Clinical Endocrinology (2011) **74**, 513–519 doi: 10.1111/j.1365-2265.2010.03974.x

ORIGINAL ARTICLE

Thyroid autoimmunity and miscarriage: a meta-analysis

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Summary

Objective To investigate whether thyroid autoimmunity (TAI) is associated with increased risk of miscarriage in euthyroid women.

Methods An electronic search was conducted using the databases Medline, PubMed, EMBASE and the Cochrane library, from inception to October 2010. A systematic review of the studies on the association between TAI and miscarriage was performed. The odd ratios of case–control studies and relative risks of cohort studies were pooled respectively. The software Review Manager (version 4.3.1) was applied for meta-analysis.

Results The search strategy identified 53 potentially relevant publications, 22 of which were included in the meta-analysis. A clear association between thyroid autoimmunity and miscarriage was observed with a pooled odds ratio of 2·55 (95% CI 1·42–4·57, $P = 0·002$) in eight case–control studies and a pooled relative risk of 2·31 (95% CI 1·90–2·82, $P < 0·000\ 01$) in 14 cohort studies. Women with TAI were found to have slightly higher age [age difference, 1·29 years] (95% CI 0·43–2·16, $P = 0·003$) and thyroid-stimulating hormone (TSH) levels [TSH difference, 0·61 mIU/l] (95% CI 0·51–0·71, $P < 0·000\ 01$) compared with those without TAI.

Conclusion Based on the currently available evidence, it appears that the presence of thyroid autoimmunity is associated with an increased risk of spontaneous miscarriage in euthyroid women.

(Received 11 November 2010; returned for revision 22 November 2010; finally revised 18 December 2010; accepted 24 December 2010)

Introduction

According to epidemiological research, 31% of pregnancies end in abortion.[1] Because human chorionic gonadotrophin (hCG) was applied to the detection of early gestation, about one-third of miscarriages could be discovered in time.[1] The prevalence of two consecutive abortions is approximately 2–4%, while the prevalence of three consecutive abortions is <1%.[1] Many factors have been associated with miscarriage, such as hereditary defects, developmental deformities, peripartum infection, environmental exposure (smoking, alcohol abuse and intoxication) and some endocrine disorders (diabetes mellitus, thyroid diseases and hyperprolactinaemia).[2] Recurrent spontaneous abortion has been associated with several autoimmune diseases, especially systemic lupus erythematous (SLE) and antiphospholipid syndrome (APS).[3] The fact that overt hypothyroidism negatively affects pregnancy outcome has been affirmed. However, the effect of subclinical hypothyroidism on pregnancy outcome, particularly in euthyroid women with positive thyroid autoantibodies is still controversial. In 1990, Stagnaro-Green[4] initially reported that euthyroid women with positive thyroid autoantibodies (TA) are more liable to abortion. Since then, numerous studies on the association between thyroid autoimmunity (TAI) and miscarriage have been issued. In a recent meta-analysis,[5] the presence of TAI was associated with an increased risk for spontaneous miscarriage in subfertile women achieving a pregnancy through an *in vitro* fertilization (IVF) procedure. Considering the heterogeneity of the design and methodology of these studies and the conflicting study results, we have conducted a meta-analysis to provide more persuasive evidence for clinical practice.

Materials and methods

A systematic evaluation of the association between TAI and miscarriage was based on a search and data analysis of the published case–control studies and cohort studies. TAI prevalence was compared between aborters and controls in case–control studies. The pooled odds ratio (OR) and its 95% confidence interval (CI) were then calculated. Likewise, the abortion rates for TA-positive and TA-negative groups were compared, and the pooled relative risk (RR) and its 95% CI were calculated.

Study inclusion criteria

(i) All published studies were included in our research, regardless of their publication language or date. (ii) The cohort studies had to be prospectively designed. (iii) Overt thyroid dysfunction in gestation was excluded, while euthyroidism was defined as serum thyroid-stimulating hormone (TSH) between 0·3 and 5·0 mIU/l. (iv) TAI was defined as one or more types of TA positive. TA refers to thyroid microsome antibody, thyroglobulin antibody and thyroid peroxidase antibody. (v) OR or RR and its 95% CI were calculated from the raw data extracted from the original literature. (vi) The studies involving multiple IVF procedures were excluded.

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Search strategy

The literature search, as well as screening of titles, abstracts and full-text articles, was completed independently by two investigators, according to the inclusion criteria mentioned earlier. An electronic search was conducted using the databases Medline, PubMed, EMBASE and the Cochrane library, from inception to October 2010. The terms used for electronic search were miscarriage, abortion, misbirth, pregnancy loss, thyroid autoimmunity, autoimmune thyroid disease, thyroid antibodies, thyroid autoantibodies, thyroid microsome antibody, thyroglobulin antibody and thyroid peroxidase antibody. Various combinations of the keywords were applied. Moreover, the references of included literature were searched manually, and the related articles provided by PubMed were screened.

Data extraction

Information from each study was extracted independently by two investigators, using a standardized data extraction form. Any dispute was solved unanimously via discussion. The literature approved by both investigators was included in this meta-analysis. If two or more studies had shared research data, then the study with the largest number of samples was included, while others were excluded. General characteristics of the study (author, year of publication, country, study design, sample size), characteristics of the study groups, their comparability on baseline characteristics (age, thyroid function tests), definition of TAI, recurrent aborters and controls (types of thyroid autoantibodies measured, times of consecutive miscarriages) and outcomes (miscarriages, TA-positive rate) were recorded, wherever available, and double-checked. Where appropriate, efforts were made to complete the data set through communication with the authors.

Statistical analysis

If the *chi-square* test showed there was no significance of heterogeneity among the included studies ($P > 0{\cdot}10$), then Mantel–Haenszel formula (fixed model) was applied to calculate OR_P (RR_P) and its 95% CI. In contrast, the Dersimonian–Laird formula (random model) was applied to calculate OR_P (RR_P) and its 95% CI when there was significant heterogeneity among the included studies ($P \leq 0{\cdot}10$). Finally, the *u*-test of OR_P (RR_P) was performed.

Statistics were performed with the software RevMan 4.3.1. (The Nordic Cochrane Centre, Copenhagen, Denmark). To evaluate publication bias, we set the OR (RR) of included studies as x-co-ordinate and 1/SE as y-co-ordinate to generate a funnel plot.

Results

Search results

The search strategy identified 53 potentially relevant studies, five of which were acquired through reference sections of relevant publications or manual search. A flow chart summarizing search results is provided in Fig. 1. Four publications were excluded because it was clear from the titles that they did not fulfil the selection criteria. From the remaining 49 publications, 21 reviews were excluded. Twenty-eight articles were read in full, independently by two investigators, to assess their accordance with the predefined inclusion criteria. One study was excluded because of research data overlap.[6] Three cohort studies were excluded because of their retrospective design.[7–9] Another two publications were excluded because of multiple IVF procedures involved.[10,11] Finally, 22 studies were included in the meta-analysis, eight of which were case–control studies,[12–19] and 14 cohort studies.[4,20–32]

Systematic review

Case–control studies. The eight case–control studies included in the systematic review were published between 1993 and 2008. They reported data on 1077 recurrent aborters, all of whom were Caucasian. The main data are displayed in Table 1. Most aborters had two or more consecutive miscarriages ($n = 1341$), while women without history of abortion ($n = 747$), female blood donors ($n = 300$) and parous women ($n = 284$) served as most of controls. In six studies,[12–14,16,17,19] both thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were detected. Only in one

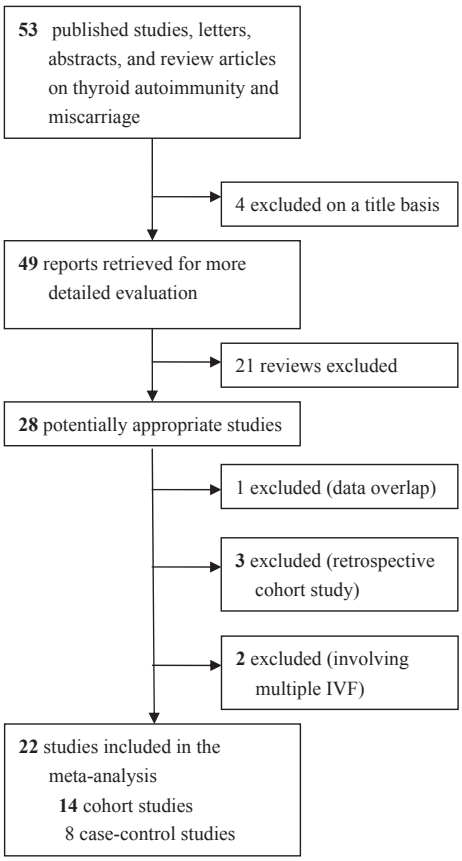

Fig. 1 Flow chart for the systematic review and meta-analysis.

Table 1. Primary information of the included case–control studies

Author and year	Country	Thyroid autoantibodies	Abortion group		Control group			
			Consecutive abortions	Positive rate of TA n/N (%)	Control definition	Positive rate of TA n/N (%)	OR	95% CI
Pratt,1993[12]	USA	TgAb, TPOAb	≥3	14/45 (31)	Blood donors	19/100 (19)	1·93	0·86–3·37
Bussen,1997[13]	Germany	TgAb, TPOAb	≥3	11/28 (39)	No abortions	2/28 (7)	8·41	1·70–42·8
Esplin,1998[14]	USA	TgAb, TPOAb	≥3	22/74 (29)	≥3 pregnancies	28/75 (37)	0·71	0·50–1·01
Kutteh,1999[15]	USA	TgAb, TPOAb, TmAb	≥2	158/700 (23)	Blood donors	29/200 (15)	1·72	1·12–2·65
Dendrinos,2000[16]	Greece	TgAb, TPOAb	≥3	11/30 (37)	Parous	2/15 (13)	3·76	0·71–19·87
Bagis,2001[17]	Turkey	TgAb, TPOAb	≥1	54/162 (33·3)	No abortions	54/714 (8)	5·98	3·98–9·38
Marai,2004[18]	Israel	TPOAb	≥3	8/38 (21)	Infertile, no abortions	0/20 (0)	11·43	0·62–209·03
Iravani,2008[19]	Iran	TgAb, TPOAb	≥3	157/641 (24·5)	Parous	34/269 (12·6)	2·24	1·5–3·35
In total	–	–	–	435/1718 (25·3)	–	168/1421 (11·8)	2·55	1·42–4·57

TA, thyroid autoantibodies; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TmAb, thyroid microsome antibody.

study[15] were thyroid microsome antibody (TmAb), TgAb and TPOAb all tested. One study [18] measured only TPOAb.

Six studies reported the prevalence of TAI in women with recurrent spontaneous abortion (RSA, three or more consecutive miscarriages), of which five studies [12,13,16,18,19] concluded that the prevalence of TAI in RSA women is significantly higher than in controls. Only one study [14] claimed that the prevalence of TAI in RSA women is lower than in controls. Kutteh [15] compared the TAI prevalence of women that have two or more consecutive miscarriages (n = 700) with female blood donors (n = 200) and found the prevalence of TAI in aborters to be significantly higher (23% *vs* 15%). Bagis [17] studied the TAI prevalence of women (n = 162) with and without (n = 714) a history of abortion and concluded that the prevalence of TAI in aborters is far higher (33·3% *vs* 8%).

Cohort studies. Fourteen prospective cohort studies published from 1990 to 2009 assessed the influence of TAI on pregnancy outcome. The characteristics of the cohort studies are listed in Table 2. In all, 598 TA-positive pregnancies and 4870 TA-negative pregnancies were followed up. The result was that 120 aborted in the TA-positive group, while 313 aborted in the TA-negative group. Only one study[24] was undertaken in Asia. Among the 14 cohort studies, four[25,30–32] observed pregnancies in which assisted reproduction technology (ART) had been applied, while the rest surveyed spontaneous pregnancies.

Diversity in the methodology applied to measure thyroid autoantibodies was also observed. Both TPOAb and TgAb were determined in five studies.[20,22,28,29,32] In three studies,[4,21,23] TgAb, TmAb and TPOAb were detected, whereas only TPOAb was tested in five studies.[25–27,30,31] In another study,[24] only TmAb was detected. Nine studies drew a conclusion that TAI increased the risk of miscarriage. However, according to the remaining five studies,[23,25,28,29,32] the abortion rate in the TAI group was higher than in controls, but not significantly.

Table 2. Primary information of included cohort studies

Author and year	Country	Thyroid autoantibodies	Abortion rate in TA+ women n/N (%)	Abortion rate in TA− women n/N (%)	RR	95% CI
Stagnaro-Green,1990[4]	USA	TgAb, TmAb, TPOAb	17/100 (17)	33/392 (8)	2·02	1·17–3·47
Glinoer,1991[20]	Belgium	TgAb, TPOAb	6/45 (13)	20/603 (3)	4·02	1·70–9·51
Lejeune,1993[21]	Belgium	TgAb, TmAb, TPOAb	5/23 (22)	16/340 (5)	4·62	1·86–11·49
Pratt,1993[22]	USA	TgAb, TPOAb	8/13 (62)	4/29 (14)	4·46	1·63–12·20
Glinoer,1994[23]	Belgium	TgAb, TmAb, TPOAb	6/87 (6·9)	20/606 (3·3)	2·09	0·86–5·06
Iijama,1997[24]	Japan	TmAb	13/125 (10)	52/951 (5)	1·90	1·07–3·39
*Muller,1999[25]	Netherlands	TPOAb	4/12 (33)	8/42 (19)	1·75	0·63–4·83
*Poppe,2003[30]	Belgium	TPOAb	9/17 (52·9)	20/87 (23·0)	2·30	1·28–4·16
Sieiro,2004[26]	Brazil	TPOAb	3/29 (10·3)	10/505 (2·0)	5·22	1·52–17·96
*Negro,2005[31]	Italy	TPOAb	11/21 (52)	82/318 (26)	2·03	1·30–3·18
Negro,2006[27]	Italy	TPOAb	8/58 (13·8)	21/869 (2·4)	5·71	2·64–12·32
Todorova,2008[28]	Bulgaria	TgAb, TPOAb	19/30 (63·3)	4/12 (33·3)	1·90	0·82–4·42
*Kilic,2008[32]	Turkey	TgAb, TPOAb	3/10 (30)	3/16 (18·7)	1·60	0·40–6·43
Sezer,2009[29]	Turkey	TgAb, TPOAb	8/28 (28·6)	20/100 (20)	1·43	0·71–2·89
In total	–	–	120/598 (20·1)	313/4870 (6·4)	2·31	1·90–2·82

The abbreviations are the same as in Table 1.
*Pregnancy achieved by assisted reproductive technologies.

Meta-analysis

The funnel plot (not shown) indicated that there was no significant publication bias. The main results of the meta-analysis are summarized in Table 3. The heterogeneity test of eight case–control studies suggested that the random model should be applied ($P < 0{\cdot}00001$). The pooled OR was 2·55 (95% CI 1·42–4·57, $P = 0{\cdot}002$), which means thyroid autoimmunity was more prevalent in recurrent aborters. Heterogeneity test of 14 cohort studies suggested a fixed model should be applied ($P = 0{\cdot}25$). The pooled RR was 2·31 (95% CI 1·90–2·82, $P < 0{\cdot}00001$), which implies that thyroid-autoantibody-positive women were more liable to miscarriage.

Discussion

The present meta-analysis attempts to provide an estimate of the risk of miscarriage for euthyroid women in the presence of thyroid autoantibodies. According to the present meta-analysis, TAI is significantly associated with miscarriage. However, it does not mean that the relationship is causal. Many factors could affect the outcome of pregnancy, of which TAI is just one aspect. The factors affecting the result of this meta-analysis will be discussed in the following sections.

Other autoimmune diseases

Miscarriage is associated with several autoimmune diseases, especially APS and SLE. The abortion rates of pregnancies complicated with APS and SLE are 7–8% and 22%, respectively.[3] Moreover, autoimmune diseases can lead to stillbirth in the middle and late stages of gestation. In fact, TA may coexist with antiphospholipid antibodies.[33] Hence, subjects with other autoantibodies were excluded or analysed separately in all the studies included in this meta-analysis.

Autoimmunity against foeto-placental unit

TAI could be an indication of autoimmune dysfunction. In this way, autoimmunity against the foeto-placental unit is heightened. The CD5/20 + B-lymphocyte counts of RSA women are much higher than those of women without a history of miscarriage.[34] T lymphocytes of TAI women function abnormally. T-lymphocyte infiltration of the uterine endometrium leads to decreased secretion of interleukin-4, interleukin-10 and increased secretion of γ-interferon.[35] Moreover, pregnancy complicated by thyroid microchimerism is prone to abortion in some animal models.[36] If a pregnant mouse is immunized with human thyroglobulin, TgAb will be detected in the serum. Moreover, TgAb can bind with mouse placenta antigen and lead to a decrease in mouse foeto-placental unit weight.[37]

Table 3. Meta-analysis of studies on association between TAI and miscarriage

	Heterogeneity test	Model type	Pooled OR(RR) (95% CI)	OR(RR) *significance test*
Case–control studies	$\chi^2 = 36{\cdot}89$, $P < 0{\cdot}000\,01$	Random effect model	2·55 (1·42–4·57)	$Z = 3{\cdot}13$, $P = 0{\cdot}002$
Cohort studies	$\chi^2 = 16{\cdot}01$, $P = 0{\cdot}25$	Fixed effect model	2·31 (1·90–2·82)	$Z = 8{\cdot}35$, $P < 0{\cdot}00001$

Direct involvement of TA

If TA causes miscarriage directly, then a dose-dependent effect between the titre of TA and risk of abortion would be expected. However, most studies have not paid attention to the titre of TA. Some studies declare that there is no significant association between the titre of TA and risk of abortion.[4,24] Only one study[38] claimed that the TPOAb titre and affinity of aborters were significantly higher in miscarriage than in full-term pregnancies.

Nonimmunological factors

There are some nonimmunological differences between TA-positive and TA-negative women, such as age and thyroid function. A cohort study observed that euthyroid women with positive TPOAb were 6 years older than women without TPOAb on average. The serum TSH of TPOAb-positive women was higher than that in TPOAb-negative women.[39] All these factors may contribute to the elevated risk of miscarriage.

Age. Owing to the correlation between TAI and infertility, the fertility of TAI women is slightly impaired, which in turn leads to higher age of pregnancy. It has been clarified that higher age is an independent risk factor for miscarriage.[2] Most TA-positive women are older than TA-negative women. There is found in most of the studies included in this meta-analysis (Table 4). In some studies, age data are not provided. According to a weighted mean difference (WMD) calculation, TA-positive women are 1·29 years older than TA-negative women (95% CI 0·43–2·16, $P = 0{\cdot}003$). Although the

Table 4. Age of TA-positive women when compared with TA-negative women [$\bar{x}$±s or M(Quartile range)]

	Age (year)			
	TA+ women	TA− women	Difference	*P*
Bagis[17]	27·7 ± 6·2	25·9 ± 5·2	+1·8	<0·0009
Stagnaro -Green[4]	33 (25–40)	34 (21–41)	−1·0	NS
Glinoer[20]	29·3 ± 1	27·3 ± 1	+2·0	<0·001
Lejeune[21]	28·2 ± 9·5	27·2 ± 6·8	+1·0	0·06 (NS)
Pratt[22]	33 ± 2·9	34 ± 3·4	−1·0	NS
Glinoer[23]	30 ± 5	27 ± 6	+3·0	<0·001
Iijama[24]	30·2 ± 4·8	30·0 ± 4·3	+0·2	NS
Muller[25]	32·4 ± 3·3	32·4 ± 4·4	0	NS
Negro[27]	30 ± 6	28 ± 5	+2·0	<0·05
WMD	+1·29 (95% CI 0·43–2·16)			$P = 0{\cdot}003$

age difference seems negligible, the risk of abortion increases dramatically as a woman ages. The prevalence of miscarriage in women aged 25–29 is 10·7%. This increases to 14·2% in women aged 30–34 and rises as high as 26·2% in women aged 35–39.[40] Therefore, the slightly higher age is a potential cause of miscarriage in TA-positive pregnancies.

Thyroid function. With the traditionally used, but in our view too high, TSH cut-off value of 4·5 mU/l, the prevalence of hypothyroidism has been found to be 1·1% and 4·5% in black and white pregnant women, respectively.[41] Factors that are thought to be associated with increased likelihood of mild hypothyroidism include white race, high iodine intake and positive antithyroid antibodies. Hypothyroidism may lead to infertility and increases the risk of miscarriage.[2] The risk of abortion caused by overt and subclinical hypothyroidism is similar. If hypothyroidism is diagnosed in the early stages of gestation, levothyroxine ($L\text{-}T_4$) replacement therapy should be initiated in time to avoid an unfavourable pregnancy outcome. The abortion rate falls to 4% if hypothyroidism is managed with $L\text{-}T_4$ replacement therapy.[41]

Subjects with overt thyroid dysfunction were excluded in all of the studies in this meta-analysis. However, some studies did not provide TSH data. Glinoer[23] reported that the TSH increment in the first trimester of pregnancy complicated with TAI was significantly higher than in controls, while serum free thyroxine (FT_4) in the third trimester was significantly lower. Bagis[17] concluded that if the outcome of pregnancy complicated with TAI was miscarriage, the serum TSH was higher and FT_4 lower compared to TA-negative pregnant women. During gestation after ART, the TSH increment and FT_4 decrement were much more notable in TA-positive women, which indicates insufficient compensatory ability of the thyroid to the hyperestrogenism induced by ovarian hyperstimulation and pregnancy.[6] Although within the normal range, the TSH of TA-positive women was slightly higher than that of TA-negative women (Table 5). On WMD calculation, the TSH of TA-positive women was 0·61 mIU/l higher than that of TA-negative women (95% CI 0·51–0·71, $P < 0·00001$), which indicates that insufficiency of thyroid compensatory ability or mild hypothyroidism is another potential cause of miscarriage in TA-positive pregnancies.

Negro[27] reported that euthyroid pregnant women who are positive for TPOAb develop impaired thyroid function, which is associated with an increased risk of miscarriage and premature deliveries. Substitutive treatment with $L\text{-}T_4$ was able to lower the chance of miscarriage and premature delivery.[27] Vaquero[42] compared intravenous immunoglobulin (IVIG) therapy ($n = 11$) and $L\text{-}T_4$ replacement therapy ($n = 16$) for TAI during pregnancy. The conclusion was that the abortion rate in the $L\text{-}T_4$ replacement group was significantly lower than in the IVIG group (19% *vs* 45%). Will $L\text{-}T_4$ intervention in euthyroid women with TAI improve the pregnancy outcome? This is still subject to further confirmation from more prospective clinical trials.

Table 5. TSH levels in women with TA compared with those without [$\bar{x}\pm s$, $\bar{x}$, or M(Quartile range)]

	TSH (miu/l)			
Author	TA+ women	TA− women	Difference	*P*
Bagis[17]	1·86 ± 1·8	1·17 ± 0·9	+0·69	<0·000 1
Stagnaro -Green[4]	2·35	1·60	+0·75	0·12 (NS)
Glinoer[20]	1·4	0·9	+0·5	<0·01
Glinoer[23]	1·6	0·9	+0·7	<0·001
Muller[25]	3·5 ± 3·6	1·7 ± 0·9	+1·8	<0·05
Sieiro[26]	1·9 (1·2–3·3)	1·1 (0·6–1·8)	+0·8	0·001
Negro[27]	1·7 ± 0·4	1·1 ± 0·4	+0·6	<0·05
WMD	+0·61 (95% CI 0·51–0·71)			$P < 0·00001$

Future prospects

TAI is closely related to miscarriage. The underlying mechanism consists of four aspects: heightened autoimmunity against the foeto-placental unit, direct involvement of TA, higher age and mild hypothyroidism. Regarding the first three aspects, there is no safe and efficient intervention therapy at the present time. Nevertheless, intervention regarding the last aspect is much easier. The serum TSH of TA-positive women is slightly higher than that of TA-negative women. The optimal TSH range during gestation is 0·4–2·0 mIU/l.[42] As TSH reference ranges vary in different laboratories, L-thyroxine replacement during pregnancy, aiming for a TSH at the lower third of the normal range, is strongly recommended. The TSH levels of women planning for pregnancy should also be titrated to this lower target value, if possible.

Acknowledgement

Nothing to declare.

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