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INVITED REVIEW

Thyroid autoimmunity and miscarriage

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Abstract

To ascertain the strength of the association between thyroid autoimmunity and miscarriage, we performed a meta-analysis of both case–control and longitudinal studies performed since 1990 when this association was first described. A clear association between the presence of thyroid antibodies and miscarriage was found with an odds ratio (OR) of 2.73 (95% confidence interval (CI), 2.20–3.40) in eight case–control and ten longitudinal (OR, 2.30; 95% CI, 1.80–2.95) studies. This association may be explained by a heightened autoimmune state affecting the fetal allograft, of which thyroid antibodies are just a marker. Alternatively, the association can be partly explained by the slightly higher age of women with antibodies compared with those without (mean±S.D. age difference, 0.7±1.0 years; $P < 0.001$). A third possibility is mild thyroid failure, as thyroid-stimulating hormone (TSH) levels in antibody-positive but euthyroid women are higher than in antibody-negative women: difference 0.81±0.58 mU/l ($P = 0.005$). Randomized clinical trials with L-thyroxine (aiming at TSH values between 0.4 and 2.0 mU/l) and with selenium (to decrease antibodies against thyroid peroxidase) are clearly needed to elucidate further the nature of this association.

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Introduction

Miscarriage is a common occurrence and as many as 31% of pregnancies end in a miscarriage when sensitive human chorionic gonadotropin (hCG) assays are used, of which about one-third will be noticed by the mother (1). The incidence of two miscarriages is 2–4% and the incidence of three consecutive losses is less than 1%. These recurrent losses 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 (2). Recurrent pregnancy loss is also associated with several autoimmune diseases, most notably systemic lupus erythematosus and antiphospholipid syndrome (3). There are also reports linking thyroid autoimmunity with recurrent abortions and we will here review the evidence for this association.

Studies on the association between miscarriage and thyroid autoimmunity

Using the PubMed search strategy 'miscarriage AND thyroid', and studies cited in several published review articles (4–7), we identified 18 controlled studies in which data were available to calculate the odds ratios (ORs). Of these, 8 were case–control studies (8–15) and 10 were prospective (16–25). For all the studies, we have calculated the OR with 95% confidence interval (95% CI) according to Sandercock (26). The meta-analysis of the case–control studies is presented in Table 1, where the prevalence of thyroid autoantibodies in patients with recurrent abortions is compared with controls. In Table 2 the meta-analysis represents the miscarriage rates in subjects with thyroid antibodies compared with the abortion rates in controls. Both types of studies revealed a similar and significant relationship between thyroid autoantibodies and miscarriage: the cumulative OR was 2.73 in the 8 case–control studies and 2.30 in the 10 prospective studies.

Nature of the association

From the meta-analysis it is clear that there is a significant association between the presence of thyroid autoimmunity and a higher miscarriage rate, but of course the presence of an association does not mean that there is a causal relationship. There are a number of possible explanations.

Co-segregation with other autoimmune syndromes

Miscarriage is also associated with other autoimmune syndromes such as the antiphospholipid syndrome

Table 1 Meta-analysis of case–control studies on the association between miscarriage and the presence of antithyroid autoantibodies.

Reference	Patients No. of Ab +ve (%)	Controls No. of Ab +ve (%)	Odds ratio	95% CI
Pratt *et al.* (8)	≥3 abortions 14/45 (31%)	Blood donors 19/100 (19%)	1.93	0.86–3.37
Bussen & Steck (9)	≥3 abortions 8/22 (36%)	No abortions 3/44 (7%)	7.81	1.82–33.6
Bussen & Steck (10)	≥3 abortions 11/28 (39%)	No abortions 2/28 (7%)	8.41	1.70–42.8
Esplin *et al.* (11)	≥3 abortions 22/74 (29%)	≥3 pregnancies 28/75 (37%)	0.71	0.50–1.01
Kutteh *et al.* (12)	≥2 abortions 158/700 (23%)	Blood donors 29/200 (15%)	1.72	1.12–2.65
Mecacci *et al.* (13)	≥2 abortions or ≥1 fetal death 20/51 (39%)	Unknown 10/69 (15%)	3.81	1.95–9.14
Dendrinos *et al.* (14)	≥3 abortions 11/30 (37%)	≥1 pregnancies 2/15 (13%)	3.76	0.71–19.87
Bagis *et al.* (15)	≥1 abortion 54/162 (33%)	No abortions 54/714 (8%)	5.98	3.98–9.38
Total	298/1112 (27%)	147/1245 (12%)	2.73	2.20–3.40

(lupus anticoagulant, anticardiolipin antibodies) and systemic lupus erythematosus (3). These syndromes carry a miscarriage rate of 7–8 and 22% respectively but, unlike thyroid antibodies, these syndromes also carry a higher risk for fetal death after the first trimester. Indeed, antithyroid antibodies are sometimes present together with anticardiolipin antibodies (27). However, in the above-mentioned studies women with other than thyroid antibodies were excluded or were analyzed separately (8, 10, 13, 16, 19, 21, 23, 24) and it appears that the observed association is not due to the co-presence of any of these antibodies.

However, this does not exclude the possibility that the thyroid antibodies are a marker of an as yet unidentified more generally heightened autoimmune state against the fetal–placental unit. This notion is supported by the observation that women with recurrent abortions have an increased number of CD5/20-positive B cells as compared with women with a normal pregnancy or with only one abortion (28), and others found an abnormal T cell function in women with thyroid antibodies (6). Women with thyroid antibodies have higher numbers of endometrial T cells than controls, and these cells produced less interleukin (IL)-4 and IL-10, but more interferon-γ (29).

Direct involvement of thyroid antibodies

If this were the case, one would expect that there would be a 'dose–response' relationship between antibody titers and miscarriage. Surprisingly, this has not been analyzed frequently. Some studies do mention that the antibody titers are not related to miscarriage (16, 21) but they sometimes calculated the titers including the antibody-negative subjects (9). There is one study that did find higher thyroperoxidase (TPO) antibody titers and avidity in TPO-positive women who aborted than in women with TPO antibodies who had a term delivery (30).

Table 2 Meta-analysis of prospective studies analyzing abortion rates among women with thyroid autoantibodies (Ab +ve) versus women without antibodies (Ab −ve).

Reference	Abortion rate in Ab +ve women	Abortion rate in Ab −ve women	Odds ratio	95% CI
Stagnaro-Green *et al.* (16)	17/100 (17%)	33/392 (8%)	2.23	1.19–4.20
Glinoer *et al.* (17)	6/45 (13%)	20/603 (3%)	4.48	1.70–11.81
Lejeune *et al.* (18)	5/23 (22%)	16/340 (5%)	5.63	1.82–17.1
Pratt *et al.* (19)	8/13 (62%)	12/42 (29%)	10.0	2.20–46.5
Singh *et al.* (20)	28/87 (32%)	49/301 (16%)	2.44	1.42–4.20
Iijama *et al.* (21)	13/125 (10%)	52/951 (5%)	2.01	1.06–3.80
Kim *et al.* (22)	4/10 (40%)	4/35 (11%)	5.17	2.72–26.54
Muller *et al.* (23)	4/12 (33%)	8/42 (19%)	2.13	0.51–8.87
Rushworth *et al.* (24)	10/24 (42%)	30/77 (39%)	1.12	0.44–2.84
Poppe *et al.* (25)	9/17 (53%)	20/87 (23%)	3.77	1.34–10.63
Total	104/456 (23%)	336/2957 (11%)	2.30	1.80–2.95

Confounders: non-immunological factors different in antibody positive and negative women

Women with TPO antibodies differ from TPO-negative women in a number of non-immunological factors such as age and thyroid function. In a cohort of euthyroid female relatives of patients with documented autoimmune thyroid disease, we found that TPO-antibody-positive women were on average 6 years older and had slightly, but significantly, higher TSH levels (31). Could these factors explain the observed difference in miscarriage rate?

Miscarriage and age

Higher age is a definite risk factor for miscarriage (2) and TPO-antibody-positive women are in general older than TPO-antibody-negative women. This was also the case in most, though not all, of the studies used here (Table 3). A crude estimation of the age difference is that the TPO-positive women are 0.7 years older than their TPO-negative counterparts ($P < 0.001$). This appears to be a small and negligible difference, but around this age especially there is a sharp increase in the rate of spontaneous abortions. The rate among women aged 25–29 is 10.7 %, in the age group 30–34 it is 14.2 % and in the group aged 35–39 years it is 26.2 % (32). It thus may be that the slightly higher age explains a small part of the observed difference in miscarriage rates.

Miscarriage and mild thyroid failure

Euthyroid women with TPO antibodies have slightly higher TSH values than those without antibodies; this may indicate less thyroidal reserve in times of greater demand for thyroid hormones, such as in pregnancy (5). Hypothyroidism is associated with infertility, but also with a higher miscarriage rate (2). In a recent study among women treated with thyroxine (T_4) for hypothyroidism, the miscarriage rate in hypothyroid women was 31.4 % as compared with 4 % in euthyroid women on T_4 substitution (33). The miscarriage rate was similar in overtly hypothyroid (38 %) and subclinically hypothyroid (48 %) women. Importantly, when hypothyroidism was detected early in pregnancy and adequate T_4 substitution was given from then on, the abortion rate fell to 0 %, indicating that rapid treatment prevents miscarriage. In another study, women with recurrent abortions and with TPO antibodies but normal thyroid function were either treated with intravenous immunoglobulin (IVIG) ($n = 11$) or with thyroid hormone extract ($n = 16$) (34). The miscarriage rate was 45 % in the IVIG-treated women, but only 19 % ($P < 0.05$) in the T_4/3,5,3′-triiodothyronine (T_3)-treated mothers.

In the reports studied in this review, most included euthyroid women only. However, in these euthyroid women, the TSH levels tended to be slightly higher in females with antibodies (Table 4). On average, TSH levels were 0.81 mU/l higher ($P = 0.005$) in antibody-positive women, and this may indicate a lessened thyroid reserve, or very mild thyroid failure.

It may thus be that mild thyroid failure forms part of the explanation for the association between thyroid autoimmunity and miscarriage. This is underscored by the fact that in women with a history of abortion, those with antibodies had significantly higher TSH values than women with recurrent pregnancy loss who did not have those antibodies (13, 15).

Future developments

It is possible, therefore, that the association between thyroid antibodies and miscarriage has to be explained by a general increase in autoimmunity against the fetal allograft. If this were to be the case, there are almost no therapeutic interventions to offer to these women. The two other explanations, i.e. mild thyroid failure or the TPO antibodies themselves, do hold a promise for successful intervention. The higher TSH values in antibody-positive women warrant a randomized clinical trial to evaluate the effect of T_4 substitution therapy aiming at TSH values between 0.4 and 2.0 mU/l.

Table 3 Age difference (in years; mean±S.D.) among women positive for thyroid autoantibodies as compared to antibody-negative women in studies on the association between thyroid antibodies and miscarriage where these data were available.

Reference	Age in TPO +ve women	Age in TPO −ve women	Difference	*P*
Bussen & Steck (9)	31.0±5.2	30.3±4.5	+0.7	NS
Bagis *et al.* (15)	27.7±6.2	25.9±5.2	+1.8	<0.0009
Glinoer *et al.* (17)	29.3±1	27.3±1	+2.0	<0.001
Lejeune *et al.* (18)	28.2±9.5	27.2±6.8	+1.0	0.06
Pratt *et al.* (19)	33±2.9	34±3.4	−1.0	NS
Iijama *et al.* (21)	30.2±4.8	30.0±4.3	+0.2	NS
Muller *et al.* (23)	32.4±3.3	32.4±4.4	0	NS
Rushworth *et al.* (24)	34 (20–41)*	34 (22–46)	0	NS
Poppe *et al.* (25)	33.2±4.6	31.6±5.4	+1.6	NS
Average±S.D.	31.0±2.3	30.3±3.0	+0.7±1.0	

*Median (range).

Table 4 TSH levels (mean±S.D., or median with range) in women with thyroid antibodies, compared with those without, in studies on the association between thyroid autoimmunity and miscarriage where these data were available.

Reference	TSH levels in Ab +ve women	TSH levels in Ab −ve women	Difference	*P*
Stagnaro-Green *et al.* (16)	2.35	1.60	0.75	0.12
Glinoer *et al.* (17)	1.4	0.9	0.5	<0.01
Muller *et al.* (23)	3.5±3.6	1.7±0.9	1.8	<0.005
Bagis *et al.* (15)	1.86±1.8	1.17±0.9	0.69	<0.001
Poppe *et al.* (25)	1.6 (0.02–4.1)	1.3 (0.05–3.6)	0.3	NS
Average±S.D.	2.14±0.84	1.33±0.32	0.81±0.58	

Regarding TPO antibodies, we suggest that selenium substitution may have a role that can be ascertained via a randomized clinical trial. Selenium, a trace element also called the 21st amino acid, is essential in thyroid hormone synthesis because several enzymes involved are selenoproteins (35). Selenium also plays a role in the immune system, and in the coagulation system (36, 37). Selenium substitution decreased TPO antibody levels in euthyroid subjects (and increased quality of life) in a recent double-blind randomized clinical trial (37). It also decreased TPO antibody levels in hypothyroid patients treated with T_4 substitution in another trial (38). In this respect, it is of interest to note that women with recurrent pregnancy loss had lower selenium levels in their hair than controls: 0.14±0.09 versus 0.34±0.25 μg/g ($P < 0.001$) (36).

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