The Immunology of Autoimmune Thyroid Disease in Pregnancy

Francis Balucan and Terry F. Davies

Mount Sinai School of Medicine and the James J. Peters VA Medical Center, New York, New York, USA

Abstract

In pregnancy, complex physiologic changes in the immune system alters the environment for the “non-self” fetus allowing it to be tolerated in the maternal womb, while the immune system is still able to counteract external pathogens. The interplay of the immune system and the physiologic changes induced by pregnancy on the thyroid induce changes in the natural history of the autoimmune thyroid diseases (AITD). This review discusses the various players in creating this milieu, including the MHC, the T- and B-cells, sex steroids and the possible role of microchimerism. The participants provide a variety of mechanisms that create the clinical scenarios that we see in patients with AITD – most commonly the improvement in Grave’s Disease during pregnancy and the rebound in thyroid autoantibodies and recurrence, or new onset, of Graves’ and Hashimoto’s diseases in the post-partum.

Keywords: immunology, autoimmune thyroid disease, pregnancy

Introduction

Pregnancy is a state that induces significant changes in the immune system. It is an immunotolerogenic state, allowing a semi-allogeneic fetus to exist within an environment that must still allow maternal detection and destruction of pathogens. This paradox is unique and necessary since a state of systemic immunosuppression would be disadvantageous to both the fetus and the mother. Pregnancy itself has a complex relationship with the normal thyroid, and with thyroid disease, and pregnancy complicating the course of autoimmune thyroid disease is a common clinical problem. However, the converse is also true with autoimmune thyroid disease increasing a variety of risks associated with pregnancy and its association with recurrent miscarriages.

The thyroid in pregnancy

The thyroid undergoes transformation during pregnancy (Table 1). The thyroid gland itself may enlarge under the stimulation of hCG and the increased demand for thyroid hormones. Pregnancy is a hypervolemic state, a greater water volume increases body weight and body mass index, both of which increase thyroid volume and enlarge the distribution space for thyroid hormones. There is a rise in urinary excretion of iodide owing to an increased glomerular filtration rate which has to be corrected by increased dietary intake. All of this results in increased thyroid activity and a variable degree of TSH suppression. Thyroid binding globulin (TBG) production is increased in the pregnant liver, and its half-life prolonged because of estrogen-induced changes in sialylation resulting in increased TBG levels. Many of these physiological changes associated with pregnancy are an adaptation to improve thyroxine delivery to fetal cells, particularly neuronal cells.

<table>
<thead>
<tr>
<th>Physical Changes</th>
<th>Change</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Increased</td>
<td>Increased in size in iodine-deficient areas, but less change in iodine replete areas.</td>
</tr>
<tr>
<td>Intra-thyroidal blood volume</td>
<td>Increased</td>
<td></td>
</tr>
</tbody>
</table>

Biochemical Changes

- Thyroid binding globulin
- TSH

<table>
<thead>
<tr>
<th>Comment</th>
<th>Associated with estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodide availability</td>
<td>Decreased</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Thyroid and pregnancy risks

As mentioned earlier, the normal physiologic changes of pregnancy may result in a subsequent decrease in TSH levels during many early normal pregnancies. Such a normal state is referred to as “gestational thyrotoxicosis.” However, the greater influence of a pathologically overactive or underactive thyroid gland should not be underestimated. Thyroid hormones change several aspects of reproduction directly through their impact on sex hormone binding globulin, prolactin and GnRH secretion. The interplay of thyroid hormones, autoimmunity, and the physiologic changes of pregnancy significantly influences the risks of pregnancy: ranging from early pregnancy losses to the development of infertility (Table 2). Hence, many pregnancy risks are increased by an overactive or underactive thyroid gland regardless of immune changes (Table 3).
Table 2. Interplay of thyroid hormones on pregnancy outcomes. Hypothyroidism and hyperthyroidism may have an effect on infertility indirectly, through its interaction with menstrual dysfunction. Adapted from 87, 78, 89

<table>
<thead>
<tr>
<th>Condition</th>
<th>Thyroid Disease</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Increased risk</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Increased risk</td>
<td>Increased risk</td>
</tr>
</tbody>
</table>

Table 3. Maternal and fetal complications associated with thyroid dysfunction in pregnancy. Adapted from 90, 91, 92

<table>
<thead>
<tr>
<th>Complications</th>
<th>Maternal</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>Anemia</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>Gestation-Induced</td>
<td>Pre-Eclampsia</td>
<td></td>
</tr>
<tr>
<td>Hypertension and Pre-Eclampsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placental Abruption</td>
<td>Gestational Diabetes Mellitus</td>
<td></td>
</tr>
<tr>
<td>Post-Partum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Placental Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Frequency of Caesarean Section</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Fetal Loss</td>
<td>Neontal Mortality</td>
<td></td>
</tr>
<tr>
<td>Fetal Complications</td>
<td>Cretinism</td>
<td>Intrauterine Growth Restriction</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>Preterm Delivery</td>
<td></td>
</tr>
<tr>
<td>Stillbirths/Perinatal Death</td>
<td>Still Births</td>
<td></td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>Low Birth Weight</td>
<td></td>
</tr>
<tr>
<td>Fetal Distress in Labor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thyroid disease and infertility
Infertility is defined as the absolute inability to conceive after approximately 1 year of regular intercourse without contraception. A pooled review of the multiple studies involving autoimmune thyroid disease (AITD) in women with infertility compared to controls showed an overall relative risk of 2.1 (P<0.0001). Infertility may be due to the hormonal changes associated with AITD or to problems with implantation of the embryo reflected more clearly in established pregnancies by early miscarriages (see below). It remains unclear whether AITD is simply a marker for an autoimmune imbalance in such patients or reflective of subtle thyroid hormone changes. Of interest, AITD may also occur in patients with endometriosis which is a frequent association with infertility. Endometriosis has also been associated with immunological changes—including endometrial autoantibodies and deposition of complement, cytotoxic effects on the endometrium, and contradictory declining levels, or functional defects in natural killer (NK) cells have all been reported. Such NK cell dysregulation may activate Graves’ disease or Hashimoto’s thyroiditis.

Autoimmune thyroid disease (AITD)
The autoimmune thyroid diseases include Graves’ disease, Graves’ orbitopathy (ophthalmopathy), Hashimoto’s thyroiditis and the post partum thyroid syndromes. While the immune response is very different in these diseases (Table 4) they each are considered to be caused by the combination of an environmental insult and a genetic predisposition (Table 5). Some of these insults have been well described but they can be ascribed to only a small proportion of patients and much still needs to be learned about the causality of AITD.

The effect of pregnancy on autoimmune disease
With the physiological changes of pregnancy changing the immunologic milieu of the woman, many autoimmune diseases show differing responses owing, perhaps, to differences in their pathophysiology. For rheumatoid arthritis, recent studies show a modest reduction in symptoms; with less swelling of joints, less pain and morning stiffness and improved functionality in pregnancy. Ankylosing spondylitis seems to be unaffected — neither improved nor aggravated with pregnancy. In systemic lupus erythematosus, many prospective studies have shown increased flare rates in pregnancy rather than improvement, although the flares in pregnancy are not as severe. For autoimmune thyroid disease, it is clear that Graves’ disease improves during pregnancy but sometimes flare again in the post-partum.

Table 4. A comparison between the autoimmune thyroid diseases. Adapted from 93, 94, 95, 96

<table>
<thead>
<tr>
<th>Incidence Rates</th>
<th>Graves’ Disease</th>
<th>Hashimoto’s Disease</th>
<th>Postpartum Thyroiditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Examination</td>
<td>Enlarged, and soft</td>
<td>Enlarged and firm</td>
<td>Variable</td>
</tr>
<tr>
<td>Pathological Findings</td>
<td>Hyperplasia</td>
<td>Follicular atrophy</td>
<td>Paucity of follicular atrophy</td>
</tr>
<tr>
<td>Timeframe</td>
<td>Permanent</td>
<td>Diffuse with B-cell germinal centers</td>
<td>Patchy</td>
</tr>
<tr>
<td>Primary Immune Defect</td>
<td>Antibodies to the TSH-R</td>
<td>Permanent</td>
<td>Transient</td>
</tr>
<tr>
<td>Extrathyroid Manifestations</td>
<td>Yes</td>
<td>Cytotoxic T-cells</td>
<td>Cytotoxic T-cells</td>
</tr>
<tr>
<td>Environmental factors involved</td>
<td>Graves Ophthalmopathy, prelateral myxedema</td>
<td>Rare</td>
<td>No</td>
</tr>
<tr>
<td>Iodine Excess</td>
<td>Selenium Deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>Drugs: Amiodarone, Interferon-γ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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As far as Hashimoto’s thyroiditis is concerned, while there is suggestive evidence of deterioration during pregnancy, the main clinical event is post-partum thyroiditis which can be considered new onset, but is usually transient Hashimoto’s thyroiditis.\textsuperscript{18} However, established Hashimoto’s thyroiditis may deteriorate in the post partum as evidenced by a need for increased thyroxine intake.\textsuperscript{19}

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>Chromosome Location</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA</td>
<td>Major histocompatibility complex</td>
<td>6q21</td>
<td>2.0-4.0</td>
</tr>
<tr>
<td>CTLA4</td>
<td>Cytotoxic T-lymphocyte-associated protein 4</td>
<td>2q33</td>
<td>1.5-2.2</td>
</tr>
<tr>
<td>PTPN22</td>
<td>Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)</td>
<td>1p13</td>
<td>1.4-1.9</td>
</tr>
<tr>
<td>CD40</td>
<td>CD40 molecule, TNF receptor superfamily member 5</td>
<td>20q11</td>
<td>1.3-1.8</td>
</tr>
<tr>
<td>IL2RA (CD25)</td>
<td>Interleukin 2 receptor, alpha</td>
<td>10p15</td>
<td>1.1-1.4</td>
</tr>
<tr>
<td>FGL3</td>
<td>Fc receptor-like 3</td>
<td>1q23</td>
<td>1.1-1.3</td>
</tr>
<tr>
<td>TG</td>
<td>Thyroglobulin</td>
<td>8q24</td>
<td>1.3-1.6</td>
</tr>
<tr>
<td>TSIR</td>
<td>Thyroid-stimulating hormone receptor</td>
<td>14q31</td>
<td>1.4-2.6</td>
</tr>
</tbody>
</table>

The paradoxical immunotolerogenic state of pregnancy
The paradoxical immunotolerogenic state of pregnancy was explained by Medawar using three hypotheses: a) the anatomic separation of the fetus from the mother, b) the antigenic immaturity of the fetus, and c) the indolence or inertness of the mother.\textsuperscript{20} Although newer studies have challenged these hypotheses it is now clear that each of these factors may have a role in creating this environment.

The MHC
MHC molecules are polymorphic cell surface proteins that bind with antigenic peptides. They are widely expressed, especially in inflammatory areas typical of autoimmune disease.\textsuperscript{21} Their role includes the presentation of such peptides to the immune system via antigen-specific T cells. These proteins are divided into MHC class I and MHC class II molecules interacting with CD8+ and CD4+ cells respectively. In humans they are referred to as human leukocyte antigens (HLA) and are derived from a highly complex gene region on chromosome 6.\textsuperscript{22} All auto-immune diseases have shown a genetic association with the HLA gene locus as manifested by the prevalence of certain HLA alleles in the patient populations.\textsuperscript{23} For example, Graves’ disease has been widely associated with HLA-DR3 in Caucasians and further investigation has suggested that it is residue 74 (Arginine) in the molecule which is the major influence.\textsuperscript{24}

The fetomaterial interface, which includes the villous trophoblasts and syncytiotrophoblast microparticles, avoid allogenic responses because they lack HLA class I and class II proteins and only express other MHC molecules such as HLA-S, -E, -F and HLA-G.\textsuperscript{25} In fact, extravillous trophoblasts migrate from tips of placental villi into maternal decidual tissue where they appear to promote immune regulation and spiral artery remodeling.\textsuperscript{25} HLA-G expression can also be found on thymic epithelial cells, the cornea, and the nasal matrix which are also considered to be immunologically privileged sites. It can be induced in other cell types during pathologic processes including cancer, inflammatory disorders, infections and allotransplantation and is thought to confer resistance to NK cells.\textsuperscript{26}

T Lymphocytes
T-cells play an important role in the immune response in pregnancy. T-helper cells are classically divided into Th1 cells, characterized by IL-2, and IFN-γ production involved in cellular immunity and Th2 cells which are characterized by the production of IL-4, IL-5 and IL-13 which are involved in humoral immunity (Figure 2).\textsuperscript{22} Although studies of CD4+ T Cells in pregnancy have shown very modest changes in absolute numbers,\textsuperscript{27} the Th1/Th2 ratio has been proposed to indicate a successful pregnancy as a Th2 phenomenon, with the Th2 chemokines downregulating the Th1 response.\textsuperscript{28} Hence the Th1/Th2 ratio is low in pregnancy but remains particularly high in the proliferative endometrium.\textsuperscript{29} The variation in the ratio of these cells has been used to explain the various phenotypes of autoimmune diseases in relation to pregnancy. For example, multiple retrospective and cohort studies have shown that cell-mediated autoimmune diseases improve during pregnancy, and worsen in the post-partum.\textsuperscript{30} However, this Th1/Th2 dichotomy is not able to explain the multitude of immune responses in pregnancy, among them the fact that some Th1 cytokines are necessary in some aspects of pregnancy\textsuperscript{31} Furthermore, although the Th2 predominance suggested an explanation for the exacerbation of humoral autoimmune diseases in pregnancy such as lupus\textsuperscript{32} it does not explain the suppression of autoantibodies, including thyroid autoantibodies (Figure 1), seen in many autoimmune diseases and as exemplified by the improvement of Graves’ disease in pregnancy.\textsuperscript{2} Newer studies have shown a multitude of T-cells that share a common lineage with the Th1 and Th2 (Figure 2) cells and which helps explain the complex interplay of immune responses in pregnancy as described below.

Regulatory T Cells
A third subset of CD4+ T cells (Tregs) have been implicated in the regulation of tolerance and have helped explain some of the problems with the Th1/Th2 ratio hypothesis. It is important to note that two particular subsets of regulatory cells occur, the CD4+CD25+FoxP3+ cells that are thymus-generated and termed, natural T-regulatory cells (nTreg), while a second subset of Treg cells can be induced by antigens presented in a tolerogenic form.\textsuperscript{33,34} A schematic is shown in Figure 3.
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Figure 1. Thyroid autoantibodies in pregnancy. There is a modulation of TPO autoantibodies in pregnancy, but this rebounds postpartum, characterized clinically as Postpartum Thyroiditis (PPTD). Adapted from 56

Figure 2. The common lineage of CD4+ T-Cells. This simplified model shows the common lineage of the various T-cells, including the helper cells, CD4+ Th1, Th2, Th17, which are implicated in immunity, and the regulatory T-cells. A balance of these cells and their cytokines are essential in maintenance of pregnancy. References 39 97

We now know that the CD4+CD25+FoxP3+ regulatory T cells are the most potent and widespread lineage of immune cells that are capable of regulating immune function.35 They have major protective functions in autoimmune disease, transplantation tolerance, gastrointestinal homeostasis and inflammatory disease. The role of induced T-regulatory cells is unclear; speculation exists whether they may have a role in bystander suppression. Bystander suppression is the modulation of effector T-cells that are specific to a particular antigen, if it arises in the same antigen presenting cell, or target cell, or is within the vicinity.34

The mechanism of action of how Treg cells are able to regulate immune tolerance is still being defined, but they appear capable of suppressing proliferation and cytokine production in both the CD4+ and CD8+ T cell lineages, and are also able to inhibit B-cell proliferation and immunoglobulin production. The Treg cells are also able to inhibit the maturation and function of antigen presenting cells. Of direct relevance to our discussion, Treg cells may proliferate peripherally after encountering foreign antigens (such as fetal antigens), and migrate towards the feto-maternal interface generating a tolerant environment characterized by cytokines such as TGF-β, Leukemia Inhibitory Factor (LIF), and Hemooxygenase 1 (HO-1) which are proposed to protect pregnancy.36 The hemooxygenases break down heme into bilirubin and CO, stopping the increase in toxic free heme.37 Hence, increases in Treg cells during pregnancy have been well documented and clearly are major contributors to the dampening of autoimmune responses in pregnancy. It is also likely that deficiency in their function or proliferative responsiveness may endanger pregnancy.38

Th17 cells

Th-17 cells are a unique effector subset that share the same lineage with Th1 and Th2 and which have recently been recognized to have an important role in immune regulation, immune pathogenesis and host defense.39 In normal pregnant women, the values of IL-17 are present throughout the whole pregnancy, although higher during the third trimester.40 In-vitro studies have shown that IL-17 increases the invasive potential of choriocarcinoma cells.41,42 The studies reflect a potential role of these cytokines in implantation and placentation. Additionally, IL-17 increases progesterone secretion,43 which is needed in pregnancy maintenance.

With regard to autoimmunity, enhanced IL-17 expression has been seen in various autoimmune diseases such as rheumatoid arthritis, psoriasis and multiple sclerosis.44 Its role in autoimmunity has been theorized from increased levels of IL-17 found in an acute renal rejection model 45, and neutralization of IL-17 prevented acute rejection of aortic and cardiac allografts.46 However, its role in the immunotolerogenic pregnancy is unclear. Some studies have shown increased Th17 cells in the blood and decidua in unexplained recurrent spontaneous abortion patients,47 while the levels of circulating and decidual Th17 cells in healthy pregnancy are stable.48

B Cells

B cells are not only capable of antibody secretion but are also potent antigen presenting cells interacting with the T cell receptors.22 However, there appear to be no significant changes in the quantity of B-cells in the circulation during normal human pregnancy yet one unifying characteristic is the fall in autoantibody titers (Figure 1). As discussed earlier, this is most likely secondary to the increase in Treg cells. However, estrogen has also been shown to deliver a negative signal towards B cell function in pregnancy, 49 and this effect is lost in the postpartum period. Newly described B regulatory cells
have also been shown to modulate immune response and inflammation but their role in pregnancy still remains to be elucidated.

**Thyroid autoantibodies**

Grave’s Disease and Hashimoto’s Thyroiditis differ in clinical presentation but have commonalities in some of their immunological characteristics (Table 4). This similarity includes lymphocytic infiltration of the thyroid and autoantibodies against various thyroid antigens, including thyroid peroxidase (TPO) and thyroglobulin (Tg) and perhaps also pendrin, and the Na+/I-cotransporter. However, the major autoantibodies in Hashimoto’s Thyroiditis are the antithyroid peroxidase antibodies (TPOAb) and antithyroglobulin antibodies (TgAb). In pregnancy, as mentioned earlier there is a marked fall in both TPOAb and TgAb levels, and both increase 6 months postpartum.

**TSH receptor antibodies**

Stimulation of the TSH receptor (TSHR) by autoantibodies is the primary immunopathogenesis of Grave’s disease (Table 4). Stimulating TSHR antibodies interact with conformational epitopes in the TSH receptor ectodomain, and consequently initiate TSH signaling (Figure 4). Early studies demonstrated a decrease in the levels of TSHR antibodies in pregnancy, with the lowest point in the third trimester, and a rising trend again in the post partum. Patients may also develop blocking TSHR antibodies which have been reported to cause neonatal hypothyroidism and/or neutral TSHR antibodies which may contribute to the persistence of the disease by their apoptotic action on thyroid cells which acts as an immune stimulant.

**Other immune cells**

The role of NK cells involves cell lysis and cytokine production directed against virally infected cells and tumor cells. Interferon (IFN-γ) is one of the key products which restrict viral infection. The number of peripheral NK cells is only moderately decreased in pregnant women compared with non pregnant women while the expression of HLA-G at the feto-maternal interface suggests they have
an integral role in pregnancy.\textsuperscript{27} Dendritic cells have a major role in the adaptive immune response, and literature notes the pro-activating effects of estrogen on dendritic cells, while progesterone has an inhibitory function.\textsuperscript{52} In pregnancy, the decidual dendritic cells can modulate the TH1/TH2 cytokine balance in promotion of pregnancy.\textsuperscript{65}

Microchimerism
Microchimerism is the presence of a low-level of foreign cells or their progeny in an individual\textsuperscript{64} which may have the potential to initiate an autoimmune response (Figure 5). Usually this occurs only in women after pregnancy although it may also occur after receiving a transplant or transfusion; bidirectional cell trafficking between twins \textit{in utero} has also been demonstrated.\textsuperscript{64} Paternally-derived DNA has been seen in post-partum females up to 27 years later.\textsuperscript{55} The potential role of microchimerism in autoimmune disease arose from the identification of fetal cells as male DNA in inflammatory skin lesions and peripheral blood of patients with scleroderma\textsuperscript{66}, primary biliary cirrhosis, systemic lupus erythematosus and Sjögren’s syndrome. In the thyroid gland, fetal cells have been identified in patients with nodules, Hashimoto’s thyroiditis and Graves’ disease.\textsuperscript{67} A mouse model has demonstrated the targeting of the thyroid gland by fetal cells which were primarily immune and dendritic cells.\textsuperscript{68} It is possible, therefore, that such foreign cells initiate an immune response within their targets by activating bystander cells (Figure 5). Evidence for a role for microchimerism has also come from identical twins of different sexes who are more likely to demonstrate thyroid autoantibodies than identical twins of the same sex.\textsuperscript{69} Although some studies have not shown that parity is a risk factor for autoimmune thyroid disease\textsuperscript{70} other investigators have observed this phenomenon thus supporting the microchimerism hypothesis.\textsuperscript{71}

The role of sex hormones in immunity
The difference in the prevalence of most autoimmune diseases between male and females and the major immune changes in pregnancy have led to the belief that sex steroids must have effects on both the innate and adaptive immune system.\textsuperscript{72} For example, women are 7 times more likely to develop autoimmune thyroid disease than men. One explanation is that testosterone has been implicated in apoptosis of T-cells.\textsuperscript{73} Although the absolute number of lymphocytes from either gender is the same, the percentage of T lymphocytes is lower in men.\textsuperscript{74} On the other hand, estrogen reduces bone marrow stroma, generating a faster development time for B lymphocytes, and additionally stimulating extra-marrow lymphopoiesis, that may be pro-autoimmune as the cells may avoid the deletion process during development.\textsuperscript{75} Women have greater baseline plasma levels of IgG and IgM.\textsuperscript{76} Estrogen enhances activation-induced deaminase (AID) which deaminates cytokines at immunoglobulin loci initiating somatic hypermutation.\textsuperscript{77} NK cells’ cytotoxic action is greater in postmenopausal women and in men than in women of reproductive age, suggesting a possible role for progesterone or estradiol.\textsuperscript{78} Another set of immune effector cells, dendritic cells are sentinels that recognize pathogens throughout the whole body. Evidence exists that estrogen can activate dendritic cells, while progesterone inhibits their actions.\textsuperscript{82}

Miscarriage and pre-term birth
The studies of Stagnaro-Green\textsuperscript{86} in New York and confirmed by Glinoer\textsuperscript{87} in Belgium and in multiple subsequent studies, have demonstrated increases in the miscarriage rate in women who are thyroid autoantibody positive and such women are also more likely to deliver early.\textsuperscript{80} A meta-analysis ascertaining this relationship showed an odds ratio (OR) of 2.73 (95% CI 2.20-3.40) in eight case control and ten longitudinal studies.\textsuperscript{81} A number of etiologies have been hypothesized as the cause of the relationship between spontaneous termination of pregnancy and autoimmune thyroid antibodies (Table 6).

Table 6: Possible causes of increased miscarriages in thyroid autoantibody positive women. Adapted from\textsuperscript{84}

- The existence of a subtle degree of hypothyroidism
- There is an autoimmune "imbalance" in the female merely reflected by thyroid autoantibodies.
- Thyroid autoantibodies may act directly on the placenta or the fertilized ovum causing the rejection.
- Women with thyroid autoimmunity and subfertility may become pregnant at an older age with increased risk.
In patients who have evidence of AITD, prospective studies have characterized the onset of hypothyroidism in pregnancy, although euthyroid to start with and despite a reduction in antibody titers thus suggesting the association may be secondary to subtle thyroid deficiency. Furthermore, subclinical hypothyroidism persists, with its increased levels of TSH has been shown to be related to increased early pregnancy loss when compared to euthyroid patients, or thyroid autoimmune patient’s without thyroid hormonal imbalance. This may reflect the reduced capacity of the thyroid with pregnancy’s increased demands. These hypotheses have been extrapolated to interventional studies with levotiroxine, showing a decrease in miscarriage rates in patients with AITD treated with levotiroxine compared to placebo. Such studies await confirmation before being clinically applicable but the concept that thyroid antibodies are merely markers for subtle immune abnormalities remains.

Conclusions

Pregnancy is a state of immunotolerance with the ability to continuously ward off pathogens. The unique milieu in pregnancy allows us to examine the various roles of different immune-effector cells in generating this paradoxical immune-tolerant state from changes in thyroid function. Extrapolating the information to autoimmune thyroid disease helps explain many of the clinical situations we meet and should potentially improve our management of these common disorders.

References


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