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Study of Thyroid Disorders in Pregnancy

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Abstract:
Objective*: To evaluate thyroid profile in pregnancy with special reference to anti-TPO antibodies and maternal and foetal outcomes in those with deranged thyroid profile.*
Materials and Methods*: It was a prospective study done at Rajendra Hospital and GMC, Patiala. 500 pregnant women with singleton pregnancy irrespective of age, gestational age, parity and socioeconomic status were included. Those with multiple pregnancy and known case of any thyroid disorder were excluded. Written informed consent obtained. A detailed history and examination was done .Along with routine investigations estimation of T3, T4 and TSH was done. In those with deranged thyroid function tests, anti TPO antibody levels was estimated. Patients with deranged thyroid profile were followed up for pregnancy outcomes and maternal and foetal complications during subsequent visits to the hospital or through telephonic registry.*
Results*: From this study it was concluded that prevalence of thyroid disorders in pregnant women was considerably high (11.8%) with subclinical hypothyroidism being the most common (7.6%), followed by overt hypothyroidism (2.6%), subclinical hyperthyroidism (1.2%) and overt hyperthyroidism (0.4%). In cases with subclinical hypothyroidism, pre-eclampsia was the most common maternal complication (13.16%) followed by preterm delivery (7.89%). Statistically significant association with was found in IUGR (p=0.011) and LBW (p=0.011). In overt hypothyroidism, most common maternal complication was preterm delivery (15.38%) while statistically significant association was found with low birth weight. Overall, the association of anti TPO antibody with respect to maternal and foetal complications was found to be statistically significant (p=0.034).*
Conclusion*: The presence thyroid disorders and anti TPO antibody confers a statistically significant risk with respect to increased chances of abnormal pregnancy outcomes as well as maternal and foetal complications during pregnancy. Therefore, it is essential to screen all pregnant women for thyroid dysfunctions with special reference to autoimmune evaluation to reduce maternal and foetal morbidity as well as mortality.*

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I. Introduction

Thyroid disorder comprise the second most common endocrine disease after diabetes mellitus that affects women in their reproductive years.(1) Hence, it presents commonly as an intercurrent disease during pregnancy and puerperium.(2) Pregnancy is associated with various changes in thyroid physiology in order to ensure an optimal thyroid environment for foetal growth and development. There is increased requirement for maternal thyroid hormone production and secretion during pregnancy. In order to successfully adapt to these pregnancy related alterations, a normally functioning thyroid gland and an adequate iodine intake are required. The changes in thyroid physiology during a normal pregnancy are also reflected in altered thyroid function tests. Symptoms of thyroid disease often mimic the common symptoms and complains of pregnancy, making it difficult to identify the disease. Poorly controlled or undiagnosed thyroid disease is associated with adverse maternal and foetal outcomes during pregnancy and therefore, prompt diagnosis and early treatment become essential part of prenatal care in order to to ensure maternal and fetal well-being.(1,3,4) Hypothyroidism is present in up to 3% of pregnancies, of which 0.3–0.5% is overt and 2.0–2.5% is subclinical hypothyroidism.(3,4) Western

literature shows a prevalence of hypothyroidism in pregnancy of 2.5% and prevalence hyperthyroidism in pregnancy of 0.1 to 0.4%.[5] There is scarcity of data on prevalence of thyroid disorders in pregnancy in Indian women. A few reports show a prevalence of 4.8% to 11% amongst Indian pregnant population.[6,7] The most important cause of maternal thyroid deficiency all remains to be iodine deficiency, affecting approximately 1.2 billion individuals.[8] The major maternal and foetal complications encountered in an ongoing pregnancy with hypothyroidism are:[9,10]

- Preeclampsia and gestational hypertension
- Placental abruption
- Maternal anaemia
- Nonreassuring fetal heart rate tracing
- Preterm delivery
- Low birth weight
- Increased rate of cesarean section
- Postpartum hemorrhage
- Perinatal morbidity and mortality
- Neuropsychological and cognitive impairment in the child.

Western literature shows a prevalence of hyperthyroidism in pregnancy prevalence of 0.1 to 0.4% making it relatively uncommon.[11] As far as etiology is concerned, Graves' disease (occurring in 0.1 to 1 percent of all pregnancies) and gestational transient thyrotoxicosis (1 to 3 percent of pregnancies) constitute the most common causes of hyperthyroidism in pregnancy. Pregnancy complicated by poorly controlled or overt hyperthyroidism is associated with increased risk of the following:[12]

- Spontaneous abortion
- Premature labor
- Low birth weight
- Stillbirth
- Preeclampsia
- Heart failure.

Autoimmune thyroid disease is detected mostly by measuring circulating antibodies against thyroglobulin (Tg) and thyroid peroxidase (TPO). About 5 to 15% of euthyroid women have thyroid antibodies; these women are at increased risk of developing thyroid dysfunction later in life.[13] Autoantibodies to TPO are also common in women with thyroid disorders both hypo and hyper-thyroidism and are therefore, associated with major alterations in the course of pregnancy as well as affecting the mother, fetus and/or neonate with higher rates of pregnancy complications such as miscarriage, placental abruption, pregnancy-induced hypertension, and preterm delivery.[14] There is scarcity of data with respect to thyroid disorders in pregnancy in India as compared to the western world. So, the present study was undertaken to quantify the presence of thyroid disorders in pregnancy and its association with anti-thyroid peroxidase antibody and to find out whether it is necessary to screen all pregnant women for thyroid dysfunctions or only a subset of pregnant women needs to undergo biochemical and autoimmune evaluation.

II. Material And Methods

Type of Study: Prospective observational study done in 500 antenatal females

Source of Data: Antenatal patients presenting to the department of Obstetrics and Gynaecology (OBG) and Medicine department of Rajindra Hospital and Government Medical College (GMC), Patiala.

Inclusion Criteria: Pregnant females of any gestational age presenting to the departments of OBG and Medicine, Rajindra hospital and GMC, Patiala.

Exclusion Criteria: Multifetal gestation, known chronic disorders (cardiovascular diseases, diabetes mellitus, hypertension), bad obstetric history, pre-diagnosed thyroid dysfunction or autoimmune thyroid disorders, history of previous thyroid surgery, neck irradiation or iodine therapy, lithium or amiodarone medication.

Method: After obtaining informed consent, 500 patients satisfying the inclusion and exclusion criteria were randomly selected for the study. All the patients were personally subjected to detailed history regarding name, age, sex, occupation, socio-economic status, general physical and systemic examinations with special attention to signs and symptoms of hyper/hypo-thyroidism. Routine investigations like Hb, TLC, DLC, RBS, serum creatinine, blood urea and urine examination were carried out. Thyroid function was assessed by measuring T3, T4, TSH values. In patients with deranged thyroid function tests, anti TPO antibody levels were estimated. Patients with deranged thyroid profile were followed up for pregnancy outcomes and maternal and foetal complications during subsequent visits to the hospital or through telephonic registry.

Specific investigations: Analysis of thyroid function was done based on trimester specific range of TSH, T4 and T3 levels. The reference ranges of the test values used in this study were as per the guidelines of American Thyroid Association. The following upper normal reference ranges for TSH were considered: 1st trimester - 0.1 to 2.5 mIU/L, 2nd trimester - 0.2 to 3.0 mIU/L & 3rd trimester - 0.3 to 3.0mIU/L.[26] Since trimester-specific reference ranges for T3 and T4 were not available, as per the Endocrine Society clinical practice guidelines, 2012 recommendation 1.1 which advises that the non-pregnant total T4 range (5-12 mcg/ dl) can be adapted in the 2nd and 3rd trimesters by multiplying this range by 1.5 fold, the following normal reference range for T4 were used: 7.5 to 18 µg/dl.[33] Similarly, for T3, the following normal reference range was used: 0.75 to 2.775ng/ml.

Depending on the hormonal levels, the patients were classified as:

- **Euthyroid (EU):** thyroid function tests within the normal trimester specific range.
- **Subclinical hypothyroidism (SCHO):** TSH more than trimester specific range with normal T3 and T4 levels.
- **Overt hypothyroidism (OHO):** elevated TSH with low T3 and T4 levels.
- **Subclinical hyperthyroidism (SCHY**): low TSH with normal T3 and T4 levels.
- **Overt hyperthyroidism (OHY):** low TSH with elevated T3 and T4 levels.

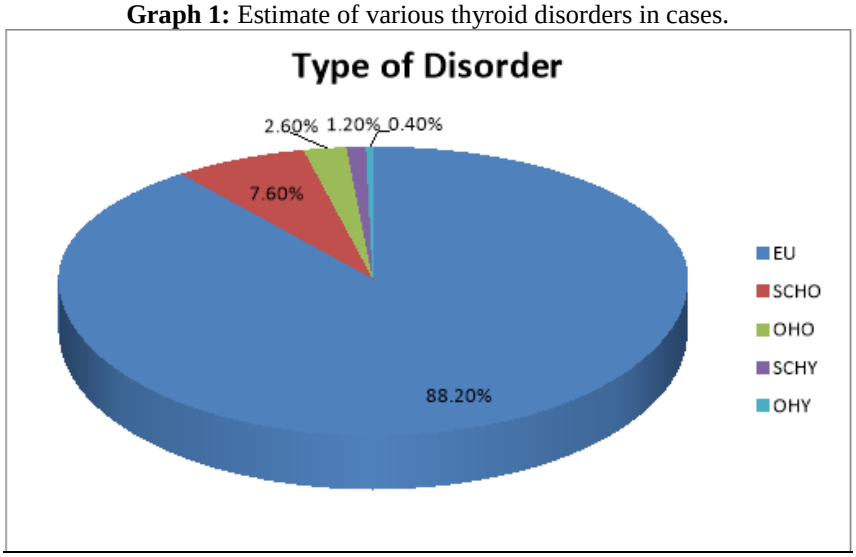
III. Results

In this study (table 1), majority of cases ie. 441/500 (88.2%) were euthyroid (EU). The most common thyroid disorder was hypothyroidism in 51 females (10.2%) with subclinical hypothyroidism (SCHO) present in 38(7.6%) and overt hypothyroidism (OHO) in 13(2.6%). 8(1.60%) cases of hyperthyroidism were found with subclinical hyperthyroidism (SCHY) in 6 (1.2%) and overt hyperthyroidism (OHY) in only 2(0.4%) as depicted in graph 1.

Table 1: Estimate of various thyroid disorders in cases.

Type of Disorder		Cases (n=500)	Percentage
EU		441	88.20%
Hypothroidism	SCHO	38 (7.60%)	
	OHO	13 (2.60%)	10.2%
Hyperthyroidism	SCHY	6 (1.2%)	
	OHY	2 (0.40%)	1.60%

Graph 1: Estimate of various thyroid disorders in cases.



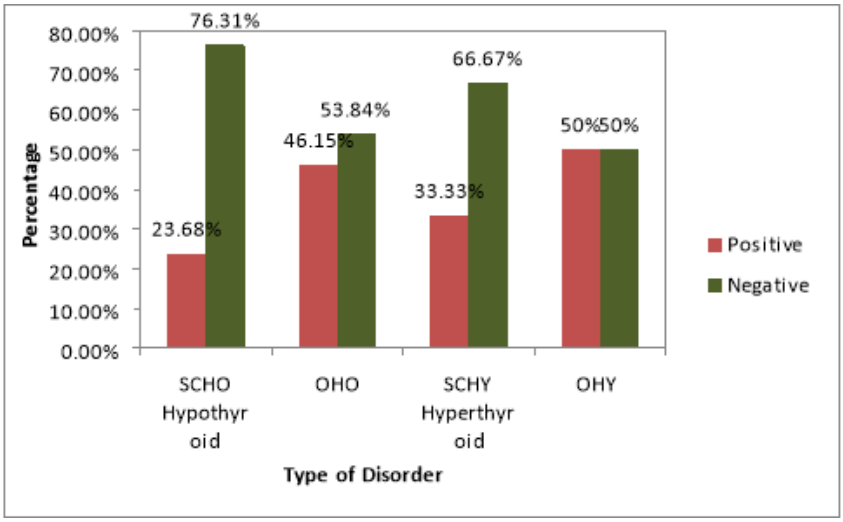
In this study, the mean TSH level in euthyroid cases was 1.67 mIU/L with range from 0.2 to 2.91 mIU/L. In subclinical hypothyroid patients, mean TSH was 6.24mIU/L with range from 4.28 to 11.61mIU/L, in overt hypothyroidism TSH ranged from 7.09/L to as high as 40mIU/L with mean of 14.79mIU/L. In patients with subclinical hyperthyroidism, mean TSH value of 0.04mIU/L with range from 0.01/L to 0.08/L and in those with overt hyperthyroidism, mean TSH of 0.01mIU/L was found (table 2).

Table 2: TSH levels in thyroid disorders.

Type of Disorder	Mean TSH (mIU/L)	SD	Range
EU	1.67	0.314	0.2 – 2.91
SCHO	6.24	1.36	4.28-11.61
OHO	14.79	8.68	7.09-40.00
SCHY	0.04	0.03	0.01-0.08
OHY	0.01	0.00	0.01-0.01

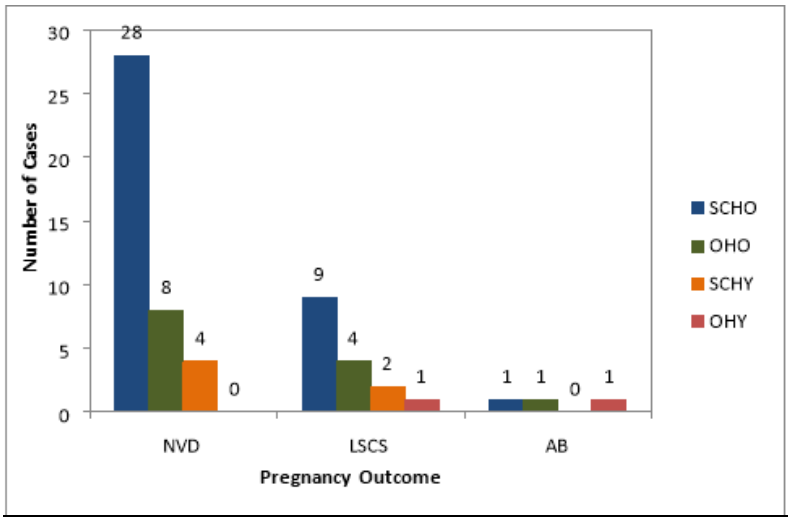
In this study (graph 2), out of total 59 cases with thyroid disorder, anti TPO ab was positive in 18 (30.51%) while negative in 41 cases (69.49%) which was statistically significant (p=0.008). 9 out 38 cases (23.68%) of SCHO were positive for Anti TPO Ab which was statistically significant (p=0.049). 6 out of 13 (46.15%) of OHO cases were positive for anti TPO ab, 2 out of 6 (33.33%) cases of SCHY and 50% ie. 1 out of 2 OHY cases tested positive for anti TPO ab.

Graph 2: Anti TPO antibody status in various thyroid disorders.



In this study (graph 3), out of 38 SCHO cases, 28(73.68%) had normal vaginal delivery, 9(23.68%) had LSCS, 1(2.63%) had spontaneous abortion. Out of 13 OHO cases, 8(61.53%) had NVD while 4(30.76%) had LSCS and 1(7.69%) had abortion. In cases of SCHY, 4 out of 6 (66.67%) had NVD while 2(33.33%) had LSCS. In OHY cases, one (50%) had LSCS and one (50%) had abortion.

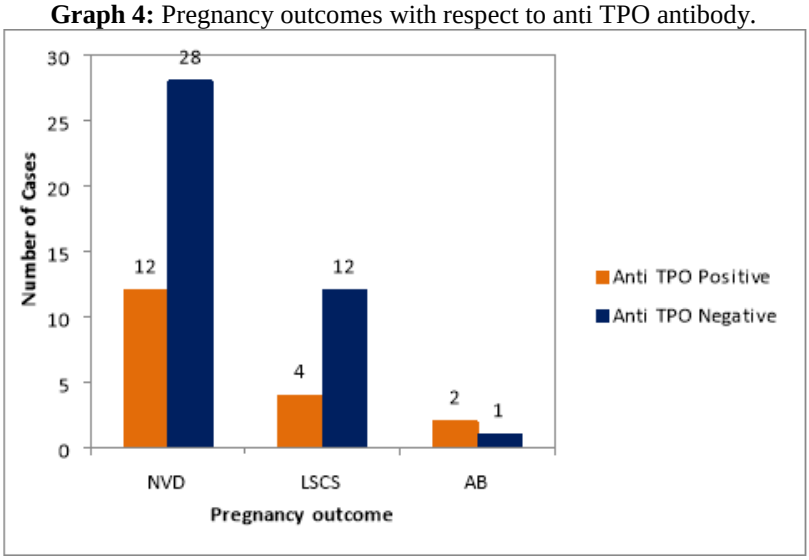
Graph 3: Pregnancy outcome in various thyroid disorders.



In this study (graph 4), anti TPO antibody was positive in 12 out of 41 cases (30%) who had NVD while 28 (70%) reported negative . Out of 16 cases with LSCS, anti TPO antibody was positive in 4(25%) while 12(75%) reported negative. The association between LSCS and anti TPO ab positivity was highly significant

(p=0.001). Out of 3 cases with abortion, 2(66.67%) were positive for anti TPO antibody while 1(33.33%) was negative.

Graph 4: Pregnancy outcomes with respect to anti TPO antibody.

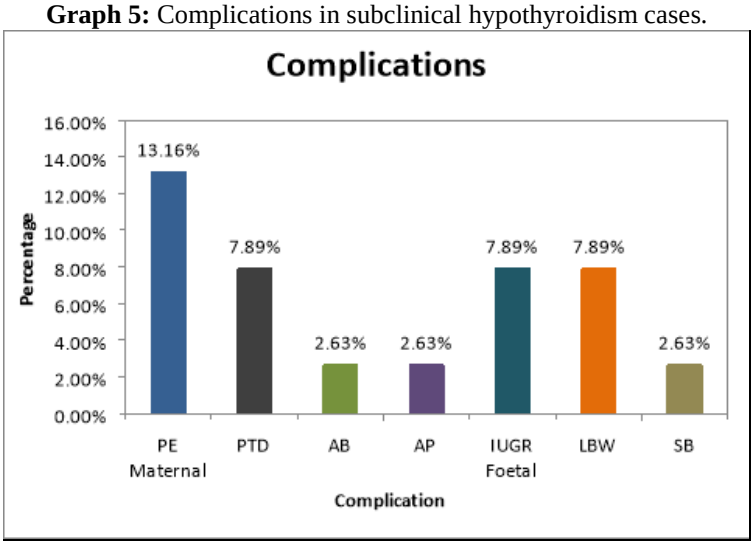


In subclinical hypothyroidism (table 3), pre-eclampsia (PE) was the most common maternal complication affecting 5 out of 38(13.16%) cases. Preterm delivery (PTD) was present in 3(7.89%), spontaneous abortion (AB) and abruption placentae (AP) in 1(2.63%) each. Statistically significant association with SCHO was found in preeclampsia (p=0.009) and preterm delivery (p=0.011). In foetal complications, 3(7.89%) cases each were affected by intra uterine growth retardation (IUGR) of the foetus and low birth weight (LBW) while one(2.63%) had stillbirth (SB). Statistically significant association with SCHO was found in cases who had IUGR (p=0.011) and LBW (p=0.011).

Table 3: Complications in subclinical hypothyroidism cases.

Complication		Cases (n=38)	Percentage
Maternal	PE	5	13.16%
	PTD	3	7.89%
	AB	1	2.63%
	AP	1	2.63%
Foetal	IUGR	3	7.89%
	LBW	3	7.89%
	SB	1	2.63%

Graph 5: Complications in subclinical hypothyroidism cases.

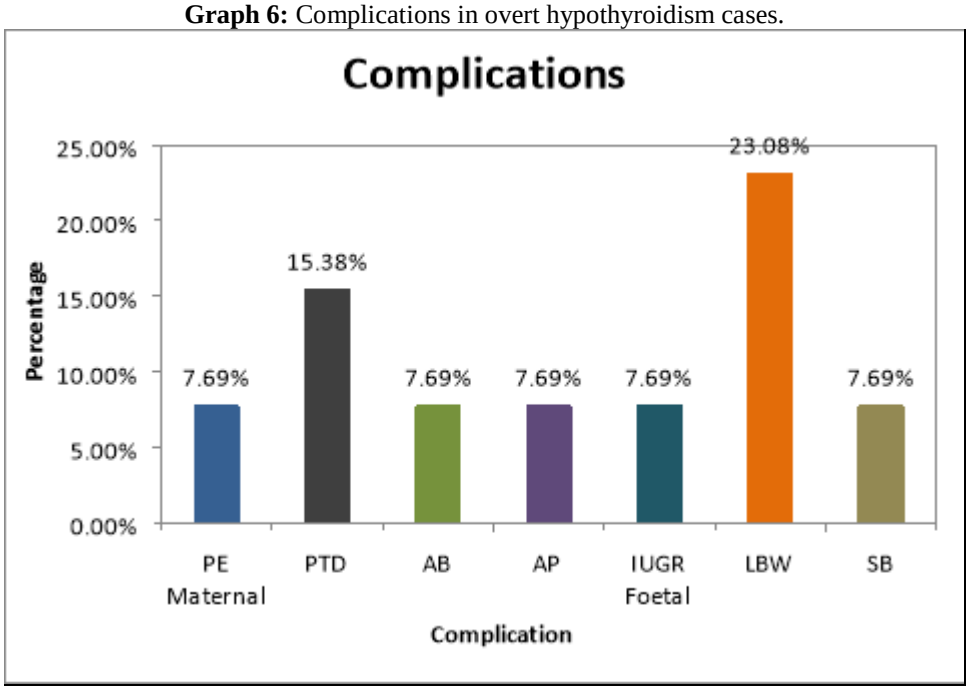


In overt hypothyroidism (table 4), most common maternal complication was preterm delivery present in 2 out of 13 cases(15.38%) while pre-eclampsia, abruption placentae and abortion were present in one case each(7.69%). The most common foetal complication was low birth weight in 3(23.08%) cases while stillbirth and intrauterine growth retardation was present in 1 case each(7.69%). Statistically significant association with OHO was found only in low birth weight cases (p=0.048).

Table 4: Complications in overt hypothyroidism cases.

Complication		Cases (n=13)	Percentage
Maternal	PE	1	7.69%
	PTD	2	15.38%
	AB	1	7.69%
	AP	1	7.69%
Foetal	IUGR	1	7.69%
	LBW	3	23.08%
	SB	1	7.69%

Graph 6: Complications in overt hypothyroidism cases.



In this study (table 5), out of 6 cases of subclinical hyperthyroidism, pre-eclampsia and preterm delivery was seen in one case each(16.67%) as part of maternal complications. In foetal complications, 1 case (16.67%) each had intrauterine growth retardation and low birth weight. No case had spontaneous abortion or stillbirth.

Table 5: Complications in subclinical hyperthyroidism cases.

Complication		Cases (n=6)	Percentage
Maternal	PE	1	16.67%
	PTD	1	16.67%
	AB	0	0%
	AP	0	0%
Foetal	IUGR	1	16.67%
	LBW	1	16.67%
	SB	0	0%

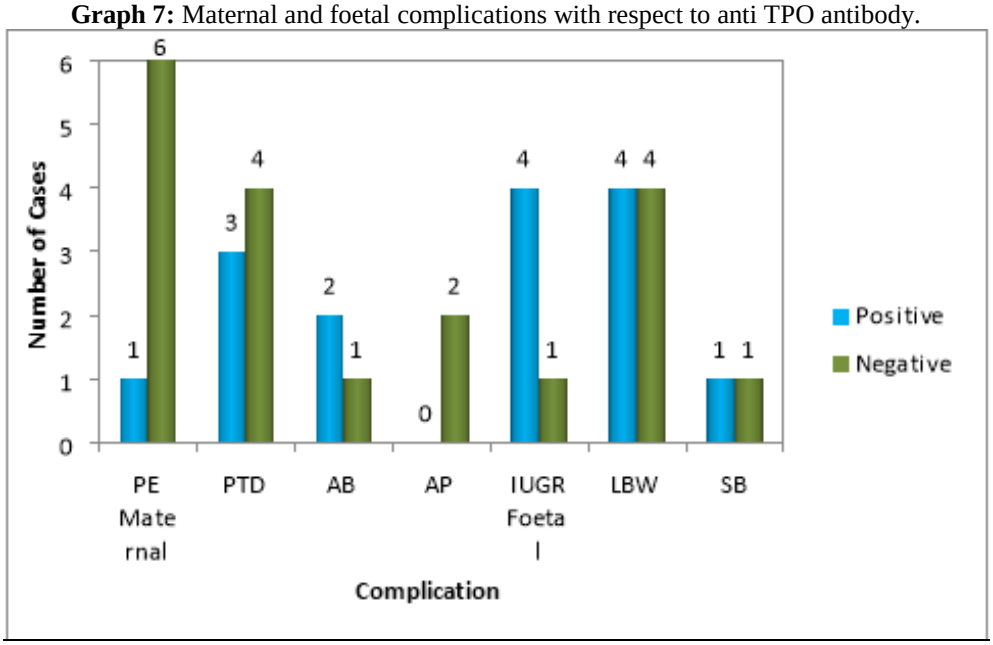
From table 6, it was seen that maternal complications in the two overt hyperthyroidism cases were present as preterm delivery in one (50%) and spontaneous abortion in the other (50%). As far as foetal complications are concerned, low birth weight was present in one.

Table 6: Complications in overt hyperthyroidism cases.

Complication		Cases (n=2)	Percentage
Maternal	PE	0	0%
	PTD	1	50%%
	AB	1	50%%
	AP	0	0%
Foetal	IUGR	0	0%
	LBW	1	50%
	SB	0	0%

In this study (graph 7), out of 34 cases presenting with various maternal and foetal complications, anti TPO ab was positive in 15 ie. 44.12% and negative in 19 (55.88%). The most common maternal complication associated with anti TPO antibody positivity was spontaneous abortion present in 2/3 cases (66.67%) followed by preterm delivery with 3/7 cases (42.85%) and 1 out of 7 (14.28%) case with preeclampsia. In foetal complications, anti TPO antibody positivity was found in 4 out of 5 cases(80%) with intrauterine growth retardation, 4/8 cases (50%)with low birth weight and 1/2 cases (50%) with stillbirth. Overall, the association of anti TPO antibody with respect to maternal and foetal complications was found to be statistically significant (p=0.034).

Graph 7: Maternal and foetal complications with respect to anti TPO antibody.



IV. Discussion

In this study (table 7), the prevalence of subclinical hypothyroidism was found to be 7.6% which was comparable to studies by Sarladevi et al (6.4%), Taghavi et al (7.4%) and Ajmani et al (9%). The prevalence was low in study by Thanuja et al (0.7%) while it was high in Murty et al (16.13%) and Rajput et al (21.5%). Overt hypothyroidism was found in 2.6% of cases which was comparable to Sarladevi et al (2.8%) and Taghavi et al (2.4%). Subclinical hyperthyroidism was present in 1.2% of cases which was comparable to study by Sarladevi et al (1.8%) and Thanuja et al (1.3%). Overt hyperthyroidism was present on in 0.4% which was comparable to studies by Sarladevi et al (0.6%), Taghavi et al (0.6%), Ajmani et al (0.5%) and Rajput et al (0.4%).

Table 7: Comparison of prevalence of various thyroid disorders.

Study	SCHO (%)	OHO (%)	SCHY (%)	OHY (%)
Present study	7.6	2.6	1.2	0.4
Sarladevi et al[15] (2015)	6.4	2.8	1.8	0.6
Taghavi et al[16] (2009)	7.4	2.4	4.2	0.6
Ajmani et al[17] (2013)	9	3	0.75	0.5
Thanuja et al[18] (2014)	0.7	1	1.3	2
Murty et al[19] (2015)	16.13	3.28	0.82	0.22
Rajput et al[20] (2015)	21.5	1.3	3.3	0.4

Table 8: Comparison of anti TPO antibody positivity in various thyroid disorders.

Disorder	SCHO(%)	OHO(%)	SCHY(%)	OHY(%)
Present study	23.68	46.15	33.33	50
Thammiah J[21] (2016)	52.6	75	50	0
Vaidya et al[22] (2007)	37.5	50	11.11	9.1
Rajput et al[20] (2015)	30.5	4.7	0	0
Goel et al[23] (2015)	15	12.5	-	-
Dhawal et al[24] (2013)	18.5	71.4	-	-

In the present study (table 8), 23.68% cases of subclincal hypothyroidism were positive for ant TPO antibody. The percentage was higher in some studies such as Thammiah J (52.6%), Vaidya et al (37.5%) and Rajput et al (30.5%) while lower in Goel et al (15%) and Dhanwal et al (18.5%). 46.15% overt hypothyroid cases were positive for anti TPO antibody which was comparable to Vaidya et al (50%). 33.33% of subclinical hyperthyroid patients in this study were positive for anti TPO ab. The percentage in Thammiah J was higher (50%) while it was lower in Vaidya et al (11.11%). 50% cases of overt hyperthyroidism were anti TPO positive. It was not comparable to other studies.

Table 9: Comparison of complications in pregnant women with subclinical hypothyroidism.

Complication	PE (%)	PTD(%)	AB (%)	AP (%)	IUGR(%)	LBW(%)	SB (%)
Present study	13.6	7.89	2.63	2.63	7.89	7.89	2.63
Leung et al[9] (1993)	15	9	-	-	-	9	-
Sahu et al[7] (2010)	9.8	10.3	-	-	2.4	-	2.5
Sarladevi et al[15] (2015)	9.3	7.81	4.68	1.56	6.25	4.68	1.56
Ajmani et al[17] (2013)	22.3	5.8	2.39	-	4.9	12.11	1.7
Pokhanna et al[25] (2017)	30	30	6.6	3.3	10	30	0

In the present study (table 9), the most common maternal complication in subclinical hypothyroid cases was pre eclampsia (13.6%), followed by preterm delivery (7.89%), abortion and abruption placentae in 2.63% each. Foetal complications were IUGR and low birth weight in 7.89% cases and still birth in 2.63%. It was comparable to studies by Sarladevi et al, Sahu et al and Leung et al. Ajmani et al and Pokhanna et al have higher percentage of complications.

Table 10: Comparison of complications in pregnant women with overt hypothyroidism.

Complication	PE (%)	PTD(%)	AB (%)	AP (%)	IUGR(%)	LBW(%)	SB (%)
Present study	7.69	15.38	7.69	7.69	7.69	23.08	7.69
Leung et al[9] (1993)	22	-	-	-	-	22	4
Sahu et al[7] (2010)	20.7	4.7	-	-	13.81	-	2.9
Sarladevi et al[15] (2015)	14.8	10.7	7.14	3.57	10.71	10.71	3.57
Ajmani et al[17] (2013)	16	33	16.6	16.6	25	50	16.6
Pokhanna et al[25] (2017)	22.2	44.4	22.2	22.2	33.3	66.6	22.2

In the present study (table 10), overt hypothyroidism was associated with 15.38% cases of preterm delivery followed by 7.69% cases of abortion, preeclampsia and abruption placentae each. In foetal complications, low birth weight was present in 23.08% cases followed by IUGR and stillbirth in 7.69% each. It was comparable to findings by Sarladevi et al whereas Ajmani et al and Pokhanna et al had higher values.

Table 11: Comparison of complications in pregnant women with subclinical hyperthyroidism.

Complication	PE (%)	PTD(%)	AB (%)	AP (%)	IUGR(%)	LBW(%)	SB (%)
Present study	16.67	16.67	0	0	16.67	16.67	0
Mannisto et al[26] (2010)	3.5	-	-	1	-	-	-
Taghavi et al[16] (2009)	4.7	4.7	-	-	-	-	-
Sarladevi et al[15] (2015)	11.11	5.55	5.55	-	11.11	-	5.55
Thanuja et al[18] (2014)	50	-	-	-	25	-	-
Pokhanna et al[25] (2017)	0	0	0	14.2	0	0	0

In this study (table 11), in cases of subclinical hyperthyroidism, preeclampsia, preterm delivery, low birth weight and IUGR were present in 16.67% each. Sarladevi et al had similar rate of preeclampsia (11.11%) and IUGR (11.11%). Thanuja et al reported higher values of PE(50%) and IUGR(25%) while Pokhanna et al showed high prevalence of abruption placentae (14.2%). Mannisto et al and Taghavi et al showed lesser values for PE at 3.5% and 4.7% respectively.

Table 12: Comparison of complications in pregnant women with overt hyperthyroidism.

Complication	PE (%)	PTD(%)	AB (%)	AP (%)	IUGR(%)	LBW(%)	SB (%)
Present study	0	50	50	0	0	50	0
Saki et al[27] 2014	0	14	-	-	28	-	-
Sarladevi et al[15] (2015)	0	0	66.67	0	0	0	0
Thanuja et al[18] (2014)	33.4	16.7	50	-	-	-	-
Pokhanna et al[25] (2017)	0	0	0	20	0	0	0

In the present study (table 12), preterm delivery, abortion and low birth weight are present in 50% of cases of overt hyperthyroidism. Sarladevi et al showed 66.67% of abortion while Thanuja et al showed 50% abortion, 33.4% preeclampsia and 16.7% preterm delivery. Saki et al had 14% preterm delivery and 28% cases of IUGR. Pokhanna et al had 20% cases with abruption placentae.

Table 13: Comparison of anti TPO positivity in maternal and foetal complications.

Complication	PE(%)	PTD(%)	AB(%)	AP(%)	IUGR(%)	LBW(%)	SB(%)
Present study	14.28	42.85	66.67	0	80	50	50
Negro et al[28] (2010)	3.3	22.4	-	-	-	6.5	-
Meena et al[29] (2016)	3.33	13.33	13.33	3.33	-	25	-
Rajput et al[30] (2017)	2.6	14	12	-	10	-	-
Bhattacharryya et al[31] (2015)	16.66	14.28	10.87	2.38	-	-	-

In the present study (table 13), the most common maternal complication associated with anti TPO antibody positivity was spontaneous abortion (66.67%) followed by preterm delivery (42.85%) and preeclampsia (14.28%). In foetal complications, 80% cases of IUGR, 50% low birth weight and stillbirth each were positive for anti TPO antibody. Meena et al had anti TPO positive in 3.33% cases with preeclampsia and abruption placentae each, 13.33% for preterm delivery and abortion each and 25% with low birth weight. Negro et al and Rajput et al had lower values while Bhattacharyya et al had higher values. The findings of this study were not comparable to any study.

V. Conclusion

From this study it can be concluded that prevalence of thyroid disorders in pregnant women is considerably high (11.8%) with subclinical hypothyroidism being the most common (7.6%), followed by overt hypothyroidism (2.6%), subclinical hyperthyroidism in 6 cases (1.2%) and overt hyperthyroidism (0.4%). Thyroid disorders are associated with abnormal pregnancy outcomes as well as various maternal and foetal complications. The presence of anti TPO antibody confers a statistically significant risk with respect to increased chances of abnormal pregnancy outcomes as well as maternal and foetal complications during pregnancy. Therefore, early identification of thyroid disorders and timely initiation of appropriate treatment is essential in pregnancy. Therefore, it is essential to screen all pregnant women for thyroid dysfunctions with special reference to autoimmune evaluation as it would be helpful in reducing maternal and foetal morbidity as well as mortality.

Limitations of study

- Study was based on single thyroid function test at screening. Data on subsequent thyroid function tests during the pregnancy were not collected.
- Urinary iodine in the study population was also not measured.
- TPO antibody levels were not examined in all the cases.

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