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The association of thyroid autoantibody in euthyroid women with early pregnancy loss

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Abstract
Introduction: Thyroid autoantibodies are seen in a significant percentage of women of reproductive age. Even in euthyroid women, a positive anti thyroid antibody has been linked to an increased risk of spontaneous and recurrent pregnancy loss, as well as premature birth. However, in Bangladesh context, data is still insufficient to practice thyroid autoantibodies screening for prevention of early pregnancy loss.
Methods: This case-control study was carried out in the Obstetrics and Gynecology department of Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh from July 2021 to June 2022. The study period was 12 months. A total of 80 patients was enrolled according to inclusion and exclusion criteria following ethical clearance. Informed written consent was taken from each patient. Patients were enrolled dividing in two groups: group 1 and group 2. Group 1 included euthyroid patients presenting with early pregnancy loss and group 2 included apparently healthy pregnant women with a gestational age from 8 to 20 weeks. Each patient was subjected to detailed history taking, thorough physical examination, and relevant investigations, including thyroglobulin antibody and thyroperoxidase antibody. For data collection, a semi-structured questionnaire was used. Collected data were checked for errors and analyzed by Statistical Packages for social sciences (SPSS 22).
Results: Mean age of the patients was 24.13±4.49 (SD) years in group 1 and 23.98±4.76 (SD) in group 2. Baseline characteristics were statistically similar in both groups. Regarding obstetric profile, multiparity and multigravidity were significantly higher in patients with early pregnancy loss ($p<.05$).Though TSH (Thyroid stimulating hormone) was statistically similar in both groups (1.88±1.00 mIU/L in group 1 and 1.85±0.95mIU/L in group 2, $p>.05$), both thyroglobulin antibody (Tg-Ab) (184.7±202.4 IU/ml vs 115.3 ±103.3 IU /ml, $p<.05$) and thyroid peroxidase antibody (TPO-Ab) (53.55±121.8 I U/ml vs 19.97±57.29I U/ml, $p<.05$) were significantly higher in women with early pregnancy loss (group-1).
Conclusion: This study observed significantly higher frequency of thyroid antibody in patients with early pregnancy loss comparing to the women with normal early pregnancy. However, further larger study is recommended.

Keywords: Thyroid Auto-Antibody, Thyroglobulin Antibody, Tg-Ab, Thyroid Peroxidase Antibody, TPO-Ab, Early Pregnancy Loss, Abortion, Miscarriage

Introduction
An abortion is the spontaneous or induced loss of early pregnancy. The pregnancy period before fetal viability outside of the uterus is considered as early pregnancy loss. Most consider early pregnancy to end at 20 weeks of gestation or when the fetus weighs 500 grams. Considering the fact that the exact cause (s) of early pregnancy loss is still not known in over half of the cases [1], this has become a topic of consideration by researchers. Early pregnancy loss is the most common adverse outcome of pregnancy that affects the physical and psychological well- being of prospective parents and has major cost implications for patients and health institutions. It is also known as spontaneous abortion, and miscarriage, typically occurs in the first trimester of gestation [2]. More than 80% of the early pregnancy loss occur within the first 12 weeks of gestation while 1 in 5 women loosed before the 24th week of gestation [3, 4]. However, an estimated 10–25% of clinically- recognized pregnancies ends in miscarriage in developed countries [5]. The prevalence of miscarriage/ early pregnancy loss in Bangladesh is 9.6% [6]. World Health Organization (WHO) estimated that 15-20% of maternal death is caused by abortion and 19 million miscarriages occur each year. This miscarriage is close to one miscarriage for every 10 pregnancies [7], the number of abortion cases in Southeast Asia was 4.2 million per year [8]. Thyroid autoantibodies are the markers, represent the generalized autoimmune imbalance that is responsible for an increased miscarriage rate, increased chances

of these women to develop subclinical, or overt hypothyroidism during pregnancy [9]. Thyroid disease is one of the most frequent endocrine conditions in women of childbearing age. The most common cause of thyroid dysfunction is thyroid autoimmunity. It is defined as the presence of antithyroid antibodies (Anti-TPO antibodies), specifically thyroid peroxidase antibodies and/or thyroglobulin antibodies [10]. Anti-TPO antibodies, which belong to the IgG immunoglobulin class, are autoantibodies directed against thyroid peroxidase protein. These antibodies are seen in patients with thyroid dysfunction (Hypothyroidism or hyperthyroidism), but there is also evidence of these antibodies in euthyroidism. However, the mechanism linking thyroid autoimmunity with increased risk of miscarriage and preterm birth in women without overt hypothyroidism is unclear. Two competing mechanistic theories propose that thyroid autoantibodies are a marker of a hostile immune environment or thyroid autoantibodies act as a surrogate biomarker of impaired thyroid hormone reserves, despite normal thyroid function tests. If the latter theory is true, one hormone reserves, despite normal thyroid function tests [11]. Early pregnancy loss (Unintended pregnancy loss before 20 completed weeks of gestation) is a common adverse pregnancy outcome with reported incidence ranging from 10 to 30% of detected pregnancies. It spans a range of subtypes, including spon-taneous abortion, missed abortion, incomplete abortion, molar pregnancy, and others [12]. Even in euthyroid women, there is a link between thyroid autoantibodies, specifically antithyroid peroxidase antibodies, and an increased risk of pregnancy loss and preterm delivery [13-16]. Therefore, the purpose of the study is to evaluate the association of thyroid autoantibody in euthyroid women with early pregnancy loss.

Methodology

- **Study design:** This was a case-control study.
- **Study place:** Department of Obstetrics and Gynaecology, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh.
- **Study period:** From July 2021 to June 2022.

Study population

- **Case group (group 1):** Euthyroid Pregnant women in the process of abortion in between 8 to 20 weeks fulfilling the inclusion criteria were included as a case group.
- **Control group (group 2):** Study sample included euthyroid normal pregnant women without process of abortion between 8 to 20 weeks as the control group.
- **Sample method**: The sample was collected by purposive sampling.
- **Sample size:** The targeted sample size was 103 in each group. But due to limited resources and COVID-19 pandemic situation a total (40x2) subjects were included in the study.

Selection Criteria

Inclusion criteria

- Pregnant women with the age between 18 to 35 years old.
- Gestational age less than 20 weeks of gestation calculated according to last menstrual period (LMP) and or an early ultrasound confirmation.
- Euthyroid women (TSH ≥0.2 and ≤3 mIU / L) (As first trimester reference ranges 0.1 – 2.5 mIU/L; second trimester, 0.2-3.0 mIU/L) [15].

Exclusion criteria both

- Known case of thyroid disease.
- Women with known chronic medical disorder (Diabetes, Hypertension etc.).
- Women with known autoimmune disorder (Like SLE, anti-phospholipid antibody syndrome etc.)
- Women with history of habitual abortion due to cervical incompetence, bicornuate uterus, uterine septam, any other uterine pathology.
- History of birth of major fetal abnormalities.

Data collection Procedure

This case-control study was carried out in the Obstetrics and Gynecology department of Sir Salimullah Medical College Mitford Hospital, Dhaka, from July 2021 to June 2022. A total of 80 patients were enrolled according to inclusion and exclusion criteria and following ethical clearance and informed written consent.

Patients were enrolled dividing in two groups: group 1 and group 2. Group 1 included patients presenting with early pregnancy loss and group 2 included apparently healthy pregnant women with a gestational age from 8 to 20 weeks. All selected respondents were euthyroid according to operation definition and confirmed by laboratory test (Thyroid Stimulating Hormone). Each patient was subjected to detailed history taking, thorough physical examination, and relevant investigations, including anti thyroglobulin antibody and anti thyroperoxidase antibody.

Data processing and analysis

Statistical analysis was performed using statistical package for social science (SPSS) statistical software version 22.0. Socio-demographic characteristics, clinical and laboratory parameters were measured and reported for the respondents. Continuous data were expressed as mean and standard deviation and categorical data were expressed as frequency and percentage. Comparisons between groups were assessed by chi-square test and independent student t-test for categorical and continuous value respectively. A probability (p) value of < 0.05 ($p<0.05$) were considered statistically significant.

Results

Table 1: Distribution of Baseline characteristics among the study subjects (n=80)

Demographic and obstetric characteristics	Group-1 (cases) n=40 Mean ±SD	Group-2 (controls) n=40 Mean ±SD	p value
Age (in years)	24.13±4.49	23.98±4.76	0.349
Height (in meters)	1.87±1.06	1.87±1.06	1
Weight (in kgs)	58.7±4.94	58.71±4.93	.921
BMI (kg/m^2)	19.87±3.56	19.59±3.92	0.588

Abbreviation: BMI-body mass index

The majority of the study population was in their early twenties, with the mean age of the pregnant women in both group-1 and

group-2 being 24.13±4.49 years and 23.98±4.76, respectively. The mean height of the pregnant women was 1.87 meters, and the mean weight was approximately 58 kgs in both groups. Moreover, the BMI reported by both the groups was 19.87±3.56 and 19.59±3.92, with no significant difference between the groups.

Table 2: Obstetric profile of the study respondents (n=80)

Obstetric profile	Group-1 (Cases) n=40 n (%)	Group-2 (controls) n=40 n (%)	p value
Duration of pregnancy (in weeks)			
Mean ±SD	12.00±2.42	12.8±2.97	0.052
Gravida			
Primigravida	6(15%)	25(62.5%)	<0.001
Multigravida	34(85%)	15(37.5%)	
Parity			
Nulliparous	6(15%)	25(62.5%)	0.034
Primiparous	16(40%)	1(2.5%)	
multiparous	18(45%)	14(35%)	

The mean duration of the pregnancy was 12 weeks and 14.28 weeks in group-1 and group-2 respectively. Nulli parity was significantly more common in normal pregnant women compared to pregnant women in the process of abortion. Multigravida was significantly higher in pregnant women in the process of abortion (group-1:85%) compared to normal pregnant women (group-2:37.5%). Multiparity were significantly higher in pregnant women with early pregnancy loss compared to normal pregnant women.

Table 3: Thyroid profile of the respondents in both group-1 and group-2 (n=80)

Thyroid profile	Group-1 (Cases) n=40 n (%)	Group-2 (Controls) n=40 n (%)	p value
TSH (mIU/L)*	1.88 ±1.00	1.85 ±0.95	0.043
Tg-Ab positive (>116 IU/ml)**	16(40%)	4(10%)	0.002
TPO-Ab positive (>35 IU/ml) **	15(37.5%)	6(15%)	0.022
Tg-Ab (IU/ml)*	184.7 ±202.4	115.3 ±103.3	0.005
TPO-Ab (IU/ml)*	53.55 ±121.8	19.97 ±57.29	0.032

Abbreviation: Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid-peroxidase antibody; TSH, thyroid-stimulating hormone
Variables were presented as mean± SD* and frequency (Percentage)**

While assessing the thyroid profile of the study participants, it was reported that the mean average level of TSH was 1.88 ±1.00 IU/ml and 1.85 ±0.95 IU/ml and there was no significant difference in the TSH level in both group-1 and group-2 respectively. Anti-thyroglobulin antibody (Tg-Ab) was positive in 40% of the women with early loss of pregnancy along with 37.5% of them having positive TPO-Ab. The Tg-Ab and TPO-Ab was significantly higher in women in the process of aborting their child (group-1) compared to women with normal pregnancy (group-2). The mean value of Tg-Ab was 184.7 ±202.4 IU/ml and TPO-Ab was 53.55±121.8 IU/ml in women with the early loss of pregnancy (group-1).

Discussion

The presence of thyroid peroxidase (TPO) or thyroglobulin antibodies in the first trimester of pregnancy is a risk factor for subsequent spontaneous pregnancy loss obtained [17] studied the significance of the presence of thyroid antibodies before pregnancy in women with a history of habitual abortion and found these antibodies to increase the risk for yet another abortion significantly. Impaired maternal thyroid hormone availability may induce irreversible brain damage with consequent neurological abnormalities [18]. The prevalence of anti-thyroid antibodies among women is 10 fold that in men and its prevalence among reproductive aged women has been reported at 2-6% [19]. The prevalence of TPOAb in women with unexplained recurrent miscarriage is 11.8% [19] and it is 18% in women with female factor infertility [20]. In the current study, majority of the pregnant women were in their 1st trimester (mean duration of pregnancy: 12-12.8 weeks) and the thyroid profile of the women in case group, reported that the mean average level of TSH was 1.88±1.00 mIU/L and 1.85±0.95 mIU/L in women of control group. it was observed that the level of TSH was significant in the cases (Women with early loss of pregnancy) than in controls in this study which is similar to findings in a case-control study conducted among 2105 pregnant women in china, were it was reported that the TSH levels between 2.5 and 4.87 mIU/L were correlated with increased risk of miscarriage [21]. Tg-Ab and TPO-Ab was significantly higher in women with early loss of pregnancy (group-1) compared to women with normal pregnancy (group-2). The mean value of Tg-Ab was 184.7 ±202.4 IU/ml and TPO-Ab was 53.55±121.8 IU/ml in women with early loss of pregnancy (group-1). In contrary to this study, Hafez *et al*., [22] reported that early loss and adverse pregnancy outcomes were higher in patients with thyroid dysfunction, than normal control group, but this difference was not statistically significant. Dendrinos *et al*., [23] on the other hand, in a case control study done on women with history of recurrent abortion and fertile women reported higher frequency of Tg-Ab in women with recurrent abortion compared to controls (37% versus 13%). As demonstrated in the present study, TSH tend to be higher among women with higher levels of Thyroid antibodies and early pregnancy loss. Detectable serum TPO-Ab has been reported in up to 37.5% of women with early loss of pregnancy. This percentage is twice the times higher (18%) than a case-control study conducted among 60 women in a tertiary hospital of Bangladesh Ohida *et al*. [24] and 17% of US adult women reported higher level of TSH and TPO-Ab [25]. The presence of detectable maternal thyroid antibodies is said to be a risk factor for postpartum thyroiditis, miscarriage, and premature babies [26-28]. In fact, findings from a recent study suggest that treatment of TPO-Ab–positive euthyroid women with levothyroxine results in improved obstetric outcomes [29]. Thus, information about TPO-Ab positivity is important for the

development of trimester-specific reference ranges for thyroid function test values. Growing fetus release enough antigen to stimulate the maternal immune system which subsequently produce thyroid per oxidase antibodies and exerts inverse effect on maternal thyroid hormone synthesis [30]. Antibody against thyroid peroxidase enzyme (TPO-Ab) blocks each steps of thyroid hormone synthesis and causes a decrease in serum free thyroxine (FT4) and increase in serum TSH levels in TPO-Ab positive women in comparison to those of TPO-Ab negative women during 1st trimester [31].

Limitation

- However, this study has several limitations. First, it lacks data on some potential confounding factors such as environmental toxins, irregular menstruation, family history of miscarriage, and anti-phospholipid antibodies.
- Second, chromosomal anomalies and HCG values were not evaluated.
- Third, matched case–control study wastes some data and reduces the amount of statistical information.
- Fourth, this study may lead to measurement bias or omission.
- Fifth, the study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the country.
- Sixth, sample size was also a limitation of the present study.

Conclusion

Early pregnancy loss or abortion may result in devastating consequences in physical health, mental health, and social status. A significant amount of pregnancy loss could be prevented through early risk assessment. In this study, both thyroglobulin anti body and thyro peroxidase antibody were significantly higher in patients with early pregnancy loss. Indicating importance of assessment of these antibodies in early pregnancy loss even though patient are euthyroid. But before establishment of routine prenatal and antenatal screening of thyroid antibodies, further larger study should be conducted in large scale.

Recommendations

- Further studies with a larger sample size are recommended.
- Pregnant women with history of early pregnancy loss should be routinely checked for antithyroid antibodies soon after the confirmation of conception.
- During pre-natal checkup, antithyroid antibodies should be checked.
- Women with the presence of thyroid antibodies during prenatal and antenatal check-up should be considered as vulnerable and treated accordingly even though they are euthyroid.

Conflict of Interest

Not available

Financial Support

Not available

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