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Original Article

Effect of thyroid autoimmunity *per se* on assisted reproduction treatment outcomes: A meta-analysis

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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.

Introduction

Thyroid autoimmunity (TA) is defined as the presence of antithyroid 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 ($p = 0.782$).