



Review Article

# Miscarriage and Anti-TPO antibodies

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## ABSTRACT

Autoimmune thyroid disorders are common in women of reproductive age. Anti-TPO antibody and thyroglobulin antibody are frequently found to be associated. Anti-TPO antibodies are responsible for the activation of complement and are thought to be significantly involved in thyroid dysfunction. In early pregnancy women with anti TPO antibodies are prone to develop subclinical or overt hypothyroidism leading to adverse obstetric and fetal outcomes. An association between the risk of a miscarriage and anti TPO antibodies has also been reported even in absence of overt thyroid dysfunction. However, screening for these antibodies and Levothyroxin supplement in anti TPO antibodies -positive euthyroid pregnant women has not been established yet.

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## INTRODUCTION

Miscarriage also known as spontaneous abortion is defined as loss of previable pregnancy. Previability means a fetus weighing <500 gram or at gestational age < 20 weeks.<sup>1</sup> After 20 weeks of gestation, fetal death is known as a stillbirth.<sup>2</sup> However the gestational threshold for the definition varies between countries. In the US it is usually 20 weeks (but may vary in different states)<sup>3</sup>, whereas in the UK, the Royal College of Obstetricians and Gynecologists defines it as 24 weeks. Three or more consecutive pregnancy losses prior to 20 weeks gestation is defined as recurrent miscarriage.<sup>4</sup>

The overall miscarriage rate is reported as 15-20% and that for recurrent miscarriage is 1-3% of reproductive age women.<sup>5</sup> The true rate of miscarriage is probably higher because many losses occur preclinically, before a menstrual period is missed.<sup>6</sup> About 80% of miscarriages occur within the first trimester. The frequency of miscarriage decreases with increasing gestational age.<sup>1</sup> Signs and symptoms of a miscarriage might include vaginal spotting or bleeding, abdomen cramp, pain in lower back, fluid or tissue passing from vagina.<sup>7</sup>

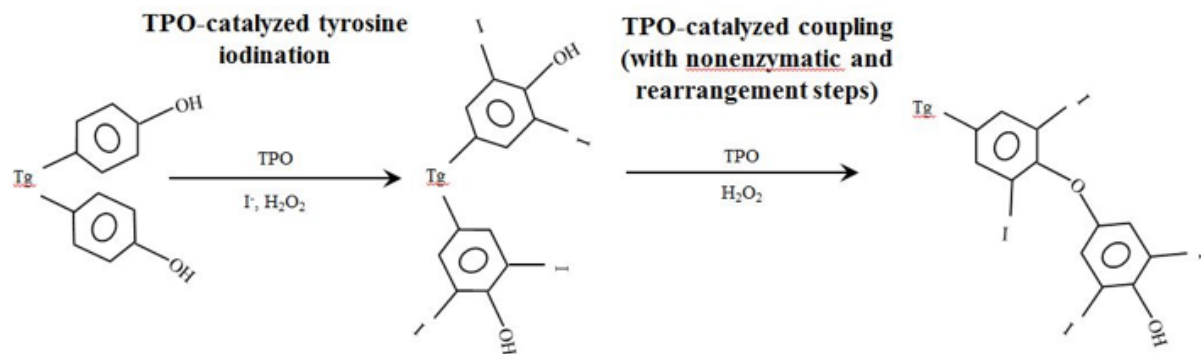


Figure 1: Role of TPO in Thyroid Hormone Synthesis.

Diagnosis of miscarriage can be reached on the basis of clinical findings, imaging and biochemical markers. As clinical diagnosis of miscarriage is unreliable, transvaginal ultrasonography has become the accepted standard for examining women with suspected complications of early pregnancy in modern practice.<sup>8,9</sup> Biochemical markers for diagnosis of miscarriage are not routinely used, however, they might be useful to confirm the early pregnancy failure in women in whom ultrasound findings are non-diagnostic. Serum human chorionic gonadotrophin and progesterone are frequently assessed biomarkers in miscarriage. Declining human chorionic gonadotrophin values can diagnose a complete miscarriage with a sensitivity of 93-97 percent.<sup>10</sup>

Miscarriage can be caused by genetic, anatomic, infectious and endocrine factors such as diabetes mellitus and hyperprolactinemia and by environmental insults such as smoking, alcohol abuse and exposure to toxic substances.<sup>11</sup> It is also associated with several autoimmune diseases, most notably systemic lupus erythematosus, antiphospholipid syndrome and inherited thrombophilias (antithrombin deficiency, deficiency of protein C and protein S, factor V Leiden mutation, and mild hyper homocysteinaemia).<sup>12</sup> There now have been several reports in the literature of an increased incidence of thyroid antibodies in the sera of women with a history of miscarriage, and it has been suggested that thyroid antibodies may serve as a marker for women at risk for miscarriage.<sup>13</sup>

#### ANTI THYROPEROXIDASE (TPO) ANTIBODIES AND MISCARRIAGE

Thyroid peroxidase (TPO) is an enzyme responsible for thyroid hormone synthesis. It catalyzes the oxidation of iodide on tyrosine residues in thyroglobulin and coupling for the synthesis of triiodothyronine and thyroxine (fig.1). TPO is a membrane-associated hemoglycoprotein which is expressed in thyrocytes and is one of the most important thyroid gland antigens.<sup>14</sup>

Disorders of the thyroid gland are frequently caused by autoimmune mechanisms with the production of

autoantibodies. Anti-TPO antibodies are one of the common thyroid antibodies that activate complement and are thought to be significantly involved in thyroid dysfunction and the pathogenesis of hypothyroidism.<sup>15</sup> The majority of anti-TPO antibodies are produced by thyroid infiltrating lymphocytes, with minor contributions from lymph nodes and the bone marrow.<sup>16</sup> Anti-TPO antibodies are an anti-microsomal antibody and can be of any class of IgG, although some studies indicated a higher prevalence of IgG1 (70%) and IgG4 (66.1%) compared to IgG2 (35.1%) and IgG3 (19.6%). Low levels of IgA antibodies have also been reported.<sup>17</sup>

These antibodies are associated with approximately 90% of Hashimoto's thyroiditis, 75% of Graves' disease and 10-20% of nodular goitre or thyroid carcinoma. About 10-15% of normal individuals can also have high level anti-TPO antibody titres.<sup>18</sup> In patients with subclinical hypothyroidism, presence of anti TPO antibodies is associated with an increased risk of developing overt hypothyroidism.<sup>19</sup>

Thyroid disorders especially those of autoimmune origin are common in women of reproductive age. Anti-TPO antibody and thyroglobulin antibody being the two main autoantibodies. In an "unselected" population of women, the prevalence of Anti TPO antibodies range from 6% to 20%, being even higher in women with a history of recurrent pregnancy loss, at around 17-33%, and in women with a history of subfertility, at around 10-31 percent.<sup>20</sup>

In early pregnancy, women with anti TPO antibodies have higher serum thyrotropin-stimulating hormone (TSH) levels compared with anti TPO antibodies-negative women, although the mean TSH levels may still fall within the normal range. These antibodies-positive women are prone to develop subclinical or overt hypothyroidism during pregnancy owing to the reduced functional reserve of their thyroid, which is unable to compensate for the increased hormone requirement of pregnancy and contributes to adverse obstetric and fetal outcomes.<sup>21, 22</sup>

Although the effects of anti TPO antibodies in patients with thyroid disorders have been identified long ago, their

adverse outcome in euthyroid women with pregnancy was brought to the attention by the landmark study by Stagnaro et al.<sup>21</sup> Since that time, numerous other studies have examined the association between maternal anti thyroid antibodies status and pregnancy loss risk, showing similar findings. An association between the risk of a miscarriage and autoimmune thyroid disease has been largely confirmed in several population studies, suggesting that anti TPO antibodies presence without overt thyroid dysfunction was significantly associated with a 3- to 5-fold increase in overall miscarriage rate.<sup>23,24</sup> Three hypotheses may underlie the association of thyroid autoimmunity with pregnancy complications: first, the fact that the presence of thyroid antibodies may represent a marker of a generalized autoimmune imbalance that is responsible for an increased miscarriage rate; second, increased chances of these women to develop subclinical, or overt hypothyroidism during pregnancy and third, these women are often older than those without, so an older age, per se, may explain the increased rate of fetal loss.<sup>25</sup>

### SCREENING AND TREATMENT

American Thyroid Association (ATA) and Endocrine Society both are against the screening for anti TPO antibodies in pregnancy to prevent spontaneous abortion and preterm delivery or even screening euthyroid women with sporadic or recurrent abortions. But if identified then serum TSH should be evaluated at time of pregnancy confirmation and every 4 weeks through mid pregnancy as per recommendation of ATA and Endocrine Society recommends that these women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy.<sup>26,27</sup>

Regarding treatment, there is little doubt that during pregnancy even mild abnormalities in thyroid function, for example, subclinical hypothyroidism, should be treated with levothyroxine (LT4). Insufficient evidence exists to conclusively determine whether levothyroxin therapy decreases pregnancy loss risk in anti TPO antibodies-positive euthyroid women who are newly pregnant. However, administration of LT4 to anti TPO antibodies -positive euthyroid pregnant women with a prior history of loss may be considered given its potential benefits in comparison with its minimal risk. In such cases, 25–50 µg of LT4 is a typical starting dose.<sup>26</sup> Some studies evaluating euthyroid anti TPO antibodies-positive pregnant women have shown that selenium can diminish anti TPO antibodies concentrations. However, this reduction has not been observed in all studies.<sup>28,29</sup> In addition, patients treated with selenium could be at higher risk for developing type 2 diabetes mellitus. For these reasons ATA does not recommended Selenium supplementation for the treatment of anti TPO antibodies-positive women during pregnancy.<sup>26</sup>

### CONCLUSION

An association between the risk of a miscarriage and anti TPO antibodies has been largely confirmed in several population studies even in absence of overt thyroid dysfunction. However, the screening for these antibodies in pregnancy to prevent spontaneous abortion and preterm delivery has not been recommended. Levothyroxin supplement in anti TPO antibodies -positive euthyroid pregnant women has not been established yet but might have potential benefit if there is prior history of pregnancy loss.

Conflict of Interest: **None**

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