Evaluation of the diagnostic utility of thyroid profile and thyroid antibodies in detecting subclinical hypothyroidism as part of a routine workup for women with infertility

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ABSTRACT:

OBJECTIVE:

To evaluate the diagnostic utility of thyroid profile and thyroid antibodies in detecting subclinical hypothyroidism as part of a routine workup for women with infertility.

MATERIALS AND METHODS:

Prospective case-control investigation was done in physiology department in collaboration with the department of gynecology and obstetrics at the JPMC Karachi, BMSI. Ethical approval for the study was obtained from IRB JPMC Karachi. Duration of study was 1 year from Jan 2018 till Jan 2019. There were 88 participants in the sample, who were split into two groups. Infertile group (group A) and control group (group B). Non-probability purposive sampling was employed because each group's subjects were chosen based on specified standards. In the current investigation, all subjects who met the eligibility requirements were registered. Each subject who took part gave their written consent. Information obtained was held in strict confidence. Data was analyzed using IBM SPSS version 23.

RESULTS:

Serum T3, T4, TSH, anti TPOAb, and TBG levels differed significantly between the two study groups. There was significant mean difference obtained for TSH and antiTPO antibodies between fertile and infertile samples with p-value less than 0.05.

CONCLUSIONS:

A trend towards subclinical hypothyroidism and the incidence of anti-thyroid antibodies was observed within females who had UE infertility, when their thyroid hormone profile was compared with fertile females. Anti TPO-Ab can be used as a screening tool as well as a marker for identification of the risk factors of infertility.

KEY WORDS:

Thyroid, Hypothyroidism , Infertility, Antibodies

INTRODUCTION:

Hypothyroidism can be the cause of various gynecological problems including disturbance of the menstrual cycle, infertility and increased risk of miscarriage [1]. Several mechanisms have been proposed. Elevated levels of thyrotropin-releasing hormone (TRH) caused by hypothyroidism, via a feedback loop, which causes excess secretion of prolactin. Moreover, metabolism of dopamine is changed by hypothyroidism that lowers dopamine levels and increases prolactin production. In addition, altered dopamine metabolism results in reduces levels of dopamine and increased prolactin secretion. Thus**,** hypothyroidism, followed by hyperprolactinemia, can lead to ovulatory dysfunction, luteal phase abnormalities**,** and even oligomenorrhea and amenorrhea. [2]. Additionally, dopamine slows the pulsation of gonadotropin-releasing hormone, which may result in an increase in lutenizing hormone (LH) [2–4]. Decrease in sex hormone-binding globulin (SHBG), a decrease in total estradiol, and an increase in the unbound fraction of testosterone and estradiol cused by hypothyroidism [2–4]. Reduced metabolic clearance of estrone and androstenedione [5]. Finally, increases in thyroid-stimulating hormone (TSH) and TRH may exacerbate luteal dysfunction through direct effects on the thyroid gland [6]. Lower levels of free thyroxine (T4), typically induced by lowered thyroid hormone release, are the cause of the clinical signs of hypothyroidism. Normal definitions of subclinical hypothyroidism (SH) include a high serum TSH level, normal free T4 levels, and a lack of overt hypothyroidism symptoms. [7]. It has long been standard practise to use the TRH stimulation test as an adjuvant in the evaluation or differential diagnosis of thyroid disorders [8,9]. Early-stage SH may be implicated by an aberrant TRH stimulation test, which is defined as an inflated TSH response to TRH challenge. According to various TRH stimulation test methods used to detect SH, between 11.3 and 24% of infertile women with ovulation disorder or corpus luteum insufficiency have the condition [10–14]. This variety is due to the diverse populations of women investigated, the various protocols, and the various TSH

measuring techniques. Some studies defined SH as having both abnormally high basal TSH levels and an aberrant response to the TRH test. But there is a dearth of conclusive information on the prevalence of SH among people who are infertile. [15], and As a result, there are no universally established standards for using TRH testing in infertile women who have ovulation disorders [2,16] and women with other causes for infertility versus not at all [15]. Furthermore, the question of how frequently to repeat endocrine examinations, particularly those that examine thyroid function, has not been well addressed because fertility treatments might last for months or even years. Antithyroid antibodies are frequently examined, even though they are not used to make the diagnosis of SCH; excessive levels have been linked to a higher chance of developing overt hypothyroidism.

The current study's objective was to assess the diagnostic value of thyroid antibodies and thyroid profiles in identifying subclinical hypothyroidism as part of a regular workup for infertile women.

RESULTS:

Table 1

Baseline characteristics of study groups

	Group A	Group B	P Value
Age (years)	31.57 ± 6.12	32.33 ± 5.83	0.556
Age of marriage (years)	23.32 ± 4.84	20.13 ± 6.32	0.025*
Duration of Marriage (years)	8.25 ± 4.43	10.35 ± 6.81	0.097
BMI kg/m^2	28.53 ± 4.38	23.41 ± 1.67	<0.001*

Group A: Women with unexplained infertility (cases)

Group B: Healthy parous women (controls)

Mean ± SD is given in table

***p<0.05 was considered significant using independent sample t-test**

Figure 1

Comparison of Thyroid Profile and antiTPO Antibodies

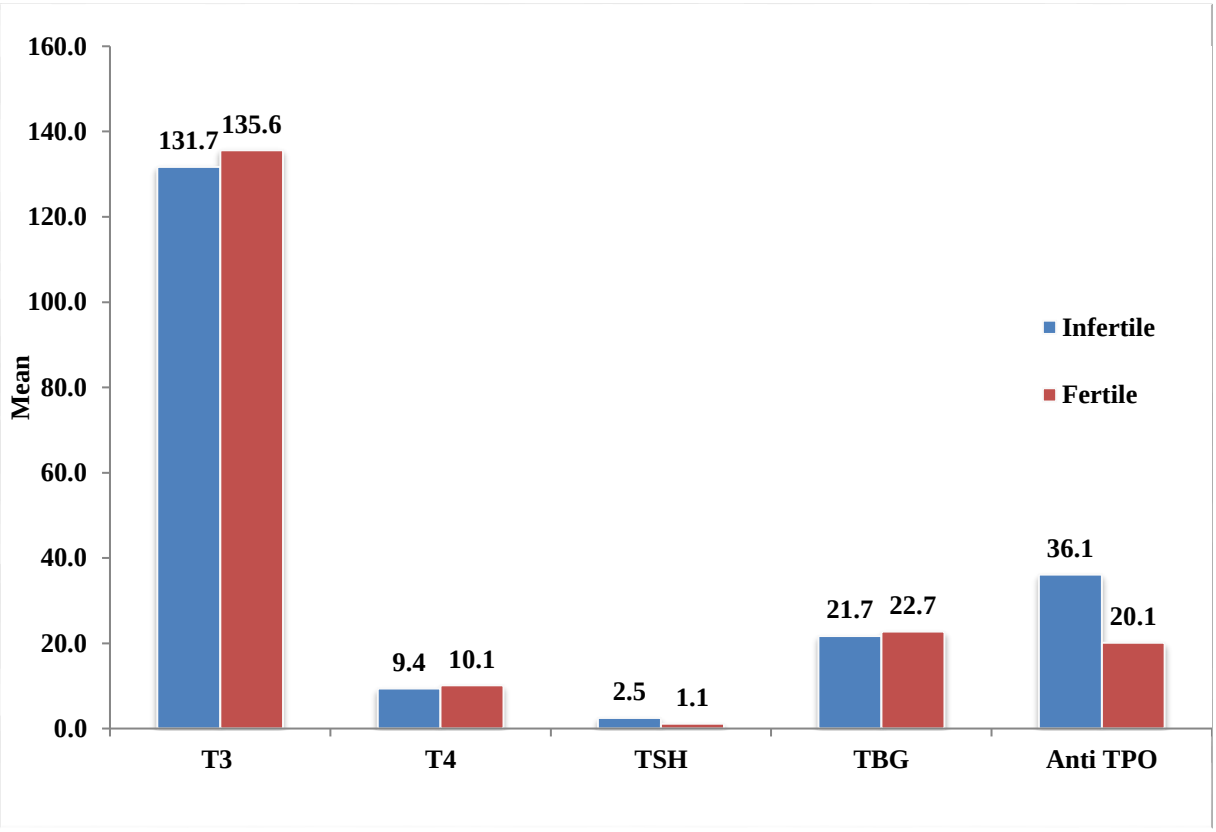

160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Mean
131.7
135.6
9.4
10.1
2.5
1.1
21.7
22.7
36.1
20.1
T3
T4
TSH
TBG
Anti TPO
Infertile
Fertile

Table 2

Correlation among Thyroid Profile and anti TPO

Parameters	T3	T4	TSH	TBG	antiTPO
T4	0.423 (0.0**)	1			
TSH	-0.002 (0.985)	-0.111 (0.304)	1		
TBG	-0.007 (0.948)	0.037 (0.735)	-0.068 (0.526)	1	
antiTPO	-0.212 (0.047)*	-0.292 (0.006)*	0.059 (0.582)	-0.146 (0.175)	1
BMI	-0.055 (0.608)	-0.087 (0.422)	0.155 (0.15)	-0.028 (0.797)	0.37 (0.0)**

Above values are: (p-value)

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

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

Figure 2

Association of T3 and antiTPO

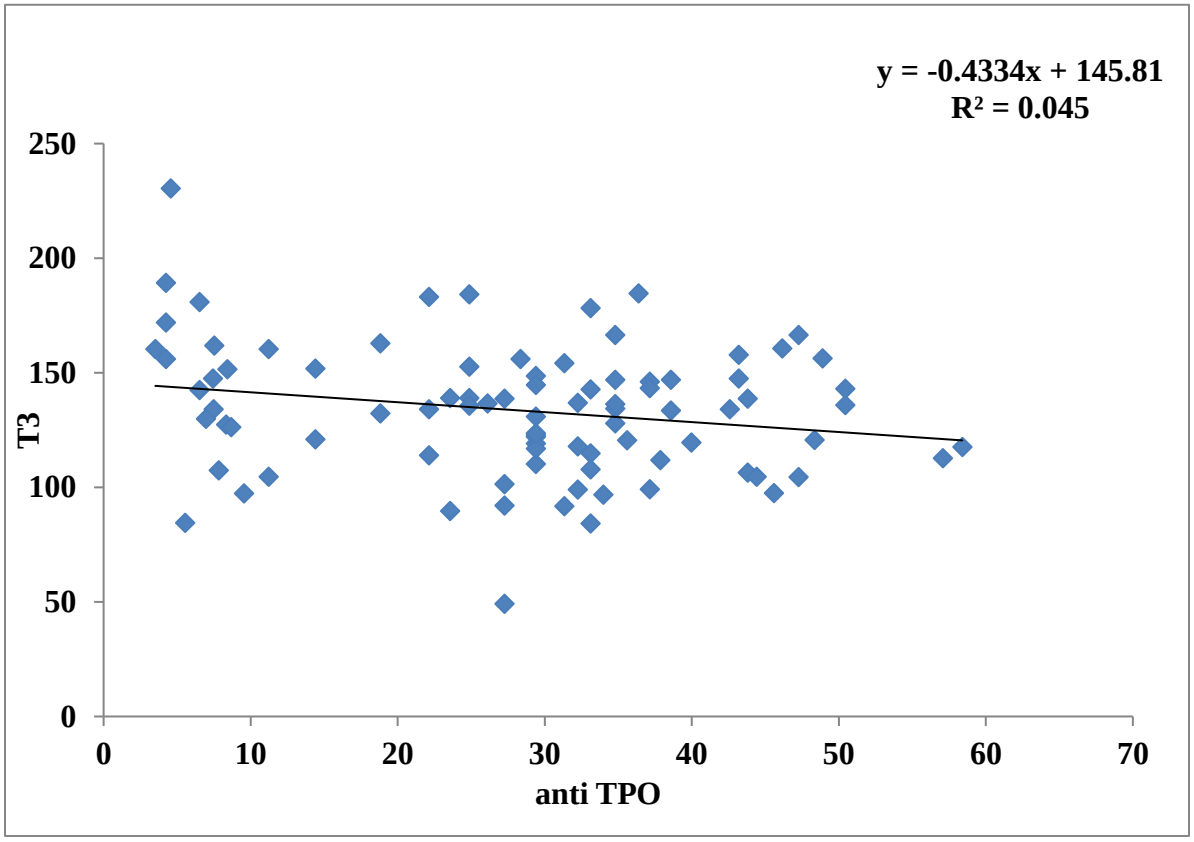
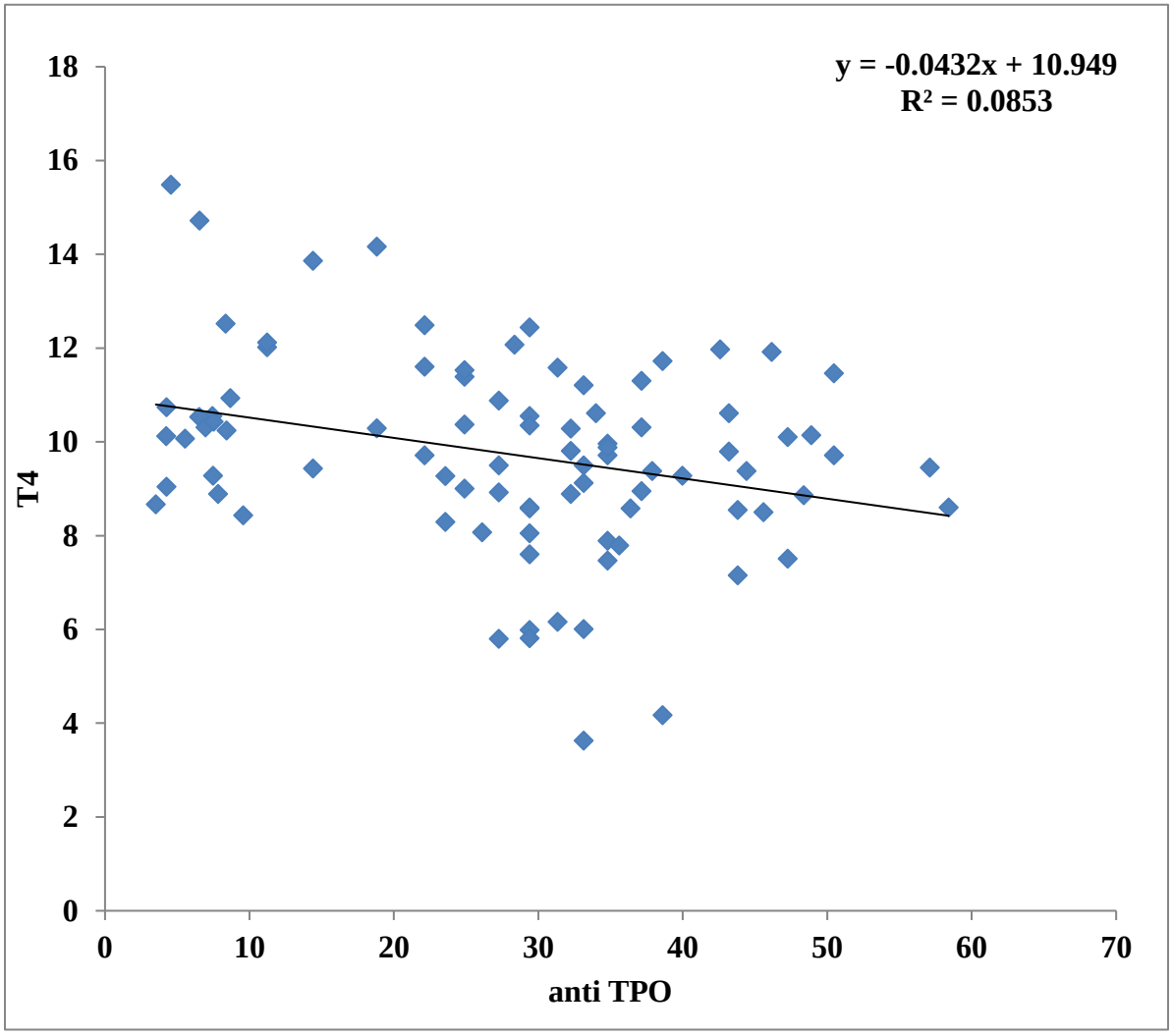


Figure 3

Association of T4 and antiTPO



DISCUSSION:

Infertility, a common problem among the general population, even though having numerous known reasons, there are still couples who are categorized as unexplained infertility (UI) as of the principal mechanism are not discovered [17]. Endocrine as well as immune system abnormalities can impair fertility [18]. A strong interaction among thyroid hormones and usual steroid action and secretion occurs, needed for the ovarian function and hence leading to fertility. Major studies have disclosed in the relevant literature concerned that association of hypothyroidism with disorders in fertility. In a recent systemic review it has been reported that the presence of thyroid antibodies was associated with an increased risk of unexplained subfertility UE miscarriage, recurrent miscarriage, preterm birth and maternal post-partum thyroiditis ,when compared with the absence of thyroid antibodies.

The purpose of the study was to assess the link of mild thyroid functional variation with the phenotype of UI. Conclusively, it was evident that women had a significantly higher TSH levels unknowingly. The mean of TSH was 2.47±1.97mIU/L in women with UI, as compared to 1.10±2.14mIU/L TSH levels in controls which suggested that mild abnormalities in thyroid function may contribute to some cases of UI. Thus, it is important to go for complete thyroid evaluation in all the patients with UI. It also raises the question of whether thyroid hormone replacement in women with TSH levels ≥2.5 mIU/L may be an economical first step in treating UI. Although, in current practices, guidelines do not recommend treating women with a TSH ≥2.5 mIU/L who are attempting to conceive naturally, however, some practitioners use this lower cutoff to initiate treatment [19].

Age distribution of the women of both the groups varied between 20-35 years. When we studied the descriptive analysis of the group A and group B, we found that infertile sample had mean age 31.57 ±6.12, whereas fertile samples had mean age 32±6.15 with p value (>0.05) showing no significant difference between both the groups.

In current study, mean T3 levels was 131.6±24.04 ng/dl in cases as compared to135.57±32.55ng/dl in controls, showing no significant difference. Although the T3 levels in infertile samples are decreased as compared to controls but important point is that the levels are within the normal, pre-pregnancy reference range.

When we compared T3 with other parameters, Pearson's correlation of T3 gives 42.3% significant positive correlation with T4, and 21.2% significant negative correlation with antiTPO. Rest of the correlations were insignificant.

Insufficient triiodothyronine (T3) results in hypothyroidism which is usually due to thyroid failure but can also be due to diseases of the pituitary or hypothalamus. Thyroid dysfunction has been recognized as an entity in a wide variety of gynaecological disorders ranging from abnormal sexual development to menstrual disorders, anovulation, infertility and reproductive wastage when pregnancy is achieved [20].

In present study mean tetraiodothyronine (T4) levels was 9.37±1.44 µgram/dl in infertile samples as compared to10.10±2.51µgram/dl in controls, showing no significant difference. Although, the T4 levels are comparatively low in infertile samples however, the levels are within the normal, pre-pregnancy reference range. When we compared T4 with other parameters, Pearson's correlations of T4 gives 29.2% significant negative correlation with antiTPO and 42.3% significant positive correlation with T3. Rest of the correlations of T4 are insignificant.

In present study mean TSH levels in infertile samples were 2.47±1.97mIU/L as compared to 1.10±2.14mIU/L in controls, difference was significant.

When we compared TSH with other parameters, Pearson's correlations of TSH gives 22.1% significant correlation with BMI. Rest of the correlations were insignificant.

Interestingly, in our study we found a significant increase in anti TPO-Ab titers in infertile patients .Mean anti TPO- Ab levels in infertile samples were 36.08±10.60 IU/ml as compared to20.13±12.30IU/ml in controls .showing highly significant difference.(<0.05) When we compared anti TPO- Ab levels with other parameters, Pearson's correlations of TPO-Ab gives 40% significant positive association with BMI, 21.2% significant negative correlation with T3,and 29.2% significant negative correlation with T4 .all other correlations were negligible

In the most studies for determining the relationship between autoantibodies and infertility, TPO-Ab have been measured, in addition to TSH , T3 and T4 levels. Our results are in agreement with other researchers who found a relationship between thyroid autoantibodies, and infertility.

A relatively elevated frequency of anti-thyroid antibody was seen among the women having infertility in contrast to the women having good health, indicating a probably autoimmune dysfunction as the core reason of their infertility, as previously suggested by some researchers.

This study recommends the Screening for thyroid function and thyroid auto-immunity as an essential part of the work-up of women with UE infertility. It also recommends that variations in TSH levels in the narrower range or borderline cases, ≥2.5 mIU/L should not be ignored in infertile women which are otherwise asymptomatic for clinical hypothyroidism. This 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.

CONCLUSIONS:

A trend towards subclinical hypothyroidism and the incidence of anti-thyroid antibodies was observed within females who had UE infertility, when their thyroid hormone profile was compared with fertile females. Anti TPO-Ab is independently associated with infertility irrespective of thyroid hormones levels and can be used for screening as well as the marker for identifying the risk factor of infertility.

REFERENCES:

1. Javaid S, Mastoi SW, Jahan E, Khalid S, Jabeen A, Mahajan N. Prevalence of Infertility and Its Causes in the Population of Pakistan: A Cross-Sectional Study. Annals of the Romanian Society for Cell Biology. 2022 Feb 6;26(01):129-33.
2. Geno KA, Nerenz RD. Evaluating thyroid function in pregnant women. Critical Reviews in Clinical Laboratory Sciences. 2022 Mar 15:1-20.
3. Poppe K, Bisschop P, Fugazzola L, Minziori G, Unuane D, Weghofer A. 2021 European thyroid association guideline on thyroid disorders prior to and during assisted reproduction. European thyroid journal. 2021 Feb 1;9(6):281-95.
4. Li L, Li L, Li P. Effects of controlled ovarian stimulation on thyroid function during pregnancy. Biology of Reproduction. 2022 Aug 12.
5. Poppe K. MANAGEMENT OF ENDOCRINE DISEASE: Thyroid and female infertility: more questions than answers?!. European journal of endocrinology. 2021 Apr 1;184(4):R123-35.
6. Ramees Fathima J. *A Study on Role of Thyroid Dysfunction and Thyroid Autoimmunity in Infertile Women: A Case control study* (Doctoral dissertation, Stanley Medical College, Chennai).
7. Anandappa S, Joshi M, Polanski L, Carroll PV. Thyroid disorders in subfertility and early pregnancy. Therapeutic Advances in Endocrinology and Metabolism. 2020 Oct;11:2042018820945855.
8. Silva JF, Ocarino NM, Serakides R. Thyroid hormones and female reproduction. Biology of reproduction. 2018 Nov 1;99(5):907-21.
9. Das D, Banerjee A, Jena AB, Duttaroy AK, Pathak S. Essentiality, relevance, and efficacy of adjuvant/combinational therapy in the management of thyroid dysfunctions. Biomedicine & Pharmacotherapy. 2022 Feb 1;146:112613.
10. Colella M, Cuomo D, Giacco A, Mallardo M, De Felice M, Ambrosino C. Thyroid hormones and functional ovarian reserve: systemic vs. peripheral dysfunctions. Journal of clinical medicine. 2020 Jun;9(6):1679.

11. Safarian GK, Gzgzyan AM, Dzhemlikhanova Lyailya K, Niauri DA. Does subclinical hypothyroidism and/or thyroid autoimmunity influence the IVF/ICSI outcome? Review of the literature. Gynecological Endocrinology. 2019 Jul 31;35(sup1):56-9.
12. Medenica S, Abazovic D, Ljubić A, Vukovic J, Begovic A, Cucinella G, Zaami S, Gullo G. The Role of Cell and Gene Therapies in the Treatment of Infertility in Patients with Thyroid Autoimmunity. International Journal of Endocrinology. 2022 Aug 30;2022.
13. Dosiou C. Thyroid and fertility: recent advances. Thyroid. 2020 Apr 1;30(4):479-86.
14. Oiwa A, Minemura K, Nishio SI, Yamazaki M, Komatsu M. Implications of thyroid autoimmunity in infertile women with subclinical hypothyroidism in the absence of both goiter and anti-thyroid antibodies: lessons from three cases. Endocrine Journal. 2019;66(2):193-8.
15. Chitme HR, Al Azawi E, Al Farsi MK, Abdul DM, Jalil MS. Thyroid Health and its Correlation to Female Fertility: A Pilot Study. INDIAN JOURNAL OF PHARMACEUTICAL EDUCATION AND RESEARCH. 2019 Jul 1;53(3):S404-15.
16. Inagaki Y, Takeshima K, Nishi M, Ariyasu H, Doi A, Kurimoto C, Uraki S, Morita S, Furukawa Y, Inaba H, Iwakura H. The influence of thyroid autoimmunity on pregnancy outcome in infertile women: a prospective study. Endocrine Journal. 2020:EJ19-0604.
17. Poppe K, Autin C, Veltri F, Kleynen P, Grabczan L, Rozenberg S, Ameye L. Thyroid autoimmunity and intracytoplasmic sperm injection outcome: a systematic review and meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2018 May;103(5):1755-66.
18. Wali AA, Abdelfattah W, Abd-El-Fatah SM. Prevalence of thyroid dysfunction and thyroid autoimmunity in infertile women. Evidence Based Women's Health Journal. 2020 Nov 1;10(4):308-15.
19. Ramees Fathima J. *A Study on Role of Thyroid Dysfunction and Thyroid Autoimmunity in Infertile Women: A Case control study* (Doctoral dissertation, Stanley Medical College, Chennai).
20. Andrisani A, Sabbadin C, Marin L, Ragazzi E, Dessole F, Armanini D, Dona G, Bordin L, Ambrosini G. The influence of thyroid autoimmunity on embryo quality in women undergoing assisted reproductive technology. Gynecological Endocrinology. 2018 Sep 2;34(9):752-5.