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Assessment And Co-Relation Of Thyroid Function Parameters In Pregnancy With First Trimester Vaginal Bleeding And Its Outcome In Early Pregnancy

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ABSTRACT

Background: To study the assessment and co-relation of thyroid function parameters in patients with first trimester vaginal bleeding and to study its pregnancy outcome.

Method: The prospective observational study was conducted in the department of obstetrics and gynecology, MRAMC Ambedkar nagar during one year period from march 2023 to march 2024 with the sample size of 151 patients who fit the inclusion criteria were included in the study after obtaining an informed and written consent.

Results: Among the 151 patients, a total of 89 (58.94%)were Euthyroidism, 57 (37.75%) were hypothyroidism, 3 (1.99%) were hyperthyroidism and 2 (1.32%) were patients with autoimmune thyroid disease. Among the 151 patients, 18 (31.58%) with hypothyroidism and 2 (100%) with autoimmune thyroid disease tested positive for TPO antibodies. . Abortions occurred more frequently in hypothyroidism in 24 patients (42.11%) followed by 9 in euthyroidism (10.11%). In normal TSH levels i.e Less than 2.5 µIU/L, abortion was found in 27.27%. Moreover the TSH more than 2.5 µIU/L was found significantly more in aborted as compared to continued pregnancy.The Anti-TPO antibodies level more than 9 IU/ml was significantly more (48.48%) in aborted as compared to continued pregnancy (3.39%).

Conclusion: There is positive correlation between thyroid disorders and adverse outcome in early pregnancy. The patients are in increased risk of having miscarriage in early pregnancy. Among the thyroid function test parameters ,serum TSH and anti TPO Antibodies have positive correlation with adverse outcome like miscarriage in early pregnancy .Hence Serum TSH And Anti TPO antibodies can be used as predictor for adverse outcome in early pregnancy so it can be routinely recommended for screening for adverse outcome in the first trimester.

Keywords: Thyroid function test, First trimester vaginal bleeding, Outcome, early Pregnancy

Introduction

Thyroid hormones are very important for the development and growth of the fetus. There are significant anatomical, physiological and biochemical changes in pregnancy including thyroid gland. It is very important to differentiate the physiological changes from the pathological. Thyroid gland undergoes significant changes in pregnancy anatomically and physiologically. In anatomical changes there is moderate enlargement with increasing vascularization of thyroid gland. Metabolic

demands and hormonal changes during pregnancy result in significant alterations in the biochemical parameters of thyroid function. Due to structural similarity of B –HCG with thyroid stimulating hormone , thyrotrophic activity of B –HCG also cause a decrease of serum TSH in pregnancy. Hence, serum TSH are lower in pregnant woman than non pregnant woman[1].

Total concentrations of thyroxine (T4) and of triiodothyronine (T3) increase in early pregnancy and achieve a plateau early in the second trimester, reaching a concentrations value of 30-100% greater than pre-pregnancy levels, primarily following the rise in TBG[2]. ·Some authors have reported a decrease of free T4 and T3 concentrations, whereas others have reported no change or even an increase; therefore changes in free-hormone during pregnancy are controversial, though pregnant women in general have lower free-hormone concentrations at term than non-pregnant women [3,4].Anti-TPO antibodies are auto-antibodies directed against thyroid peroxidase protein which belong to the IgG immunoglobulin c. These antibodies are found in people who have thyroid disease , but also noticed in healthy people[5].

The thyroid-binding globulin (TBG) circulating levels are also increased by estrogen level. The circulating level of TBG increases due to increased hepatic synthesis and estrogen mediated prolongation of TBG half-life from 15 minutes to 3 days, after few weeks of conception and reaches a plateau during mid of the gestation[6].

First trimester vaginal bleeding is one of the most common complication encountered in early pregnancy and its incidence is 15-25%[7,8].Vaginal bleeding in pregnancy is a warning sign prompting for immediate assessment of the early pregnancy to identify the cause of the bleeding, complication and risk factor associated with the pregnancy at the earliest. There are various causes of first trimester vaginal bleeding, among them miscarriage and ectopic pregnancy are the most common causes. It can be physiological and pathological. It is very important to identify the pathological cause and treat at the earliest to prevent further complications and pregnancy loss.

There are various causes of miscarriage in first trimester including genetic factors, infections, endocrine disorders, medical disorders, anatomical abnormalities of uterus among these genetic factors is the most common cause in the early pregnancy loss.Thyroid disorders is one of the most common endocrine disorders in pregnancy. Thyroid disorders can be hypothyroidism or hyperthyroidism, it can be subclinical or overt. Thyroid disorders in early pregnancy can cause adverse effects like miscarriage.

Thyroid dysfunctions are common in women during 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 the population[9,10]. Among the thyroid function test ,S TSH and Anti TPO antibodies are implicated the adverse outcome in the pregnancy in many studies..

This study is being undertaken to study the thyroid function parameters in pregnancy with first trimester vaginal bleeding and its correlation with early pregnancy loss and outcome of early pregnancy is noted.

Methods

The Prospective Observational Study was conducted in the department of obstetrics and gynaecology, MRAMC, Ambedkar nagar during one year period from march 2023 to March 2024. This clinical study comprises of 170 women who fulfilled the criteria but 19 woman didn't follow up hence they were left out of the study, hence only 151 patients were considered for the study. The study protocol was approved by institutional ethical committee. All subjects were included in the study after obtaining an informed and written consent. Participation in the study was voluntary.

Inclusion criteria

All pregnant patients of singleton pregnancy presented with first trimester vaginal bleeding delivering at study institutions were chosen for the study

Exclusion criteria

Twin pregnancy, high risk pregnancy (hypertension, diabetes, severe anaemia), non-obstetrical causes of vaginal bleeding in pregnancy and medical causes like coagulopathies were excluded from the study.

Methodology

Pregnant women as per exclusion and inclusion criteria was considered and taken into the study. Pregnancy was confirmed by a pregnancy test. A detailed clinical history, clinical examination, systemic examination of the patient who satisfy the criteria. A detailed information of associated symptoms as well as bleeding regarding timing, heaviness, duration with the bleeding was noted.

Heaviness was defined according to the heaviest bleeding in an episode, and was compared to heaviness of usual menses. A 'spotting' episode was only noticed when wiping, a 'light bleeding' episode was defined as having the heaviest day(s) of flow being lighter than the heavy flow of a usual menstrual period, and a heavy bleeding episode was defined as having the heaviest day(s) of flow as heavy or heavier than the heavy flow of a usual menstrual period[11]. All patients were closely monitored by frequent follow up till the end of first trimester.

Biochemical investigations like thyroid function test, kidney function test, liver function test, clotting time, bleeding time, complete haemogram , reticulocyte count, coagulation profile, viral markers including VDRL were done in all patients.

In thyroid function test free T3, free T4,Serum TSH, Anti-TPO was assesed. Blood sample was collected in fasting state by venupuncture ,allowed to clot, and serum is separated by centrifugation at room temperature. The serum is stored at 2 to 8°C and all parameters was estimated by using enzyme-linked immunoassay (ELISA) method.

Thyroid disorders can be classified as either hypothyroidism or hyperthyroidism. Euthyroid in first trimester are defined as those having normal TSH (0.1-2.5 μIU/l). Subclinical hypothyroidism is defined as high TSH (>2.5 μIU/l) with normal levels of Free T4 (0.8-2.0ng/dl). Overt hypothyroidism in pregnancy is defined when there is high TSH (>2.5 μIU/l) with low Free T4 (<0.8 ng/dl). overt hyperthyroidism is thyroid condition when there is high Free T4 (>2.0 ng/dl) with decreased TSH(<0.2 μIU/l) and Subclinical hyperthyroidism is when there is low serum TSH (<0.2 μIU/l) concentration with normal Free T4 (0.8-2.0 ng/dl).

Ultrasound to identify the location of pregnancy, gestational age and presence of cardiac activity was done at the first point of contact and review ultrasound was done at the end of first trimester including NTNB Scan. The feto-maternal outcome of the pregnancy at the end of first trimester and the complications associated will be noted. Fetal outcome was assessed by viability at the end of first trimester.

The statistical analysis of results was done by using SPSS (Statistical package for social science) versions 16 statistical analysis software. Discrete (categorical) data were summarized as in proportions and percentages (%) and mean ± SD (standard deviation). The values were represented in number (%) and mean ± SD.**Results**

A total of 151 patients were included in this study. Of the 151 patients, a total of 89 (58.94%)were Euthyroidism, 57 (37.75%) were hypothyroidism, 3 (1.99%) were hyperthyroidism and 2 (1.32%) were patients with autoimmune thyroid disease The baseline characteristics of socioeconomic

status, residence, education, religion, parity, abortion history and complications differed significantly between thyroid conditions, as shown in Table 1.

Table 1: Association of baseline characteristics of the patients with different thyroid States

		Euthyroidism (n=89)		Hypothyroidism (n=57)		Hyperthyroidism (n=3)		Autoimmune thyroid disease (n=2)		p-Value
		n	%	n	%	n	%	n	%	
Age (years)	Mean± SD	25.20±3.18		26.84±4.85		24.33±4.93		26.00±2.83		0.094
SES	Lower	56	62.92	42	73.68	3	100.00	0	0.00	<0.001*
	Middle Lower	31	34.83	11	19.30	0	0.00	0	0.00	
	Middle	2	2.25	4	7.02	0	0.00	2	100.00	
Residence	rural	44	49.44	49	85.96	3	100.00	0	0.00	<0.001*
	urban	55	61.80	8	14.04	0	0.00	2	100.00	
Education	Primary	32	35.96	21	36.84	0	0.00	0	0.00	0.039*
	Secondary	18	20.22	8	14.04	0	0.00	2	100.00	
	Graduate	39	43.82	28	49.12	3	100.00	0	0.00	
Religion	Hindu	23	25.84	55	96.49	3	100.00	0	0.00	<0.001*
	Muslim	66	74.16	0	0.00	0	0.00	0	0.00	
	Christian	10	11.24	0	0.00	0	0.00	2	100.00	
	Sikh	0	0.00	2	3.51	0	0.00	0	0.00	
Parity	Nulliparous	0	0.00	40	70.18	0	0.00	0	0.00	<0.001*
	multipara	89	100.00	17	29.82	3	100.00	2	100.00	
Abortion History	Yes	0	0.00	48	84.21	3	100.00	0	0.00	<0.001*
	No	89	100.00	8	14.04	0	0.00	2	100.00	
Complications	Yes	13	14.61	29	50.88	0	0.00	0	0.00	<0.001*
	No	76	85.39	28	49.12	3	100.00	2	100.00	

*=Significant (p<0.05)

Table 2: Association of mean thyroid function, Anti TpO (IU/L) and GA Bleeding of the patients with different thyroid States

	Euthyroidism (n=89)		Hypothyroidism (n=57)		Hyperthyroidism (n=3)		Autoimmune thyroid disease (n=2)		p-Value
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	
S. TSH (mIU/l)	1.27	0.47	6.26	2.39	0.02	0.02	1.80	0.42	<0.001*
Free T4 (ng/dl)	1.06	0.16	1.33	1.97	0.94	0.37	1.08	0.11	0.638
Free T3 (pg/ml)	3.26	0.82	1.93	1.27	2.80	1.65	3.90	0.57	<0.001*
Anti TpO (IU/L)	2.99	1.16	103.32	194.21	3.07	1.15	885.00	261.63	<0.001*

GA Bleeding	7.35	1.58	8.41	1.64	7.60	2.18	7.20	1.56	0.002*

*=Significant (p<0.05)

Table 2 shows the relationship between mean thyroid function, anti-TpO (IU/L) and GA bleeding in the patients with different thyroid conditions. The TSH value was significantly higher in hypothyroidism, followed by autoimmune thyroid disease and euthyroidism. In addition, the mean free T3 (pg/ml) differed significantly between the different thyroid stages. The mean anti-TpO level was significantly higher in autoimmune thyroid disease than in hypothyroidism. Mean GA bleeding was significantly higher in hypothyroidism than in euthyroidism and autoimmune thyroid disease.

Table 3: Association of TPO Antibody status, Type of Bleeding, Associated Symptom and Viability of the patients with different thyroid States

		Euthyroidism (n=89)		**Hypothyroidism (n=57)**		**Hyperthyroidism (n=3)**		**Autoimmune thyroid disease (n=2)**		**p-Value**
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
TPO Antibody status	Positive	0	0.00	18	31.58	0	0.00	2	100.00	<0.001*
	Negative	89	100.00	39	68.42	3	100.00	0	0.00	
Type of Bleeding	Spotting	76	85.39	5	8.77	1	33.33	2	100.00	<0.001*
	Mild	0	0.00	32	56.14	0	0.00	0	0.00	
	Moderate	12	13.48	5	8.77	2	66.67	0	0.00	
	Heavy	1	1.12	17	29.82	0	0.00	0	0.00	
Associated Symptom	Pain abdomen	15	16.85	18	31.58	2	66.67	0	0.00	0.001*
	Nausea	11	12.36	5	8.77	1	33.33	0	0.00	
	Weakness	0	0.00	16	28.07	0	0.00	0	0.00	
	Back pain	0	0.00	2	3.51	0	0.00	0	0.00	
	Loss of appetite	0	0.00	11	19.30	0	0.00	0	0.00	
Viability	Non-viable	11	12.36	23	40.35	0	0.00	0	0.00	0.001*
	Viable	78	87.64	34	59.65	3	100.00	2	100.00	

*=Significant (p<0.05)

The above table shows the association of TPO antibody status, type of bleeding, associated symptom and viability of the patients with different thyroid states. Among the 151 patients, 18 (31.58%) with hypothyroidism and 2 (100%) with autoimmune thyroid disease tested positive for TPO antibodies. Patients with hypothyroidism were higher likely to experience heavy bleeding.

Abdominal pain was frequently observed in patients with hyperthyroidism and less frequently in patients with hypothyroidism. The prevalence of nausea is higher in hyperthyroidism than in euthyroidism. In addition, hypothyroidism has been associated with a higher prevalence of weakness, back pain and loss of appetite .The term "not viable" was found most frequently in hypothyroidism, while euthyroidism was the second most common.

Table 4: **Association of different thyroid States with pregnancy outcome**

Outcome	Euthyroidism (n=89)		Hypothyroidism (n=57)		Hyperthyroidism (n=3)		Autoimmune thyroid disease (n=2)		p-Value
	n	%	n	%	n	%	n	%	
Aborted	9	10.11	24	42.11	0	0.0	0	0.0	
Pregnancy continued	80	89.89	33	57.89	3	100.0	2	100.0	<0.001*

*=Significant (p<0.05)

Table 4 shows the relationship between the different thyroid conditions and pregnancy outcome. Abortions occurred more frequently in hypothyroidism in 24 patients (42.11%) followed by 9 in euthyroidism (10.11%).

Table 5: **Association of different TSH level and Anti- TPO level with pregnancy outcome**

		Aborted (n=33)		Pregnancy continued (n=118)		p-Value
		n	%	n	%	
TSH level	≤2.5	9	27.27	85	72.03	<0.001*
	2.6-5.0	8	24.24	16	13.56	
	5.1-7.5	7	21.21	11	9.32	
	7.6-10	5	15.15	6	5.08	
	>10	4	12.12	0	0.00	
Anti-TPO	>9 IU/ml	16	48.48	4	3.39	<0.001*
	≤9 IU/ml	17	51.52	114	96.61	

*=Significant (p<0.05)

In normal TSH levels i.e Less than 2.5 µIU/L, abortion was found in 27.27%. Moreover the TSH more than 2.5 µIU/L was found significantly more in aborted as compared to continued pregnancy. The Anti-TPO antibodies level more than 9 IU/ml was significantly more (48.48%) in aborted as compared to continued pregnancy (3.39%).

Table 6: Correlation of thyroid function, Anti TPO (IU/L) and GA bleeding of the patients with adverse outcome

	Pearson Correlation	p-Value
S. TSH (mIU/l)	0.299	<0.001*
Free T4 (ng/dl)	-0.131	0.108

Free T3 (pg/ml)	-0.086	0.292
Anti TpO (IU/L)	0.077	0.347
GA Bleeding	0.277	0.001*

*=Significant ($p<0.05$)

Table 6 shows the correlation of thyroid function parameters, anti-TpO (IU/L) and GA bleeding of the patients with adverse outcome. S. TSH and Anti-TPO was significantly positively correlated with unfavourable outcome, while GA bleeding was significantly negatively correlated with adverse outcome. In addition, free T4 (ng/dl), free T3 (pg/ml) and anti TpO (IU/L) were not significantly correlated with adverse outcome.

Discussion:

Thyroid function is of paramount importance during pregnancy as thyroid hormones are vital for the development of the unborn foetus and health of the mother. Physiological changes that occur during pregnancy can affect thyroid hormone levels. In addition, pre-existing thyroid problems or abnormalities in TSH levels can alter pregnancy outcomes[12]. Alteration in endocrine and metabolic status during pregnancy could potentially affect thyroid hormone levels. There are several factors that may explain the changes in thyroid function during pregnancy: (1) inadequate iodine levels during pregnancy; (2) the effects of human chorionic gonadotropin (hCG) on the activation of thyroid function, which stimulates the release of thyroid hormones. This can interfere with adenohypophyseal function and decrease thyrotropin levels; (3) higher estrogen levels during pregnancy, which increase blood levels of thyroid-binding globulin (TBG) and increase the concentration of total thyroxine; and (4) the influence of the placenta on thyroxine degradation[13]. Therefore, the standard TSH reference ranges for pregnant women differ from those for non-pregnant women. To avoid confusion between euthyroid function and thyroid disease, it is essential to use accurate reference ranges for TSH and thyroid hormones during pregnancy.

1.Our study showed a strong positive correlation between S. TSH levels and poor early pregnancy outcome, especially miscarriages. In addition, the presence of more than 2.5 S.TSH was found to be significantly higher in terminated pregnancies than in continuing pregnancies.

Studies suggest that both underactive (hypo-) and overactive (hyper-) thyroid can lead to adverse pregnancy outcomes if not well controlled. Hypothyroidism, which is characterised by elevated TSH levels and reduced thyroid hormone levels, has been associated with miscarriage, premature birth, low birth weight and developmental problems in children[14].

Monitoring thyroid function is essential in the context of abortion, especially in those with thyroid problems or high TSH levels. Thyroid disease can exacerbate the risks associated with pregnancy and influence the abortion decision-making process[15].

Recent studies have shown an association between subclinical hypothyroidism during pregnancy and adverse outcomes such as preterm delivery, placental abruption and gestational diabetes[16.17.18.19]. However, the effect of subclinical hypothyroidism on the likelihood of miscarriage is still uncertain. Zhang et al (2017) found that women with untreated subclinical hypothyroidism (SCH) in early pregnancy had a 1.9-fold higher risk of miscarriage than women with normal thyroid function. This suggests that SCH may serve as a predictive factor for miscarriage[20].

A study conducted by Casey et al (2005) found that women with subclinical hypothyroidism, characterized by elevated TSH levels but normal thyroid hormone levels, had a greater susceptibility to miscarriage compared to women with normal thyroid function, referred to as euthyroid women. This study suggested a possible link between elevated levels of thyroid

stimulating hormone (TSH) and the occurrence of miscarriage during pregnancy. However, other studies have produced contradictory results[21].

2. The Anti-TPO antibodies level more than 9 IU/ml was significantly more (48.48%) in aborted as compared to continued pregnancy (3.39%).

A meta-analysis conducted by Thangaratinam et al (2011) found that thyroid auto-antibodies were positively correlated with a higher likelihood of miscarriage. However, the study found no significant correlation between TSH levels and the risk of miscarriage[22].

A study by Wang et al. (2020) found that maternal subclinical hypothyroidism (SCH) was associated with a significantly higher likelihood of miscarriage compared to normal thyroid function (euthyroidism)[23].

However, in a study conducted by Korevaar et al. (2019), it was found that there was no significant association between TSH levels and the likelihood of spontaneous abortion, even after accounting for possible factors that could influence outcomes[24].

According to Maraka et al (2019), women who tested positive for TPOAb and had a TSH level greater than 2.5 mIU/L during early pregnancy were more likely to miscarry. These results suggest that the presence of thyroid autoimmunity together with elevated TSH levels may increase the likelihood of miscarriage[25]. In their study, Liu et al (2021) investigated the association between TSH levels and the likelihood of miscarriage in a large group of expectant mothers. The results suggest that elevated or decreased TSH levels in the early stages of pregnancy were associated with a higher likelihood of miscarriage. The highest risk was found in women whose TSH levels were outside the range considered normal[26].

Conclusion

There is positive correlation between thyroid disorders and adverse outcome in early pregnancy. The patients are in increased risk of having miscarriage in early pregnancy. Among the thyroid function test parameters ,serum TSH and anti TPO Antibodies have positive correlation with adverse outcome like miscarriage in early pregnancy .Hence S TSH And Anti TPO antibodies can be used as predictor for adverse outcome in early pregnancy so it can be routinely recommended for screening for adverse out in the first trimester.

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