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RESEARCH ARTICLE

SUB CLINICAL HYPOTHYROIDISM: A POSSIBLE CAUSE OF PRIMARY INFERTILITY

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ABSTRACT

Background and Aim: Infertility is a common condition with a prevalence of 12-14%. It has important medical, economic and psychological implications. Thyroid hormones play an important role in menstural health and fertility. The aim of the study was to study serum gonadotrophins in hypothyroid females in reproductive age group and to find a correlation if any amongst the two and also study the prevalence of infertility in hypothyroid and subclinical hypothyroid patients.
Design and Methods: In this study Thyroid function tests (T_3, T_4, TSH) and serum Prolactin, FSH and LH was estimated in 150 individuals, out of which 75 females were having primary infertility and 75 females were normal.
Statistical analysis: Data collected is presented as mean± S.D. Pearson's coefficient of correlation was calculated to study the correlation between different parameters.
Results: The prevalence of sub clinical hypothyroidism was 81% with increased serum prolactin. A Significant positive correlation was found between TSH and LH and a negative correlation between TSH and FSH
Conclusions: Prevalence of sub clinical hypothyroidism is more than overt hypothyroidism in the infertile females enrolled in the present study. A small deviation from the normal levels of TSH should be taken into consideration and treated accordingly so as to prevent primary infertility.

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INTRODUCTION

Infertility is defined as the inability to conceive after one year of regular intercourse without contraception. Currently the estimated rate of infertility is between 12-14% (Padubidri and Daftary, 2002). Thus representing a common condition with important medical, economic and psychological implications. Proper evaluation of these disorders involves a multidimensional diagnostic approach. The thyroid hormones have profound effects on reproduction and pregnancy, ranging from abnormal sexual development to menstrual irregularities and infertility. Thyroid dysfunction is a condition known to reduce the likelihood of pregnancy and to adversely affect pregnancy outcome (Larsen and Daves, 2003; Larsen and Daves, 2003; Thomas and Ried, 1987). Patients suffering from hypothyroidism have various abnormalities ranging from menorrhagia, polymenorrhoea, oligomenorrhoea, anovulatory cycle and infertility. Hypothyroidism leads to increase levels of thyroid releasing hormone (TRH), which in turn stimulates secretion of TSH and PRL (prolactin) and PRL inhibits gonadotrophins i.e. FSH and LH. Numerous studies have also documented abnormal menstrual patterns in hypothyroidism (Veeres *et al*., 2015; Goswami *et al*., 2009). But it was found that very little work has been done about the relationship of thyroid dysfunction and serum Prolactin, FSH and LH. Hence the present study was conducted to study of serum gonadotrophins in hypothyroid females in reproductive age group and to find a correlation if any amongst the two and also study the prevalence of infertility in hypothyroid and subclinical hypothyroid patients.

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Study design

The study was conducted in the Department of Biochemistry in association with department of Obstetrics and Gynecology, GMC, Amritsar. A total of 150 individuals were recruited for the present study out of which 75 females belonging to the age range of 20 to 35 years diagnosed of primary infertility for at least one year with normal semen analysis of husband were recruited, with an equal number of age matched normal

females to serve as control. Written informed consent was obtained from all the participants.

Exclusion criteria

Cases of infertile women having tubular blockage, Pelvic inflammatory disease, Endometriosis, Genital TB, females with liver disorders, cardiac disease, with any history of thyroid disease or previous thyroid surgery or being on treatment with thyroid hormones and cases where abnormality was found in husband's semen analysis were excluded from the present study. Fasting, mid morning venous sample in follicular phase of menstrual cycle were collected under aseptic conditions. In vitro quantitative determination of hormones TSH (Bristow *et al*., 1982), T3 (Agharanya, 1990), T4 (Barker, 1948), Prolactin (Maddox *et al*., 1991), FSH (Odell *et al*., 1981) and LH (Kosasa, 1981) was carried out by using direct solid phase immunoassay based ERBA Thyrokit on ERBA Mannheim LISA Scan. Blood glucose was estimated by glucose oxidase method as described by Trinder (1969). Total Cholesterol was estimated by enzymatic method as described by Charles (1974) using kits from Biosystems (SA Costa Brava, 30-Barcelona Spain), HDL-C was estimated by method described by Burstein (1970) using kits from Transasia Biomedicals Ltd. Serum Triglycerides was estimated by Trinder's method described by Gowen (1983) using kits from Transasia Biomedicals. Serum LDL was determined by using Friedwald's and Fredrickson's formula (Friedwald and Levy, 1982) LDL=TC-(HDL+ VLDL). VLDL was estimated using VLDL= Triglycerides/5 based on the average ratio of TG to cholesterol in VLDL. Serum Uric Acid was estimated by Caraway's method (Caraway, 1955) using kits from Transasia Biomedicals. The data thus generated was analyzed using ANOVA (spss 19.0 inc. Chicago U.S.A computer software), student's 't' test was done to study the variance of mean between two groups. p value of 0.05 was taken as statistically significant.

RESULTS

The females included in the present study belonged to age group of >19-35 years with a mean age of 25 years whereas the mean age of control group was 26 years. The mean duration of infertility in the study group was 3.28 years and all these females were having primary infertility. Comparison of baseline parameters in fertile and infertile patients revealed a statistically significant increase in the levels of lipid profile and uric acid in infertile females (Table 1). Mean fasting plasma glucose levels indicated impaired fasting glucose in infertile females. Comparison of hormonal profile revealed a significant increase in the levels of TSH, Prolactin and FSH in infertile females as compared to normal females (Table 2). Based on the levels of TSH (according to Indian Thyroid Society) (Agarwa *et al*.; Donangelo and Brawnstein, 2011) all the infertile females were classified as normal, having sub clinical hypothyroidism and overt hypothyroidism (Table 3). It was observed that mean levels of TSH in normal females was 2.58±1.1 µIU/ml. In sub clinical hypothyroidism it was 6.24±1.71µIU/ml whereas in hypothyroid females it was 18.17±3.35µIU/ml. According to this classification it was observed that 61 (81.33%) females had sub clinical hypothyroidism and 12 (16.4%) had clinical hypothyroidism whereas only 2 (2.6%) females had normal levels of TSH. The incidence of hyperprolactinemia i.e. serum prolactin levels > 25 ng/mL was found both in subclinical and clinical hypothyroid women and the mean serum prolactin level in hyperprolactinemic women was 52.13±23.06 ng/mL and 55.05 ±38.41ng/mL in subclinical and clinical hypothyroid patients respectively. In both sub clinical and overt hypothyroid females a statistically significant positive correlation was found between increased levels of TSH and LH, whereas statistically significant negative correlation was found between increased levels of TSH and FSH.

Table 1. Comparison of baseline parameters of fertile and infertile females

Parameter	Infertile	Fertile	p value
Cholesterol mg%	203.24± 10.8	171.34± 9.7	<0.001
Triglycerides mg%	216.16±15.4	183.44±1 3.2	<0.001
HDL mg%	38.34±6.8	52.08±9.7	<0.001
LDL mg%	121.7±12.3	94.76±10.4	<0.001
VLDL mg%	43.2±5.6	36.6±6.8	<0.001
Glucose mg%	116.48±10.4	95.9±8.4	<0.001
Uric Acid mg%	7.2 ±2.3	5.4±2.0	<0.001

Table 2. Comparison of hormonal profile of normal and infertile females

Group	T_3 ±S.D ng/ml	T_4 ± S.D µg/dl	TSH± S.D µIU/ml	Prolactin± S.D ng/ml	LH± S.D mIU/ml	FSH± S.D mIU/ml
Normal females	0.96±0.24	12.1±3.96	2.58±1.11*	14.04±2.14*	5.16±2.11	3.85±1.31
Infertile females	0.87±0.39	10.6±2.70	8.17±2.92*	34.7±9.57*	5.46±2.26	9.53±4.5

* p<0.001 when normal and infertile females were compared amongst each other

Table 3. Fertility profile of infertile patients according to their TSH levels

S.No	TSH levels (µIU/ml)	No.	Prolactin (Mean ±S.D.)	FSH (Mean ±S.D.)	LH (Mean ±S.D.)
1.	Normal: (2.58±1.11)	2 (2.6%)	30.38±13.14	10.28±2.84	3.89±2.29
2.	Subclinical :(6.24±1.71)	61 (81.3%)	52.31±23.06	8.72±3.35	5.18±1.70
3.	Clinical : (18.17±)	12 (16.1%)	55.05±38.41	11.79±7.34	7.21±4.28

DISCUSSION

In the present study patients were selected from the age group of (19-35) years, which included more than 19 years but less than 35 years and maximum number of patients were belonged to the age group 24-30 years with a mean duration of infertility as 3.28 years as reported by previous studies (Shivaleela M Biradar *et al*., 2012). As reported in previous studies (Navreet Kaur *et al*., 2014) females with hypothyroidism especially sub clinical hypothyroidism is at more risk for insulin resistance and its related disorders. Uric acid an endogenous antioxidant (Mridula Mahajan and Sukhraj Kaur, 2009) was found to be significantly increased in individuals with infertility thus indicating predisposition of these females to oxidative stress thereby indicating that change in the levels of thyroid hormones leads to change in normal metabolic homeostasis of infertile females. The increased levels of TSH in infertile females indicated thyroid dysfunction which has been reported by various studies ranging from 23% to 33.3% (Rahman *et al*., 2008; Goswami *et al*., 2009; Sharma and Parmar, 2007) but in the present study it was found to be 61% indicating that fertility of female reproductive system is hampered by altered thyroid hormone levels. The prevalence of clinical hypothyroidism in the reproductive age group is reported to range from 2 % to 20 % by various studies (Bals Pratsch *et al*.,1997; Grassi *et al*., 2001), while in our study this prevalence is 16% on the contrary prevalence of subclinical hypothyroidism was highest amongst all the reported previous studies and it was 81%.

The impact of hypothyroidism on ovulation and menstrual function is related to numerous interactions of thyroid hormones with the hypothalamic pituitary ovarian axis, thus finally leading to Infertility. In hypothyroidism, increased TRH production leads to hyperprolactinaemia and altered GnRH pulsatile secretion. This leads to a delay in LH response leading to abnormal follicular development and ovulation. Thyroid hormone receptors are expressed in human oocytes and granulosa cells. At the cellular level, thyroid hormones synergize with the FSH-mediated LH / hCG receptor to exert direct stimulatory effects on granulosa cell function (Poppe and Velkeniers, 2004). Another pathway by which hypothyroidism may impact on fertility is by altering the peripheral metabolism of estrogen and by decreasing Sex Hormone Binding Globulin production. (Krassas, 2000) Both pathways may result in an abnormal feedback at the pituitary level. Disturbances in normal pulsatile release of LH and hyperprolactinaemia can result in menstrual dysfunction, ranging from anovulatory cycles with menorrhagia, oligomenorrhea or amenorrhea. In a study on Indian women, Joshi *et al*. (1993) found 68.2% of menstrual abnormalities in hypothyroid women compared with 12.2% of healthy controls. The mean serum prolactin level in hyperprolactinemia women was 76.53 ± 15.97 ng/ml (range 48.3 to 200 ng/ml). The incidence of hypothyroidism in hyperprolactinemia was 25.5% in a study by Avasthi Kumkum *et al.* 2005 whereas in present study, the incidence of hyperprolactinemia i.e. serum prolactin levels > 25 ng/ml was found both in subclinical and clinical hypothyroid women and the mean serum prolactin level in hyperprolactinemic women was 52.13±13.06 ng/ml and 55.05 ±18.41ng/ml in subclinical and clinical hypothyroid patients respectively. Increased levels of thyroid leads to hyperprolactinemia and it was also proved statistically ($p<0.01$). Our incidence of hyperprolactinemia is more, probably because the cases of tubal factor infertility were excluded. Our incidence of hypothyroidism in hyperprolactinemic women is 46.50% (69/150). So, a positive correlation of more than 1:2 was found between hypothyroidism and hyperprolactinemia as observed in previous studies ranging from 16.6% to 57% (Choudhary and Goswami, 1995; Singh *et al*., 1990). Thyroid dysfunction is a common cause of infertility which can be easily managed by correcting the appropriate dose of thyroid hormones. The decision to initiate thyroid correction therapy in subclinical thyroid dysfunction at early stage is justified in infertile women. The group of infertile women, if only carefully diagnosed and treated for sub clinical hypothyroidism, can benefit a lot rather than going for unnecessary battery of hormone assays and costly invasive procedures. For better management of infertility cases, we should plan further studies with the large sample size and investigate the beneficial effect of drug treatment by long-term follow-up, which are necessary to validate the variation in T3, T4 and TSH levels. In addition to thyroid profile other endocrine hormones like prolactin should be considered in infertility.

Conclusion

Our study reveals that subclinical thyroid dysfunction (81.3%) is more prevalent than overt thyroid dysfunction (16.1%) in infertile women. Sub clinical Hypothyroidism seems to be dominant thyroid dysfunction in infertile women. A small deviation from the normal levels of TSH should be taken into consideration and should be treated accordingly so as to prevent primary infertility.

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