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## DETERMINATION OF THE FREQUENCY OF THYROID DYSFUNCTION IN PRIMARY INFERTILE WOMEN WITH MENSTRUAL IRREGULARITIES

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**Abstract:**

**Background:** Thyroid disease is the second most common endocrine condition in women of childbearing age and common endocrine disorders worldwide with females having infertility. The prevalence of infertility in Pakistan is 21.9% where, primary infertility is 3.9%, while prevalence of thyroid disorders in infertile women is variable globally.

**Study Design:** Cross sectional study. Setting: Department of Gynae & OBS: Unit-II, Shaikh Zayed Women Hospital Larkana. Duration: From 30th OCTOBER 2018 to 29th APRIL 2019.

**Material and Methods:** Total 67 Primary infertile patients of age between 15- 35 years were included. A 3ml blood was sent laboratory for serum TSH, Free T3, Free T4 level. Patient with the following values above or below were considered as abnormal thyroid function i.e., TSH 0.35-5.50mIU/L, Free T3 0.9-2.8pmol/L, Free T4 10.5-20pmol/L.

**Results:** There was total 67 primary infertile patients aged between 15 to 35 years were included. Mean age was 26.88±3.898 years. Around 32 (47.8%) have BMI of >27 while 35 (52.2%) patients were having BMI of <27. No significant association found between smoking and thyroid dysfunction. 37 (55.20%) of total have thyroid dysfunction. Hypothyroidism with Menorrhagia was common i.e., 8 (11.8%). Obesity and menstrual irregularities have significant association with thyroid dysfunction with the (p=0.001 and p=0.011) respectively. While no significant (i.e., p=0.556 and 0.508) association with age and smoking was observed.

**Conclusion:** Our study showed, patients have complained of primary infertility with menorrhagia have high percentage of hypothyroidism, while patients had a history of infertility with amenorrhea had hyperthyroidism in common.

**Keywords:** Thyroid hormone, hypothyroidism, menstrual irregularities

## INTRODUCTION

Thyroid disease is the second most common endocrine condition in women of childbearing age and commonest endocrine disorders worldwide with females having higher dysfunction rate than male (1-3). It is estimated that approximately 8-12% of all pregnancy losses are the result of endocrine factors. At least 2-3% of women have some form of thyroid dysfunction during pregnancy (1). Thyroid hormones are involved in control of menstrual cycle and in achieving fertility affecting the actions of follicle stimulating hormone and luteinizing hormone on steroid biosynthesis by specific triiodothyronine sites on oocytes, sperm and embryo during fertilization, implantation and placentation (1-5) therefore affect, numerous aspects of reproduction and pregnancy and an association of thyroid dysfunction with menstrual disturbance, anovulatory cycles, decreased fecundity and increased morbidity during pregnancy has been observed (2, 3). Subclinical forms of disease are very frequent but not easily recognized without specific screening programs. If left untreated, these conditions may affect mother and fetus (2, 3). A study conducted in Nepal over 233 females and thyroid dysfunction was seen in 25.8% (n=60) women. Most common thyroid dysfunction was subclinical hypothyroidism (14.2%, n=33) followed by subclinical hyperthyroidism (6.9%, n=16), overt hyperthyroidism (3%, n=7) and overt hypothyroidism (1.7%, n=4) (2).

Infertility is defined as the failure to conceive after one year of regular intercourse in women < 35 years not using contraception and after six months in women > 35 years. Epidemiological data suggest that



about 10% to 15% of all couples will experience difficulties to conceive (primary infertility) or to conceive the number of children they wanted (secondary infertility) (6). Infertility is a global phenomenon that affects between 60 million and 168 million people worldwide. The majority suffers those who live in the developing world. WHO-DHS Comparative Report in 2004 states that more than 186 million ever-married women in developing countries (excluding China) were infertile because of primary or secondary infertility. This number represents more than one in four ever-married women of reproductive age in these countries. Knowledge about infertility is inadequate in many parts of the world. A global survey of almost 17,500 women (mostly of childbearing age) from 10 countries revealed that knowledge regarding fertility and biology of reproduction was poor. Many women have little awareness of the period of the month in which they are most fertile and when to seek treatment. In addition to the low level of knowledge, there are several misconceptions regarding infertility all over the world (4).

The prevalence of infertility in Pakistan is 21.9% where, primary infertility is 3.9% and secondary infertility is 18.0% (4). The prevalence of thyroid disorders in infertile women is variable globally. Failure to ovulate regularly in women of the reproductive age group may occur owing to have hypothyroidism. Hyperthyroidism ranges from 2.1% to 5.8% and hypothyroidism ranges from 2.3% to 6% in different studies in infertile women (7,8). A study in tertiary-care hospital in northeast India, conducted over 53 diagnosed female subjects of primary infertility who were sent to the Department of Biochemistry for hormonal investigation. Of 53 infertile patients, 24% (13) were found to present hypothyroidism and only 3% (2) hyperthyroid (7). A local study done at Peshawar Medical College, Pakistan total 168 subjects comprising of 106 primary and 62 secondary infertile women were evaluated. Out of 168 infertile patients 134(79.76%) had euthyroid, 31(18.45%) hyperthyroid and only 3(1.78%) patients had hypothyroid profile. Irregular menstrual cycles were found in 10 out of 31 (32.25%) hyperthyroid, 2 out of 3 (66.66%) hypothyroid and 21 out of 134 (15.67%) euthyroid infertile women (9). Feldthusen AD *et al.* study over, total 758 (6.7%) had mild (subclinical) hypothyroidism, 9.4% prevalent hypothyroidism, and 4.2% prevalent hyperthyroidism (10).

## MATERIAL AND METHODS

### STUDY DESIGN

This cross-sectional study was conducted at the Department of Gynecology & Obstetrics, Unit-II, Shaikh Zayed Women Hospital Larkana, Pakistan between the period of 30th October, 2018 to 29th April, 2019.

### SAMPLE SIZE

Sample size was calculated by using software package WHO for determination of sample size. The frequency of Thyroid dysfunction in primary infertile women with menstrual irregularities was 9.4%. 1067 patients was required to achieve 95% of confidence interval and 7% margin of error.

### SAMPLING TECHNIQUE

Non - Probability consecutive sampling was used for this study as sampling technique.

### INCLUSION CRITERIA AND EXCLUSION CRITERIA

Female patients having age between 15 to 35 years with history of primary infertility and menstrual irregularity were included in the study. While patients having previous history of thyroid dysfunction, goiter, cervical irradiation or thyroid surgery, family history of thyroid disease, presence of clinical signs or symptoms of thyroid dysfunction except menstrual irregularity, pelvic inflammatory disease, tubal occlusion, endometriosis, uterine abnormality, or polycystic ovarian syndrome, diagnosis of type 1 diabetes mellitus or any other autoimmune disease, history of repeated abortions, prematurity, or secondary infertility, treatment with lithium, anti-thyroid, amiodarone or recent administration of iodinated contrast, living in an area with moderate to severe deficiency of iodine, major medical disorders, including conditions with indication for anticoagulation therapy were excluded from the study.

### DATA COLLECTION PROCEDURE



The study was conducted at Department of Gynecology and Obstetrics, Unit-II, after approval by ethical review committee of the Shaikh Zayed Women Hospital Larkana. Informed written consent was obtained from the patients; the cases fulfilled the inclusion criteria were included in the study. Then their TSH, T3 and/or T4 were done from diagnostic laboratory of LINAR Hospital Larkana and the results were collected on reporting date and put onto the worksheet.

## DATA ANALYSIS PROCEDURE

Data was analyzed on computer using SPSS software version 20.0. Description statistics like frequency and percentage was measured for age, obesity (BMI >27), smoking, menstrual cycle, oligomenorrhea, amenorrhea, polymenorrhea, menorrhagia, thyroid dysfunction, hyperthyroidism, hypothyroidism, subclinical-hypothyroid, subclinical-hyperthyroid and sick-euthyroid. Mean  $\pm$  SD (standard deviation) were calculated for age, duration of primary infertility. Effect modifiers were specified like age, obesity (BMI >27), smoking, oligomenorrhea, amenorrhea, polymenorrhea, menorrhagia to see the effect of these on outcome variable post stratification applying chi-square test with  $p$  value <0.05 as significant.

## RESULTS

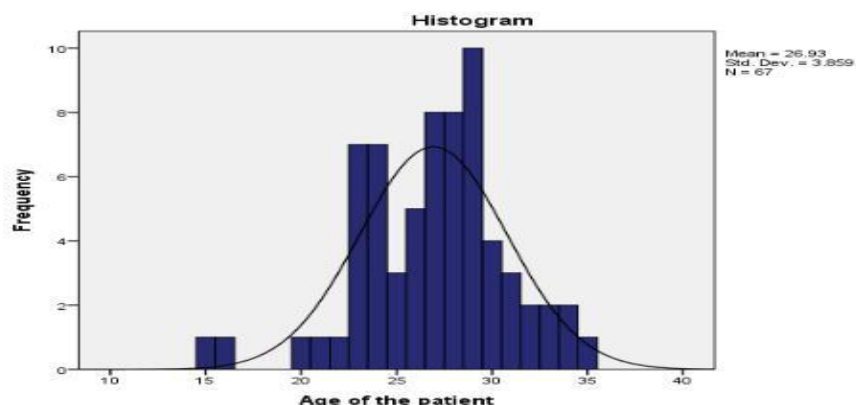
Total 67 patients aged between 15 to 35 years who fulfilled the inclusion criteria and were enrolled in the study. Frequency of thyroid dysfunction in patients have primary infertility with menstrual irregularities was observed along with effect modifiers. Statistical package for social sciences (SPSS 20) was used for data compilation and analysis.

Mean  $\pm$  SD was calculated for quantitative variables. Frequency and percentage were calculated of qualitative variables. Effect modifiers were controlled by stratification. Post stratification, chi-square test was applied. P-value  $\leq$ 0.05 was considered as significant.

Descriptive statistics of age was calculated, and it was found that mean age of the study subjects was  $26.88 \pm 3.898$  years. The detailed descriptive statistic of age is presented in Table I. The distribution of overall age is presented in Fig. 1.

**Table I.** Descriptive statistics of age in years (n=67)

Mean $\pm$ SD	95%CI (LB – UB)	Median (IQR)	Range	Minimum	Maximum
26.93 $\pm$ 3.859	25.93–27.87	27.00 (5)	20	15	35



**Fig. 1.** Histogram presenting distribution of age (n=67)

The age was stratified into two groups. The frequency and percentages are presented in Table-2. The detailed descriptive statistics of age according to age groups are presented in Table III frequency and percentages distribution of obesity is presented in Table-4 showed that out of total, 32 (47.8%) have BMI of >27 while 35 (52.2%) patients were having BMI of <27.

**Table II.** Frequency and percentage of patients according to age groups (n=67)

Age Groups (In years)	Frequency	Percentage
15-24	19	28.4%
25-35	48	71.6%
Total	67	100%

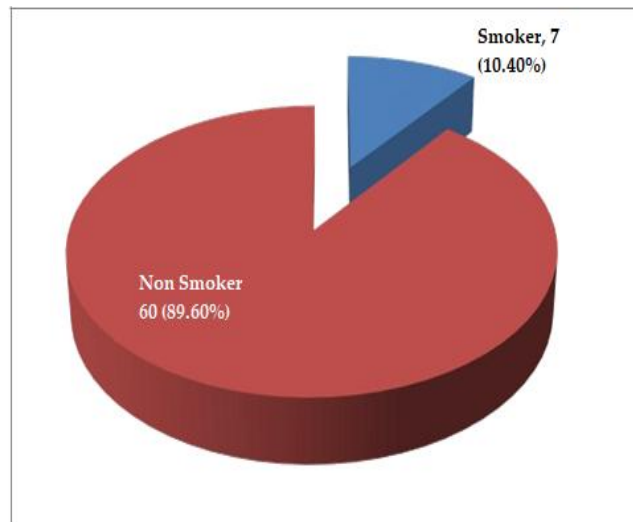
**Table III.** Descriptive statistics of age according to age groups (n=67)

	Mean $\pm$ SD	95%CI (LB - UB)	Median	Range	Minimum	Maximum
15-24 years (n=19)	22.26 $\pm$ 2.621	21.00-23.53	23 (2)	9	15	24
25-35 years (n=48)	28.77 $\pm$ 2.452	28.06-29.48	28.50 (3)	10	25	35

**Table IV.** Frequency and percentage of OBESITY (n=67)

OBESITY (BMI >27)	Frequency	Percentage
Present	32	47.8%
Absent	35	52.2%
Total	67	100%

Frequency and percentage of smoking was calculated, it was found that, out of total study subjects 07 (10.40%) patients were smoker, while 60 (89.6%) were non-smoker, shown in Fig. 2.

**Fig. 2.** Frequency and percentage of smoking (n=67)

Descriptive statistics of duration of primary infertility was calculated and it was found that Mean  $\pm$  SD was 3.03 $\pm$ 2.296 in years. Detail results are presented in Table V.

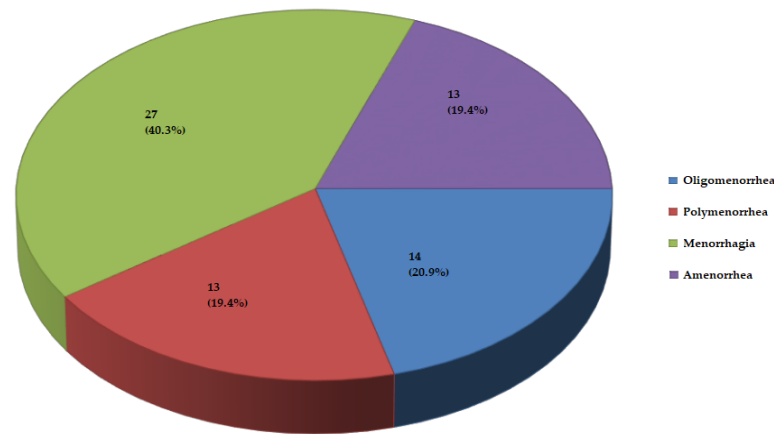


Fig. 3. Frequency and percentage of menstrual Irregularities (n=67)

Table V. Descriptive statistics of duration of infertility (in Years) (n=67)

Mean ±SD	95%CI (LB – UB)	Median (IQR)	Range	Minimum	Maximum
3.03±2.296	2.47–3.59	2.0 (3)	09	01	10

Frequency and percentages distribution of thyroid dysfunction is presented in Table-6 showed that out of total study patients 37(55.20%) had thyroid dysfunction, out of 8(11.9%), 15(22.4%), 3(4.5%), 8(11.9%) and 3(4.5%) have Hyperthyroidism.

Table VI. Frequency and percentage of thyroid dysfunction (n=67)

Thyroid Function	Frequency	Percentage
Normal TFT	30	44.8%
Hyperthyroidism	8	11.9%
Hypothyroidism	15	22.4%
Subclinical-Hyperthyroidism	3	4.5%
Subclinical-Hypothyroidism	8	11.9%
Sick-Euthyroid	3	4.5%
Total	67	100.0%

Hypothyroidism, Subclinical Hyperthyroidism, Subclinical Hypothyroidism and Sick euthyroid, respectively. While 30(44.8%) have normal thyroid function test.

Frequency and percentages distribution of menstrual irregularities is presented in Graph-3 showed that out of total, 14 (20.9%), 13 (19.4%), 27 (40.3%) and 13 (19.4%) patients were having Oligomenorrhea, Polymenorrhea, Menorrhagia and Amenorrhea, respectively.

Stratification of thyroid dysfunction with respect to age group, obesity, smoking, and menstrual irregularities were done to see the association by applying chi-square test. P-value ≤0.05 was considered as significant. The results have shown that obesity and menstrual irregularities have significant association i.e., <0.05 with thyroid dysfunction; but stratification of age and smoking showed non-significant association was found i.e., P >0.05. Detailed results are presented in Table VII, Table VIII, Table IX, and Table X.

**Table VII.** Frequency and association of thyroid dysfunction with age groups (n= 67)

Thyroid Function	Age Groups in Years				P-value
	15-24 Years		25-35 Years		
	(n)	%	(n)	%	
Normal TFT	08	11.94%	22	32.85%	0.556*
Hyperthyroidism	03	4.47%	05	7.46%	
Hypothyroidism	03	4.47%	12	17.91%	
Subclinical Hyperthyroidism	00	00	03	4.47%	
Subclinical Hypothyroidism	04	5.97%	04	5.97%	
Sick-euthyroid	01	1.49%	02	2.99%	
Total	19	28.35%	48	71.65%	

**Table VIII.** Frequency and association of thyroid dysfunction with obesity (n= 67)

Thyroid Function	Obesity (BMI>27)				P-value
	(n)	%	(n)	%	
Normal TFT	20	29.85%	10	14.92%	0.001**
Hyperthyroidism	08	11.94%	00	00	
Hypothyroidism	00	00	15	22.38%	
Subclinical Hyperthyroidism	03	4.47%	00	00	
Subclinical Hypothyroidism	02	2.98%	06	8.96%	
Sick-euthyroid	02	2.98%	01	1.49%	
Total	35	52.23%	32	47.77%	

**Table IX.** Frequency and association of thyroid dysfunction with menstrual irregularities = (n 67)

Thyroid Function	Oligo-Menorrhoea		Polymenorrhoea		Menorrhoea		Amenorrhoea		P-Value
	(n)	%	(n)	%	(n)	%	(n)	%	
Normal TFT	07	10.45%	05	7.46%	13	19.40%	05	7.46%	0.011**
Hyperthyroidism	03	4.47%	00	00	00	00	05	7.46%	
Hypothyroidism	01	1.49%	06	8.95%	08	11.94%	00	00	
Subclinical Hyperthyroidism	01	1.49%	00	00	00	00	02	2.99%	
Subclinical Hypothyroidism	01	1.49%	02	2.98%	04	5.97%	01	1.49%	
Sick-Euthyroid	01	1.49%	00	00	02	2.98%	00	00	
Total	14	20.90%	13	19.40%	27	40.29%	13	19.41%	

## DISCUSSION

Thyroid dysfunction is a large public health problem which affects more than 1.5 to 6% of population, with significant morbidity and mortality worldwide. Normal thyroid function is necessary to maintain reproductive physiology. An abnormality in its function may be the cause of infertility manifesting as abnormal menstrual cycle (9). However, it is likely that the thyroid system is important for both follicular and embryo development. The association between thyroid disease and infertility indicate that TH and TSH affect the endometrium and ovary on the paracrine level (11).



**Table X.** Frequency and association of thyroid dysfunction with smoking (n= 67)

Thyroid Function	Smoker		Non-smoker		P-value
	(n)	%	(n)	%	
Normal TFT	04	5.97%	26	38.81%	
Hyperthyroidism	00	00	08	11.94%	
Hypothyroidism	03	4.47%	12	17.91%	
Subclinical Hyperthyroidism	00	00	03	4.47%	0.508*
Subclinical Hypothyroidism	00	00	08	11.94%	
Sick-euthyroid	00	00	03	4.47%	
Total	07	10.44%	60	89.56%	

In current study, 67 cases of primary infertility presented with menstrual disturbances consisted of age between 15-35 years were taken, compare with the study conducted at India by Nath C et al., (7). Our study showed high prevalence of thyroid dysfunction i.e., hypothyroidism 12 (17.91%) and hyperthyroidism 5 (7.46%) in age group between 25-35 years similarity compared with study conducted by Joseph J et al., (12) Relationship of thyroid dysfunction and menstrual irregularity has been of immense help in the clinical understanding of thyroid dysfunction in primary infertile patients. Out of total 30 (44.8%) have normal thyroid function similar to study done by Sangita AN (13). Thyroid dysfunction was evaluated and labeled in a light of abnormal lab results of serum TSH, Free T3 and Free T4, similar to study conducted by Boelaert K (14).

The results have shown that thyroid dysfunction have insignificant and inverse association with smoking that showed, smokers have 3 (4.47%) of thyroid dysfunction, compared with non-smoker having 34 (50.74%) of thyroid dysfunction. This finding not supported by the study conducted at Korea by Chung SM et al., (15) while Wiersinga WM et al. (16) Vestergaard P *et al* (17) and Schlienger JL et al (18) have found that the relapse of Graves' disease and the incidence and severity of Graves' ophthalmopathy have been seen reported in smokers, while no other significant effects were noted.

Reproductive function in women can be altered by thyroid disorders. Menorrhagia and Polymenorrhoea was common reported menstrual disturbance to occur in subclinical/overt hypothyroid cases while hyperthyroidism has either Oligomenorrhoea or a menorrhoea. This sort of presentation reported in our study which have similarity with studies conducted by Joshi JV et al. (19) Krassas GE et al. (20) and Dittrich R et al. (21).

In our study results, subclinical/overt hypothyroidism has shown significant correlation with obesity, concluded that hypothyroid patients have obesity (BMI>27) in common, while BMI <27 was seen in patients of subclinical/overt hyperthyroidism, these similar results was found in study conducted by Knudsen N et al. (22) and Asvold BO (23). While Manji N et al. (24) concluded that no evidence for an association between thyroid status within the normal range and BMI.

Strength of our study was use of consecutive sampling best suited for our study design, primary infertile patients having menstrual irregularity were categorized and evaluated for thyroid dysfunction and sample selection, as our inclusion and exclusion criteria was stringent.

## STUDY LIMITATIONS

The main limitations of the present study include the cross-sectional design where cause cannot be attributed, a single-center experience, young age representation in the study cohort and nonrandomized study design. Hence the figure does not reflect true frequency and severity of the disease. Secondly, there were some confounding factors in this study, such as age, race, diet, obesity, physical activity, depression and so on. Some, but not all, of the studies generated adjusted. Moreover, this study was conducted with small sample size and in urban environment therefore, the results might not be generalizable to larger populations.

## CONCLUSION

This study concludes that thyroid dysfunction plays a significant role in primary infertility which may manifest as menstrual disturbances. However, further well-designed randomized controlled trials are needed to determine the frequency of thyroid dysfunction in primary infertile women with menstrual disturbances for the better understanding of relationship between thyroid dysfunction and primary infertility. Therefore, in our setup thyroid hormone profile must be included in the routine workup of primary infertile women those presented with irregular menstrual history.

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