Determinants of Thyroid Autoimmunity in Pregnant Women of Rural Central India- A Cross Sectional Study

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Abstract: *Background:* Thyroid autoimmunity (TAI) is the most common autoimmune disorder in women of reproductive age. TAI in pregnancy is seen to rise markedly all over the world & can remain undiagnosed as it may present without thyroid dysfunction. It is seen to be associated with a number of feto-maternal disorders and may affect pregnancy outcome. The occurrence of TAI in pregnancy, in the present rural community is not known, hence this study was carried out to determine the occurrence of thyroid autoimmunity in pregnant women from rural area.

Methods: A hospital based, cross-sectional, observational study was carried out among pregnant women seeking antenatal care at Kasturba Hospital of MGIMS, Sewagram, a rural tertiary care institute in central India. Information was collected about demographic variables. Family history and other determinants. Serum TSH, Free T4, and antithyroglobulin antibody levels were in the first trimester. Thyroid status was labelled as euthyroid, overt hypothyroid, subclinical hypothyroid, overt hyperthyroid and subclinical hypothyroid and correlation was done with antibody positivity and various determinants.

Results: Among 250 pregnant women of first trimester, antithyroglobulin antibody was positive in 32 (12.8%) of which 22 (68.75%) had thyroid dysfunction in the form of hypo or hyperthyroidism, and 10 (31.25 %) were euthyroid. Of 218 with negative antibody, 24 (11%) had thyroid dysfunction and 194 (88.99%) were euthyroid with a significant difference. Though TAI was present in all age groups, the numbers increased with increasing age. Among study subjects, 9.95 % from rural compared to 28.20 % from urban residential area had TAI indicating higher occurrence in urban population. TAI was observed in all socioeconomic classes but more so in middle, lower middle and lower economic class. Positive family history was noted in 18.75 % women with positive antibody compared to 3.71 % negative women (p value 10.62, chi square 0.002). More number of pregnant women with negative antibody had an average BMI compared to positive (77.06% vs 31.25%), more positive PW were overweight compared to negative (37.5% vs 18.34%) and also obese (15.62% vs 0.91%) (Chi square – 26.67, p value – 0.00002). As BMI increased proportion of PW with positive antibody increased with a significant difference

Conclusions: Thyroid autoimmunity was seen in 12.8% pregnant women of the rural area of present study site. A substantial number of women with TAI had thyroid dysfunction and some were found to be euthyroid too. Older age, socioeconomic status, urban residence, high BMI and positive family history were risk factors for thyroid autoimmunity. Screening for thyroid antibodies in high risk pregnant women and those with thyroid dysfunction is suggested.

Keywords: Thyroid autoimmunity, Pregnant women, Determinants, Thyroid dysfunction, Rural India.

INTRODUCTION

Anti-thyroid autoantibodies (or simply anti-thyroid antibodies) are autoantibodies targeted against one or more components of thyroid, the most clinically relevant of which are anti-thyroperoxidase antibodies (anti-TPO antibodies), thyrotropin receptor antibodies (TRAbs) and antithyroglobulin antibodies (Anti-Tg). TRAbs are subdivided into activating, blocking and neutral antibodies, depending on their effect on the TSH receptor. Graves' disease and Hashimoto's thyroiditis are commonly associated with the presence of anti-thyroid autoantibodies, anti-TPO antibodies with Hashimoto's thyroiditis & activating TRAbs are most commonly associated with Graves' disease [1]. Thyroid autoimmunity (TAI) the most common autoimmune disorder in women of reproductive age, with a prevalence varying between 5 -15%, is 5-10 times more common in women than in men & can remain undiagnosed as it may present without TD [2]. Hashimoto's thyroiditis is often defined as the simple presence of serum thyroid autoantibodies which, pathologically, correlate well with an intrathyroidal lymphocytic infiltrate [3]. It requires more than 75% compromise of thyroid function before thyroid failure is reflected in serum thyroid hormone levels, the disease existing for many years before getting diagnosed & is the most common cause of hypothyroidism in pregnancy [4]. In early pregnancy, women with thyroid antibodies (Abs) have higher serum TSH compared with Ab-negative, although the mean may still fall within the normal range. These Ab-positive women are prone to develop SCH or OH during pregnancy [5] owing to reduced functional reserve of thyroid, which is unable to compensate for the increased demand of hormone in pregnancy [6]. Thus this study was carried out to

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determine the occurrence of thyroid autoimmunity in pregnant women from rural area.

METHODS

Study Design and Study Site

This hospital based, cross sectional, observational study was conducted in the Kasturba Hospital, placed in rural central India which is attached to Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha, a tertiary level institute serving underprivi-leged rural masses. The hospital has separate maternal and Child Health wing which caters to around 5000 deliveries per year. The antenatal and high risk antenatal clinic is conducted every day and serves rural antenatal women and offers high quality, low cost, diagnostic and therapeutic care.

Study Population & Ethical Considerations

Study participants were 250 consenting women with singleton pregnancy, attending antenatal clinic at Kasturba Hospital and were recruited in first trimester. Women with multiple pregnancy known thyroid disorders and those with diabetes mellitus were excluded. Ethical approval was obtained from institutional ethical committee, informed written consent was sought from participants and the research was conducted with no financial burden to the participants.

Methods

Participants were recruited in the first trimester, pregnancy was diagnosed with urine pregnancy test and confirmed with ultrasonography. Demographic information and relevant obstetric and clinical history was obtained in a pretested, validated questionnaire. Socioeconomic status was classified using Modified Prasad's classification as upper, upper middle, middle, lower middle and lower using per capita income. Body mass index was calculated and classified according to WHO classification as underweight (< 18.5kg/m2), normal weight (18.5-24.9 kg/m2), overweight 25.0-29.9 kg/m2 and obese (>30 kg/m2). Serum thyroid stimulating hormone (TSH), free thyroxine (fT4), and Antithyroglobulin (ATG) antibody was quantitatively determined using enzyme-linked immuno-assays in the first trimester by obtaining around 5 ml of venous blood sample. Trimester specific values of 0.1-2.5mIU/L were considered normal for TSH. Serum FT4 values between 0.7-1.8 mg/dl was considered normal. Thyroid function was classified as [7] – a) Overt hypothyroidism (OH) – elevated TSH levels & low free T4, defined with trimester specific reference ranges or TSH > 10 mIU/L irrespective of FT4, b) Subclinical hypothyroidism (SCH) - Elevated TSH, but less than 10 mIU/L and normal FT4, c) Overt hyperthyroidism (OHr)- Low TSH (Trimester Specific) with free T4 that exceeded normal reference range, and d) Subclinical hyperthyroidism (SCHr)- Low TSH, with normal free T4 within normal reference range. Antithyroglobulin antibody values >115 IU/ml were considered positive

Statistical Analysis

Data was entered in a spread sheet (Excel) and analysis was done by using descriptive statistics using SPSS 17.0 version. Normal distribution of the data was examined by Kolmogorov-Smirnov test & reported as arithmetic means ± SD, non-normally distributed data as medians (quartiles) and categorical data as numbers and percentages. The proportions were compared by chi square test & a two-level P value <0.05 was considered as significant.

RESULTS

A total of 250 participants from first trimester of gestation were involved in the study with a mean age of 26.53 ± 3.67 years. Maximum were gravida two. Antithyroglobulin antibody was positive in 32 (12.8%) (Table **1**). Of 32 study subjects with positive antibody 22 (68.75%) had thyroid dysfunction in the form of hypo or hyperthyroidism, and 10 (31.25 %) were euthyroid. Of 218 with negative antibody, 24 (11%) had thyroid dysfunction and 194 (88.99%) were euthyroid with a statistically significant difference. Thyroid dysfunction, mostly in the form of overt or subclinical hypothyroidism was more commonly observed in study subjects with thyroid autoimmunity (TAI) (Table **2**). No pregnant woman (PW) below 19 years of age in had TAI; 8 of 80 (10%) between age 20-24 years; 11 of 104 (10.57%), between ages 25- 29 years; 11 of 60 (18.33%) between ages between 30 - 34 years and 2 of 5 (40 % who were 35 years and above had TAI. Though TAI was present in all age groups, the numbers increased with increasing age (Table **3**). Among study subjects, 21 of 211 (9.95 %) from rural as compared to 11 of 39 (28.20 %) from urban had TAI indicating higher occurrence in urban population with a significant difference (p value < 0.001). Among study subjects, 1 of 15 (6.66%) from upper class, 2 of 31 (6.45%) from upper middle; 8 of 52 (15.38 %) from middle class; 9 of 58 (15.51%) of lower middle class and 12 of 66 (18.88 %) of lower class had TAI indicating occurrence in all

classes but more so in middle, lower middle and lower economic class (Table **3**). Of 32 PW with positive antibody, 6 (18.75%) had family history compared to 7 of 218 (3.71 %) (p value 10.62, chi square 0.002). Similar proportion of PW with positive and negative antibody had below average BMI, however more number of negative PW had an average BMI compared to positive (77.06% vs 31.25%), more positive PW were overweight compared to negative (37.5% vs 18.34%) and also obese (15.62% vs 0.91%) (chi square – 26.67, p value – 0.00002). As BMI increased proportion of PW with positive antibody increased with a significant difference (Table **4**).

Table 1: Antithyroglobulin Values in Study Subjects

Parameter	Grading	Values	
		n	%
Antithyroglobulin antibody	Positive	32	12.8
	Negative	218	87.2

DISCUSSION

Thyroid autoimmune disease, a multifactorial organ-specific autoimmune disorder, is constantly increasing worldwide and is common in women of childbearing age. These disorders are significantly influenced by a variety of changes in thyroid function that take place during normal gestation and also by the privileged immune status of pregnancy [8]. TAI has been closely linked with thyroid function. Graves' disease and Hashimoto's thyroiditis are being commonly associated with anti-thyroid antibodies [1]. Hashimoto's thyroiditis required more than 75% compromise of thyroid function before thyroid failure isreflected in serum thyroid hormone levels. The disease actually exists for many years before getting diagnosed & is the most common cause of hypothyroidism in pregnancy [4].

In the present study, thyroid autoimmunity was found in 12.8 % pregnant woemn in first trimester. Kayode *et al.* in 108 pregnant women found elevated antithyroid antibody in 27 (25%) as against about 2% of

Table 2: Antithyroglobulin Antibody and Thyroid Function

Antithyroglobulin Antibody	Thyroid Function										Total
	Normal		OH		SCH		OHr		SCHr		
	n	%	n	%	n	%	n	%	n	%	
Positive	10	31.25	18	56.25	3	9.37	1	3.13	0	0	32
Negative	194	88.99	5	2.29	18	8.26	1	0.46	0	0	218
ϰ2-value, p value	107.32, p-value=0.0001, S										

OH-Overt Hypothyroidism, SCH- Subclinical Hypothyroidism, OHr-Overt Hyperthyroidism, SCHr- Subclinical hyperthyroidism.

Table 3: Age and Socioeconomic Status of Study Subjects of Study Subjects

Parameter	Categories	ATG Positive n=32	
		n	%
Age in years	Below 19 n=19	0	0
	20-24 n=80	8	10
	25-29 n=104	11	10.57
	30-34 n=60	11	18.33
	35 and above n=5	2	40
Socioeconomic Status	Upper n=15	1	6.66
	Upper middle n=12	2	6.65
	Middle n=52	8	15.38
	Lower Middle n=58	9	15.51
	Lower n=66	12	18.18

ATG- Antithyroglobulin antibody.

Table 4: Family History and Body Mass Index of Study Subjects

Determinants	Value	ATG Positive n=32		ATG Negative n=218		Chi Square	p-value
		n	%	n	%		
Family History	Yes	6	18.75	7	3.21	10.62	0.002
BMI in kg/m2	<18.5	3	9.37	21	9.63	26.67	0.00002
	18.5-24.9	10	31.25	168	77.06		
	25-29.9	12	37.5	40	18.34		
	>30	5	15.62	2	0.91		

ATG- Antithyroglobulin antibody.

the nonpregnant women levels ($P < 0.001$) [9]. Various other studies in pregnant women from Tunisia, Belgium, Japan, Turkey, Spain and the United States reported TAI in 6.5%, 6.3%, 10%, 12%, 14.8%, and 20% respectively [10-14].

In early pregnancy, women with thyroid antibodies have higher serum TSH compared with antibody negative, although the mean may still fall within the normal range. These women are prone to develop subclincal/overt hypothyroidism during pregnancy during pregnancy [5] owing to reduced functional reserve of thyroid, which is unable to compensate for the increased demand of hormone in pregnancy [6]. The present study found that 68.75 % study subjects with positive antibody had thyroid dysfunction in the form of hypo or hyperthyroidism, and 31.25 % were euthyroid compared with PW with negative antibody, in whom thyroid dysfunction was present in 11% and 88.99% were euthyroid with a significant difference. Kayode *et al.* found that hypothyroidism was associated with elevated levels of TPO-Ab in 33.3% of women [9]. Prevalence of subclinical hypothyroidism in women with thyroid autoimmunity was 12.6% in the study by Sailakshmi *et al.* [15]. Prevalence of thyroid autoimmunity and subclinical hypothyroidism was 18.5% in studies of Dhanwal *et al.* [16]. This shows that auto immunity is a common cause of hypothyroidism in pregnant women.

Iodine defiiency and TAI may go hand in hand too. In Denmark, comparison of two appropriately matched cross-sectional groups with and without iodine supplementation showed a marked increase in thyroid antibodies with iodine supplementation probably secondary to the increased iodination of thyroglobulin which enhanced its immune-reactivity [17]. This is more marked in mild iodine deficient areas.

Age can be considered as a co factor for higher thyroid antibody titers. Seroconversion with increasing age and subsequent affection of pregnancy outcome has been suggested [18]. In the present study it was seen that though TAI was seen in all age groups, the incidence was higher with increasing age. Few longitudinal studies exists in the population as regards to conversion to thyroid antibody positivity with age. Turnbridge revealed that individuals with antibody positivity developed increased titers as they grew older [19] and the original Whickham cohort, revealed that 21% women at 55–65 years had developed TAI [20]. Muller *et al.* found that the mean age of antibody positive pregnant women was 32.4 +/- 3.3 years [21]. Bagis *et al.* found that mean age in antibody-positive was higher than antibody-negative (27.7 +/-6.2 years, vs. 25.9 +/- 5.2 years) [13]. Similar findings were reported by other researchers [22-24].

Pregnant patients screened during the first trimester of pregnancy have an increased prevalence of thyroid autoantibodies (up to 20%) reflective of the greater prevalence in this age group rather than secondary to the pregnancy itself [25]. In fact the physiologic changes surrounding pregnancy include changes allowing an immune-tolerant environment for the non-self fetus, and this results in a decline in autoantibodies. So in pregnancy, there is a marked fall in both TPO-Ab and Tg-Ab levels followed by an increase in postpartum [25]. An increase in cases of different autoimmune and inflammatory disorders in families with an index case of a given autoimmune disease is a consistent finding in many autoimmune disorders [26], and suggests a shared genetic etiology [27] of immune dysregulation. The present study observed that family history was positive in more PW with positive antibody compared with negative antibody.

In the present study, PW with all socioeconomic backgrounds showed TAI however it was more commonly observed in middle, lower middle and lower socioeconomic group. The positive correlation of SES

with autoimmunity is frequently attributed to biological etiological factors rather than differential diagnosis of disease in the context of access to health care resources. This often focuses on factors modulating the developing prenatal and neonatal immune system [28].

Increased body mass index was also shown to be a risk factor for TAI by some researchers. Meena *et al.* found an association between BMI and anti-TPO positivity in pregnant woman [29]. The majority of the studies showed a positive correlation between the TSH values and BMI [30, 31]. Pop and Nyrnes positively correlated TAI with BMI [30, 31]. Present study agrees that TAI increases with increased BMI.

Environmental factors may induce or suppress the development of autoantibodies. The "Hygiene Hypothesis" has been supported by observations of increased thyroid antibodies in more affluent towns [1]. It is thought to be caused by multiple environmental factors triggering autoimmune response in genetically susceptible individuals, though the exact mechanisms linking environmental factors to thyroid autoimmunity are not as yet well understood. Nevertheless, there is increasing evidence that mainly nutritive factors and environmental pollution by metals and chemicals (*e.g*. organochlorines, pesticides) are the main factors in the present-day spread of this disease [32]. Present study found that PW from urban residential area were more prone to develop TAI. Screening for antibodies in the early months of pregnancy is justified to reduce adverse pregnancy outcomes like progressive hypothyroidism during gestation with the increased risk of spontaneous miscarriage, postpartum thyroiditis after pregnancy; and the long-term risk of developing definitive hypothyroidism later on in life. It is important that all pregnant women with TAI should be monitored closely and jointly by obstetricians and endocrinologists.

CONCLUSION

In the present geographic area of rural central India, thyroid autoimmnity was found in 12.8 % pregant women in the first trimester. A substanstial proportion of pregnant women with thyroid autoimmune disorder had thyroid dysfunction, however a number of them were euthyroid. Older age, socioeconomic status, urban residence, high BMI and positive family history were risk factors for thyroid autoimmunity. Screening women with these high risk factors in pregnancy and appropriately performing thyroid function tests is the suggested approach for cost effectivley diagnosing and managing pregnant women with thyroid autoimmunity and associated dysfunction.

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DECLARATIONS

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CONFLICT OF INTEREST

No conflict of interest

ETHICAL APPROVAL

Ethical approval was obtained from the institutional ethical committee. Informed written consent was taken from study participants and the cost of research was borne by the study team

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