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Correlation of Thyroid Function Test and Cytomorphology with Obstetric Outcome in Females of Reproductive Age Group

Dr Varsha kumar, Pragya Pandey, Vatsala Mishra, Anshul Singh and Amrita Chaurasiya

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I. Introduction

Laboratory measurement of thyroid function plays an important role in the assessment of thyroid health. Maternal thyroid dysfunction has been associated with a variety of adverse pregnancy outcomes. Laboratory evidence of thyroid dysfunction is common in women of reproductive age, with the prevalence of elevated TSH ranging from 4 to 9%, and the prevalence of TPO-Ab ranging from 11.3 to 18% in this population.[1]Elevated maternal thyroid-stimulating hormone (TSH) has been associated with an increased risk of pre-term birth, placental abruption, fetal death, and impaired neurological development in the child.[1] Similarly, the presence of antibodies to thyroid peroxidase (TPO-Ab) has been associated with increased risk of miscarriage, preterm birth, and maternal post partum thyroid disease.[1]

Fine needle aspiration cytology of the thyroid gland is a well established, first-line diagnostic test for the evaluation of thyroid lesions with the main purpose of confirming their benign nature and thereby, reducing unnecessary surgery.[2] Due to its simplicity, low cost, and absence of major complications, it is the initial investigation in the management of thyroid disease. FNAC along with clinical examination and Ultrasound scanning forms the basis of a triple test for a thyroid nodule.[3]

II. Aims And Objectives

The present study was undertaken to study the correlation between thyroid function test, spectrum of cytomorphological findings of the various thyroid lesions and obstetric outcome in women of the reproductive age group. Antithyroid antibodies were measured wherever required.

III. Materials And Methods

This study included female patients between 15-45 years of age presenting in the OPD with thyroid gland enlargement. After informed consent, complete evaluation of all the patients was done including reproductive history and clinical examination. Females outside the reproductive age group, those presenting with acute inflammatory lesion and who had undergone biopsy previously were excluded from the study.

Detailed reproductive history was taken for each patient and included gravida, parity, history of missed, spontaneous, recurrent abortions, PIH, preeclampsia etc. Relevant gynaecological history i.e. abnormal uterine bleeding, primary/secondary infertility etc. was also recorded. The thyroid gland was examined with the patient sitting upright. Fine needle aspiration was performed using 24 gauge needle with the patient lying in supine position with hyperextension of the neck. The material was smeared on clean glass slides. Half of the smears were air-dried for Romanowsky stain (Leishman Giemsa) while the rest were wet-fixed in ethanol for Papanicolaou stain. If the aspirate was scanty, only Romanowsky stain was done as it ensures retention of 100% of cells on the slide.

Quantitative analyses of thyroid hormones (TSH, fT3 and fT4) and antibodies (TPO-Ab and TG-Ab) was performed using IMMULITE 1000 solid phase enzyme labelled chemiluminescent immune assay analyser. Manufacturer's reference intervals for various tests were as follows 0.4–5.4 mU/ml for TSH, 0.71-1.85 ng/dL for T4 , 1.4-4.2 pg/dL for fT3, non-detectable to 40 IU/ml for anti TPO and non-detectable to 20 IU/ml for anti TG-Ab as calculated by using serum specimens from individuals with normal thyroid function. Statistical analysis was performed using the Chi square test with and without Yates correction. $p \leq 0.05$ was taken as critical level of significance.

IV. Results

Seventy females of age ranging from 15-45 years and presenting with enlarged thyroid gland were included in the study. The most common age group involved was 15-25 and 36-45 years. 31.4 %(22/70) of these women presented with thyroid dysfunction with 15.7% cases of hypothyroidism and hyperthyroidism

each. 65.7% (46/70) females had an uneventful reproductive process and were categorised as normal reproductive performance group (NRP). 34.2 % (24/70) patients had history of spontaneous abortion, recurrent abortion, menstrual irregularities or infertility and were categorised as poor reproductive performance (PRP) group.

In the poor reproductive performance group, 33.3%(8/24) females were hypothyroid, 29.2%(7/24) were hyperthyroid and 37.5%(9/24) were euthyroid, on the basis of thyroid function tests. Patients with both hypothyroid and hyperthyroid status showed a significantly high prevalence of poor reproductive performance as compared to euthyroid patients.(p=0.0004; <0.05; p=0.0025 respectively) (Table 1)

On the basis of cytomorphology, sixty seven had non neoplastic (95.7%) and three had neoplastic lesions(4.3%). Colloid goiter was the most common non neoplastic lesion seen in 40 cases (59.7%) followed by autoimmune thyroiditis in 27/67 cases(40.2%). The neoplastic lesions included 2 cases (2.8%) of papillary carcinoma and 1 (1.4%)case of follicular neoplasm.

On cytological smear examination, 77.5% (31/40) cases showed clusters of follicular epithelial cells arranged in monolayered sheets and poorly cohesive groups in a background of abundant thin colloid. 22.5% (9/40) cases showed numerous macrophages in the background admixed with abundant colloid suggesting cystic degeneration. These cases were diagnosed as colloid goitre.(Fig 1) On assesment of the thyroid status in cases with colloid goitre, 62.5% (25/40) were euthyroid, 22.5%(9/40) patients were hypothyroid and 15%(6/40) were hyperthyroid. Out of 40 cases of colloid goitre included in the study, 22.5% (9/40) had associated cystic degeneration.

Poor reproductive performance was observed in 27.5%(11/40) cases of colloid goitre, out of which 20%(8/40)had associated cystic degeneration also. When compared the difference between colloid goitre with and without cystic degeneration (88.9%; 9.7% respectively) for poor reproductive performance was statistically significant. (p<0.00001) table 2

FNA smears from 27 cases showed the presence of follicular epithelial cells admixed with lymphocytes. Hurthle cells were seen in various proportions. Lymphocytes were seen infiltrating follicular cell clusters.(Fig2) Occasionally multinucleated giant cells, epithelioid cells and squamoid changes were seen. Cytological diagnosis of autoimmune thyroiditis was rendered in these cases.

In 11.1% cases(3/27) clusters of follicular epithelial cells showed peripheral fire flares and were found to be hyperthyroid. 22.2% cases (6/27) showed heavy lymphoid infiltrate on cytological smears. These cases had raised anti TPO levels compared to the rest of the cases, five out of these had levels exceeding 1000 IU/ml. Such relation was not observed with anti-TG levels.

In autoimmune thyroiditis, 74.1% (20/27) were euthyroid, 7.4% (2/27)were hypothyroid and 18.5% (5/27) had hyperthyroidism. Poor reproductive performance was seen 44.4% (12/27) cases of Autoimmune thyroiditis. On comparing the reproductive performance between colloid goitre and autoimmune thyroiditis, the results were not statistically significant when all the cases of goitre were included irrespective of cystic degeneration (p=0.1519). However upon excluding cases of colloid goitre undergoing cystic degeneration, the results were statistically significant. (p=0.0025)

Autoimmune thyroiditis was evaluated by the serum measurement of antithyroid antibodies. It was seen that in 25 out of 27 cases (92.6%) raised levels of Anti TPO levels were noted whereas 21 out of 27 cases (77.8%) displayed elevated levels of Anti TG. 44% cases of autoimmune thyroiditis showing positivity for anti TPO and 47.6% cases positive for anti TG had poor reproductive performance.

Comparison of reproductive performance between anti TPO and anti TG positive cases did not yield statistically significant results.(p=0.8)

Only 4.3% cases (3/70) represented neoplastic lesions comprising of two cases of papillary carcinoma and one case of follicular neoplasm. All three were euthyroid. Follicular neoplasm had a history of spontaneous abortion whereas both cases of papillary carcinoma had uneventful reproductive history. However in view of the lesser number of cases of neoplastic lesions, it would be futile to draw any conclusion.

V. Discussion

Thyroid gland influences almost all the metabolic processes in our body. Thyroid dysfunction leads to various metabolic disorder which is manifested in the form of hypothyroidism, hyperthyroidism and poor reproductive performance. One of the initial studies done by Glinoer et al in 1991 showed that thyroid function is intimately related to reproductive performance in female.[4] The menstrual pattern is influenced by thyroid hormones directly through impact on the ovaries and indirectly through impact on SHBG, PRL and GnRH secretion and coagulation factors. Subtle changes in thyroid hormones or the presence of autoantibodies leads to menstrual irregularities, infertility, abortions, still births and prematurity.

In our study, prevalance of thyroid dysfunction in women of the reproductive age was 31.4% with 15.7% cases of hyperthyroidism and hypothyroidism each. Prevalence of thyroid dysfunction in pregnancy in a study by Wang et al. was 10.2%; hyperthyroidism, hypothyroidism and hypothyroxinemia were 1.8, 7.5 and

0.9% respectively.[5]Studies from the Indian subcontinent reported prevalance of thyroid dysfunction in pregnant females ranging from 8.25%-12.46%.[6-7]

45.5% hypothyroid cases, 36.4% hyperthyroid and 12.5% euthyroid cases had poor reproductive performance in the present study. Patients with hypothyroid and hyperthyroid status showed a significantly high prevalence of poor reproductive performance as compared to euthyroid patients.($p=0.0004$; $p=0.0025$ respectively). Joshi et al reported a much higher prevalence of poor reproductive performance of approximately 74% in the form of infertility(6.2%) and menstrual iregularities(68%) in hypothyroidism.[8] Joshi et al reported 13.6% cases of infertility and 65% menstrual irregularities in hyperthyroid females. 44% euthyroid females had abnormal menstrual pattern while 19.3% had poor reproductive performance.[8] Various studies report prevalence of menstrual disturbances in hyperthyroidism ranging from 21.5%-65%.[9]

Studies that examined the incidence of infertility in hypothyroid patients are few and most studies revealed data on the prevalence of hypothyroidism in patients presenting to the infertility clinic. Gerhard et al, Raber et al reported prevalence of subclinical hypothyroidism of 43%, 34% in infertile women respectively.[10,11]This finding is in concordance with our study where 45.5% hypothyroid cases had poor reproductive performance.

In this study an attempt has been made to categorise lesions based on cytomorphology. Correlation of reproductive health with thyroid functions has been done in earlier studies but this is the first study where lesion has been categorized into benign and malignant and subtyped based on cytomorphology and results correlated with reproductive health.

On comparing the reproductive performance between colloid goiter and autoimmune thyroiditis, the results were not statistically significant($p=0.1519$). However upon excluding cases of goiter undergoing cystic degeneration, the results were statistically significant. ($p=0.0025$)

Poor reproductive performance was observed in 27.5% cases (11/40) of colloid goitre, out of which 20% (8/40) had associated cystic degeneration also. When compared, the difference between colloid goitre with and without cystic degeneration (88.9%; 9.7% respectively) for poor reproductive performance was statistically significant. ($p<0.00001$). Extensive pubmed search did not show any literature in which the pregnancy outcome in colloid goiter with and without cystic degeneration was compared. Adverse pregnancy outcome can be related to certain immunological mechanism underlying cystic degeneration in colloid nodule. Nguyen et al stated that the benign cysts are formed as a result of haemorrhagic degeneration of a benign colloid nodule.[12]

Poor reproductive performance was seen 44.4% (12/27) cases of Autoimmune thyroiditis, of which 18.5% (5/27) had normal thyroid function tests. This finding is in concordance with the study by Thangaratinam et al who concluded that in women with thyroid antibodies the risk of miscarriage is more than tripled and the risk of preterm birth is doubled, inspite of normal thyroid functions. [13]

Anti TPO was raised in 92.6%(25/27) of AIT whereas anti TG was raised in 77.8% cases(21/27). 44% (11/25) of anti TPO positive cases and 47.6% (10/21) of anti-TG positive cases had poor reproductive performance. Meta-analysis of case control studies on the association between miscarriages and the presence of antithyroid antibodies found odds ratio ranging from 0.71-8.41.[13]

Certain cytomorphological changes that correlated with serological profile were noted in our study. 18.5% cases (5/27) of autoimmune thyroiditis showed dense lymphocytic infiltrate so much so as to obscure the follicular epithelial cells.(ratio of lymphocytes: follicular epithelial cells >40:1) The heavy lymphoid infiltrate correlated with markedly raised levels of anti TPO to the range of >1000 IU/ml. One case had moderate lymphocytic infiltrate with anti TPO levels of 642 IU/ml. These findings were in concordance with that of Jayaram et al who showed TPO antibodies to bear a significant correlation with high lymphoid:epithelial ratio. Such a relationship was not observed for anti-TG levels.[14]

11.1% (3/27) cases of AIT showed abundant marginal vacuoles/fire flares and were found to be hyperthyroid. Findings were in concordance with the study by Gupta et al, who postulated that marginal vacuoles represent diffusing out of thyroid hormones and hence are representative of hyperthyroid status. [15]

VI. Conclusion

Thyroid function tests and thyroid autoantibodies should be mandatory in females presenting with a history of poor reproductive performance. During the ante natal check up, even in case of normal thyroid function, thyroid auto antibodies should be investigated for timely management of such cases and for early detection of subtle alterations which may lead to adverse pregnancy outcome.

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Table 1: Thyroid Status And Reproductive Performance

THYROID STATUS	NRP	PRP	TOTAL
EUTHYROID	39	9	48
HYPERTHYROID	4	7	11
HYPOTHYROID	3	8	11
	46	24	70

TABLE 2: REPRODUCTIVE PERFORMANCE AND CYTOMORPHOLOGICAL DIAGNOSIS

CYTOMORPHOLOGICAL DIAGNOSIS	NRP	PRP	TOTAL
COLLOID GOITRE	28	3	31
COLLOID GOITRE UNDERGOING CYSTIC DEGENERATION	1	8	9
AUTOIMMUNE THRYOIDITIS	15	12	27
TOTAL	44	23	67

TABLE 3: REPRODUCTIVE PERFORMANCE AND THYROID AUTOANTIBODIES

ANTIBODY STATUS	TPO		TG	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
NRP	14	1	11	2
PRP	11	1	10	2
	25	2	21	6

Figure legends :
Figure 1 – LG 100X- Cluster of follicular epithelial cells admixed macrophages in a background of thin colloid.
Figure 2- LG 100X- Lymphocytes infiltrating cluster of follicular epithelial cells in a haemorrhagic background.

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