

**Review****Thyroid autoimmunity and miscarriage**

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**The relation of thyroid autoimmunity to miscarriage is an important issue that has attracted the interest of many investigators. A number of papers have been published so far, which include healthy women, women with recurrent miscarriage and those undergoing assisted reproductive techniques. Most studies have shown a significant positive association between the presence of thyroid autoantibodies and miscarriage rate. It is of interest that women with high titers do not show a higher miscarriage rate when compared with women having low titers, although, there is no general agreement on this issue. There are three possible explanations for the assumed association of thyroid autoimmunity with miscarriage: 1) pregnancy loss is an epiphenomenon and not a direct effect of the thyroid autoantibodies, the presence of thyroid autoantibodies reflecting a generalized activation of the immune system; 2) delayed conception from the presence of thyroid autoantibodies; hence, when women with thyroid autoimmunity become pregnant, face a higher risk of miscarriage because of older age; and 3) the pregnancy loss is secondary to a subtle deficiency in thyroid hormone concentrations or a lower capacity of the thyroid to adequately adapt to the demands of pregnancy.**

**Key words:** Autoimmunity, Miscarriage, Pregnancy loss, Thyroid

**INTRODUCTION**

Spontaneous pregnancy loss is a common clinical problem. With the use of sensitive human chorionic gonadotropin (hCG) assays, it has been shown that 31% of pregnancies end in a miscarriage, with two-thirds of the losses occurring before clinical detection.<sup>1,2</sup> In approximately 50% of women with habitual abortions,

defined as three or more spontaneous miscarriages, the etiology remains elusive.<sup>3</sup> Previous studies have suggested that anatomical, hormonal, thrombotic, genetic, infectious, autoimmune, environmental and other unrecognised factors may be involved.<sup>4</sup> Diseases of the thyroid gland such as hypo- and hyperthyroidism have also been associated with fetal loss. Over the past decade, many reports have linked thyroid autoimmunity (TA) with recurrent abortions and it has been suggested that thyroid autoantibodies may serve as a marker for at-risk pregnancies.<sup>5-7</sup>

Furthermore, it was recently shown that thyroxine administration to pregnant women with positive thyroid autoantibodies and a history of recurrent abortions may improve the final outcome.<sup>8</sup>

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In this communication, an overview of recent knowledge regarding TA and miscarriage is presented.

#### AUTOIMMUNE DISEASES AND MISCARRIAGE

Pregnancy affects the immune system in such a way as to maintain the fetal-maternal allograft, which displays paternal antigens.<sup>9</sup> Autoimmune diseases (ADs), such as rheumatoid arthritis, psoriatic arthritis and possibly ankylosing spondylitis, may show clinical improvement during pregnancy.<sup>10</sup> However, recurrent miscarriage has been associated with several ADs. The first such case report suggesting this correlation was published in 1975 and described the presence of a circulating anticoagulant in a woman with recurrent abortions.<sup>11</sup> This anticoagulant was later found to be the lupus anticoagulant. Since that time many studies have confirmed the association of ADs such as antiphospholipid syndrome,<sup>12</sup> rheumatoid arthritis<sup>13</sup> and systemic lupus erythematosus,<sup>14,15</sup> with miscarriage. Thus, antiphospholipid syndrome and systemic lupus erythematosus carry a miscarriage rate of 7-8 and 22%, respectively, with a higher risk for fetal death after the first trimester.<sup>16</sup>

A number of studies have linked TA with recurrent abortions, although the mechanism involved is not clear. It is postulated that the presence of thyroid autoantibodies reflects a generalized activation of the immune system and a generally heightened autoimmune reactivity against the fetoplacental unit.<sup>7</sup> Thus in 1990, Stagnaro-Green et al<sup>7</sup> screening 552 women in the first trimester of pregnancy for thyroid autoantibodies were the first to report a doubling of the miscarriage rate in women who were antibody positive in the first trimester as compared to an antibody negative cohort (17% vs 8.4%,  $p=0.011$ ). The miscarriage rate was found to be independent of demographic data, serum TSH level, thyroid antibody titer, prior obstetrical history, maternal age or presence of anticardiolipin antibodies. However, as noted by Abramson et al,<sup>17</sup> 10.3% of the study population was lost to follow-up, while other causes of abortion were not excluded.

Glinoe et al<sup>18</sup> documented a four-fold increase in the rate of pregnancy loss in euthyroid women with thyroid autoantibodies compared to thyroid

autoantibodies negative pregnant women (13.3% vs 3.3%,  $p<0.001$ ).

Lejeune et al<sup>19</sup> evaluated 363 women in the first trimester of their pregnancy, 21 of whom spontaneously miscarried. In this cohort, 22% with positive thyroid antibodies aborted compared to 5% with antibody negative ( $p<0.005$ ). The miscarriages associated with thyroid autoimmunity took place early, within the first trimester of pregnancy.

In the study of Pratt et al,<sup>20</sup> 45 women with recurrent abortions were evaluated for the presence of thyroid autoantibodies as well as for 15 non-organ-specific autoantibodies. The women with habitual miscarriages did not have significantly higher incidence of thyroid autoantibodies as compared to the controls (31% vs 19%). In a follow-up study in which pregnancy outcome was evaluated in 42 euthyroid women with a history of three or more consecutive, first trimester abortions, 31% had thyroid autoantibodies. The presence of thyroid autoantibodies before conception carried a significantly increased risk of miscarriage, because 8 of 13 thyroid autoantibody positive women and only 4 of 29 thyroid autoantibody negative women miscarried (62% vs 14%,  $p=0.003$ ).<sup>21</sup>

Singh et al<sup>5</sup> studied 487 women who conceived with assisted reproductive techniques. Twenty-two per cent of them were positive for either TPOAbs or TgAbs or both. It was found that determining the presence of thyroid autoantibodies 14 days after embryo transfer was useful in identifying women at risk for miscarriage after the pregnancy was clinically recognized (visualization of gestation sac) but not before. There was significant statistical difference in clinical miscarriage rate between the antibody positive group (32%) compared to the antibody negative one (16%).

In a study<sup>6</sup> of 22 euthyroid non-pregnant habitual aborters it was found that thyroid autoantibodies were significantly higher compared to two control groups: 22 multigravidae and 22 nulligravidae (36% vs 5% and 9%, respectively). It was also shown that 11 of 28 women with recurrent abortions were thyroid antibody positive, as compared to 2 of 28 controls (39% vs 7%,  $p<0.004$ ).<sup>22</sup>

In 45 women with recurrent abortions and 15 con-

trols, Roussev et al<sup>23</sup> found that 9% of the women in the recurrent abortion group were thyroid antibody positive as contrasted to 0% in the controls.

Roberts et al<sup>24</sup> compared 11 women with a history of recurrent abortions with four other groups (10 non-pregnant controls, 11 healthy pregnant women, 11 women with spontaneous abortion and 10 women with elective termination of pregnancy). They found a statistically significant increase in the rate of thyroid autoantibodies in the group with recurrent pregnancy loss. No information for TA was available before pregnancy.

Iijima et al<sup>25</sup> showed that women positive for thyroid autoantibodies had a higher miscarriage rate than women who were negative (10.4 vs 5.5%,  $p < 0.05$ ). The titer of the thyroid autoantibodies had no effect.

In 74 women with recurrent abortion and in 75 controls it was shown<sup>26</sup> that women with a history of recurrent pregnancy loss were no more likely than controls to have thyroid autoantibodies. The conclusions of this study have been questioned due to the unusually high incidence of thyroid autoantibodies in the control group (37%).<sup>17,27,28</sup>

In women undergoing in vitro fertilization (IVF), Kim et al<sup>29</sup> found that the miscarriage rate was significantly higher in the group of 28 women who were positive for thyroid autoantibodies compared with the control group (40% vs 11.4%,  $p < 0.05$ ).

Kutteh et al<sup>27</sup> investigated 1588 women who were divided into 3 groups: 700 women with two or more consecutive pregnancy losses, 688 with a history of infertility who underwent assisted reproductive techniques and 200 control women. The percentage of women with thyroid autoantibodies was significantly higher in the abortion group compared with the controls (22.5% vs 14.5%,  $p = 0.01$ ).

Muller et al<sup>30</sup> found no difference between antibody negative and antibody positive women regarding miscarriage rate.

Dendrinis et al<sup>31</sup> found that 37% of women with recurrent abortions had positive thyroid autoantibodies compared with 13% of controls ( $p < 0.05$ ).

Mecacci et al<sup>32</sup> found 37.9% of 29 women with a

history of early pregnancy loss had positive thyroid antibodies.

In a study<sup>33</sup> of 870 women, thyroid autoantibodies were found in 19% (TgAbs 5%, TPOAbs 60% and both Abs 35%). Fifty-eight per cent of pregnancies in women with thyroid positive autoantibodies and 58% of the thyroid negative pregnancies resulted in live births. They concluded that future risk of pregnancy loss in women with unexplained recurrent miscarriages is not affected by their thyroid antibody status.

In a prospective study, Bagis et al<sup>34</sup> evaluated 876 women who were followed during their pregnancy starting on the 12<sup>th</sup> week and subsequently up to one year post partum. In the total group 12.3% of women were thyroid autoantibody positive. In the antibody positive group, 54 women (50%) had at least one previous miscarriage and 12 of them (11.1%) had more than 2, as compared to 14.1% and 3.1%, respectively, of women who were thyroid autoantibody negative ( $p < 0.001$ ). The women who were antibody positive had a significantly higher TSH and lower free thyroxine, as compared to women with negative thyroid autoantibodies.

Poppe et al<sup>35</sup> evaluated 234 women presenting for their first IVF cycle and found that the miscarriage rate was significantly higher in the thyroid antibody positive women as contrasted to thyroid antibody negative women (53% vs 23%,  $p = 0.016$ ).

Sieiro Netto et al<sup>36</sup> in a study of 534 pregnant women found that 5.4% of them were thyroid autoantibody positive. The risk of miscarriage was significantly higher among thyroid autoantibody positive women (10.3%) and especially among those presenting high TSH levels (12.5%).

In 984 euthyroid pregnant women Negro et al<sup>37</sup> found that the miscarriage rate was 13.8% in the thyroid autoantibody positive group and 2.4% in the antibody negative group ( $p < 0.05$ ).

In a retrospective study<sup>38</sup> of 416 euthyroid women undergoing assisted reproduction technologies 10.1% had thyroid autoantibodies. The miscarriage rate was 23.8 in the thyroid autoantibody positive group and 11.5% in the thyroid autoantibody negative group. The conclusion of this study was that in euthyroid women undergoing assisted reproduction technologies,

the delivery rates were not affected by the presence of thyroid autoantibodies. However, in women with autoimmune thyroid disease, high-normal TSH values were associated with increased risk of miscarriage.

Thus most of the published studies indicate an association between positive thyroid autoantibodies and miscarriage. A summary of pertinent studies is presented in Tables 1 and 2. There are limited data on the relationship between thyroid autoantibody titers and miscarriage rate and these are controversial. Two such studies have found no correlation,<sup>7,25</sup> while one study had different results.<sup>39</sup>

#### POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS OF THE ASSOCIATION OF THYROID AUTOIMMUNITY WITH MISCARRIAGE

The exact mechanism of an association of thyroid autoimmunity with miscarriage remains largely unknown. Three mechanisms have been postulated.<sup>40,41</sup>

1) The presence of thyroid autoantibodies reflects

a generalized activation of the immune system and specifically a heightened reactivity of the immune system against the feto-placental unit;<sup>7</sup> women with thyroid autoantibodies could have a more generalized immune imbalance. It must be noted that, pertinent studies have shown that in the presence of antiphospholipid antibodies, miscarriages occur at 22 weeks,<sup>42</sup> whereas miscarriages in women with positive thyroid autoantibodies occur within the first trimester of gestation<sup>35</sup> when the fetus is critically dependent on maternal thyroid hormones.<sup>43</sup> It is of interest that in mice a direct action of TgAbs on the placenta has been described, but analogous data in humans are not available.<sup>44-46</sup> 2) The presence of thyroid autoantibodies may act as an infertility factor and may delay conception. Thus, when women with thyroid autoantibodies do become pregnant, they are older and face a higher risk of miscarriage.<sup>19,47,48</sup> The study of Poppe et al,<sup>35</sup> showed that age was an independent risk factor for miscarriage. However, the mean age of the thyroid autoantibody positive women was not significantly different from that of thyroid autoanti-

**Table 1.** Studies published to date regarding the relationship between recurrent miscarriage and thyroid autoimmunity

A/A	Name of first author (Ref N°)	Year of publication	Number of TPOAb(+) women	Number of TPOAb(-) women	Age at detection of TPOAb(+)	Age at detection of TPOAb(-)	Miscarriage rate in TPOAB(+) vs TPOAB(-)	P
1	Stagnaro-Green et al <sup>(7)</sup>	1990	100	392	NA	NA	17.0% vs 8.4%	0.011
2	Glinoeer et al <sup>(18)</sup>	1991	45	603	29.0±1.0	27.0±1.0	13.3 vs 3.3	<0.001
3	Lejeune et al <sup>(19)</sup>	1993	23	340	28.2±9.5	27.2±6.8	22.0% vs 5.0%	<0.005
4	Pratt et al <sup>(21)</sup>	1993	13	29	33.0±2.9	34.0±3.4	64.0% vs 14.0%	0.003
5	Singh et al <sup>(5)</sup>	1995	106	381	NA	NA	32.0% vs 16.0%	NA
6	Iijima et al <sup>(25)</sup>	1997	125	951	30.2±4.8	30.0±4.3	10.4% vs 5.5%	<0.05
7	Kim et al <sup>(29)</sup>	1998	28	51	32.1±3.7	31.6±3.1	40.0% vs 11.4%	<0.05
8	Muller et al <sup>(30)</sup>	1999	25	148	32.4±3.3	32.4±4.4	33.0% vs 19.0%	0.29
9	Rushworth et al <sup>(33)</sup>	2000	24	81	34 (20-41)	34 (22-46)	42.0% vs 42.0%	NA
10	Bagis et al <sup>(34)</sup>	2001	108	768	27.7±6.2	25.9±5.2	11.1% vs 3.1%	<0.0001
11	Poppe et al <sup>(35)</sup>	2003	32	202	33.2±4.6	31.6±5.4	53.0% vs 23.0%	0.016
12	Sieiro Netto et al <sup>(36)</sup>	2004	29	505	NA	NA	10.3% vs 2.0%	0.029
13	Negro et al <sup>(37)</sup>	2006	57 <sup>a</sup> 58 <sup>b</sup>	869	30.0±6.0	28.0±5.0	3.5 <sup>a</sup> vs 13.8 <sup>b</sup> vs 2.4%	<0.05 between control and subgroup b
14	Negro et al <sup>(38)</sup>	2007	21	234	NA	NA	23.8% vs 11.5%	NA

NA: Not Available, a: Subgroup given LT4, b: Subgroup not given LT4

**Table 2.** Studies published to date on the rate of positive thyroid autoantibodies in women with recurrent miscarriage and controls.

A/A	Name of first author (Ref N <sup>o</sup> )	Year of publication	Number of women with RSM	Number of controls	Age of women with RSM	Age of controls	Rate of TPOAbs in women with RSM vs controls	P
1	Pratt et al <sup>(20)</sup>	1993	45	100	35.5±0.68	37.5±12.2	31.0% vs 19.0%	NA
2	Bussen et al <sup>(6)</sup>	1995	22	22 <sup>a</sup> 22 <sup>b</sup>	30.5±4.6	29.0±4.7 32.5±5.1	36.0% vs 9.0% and 5.0%, respectively	0.03 0.009
3	Roussev et al <sup>(23)</sup>	1996	45	15	NA	NA	9.0% vs 0%	NA
4	Roberts et al <sup>(24)</sup>	1996	11	10 <sup>c</sup> 11 <sup>d</sup> 11 <sup>e</sup> 10 <sup>f</sup>	30.4±4.8	28.4±3.2 24.5±4.1 25.5±3.8 25.7±6.9	36.3% vs 4.7%	<0.01
5	Bussen et al <sup>(22)</sup>	1997	28	28	32.4±4.5	31.2±5.9	39.0% vs 7.0%	0.004
6	Esplin et al <sup>(26)</sup>	1998	74	75	33.6±6.9	38.6±5.6	29.0% vs 37.0%	>0.05
7	Kutteh et al <sup>(27)</sup>	1999	700	200	33.3±5.0	30.8±6.2	22.5 vs 14.5%	0.01
8	Dendrinou et al <sup>(31)</sup>	2000	30	15	25-37	26-36	37.0% vs 13.0%	<0.05
9	Mecacci et al <sup>(32)</sup>	2000	29	69	33.7±0.8	33.7±0.8	37.9% vs 14.5%	<0.02

RSM: recurrent spontaneous miscarriage, NA: Not Available, a: nulligravidae, b: multigravidae, c: non-pregnant women, d: healthy women in the first trimester of an ongoing pregnancy, e: women admitted with spontaneous abortion (no history of recurrent miscarriage), f: healthy women admitted for termination of pregnancy

body negative women. It is of note that the study of Poppe et al is restricted to a specific population, i.e. women scheduled for assisted reproduction, so that age findings from this study cannot be generalized to the whole population of pregnant women. Moreover, Kontiainen et al<sup>49</sup> found an increase in the titer of TPOAbs with age, but this correlation was not statistically significant. In a study of Kutteh et al,<sup>27</sup> a high number of patients with recurrent pregnancy loss demonstrated elevated autoantibody titer as age increased, up until the age range of 31-35, after which a decreased frequency was observed. 3) The presence of thyroid autoantibodies in euthyroid women could be associated with a subtle deficiency in thyroid hormone concentrations or a lower capacity of the thyroid gland to adequately adapt to the demands of pregnancy. Indeed, the mean serum TSH values, while being within normal range, were significantly higher in thyroid autoantibody positive women compared to women with negative thyroid autoantibodies. This may reflect lower thyroidal reserve during pregnancy when a greater amount of thyroid hormones is demanded.<sup>50</sup> Moreover, it was shown that in thyroid autoantibody

positive women, serum TSH levels gradually increased as gestation progressed, with 19% of them having an increased serum TSH at delivery. Serum TSH levels also increased in the group with negative thyroid autoantibodies but to a lesser extent.<sup>37,51</sup>

Imaizumi et al<sup>45</sup> investigated the impact of experimentally induced thyroiditis on pregnancy loss in a murine model. The immunized mice that mated with a similar but not identical strain had a significantly lower percentage of pregnancy maintenance (57%) as compared with the immunized mice that mated with an identical strain (98%,  $p < 0.05$ ). Moreover, Matalon et al<sup>46</sup> expanding on the findings by Imaizumi et al revealed an increase in fetal wastage ( $p = 0.04$ ) and decrease in fetal and placental weights ( $p < 0.001$ ) in the immunized mice.

The various explanations stated above are not in contradiction with one another. It is possible that the increased risk of miscarriage in thyroid antibody positive women results from several influences acting in concert.

### THE EFFECT OF THYROXINE ADMINISTRATION ON MISCARRIAGE RATE IN WOMEN WITH POSITIVE THYROID AUTOANTIBODIES

It is obvious that the final goal of clinicians and researchers is to decrease miscarriage rate in women with thyroid autoimmunity to that of the general population. Autoimmunity may play a major role in fertilization, implantation and placenta development.

Therapeutic interventions aiming at modulating the immune system of women with autoantibodies have included intravenous immunoglobulin administration. This treatment resulted in an increase in the percentage of women who had successful pregnancies.<sup>52,53</sup> In addition to this, the combination of immunoglobulin, heparin and aspirin had better results than the administration of only heparin and aspirin.<sup>54</sup>

The first study in which thyroid hormone replacement therapy was applied was conducted by Vaquero et al.<sup>8</sup> It was a prospective study in women with two or more previous first trimester miscarriages and positive thyroid autoantibodies. Eleven women were treated with intravenous immunoglobulin during pregnancy and 16 women were treated with thyroid hormone replacement therapy (66 mg of thyroid extract, started before conception and continued until the 20<sup>th</sup> week). The conclusion was that thyroid hormone supplementation was more effective than intravenous immunoglobulin in the prevention of recurrent abortions. Indeed, 81.2% of the women treated with thyroid extract had a successful pregnancy outcome contrasted to 54.5% of the group treated with immunoglobulin ( $p < 0.05$ ). However, it has been argued that the number of patients was small and that the thyroid extract administration was initiated before conception in contrast to the administration of intravenous immunoglobulin that was initiated after the onset of pregnancy.<sup>55</sup>

Negro et al<sup>56</sup> also reported results on levothyroxine (LT4) administration to euthyroid women who underwent IVF and were thyroid autoantibody positive. The women were randomly divided into two groups. One received LT4 and the other placebo. The miscarriage rate in the untreated group was 52% compared to 33% in the group in which LT4

was given. However, the difference was not statistically significant, most probably because the number of patients investigated was small.

In another study, Negro et al<sup>37</sup> divided thyroid autoantibody positive women into two groups. One group was treated with LT4 ( $49.7 \pm 14$   $\mu\text{g}$  daily) in a dose based on the TSH starting values. The other group was not treated. A third group served as a normal general population control. Forty percent of the women in the treated group started LT4 treatment by the 8<sup>th</sup> week and 79% by the 12<sup>th</sup> week. Initially, the mean TSH values were significantly higher in the treated and untreated groups compared to the control group ( $1.6 \pm 0.5$  and  $1.7 \pm 0.4$ , respectively vs  $1.1 \pm 0.4$  mU/L,  $p < 0.05$  and  $p < 0.05$ , respectively). The TSH values of the untreated group remained significantly higher than those of the other 2 groups during the entire gestational period. TSH and FT4 values in the treated group were not significantly different from the control group. The treated group and the controls showed a similar miscarriage rate (3.5% and 2.4%, respectively), which was lower than that of the second group who did not receive LT4 (13.8%,  $p < 0.05$ ).<sup>37</sup> The conclusion of this study was that thyroid autoantibody positive women have an increased risk of miscarriage but when given the benefit of treatment with thyroid hormone, they behave as the normal ones.

It is not entirely clear whether the development of hypothyroidism can be predicted at the beginning of gestation. Glinioer et al<sup>57</sup> mentioned that women who developed hypothyroidism had higher TPOAb titers at delivery and in the first trimester and a slightly but significantly higher TSH level at the beginning of their pregnancy compared to women with autoimmune thyroid disease who maintained normal thyroid function during pregnancy. They therefore suggested that women with TPOAb titers greater than 2000 U/ml or TSH greater than 2mU/ml require close monitoring during gestation and probably systematic treatment with thyroid hormones. In a recent study, Negro et al<sup>38</sup> stressed that, at least for TPOAb positive women desiring pregnancy, TSH value  $> 2.5$  mU/L is to be considered abnormal.

Thyroxine administration seems to be effective in reducing the number of miscarriages when given during the early stages of pregnancy, because miscar-

riages with maternal thyroid autoimmunity generally occur within the first trimester. Nevertheless, in a study carried out in infertile women undergoing assisted reproduction technologies, LT4 treatment was not found to be beneficial.<sup>56</sup>

Poppe and Glinoe have proposed that serum TSH, free T4 and thyroid autoantibodies should be measured in early gestation. When serum TSH is elevated or free T4 is below normal, LT4 should be administered during pregnancy. In women with thyroid autoantibodies and serum TSH < 2 mU/L, LT4 treatment is not warranted; however, serum TSH and free T4 should be measured later in gestation, preferably at the end of the second trimester. For women with thyroid autoantibodies and TSH between 2-4 mU/l in early gestation, treatment with LT4 should be considered. It is important to consider that serum TSH is down-regulated during the first half of gestation by hCG.<sup>28</sup>

It has to be mentioned that other substances, such as selenium, that are essential to thyroid hormoneogenesis may play a role in repeated miscarriages. It has been reported that selenium administration during pregnancy decreases thyroid autoantibodies concentration.<sup>58</sup>

Over the past fifteen years a positive association between thyroid autoantibodies and fetal loss in unselected women has been clearly established. Recent studies, although limited in number and not well designed, have suggested that thyroxine therapy in women with thyroid autoantibodies decreases fetal loss. It is, however, too early to draw final conclusions regarding a very important question, namely if women with positive thyroid autoantibodies should be started on LT4 therapy during their pregnancies to minimize abortion rate. Further studies are needed before we can answer this question.

## CONCLUSIONS

Most but not all studies have shown a significant association between the presence of thyroid antibodies and a higher miscarriage rate. However, patients with high titers of thyroid autoantibodies do not show a higher rate of miscarriages compared with patients with low titers. The mechanisms involved

remain speculative.

Regarding prevention of miscarriage, there are a few studies showing that thyroxine treatment may be effective in reducing the number of miscarriages when given during the early stages of pregnancy. Further studies are required with a greater number of women in order to reach definitive conclusions.

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