

Original Article

Effect of thyroid autoimmunity *per se* on assisted reproduction treatment outcomes: A meta-analysisHui He^{a, b}, Shuang Jing^{a, b}, Fei Gong^{a, b, c}, Yue Qiu Tan^{a, b, c}, Guang Xiu Lu^{a, b, c}, Ge Lin^{a, b, c, *}^a Institute of Reproductive & Stem Cell Engineering, Central South University, Changsha, China^b Key Laboratory of Reproductive & Stem Cell Engineering, Ministry of Health, Changsha, China^c Reproductive Center, Reproductive & Genetic Hospital of CITIC-Xiangya, Changsha 410078, China

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ABSTRACT

Objective: Thyroid autoimmunity (TA) is the most prevalent autoimmune disease in women of reproductive age and is often accompanied by subclinical hypothyroidism (SCH). Both TA and SCH have been associated with adverse pregnancy outcomes, but their relative influence is unclear. Therefore, we carried out a meta-analysis to evaluate the sole effect of TA on pregnancy outcomes in euthyroid women undergoing assisted reproductive technology.

Materials and Methods: Literature searches were conducted on Pubmed, EMBASE, and the Cochrane Controlled Trials Register Database from inception to May 2014.

Results: In euthyroid women whose SCH status is unknown, those with positive antithyroid antibodies (ATA) had a higher miscarriage rate [pooled relative risk (RR) = 1.638; 95% confidence interval (CI), 1.228–2.185] and a lower delivery rate (pooled RR = 0.856; 95% CI, 0.759–0.965) than those with negative ATA. Clinical pregnancy rates were similar between groups. However, clinical pregnancy rate, miscarriage rate, and delivery rate were all comparable between ATA-positive and ATA-negative euthyroid women without SCH.

Conclusion: TA *per se* does not impair assisted reproductive treatment outcomes in women without SCH. Copyright © 2016, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Thyroid autoimmunity (TA) is defined as the presence of anti-thyroid antibodies (ATA), specifically antithyroglobulin (anti-TG) and antithyroid peroxidase (anti-TPO). It is the most prevalent autoimmune disease in women of reproductive age, with a prevalence of 5–15% [1], and in women with infertility, the prevalence is 10–31% [2]. TA was shown to be associated with many kinds of adverse obstetric outcomes, such as preterm delivery, placental abruption, and low birth weight [3]. The association with miscarriage was first reported in 1990 [1]. Subsequently, the number of studies on the association between TA and miscarriage increased substantially, however, the results were conflicting. Although several meta-analyses showed that TA was associated with a higher

risk of miscarriage in women who had conceived spontaneously [4,5], the association between TA and miscarriage was still unclear in infertile women undergoing assisted reproductive technologies (ART).

TA has been found to be related to subclinical hypothyroidism (SCH) [6–8], which is characterized by increased serum thyroid stimulating hormone (TSH) concentration but normal concentration of free thyroxine (FT4) [9]. A study investigated 6288 euthyroid women with no history of thyroid disorder undergoing their first *in vitro* fertilization (IVF) cycle and found that 26% of ATA-positive women also had SCH compared with 16.8% of ATA-negative women, suggesting that women with positive ATA were more likely to have SCH [8]. In another study [10], thyroid function values and anti-TPO status were measured in 668 pregnant women without known thyroid disease to determine the 1st-trimester thyroid function values and associations with anti-TPO status. It was found that TSH concentration in anti-TPO-positive women was nearly double that of anti-TPO-negative women (1.1 mIU/L vs.

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1.8 mIU/L). In addition, it has also been shown that TSH values prior to ART treatment, at 12 and 30 weeks after conception, were all significantly higher in anti-TPO positive women [11].

However, SCH has also been reported to be associated with a higher risk of miscarriage [3]. It is therefore difficult to determine if miscarriage resulted from TA or underlying SCH, especially when previous meta-analyses [4,12] only included euthyroid women without overt thyroid disorder, and did not take SCH into consideration. We undertook this meta-analysis again to observe the effect of TA *per se* on pregnancy outcomes in euthyroid women undergoing ART, and also the effect of excluding patients with SCH.

Materials and methods

Search strategy and identification of literature

Literature searches were conducted via Pubmed, EMBASE, and the Cochrane Controlled Trials Register Database from inception to May 2014. A combination of medical subject headings (MeSH) and text words were used for search: “Fertilization in Vitro [MeSH],” “Reproductive Techniques, Assisted [MeSH],” “Sperm Injections, Intracytoplasmic [MeSH],” “IVF,” “ART,” “ICSI,” “Thyroid Gland [MeSH],” “autoantibodies [MeSH],” “(Thyroid) AND antibody,” “thyroglobulin [MeSH Terms],” “thyroid microsomal antibodies,” [Supplementary Concept],” “thyroperoxidase,” “thyroid peroxidase,” “Thyroid Autoimmunity,” “Pregnancy Outcome[MeSH Terms],” “Pregnancy[MeSH Terms],” “Abortion, Spontaneous[MeSH Terms],” “Delivery, Obstetric[MeSH Terms],” “abortion,” “miscarriage,” “labor,” “delivery,” “parturition.” The search items were set by the authors and a professional information retrieval practitioner. No language restrictions were placed on any search. A manual search was also applied to identify as many relative articles as possible.

Study selection and outcome measures

Studies were selected if the target population was euthyroid women undergoing ART whose level of thyroid function and ATA was measured. “Euthyroid” women were defined as those with normal concentrations of triiodothyronine (T3) and thyroxine (T4), with no overt thyroid disorders, and with no history of thyroid diseases. To eliminate the influence of failed IVF treatment on thyroid function and pregnancy, studies involving multiple IVF procedures were excluded. In addition, studies were excluded if participants had SCH, or the data of SCH patients could not be separated.

Studies were included if they were a cohort design, including prospective and retrospective, comparing ATA-positive women with ATA-negative controls. There were no limitations for language or publications type, therefore, conference abstracts could be included.

The outcome measures of interest were clinical pregnancy, miscarriage, and delivery rates. For the purpose of this review, clinical pregnancy was defined as the observation of a pregnancy sac on ultrasound at least 4 weeks after embryo transfer. Miscarriage was defined as the loss of clinical pregnancy.

Data extraction

Two reviewers independently selected eligible studies and extracted the relevant data as defined below. Any disagreements were resolved via discussion. A standardized data extraction form was used for data extraction and included general characteristics of the study (author, year of publication, country, study design, sample size, study period), characteristics of the study groups, their

comparability on baseline characteristics (age, body mass index, etiology of infertility, number of oocytes retrieved and embryos transferred, hormone concentrations, thyroid function tests), methodology (ART types, protocol, definition of measure outcomes, thyroid autoantibodies and hormone measurement method, threshold and time of measurement, study quality), and outcomes (clinical pregnancies, miscarriages, deliveries).

The Newcastle–Ottawa Scale [13] was applied for quality assessments, including selection of cases and controls, comparability at baseline, and completeness of follow up. A quantitative appraisal of overall quality of each observational study was obtained, and scores ranged from 0 to 9.

Statistical analysis

If the chi-square test showed there was no significance of heterogeneity among the included studies ($p > 0.05$), the fixed model was applied to calculate the pooled relative risk (RR) and its 95% confidence interval (CI). When heterogeneity among the included studies was significant ($p < 0.05$), the random model was applied to calculate the pooled RR and its 95% CI. Egger's test was applied to assess the publication bias.

Statistical analyses were performed using Stata/SE 12.0 for Windows (StataCorp. LP, College Station, TX, USA). The study was completed in accordance with the standards of meta-analysis of observational studies in epidemiology groups [14].

Results

Search results

The search strategy identified 300 potentially relevant studies, and a flowchart summarizing the search results is provided (Figure 1). Of these 300 publications, 280 were excluded on the basis of title and abstract. The remaining 20 publications were read independently by two reviewers in full. Among these, 10 articles were excluded because the women were not undergoing their first ART procedure [15–24], one because no data were given [25], and one because thyroid function was not tested [26]. Of the eight articles remaining [8,11,27–32], four were used in the final analysis [8,27,28,32] once patients with SCH were excluded.

The eight studies included in the systematic review were published between 2003 and 2014 and report data on 5286 infertile women including 675 ATA-positive and 4611 ATA-negative women (Table 1). In the final analysis, four studies were included with data on 1855 infertile women including 292 ATA-positive and 1563 ATA-negative women. The quality assessments of all studies are presented in Table 2.

Outcomes

Clinical pregnancy rate

In subfertile euthyroid women whose SCH status is unknown undergoing ART, positive-ATA women showed a similar clinical pregnancy rate compared with negative-ATA women (fixed-effects RR = 0.967; 95% CI, 0.883–1.059; $p = 0.467$; Figure S1). The heterogeneity test result was low ($I^2 = 11.2\%$), and Egger's test result was not significant ($p = 0.960$).

Similar results were shown in subfertile euthyroid women without SCH undergoing ART (fixed-effects RR = 0.993; 95% CI, 0.853–1.155; $p = 0.923$; Figure 2). Again, heterogeneity was low ($I^2 = 0\%$) and Egger's test result was nonsignificant ($p = 0.782$).

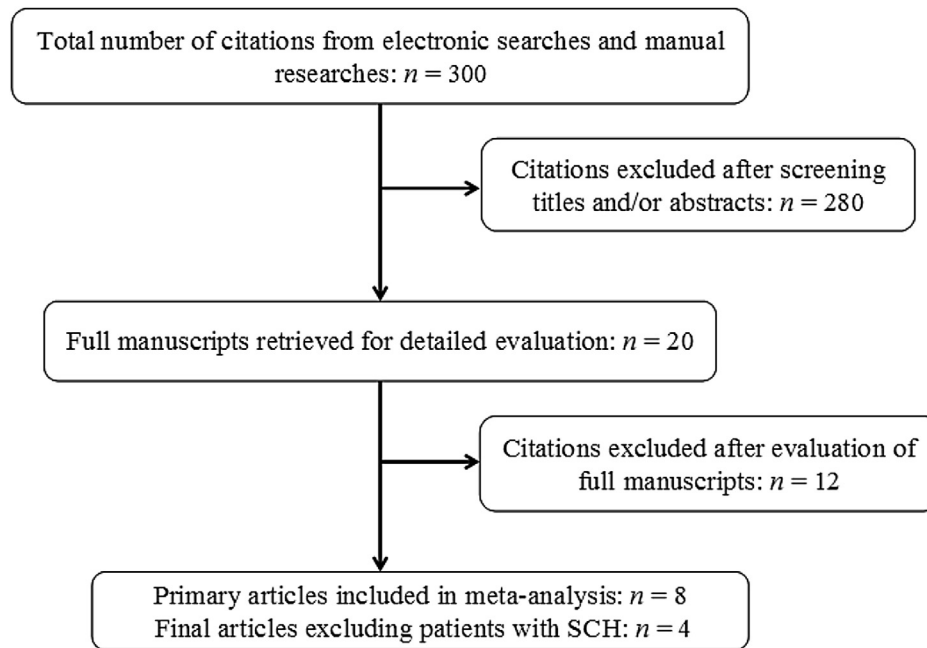


Figure 1. Study selection process for meta-analysis of effect of thyroid autoimmunity on assisted reproduction treatment outcomes. SCH = subclinical hypothyroidism.

Miscarriage rate

In subfertile euthyroid women whose SCH status is unknown undergoing ART, women with positive ATA had a significantly higher miscarriage rate compared with those with negative ATA (fixed-effects RR = 1.580, 95% CI, 1.297–1.925; $p < 0.001$; [Figure S2](#)). No sign of heterogeneity was detected ($I^2 = 0\%$), and Egger's test showed no sign of publication bias ($p = 0.428$).

However, in subfertile euthyroid women without SCH undergoing ART, the women with positive ATA showed a similar miscarriage rate to those with negative ATA (fixed-effects RR = 1.445; 95% CI, 0.970–2.154; $p = 0.070$; [Figure 3](#)). No sign of heterogeneity was detected ($I^2 = 0\%$), and Egger's test showed no sign of publication bias ($p = 0.158$).

Delivery rate

In subfertile euthyroid women whose SCH status is unknown undergoing ART, women with positive ATA had significantly lower delivery rates than those with negative ATA (fixed-effects RR = 0.856; 95% CI, 0.759–0.965; $p = 0.011$; [Figure S3](#)). The heterogeneity test found low heterogeneity ($I^2 = 28.3\%$) and Egger's test found no sign of publication bias ($p = 0.614$).

However, in subfertile euthyroid women without SCH undergoing ART, women with positive ATA showed a similar delivery rate to those with negative ATA (fixed-effects RR = 0.935; 95% CI, 0.785–1.112; $p = 0.446$; [Figure 4](#)). No sign of heterogeneity was detected ($I^2 = 0\%$) and Egger's test found no sign of publication bias ($p = 0.955$).

Discussion

The present meta-analysis sought to estimate the effect of ATA status alone on pregnancy outcomes in euthyroid women undergoing ART. It was found that in subfertile euthyroid women whose SCH status is unknown, ATA was associated with increased miscarriage rate and decreased delivery rate, but was not related to pregnancy rate. In subfertile euthyroid women without SCH, the present study did not detect a significant effect of ATA status on pregnancy rate, miscarriage rate, and delivery rate.

An unexpected result was that the pooled miscarriage and delivery rate in subfertile euthyroid women whose SCH status is unknown were contrary to those in subfertile euthyroid women without SCH. We propose three reasons for this: (1) that the number of studies on women without SCH may have been insufficient to detect a difference; (2) that TA *per se* may not affect miscarriage and delivery rates; or (3) it may only occur in women with high concentrations of TSH.

Our findings could provide useful inferences on the importance of TA on miscarriage, although its direct influence on miscarriage is still unclear. The most popular hypothesis is that TA exerts its effect in both a TSH-independent and TSH-dependent manner [33]. The former implies that ATA level may be an indication of autoimmune dysfunction such as increased endometrial T cell population, hyperactivity, and elevated mass of natural killer cells and activated polyclonal B cells. In ATA-positive women, these immunological factors were activated, and attacked trophoblast-placental tissue, leading to miscarriage and fetal wastage. One study [18] concluded that ATA *per se* may play a role, because it interferes with fertilization and subsequent embryo development or implantation by binding to the surface of the egg and/or embryo or attacking the endometrium. However, evidence of a TSH-independent mechanism was limited. First, there was no dose-dependent effect between the titer of ATA and miscarriage [1]. In addition, the effect of immunological therapy is still in doubt. Only one study [34] compared the effect of heparin/aspirin therapy alone versus heparin/aspirin in combination with intravenous immunoglobulin (IVIg) immunotherapy on IVF outcomes of patients with positive ATA. The study found that IVIg was linked to increased live birth rate, but had no effect on miscarriage rate. Finally, there was no direct evidence to prove any of the above proposed mechanisms.

Owing to the association between TSH levels and TA, a TSH-dependent mechanism was also proposed. Our study may provide evidence for the existence of a TSH-dependent mechanism, but the pathogenesis is still unclear. It has been found that TSH could stimulate the immune system by increasing the proliferative capacity and activity of natural killer cells, which might be responsible for miscarriage [35]. Another hypothesis was that it was high-

Table 1
Characteristics of the included studies.

Source	Inclusion criteria, patient characteristics	Study groups	Outcome measures	ATA type, threshold
Karacan et al [28], Turkey, 253 women, prospective, ICSI	Women <42 y, with normal TSH and fT4, ACA(−) and LAC(−), normal uterine cavity, no adjuvant treatment (thyroid hormones and glucocorticoids) during study, produced at least three oocytes in response to ovarian stimulation, first ART procedure, men with morphologically normal spermatozoa	n = 34 ATA(+) n = 219 ATA(−)	Implantation rate, positive pregnancy test rate, biochemical pregnancy rate, clinical pregnancy rate, miscarriage rate, ongoing pregnancy rate	TPO-Ab and Tg-Ab, threshold <35 IU/ml (TPO-Ab), <115 IU/ml (Tg-Ab)
Chai et al [8], Hong Kong, 627 women, prospective, IVF/ICSI	First IVF/ICSI cycles, serum samples were taken 6 mo prior to ovarian stimulation, women with history of thyroid disease, cycles for PGD and using donor oocytes were excluded	n = 89 ATA(+) and euthyroid n = 33 ATA(+) and subclinical n = 419 ATA(−) and euthyroid n = 86 ATA(−) and subclinical	Clinical pregnancy rate, miscarriage rate, live birth rate	TPO-Ab and Tg-Ab, threshold <9 IU/ml (TPO-Ab), <4 IU/ml (Tg-Ab)
Kilic et al [30], Turkey, 79 women, prospective, ICSI	First ART procedure, women with thyroid pathologies, endocrine or systemic diseases, history of miscarriage were excluded	n = 31 ATA(−) n = 23 ATA(+) without treatment n = 23 ATA(+) with treatment	Biochemical pregnancy rate, clinical pregnancy rate	TPO-Ab and Tg-Ab, threshold <34 IU/ml (TPO-Ab), <115 IU/ml (Tg-Ab)
Poppe et al [32], Belgium, 234 women, prospective, IVF/ICSI	First ART procedure, women with overt thyroid dysfunction were excluded	n = 32 ATA(+) n = 202 ATA(−)	Pregnancy rate, miscarriage rate, delivery rate	Only TPO-Ab, threshold <100 kU/L
Negro et al [11], Italy, 416 women, retrospective, IVF/ICSI	First ART procedure, women with overt thyroid dysfunction or age >35 y were excluded	n = 42 ATA(+) n = 374 ATA(−)	Pregnancy rate, miscarriage rate, delivery rate	Only TPO-Ab, threshold <100 kU/L
Chi et al [29], China, 2419 women, retrospective, IVF	First IVF procedure, euthyroid infertile women	n = 276 ATA(+) n = 2143 ATA(−)	Clinical pregnancy rate, miscarriage rate, live birth rate	TPO-Ab and Tg-Ab, threshold was not clearly stated
Tan et al [27], Greece, retrospective, 835 women, ICSI	First ICSI procedure, euthyroid healthy women receiving ART exclusively for male infertility reasons, women with reported thyroid disease, intake of thyroid medication and incomplete questionnaire data were excluded	n = 110 ATA(+) n = 725 ATA(−)	Clinical pregnancy rate, miscarriage rate, birth rate, gestational age, preterm rate, very preterm rate	TPO-Ab and Tg-Ab, threshold <100 U/L (TPO-Ab), <100 U/L (Tg-Ab)
Negro et al [31], Italy, prospective, 484 women, IVF/ICSI	First ART procedure, women with overt thyroid dysfunction were excluded	n = 36 ATA(+) with treatment n = 36 ATA(+) without treatment n = 412 ATA(−)	Pregnancy rate, miscarriage rate, delivery rate	Only TPO-Ab, threshold <100 kU/L

ART = assisted reproductive technologies; ATA = positive antithyroid antibodies; ICSI = intracytoplasmic sperm injection; IVF = *in vitro* fertilization; LAC = lupus anticoagulant; SCH = subclinical hypothyroidism; Tg-Ab = antibodies against thyroglobulin; TPO-Ab = antibodies against thyroid peroxidase; TSH = thyroid stimulating hormone.

normal TSH values, rather than ATA levels, that lead to miscarriage [11]. This could account for the difference in the effect of ATA between subfertile euthyroid women whose SCH status is unknown and subfertile euthyroid women without SCH in our meta-analysis.

The evidence for the effect of SCH on miscarriage is more compelling than that for TA. First, in a recent meta-analysis [3], it

was found that SCH was associated with a significantly increased risk of pregnancy loss, including miscarriages, stillbirths, and perinatal deaths. Second, the correlation between SCH and miscarriage was more robust. It was proposed that mothers' demand for thyroid hormone increased during gestation, resulting in a more severe degree of SCH and a decrease in serum

Table 2
Quality assessment of included studies.

Source	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Incident disease		Assessment of outcome	Length of follow up	Adequacy of follow up	
Karacan et al [28]	☆	☆	☆	☆	☆☆	—	☆	☆	8
Chai et al [8]	☆	☆	☆	☆	☆☆	—	☆	☆	8
Kilic et al [30]	☆	☆	☆	☆	☆☆	—	☆	☆	8
Poppe et al [32]	☆	☆	☆	☆	—	—	☆	☆	6
Negro et al [11]	☆	☆	☆	☆	☆☆	—	☆	☆	8
Chi et al [29]	☆	☆	☆	☆	—	—	☆	—	5
Tan et al [27]	☆	☆	☆	☆	☆☆	—	☆	☆	8
Negro et al [31]	☆	☆	☆	☆	☆☆	—	☆	☆	8

A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars (☆☆) can be given for comparability.

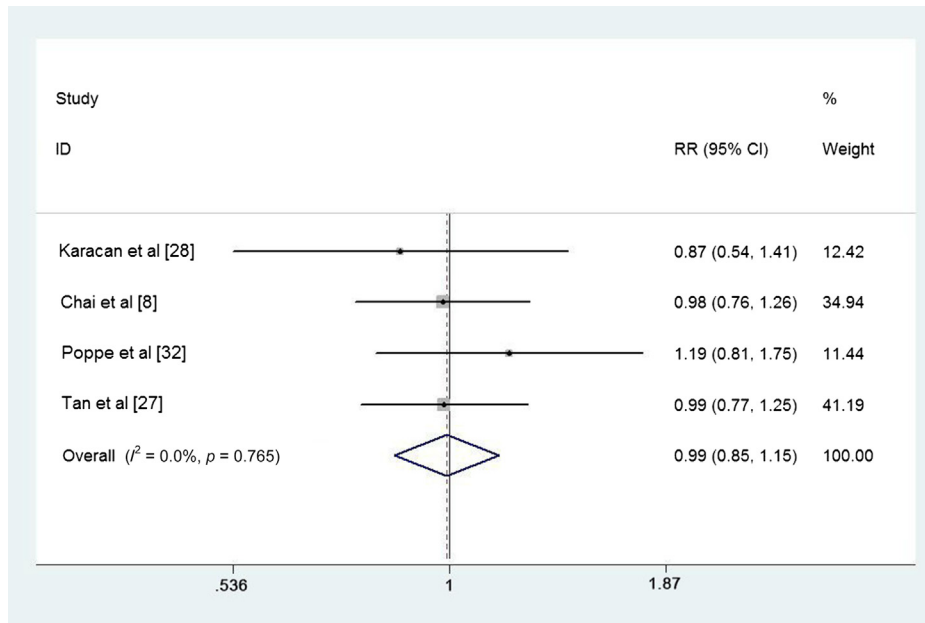


Figure 2. Forest plot of risk ratios (RR) and 95% confidence interval (CI) of pooled studies comparing ATA-positive patients with ATA-negative controls in subfertile euthyroid women without SCH undergoing ART according to clinical pregnancy rate. ART = assisted reproductive technologies; ATA = positive antithyroid antibodies; SCH = subclinical hypothyroidism.

concentrations of T3 and T4. However, the fetuses were sensitive to changes in T3 and T4 serum concentrations in mothers. One study reported that fetal concentrations of T3 and T4 were 100 times lower than those in maternal serum, and serum FT4 concentrations were about one-third in their euthyroid mothers [36]. As a result, even a slight reduction in maternal serum FT4 concentrations may result in a significant decrease in fetal concentration, which may lead to the loss of pregnancy. Finally, a meta-analysis of three randomized controlled trial with data on 220 patients found that levothyroxine supplementation resulted in a significantly higher

delivery rate and lower miscarriage rate in women with SCH undergoing ART [3].

Two meta-analyses on the effect of TA on women undergoing ART have been reported previously, but the results were conflicting. Although one study [5] found no association between TA and miscarriage in women undergoing IVF, another [12] reported that TA was associated with a higher risk of miscarriage in euthyroid, subfertile women undergoing IVF. The contrasting results may be attributable to different study populations and design: whereas the meta-analysis by Toulis et al [12] included only prospective studies

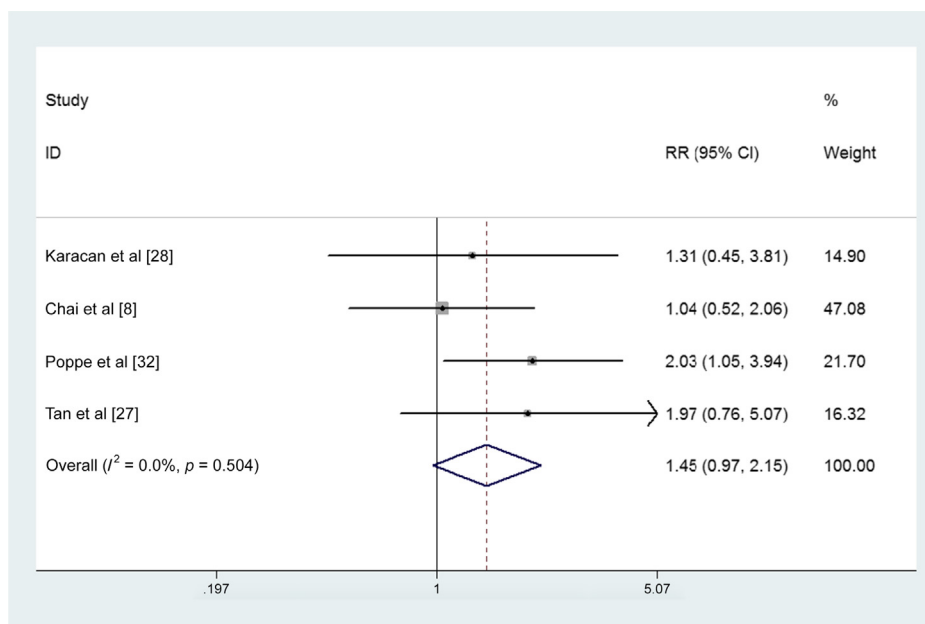


Figure 3. Forest plot of risk ratios and 95% confidence interval of pooled studies comparing ATA-positive patients with ATA-negative controls in subfertile euthyroid women without SCH undergoing ART according to miscarriage rate. ART = assisted reproductive technologies; ATA = positive antithyroid antibodies; SCH = subclinical hypothyroidism.

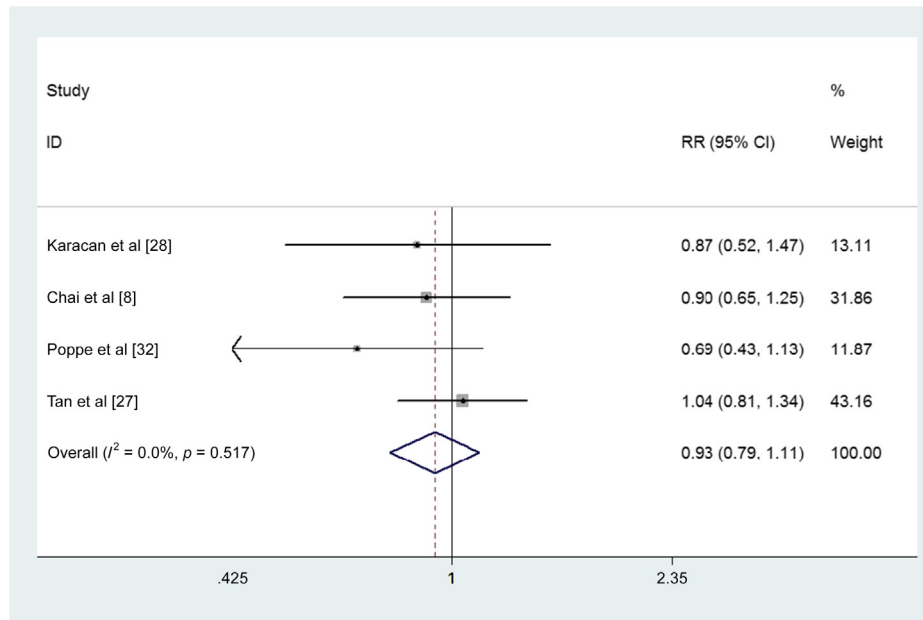


Figure 4. Forest plot of risk ratios and 95% confidence interval of pooled studies comparing ATA-positive patients with ATA-negative controls in subfertile euthyroid women without SCH undergoing ART according to delivery rate. ART = assisted reproductive technologies; ATA = positive antithyroid antibodies; SCH = subclinical hypothyroidism.

on euthyroid patients who were undergoing their first ART cycle, the study by van den Boogaard [5] had no rigorous inclusion criteria on either patients or design. With a similar study population to the study by Toulis et al [12], our results in euthyroid women with/without SCH were consistent with their data on miscarriage, but our study also detected a significant difference in delivery rates between ATA-positive and ATA-negative patients.

However, several limitations of the present study should be considered. As mentioned above, the included studies used different cutoff levels and different laboratory methods to measure TSH concentration, therefore, the effects of SCH could not be totally eliminated. In addition, although patients with SCH were excluded as far as possible, TSH levels may not be equal between positive-ATA and negative-ATA patients. Unfortunately, the pooled difference of TSH levels between groups could not be calculated because of the lack of relative data in some articles, so the effect of normal-range TSH in patients without SCH could not be determined. Another limitation of our study is the small sample size, especially the number of patients without SCH. Only four articles, including 1855 patients, met our inclusion criteria when we limited the TSH concentration to within 5 mIU/mL, so the results should be regarded with caution.

In conclusion, TA *per se* does not impair assisted reproductive treatment outcomes in women without SCH, and the apparent association between TA and miscarriage in women whose SCH status is unknown may be related to underlying SCH or TSH-dependent mechanisms. Our study has potentially provided useful data on the association between TA and miscarriage. However, it is recommended that women with TA undergoing ART, especially combined with SCH, be carefully monitored in case of miscarriage. Finally, more randomized controlled trials should be conducted to determine whether supplemental levothyroxine is needed for patients with TA.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tjog.2015.09.003>.

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