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Full Length Research Paper

Role of Thyroid Antibodies in Recurrent Miscarriage: A Case Control Study

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Abstract
Thyroid antibody positivity during pregnancy has been associated with adverse outcomes including miscarriage. The aim of the study is to shed light on relation between presence of thyroid antibodies and occurrence of recurrent miscarriage. It is a case control study. This study was conducted on 80 pregnant women attended to outpatient clinic of Al-Azhar university hospital (New Damietta) between October 2015 and September 2016, 40 of them with history of two or more consecutive miscarriages (study) and other 40 without history of miscarriage (controls). The mean age of the patients included in the study was 25.75 ± 4.1 years. Thyroid autoimmunity (thyroid peroxidase antibody (TPO Ab +ve) >34 U/ml) was found in 27.5% of the cases and 4% of controls, P=0.045. There was a difference in the prevalence of miscarriage between recurrent miscarriage (cases) and healthy pregnant women group (controls) (17.5 vs 7.5%). Abortion outcome was high in TPO +ve than TPO –ve of study cases (54.5 vs 3.4), P=0.0007. Family history of thyroid disorders was high in TPO +ve than TPO –ve (36.4 vs 6.9), p =0.038.There is an association between thyroid autoimmunity and increase prevalence of recurrent miscarriage and an association between thyroid autoimmunity and family history of thyroid diseases.

Keywords: *Recurrent miscarriage, Thyroid autoimmunity, TPO Ab.*

Introduction

Recurrent miscarriage (RM) is a very frustrating condition for both the couple and the clinician, because it is difficult to find a distinct reason for the repeated failure to sustain a pregnancy and eventually have a successful pregnancy outcome. Epidemiologically advanced maternal age is a strong risk factor for both spontaneous abortion (SA) and RM. The number of good quality oocytes in older mothers is fewer than younger mothers, which increase the frequency of chromosomal abnormalities leading to miscarriage. The risk of further miscarriage increases to approximately 50% for women with three or more losses without a liveborn infant (1). During the last decade, much work has been done in the area of thyroid and pregnancy, and significant advances in the understanding of thyroid function modifications have been reached. A general agreement has developed in the potential relationship between different pregnancy pathologies, such as abortion, gestational hypertension, and diabetes, and even subclinical thyroid disorders such as subclinical hypothyroidism and the presence of thyroid antibodies (TAI) (2). Miscarriage is the spontaneous loss of the conceptus before 20 weeks of gestation. Potential amount of possible miscarriage before pregnancy is recognized to be about 30%. In clinically recognized pregnancy, it is 10–15% before 8th week and 3% between 8th and 28th weeks. Recurrent miscarriage, defined as loss of two or more consecutive pregnancies, occurs in 1–2% of couples attempting to bear children (3) (4). The etiology of recurrent spontaneous miscarriage is often unclear and with much controversy regarding diagnosis and treatment. Reasonably accepted etiologic causes include, genetics 5%, anatomical 10%, hormonal problems, infections 5% and responsible for sporadic miscarriage rather than consecutive miscarriage. Anti-phospholipids antibody (APA) 7% to 25%, certain coagulation and immunoregulatory protein defects cause miscarriage. However, the majority of cases of RSM remain unexplained 60% (5). Although the great majority of pregnant women have no preexisting endocrine abnormalities, a small number of women can have certain endocrine alterations that could potentially lead to recurrent pregnancy losses. It is estimated that approximately 8 to 12% of all pregnancy losses are the result of endocrine factors. Several endocrinological abnormalities such as thyroid disease, hypoparathyroidism, uncontrolled diabetes, and decreased ovarian reserve have been implicated as etiologic factors for recurrent pregnancy loss (6). With regard to AITDs, other accelerators in addition to obesity include low selenium (Se) and a high iodine intake. Obese are hyperleptinemic, and leptin, with its numerous functions including the promotion of cell-mediated immune responses, is a good candidate for contributing to the pathogenesis of autoimmune diseases. Obese have been found to have increased interferon (IFN) secreting T helper cells and altered thyroid structure and hormonal status (7). Autoimmune disorders result from a complex interplay of genetic, environmental, and endogenous factors (antibodies), and a combination of these factors is required to initiate thyroid autoimmunity (8).

Patients and methods

This study was a case control study conducted on 80 women between 20 and 40 years of age attended to outpatient clinic of Al-Azhar university hospital (New Damietta). The cases of the study divided to two groups.

1st group: 40 pregnant women with a history of two or more consecutive miscarriages (study group).
2nd group: 40 pregnant women without history miscarriages were taken as healthy controls cases.

A- Inclusion criteria:

- All pregnant women with a history of two or more consecutive miscarriages.
- All pregnant women before 10 weeks who have no history of miscarriage (control cases).

B- Exclusion criteria:

- Women already on treatment for thyroid dysfunction.
- History of cervical incompetence and uterine pathology.
- Women with history of induced abortion.
- Positive to antiphospholipid syndrome.
- Women under treatment of chronic diseases. **All the included cases were subjected to:**

Detailed history taking, Personal history, menstrual history, Obstetric history, history of other autoimmunological diseases, symptoms of thyroid disorders, family history of thyroid disorders and other autoimmunological disease. Physical examination including general examination and thyroid examination. Obstetric U/S will be done for all cases at 8 weeks, and another scan repeated at 18 weeks, then once monthly till 28 week. TSH and thyroid peroxidase (TPO) antibodies also will do. All cases will be followed every 4 wks till 28 weeks and results will be recorded. All data were organized, tabulated, and statistically analyzed.

Results

In the present work, Table 1 shows age distribution of the 80 cases recruited. age of patients ranged from 20 to 40 years with mean (25.3 ± 3.5) in the study group and (26.2 ± 4.7) in controls. BMI ranged from (22.57-33.17) with mean (27.87) in study group and from (22-31.60) with mean (26.80) in controls. According to parity, it was higher in controls than study with a mean of (1.80 ± 1.20) and (2.35±1.62) respectively.

History of Consecutive abortion was high in study group ranged from (2 -8) with mean (2.85 ± 1.2). History of presence of other autoimmune diseases was higher in study group (10%). Presence of family history of thyroid diseases was higher in study group (15%). Presence of family history of other autoimmune diseases was higher in study group (5%). (Table 2).

TSH was nearly comparable in the 2 groups with mean (2.94 vs 2.32) in study and controls respectively. There were much difference in TPO Ab between the 2 groups with mean (27.6 vs 16.27) in study and controls respectively. P-value:< 0.001.TPO Ab +ve cases were high among study group than controls (27.5% vs 10%), which show significant difference between the two groups. P-value: 0.045. (Table 3).

Table 4 Abortion outcome among women with TPO Ab+ve was nearly comparable (54.5% vs 50%) in study and controls respectively. Abortion outcome was high (50%) among women with +ve family history of thyroid diseases in study group. General Abortion outcome was high among study than controls (17.5% vs 7.5%) respectively, with no significant difference between the two groups.

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Table 5 which compare between TPO +ve and TPO –ve in the (study) group in which age is nearly comparable with mean (28.9 vs 25.2) in +ve and -ve TPO women respectively. BMI is nearly comparable with mean (28.3 vs 26.8) in +ve and -ve TPO women respectively. History of presence of other autoimmune diseases was high among TPO +ve than TPO-ve (27.3% vs 3.4%) respectively, but with no significant statistical difference between the two groups. presence of family history of thyroid diseases was high among TPO +ve than TPO-ve (36.4% vs 6.9%) respectively, with significant difference between the two groups. P-value: 0.038. Presence of family history of other autoimmune diseases was high among TPO +ve than TPO -ve (18.2% vs 0%) respectively, but with no statistical significant difference between the two groups. Abortion outcome was high among TPO+ve than TPO-ve (45.5% vs 3.4%) respectively, with significant difference between the two groups. P- value: 0.0007.

Table 1. Demographic data of the studied groups.

Items	Study n=40	Controls n=40	P-value
Age/years			
Mean ± SD	25.3 ± 3.5	26.2 ± 4.7	0.16
Min-Max	20 -38	20 - 36	
<25 yrs	15 (37.5%)	14 (35%)	
25 – 30	19 (47.5%)	23 (57.5)	
>35 yrs	6 (15%)	3 (7.5%)	
Weight (kg)			

Mean ± SD	69.59±9.88	65.23±5.21	0.016*
Height (meter)			
Mean ± SD	1.58±0.06	1.56±0.05	0.071
BMI (kg/m2)			
Mean ± SD	27.87±2.44	26.80±1.39	0.018*
Min-Max	22.57-33.17	22-31.60	
Parity			
Mean ± SD	1.80 ± 1.20	2.35±1.62	0.088
P0	11 (27.5%)	6 (15%)	*0.305*
P1	12 (30%)	12 (30%)	
P2	10 (25%)	17 (42.5%)	
> P2	7 (17.5%)	5 (12.5)	

Table 2. History and Family history of the studied groups

Items	**Study n=40**
History of consecutive abortion	
Mean ± SD	2.85 ± 1.2*
History of other autoimmune dis	
No. (%)	4 (10%)
	2 SLE (5%) 1 Rh Arthritis (2.5%) 1 vitiligo (2.5%)
Family history of thyroid dis.	
No (%)	6 (15%)
Family history of other Autoimmune dis.	
No (%)	2 (5%) SLE
NB: control group was normal with no family history	

Table 3. Lab profile in the two groups

Items	**Group (1) n=40**	**Group (2) n=40**	**P-value**
TSH (m IU/mL)			
Mean ± SD	2.94 ± 1.13	2.32 ± 1.05	0.273
TPO ab(IU/mL)			
Mean ± SD	27.6 ± 12.6*	16.27 ± 10.25	0.001*
TPO Ab +ve patients			
N / %	11 (27.5%)	4 (10%)	0.045*

Table 4. Abortion outcome in the studied groups.

Items	**Study**	**controls**	**P-value**
Abortion outcome in +ve TPO			
N / %	6/11 (54.5%)	2/4 (50%)	1
Abortion outcome in +ve Thyroid Family history			
N / %	3/6 (50%)	0 (0%)	1
General Abortion outcome			
N / %	7/40 (17.5%)	3/40 (7.5%)	0.176*

Table 5. Comparison between +ve and –ve TPO women of (study) group.

Items	**Positive TPO (n=11)**	**Negative TPO (n=29)**	**P-value**
Age	28.9±3.4	25.2±3.7	0.006*
BMI	28.3±2.32	26.8±2.56	0.098
Other Autoimmune Dis (n / %)	3 (27.3%)	1 (3.4%)	0.056
F.H of thyroid	4 (36.4%)	2 (6.9%)	0.038*
F.H of Autoimmune Dis	2 (18.2%)	0	0.070
Abortion	6 (54.5%)	1 (3.4)	0.0007*

Discussion

It has been twenty years since publishing the first paper reporting the association between thyroid antibodies (TAIs) and spontaneous miscarriage. Following this observation, several studies have clearly demonstrated an increased prevalence of TAI in patients with recurrent miscarriage (RM). However, the exact mechanism underlying this association remains a matter of debate [(9)]. In current study, the prevalence of thyroid autoimmunity was higher in pregnant women with a history of recurrent abortion compared with the healthy pregnant control population.

The prevalence of thyroid autoimmunity in our study was 18.75% (27.5%in pregnant women with recurrent abortion) while it was significantly lower (10%) in the healthy group (27.5 vs 10%, P=0.045). The prevalence in the general population described in the literature is 10–15% [(10)]. The odds ratio of having TPO Ab +ve was higher in the miscarriage group, indicated a strong association between them. General abortion outcome which was nearly comparable between both cases and controls (17.5% Vs 7.5%). But was high in TPO +ve than TPO –ve women of the study group (54.5 vs 3.4) respectively, with statistically significant difference. P-value= 0.0007.

Anita Singh *et al.,* 1995 [(11)] observe that; of the 487 patients studied, there were 106 women who were antibody positive for anti-TG, antithyroid peroxidase, or both, and 381 who were negative. The overall incidence of positivity was 22%. In the antibody-positive group there was a 32% clinical miscarriage rate in comparison to 16% in the antibody-negative group. This did reach statistical significance. There was no significant difference between the two groups in the incidence of biochemical or ectopic pregnancies. There also was no significant difference between the groups in age, gravidity; or number of prior pregnancy losses. so, thyroid antibodies proved to be a useful marker for identifying women at risk for clinical miscarriage but they appear not to have an association with biochemical pregnancies.

A similar study was carried out by Prummel *et al.,* 2004 [(12)], showed that TPO Ab +ve was associated with a twofold increased risk of miscarriage. In both the groups, the outcome of current pregnancy was not influenced by TPO positivity or by TSH values. This could be because all cases of either isolated TPO Ab positivity or of elevated TSH were treated during pregnancy. Similar results were found by (Negro *et al.,* 2006) [(13)], who found the miscarriage rate in the TPO Ab +ve group supplemented with T4 was comparable to healthy controls (3.5 vs 2.4%). However, unlike our study population, these patients had no history of recurrent miscarriage. This agree with the study by Carlo Ticconi et al.,2011 [(14)], Antithyroid autoantibodies were detected in 46 of 160 RM women, while the remaining 114 women were ATA negative. The results of the study show that ATA have been detected more frequently in women with RM than in healthy women without any abortion. The frequency of ATA positivity in RM women (28.75%) resulted within the range observed in the previous published studies on this subject (6.4–32.5%).

Observation of present study is in harmony with previous meta-analysis study by Shakila Thangaratinam *et al.,* 2011 [(15)] showed, 30 articles with 31 studies (19 cohort and 12 case-control) involving 12126 women assessed the association between thyroid autoantibodies and miscarriage. Of the 31 studies evaluating miscarriage, 28 showed a positive association between thyroid autoantibodies and miscarriage. Meta-analysis of the cohort studies showed more than tripling in the odds of miscarriage with the presence of thyroid autoantibodies (odds ratio 3.90, 95% confidence interval 2.48 to 6.12; P<0.001). For case-control studies the odds ratio for miscarriage was 1.80, 1.25 to 2.60; P=0.002). There was a significant doubling in the odds of preterm birth with the presence of thyroid autoantibodies (2.07, 1.17 to 3.68; P=0.01). Two randomized studies evaluated the effect of treatment with levothyroxine on miscarriage. Both showed a fall in miscarriage rates, and meta-analysis showed a significant 52% relative risk reduction in miscarriages with levothyroxine (relative risk 0.48, 0.25 to 0.92; P=0.03). One study reported on the effect of levothyroxine on the rate of preterm birth, and noted a 69% relative risk reduction (0.31, 0.11 to 0.90).

The previous findings was in accordance with the work of Yi-ping Zhong *et al.,* 2012 [(16)] of two groups, in the ATA +ve group, 90 women (were positive for TG-Ab and/or TPO-Ab), 676 women (negative for TG-Ab and/or TPO-Ab served as controls). The abortion rate was significantly higher in patients with antithyroid antibody (26.9% vs 11.8%). and agree the study by (Juneau Yan et al.,2012)[(17)] A total of 496 women with unexplained RM and a control group of 220 women with a known cause for RM were included in the study. The mean age of the two groups of subject was similar (women with unexplained RM, 32.7 ± 5.5 years; women with a known cause, 32.2 ± 5.6 years. Among 496 women with unexplained RM, 53 subjects (10.7%) tested positive for TPO Ab, whereas 26 of 220 (11.8%) of women with a known cause for their RM tested positive. but this study differs from our study in that, women in the control group have RM but of known cause.

Finally, this present study agrees with the study by (K Lata *et al.,* 2013) [(18)] 100 pregnant and 25 non-pregnant women between 21 and 35 years of age with a history of two or more consecutive miscarriages were included in the study. A third group comprising 100 pregnant women without a history of miscarriage was taken as healthy controls. The prevalence of thyroid autoimmunity was higher in pregnant women with a history of recurrent abortion compared with the healthy pregnant control population. Even though the TSH value was higher in the TPO Ab +ve group than in the TPO Ab -ve group.

On the other hand, which disagree with the results of present study by Esplin *et al.,* 1998 [(19)] failed to find a significant association between positive thyroid antibodies and recurrent abortion in a group of 74/149 women from the Salt Lake City area. This study constitutes an exception, as it is still unclear today why this studies yielded results that were at variance with almost all others. Referral biases and population differences may be a partial explanation for the negative findings. Also, the unusual and extremely

high incidence of TAI-positive controls (>30%) may have impacted on the results of the study.

In present study Family history of thyroid diseases was high among study (15%) than among control cases (0%) and abortion outcome was high (3/6) (50%) among women with +ve family history of thyroid diseases in study group, which is an indicator to familial cause of autoimmunity.

This is in accordance with study by Thea G. A. Strieder *et al.,* 2003 [20] done on 803 subjects, 440 came from families with more than one patient with documented AITD. Of these families, 33% had documented cases of both Graves' disease and Hashimoto's thyroiditis. Although the subjects were in self-proclaimed good health, 3·6% were found to have hypothyroidism and 1·9% had hyperthyroidism. These patients were older than the euthyroid subjects and were mostly positive for thyroid peroxidase (TPO) antibodies. Smoking and estrogen use were negatively correlated with the presence of TPO antibodies. In the euthyroid subjects, TPO antibody titer correlated positively with TSH levels ($rP < 0{\cdot}001$).

And this in harmony with a study by N. Manji *et al.,* 2006 [21] which reported a family history (FH) of thyroid dysfunction. In GD, a FH of hyperthyroidism in any relative was more frequent than hypothyroidism (30.1 *vs.* 24.4% in affected females, $P < 0.001$). In HT, a FH of hypothyroidism was more common than hyperthyroidism (42.1 *vs.* 22.8% in affected females, $P < 0.001$). For GD ($P < 0.001$) and HT ($P < 0.05$), a FH was more common in maternal than paternal relatives. The reporting of a parent with thyroid dysfunction (hyper or hypo) was associated with lower median age at diagnosis of both GD (mother with hyperthyroidism, $P < 0.001$) and HT (father with hypothyroidism, $P < 0.05$). In GD and HT, there was an inverse relationship between the number of relatives with thyroid dysfunction and age at diagnosis ($P < 0.01$).

And this agree another study by Magdalena Kochman *et al.,* 2014 [22] which was carried out on a group of 480 adolescents (285 girls and 195 boys), aged 17–18 years. All subjects were asked to answer questionnaire regarding family history of thyroid disease. Serum levels of TSH and anti-TPO were measured and performed thyroid ultrasound. Positive family history of thyroid disease declared 43% of the subjects. The mean thyroid volume was 9.85 ml (4.54–24.69, S.D.±3.31) for females, and 13.31 ml (5.46–60.95, S.D.±6.89) for males and did not differ significantly between subjects with and without thyroid disease in family. In the group with positive family history of thyroid disease abnormal TSH concentration was found in 3.2%, elevated anti-TPO concentration in 6.4% and abnormal ultrasound thyroid image in 30% of subjects, while in the group with negative family history in 2.6, 2.6 and 14% respectively.

Conclusion

Based on this study and previous studies done by other authors, there is an association between thyroid autoimmunity and increase prevalence of recurrent miscarriage and an association between thyroid autoimmunity and family history of thyroid diseases.

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