



## Original Article

# Thyroid Autoimmunity is a Risk Factor for Recurrent Pregnancy Loss

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### Abstract

This was a hospital based case control study. The study included patients attending in outdoor and indoor Department of Obstetrics and Gynaecology of Rajshahi Medical College, Hospital since July 2014 to June 2016.

The aim of this study was to determine thyroid antibodies is a risk factor for recurrent pregnancy loss. Sixty seven pregnant or non pregnant women with history of recurrent miscarriage during 1<sup>st</sup> trimester were selected as case group and another sixty seven pregnant women who reached their 12 weeks uneventfully with no history of recurrent miscarriage were selected as control group. Patients with other cause of recurrent miscarriage such as metabolic or endocrinologic disorders, genital organ anomaly, uterine fibroid were excluded from the study. Thyroid function test and thyroid antibodies (FT<sub>4</sub>, TSH and TPO-Ab) were measured for the two groups. The result of this study showed that the percentage of positive TPO-Ab in target and control group is 67.16% and 5.95% respectively.

The study observed that the mean serum concentrations of FT<sub>4</sub> in the control subject was significantly higher than the mean of the target group (p-value <0.05). The TSH concentration was increased in miscarriage women with positive antibodies compared with the concentration of TSH in the control group with positive antibodies. The conclusions are that there is a deficiency in thyroid hormones or thyroid's functional capacity is unable to meet the extra demands of pregnancy which may be one of the causes of recurrent miscarriage. Moreover positive thyroid antibodies pregnant women can reach term and have babies when the concentration of TSH is low during the first trimester, so the risk of miscarriage could be high in positive thyroid antibodies.

**Key words:** Autoimmunity, TPO-Ab, Miscarriage, Thyroxin.

TAJ 2017; 30: No-1: 49-55

### Introduction

Recurrent pregnancy loss is defined as three or more consecutive spontaneous pregnancy losses before 20 weeks of gestation. Pregnancy loss in the first trimester is the most common complication affecting approximately 15-20% of

clinically recognized pregnancies.<sup>1</sup> Potential amount of possible miscarriage before pregnancy is recognized to be about 30%.

Recurrent miscarriage defined as loss of two or more consecutive pregnancies (ASRM practice

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committee Report, 2008), occurs in 1-2% of couples attempting to bear children.<sup>2,3</sup> Several disorders are associated with recurrent pregnancy loss. Diseases of the thyroid gland such as hypo and hyperthyroidism have also been associated with fetal loss. Over the past decade, many reports have linked thyroid autoimmunity (TA) with recurrent abortion and it has been suggested that thyroid auto antibodies may serve as a marker for at-risk pregnancies.<sup>4,5</sup> Furthermore, it was recently shown that thyroxine administration to pregnant women with positive thyroid auto antibodies and a history of recurrent abortions may improve the outcome.<sup>6</sup>

Thyroid hormones are essential for the growth and metabolism of the growing fetus. Early in pregnancy, the mother supplies her fetus with thyroid hormones. The fetal thyroid gland is not fully functional until after 12 weeks. If the mother is hypothyroid, she cannot supply her fetus with enough thyroid hormones. Hence hypothyroidism is a risk factor for pregnancy loss. Thyroid disorder in early pregnancy may lead to grave consequences, and therefore testing may be appropriate.<sup>7</sup> The prevalence of sub-clinical hypothyroidism in women in the childbearing age may be as high as 5%.<sup>8,9</sup> Hence, there is a need to screen for subclinical hypothyroidism and thyroid autoimmunity in pregnancy, especially in women with a history of miscarriage. Even minimal hypothyroidism can increase rates of miscarriage and fetal death and may also have adverse effects on later cognitive development of the offspring. The thyroid gland and gonadal axes interact continuously before and during pregnancy. Hypothyroidism influences ovarian function by decreasing levels of sex-hormone-binding globulin and increasing the secretion of prolactin.<sup>10</sup>

Pregnancy is also accompanied by immunologic changes, mainly characterized by a shift from a T helper-1 lymphocyte to a T helper-2 lymphocyte state. Thyroid peroxidase antibodies are present in 10% of women at 14 weeks' gestation, and are associated with (a) an increased pregnancy failure (i.e., abortion), (b) an increased incidence of gestational thyroid dysfunction, and (c) a predisposition to postpartum thyroiditis.<sup>11</sup> During

the first trimester, however, pregnant women with autoimmune thyroiditis (AITD) carry a significantly increased risk for miscarriage compared to women without AITD, even if euthyroidism.<sup>12</sup> Presence of thyroid autoimmunity does not interfere with normal embryo implantation, but the risk of early miscarriage is substantially raised.

### Materials and Methods

This is a case control study. Sixty seven pregnant or non pregnant women with history of recurrent miscarriage during 1<sup>st</sup> trimester were selected as case group and another sixty seven pregnant women who reached their 12 weeks uneventfully with no history of recurrent miscarriage were selected as control group. This study was carried out in outdoor and indoor Department of Obstetrics and Gynaecology of Rajshahi Medical College Hospital, Rajshahi. The patients are selected by purposive sampling method.

### Results

**Table I:** Distribution of the study patients by age (years) (n=134)

Age (years)	Target group (n=67)		Control group (n=67)		P value
	No. of patients	%	No. of patients	%	
18-22	13	19.4	19	28.36	0.35
23-27	17	25.37	23	34.32	
28-32	26	38.81	15	22.39	
33-37	11	16.42	10	14.93	

Table I shows 38.81% patients were belonged to age 28-32 years among cases and 34.32% of 23-27 years age group in control. There is no significant difference.

**Table I** shows 38.81% patients were belonged to age 28-32 years among cases and 34.32% of 23-27

years age group in control. There is no significant difference.

**Table II:** Distribution of the study patients by BMI (Kg/m<sup>2</sup>) (n=134)

BMI (Kg/m <sup>2</sup> )	Target group (n=67)		Control group (n=67)		P value
	No. of patients	%	No. of patients	%	
18.5-22.99 (normal)	12	17.91	27	40.29	0.04
≥ 23.0 (over wt)	55	82.09	40	59.71	

P value reached from chi square test.

**Table II** shows 82.09% patients had BMI ≥ 23.0 kg/m<sup>2</sup> among cases and 59.71% in controls. There is no significant difference.

**Table III:** Distribution of the study patients by TSH (n=134)

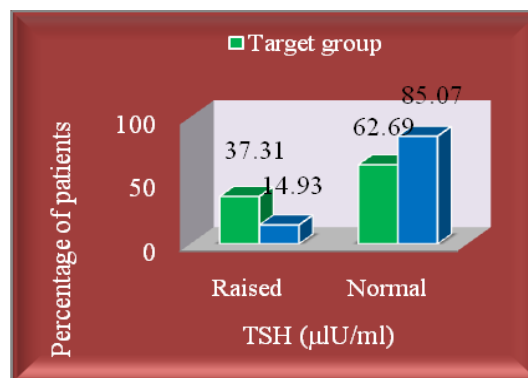
TSH (μIU/ml)	Target group (n=67)	Control group (n=67)	P value	95% CI (Lower, Upper)	OR
	No. of patients	No. of patients			
Raised	25	10	0.03	1.47, 7.81	3.39
Normal (0.3-5.0)	42	57			

**Table III** shows raised TSH level compared to normal TSH level is 3.39 times more likely to have recurrent pregnancy loss with 95% CI 1.47-7.81%. The difference was significant (p<0.05) between two groups.

**Table IV:** Distribution of the study patients by mean TSH level (n=134)

TSH level	Target group (n=67)	Control group (n=67)	P value
	Mean ± SE	Mean ± SE	
TSH (μIU/ml)	4.31 ± 2.74	2.56 ± 0.89	0.02
Range (min, max)	0.79, 12.98	1.01, 6.48	

Mean TSH level was found 4.31±2.74μIU/ml in target group and 2.56±0.89 μIU/ml in control group. The mean difference was significant (p<0.05) between two groups.



**Figure 1:** Bar diagram showing TSH level of the patients.

**Table V:** Distribution of the study patients by FT<sub>4</sub> (n=134)

FT <sub>4</sub> (fmol/ml)	Target group (n=67)	Control group (n=67)	P value	95% CI (Lower, Upper)	OR
	No. of patients	No. of patients			
Low	48	5	0.001	10.91,	31.33

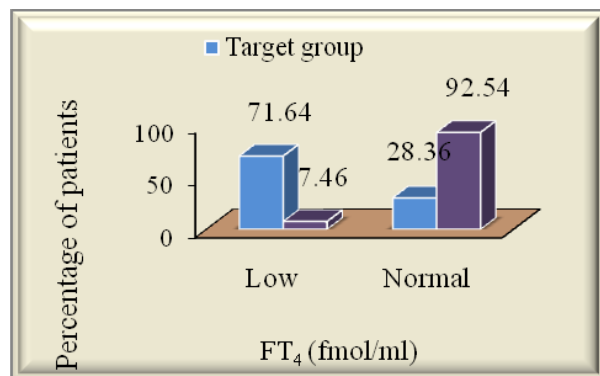
Normal (8.56-25.6)	19	62		89.94	
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**Table V** shows low FT<sub>4</sub> level compared to normal FT<sub>4</sub> level is 31.33 times more likely to have recurrent pregnancy loss with 95% CI 10.91-89.94. the difference was significant (p<0.05) between two group.

**Table VI:** Distribution of the study patients by mean FT<sub>4</sub> level (n=134)

FT <sub>4</sub> level	Target group (n=67)	Control group (n=67)	P value
	<b>Mean ± SE</b>	<b>Mean ± SE</b>	
FT <sub>4</sub> (fmol/ml)	10.53 ± 3.38	18.67 ± 4.81	0.007
Range (min, max)	3.69, 21.35	7.83, 25.6	

Mean FT<sub>4</sub> level was found 10.53±3.38 fmol/ml in cases and 18.67±4.81 fmol/ml in controls. The mean difference was statistically significant (p<0.05).

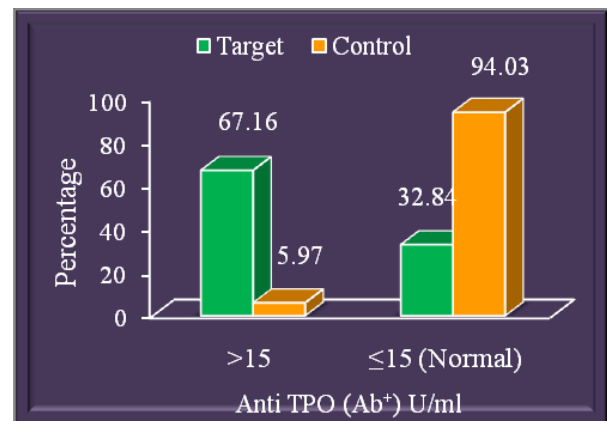


**Figure 2:** Bar diagram showing FT<sub>4</sub> of the patients.

**Table VII:** Distribution of the study patients by thyroid antibody (n=134)

Anti TPO (Ab <sup>+</sup> ) U/ml	Target group (n=67)	Control group (n=67)	P value	95% CI (Lower, Upper)	OR
	No. of patients	No. of patients			
> 15	45	4	0.001	10.38, 64.13	32.21
≤15 (Normal)	22	63			

**Table VII** shows the more number of patients among cases had positive TPO-Antibody compared to controls. A subject with TPO Ab>15 IU/ml vs TPO Ab ≤ 15 IU/ml had 32.21 (95% CI 10.38-64.13) times increase to developed recurrent pregnancy loss.



**Figure 3:** Bar diagram showing Anti TPO (Ab<sup>+</sup>) of the patients.

**Table VIII:** Status of thyroid antibody of miscarriage women (target) and control group (n=134)

Antibody U/ml	Target group (n=67)	Control group (n=67)	P value	95% CI (Lower, Upper)	OR
	No. of pts(%)	No. of pts(%)			
TPO-Ab <sup>+</sup> (positive)	55 (82.09%)	21 (31.34%)	0.001	4.47, 22.57	10.04
TPO-Ab <sup>-</sup> (negative)	12 (17.91%)	46 (68.66%)			

**Table VIII** shows the cases had higher percentage (82.09%) of positive antibody compared to controls (31.34%).

Positive TPO Ab compared to negative TPO Ab is 10 times more likely to have recurrent pregnancy loss with 95% CI 4.47- 22.57. The difference was significant ( $p < 0.05$ ) between two groups.

## Discussion

This is a case control study carried out with an aim to find out the association of thyroid autoimmunity with recurrent pregnancy loss. The study population consisted of pregnant women with a history of recurrent pregnancy loss during first trimester. Depending on the increased necessity of the thyroid gland for normal development, growth and metabolic homeostasis during pregnancy and fetal life, changes associated with pregnancy require an increased availability of thyroid hormones by 40% to 100% in order to meet the needs of mother and fetus during pregnancy.<sup>13</sup>

A number of researches have been published concerning the relation of thyroid autoimmunity and miscarriage. All studies are not easily comparable due to the different selection criteria employed for specific aims for each study, but most studies have shown a significant positive association between the presence of thyroid autoantibodies and miscarriage rate.<sup>12</sup> It was

suggested that those autoantibodies, which can also be higher in the euthyroid patients, may produce a threat for miscarriage in the subsequent pregnancy. Thyroid peroxidase antibodies target the thyroid peroxidase enzyme that assists in the production and metabolism of thyroid hormone.

Although they are widely seen in autoimmune thyroid disorders, thyroid peroxidase antibodies are not necessarily a sign of disease. In the normal healthy population, when TPO antibodies are accompanied by a higher TSH level ( $> 2.0 \text{ mu/L}$ ) they suggest an increased risk for developing Hashimoto's thyroiditis<sup>14</sup>. In spite of many studies available regarding the physiological changes in the thyroid function during pregnancy, it is uncertain if functional disorders of the thyroid gland play a role in the etiology of spontaneous miscarriages. However, the present study was trying to evaluate both thyroid hormones and thyroid antibodies as causative agent for miscarriage. The results of present study (Table-VI) showed decrease concentration of  $\text{FT}_4$  level, decrease of  $\text{FT}_4$  level may be due to non-pituitary stimulation of thyroid hormone secretion (hCG concentration).<sup>15</sup>

The higher TSH values (Table-III) that reported in the recurrent miscarriage group means that the TH in blood circulation is not high enough to stop the stimulation of the hypothalamus of release TRH to the anterior pituitary to inhibit the stimulation of the synthesis and secretion of TSH. Consequently the TH is not sufficient to meet the need of both mother and fetus resulting in termination of the pregnancy.<sup>16,17</sup> The low levels of TSH in miscarriage women is associated with small percentage of increased  $\text{TT}_4$  levels and high percentage of normal  $\text{FT}_4$  levels so most of miscarriage women are euthyroid according to the evaluation strategy of low serum TSH level.<sup>18</sup> This may be due to either IDD which diminishes the biosynthesis of thyroid hormones or to the lack of response of estrogen which affect the level of TBG, that is, the H-P-T axis work as if the women are not pregnant.

Euthyroid women in early gestational stages tend to have a reduced thyroid function reserve and

they have an increased risk for obstetrical complications such as miscarriage and premature delivery.<sup>19</sup>

Most of the studies reported that there was significant negative correlation between the T<sub>4</sub> and TSH levels in normal pregnancy.<sup>20,21</sup> Free thyroid hormones in both normal pregnant and recurrent miscarriage women were within the normal levels and this finding was disagreed with some study.<sup>22</sup>

The present study is indicating positive thyroid antibodies in both groups. The control pregnant women with positive thyroid antibodies can reach the term and have babies due to the suppression in the level of the TSH through the feedback mechanism.

Thyroid hormones are essential for the developing fetus. Hence a pregnant women needs thyroxin more than non-pregnant lady to provide T<sub>4</sub> to both herself and her developing fetus. It is advisable to suggest thyroid investigation to the pregnant women with history of recurrent miscarriage as soon as possible after knowing they are pregnant. Management of thyroid diseases during pregnancy required special considerations because pregnancy induces major changes in thyroid function, and maternal thyroid disease can have adverse effects on the pregnancy and the fetus.

### Conclusion:

Most of the women with recurrent miscarriage were euthyroid. The TSH levels were found to be normal in miscarriage women compared with healthy pregnant women. The feedback mechanism of thyroid-pituitary glands is profound or not properly works in women with recurrent miscarriage. The mean serum concentration of TPO-Ab(positive) in miscarriage women was significantly higher than mean concentration of TPO-Ab(positive) in healthy pregnant women. The thyroid antibodies can only affect pregnant women when there serum TSH level is relatively within actual normal range and free T<sub>4</sub> level in miscarriage women does not affected by the decreased TSH values. Pregnant women can reach term and have babies when their TSH levels are relatively lower.

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