

## Thyroid Autoimmunity and Reproduction

BY MARIA KRAW, MD

Autoimmune thyroid disease (AITD) is characterized by the presence of antithyroid antibodies, specifically antibodies to thyroglobulin and thyroid peroxidase. These antibodies have been reported in 5%-10% of reproductive-aged women, making AITD the most common autoimmune disorder affecting this population. Although the most frequent cause of thyroid failure (overt or subclinical hypothyroidism), AITD can present without thyroid dysfunction and, thus, remains undiagnosed.

Immunological factors appear to play an important role in the reproductive processes of fertilization, implantation, and fetal-placental development. The presence of auto-antibodies has been associated with reproductive failure, these include antiphospholipid antibodies, anti-nuclear antibodies, and organ-specific autoimmunity, particularly, thyroid antibodies. This issue of *Endocrinology Rounds* explores the association between AITD and the reproductive problems of infertility and miscarriage, discusses possible etiologies for this association, and reviews intervention/prevention studies.

### Thyroid autoimmunity and infertility

Infertility is defined as the inability to conceive after 1 year of regular intercourse without contraception. The prevalence of infertility has remained stable at around 13%-14% over the past few decades.<sup>4</sup> Causes of infertility include female factors (35%), male factors (30%), a combination of both female and male factors (20%), and unexplained infertility (15%).<sup>5</sup>

The impact of AITD without thyroid dysfunction on fertility has been examined in several studies. These results are difficult to interpret due to the inclusion of heterogeneous groups of infertility problems, retrospective designs, lack of appropriate control groups, differences in antibody assays (antimicrosomal antibodies, thyroperoxidase antibodies [TPOAb] and thyroglobulin antibodies [TgAb]), small sample sizes, and different geographical locations. Nevertheless, a pooled analysis of these data reveals that for female partners in infertile couples, the relative risk (RR) of AITD is slightly, but significantly increased: RR=1.95 (95% CI, 1.50-2.53;  $p < 0.0001$ ).<sup>6</sup>

Studies have shown an association between AITD and endometriosis, a common cause of female infertility. In a study of women with female causes of infertility, the risk of associated AITD was 2.25 (95% CI, 1.02-1.52) compared with fertile controls. This risk increased with the presence of endometriosis to 3.57 (95% CI, 1.09-11.8).<sup>7</sup> Gerhard et al reported that 44% of women with AITD had endometriosis compared with only 9% of women without AITD.<sup>8</sup> This association suggests a common link of altered immune function. Endometriosis has been associated with non-organ-specific antibodies, deficient cellular immunity, reduced natural killer cell activity, and increased peritoneal immune cell concentrations.<sup>9,10</sup>

The prevalence of thyroid autoimmunity among infertile males is less well-studied, in part, due to the much lower prevalence of thyroid dysfunction in men. Compared to men without sperm autoantibodies, thyroid autoantibodies are significantly increased in men with sperm autoantibodies.<sup>11</sup> A prospective cohort study of infertile men found AITD in 7.5%.<sup>12</sup> In this study, elevated thyroid antibody titres significantly correlated with pathozoospermia and astheno-zoospermia. These abnormalities did not correlate with thyroid dysfunction, since 3% of the subjects had subclinical hypothyroidism with no effects on sperm density, motility, or morphology.

### Thyroid autoimmunity and miscarriage

Miscarriage is the most common complication of pregnancy.<sup>13</sup> The majority of pregnancy losses occur prior to a missed menses and, therefore, the mother may be unaware that she is pregnant. However, approximately 15% of clinically-recognized pregnancies end spontaneously within the first trimester.<sup>14</sup> Recurrent miscarriages, typically defined as at least 2 consecutive pregnancies ending in miscarriage, occur in about 2%-5% of pregnant women, whereas the incidence of 3 consecutive losses is  $< 1\%$ .<sup>15</sup>



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The causes of miscarriage are diverse and include uterine abnormalities, chromosomal anomalies, hormonal imbalances, and autoimmune factors. The cause for recurrent losses is found in <50% of cases. The association between miscarriage and the presence of thyroid antibodies in euthyroid women was first reported in 1990.<sup>16</sup> Since then, a multitude of studies have focused on this association.

Eighteen studies compared the risk of miscarriage between women with and without AITD.<sup>18</sup> Between 1990 and 2003, over 5,500 women were studied as specific cases and controls on three continents. A comparison between these studies is limited by several factors. Different selection criteria were employed, depending on the specific purposes of the study. Although all women were of reproductive age, their reproductive status ranged from healthy pregnancies, to recurrent losses, to those undergoing artificial reproductive technologies (ART). The prevalence of AITD varied with location, from 6% in Brussels to 33% in Salt Lake City, with an overall mean incidence of 15% among cases and controls. Most studies did not include data on the titres of thyroid antibodies, information that may relate to the intensity of autoimmune alterations.<sup>6</sup>

Given these limitations, Poppe and Glinoe<sup>6</sup> concluded that, with the exception of 2 studies, all the others concurred that AITD without thyroid dysfunction is associated with a 3.5-fold increase in the overall miscarriage rate. Another review by Stagnaro-Green and Glinoe<sup>17</sup> attempted a more detailed classification by separately examining the association between AITD and miscarriage (5 studies), AITD and recurrent miscarriage (7 studies), and between AITD and early pregnancy loss after in-vitro fertilization (5 studies). These studies are discussed separately below. Finally, Prummel and Wiersinga<sup>18</sup> published a meta-analysis of 18 case-control and longitudinal studies confirming the association between miscarriage and thyroid antibodies. They reported an overall odds ratio (OR) of 2.73 (95% CI, 2.2-3.40) among 8 case-control studies and an OR of 2.30 (95% CI, 1.80-2.95) in 10 longitudinal studies.

### ***Thyroid antibodies and miscarriage***

The 5 studies evaluating the association between thyroid autoantibodies and miscarriage all found a statistically significant correlation between the two. The relative risk of miscarriage in women with AITD ranged from 1.9 to 44 with a mean RR of 3.0.<sup>17</sup> This evidence clearly establishes a relationship between miscarriage and thyroid autoimmunity that does not appear to be associated with antibody titres or thyroid dysfunction.

### ***Thyroid antibodies and recurrent miscarriage***

Twelve studies evaluated the relationship between recurrent miscarriage and thyroid antibodies. Two studies were not included in the analysis due to the lack of a control group. Seven studies examined the prevalence of AITD in women with recurrent miscarriages compared with controls. Five of these documented a statistically significant increase in the incidence of AITD in women with recurrent miscarriages (range 23%-37%) compared to controls (range 5%-15%). One study that reached statistical significance demonstrated a similar trend (31% vs

19%), while the other had an unusually high incidence of thyroid antibodies in the control group (37%).

Three studies evaluated the impact of thyroid antibodies on the prospective outcome of pregnancy in women with recurrent abortions. Two of these found that women with AITD and a history of recurrent miscarriage had significantly higher rates of miscarriage in subsequent pregnancies compared with women with recurrent miscarriage who were thyroid antibody negative. The other study found no difference in the rate of repeat miscarriages among thyroid antibody-positive and -negative women. These data make it difficult to draw any strong conclusions about this subgroup of women.

### ***Thyroid antibodies and artificial reproductive technology***

Stagnaro-Green<sup>17</sup> and Glinoe reviewed 4 studies comparing miscarriage rates following in-vitro fertilization (IVF) in women who were thyroid antibody-positive or -negative. A comparison between studies was difficult, since each used different research designs. Two studies found a significantly higher incidence of pregnancy loss in women with positive thyroid antibodies compared to those without antibodies. One study revealed a trend towards this association, but it did not reach statistical significance, while another study found no differences between these two groups. Two studies published after this review confirmed higher miscarriage rates in AITD women compared with controls.<sup>6,19</sup> In summary, it appears that women with AITD undergoing IVF have higher miscarriage rates than thyroid antibody-negative women.

### ***Thyroid autoimmunity and obstetrical complications***

In a study by Lejeune et al, the incidence of pregnancy-induced hypertension was increased in women with thyroid abnormalities.<sup>20</sup> A prospective study of healthy euthyroid women with AITD found a 2-fold increased rate of premature delivery in women with AITD compared with healthy controls (16% vs 8%;  $p < 0.005$ ).<sup>21</sup> There was no difference in the neonates born to mothers with AITD and no increase in perinatal complications compared with controls. A study by Negro et al demonstrated an increased risk of preterm delivery (birth <37 weeks) in untreated women with thyroid antibodies.<sup>22</sup>

### ***Etiology of miscarriage with thyroid autoimmunity***

The association between pregnancy loss and thyroid autoimmunity does not imply a causal relationship. The etiology behind this association remains unknown, but several hypotheses have been proposed.

### ***Thyroid dysfunction***

In pregnancy, the thyroid gland must compensate for increased thyroid hormone requirements caused by estrogen-induced elevations in thyroid-binding globulin concentrations, increased volume of distribution of thyroid hormones, and increased placental thyroxine transport and degradation.<sup>23</sup> Fetal concentrations of total T4 and T3 are 100-fold lower compared with those of the mother in early pregnancy, whereas fetal serum free thyroxine (FT4)

levels are about one-third of maternal values.<sup>24</sup> Therefore, even slight reductions in maternal thyroxine levels may result in relevant alterations in fetal thyroid hormone concentrations.

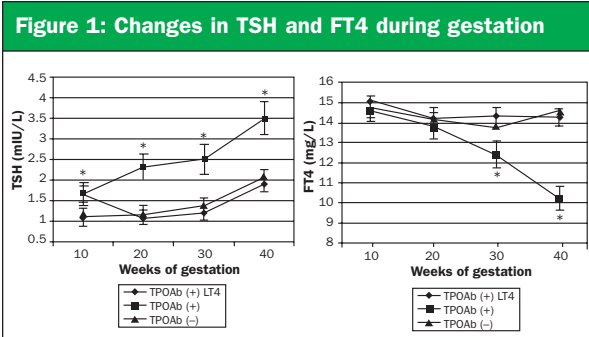
Despite their apparent euthyroidism (defined as thyroid-stimulating hormone [TSH] and thyroid hormone levels within the reference range), women with AITD may be at risk for a subtle deficiency in thyroid hormone concentration. It is known that women with AITD are at increased risk of developing subclinical or overt hypothyroidism during pregnancy, as well as thyroiditis in the postpartum period.<sup>21</sup> With the increased thyroid demands of pregnancy, these women may not be able to adequately respond due to the reduced functional reserves characteristic of chronic thyroiditis.

Changes in thyroid function were observed in a prospective longitudinal study of women with thyroid antibodies who were euthyroid during early gestation.<sup>21</sup> In the first trimester, serum TSH levels (albeit within the reference range) were significantly higher than in antibody-negative women. Although thyroid antibody titres decreased during gestation, thyroid function gradually deteriorated towards subclinical hypothyroidism (TSH >4 mIU/L) in 16% by delivery. The women with AITD required great TSH stimulation to maintain normal thyroid function, but by delivery, their FT4 levels were lower than the antibody-negative controls. In fact, almost one-half of antibody-positive women had FT4 levels below reference range at the end of pregnancy, confirming a decreased functional thyroid reserve. Serum TSH > 2.0 mIU/L and antiTPO-Ab titers >1250 u/mL before 20 weeks were indicative of women at highest risk for progression to hypothyroidism.

These findings were confirmed by Negro et al, who demonstrated significantly higher mean TSH values in women with AITD compared to women without thyroid autoimmunity (Figure 1).<sup>22</sup> At delivery, 19% of women with AITD had TSH values above the reference range (0.27-4.2 mIU/L). At 10 weeks, FT4 levels were lower in women with AITD, although not significantly. At delivery, however, there was a significant reduction in FT4 levels such that 53% revealed values under the reference range (12-23.5 pmol/L; Table 1). Thyroxine administration corrected these abnormalities in TPOAb<sup>+</sup> women to levels seen in TPOAb controls.

### Thyroid dysfunction in women undergoing artificial reproductive technologies

Ovarian hyperstimulation before IVF has been shown to impair thyroid function and cause an early decrease in serum T4 and a rise in serum TSH concentrations.<sup>25</sup> These



**Figure 1: Changes in TSH and FT4 during gestation**  
**Left:** TSH values during gestation in group A (TPOAb<sup>+</sup> treated with LT<sub>4</sub>), group B (TPOAb<sup>+</sup>), and group C (TPOAb<sup>-</sup>). At 10 wks, groups A and B were higher than group C; at 20 and 30 wks and after delivery, groups A and C were lower than group B.

**Right:** FT4 values during gestation. At 30 wks and after delivery, groups A and C were higher than group B.

\*P<0.05. (Modified from Negro<sup>22</sup> with permission of the author).

alterations take place even before the significant rise in human chorionic gonadotropin (hCG) that is known to affect the thyroid. The rapid rise in estradiol levels induced by ovarian hyperstimulation rapidly increases thyroglobulin production and hypersialylation, which increases thyroglobulin half-life. This in turn decreases total T4 levels, which initially decrease FT4 levels, stimulating TSH production by the pituitary gland.

Poppe et al reported the results from early monitoring of thyroid function in women with and without thyroid antibodies, who were undergoing ovarian hyperstimulation for IVF and became pregnant.<sup>26</sup> Although both groups had a significant increase in TSH and FT4, women with AITD had a significantly higher rise in TSH and a lower rise in FT4, followed by a fall in FT4 values, compared to antibody-negative women.

### General autoimmune imbalance

Lupus anticoagulant, anticardiolipin, antinuclear, antinative, and anti-single-stranded DNA antibodies have been associated with recurrent miscarriages. These syndromes carry a miscarriage rate of 7%-22% and a higher risk of fetal death after the first trimester.<sup>27</sup> Antithyroid antibodies can present together with anticardiolipin antibodies. The above studies, demonstrating an association between AITD and miscarriage, excluded women with antibodies other than thyroid antibodies or analyzed them separately, suggesting that the association is not due to the co-presence of other antibodies.<sup>18</sup>

It has been suggested that thyroid antibodies are a marker for an, as yet unidentified, autoimmune state against the fetoplacental unit. Compared with controls, women

Table 1: Characteristics of patients at 10, 20, and 30 weeks gestation and delivery (D)										
	n	Age	TSH (mIU/L)*				FT <sub>4</sub> (pmol/L)**			
			10 weeks	20 weeks	30 weeks	D	10 weeks	20 weeks	30 weeks	D
TPOAb <sup>+</sup> LT <sub>4</sub>	57	30±5	1.6±0.5	1.1±0.4	1.2±0.4	1.9±0.5	18.8±5.4	18.7±4.9	18.4±4.6	18.4±4.1
TPOAb <sup>+</sup>	58	30±6	1.7±0.5	2.3±0.5	2.5±0.6	3.5±0.7	18.8±5.5	17.8±6.2	16.0±6.3	13.1±5.8
TPOAb <sup>-</sup>	869	28±5	1.1±0.4	1.2±0.4	1.4±0.4	2.1±0.6	19.6±5.3	18.4±5.2	17.8±5.4	18.8±4.9

\*reference range (0.27-4.2 mIU/L); \*\*reference range (12-23.5 pmol/L)

Data are expressed as mean ± SD.

with thyroid antibodies have abnormal T cell function,<sup>28</sup> higher numbers of endometrial T cells, and these cells produce less interleukin (IL)-4 and IL-10, and more interferon- $\gamma$ .<sup>29</sup> Those with recurrent miscarriages had an increased number of CD5/20 positive B cells.<sup>30</sup>

### *Direct effects of thyroid antibodies*

Few studies have examined the potential dose-response relationship between antibody titres and miscarriage. Three studies indicated that antibody titres were not related to miscarriage<sup>16,31,32</sup> (without providing statistical analysis), while one study found that TPO-positive women who miscarried had higher TPO-antibody titres and avidity than women with TPO antibodies who carried to term.<sup>33</sup>

### *Fetal microchimerism*

The association between AITD and increased miscarriage rates may be due to the phenomenon of microchimerism. Fetal microchimerism is defined as a mixture (chimera) of cells from one individual existing within the tissue of another. Offspring can have a mixture of maternal and fetal cells. Increased transplacental passage of fetal cells into the maternal thyroid may explain an enhanced immune response against the fetoplacental unit.<sup>34</sup>

In a murine model, thyroiditis was experimentally induced by immunizing mice with thyroglobulin. Maternal cells were found in 46% of fetal thyroid glands at 5 weeks postpartum, compared with only 20% of the offspring of non-immunized mothers.<sup>35</sup> Further studies by this group demonstrated that in immunized mice, microchimerism and higher thyroid antibodies resulted in higher miscarriage rates without differences in thyroid function.<sup>36</sup> Another study revealed that mice immunized with thyroglobulin had higher rates of fetal wastage ( $p=0.04$ ), and lower fetal and placental weights ( $p<0.001$ ).<sup>37</sup> Taken together, these studies suggest a direct effect of thyroglobulin antibodies on fetal loss.

### *Age-related miscarriage rates*

Miscarriage rates are known to increase with age. The rate is 10.7% among women aged 25-29, 14.2% in women aged 30-35, and 26.2% in those 35-39 years old.<sup>38</sup> Women with AITD are generally 0.7 years older than women without AITD (average age  $31.0 \pm 2.3$  years vs.  $30.3 \pm 3.0$  years;  $p<0.001$ ).<sup>18</sup> Although this difference seems negligible, this is the age at which miscarriage rates sharply increase. In addition, since AITD is associated with infertility, pregnancy may be delayed in such women.

### **Miscarriage prevention studies in thyroid autoimmunity**

Based on the above hypothesis, several trials have investigated whether medical intervention can benefit women with AITD who experience recurrent miscarriage. If the association is due to a generalized immune disorder, immuno-modulatory drugs could be of benefit. Alternatively, if thyroid dysfunction is playing

a role in the miscarriages, early screening and thyroid replacement may be the solution.

### *Immuno-modulatory drugs*

Studies using immuno-modulatory drugs have been limited by a lack of control groups, blinding, and randomization. In a report by Kiprof et al, 35 women with AITD were treated with intravenous immunoglobulin (IVIG) prior to conception and during the first 8 months of gestation.<sup>39</sup> Although 85% of these women had a term pregnancy, there was no control group for comparison. In a study by Sher et al, 82 women with thyroid antibodies, but no antiphospholipid antibodies, undergoing IVF were randomized to receive heparin/ aspirin or heparin/ aspirin and IVIG. Live births were achieved in 51% of women treated with the addition of IVIG compared with 27% in the women receiving only heparin/ aspirin ( $p=0.027$ ), but the study was not double blinded.<sup>40</sup> Stricker et al published an unrandomized study of 47 women with autoimmunity (53% of whom had thyroid antibodies) who were offered treatment with low-dose IVIG before and monthly during pregnancy.<sup>41</sup> Those who received IVIG ( $n=36$ ) had a pregnancy rate of 66% with almost all carrying successfully to term. The pregnancy rate among those who refused IVIG was 64% with a 100% miscarriage rate.

### *Thyroid hormone treatment*

The first study demonstrating a positive effect of thyroid hormone administration was carried out in 27 women with AITD, who had experienced  $\geq 2$  first trimester miscarriages.<sup>42</sup> In this sample, 11 received IVIG during pregnancy, while 16 received levothyroxine (LT4) starting before and continuing through the pregnancy. The term delivery rate was 55% in the IVIG group compared with 81% in the LT4-treated group.

In 2005, Negro et al reported the results of LT4 treatment in infertile women with AITD undergoing IVF.<sup>19</sup> While miscarriage rates were higher in the women with AITD ( $n=86$ ) compared to those without thyroid antibodies ( $n=576$ ; RR 2.01; 95% CI, 1.13-3.56), there was a reduction in miscarriage among LT4-treated vs untreated women with AITD (33% vs 52%). This latter value did not reach statistical significance, likely due to the small number of cases (8 vs 11).

In a recently published study, Negro et al examined a group of 984 pregnant women starting from early gestation.<sup>22</sup> Women who were TPOAb+ (11.7%) were divided into two groups:

- Group A received LT4
- Group B was untreated
- Group C, TPOAb- women, served as controls.

The LT4 dose was determined by the baseline level of TSH and TPOAb titres with a mean dose of 50  $\mu\text{g}/\text{d}$ . In the majority of women in group A, LT4 treatment was started between 5-10 weeks gestational age and remained unchanged throughout the pregnancy.

The alterations in thyroid function are shown in Figure 1 and discussed in the section above, entitled

Pregnancy complication	Group A	Group B	Group C (control)
	TPOAb <sup>+</sup> LT4 (n=57)	TPOAb <sup>-</sup> (n=58)	TPOAb <sup>-</sup> (n=869)
Hypertension	5 (8.8)	7 (12)	63 (7.2)
Preeclampsia	2 (3.5)	3 (5.2)	32 (3.7)
Placental abruption	0	1 (1.7)	4 (0.5)
Miscarriage	2 (3.5)*	8 (13.8)	21 (2.4)**
Preterm delivery	4 (7)*	13 (22.4)	71 (8.2)**

Pregnancy outcome in group A (TPOAb<sup>+</sup> treated with LT4), group B (TPOAb<sup>-</sup>) and group C (TPOAb<sup>-</sup>).

\* p<0.05 group A vs. B; \*\* p<0.01 group C vs. B.

(Reproduced from Negro<sup>22</sup> with permission of the author)

“*Thyroid dysfunction.*” TPOAb<sup>+</sup> women had higher TSH values at baseline. If untreated, TSH remained higher throughout the pregnancy compared to TPOAb<sup>+</sup> women treated with LT4 and antibody-negative controls. Free T4 values were also lower in untreated women with AITD at 30 weeks and postpartum. LT4 therapy in women with AITD significantly reduced the rates of miscarriage by 72% and premature delivery by 66% (Table 2). There was no significant change in placental abruption, hypertension, or preeclampsia.

This study clearly demonstrated the benefits of LT4 treatment, not only in correcting maternal thyroid function, but also in markedly reducing the risk of obstetrical complications to the level found in healthy controls. The authors state that there was a 62% reduction in TPOAb titres at delivery compared with baseline. Unfortunately, the TPOAb titre values were not published so it cannot be determined whether LT4 administration affected the underlying autoimmunity or complications. As well, Group C was, on average, 2 years younger than groups A and B. However, the results suggest that, of all the hypotheses discussed above for an association between thyroid autoimmunity and miscarriage risk, subtle thyroid dysfunction is the main reason behind the beneficial effects of LT4 treatment.

### Other potential therapies

It has been suggested that there is a potential therapeutic role for selenium in reducing TPO antibodies.<sup>18</sup> Selenium is a trace element essential for several seleno-protein enzymes involved in thyroid hormone synthesis.<sup>43</sup> Selenium is also involved in the immune system and in coagulation. Studies of selenium therapy have shown decreased TPO antibody levels in euthyroid subjects<sup>44</sup> and hypothyroid patients treated with LT4.<sup>45</sup> To date, there have been no studies on the effect of selenium replacement on reproductive outcomes.<sup>46</sup>

### Screening of women with AITD

It has been suggested that all women at risk for thyroid autoimmunity be screened for thyroid dysfunction and antibodies before conception or during early gestation. Risk factors that may be identified in the personal and family history are indicated in Table 3. In addition, given the association between

**Table 3: Risk factors identified in personal and family history**

Personal
<ul style="list-style-type: none"> <li>• Previous thyroid dysfunction</li> <li>• Goiter</li> <li>• Surgery or radiotherapy affecting the thyroid gland</li> <li>• Diabetes mellitus</li> <li>• Vitiligo</li> <li>• Pernicious anemia</li> <li>• Leukotrichia (prematurely gray hair)</li> <li>• Medications and other compounds, such as lithium carbonate and iodine-containing compounds (eg, amiodarone hydrochloride, radiocontrast agents, expectorants containing potassium iodide, and kelp)</li> </ul>
Family
<ul style="list-style-type: none"> <li>• Thyroid disease</li> <li>• Pernicious anemia</li> <li>• Diabetes mellitus</li> <li>• Primary adrenal insufficiency</li> </ul>

AITD and reproductive failure, all women with infertility and recurrent miscarriages should be screened.

Potential benefits of systematic screening include identifying maternal hypothyroidism and the increased risk of postpartum thyroiditis, both associated with AITD. If further studies confirm the benefit of LT4 administration, women with thyroid antibodies could be offered a treatment shown to normalize thyroid function and reduce obstetrical complications.

### Conclusion

Autoimmune thyroid disease is the most common autoimmune disorder affecting reproductive-aged women. AITD has been associated with infertility and miscarriage, even in the presence of apparent euthyroidism. Possible etiologies for this association include subtle thyroid dysfunction and/or decreased thyroid reserve, direct effects of antibodies on the fetoplacental unit, and age-related differences between women with and without thyroid autoimmunity. Intervention trials aimed at reducing miscarriage rates have used immuno-modulatory drugs and thyroxine replacement. Recent trials of thyroxine replacement appear to be the most effective in normalizing thyroid function and reducing obstetrical complications. Given the possibility of effective intervention, screening for AITD in all women with infertility and miscarriage is recommended. Whether there is benefit in screening all women prior to conception or during early pregnancy for thyroid antibodies remains controversial and requires further research.

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## Upcoming Meetings

2-4 February 2007

**1<sup>st</sup> Joint Meeting: American Association of Clinical Endocrinologists / Canadian Society of Endocrinology and Metabolism / Association des médecins endocrinologues du Québec; AAACE/CSEM/AMEQ**

Mont-Tremblant, Quebec

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2-5 June 2007

**ENDO 2007: 89<sup>th</sup> Annual Meeting of The Endocrine Society**

Toronto, Ontario

CONTACT: Tel: 1-888-363-6274 or 301-941-0200

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