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THYROID DISORDERS;

PREVALENCE OF THYROID DISORDERS IN PRIMARY INFERTILE WOMEN OF REPRODUCTIVE AGE.

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ABSTRACT: Infertility has been considered as a worldwide global health issue. It is a human nature that every couple wants to have children so that the relationship can become stronger. Defect in thyroid hormone levels is one of the factors which can lead to reproductive cycle disorders and thus infertility results. **Objectives:** The purpose of current study was to investigate the levels of thyroid hormones in primary infertile and fertile females in order to evaluate the prevalence of thyroid disordsers. **Study Design:** Case control study. **Place of Study:** Outdoor of gynecology department of Madinah Teaching Hospital, Faisalabad. **Duration of Study:** 6 months from July to December 2017. **Material and Methods:** The study enrolled total 91 females of reproductive age 20-35 years which included 45 primary infertile females and 46 fertile females. They were divided into two groups. Group I: case/primary infertile women group (n= 45) and Group II: control /fertile females group (n= 46). Data was collected by taking history and clinical examination. Hormonal profile including fT_3, fT_4 and TSH was done by means of chemiluminescent immunoassay. Results were analyzed by using SPSS version 20. **Results:** Most of the infertile females were euthyroid and hyperthyroidism was the most common thyroid disorder. The prevalence of hypothyroidism and hyperthyroidism was about 9.3% and 26.7% respectively. The p-value showed the non-significant difference in the levels of fT_3, fT_4 and TSH between primary infertile and fertile females. Significant positive correlation between fT_3 and fT_4 while non-significant negative correlation was observed between fT_3 & TSH and fT_4 & TSH in primary infertile females. **Conclusion:** Infertile females with menstrual irregularities should be advised thyroid profile in order to avoid other unnecessary investigations. Evaluation of thyroid status in the infertile couple is not only important but also easy because its treatment is very simple and often has revocable effects on subfertility.

Key words: fT_3 = Free triiodothyronine, fT_4 = Free Thyroxine, TSH= Thyroid Stimulating Hormone, Primary Infertility.

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INTRODUCTION

To be a mother is a natural feeling and motherhood is a desire which is associated with the lives of all mothers.[1] Over last 30 years, infertility has become a problem but it should not be considered as a disease because the couples are healthy generally.[2] Infertility has been ranked as the fifth global disability in females.[3] It is anticipated that globally 60-80 million couples face the problem to conceive every year.[4] The prevalence of infertility in Pakistan has been estimated which is about 21.9%.[5]

WHO (World Health Organization) has defined subfertility clinically as "Inability of a couple to achieve a pregnancy after 12 months (under 35 year of age) or within 6 months (above 35 year of age) of regular unprotected sexual intercourse".[6,7]

Infertility is of two types: If a female is unable to conceive in spite of regular cohabitation then it is termed as primary infertility while secondary infertility is because of any factor in which if a female has conceived at least once but unable to pregnant again.[8] Several studies have confirmed that primary infertility is more prevalent globally.[9,10]

WHO has reported that 35% cases of infertility are due to female factors, 30% due to male factor and in 20% cases both are involved while 15%

cases are idiopathic in nature.[8,11,12,13] Also in Pakistan, about 41% cases have been reported due to female factors.[14] The most common cause of infertility in females is ovulatory dysfunction (25-53%) which usually occurs due to defect in hypothalamic-pituitary-ovarian axis[13], tubal damage (22-26%), fibroids and endometriosis accounts also for 15% cases while 11% cases are unknown in origin.[15] The simplest way to evaluate infertility is hormonal analysis[16] and thyroid ailment is one of the commonest endocrine disorders.[17]

Thyroid hormone is synthesized in thyroid gland[18] and is released in response to TSH, a glycoprotein hormone synthesized in anterior pituitary gland. TSH estimation has been recommended as the most sensitive test in order to differentiate subclinical hyperthyroidism and hypothyroidism from clinical hyperthyroidism and hypothyroidism respectively.[19] Also in females, TSH level increases after 45 years.[20] Thyroid hormone not only regulates carbohydrates, fats & protein metabolism[21] but also controls metabolic rate, thermogenesis and growth.[22] It plays a key role in body weight maintenance[23] and necessary for normal reproductive cycle and pregnancy also.[22,23]

In females, ovarian cycle is regulated by the synchronized actions of thyroid hormones, luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin on hypothalamic-pituitary-ovarian axis.[24] It has been discovered that the receptors of thyroid hormones are present on human granulosa cells and oocytes. The release of progesterone from granulosa cells takes place only when thyroid hormone acts along with FSH, LH and Hcg.[8,25] It has been evaluated by several studies that thyroid hormone controls reproductive cycle by two ways: either it affects ovaries directly or may acts indirectly with the help of sex hormone binding globulin.[26,27]

Infertility is considered as a multifactorial problem and has been deliberated as a worldwide public health issue. Deprivation of fertility may lead to psychological trauma, insecurity, social stigmatization and depression. Thyroid disorder is one of the main contributor of infertility as it can interfere with various aspects of reproductive cycle in males and females both. For thyroid hormone synthesis, iodine is required and it should be a part of diet. Endemic goiter is more common in those countries (e.g. in Pakistan) where iodine is deficient in diet. The people visiting to Madinah Teaching Hospital (MTH) Faisalabad belong to poor socioeconomic status and are generally unaware of many hazards about their life styles like smoking, alcohol use and dietary habits also. The current study was done to investigate the levels of thyroid hormones in primary infertile and fertile females at Madinah Teaching Hospital (MTH) Faisalabad and the prevalence of hypothyroidism and hyperthyroidism in primary infertile women was also ruled out.

MATERIALS AND METHODS

The approval of study was obtained from the ethical review board of The University of Faisalabad.

Setting

The study was conducted in outdoor of gynecology department of MTH (Madinah Teaching Hospital) Faisalabad in collaboration with MTH laboratory.

Study Design and Sample Size

This was a case control study and performed on 91 females of reproductive age 20-35 years. They were divided into two groups which were Group I as primary infertile females or case group (n=45) and Group II as fertile females of similar age group or control group (n=46). All participants were well informed about the purpose of study and gave written informed consents.

Inclusion and Exclusion Criteria

The duration of marriage was more than one year. Male factor was ruled out at first. Performa was prepared to obtain their medical history. On the basis of their information, females who suffered from any chronic diseases like tuberculosis, endometriosis, renal failure, hypertension, diabetes mellitus, and any liver or cardiac diseases as well as those having any history of congenital disorders (especially urogenital tract) or any tubal factor were excluded from the study. History of goiter and any previous history of

thyroid surgery accompanied by intake of drugs like L-thyroxine were also considered. Medical history including lifestyle of both partners, marital history, menstrual history, contraceptive history, lactational amenorrhea and history of previous deliveries was taken. Questions about acne, hirsuitism and any thyroid problems were also inquired. Clinical examination including general physical examination, thyroid examination and pelvic examination was done.

INVESTIGATIONS

Husband semen analysis was recommended as a definite test to evaluate any male pathology. Transvaginal ultrasonography of pelvis (TVS) was done to find out any endometrium, myometrium and ovarian pathology. The condition of adnexa was also assessed. Hormonal profile includes estimation of fT_3, fT_4 & TSH and was advised to all participants.

METHODOLOGY

After taking all aseptic measures, about 3-5 ml of venous blood sample was withdrawn from cubital vein of all individuals with the help of disposable syringes. The blood was collected in clot vial tubes without adding any anticoagulant and was properly labeled. Blood samples were allowed to clot at room temperature for 30 minutes and centrifugation was done at 5000 rpm for 10 minutes at Rotina 380 centrifuge machine in order to obtain clear, transparent serum. Quantitative estimation of TSH, fT_4 and fT_3 levels was done by using chemiluminescent Microparticle Immunoassay (CMIA) technology (Abbott / Abbott Laboratories ARCHITECT i1000SR) accompanying a flexible assay known as Chemiflex.[7,28] The commercial kits used in the laboratory of Madinah Teaching Hospital were 7K63 ARCHITECT for fT_3, 7K65 ARCHITECT for fT_4 and 7K62 ARCHITECT for TSH estimation. The reference values used in the study were 0.35 - 4.94 µ IU/mL for TSH, 0.70 - 1.48 ng/dL for fT_4 and 1.71 - 3.71 pg/mL for fT_3.

According to these levels, patients were categorized into three groups: Euthyroid, Hyperthyroid and Hypothyroid. All euthyroid females were having normal levels of fT_3, fT_4 and TSH. The cut off level of TSH for hyperthyroidism was 0.35 µ IU/mL and 4.94 µ IU/mL for hypothyroidism. They were further subdivided into clinical and subclinical groups on the basis of TSH level.[2,23]

Statistical analysis was done by using SPSS version 20.0. Descriptive statistics was used to describe the nature of data and expressed as mean ± SD values while categorical variables were expressed as number (percentage). One way ANOVA test (Analysis of variance) was applied to compare the study groups. Results were considered to be statistically significant if probability (p) value was < 0.05.

RESULTS

The mean values & standard deviation of age, fT_3, fT_4 and serum TSH were calculated in both groups and then compared with each other. This data is presented in Table-II. It was observed that TSH level was raised in primary infertile females in comparison to females of control group. Also the levels of fT_3 and fT_4 were much higher in Group I in comparison to Group II, however these differences were statistically non-significant. Mutual correlation between fT_3, fT_4 and TSH were also obtained and presented in Table-III. Subjects in both groups were categorized in relation to their thyroid status according to the mean levels of fT_3, fT_4 and TSH as shown in Table-IV. Although the levels of fT_3, fT_4 and TSH were within normal range in most of the infertile subjects but extensive variation was observed among them.

Hormones	Hyperthyroidism		Hypothyroidism	
	Subclinical	Clinical	Subclinical	Clinical
fT_3	1.71-3.71 pg/mL	> 3.71 pg/mL	1.71-3.71 pg/mL	< 1.71 pg/mL
fT_4	0.70-1.48 ng/dL	> 1.48 ng/dL	0.70-1.48 ng/dL	< 0.70 ng/dL
TSH	<0.35 µ IU/mL	<0.35 µ IU/mL	>4.94 µ IU/mL	> 4 .94 µ IU/Ml

Table-I. Levels of thyroid hormones according to thyroid disorders

Groups	Age	fT_3	fT_4	TSH
Primary Infertile Group (n=45)	27 ± 3.82	4.26 ± 7.1	3.04 ± 9.96	7.30 ± 3.73
Fertile Group (n=46)	30 ± 4.83	2.41 ± 0.35	0.92 ± 0.09	1.58 ± 1.6
*p-Value	___	0.082	0.152	0.106

Table-II. Mean values of parametres in groups ($\bar{x} \pm S\bar{x}$)
***p-value was calculated by ANOVA.**
Differences are highlighted by using * symbol.

Parameters	Age	*fT_3	fT_4
fT_3	r = 0.393 p = 0.07	—	—
*fT_4	r = 0.223 p = 0.140	r = 0.684 *p = 0.000	—
TSH	r =0.077 p = 0.631	r = - 0.118 p = 0.442	r = - 0.079 p = 0.605

Table-III. Mutual Correlation of fT_3, fT_4 and TSH in primary infertile women (n=45)

Param-eters	Hypothyroid		Hyperthyroid		Euthyroid	
	Primary	Control	Primary	Control	Primary	Control
fT_3	1.68 ± 0.51	2.83 ± 0.15	9.60 ± 12.54	2.45 ± 0.21	2.42 ± 0.45	2.36 ± 0.35
fT_4	0.56 ± 0.18	1.0 ± 0.09	8.78 ± 18.65	0.87 ± 0.07	1.02 ± 0.14	0.89 ± 0.17
TSH	57.36 ± 51.6	5.95 ± 0.46	0.047 ± 0.088	0.21 ± 0.06	1.47 ± 0.78	1.26 ± 0.85

Table-IV. Descriptive statistics of fT_3, fT_4 and TSH in primary infertile and fertile females according to thyroid disorders

The mean age of reproductive age females between 20-35 years was found as 27 ± 3.82 years in Group I and 30 ± 4.83 years in Group II. Mean age of primary infertile females was lower than fertile females although it was statistically insignificant.

Thirty (67%) females of the Group I and 13 (29%) females of Group II were presented with menstrual disorders. Thus it was clear that menstrual problems were more common in primary infertile females.

The mean level of TSH was raised in primary infertile women in comparison to females in control group, which was non-significant statistically. Also the p-value showed the statistically insignificant results of raised fT_3, fT_4 between primary infertile and control groups.

In primary infertile females, there was a non-significant negative correlation between TSH and fT_4 (p=0.605, r = -0.079) and also between fT_3 and TSH (p=0.442, r = -0.118) while a positive correlation (significant) was seen between fT_4 and fT_3 (p=0.000, r = 0.684) in the correlation analysis. Non-significant positive correlation was also detected between fT_3 and age (r = 0.393, p = 0.07), fT_4 and age (r = 0.223, p = 0.140) and TSH and age (r = 0.077, p= 0.631).

About 62.2% primary infertile females were euthyroid as compared to 82.6% females in control group. While the most common thyroid dysfunction in primary infertile females was clinical hyperthyroidism (n=9, 20%), followed by clinical hypothyroidism (n=4, 09%), then subclinical hyperthyroidism (n=3, 07%) and subclinical hypothyroidism (n=1, 02%). In contrast, about 8.7% females were diagnosed as subclinical hypothyroid and subclinical hyperthyroid both and no case of overt hypothyroidism and overt hyperthyroidism was reported in control group. In hypothyroid primary infertile women, raised TSH level along with low levels of fT_3 and fT_4 was observed. On the other hand, decrease TSH level accompanied by elevated fT_3 and fT_4 levels were found in hyperthyroid primary infertile women. Conversely the mean levels of fT_3 and fT_4 in euthyroid primary infertile women were approximately same as control group but the mean TSH level was found to be slightly higher in them.

DISCUSSION

WHO estimated that about 8-12% couples face difficulties in conception or they may not sustain a pregnancy up to term. Also the rate of divorce and remarriages are high in our population because of infertility. A number of studies have reported the significant effects of thyroid hormones on the reproductive cycle of females such as menstrual cycle irregularities, reproductive cycle disorders and infertility.[15]

Majority of females in both groups were labeled as euthyroid as they exhibited normal thyroid hormones levels.

A number of studies have confirmed that infertility may be correlated with other disorders like PID, endometriosis and anovulation etc.[15] In current study, the mean age of primary infertile females was found to be less than control group and it was also below 30 years. So this may lead to an idea that some other factors except advanced age may lead to infertility.[15] Also the incidence of infertility in higher age group (26-30 years) could be due to late marriages.[29] Most of the primary infertile females (37.8%) were belong to age group 26-28 years while 22.2% in age group between 23-25 years and 13.3% were seen in age groups of 20-22 years, 29-31years and also in 32-34 years old females. The mean age of primary infertile females were 27 ± 3.82 in current study. This was in accordance with other studies like Agrawal et al[11] and Valvekar et al[30] who reported it as 27.16 ± 3.76 and 27.80 ± 3.8 respectively.

In this study, non-significant results of TSH, fT_4 and fT_3 were exhibited between the groups which may be because of the fact that majority of the participants exhibited the normal thyroid functions (i.e euthyroid state). Similar to our findings statistically non-significant results regarding thyroid dysfunction were also observed among fertile and infertile females[7,31] while statistically significant results of raised T_3, T_4[32] and raised TSH level[4,21] were reported in primary infertile groups. In accordance to current study, statistically non-significance difference in terms of TSH between primary infertile and fertile groups was also compatible with the findings of Shalev et al. and Buyru et al. as cited by Sahin A and Onder F.[15]

Significant positive correlation was observed between fT_3 and fT_4 ($p=0.002$, $r = 0.330$)[15] which was also similar to present findings in primary infertile females ($p=0.000$, $r = 0.684$). Along with it, a negative correlation was observed between fT_4 and TSH in the same study[15] which was also according to current study. From the above findings it is clear to us that TSH is inversely correlated with T_4 and T_3 while T_3 and T_4 are positively correlated with each other. This indicates that T_4 when changed into T_3 inside pituitary cells has a negative feedback effect in TSH release.[8] Non-significant positive correlation was observed between TSH and age ($r = 0.077$, $p = 0.631$) which was supported from previous studies that the level of TSH increases with the progress of age.[20] Raised TSH level in higher age groups may be due to the increase levels of TPO-Ab (Thyroid peroxidase antibodies) titer among infertile women.[31]

The release of thyroid hormone is under the control of TSH. In hypothyroidism low levels of fT_3 and fT_4 has a positive feedback effect on pituitary gland to enhance the release of TSH. Low fT_3 and fT_4 along with raised TSH levels[2,24] in hypothyroid infertile women was reported in hypothyroid infertile women.[13,21,28] which was similar to present findings. In contrast, high levels of fT_3 and fT_4 control the release of TSH by a negative feedback mechanism. Low TSH level accompanied by higher mean levels of fT_3 and fT_4 was observed in hyperthyroid primary infertile women[13,21] and this was also compatible to our findings. However the mean levels of fT_3 and fT_4 in euthyroid primary infertile women were approximately same as control group. But mean TSH level was found to be slightly higher in them. This may be attributed to some other factors like illness or because of any drug intake etc. Conversely, TSH level was observed within normal range in euthyroid infertile women.[13]

In Pakistan, Elahi et al[31] found that thyroid disorders between fertile and infertile women were statistically non-significant. In current study almost 64% primary infertile females as compared

to 82% fertile females were euthyroid which showed that infertility may be because of some other factors except thyroid disorders. Many other studies also reported the higher prevalence of euthyroidism in infertile women like 74% by Khatiwada et al[27], 73% by Pushpagiri et al[22] and Nath et al[7] both and 66% cases according to Rahman et al.[4]

The prevalence of thyroid dysfunction in a community has been estimated to be about 10-15%. In present study thyroid disorder was common in about 36.04 % infertile females. Other studies also estimated thyroid dysfunction in infertile females as 44% cases by Ajmani and Sarbhai et al[26], 40% by Habbul and Shaikh[2] and 33.3% according to Rahman et al.[4]

The present study depicted that hyperthyroidism is more prevalent in infertile women which may be attributed to those patients who were referred by some specific areas. This was in accordance with the results of Nemade et al[32] and Biradar SM et al.[33] Conversely, hypothyroidism was more prevalent than hyperthyroidism in infertile group according to Habbul and Shaikh[2], Shende et al[13], Ajmani and Sarbhai et al[26], Valvekar et al[30] and Elahi et al[31] which was not similar to this study.

CONCLUSION

Although thyroid disorders have been considered as one of the risk factor of infertility but current study shows that thyroid disorder is not much prevalent among infertile group. Except for some differences, statistically non-significant differences in fT_3, fT_4 and TSH was found between groups in this study. This lead to an idea that although thyroid hormones have a significant role in female reproductive cycle but along with thyroid problem, some other physical or hormonal disorders should be considered as many euthyroid females were presented with menstrual irregularities. Also the level of thyroid peroxidase antibodies (anti-TPO) increases with age which may cause hypothyroidism so anti-TPO level should be a part of screening of thyroid profile among infertile females.

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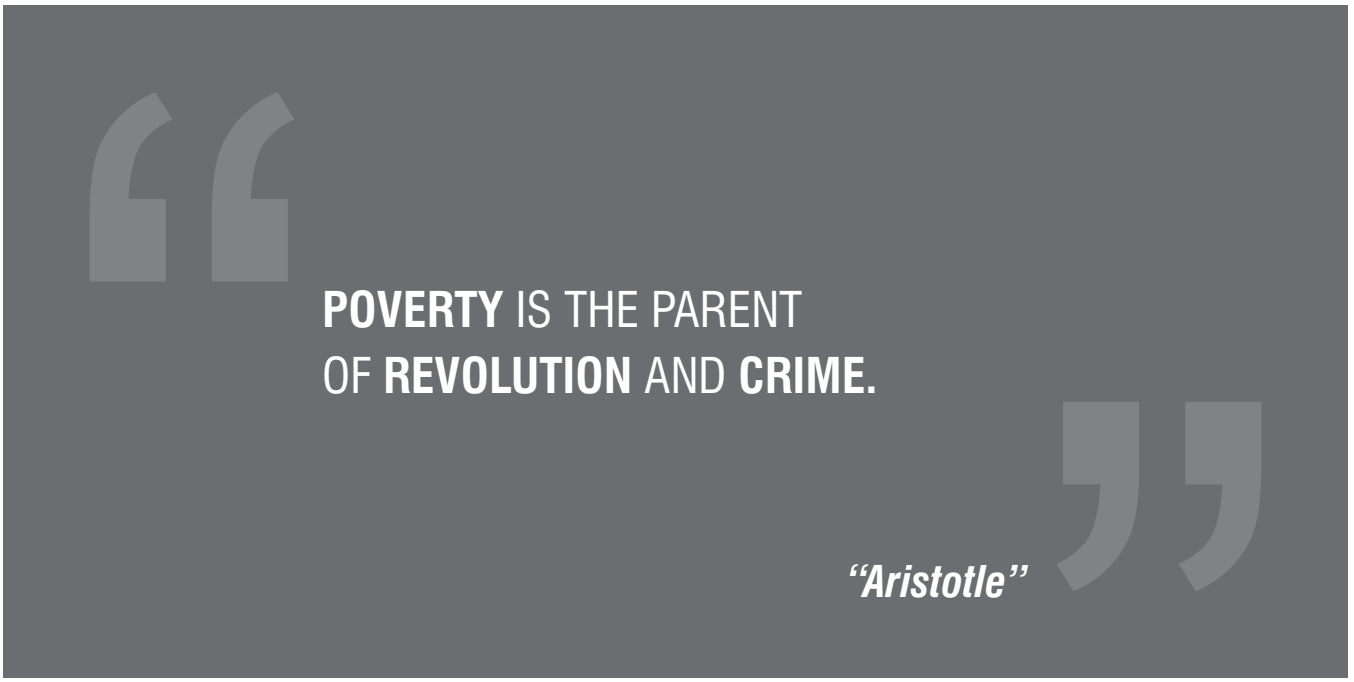

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Rahat Rahman	Performed experimental & research work.	
2	Muhammad Saeed	Conceived the idea & supervised the research.	
3	Sadaf Zia	Proof reading & correction of manuscript.	
4	Fauzia Jan	Assisted in experimentation & data collection.	
5	Sara Muzaffar	Proof reading & formatting.	
6	Anam Waheed	Literature review & Proof reading.	