present study thyroid dysfunction was observed in 42% of cases and 13% in control this difference were statistically highly significant (p = 0.0001). The 42% prevalence of thyroid dysfunction observed in the present study is consistent with similar findings observed by Raber et al[18] who observed thyroid dysfunction in 34% of infertile women. Rahman D et al[19] who observed thyroid dysfunction in 33.3% of cases. Nemade ST et al[20] found thyroid dysfunction in 48% cases. Sharma P et al[16] observed thyroid dysfunction in 38% of cases of infertility. In the present study, mean TSH value in cases and controls were 4.96 ± 5.75 µIU/ml and 2.56 ± 2.88 µIU/ml respectively and this difference was found to be statistically highly significant (p = 0.0001). In study done by Jungare S et al[17] mean TSH was significantly increased in infertile group (10.25±5.21µIU/ml) as compared to control (2.5±0.61µIU/ml). Similar pattern was noticed by Tirumalsetty S et al[21] where mean TSH of control group was 2.16±0.94 µIU/ml and 28±9.26 µIU/ml in cases. Turankar S et al[22] also observed similar findings with mean TSH levels in the infertile group (9.05±2.64 µIU/ml) higher compared to that of control group (2.41±1.03 µIU/ml).

Hyperprolactinemia is the most frequent abnormality of the anterior pituitary gland and is an extremely common disorder, especially among reproductive age group. Its prevalence is especially high in those women presenting with reproductive or menstrual dysfunction. In the present study, hyperprolactinemia 27% in cases and 8% in controls, were observed. This difference in prevalence of hyperprolactinemia between cases and controls was found to be highly significant (p = 0.0001). These findings are consistent with a study conducted by Kredentser JV et al[23] who found the incidence of hyperprolactinemia in a 19.5% infertile women. Pratibha D et al[24] observed hyperprolactinemia in 41% of the infertile women. Binita G et al[13] observed the prevalence of hyperprolactinemia in 41% of infertile women. In the present study, mean prolactin levels in cases (16.39 ± 10.38 ng/ml) and in control (10.59 ± 8.77 ng/ml). The difference between mean prolactin level in cases and controls was highly significant (p = 0.0001). Similar pattern was seen in study done by Tirumalsetty S et al[21] who observed mean prolactin in cases as 52.9 ng/ml and in controls as 12.58 ng/ml. Jungare S et al[17] in their study noted mean prolactin in cases as 67.90 ng/ml and in controls as 11.60 ng/ml. Similarly, a study done by Turankar S et al[22] also noted higher mean prolactin in cases (54.38 ng/ml) as compared to control group (18.14 ng/ml).

In this study it is observed weak positive correlation between TSH and prolactin in both cases as well as controls with rho value of 0.2497 and 0.0879 respectively. The positive correlation seen in present study is consistent with a study done by Binita Get al[13] who also reported a positive correlation between TSH and Prolactin levels in infertile women. Similarly Kumkum A et al[25] and Sharma N et al[26] observed a positive correlation between TSH and prolactin levels. While Sharma P et al[16] reported negative correlation between TSH and prolactin in infertile women and no correlation in fertile controls.

In the present study menstrual abnormalities was observed in 44% of cases and 16% in controls. This difference is highly significant (p = 0.0001). Similar findings were observed by Binita G et al[13] who detected menstrual abnormalities in 61.2% of infertile women and Kumkum A et al[25] who observed menstrual abnormalities in 57.6% of infertile women.

CONCLUSIONS:

Risk of infertility was found significantly higher in women with thyroid dysfunction, hyperprolactinemia and menstrual abnormalities. Weak, positive association was observed between hypothyroidism and hyperprolactinemia in infertile women. Oligomenorrhoea was the commonest type of menstrual abnormality associated with infertility in study subjects. As diagnostic tests are widely available for thyroid profile and prolactin level; they are non-invasive, less time consuming and relatively cost effective hence routine screening of infertile women will facilitate early diagnosis and treatment of these two disorders which will certainly help in restoring fertility in these women.

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Conflict of Interest:

NO

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