SCIENTIFIC LETTER

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Anti-Thyroid Peroxidase Antibody and Hypothyroidism in Recurrent Pregnancy Miscarriage

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ABSTRACT Thyroid disorders are one of the endocrine diseases that may develop during pregnancy. Thyroid autoimmunity (TAI) is commonly prevalent among these diseases in women of childbearing age. TAI includes thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies, and thyrotropin receptor antibodies. However, TPOAb is the most common antithyroid autoantibodies observed in women with recurrent miscarriage (RM) history. Although the precise mechanisms of the TPOAb's role in RM are not fully understood, multiple studies have found that the presence of TPOAb at a high level may increase the risk of recurrent pregnancy loss. The literature in this article was conducted based on published databases in PubMed, Web of Science, Google Scholar, and some international organizations It aims to emphasize the importance of screening for TPOAb in women with RM. It concludes that, according to published studies, the TPOAb could be considered as a good indicator of women at risk of RM.

Keywords: Abortion; antibodies; hypothyroidism; iodide peroxidase; pregnancy; thyroiditis

Recurrent miscarriage (RM) is defined as consecutive pregnancy losses at least three times or more before 20 weeks of gestational, but ectopic and molar pregnancies are not included. Nevertheless, some of the previous studies have reported that two consecutive pregnancy losses have similar factors that could be associated with three consecutive pregnancy losses. Therefore, evaluation has been advised for women with two consecutive spontaneous miscarriages to identify any causes that may be associated with their unsuccessful reproductive history.[1,2] Many factors are known to contribute to RM, such as antiphospholipid antibody syndrome, chromosome abnormalities, and structural uterine anomalies.[3] In addition to these factors, thyroid autoimmunity (TAI) disorder has been found as an independent factor that increases the risk of pregnancy losses.[4] TAI includes thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb), and thyrotropin receptor antibodies.[5] This article will focus on TPOAb because it is the one that has the most clinical importance in RM.

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TPOAB AND HASHIMOTO'S THYROIDITIS

Thyroid peroxidase (TPO) is the key enzyme stimulated by the thyroid stimulating hormone (TSH) for the biosynthesis of thyroid hormones [triiodothyronine (T3) and thyroxine (T4)] through catalyzed iodination and coupling of tyrosine residues in thyroglobulin.[6,7] TPOAb act against TPO enzymes and, as a result, cause hypothyroidism as a consequence of the insufficient synthesis of the thyroid hormones.[8,9] There are several causes for hypothyroidism, such as thyroid mastectomy, thyroid treatment, or iodine deficiency.[10] However, the primary cause is attributed to autoimmune Hashimoto's thyroiditis (HT).[11] It is characterized by normal thyroid function gland; however, hypothyroidism might develop over time.[12] The clinical symptom of HT is characterized by diffuse enlargement of the thyroid gland without pain.[13] While the clinical diagnosis of HT depends on the presence of circulating thyroid antibodies, mainly TPOAb.[14] Around 90% of HT cases have high levels of TPOAb. However, about 10-15% of euthyroid individuals also have elevated TPOAb levels.[15] Although HT is the most common autoimmune disorder globally, affecting around 4% of women during reproductive age and has been included in the causes of RMs, there are a few studies that estimate the occurrence rate of recurrent pregnancy loss (RPL) in patients with HT separated or with concurrent non-endocrine autoimmune disorders (NEAD).[16] For instance, a study conducted by Cellini et al. shows that women with HT, who also have NEAD, such as anti-phospholipid syndrome, tend to have a higher risk of RPL.[16] The presence of an anti-phospholipid syndrome may only justify some, but not all. Generally, the exact mechanism of HT-related miscarriage is not fully explained still requires more investigation.[11]

ANTI-TPO ANTIBODY AND RM

TPOAb are relatively higher in females during reproductive age.[17] Several clinical trials have examined the association between thyroid antiperoxidase antibody and RM. Some studies have found that women with positive TPOAb may have difficulty getting pregnant or, in some conditions, have a high chance for pregnancy loss or preterm delivery.[7,18] Although the exact cellular mechanisms of TPOAb on RM are not fully elucidated, there are some suggested hypotheses about the expected mechanisms of thyroid antibodies in RM cases.[3,19,20] For example, some of these hypotheses are illustrated in Figure 1.

Several systematic reviews and meta-analysis studies have discussed the presence of TPOAb in women of childbearing age as an indicator of increased incidence of RM and decreased rate of live birth, especially in those with a history of pregnancy losses. One study entitled "Effect of antithyroid antibodies on women with RM," by Xie et al. reported that women with TAI have detectable levels of thyroid antibodies such as TPOAb, TGAb, or TSH receptor antibodies. Nevertheless, most of those females have a high level of TPOAb, ranging from 8% to 14% in females of childbearing age.[21] A review study by Alexander et al. reported that TPOAb titer was higher in women with RPL history than those without a history of recurrent loss (31% vs. 18%. p=0.031). The same review study also mentioned that a meta-analysis of 8 studies showed a significant relationship between thyroid Ab positivity and RM, whereas odds ratio 2.3 (95% confidence interval 1.5-3.5) recruited 460 Ab-positive women and 1,923 controls.[22] Furthermore, a systematic study conducted by Thangaratinam et al. concludes that the prevalence of thyroid autoantibodies in women of reproductive age is about 6% to 20%, while the level is higher, around 17-33% in women with a history of RM.[23]

The Table 1 below shows the percentage of positive TPOAb in some studies involving pregnant women with RM history.

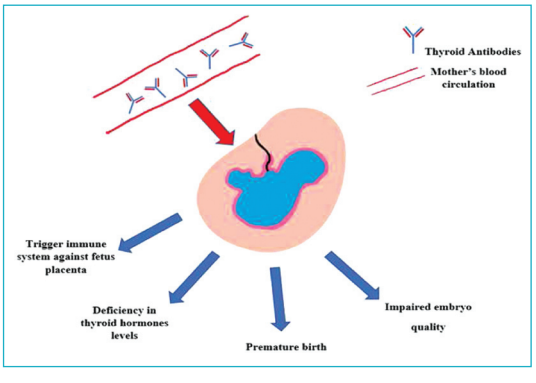

FIGURE 1: Overview of expected influences of mother's thyroid antibodies (especially thyroid peroxidase antibodies) on the fetus.

TABLE 1: Prevalence of positive TPOAb among pregnant women who participated in the target study.

Author	Number of participants	Women With RM	Prevalence of positive TPOAb	p value	Year	Reference
Mohammed Ali et al.	90	50%	18.8%	<0.001	2020	24
Rajput R et al.	1,030	15.3%	18.9%	0.004	2017	25
Meena A et al.	1,000	8%	6%	<0.001	2016	7
Vissenberg R et al.	2,020	28%	13.9%	0.023	2016	26

TPOAb: Thyroid peroxidase antibodies; RM: Recurrent miscarriage.

LEVOTHYROXINE AND PREGNANT WOMEN WITH TPOAB POSITIVE

There is no clear agreed policy for treating women with RM who tested positive for TPOAb. Levothyroxine is a treatment used in hypothyroidism conditions to replace deficient thyroid hormones.[27,28] Some published studies supported using levothyroxine to reduce TPOAb in cases with RPLs.[7,29,30] On the contrary, other studies concluded that levothyroxine does not seem to decrease the risk of miscarriage in TPOAb positive women.[31,32] So, using levothyroxine in RM cases is still a debatable issue. However, maintaining thyroid hormones within normal levels in pregnant women is very important because thyroid hormones are essential for fetal growth, especially in fetal neurocognitive development.[33]

AUTHOR'S PERSPECTIVES

According to the published data, the involvement of thyroid autoantibodies in RM is well established. Our view supports the hypothesis that proposes testing thyroid autoantibodies, especially TPOAb, including screening thyroid hormonal profiles for pregnant women. This test could be a valuable tool for women with history of RPL. It is worth noting that thyroid screening for abnormal TSH and TPO-antibody levels followed up by T4 testing in women with RPL is stated in the European Society of Human Reproduction and Embryology (ESHRE) guideline. The American Society for Reproductive Medicine (ASRM) also recommends thyroid or prolactin abnormalities tests. In addition, the American Thyroid Association (ATA) advises screening for TSH as soon as pregnancy is confirmed, especially for those with history of autoimmune thyroid disease. Furthermore, the female age should also be taken into consideration in the cases of RM, according to the Guidelines Development Group. Thus, implementing the recommendations and guidelines from accredited organizations such as ESHRE, ASRM and ATA could increase the rate of live births, subsequently raising the chance of successful pregnancy. In conclusion, although some investigators claimed that there are no significant correlations between the levels of TPOAb positive and evidence of RM, this article supports the majority of published studies that have well documented the benefits of TPOAb screening during pregnancy in helping early identification of women at risk of having RM.[34,35]

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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