Original Article

Thyroid Health and its Correlation to Female Fertility: A Pilot Study

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ABSTRACT

Background: Most of the problems in female reproductive system are due to dysfunction in hypothalamic-pituitary-ovarian axis. Our study is evaluating thyroid profile in the presence and absence of autoantibodies and how it effect the fertility of Omani women, through serum thyroid evaluation, estimation of prolactin level, autoantibodies and women fertility characteristics. **Materials and Methods:** This is a clinical cross sectional study, involves systemic random sampling of 182 patients women aged between 19-45 years visiting the study centre from September 2017 to May 2018. Study conducted according to the guidelines and ethics of the selected fertility center. Accordingly the identity and their related information is not disclosed. Data was collected retrospectively by looking at the patient profile, lab results and analyzing their blood samples by using ELISA kit to estimate Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (FT3), Free Thyroxine (FT4), Thyroperoxidase (TPO), Vitamin D and prolactin. The project was funded from Oman medical college. **Results:** The risk of female infertility is high in hyperthyroidism compared to hypothyroidism. There is no correlation between TPO, FT3 and type of menstrual cycle with fertility. There is a high significant relation between FT4 and TSH with fertility. Our results indicated that the risk of infertility was more in patient from Muscat followed by Ad Dakhiliyah, other nationalities, Al Batinah North, Al Batinah South, Dhofar, Ad Dhahirah, Ash Sharqiyah North and Ash Sharqiyah South. **Conclusion:** We have concluded form our research that FT4 and TSH are the most cause of infertility and FT3 has is considered as a cause but not as much as FT4 and TSH.

Key words: Infertility, Hypothyroidism, Hyperthyroidism, Thyroid profile, Female.

INTRODUCTION

Concerns are raised globally on rising number of cases having difficulty in becoming pregnant.[1] Approximately 22.3% of women who are married are reported with problems either carrying a pregnancy to a full term or in achieving pregnancy. The major causes of infertility are anovulation, tubal damage, endometriosis and hormone imbalance.[2] Most of the problems in female reproductive system are due to dysfunction in hypothalamic-pituitary-ovarian axis.[3] Hypothalamus releases GnRH to control the pituitary gland affecting the pituitary gland, thyroid, ovaries and resulting into hormonal abnormalities. These abnormalities may lead to hyperthyroidism, hypothyroidism and hyperprolactinemia. It is known that hyperprolactinemia causes infertility due to elevated levels of dopamine affecting steroidogenesis due to GnRH inhibition.[4] Thyroid dysfunction, including both hypothyroidism and hyperthyroidism can lead to infertility, abortions, still births, failure of lactation, menorrhagia and menstrual abnormalities. Hypothyroidism may cause failure to ovulate or regulate ovulation and subclinical hypothyroidism is reported to cause menstrual problems such as oligomenorrhea, amenorrhea, polymenorrhea and galactorrhea.[5] Severe hypothyroidism

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is known to be associated with HPO (Hypothalamus-Pituitary-Ovary) axis dysfunction and mild hypothyroidism are often associated with abortions, stillbirth or prematurity. These actions are affecting directly LH and FSH mediated control of granulosa cell function and indirect effect by decreasing binding of Sex Hormone-Binding-Globulin (SHBG) affecting the levels of estrogen and testosterone.[6] In contrast to hypothyroidism, hyperthyroidism may have irregular menses, hypomenorrhea, polymenorrhea, oligomenorrhea and menorrhagia. These adversities are mediated through their effect on altered estrogen, testosterone, GnRH and response to GnRH.[7]

Thyroid disease is estimated to cause 8-12% of total loss of pregnancies[8] and around 10% of women have thyroid dysfunction despite euthyroidism.[9] It shows that there is a two directional relationship between thyroid functioning, autoimmunity and fertility.[10] Therefore, it is important to carry out multiple hormone analysis, including ant Thyroglobulin antibody (TGB), Thyroid Peroxidase (TPO), Vitamin D and prolactin along with detailed patient history to provide better picture of the hormone imbalances that is causing menstrual problems, ovulatory dysfunction leading either primary or secondary infertility. Studies in evaluation of involvement of thyroid dysfunction in Omani women are few with very limited information.[11] It is important to mention here that there is a limited knowledge existing in Oman[11] on thyroid functioning in preconceptional, periconceptional and postconceptional period to make consensus over screening, diagnosis and treatment of thyroid disorders before treating infertility. Data on relationship between subclinical, clinical hypo/hyperthyroidism along with thyroid autoantibodies and infertility remain scarce as these groups of infertile patients ignored.[12] Study carried out in our lab in collaboration with Al Bushra Medical Specialty Complex in 2013-14 shown that the irregular periods in female increases the risk of infertility by 1.7 times. Similarly, menarche at age of 13 years, endometriosis and ectopic pregnancy increased the risk of infertility in females by 1.4, 1.05 and 2 times respectively that of control group of patients. It was also observed that thyroid disease either hyperthyroidism or hypothyroidism are significantly ($p<0.05$) associated with infertility in females.[13] Based on these results, we believe that there is a significant correlation between thyroid function and menstrual regularities affecting the fertility of Omani women. Functioning of the thyroid gland is also associated with prolactin levels and ovulatory failure. Therefore, assessment of serum T3, T4, TSH, TPO, Vitamin D and prolactin levels and their correlation will assist us to know extent of their influence on female infertility in Omani women. We hope that outcome of our study will further clarify the role of thyroid hormones should play an important role in screening, diagnosing and treatment of female infertility. In light of this we have carried out a study to evaluate thyroid profile in the presence and absence of autoantibodies and impacting fertility of Omani women and its correlation with fertility. The following, specific objectives were achieved through serum thyroid function evaluation, estimation of prolactin level, vitamin D, autoantibodies, menstrual characteristics and fertility types.

MATERIALS AND METHODS

Study Discipline

Present study is a hospital based clinical cross-sectional study involving disciplines such as pharmacology, gynecology and infertility.

Study Participants

Present pilot study involves systemic random sampling of 152 patients visiting the study centre from April 2017 to October 2017. It was carried out in collaboration with Al Bushra Medical Specialty Complex, Azaiba. Letter of permission was obtained from the Managing Director of infertility centre. The clinic has agreed to provide access to laboratory analysis. MOH licensed and trained practitioners were involved in collecting blood sample. Both used and unused biological samples were returned to the clinic for their appropriate disposal. All women aged between 19-45 years old visiting the clinic were eligible for inclusion in the study. However, those cases who were on medication affecting thyroid function such as amiodarone, beta-blockers, heparin, dopamine and phenytoin; females with tubal factors, congenital anomaly of the urogenital tract were excluded from the study.

Materials

BIOCEN 22R Refrigerated centrifuge purchased from Spain; Microplate ELISA reader CL-SPR-960 from Germany; MW12 Microplate washer from Mindray, China; ELISA diagnostic kits for FT3, FT4, TSH and TPO purchased from Wuhan Fine Biotech Co., Ltd. China; vitamin D and prolactin were estimated by using Roche diagnostic kits using Chemiluminescence method.

Methodology

2 mL of fasting venous blood was collected at the study centre in the morning of day 3-5 of menstrual cycle for serum thyroid analysis. Serum was separated at clinic and brought to OMC Bowshar campus and stored at

-20°C until the estimation of TSH, FT3, FT4 and TPO by using ELISA kits as per the kit supplier's instructions. Thyroid function was considered normal (Euthyroid) when patients were presented with normal FT3, FT4 and TSH. Abnormal thyroid function was further categorized as hyperthyroid (Increased FT3, FT4 and decreased TSH), subclinical hyperthyroid (Increased T3, T4 and normal TSH), clinical hypothyroidism (Decreased FT3, FT4 and increased TSH) and subclinical hypothyroidism (Decreased FT3, FT4 and normal TSH). Following serum thyroid profile was considered for division.

Hyperprolactinemia: prolactin >25 ng/mL,

Euthyroidism FT3 = 0.51 - 1.58 ng/mL, FT4 = 4.7 -12.8 micro gram/dL, TSH = 0.39-3.45 micro IU/mL.

Hyperthyroidism will be considered when TSH < 0.39 micro IU/mL

Hypothyroidism when TSH > 3.5 micro IU/mL.[13]

Menstrual Regularity and Fertility

Data sheet developed was used to record personal, menstrual pattern, thyroid profile and type of infertility defined as per the FIGO recommendations[14] by going through case file to have complete information.

Biomedical Ethics

The study was conducted according to the guidelines and ethics of OMC (OMC/REC-24-22/9/2016) and selected study centre the identity of the patient and their related information is not disclosed. Written consent from each case involved in the study was taken after explaining objectives, assuring privacy, maintaining anonymity and confidentiality of information shared. Participants were also informed that their non-participation would not affect their care and are free to withdraw from study at any point of time. Permission was obtained from OMC Research and Ethics Committee and Al Bushra Medical Specialty Complex, Muscat before starting the study.

Statistical Analysis

Each patient was given a separate registration number for this study and the information collected was entered directly into MS excel sheet before converting it into data sheet of SPSS version 23.0 for analysis. Various descriptive statistics such as mean and standard deviation, percentage-frequency distribution, correlation, relative risks and Confidence Intervals (CI) were obtained by Pearson correlation analysis and multiple regression analysis. Any significant difference in variables was analyzed by Chi square test and student '*t*' test.

RESULTS

Hypothesis Test Summary

Analysis of data as independent samples by Mann-Whitney U Test shows that there is a significant difference in distribution of age, TSH and FT4 in primary and secondary infertility population. Therefore, the study rejects null hypothesis in these three factors.

Incidence of Primary and Secondary Infertility

Figure 1 shows that the number of patients having primary infertility was (76%) is higher than the secondary infertility (24%). The primary infertility started in younger age compared to secondary infertility in the selected population. It is also observed that it is normally occurring between 20 years to 45 years age group women with maximum incidence between 25 years to 35 years. However, the incidence of secondary infertility is non uniform.

Thyroid Function Categorization in Study Population

Results illustrated in Figure 2 shows that about 54% of the selected population was normal, 39% of total popu-

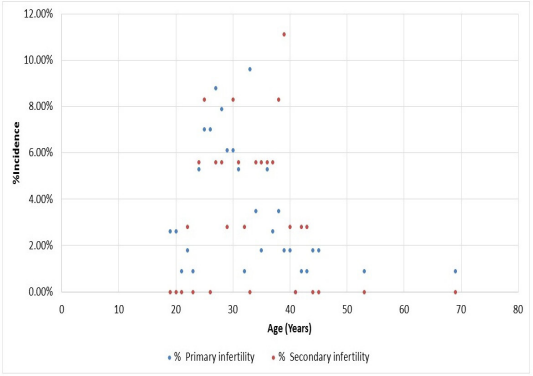

Figure 1: Incidence of Primary and Secondary Infertility.

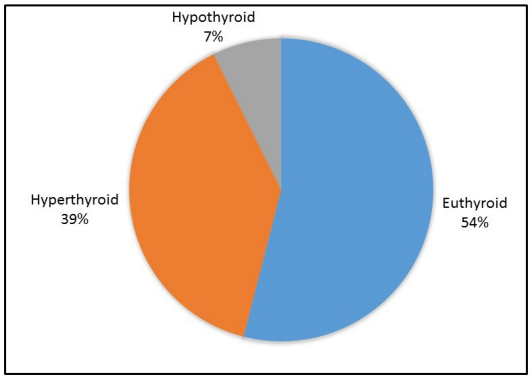

Figure 2: Thyroid Function Categorization in Study Population.

lation was with hyperthyroidism and only 7% were with hypothyroidism condition. This shows that hyperthyroidism has higher risk female infertility than compared to hypothyroidism (Figure 2).

Pattern of Menstrual Regularity

Results presented in Figure 3 and 5 shows that 91% of infertile patients had dysmenorrhea and 28% of them were having irregular menstrual cycle. Data in Figure 4 illustrates that 39% of them have mild pain more than number of patients having no pain (32%). Moderate pain was recorded in 22% patient and severe pain in 7% of patient population.

Age Distribution of Study Population

This table shows that maximum number of patients (33.33%) involved in the study belongs to the age group of 25-29 years. Second highest number of patients (24.67%) were noted in 30-34 years age group (Table 1).

Regional Distribution of Study Population

Majority of patients involved in this study were from Muscat (44) followed by Ad Dakhiliyah (27), other nationals (18), Al Batinah North (17), Al Batinah South (15), Dhofar (12), Ad Dhahirah (10), Ash Sharqiyah North (3 all primary) and Ash Sharqiyah South (4). This figure shows that patients are included from almost all regions of Sultanate of Oman. Maximum number of patients are from Muscat could be due to location of study centre and other regions nearby Muscat (Figure 6).

Linear Regression Analysis of Thyroid Profile and Infertility Types

These results shows that beta coefficient of FT3 and FT4 were 0.96 and 0.443 indicating significant $p<0.05$ and $p<0.001$ linear relationship with types of infertility respectively (Table 2). Separate primary and secondary infertility data analysis by using correlation matrix shows very interesting facts. Primary infertility has stronger correlation between age, FT3, Vit D and prolactin with TPO. It is also shown that prolactin has stronger correlation with Vit D and TSH.

Level of Significant Relation between Thyroid Profile, Menstrual Disturbance and Type of Infertility

It is evident from the results that there is a significant relation co-existing between FT3, FT4, TSH and TPO with menstrual disturbance and type of infertility (Table 3). Whereas in secondary infertility mainly the TPO has significant correlation with TSH, FT4 and prolactin. It is also seen that the FT4 has correlation with vitamin D too. Further, corrected model tests of between subject effects shows that FT3 has very strong ($r^2=0.724$) and

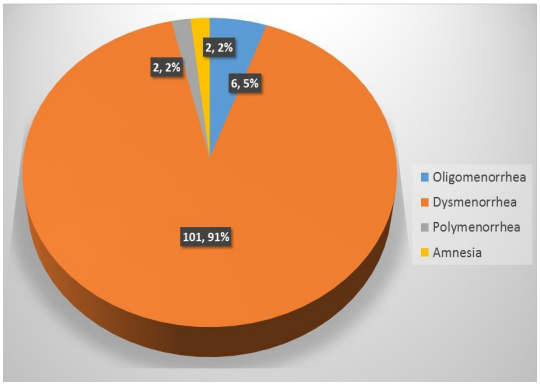

Figure 3: Menstrual Disturbance.

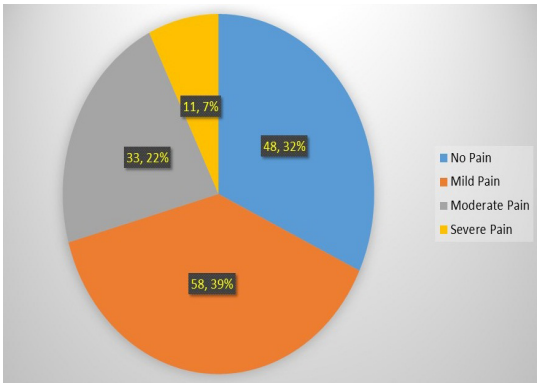

Figure 4: Frequency in Menstrual Pain Severity.

Table 1: Age Distribution of Study Population.

Age Group (Years)	Primary Infertility		Secondary Infertility		Total	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
19-24	16	84.21	3	15.79	19	12.67
25-29	42	84	8	16	50	33.33
30-34	29	78.38	8	21.62	37	24.67
35-39	17	62.96	10	37.04	27	18
40-44	6	46.15	7	53.85	13	8.67
45-49	4	100		0	4	2.67

Table 2: Linear Regression Analysis of Thyroid Profile and Infertility Types.

Linear regression analysis of thyroid profile and Infertility types						
Model	B	Unstandardized Coefficients		Standardized Coefficients	*t*	Sig.
		Std. Error	Beta			
1	(Constant)	0.078	0.620		0.126	0.902
	Age in Years	-0.008	0.011	-0.089	-0.720	0.492
	TPO	4.580	0.002	0.002	0.021	0.984
	TSH	0.048	0.034	0.278	1.425	0.192
	FT4	0.098	0.042	0.443	2.346	0.047
	FT3	0.049	0.007	0.960	6.787	0.000
	Vit D	0.002	0.013	0.020	0.175	0.865
	Prolactin	-0.007	0.005	-0.166	-1.263	0.242

a. Dependent Variable: INFERTTYPES.

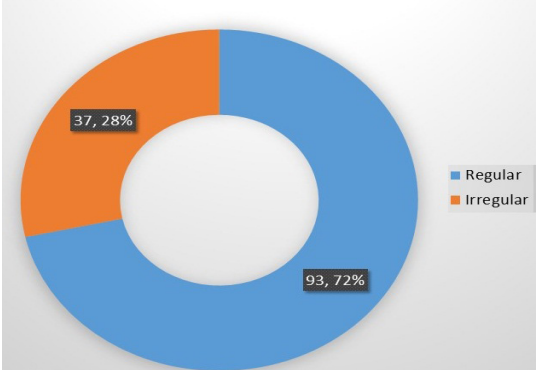

Figure 5: Pattern of Menstrual Regularity.

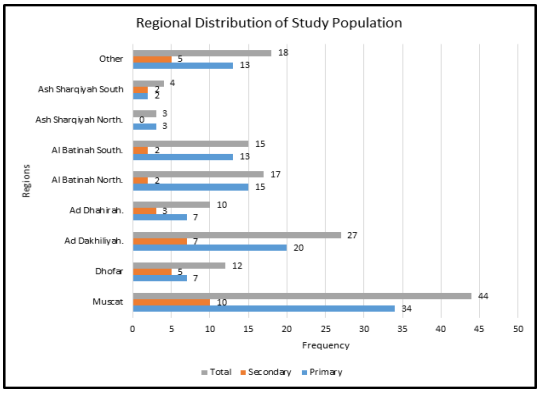

Figure 6: Regional Distribution of Study Population.

Table 3: Level of Significant Relation between Thyroid Profile, Menstrual Disturbance and Type of Infertility.

Level of Significant relation between Thyroid Profile, Menstrual Disturbance and Type of Infertility		
	Menstrual Disturbance	**Infertility Type**
Prolactin	0.057	0.063
Vitamin D	0.172	0.108
FT3	0.001	0.033
TSH	0.027	0.244
FT4	0.062	0.013
Age	0.4	0.114
TPO	0.001	0.244

significant ($p<0.001$) influence among the total population.

Independent Samples '*t*' test for Equality of Means between Primary and Secondary Infertility

Analysis of data using student *t* test shows that there is a significant ($p<0.05$) difference in levels of FT4. Secondary infertility is reported at significantly higher level (10.07 ± 3.15) compared to primary infertility (8.76 ± 3.21) (Table 4).

Correlation Analysis of Thyroid Profile and Type of Infertility

Results are summarized in Table 5 and analyzed by Chi-Square Test and Pearson correlation. Serum TPO level was normal in 86% of patients whereas 14% of patients were in the higher range. Further, it shows that 95.24% of patients higher range patients were with primary compared to 4.76% of secondary infertility. Clearly indicating that the increase in TPO level will have higher

Table 4: Independent Samples '*t*' test for Equality of Means between Primary and Secondary Infertility.

Factors	Type of Infertility	*N*	Mean ± Std. Deviation	*t*	Sig. (2-tailed)	95% Confidence Interval of the Difference	
						Lower	Upper
Age	Primary	114	30.71 ± 7.26	-1.893	0.060	-5.19	0.11
	Secondary	36	33.25 ± 6.18				
TPO	Primary	114	22.78 ± 47.4	1.821	0.071	-1.25	30.75
	Secondary	36	8.03 ± 18.23				
TSH	Primary	114	2.12 ± 2.16	1.785	0.076	-0.078	1.54
	Secondary	36	1.38 ± 2.1				
FT4	Primary	114	8.76 ± 3.21	-2.142	0.034	-2.52	-0.101
	Secondary	36	10.07 ± 3.15				
FT3	Primary	114	15.88 ± 10.89	-0.161	0.872	-4.39	3.73
	Secondary	36	16.21 ± 10.25				
Vit D	Primary	18	14.08 ± 5.62	0.191	0.850	-4.38	5.27
	Secondary	8	13.64 ± 5.2				
Prolactin	Primary	25	31.06 ± 11.52	-0.039	0.969	-8.93	8.59
	Secondary	10	31.23 ± 11.46				

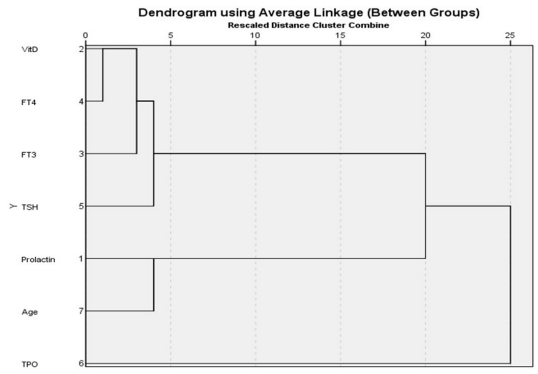

Figure 7: Dendrogram Hierarchial Clustering Analysis.

influence on incidence of primary infertility rather than secondary infertility. It is also illustrated in the table that 38.67% of patients were with clinical hyperthyroidism significantly ($p<0.05$) higher in primary infertile patients (67.24%) compared to 32.76% of patients in secondary infertility (Table 5). These observations are supported by correlation matrix analysis of primary and secondary infertility and thyroid factors as shown in Table 6 and 7. Further, corrected model analysis between subjects justifies the data. (Table 8).

Spearman's Rho Correlations Cross Tabulation

Spearman cross correlation analysis shows that there is highly significant ($p<0.001$) negative correlation is existing between TSH, TPO, FT3 and FT4. These results are in line with proven facts and figures on thyroid functioning (Table 9).

Dendrogram Hierarchial Clustering Analysis

The clustering analysis of factors considered in this study shows that there are three related clusters. The level of TSH are found to be closely associated with serum FT3 and FT4 levels. Whereas, age and prolactin levels are distantly related to types of infertility (Figure 7).

DISCUSSION

In this study we observed strong correlation between serum FT3, FT4, TSH and prolactin levels leading to dysmenorrhea and irregularities in menstrual flow affecting female fertility. The objectives of present study are achieved through estimation of thyroid hormones along with vitamin D and prolactin followed by statistical analysis.

Majority of patients involved in this study were from Muscat (44) followed by Ad Dakhiliyah (27), other nationals (18), Al Batinah North (17), Al Batinah South (15), Dhofar (12), Ad Dhahirah (10), Ash Sharqiyah North (3 all primary) and Ash Sharqiyah South (4). These results shows that patients are included from almost all part of Sultanate of Oman. However maximum number of patients were from Muscat could be due to location of study centre. Study population from other region other than Muscat were from regions nearby to Muscat. The number of patients having primary infertility was (76%) is higher than the secondary infertility (24%) supporting the prevalence of study reported from China.[15] The age of incidence of primary

Table 5: Correlation Analysis of Thyroid Profile and Type of Infertility.

		Primary		Secondary		Total			
Factors	**Levels**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**Pearson Chi-Square**	
								Value	***P***
TPO	Normal	94	72.87	35	27.13	129	86	4.955	0.017
	High	20	95.24	1	4.76	21	14		
TSH	Normal	63	81.82	14	18.18	77	51.33	4.824	0.09
	Low	40	66.67	20	33.33	60	40		
	High	11	84.62	2	15.38	13	8.67		
FT4	High	114	76	36	24	150	100	--	--
FT3	Normal	7	63.64	4	36.36	11	7.33	0.995	0.254
	High	107	76.98	32	23.02	139	92.67		
Vit D	Low	18	69.23	8	30.77	26	17.33	--	--
Prolactin	Normal	8	80	2	20	10	6.67	0.604	0.367
	High	16	66.67	8	33.33	24	16		
Regularity of Cycle	Regular	68	73.12	25	26.88	93	62	1.658	0.144
	Irregular	31	83.78	6	16.21	37	24.67		
Pain	No	36	75	12	25	48	32	0.232	0.972
	Mild	44	75.86	14	24.14	58	38.67		
	Moderate	26	78.79	7	21.21	33	22		
	Severe	8	72.73	3	27.27	11	7.33		
Menstrual Disturbance	Oligomenorrhea	3	50	3	50	6	4	3.64	0.303
	Dysmenorrhea	78	77.23	23	22.77	101	67.33		
	Polymenorrhea	1	50	1	50	2	1.33		
	Amenorrhea	2	100	0	0	2	1.33		
Hyperthyroidism Types	Normal	75	81.52	17	18.48	92	61.33	3.977	0.037
	Clinical	39	67.24	19	32.76	58	38.67		
Hypothyroidism types	Normal	105	75.54	34	24.46	139	92.67	0.22	0.482
	Clinical	9	81.82	2	18.18	11	7.33		
Thyroid Function	Euthyroid	66	81.48	15	18.52	81	54	3.978	0.137
	Hyperthyroid	39	67.24	19	32.76	58	38.67		
	Hypothyroid	9	81.82	2	18.18	11	7.33		

Table 6: Correlation Matrix of Factors in Primary Infertility Sig. (1-Tailed).

	Age	**TPO**	**TSH**	**FT4**	**FT3**	**VitD**	**Prolactin**
Age		0.444	0.012	0.084	0.103	0.447	0.289
TPO	0.444		0.242	0.390	0.426	0.420	0.468
TSH	0.012	0.242		0.033	0.357	0.362	0.488
FT4	0.084	0.390	0.033		0.006	0.166	0.147
FT3	0.103	0.426	0.357	0.006		0.203	0.282
Vit D	0.447	0.420	0.362	0.166	0.203		0.405
Prolactin	0.289	0.468	0.488	0.147	0.282	0.405	

Only cases for which INFERTTYPES = Primary are used in the analysis phase.

Table 7: Correlation Matrix of Factors in Secondary Infertility Sig. (1-Tailed).							
	Age	**TPO**	**TSH**	**FT4**	**FT3**	**VitD**	**Prolactin**
Age		0.256	0.150	0.230	0.013	0.198	0.159
TPO	0.256		0.406	0.486	0.243	0.058	0.415
TSH	0.150	0.406		0.080	0.163	0.348	0.010
FT4	0.230	0.486	0.080		0.243	0.428	0.070
FT3	0.013	0.243	0.163	0.243		0.185	0.173
VitD	0.198	0.058	0.348	0.428	0.185		0.357
Prolactin	0.159	0.415	0.010	0.070	0.173	0.357	

Only cases for which INFERTTYPES = Primary are used in the analysis phase.

Table 8: Corrected Model Tests of between-Subjects Effects.				
	Type III Sum of Squares	**Mean Square**	**F**	**Sig.**
TPO	390.860[a]	390.860	0.537	0.479
TSH	11.933[b]	11.933	1.823	0.204
FT4	2.467[c]	2.467	0.418	0.531
FT3	723.304[d]	723.304	32.442	0.001
Vit D	9.032[e]	9.032	0.353	0.564
Prolactin	5.357[f]	5.357	0.031	0.863

a. R Squared = 0.047 (Adjusted R Squared = -0.040)
b. R Squared = 0.142 (Adjusted R Squared = 0.064)
c. R Squared = 0.037 (Adjusted R Squared = -0.051)
d. R Squared = 0.747 (Adjusted R Squared = 0.724)
e. R Squared = 0.031 (Adjusted R Squared = -0.057)
f. R Squared = 0.003 (Adjusted R Squared = -0.088)

Table 9: Spearman's Rho Correlations Cross Tabulation.								
		Age	**TPO**	**TSH**	**FT4**	**FT3**	**Vit D**	**Prolactin**
Age	Correlation Coefficient	1.000	0.073	-0.140	0.058	-0.092	-0.064	0.174
	Sig. (2-tailed)	--	0.373	0.087	0.480	0.262	0.756	0.318
TPO	Correlation Coefficient	0.073	1.000	0.131	-0.332**	-0.108	-0.284	-0.081
	Sig. (2-tailed)	0.373	--	0.110	0.001	0.188	0.159	0.643
TSH	Correlation Coefficient	-0.140	0.131	1.000	-0.510**	-0.454**	-0.049	0.249
	Sig. (2-tailed)	0.087	0.110	--	0.001	0.001	0.811	0.150
FT4	Correlation Coefficient	0.058	-0.332**	-0.510**	1.000	-0.353**	0.418*	0.008
	Sig. (2-tailed)	0.480	0.001	0.001	--	0.001	0.034	0.964
FT3	Correlation Coefficient	-0.092	-0.108	-0.454**	-0.353**	1.000	-0.047	-0.023
	Sig. (2-tailed)	0.262	0.188	0.001	0.001	--	0.822	0.895
Vit D	Correlation Coefficient	-0.064	-0.284	-0.049	0.418*	-0.047	1.000	-0.060
	Sig. (2-tailed)	0.756	0.159	0.811	0.034	0.822	--	0.845
Prolactin	Correlation Coefficient	0.174	-0.081	0.249	0.008	-0.023	-0.060	1.000
	Sig. (2-tailed)	0.318	0.643	0.150	0.964	0.895	0.845	--

*Correlation is significant at the 0.05 level (2-Tailed)
**Correlation is significant at the 0.01 level (2-Tailed).

infertility is commonly observed between 20 years to 45 years age group women with maximum incidence between 25 years to 35 years. However the incidence of secondary infertility is not-uniform in occurrence with respect to age supporting a systemic metanalysis on global trends in infertility prevalence.[16]

Present study outcomes shows that about 52.96% of the selected population was normal, 41.77% of total population was with hyperthyroidism and only 7.13% was with hypothyroidism condition. This shows that hyperthyroidism has higher risk for female infertility than compared to hypothyroidism.[17-20]

Serum TPO level was normal in 88.2% of patients whereas 11.8% of patients were in the higher range having very significant ($p<0.01$) negative correlation and the trend with female fertility. The serum TSH level was lower than normal in 43% of patients whereas 48.9% were normal and 8.1% were higher than normal. Further correlation analysis predicts that there is a highly significant ($p<0.001$) correlation and trends with lower level of serum TSH level. It is important to note that in all of the patients whom we considered for the study have higher than normal levels of serum FT4. Similarly serum FT3 levels was higher in 91.9% of patients and only 8.1% of patients were in normal range. Correlation analysis proves that again increase in FT3 level will significantly ($p<0.01$) correlated negatively with fertility of women. A significant ($p<0.05$) correlation between severity of pain and incidence of infertility with a positive trend (0.21) was observed in this study.

Supporting previous studies which have reported that all types and level of severity of hypothyroidism are known to cause failure to ovulate or regulate ovulation and menstrual problems.[21] These actions are mediated directly by LH and FSH and control of granulosa cell function and indirect effect by decreasing binding of sex hormone-binding-globulin affecting the levels of estrogen and testosterone.[22] In contrast to hypothyroidism, hyperthyroidism alters estrogen, testosterone, GnRH and response to GnRH leading to irregular menses, hypomenorrhea, polymenorrhea, oligomenorrhea and menorrhagia.[23] One of the study carried out in Oman compared guidelines on thyroid care during pregnancy.[24]

Our results illustrate that all our patients were noted to have Vitamin D deficiency with an insignificant ($p>0.05$) difference in levels with respect to euthyroid, hyperthyroid and hypothyroid condition of patients. These results supports the concern raised by recently published research article.[25] It also supports that having Vitamin D deficiency is an independent risk factors for women primary infertility. Supplementation of Vitamin D might be useful for pregnancy outcome.[26] Study involving Brazilian women of reproductive age exhibited Vitamin D deficiency, regardless of their fertility status.[27]

Serum prolactin level was 29.71±8.11, 29.69±11.52 and 45.9 ± 5.3 in euthyroid, hyperthyroid and hypothyroid patients respectively differing significantly ($p<0.05$). However, patients with hypothyroidism have significantly ($p<0.01$) higher levels of prolactin compared to control group of patients. Serum FT3 was highly significantly ($p<0.001$) lower (11.32±12.27) compared to control (19.14±7.45) group of patients. Number of patients diagnosed with hyperthyroidism (33.06±7.43 years) were significantly ($p<0.05$) older compared to control group of patients (30.99±6.4 years). Normal thyroid patients were diagnosed with TPO levels (26.09 ±9.51) significantly ($p<0.001$) higher compared to both hypothyroid and hyperthyroid patients. Serum TSH levels was significantly ($p<0.001$) lower in hyperthyroid and higher in hypothyroid patients compared to control group of patients.

Free serum thyroxine level was highly significantly ($p<0.001$) higher (11.47±1.98) higher compared to normal group of patients (7.73±3.13). These results are in line with the observation that the functioning of female reproductive system is regulated by functioning of hypothalamic-pituitary-ovarian axis. Hypothalamus releases GnRH to control the pituitary gland alterations in the hypothalamus affecting the pituitary gland, ovaries, thyroid and hence, hormonal abnormalities.[28] The sequence run chart analysis predicts that the change in level of TPO and age are independent factors in female fertility. However, to some extent there is an autocorrelation exists between TSH, FT4, FT3, Vitamin D and prolactin levels. A Study done in University of North Carolina in 2016 proving that thyroid hormones are important for normal reproductive function and concluded that women with thyroid autoimmunity, even with normal thyroid function, appear to be at a higher risk for poor reproductive outcomes and thyroxine replacement in women with thyroid autoimmunity will improve pregnancy outcomes.[29]

Pearson cross correlation analysis shows that there is a significant ($p<0.05$) correlation (0.417) between various thyroid group of patients and level of prolactin. It is also seen that serum TSH levels has significant positive correlation of 0.524 and 0.44 with group of patients and level of prolactin respectively. Whereas significant negative correlation is associated with FT3 and FT4 (-0.691, -0.511). A study was done to estimate the serum prolactin concentration in primary and secondary subfertile women.

Laboratory investigation included serum prolactin level, as well as LH, FSH and TSH of 50 women who attended infertility unit Dhaka, Bangladesh. They conclude that Serum prolactin concentration may have role to play in subfertility of women.[30] Hyperprolactinemia causes infertility by increasing the release of dopamine from the hypothalamus which inhibit GnRH and thus gonadal steroidogenesis.[31] Similarly, a study conducted on 69 female infertile patients concluded that high successful pregnancy rate and shorter duration of infertility until pregnancy after T4 treatment strongly suggest that T4 enhanced fertility in infertile patients.[32]

The stepwise multiple linear regression has shown that TSH and FT4 only have significant correlation with r^2= 0.275 and r^2= 0.571 (p<0.05 and p<0.01) respectively. The Durbin-Watson analysis indicates a first order linear auto-correlation in our multiple linear regression data which shows that approximately 27.5% and 57.1% of infertility cases could be associated with TSH levels and FT4 abnormalities. This also shows that decline in every 1.67 units of TSH will increase the risk for infertility by 24.3% whereas FT4 will increase the risk by 22.7%. Thus the predicted regression equation for infertility could be equal = (0.243 x TSH) + (0.227 x FT4) – 1.672. These results are more specific and could be more precise compared to earlier study results.[33-35]

A study done to assess reciprocal relationship of thyroid autoimmunity and pregnancy. TSH and antithyroid peroxidase autoantibodies (Anti-TPO) were evaluated retrospectively over an eight-year period in 444 Greek women who had previously none or at least one pregnancy (>28 weeks) concluded that pregnancy might contribute to the development of thyroid autoimmunity, women should be monitored for development of thyroid autoimmunity long after their pregnancies, even after an uneventful first conception, pregnancy and delivery of a live infant.[36] The sequence run chart analysis in our study predicts that the change in level of TPO is unpredictable of infertility and its type supporting above study. However, to some extent there is an autocorrelation exists between TSH, FT4, FT3, Vitamin D and prolactin levels.

The clustering analysis of factors considered in this study shows that there are three related clusters. The level of TSH are found to be closely associated with type of infertility and then FT3, FT4 and Vitamin D whereas age and prolactin level is distantly related to types of infertility. These results are supported by an extensive retrospective cross sectional study of 11254 women participating in The Danish General Suburban Population Study (GESUS) on the number of children born, the number of pregnancies and the number of spontaneous abortions. The conclusion was Impaired fertility is associated with TSH followed by TPOAb, FT3 and FT4.[37] Present study involves only patients visiting only one private hospital in Muscat and do not involve other hospitals in Oman.

Present study was carried out for a limited period i.e. from April 2017 to November 2017. The female infertility is a highly complex condition varying with multiple factors such as genetic, environmental, social, dietary, endocrine, neuronal and family environment. Therefore it is important to consider the influence of other factors. Weakness of our study includes that we missed significant data on serum Vitamin D levels and even data on menstrual disturbance, regularity of menstrual cycle and prolactin levels. This should be taken into consideration while interpreting the data. It is also important to mention here that the present study was carried out by involving students of graduation students of OMC.

CONCLUSION

In this project we aimed to find whether there is a relationship between thyroid health profile and female infertility. Results of our study shown a strong relationship FT3, FT4 and TSH with infertility. A distant relationship was seen with level of TPO, prolactin and age factors with types of infertility. We also found a strong relationship between TSH and prolactin levels. The primary infertility has stronger correlation between age, FT3, Vit D and prolactin with TPO. It is also shown that prolactin has stronger correlation with Vit D and TSH. Whereas in secondary infertility mainly the TPO has significant correlation with TSH, FT4, Vitamin D and prolactin. These results are in line with the observation that the functioning of female reproductive system is regulated by functioning of hypothalamic-pituitary-ovarian axis. We recommend further studies by involving more patients, hospitals and regions of Oman for an extended period for concrete outcomes and their possible implementation in practice.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TSH: Thyroid Stimulating Hormone; **FT3:** Free Triiodothyronine; **FT4:** Free Thyroxine (FT4); **TPO:** Thyroperoxidase; **TPOAb:** Thyroperoxidase Antibody.

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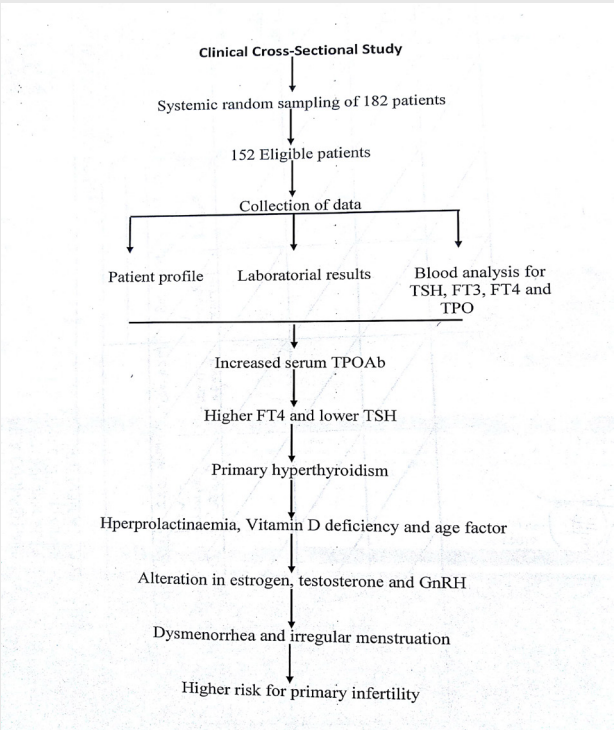
PICTORIAL ABSTRACT



SUMMARY

Based on results of our clinical cross sectional study among 152 patients shows that there is a highly significant relation between FT4 and TSH with fertility. FT3 could be considered as an additional cause for infertility in women.

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