BMC Women's Health

SYSTEMATIC REVIEW Open Access

Prevalence of thyroid autoantibody positivity in women with infertility: a systematic review and meta-analysis

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Abstract

Background Thyroid autoimmunity (TAI) is associated with infertility and complications during pregnancy. However, the prevalence of thyroid autoantibodies in women with infertility remains unclear due to variability in study designs, sample sizes, and populations. In this meta-analysis, we aimed to assess the prevalence of thyroid autoantibodies in women with infertility compared with that in healthy controls.

Methods Systematic searches were conducted across PubMed, Embase, Web of Science, and the Cochrane Library from inception to February 5, 2024. The inclusion criteria were women with infertility and those with autoimmune thyroid antibodies. Studies in which relevant data could not be extracted, randomized control trial reports, studies with non-original or duplicate data, and non-English articles were excluded. The main outcome was prevalence rate.

Results The worldwide pooled prevalence of thyroid autoantibody positivity was 20%. In contrast, a significantly higher TAI prevalence was noted in the population with infertility than in healthy controls (risk ratio [RR] = 1.51). Subgroup analyses indicated that TAI prevalence was higher in patients receiving both assisted reproductive technology (ART) and non-ART treatments than in healthy controls (RR = 1.37 and 3.06, respectively). TAI prevalence was also higher in the recurrent abortion and non-recurrent abortion groups of infertility than in healthy controls (RR = 1.80 and 1.39, respectively). Additionally, a higher TAI prevalence was found in the euthyroid and non-simple euthyroid groups than in the control group (RR = 2.77 and 1.43, respectively). The prevalence was significantly higher in cases of unexplained infertility, endometriosis, ovulation disorders, and fallopian tube factors among women with infertility than among the control group (RR = 1.53, 1.83, 1.42, and 2.00, respectively).

Conclusions Thyroid autoantibodies are more prevalent in patients with infertility than in healthy controls. Given the presence of thyroid autoantibodies, screening patients with infertility is clinically important.

Keywords Thyroid autoantibody, Infertility, Meta-analysis, Thyroglobulin, Thyroid

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Background

Thyroid autoimmunity (TAI), defined by the presence of circulating anti-thyroid antibodies targeting thyroid peroxidase (TPOAb), thyroglobulin (TgAb), and anti-microparticle protein (TmAb), is the most frequent cause of thyroid dysfunction [1, 2]. TAI comprises a spectrum of conditions, including hyperthyroidism, subclinical or overt hypothyroidism, and less frequently, transient thyrotoxicosis [3]. TAI affects nearly 10% of women of reproductive age and evokes significant interest from clinicians owing to its potentially negative impact on female fertility and pregnancy outcomes [4, 5]. TAI-related thyroid dysfunction, mainly overt and subclinical hypothyroidism, adversely affects conception and pregnancy outcomes [6].

Infertility is defined as the failure to achieve a clinical pregnancy after 12 months or more [7]. Female-related causes of infertility, such as ovulation disorders, endometriosis, pelvic adhesions, tubal obstruction/abnormalities, and hyperprolactinemia, account for approximately 35% of cases, while male factors account for 30%, and combined factors for 20%. In approximately 15% of the cases, the cause remains unknown, referred to as idiopathic or unexplained infertility (UI) [8, 9]. The prevalence of infertility varies worldwide, affecting approximately 8–12% of couples of reproductive age [9, 10].

There is evidence suggesting that TAI may have a detrimental impact on natural fertility and suggesting the success rates of assisted reproductive technology (ART) [11]. A meta-analysis of 12 cohort studies found that women with positive TAI undergoing ART had a lower live birth rate (odds ratio [OR] = 0.69; 95% confidence interval [CI], 0.49–0.87), higher miscarriage rate (OR = 1.44; 95% CI, 1.06–1.95), and similar clinical pregnancy rate (OR = 0.90; 95% CI, 0.77–1.06) [12]. Similarly, a 2022 meta-analysis by Busnelli et al. suggested a higher risk of adverse ART outcomes in women with positive TAI, which was associated with a higher risk of miscarriage and lower chances of embryo implantation and live birth [13]. A meta-analysis by Thangaratinam et al. included 31 studies evaluating the association between thyroid autoantibodies and miscarriage, with 28 of these studies revealing a positive correlation [14]. The meta-analysis of cohort studies revealed over three times the odds of miscarriage in the presence of thyroid autoantibodies. A recent study revealed that TPO is expressed at the gene and protein levels in the endometrium and placenta, which may explain the higher frequency of miscarriages in patients with TAI [15]. Furthermore, a meta-analysis of 11 prospective cohort studies involving 35,467 participants suggested that the presence of TPOAb in pregnant women significantly increases the risk of preterm delivery [16]. A recent meta-analysis of 19 cohort studies, which pooled data from 47,055 pregnant women, found that women with euthyroidism who were TPOAb-positive had a higher risk of preterm delivery than women who were TPOAb-negative [17]. Several retrospective studies have reported an increased risk of preeclampsia, gestational diabetes mellitus, anemia, placenta previa, polyhydramnios, placental abruption, and premature rupture of membranes in women with TAI [18]. Several researchers have understood the impact of TAI on clinical outcomes in patients with infertility and the importance of antibody screening and TAI testing in patients with infertility [19–22].

An increased prevalence of TAI among women attending infertility clinics has been observed in most studies, although previous studies have explored the positive rate of thyroid autoimmunity in patients with infertility, significant differences in study designs and participant characteristics have led to a lack of consensus among the results. In studies published before the early 2000s, the prevalence of TAI in women with infertility ranged from 6.8 to 14.5% [23, 24], with no significant difference compared to the control groups. However, over time, the relevant research literature is constantly updated. Therefore, in this meta-analysis, we aimed to use raw data from studies examining the relationship between thyroid autoantibodies and infertility to estimate the pooled prevalence of thyroid autoantibodies in patients with infertility and compare the prevalence of TAI in patients with infertility with that in healthy controls.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. The study was conducted according to the predefined protocol registered in PROSPERO (CRD42024503424). Systematic searches were performed on PubMed, Embase, Web of Science, and the Cochrane Library from the inception until February 5, 2024. The search strategy, which used a mixture of free terms, variants, and canonical words, such as MeSH terms and descriptors, focused on the topics of infertility and thyroid autoantibodies (Additional file 1).

Keywords included "Infertility, Female" or "Reproductive Techniques, Assisted" or "Reproductive Techniques" or "Fertilization in Vitro" or "Sperm Injections, Intracytoplasmic" or "Preimplantation Diagnosis" or "In Vitro Oocyte Maturation Techniques" or "Insemination, Artificial" or "Embryo Implantation" or "Embryo Transfer" or "Ovarian Reserve" or "Ovarian Hyperstimulation Syndrome" or "Endometriosis" or "Polycystic Ovary Syndrome" in combination with the terms "Thyroid Gland" and "Autoimmunity" or "Thyroiditis, Autoimmune" or "anti-thyroid autoantibodies" or "thyroid microsomal

antibodies" or "Hashimoto Disease" or "Graves' Disease" or "Hyperthyroidism" or "Hypothyroidism" or "Thyrotropin" or "Immunoglobulins, Thyroid-Stimulating" or "Thyroxine" or "Thyroid Diseases." The references of the retrieved studies were reviewed to identify the eligible studies.

The criteria for inclusion were as follows: (1) cohort and case-control study designs; (2) findings of the examination of the association between thyroid autoantibodies and infertility using TgAb, TPOAb, and TmAb; and (3) availability of sufficient data to calculate the prevalence of thyroid autoantibodies. The exclusion criteria included the inability to isolate or extract relevant outcome data, case reports, non-original or duplicate data, and articles not written in English.

Data collection and extraction

Two reviewers independently examined all article titles and abstracts to identify studies requiring further evaluation and omitted those deemed irrelevant. The initial screening did not consider the author, institution, publication name, or specific findings. Information was obtained from the included studies using data extraction tables created by the authors. The gathered information included publication year; first author; location of the population; study design; types of infertility; number of cases and controls; and the number of cases and controls positive for TPOAb, TgAb, or TmAb. In case of any disagreement, a consensus was achieved based on discussion between the two reviewers or through the involvement of a third reviewer.

Quality assessment

All included studies were evaluated, and the necessary data were retrieved separately by two researchers. The quality of both cohort studies and case-control trials was assessed using the Newcastle-Ottawa Scale (NOS) [26]. The three criteria for evaluating the studies were participant selection, comparability, and outcome determination (Additional files 2 and 3).

Data synthesis and analysis

All statistical analyses were performed using Stata 14.0. The I^2 statistic and chi-square test were used to assess the heterogeneity. Heterogeneity among the included studies was assessed using Cochrane's Q test, with a cut-off of $P<0.1$. Publication bias was assessed using the Begg's test. The association between infertility and thyroid autoantibodies was evaluated by the prevalence of thyroid autoantibodies in patients with infertility, followed by a Z test ($P<0.05$ considered statistically significant) to determine the significance of the risk ratio (RR). If heterogeneity was present ($P<0.1$ and $I^2>50\%$) across the included studies, a random-effects model was used for the meta-analysis. Otherwise, a fixed effects model was used. Additionally, sensitivity analysis was performed to assess the consistency and dependability of the combined data.

Results

Characteristics of included studies

Our search identified 37,821 reports (PubMed=2,603; Embase=7,235; Web of Science=27,257; and Cochrane Library=726), of which 7,049 were duplicates. After screening titles and abstracts, a total of 131 reports were deemed potentially eligible, and full texts were retrieved. Among these 131 full-text articles, 6 were excluded because the full text could not be searched. Four studies were in non-English language, and the methods and outcome indicators of 67 studies were inconsistent. Consequently, 54 relevant full articles were selected as eligible studies for this meta-analysis (Fig. 1), and their characteristics are summarized in Table 1. According to the NOS, 50 studies were classified as having high quality and 4 as having medium quality.

The study designs comprised 25 retrospective cohort studies, 15 prospective cohort studies, and 14 case-control studies. Geographically, 23 studies were conducted in Asia, 22 in Europe, 8 in America, and 1 in Africa. The studies collectively included 35,345 infertility cases and 1,279 healthy controls [19–23, 27–75].

Among the 54 studies, 6 did not provide the total number of positive thyroid autoantibodies. Of the remaining 48 studies, all included the total number of positive thyroid autoantibodies and the total number of patients with infertility. Furthermore, only 11 studies provided the total number of both patients with infertility and healthy controls, along with the number of antibody positives for each group.

Meta-analysis results

Overall pooled prevalence of thyroid autoantibody positivity in patients with infertility

The primary result was the overall prevalence of thyroid autoantibody positivity across 48 studies, which was 20% (95% CI, 18–22%) (Table 2). A high level of heterogeneity was observed ($I^2=94.45\%$). The highest prevalence, reported by Cevher Akdulum et al., was 40% [36], whereas the lowest, reported by Polyzos et al., was 10% [62].

Subgroup analyses were performed based on the geographic region, year of publication, type of infertility treatment, and thyroid function status. As shown in Table 2, studies reported the positivity rate of thyroid autoantibodies in patients with infertility in Europe, 8 in America, 18 in Asia, and 1 in Africa. The positivity rate of thyroid autoantibodies in Asia and Africa showed an increasing trend of 22% (95% CI, 18–26%), but this was

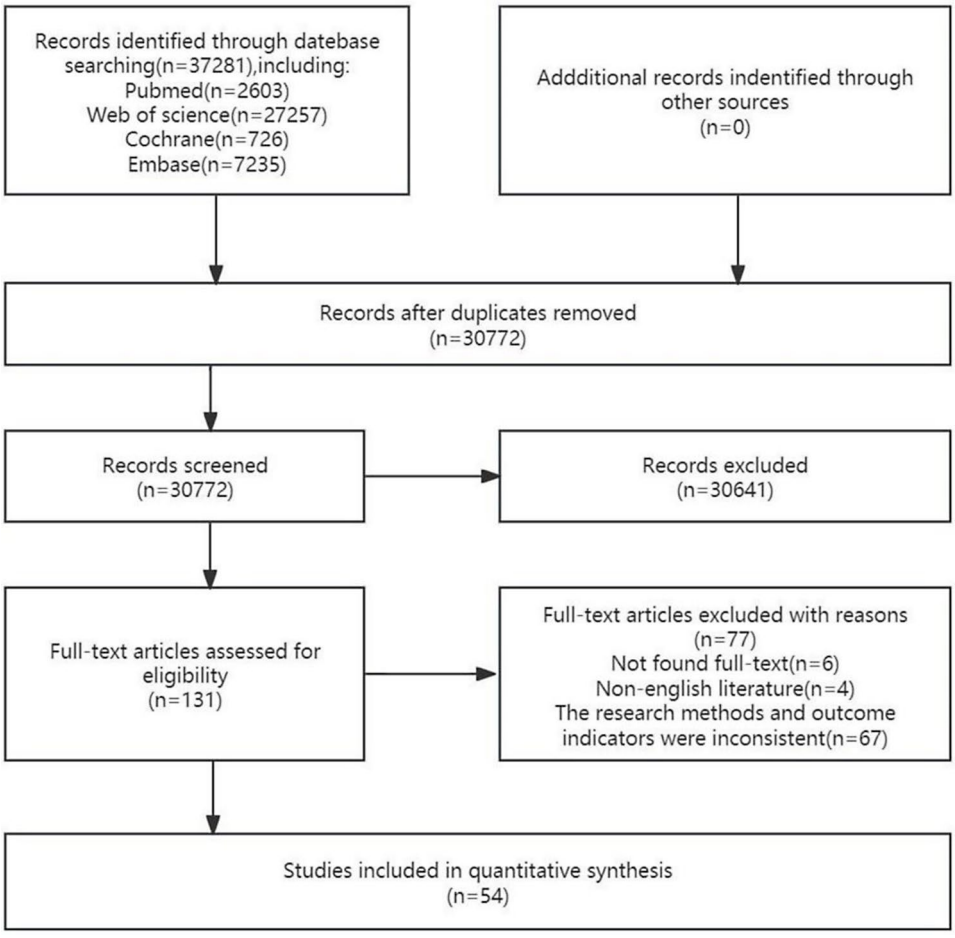

Fig. 1 Study flowchart. Preferred reporting items for systematic reviews and meta-Analyses: The PRISMA statement

not significantly different from the rates in Europe (18% [95% CI, 15–20%]) and America (18% [95% CI, 15–21%]) (P=0.131). According to the year of publication, the positivity rate of thyroid autoantibodies in patients with infertility was 21% (95% CI, 18–24%) in 11 studies published in 2000 and earlier and 15% (95% CI, 12–19%) in 8 studies published from 2001 to 2010. From 2011 to 2020, 24 studies reported a positivity rate of 18% (95% CI, 16–20%). In contrast, five studies published from 2021 onwards reported a positivity rate of 29% (95% CI, 22–37%), which was the highest rate observed and revealed a significant difference between the groups (P=0.002). Overall, 39 reports of the positivity rates of thyroid autoantibodies in patients with infertility treated with ART were similar (20% [95% CI, 18–22%]) to 9 reports in non-ART patients with infertility (18% [95% CI, 14–23%]) (P=0.668). Furthermore, the positivity rates in patients with infertility and euthyroidism, as reported in 28 studies (20% [95% CI, 17–22%]), were similar to those in 20 studies of patients with non-euthyroidism conditions (19% [95% CI, 15–23%]).

The overall pooled prevalence of TPOAb positivity across 37 studies was 12% (95% CI, 10–15%) (Table 3). A high level of heterogeneity (I^2=95.88%) was observed. The highest prevalence of 40% was reported by Cevher Akdulum et al. [36], and the lowest prevalence of 3% was reported by Karacan et al. [45].

The overall pooled prevalence of TgAb-positivity across 27 studies was 7% (95% CI, 5–10%). There was a high level of heterogeneity (I^2=95.37%), with the highest prevalence of 55% reported by Soltanghoraee et al. [69], and the lowest prevalence of 0% reported by Karacan et al. [45] and Weghofer et al. [74].

The overall prevalence of double-positive TPOAb and TgAb results across 18 studies was 7% (95% CI, 6–8%). There was high heterogeneity (I^2=66.13%), with the highest prevalence of 15% reported by Kim et al. [47], and the lowest prevalence of 1% reported by Devi et al. [40].

In the subgroup analysis, the positivity rate of TPOAb among patients with infertility in Asia was 15% (95% CI, 9–21%), which was slightly higher than that in Europe (12% [95% CI, 9–14%]) and America (10% [95% CI, 6–14%]), although the differences were not statistically

Table 1 Characteristics of the studies included in the meta-analysis

Author	Year	Country	Continent	Study design	Infertility(*n*/*N*)		Healthy controls (*n*/*N*)	
					TAI(+)	total	TAI(+)	total
S.Bussen	1995	Germany	Europe	case–control study	10	44	1	22
Anita Singh	1995	America	America	Retrospective cohort study	106	487		
E Geva	1996	Israel	Asia	Prospective cohort study	16	78		
E Geva	1997	Israel	Asia	case–control study	15	80	2	40
S.Bussen	1997	Germany	Europe	case–control study	11	28	2	28
CHUNG-HOON	1998	Korea	Asia	Retrospective cohort study	28	79		
A. F. Muller	1999	Holland	Europe	Prospective cohort study	25	173		
Willim H	1999	America	America	case–control study	290	1388	29	200
Kutteh	1999	America	America	case–control study	143	873	29	200
Rushworth	2000	UK	Europe	Retrospective cohort study	162	870		
Bussen	2000	Germany	Europe	Retrospective cohort study	15	48		
POPPE	2002	Belgium	Europe	case–control study	61	438	8	100
POPPE	2003	Belgium	Europe	Prospective cohort study	32	234		
POPPE	2004	Belgium	Europe	Prospective cohort study	9	35		
Negro	2005	Italy	Europe	Prospective cohort study	86	662		
Negro	2007	Italy	Europe	Retrospective cohort study	49	423		
Abalovich	2007	Argentina	America	case–control study	62	244	10	69
Mahnaz Ashrafi	2008	Iran	Asia	case–control study	NA	55	13	39
Bellver	2008	Spain	Europe	case–control study	17	87	5	32
Revelli	2009	Italy	Europe	Retrospective cohort study	319	3034		
Soltanghoraee	2010	Iran	Asia	case–control study	NA	285	24	95
Ticconi	2011	Italy	Europe	case–control study	46	160	13	100
Kim	2011	America	America	Retrospective cohort study	54	265		
Zhong	2012	China	Asia	Retrospective cohort study	90	766		
Karacan	2013	Turkey	Asia	Prospective cohort study	34	253		
Mintziori	2013	Greece	Europe	Retrospective cohort study	15	82		
Unuane	2013	Belgium	Europe	Prospective cohort study	163	992	60	458
Magri	2013	Italy	Europe	Retrospective cohort study	60	262		
Chai	2014	China	Asia	Retrospective cohort study	125	636		
Lukaszuk	2015	Poland	Europe	Retrospective cohort study	114	665		
Litwicka	2015	Italy	Europe	Prospective cohort study	60	194		
Magri	2015	Italy	Europe	Retrospective cohort study	55	288		
Polyzos	2015	Belgium	Europe	Retrospective cohort study	508	4864		
Weghofer	2016	America	America	Retrospective cohort study	25	225		
Unuane	2016	Belgium	Europe	Retrospective cohort study	333	2352		
Sakar	2016	Turkey	Asia	Prospective cohort study	49	251		
Chien-Wen Chen	2017	China	Asia	Retrospective cohort study	NA	840		
Chen	2017	China	Asia	Prospective cohort study	NA	1720		
Osuka	2018	Japan	Asia	Retrospective cohort study	27	153		
Korevaar	2018	America	America	Prospective cohort study	66	436		
Andrisani	2018	Italy	Europe	Retrospective cohort study	29	123		
Zhu	2019	China	Asia	case–control study	NA	214	3	59
Devi	2019	India	Asia	Prospective cohort study	17	81		
Inagaki	2020	Japan	Asia	Prospe[41]ctive cohort study	185	590		
Aubead	2020	Iraq	Asia	case–control study	NA	35		
Liu	2020	China	Asia	Retrospective cohort study	41	242		
Robert	2020	Canada	America	Retrospective cohort study	71	567		
Ke	2020	China	Asia	Retrospective cohort study	1075	6213		
Tokgoz	2020	Turkey	Asia	Retrospective cohort study	65	315		
Alikhan	2021	Iraq	Asia	Prospective cohort study	22	81		
Hamad	2021	Syria	Asia	Retrospective cohort study	148	584		

Table 1 (continued)

Author	Year	Country	Continent	Study design	Infertility(*n*/*N*)		Healthy controls (*n*/*N*)	
					TAI(+)	total	TAI(+)	total
Akdulum	2022	Turkey	Asia	Retrospective cohort study	363	918		
Bendary	2022	Egypt	Africa	case–control study	13	70	0	30
Wei	2023	China	Asia	Prospective cohort study	86	263		

Table 2 Subgroup analysis of the prevalence of positive thyroid autoantibodies in patients with infertility

Subgroup title	No. of trails	No. of participants	I^2(%)	Pooled prevalence of TAI (95%CI)	*P* for value
Overall	48	33,475	94.45	0.20(0.18 to 0.22)	
Location					
Europe	22	16,798	90.63	0.18(0.15 to 0.20)	0.131
America	8	4954	84.89	0.18(0.15 to 0.21)	
Asia and Africa	18	11,723	94.93	0.22(0.18 to 0.26)	
Year					
≤ 2000	11	4638	69.36	0.21(0.18 to 0.24)	0.002
2001–2010	8	5358	85.59	0.15(0.12 to 0.19)	
2011–2020	24	21,533	92.81	0.18(0.16 to 0.20)	
≥ 2021	5	1946	90.48	0.29(0.22 to 0.37)	
Type of infertility treatment					
ART	39	26,297	94.05	0.20(0.18 to 0.22)	0.668
Non-ART	9	7768	91.81	0.18(0.14 to 0.23)	
Thyroid function status					
Euthyroid	28	17,897	90.35	0.20(0.17 to 0.22)	0.690
Non-only euthyroid	20	15,578	96.65	0.19(0.15 to 0.23)	

Table 3 Subgroup analysis of positive rates of different types of thyroid autoantibodies in infertility patients in different regions

Antibodies	Subgroup	No. of trails	No. of participants	I^2(%)	Pooled prevalence of TAI (95%CI)	*P* for value
TPOAb	Europe	15	11,416	89.81	0.12(0.09 to 0.14)	0.308
	America	7	4267	93.38	0.10(0.06 to 0.14)	
	Asia	15	6043	97.19	0.15(0.09 to 0.21)	
	Total	37	21,726	95.88	0.12(0.10 to 0.15)	--
TGAb	Europe	7	2340	89.96	0.05(0.02 to 0.09)	0.040
	America	5	3387	90.77	0.04(0.02 to 0.07)	
	Asia	15	5020	94.58	0.09(0.06 to 0.14)	
	Total	27	10,747	95.37	0.07(0.05 to 0.10)	--
TPOAb TGAb	Europe	6	1470	22.56	0.08(0.06 to 0.11)	0.068
	America	5	3387	79.89	0.05(0.04 to 0.08)	
	Asia	7	1713	65.87	0.07(0.05 to 0.10)	
	Total	18	6570	66.13	0.07(0.06 to 0.08)	--

significant between the groups. The positivity rate of TgAb in patients with infertility in Asia was 9% (95% CI, 6–14%), which was significantly higher than that in Europe (5% [95% CI, 2–9%]) and America (4% [95% CI, 2–7%]) (P=0.04). There was no significant difference in the double-positivity rates of TPOAb and TgAb in Asia (7% [95% CI, 5–10%]), Europe (8% [95% CI, 6–11%]), or America (5% [95% CI, 4–8%]).

Prevalence of thyroid autoantibody positivity in patients with infertility and healthy controls

In 11 studies, the positivity rate of thyroid autoantibodies in patients with infertility was significantly higher than that in healthy controls (P<0.0001), with RR of 1.51 (95% CI, 1.29–1.77; I^2=32%, fixed effect). Subgroup analysis based on treatment type, abortion status, and thyroid function status revealed that the positivity rates of thyroid autoantibodies were significantly higher in patients receiving ART (seven studies) and non-ART (four studies, including three studies for recurrent abortion and one study on UI) (P=0.0003 and P<0.0001, respectively) than in healthy controls, with RRs of 1.37 (95% CI, 1.15–1.62; I^2=0%, fixed effect) and 3.06 (95% CI, 1.86–5.03; I^2=2%, fixed effect), respectively, and with a significant difference between the groups (P=0.003) (Fig. 2A). Furthermore, patients with recurrent spontaneous abortion

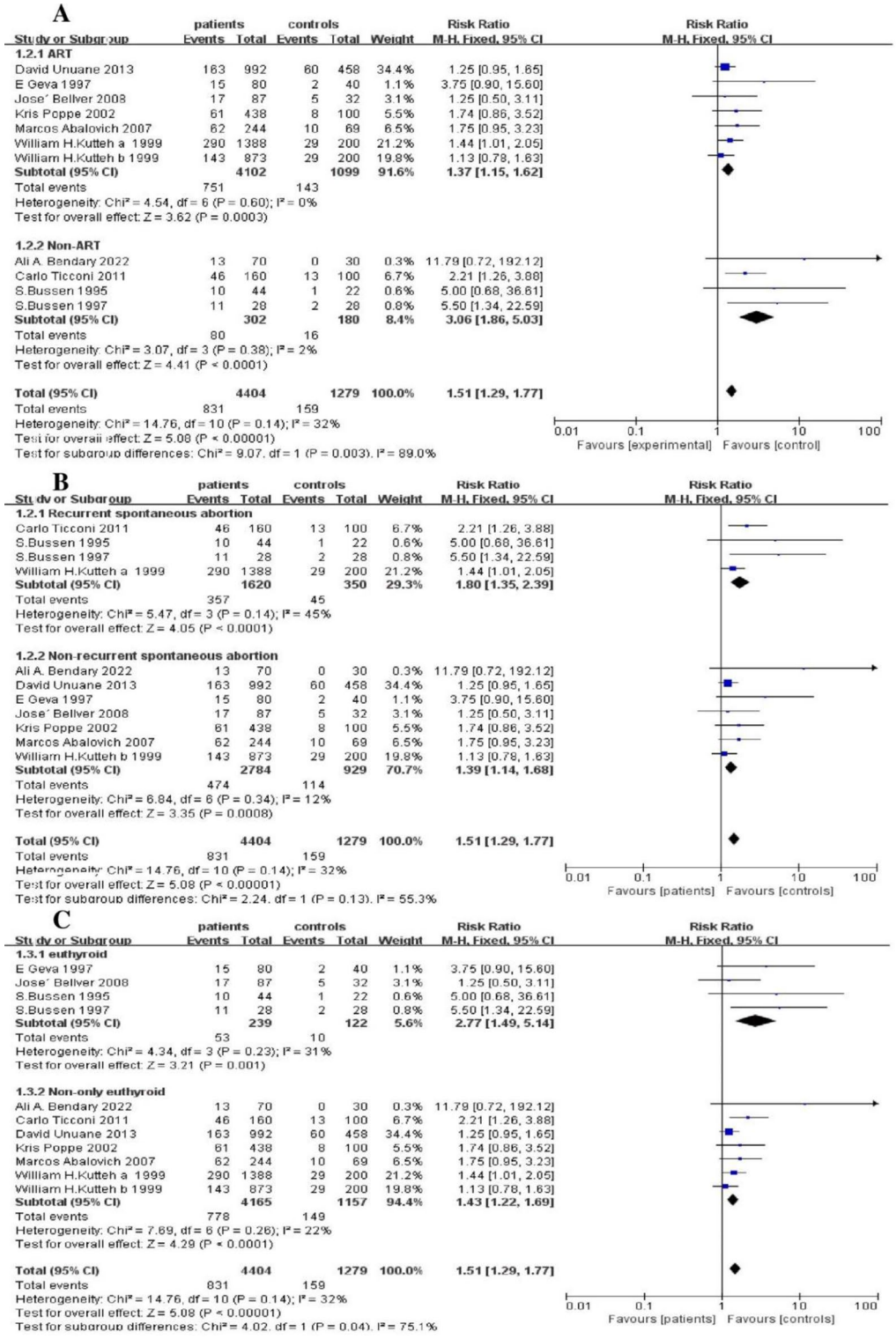

Fig. 2 Forest plots of Risk Ratio's and 95% confidence intervals for thyroid antibody positive in infertile patients with (**A**) ART and non-ART, (**B**) RSA and non-RSA, (**C**) euthyroid and non-only euthyroid compared with healthy controls

(RSA) (four studies) and non-RSA (seven studies) had higher rates of thyroid autoantibody positivity compared to those in healthy controls, with RRs of 1.80 (95% CI, 1.35–2.39; I^2=45%, fixed effect) and 1.39 (95% CI, 1.14–1.68; I^2=12%, fixed effect), respectively (P<0.0001 and P=0.0008, respectively). There was no significant difference between the groups (P=0.13) (Fig. 2B). The euthyroid group (four studies) and the non-euthyroid group (seven studies, including patients with euthyroid, hypothyroidism, and hyperthyroidism) also had significantly higher rates of thyroid autoantibody positivity compared to those in the control group, with RRs of 2.77 (95% CI, 1.49–5.14; I^2=31%, fixed effect) and 1.43 (95% CI, 1.22–1.69; I^2=22%, fixed effect), respectively (P=0.001 and P<0.0001, respectively). The difference between the groups was significant (P=0.04) (Fig. 2C).

Furthermore, based on the cause of infertility, studies reported positivity rates of thyroid autoantibodies in patients with UI (six studies), endometriosis (three studies), ovulation disorders (three studies), and tubular disturbances (four studies). All infertility subgroups had a significantly higher prevalence of TAI than that in the healthy control group, with RRs of 1.53 (95% CI, 1.04–2.24, I^2=28%, fixed effect), 1.83 (95% CI, 1.20–2.78, I^2=15%, fixed effect), 1.42 (95% CI, 1.06–1.92, I^2=0%, fixed effect), and 2.00 (95% CI, 1.39–2.89, I^2=0%, fixed effect), respectively (P<0.05 for all; Fig. 3A–D).

Sensitivity analysis

A sensitivity analysis was performed to assess the consistency and reliability of the combined data and to investigate the influence of each study on the overall meta-analysis estimate. The leave-one-out sensitivity analysis revealed that excluding any of the included studies did not substantially change the pooled prevalence estimate. A study was considered influential if the pooled estimate of the prevalence, excluding that study, was not within the 95% CI of the overall mean. The pooled prevalence estimates resulting from the sensitivity analysis were consistent with our original estimates, indicating that our findings are relatively stable and credible (Additional file 4).

Publication bias

Each study is represented by a dot, and the effect size is illustrated by a horizontal line. Begg's test was used to determine whether there is a potential publication bias in the reviewed literature. The Begg's test results did not indicate any significant publication bias regarding the prevalence of thyroid autoantibody positivity (P=0.067) (Additional file 5).

Discussion

Although TAI is not a direct cause of infertility, widespread positive rates of thyroid autoantibodies in women with infertility have been reported in the literature.

Pooled prevalence of thyroid autoantibody positivity among patients with infertility worldwide

In studies published up to the early 2000s, the prevalence of TAI in women with infertility ranged from 14 to 39% [34, 58]. More recent studies have reported a prevalence of 18–32% [21, 32]. In this meta-analysis, the overall prevalence of positive thyroid autoantibodies in patients with infertility was 20% (95% CI, 18–22%), suggesting a higher prevalence of TAI in women with infertility.

The prevalence of TAI differs according to race, age, iodine supply, and smoking status and is estimated to be as high as 5–16% in women aged 20–45 years in Europe [76–78]. Differences in iodine intake among individuals from different regions may contribute to observed differences in TAI prevalence. In iodine-repleted areas, most patients with thyroid disorders have autoimmune diseases [79].

In this study, subgroup analysis based on geographic location showed that TAI-positive rates were 18% in both Europe and the Americas, and 22% each in Asia and Africa. Although no statistically significant differences were observed between populations on different continents, the prevalence of thyroid autoantibodies was relatively high among populations with infertility in Asia and Africa.

Unfortunately, the literature on TAI-positivity rates in Africa is relatively limited, with only one study available. Therefore, the prevalence of TAI in many patients with infertility in Africa remains unknown.

With the update and promotion of international and regional guidelines, clinicians are paying more attention to thyroid function and antibody screening in patients with infertility.

The European Thyroid Association (ETA) recommends screening for serum thyroid-stimulating hormone (TSH) and TAI for all women seeking medical advice for low fertility [80]. Additionally, relevant studies have recommended the detection of related antibodies in patients with infertility [19, 21].

A subgroup analysis based on publication time revealed that the positivity rate of thyroid autoimmune antibodies in patients with infertility was 21% in studies published before 2000, 15% between 2001 and 2010, 18% between 2011 and 2020, and 29% in studies published from 2021 onwards. The data suggest a gradual increase in TAI positivity rates over time, with a particular rise after 2020. The literature reported after 2020 is mainly concentrated in Asian and African countries with high TAI positivity rates. The popularity of this screening measure has

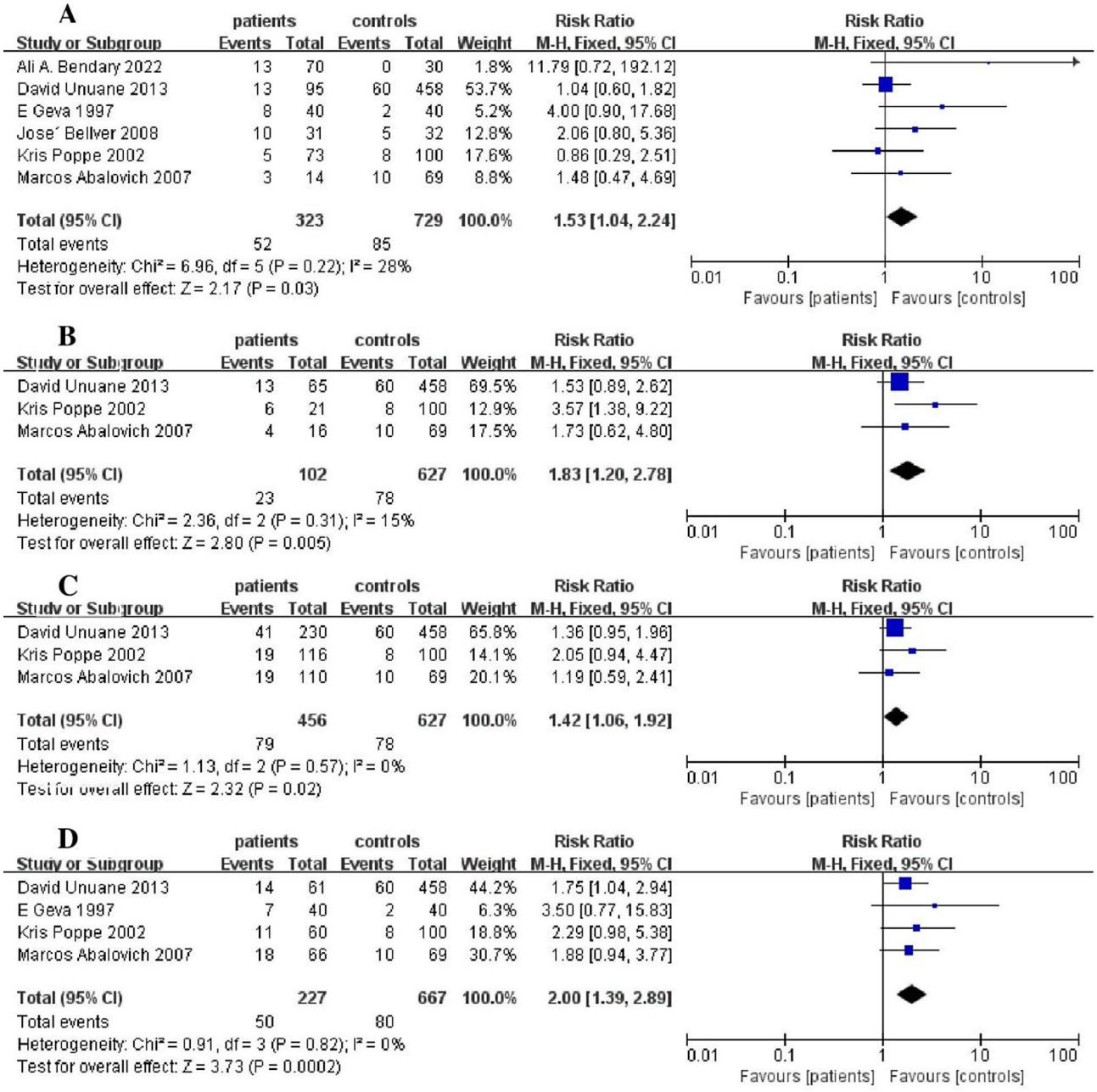

Fig. 3 Forest plot of Risk Ratio's and 95%Confidence Interval of pooled studies comparing (**A**) UI, (**B**) Endometriosis, (**C**) Ovulatory dysfunction, (**D**) Tubal disturbances patients with healthy controls according to the prevalence of positive TAI

helped to detect thyroid antibody-positive patients earlier, thus explaining the increasing trend in positive rates.

In studies based on original data, the prevalence of TAI in patients with infertility treated with ART ranged from 11 to 40% [36, 65, 74]. This meta-analysis, which includes 39 studies on ART, found a TAI positivity rate of 20%. TAI-positive patients treated with ART have higher abortion rates, lower chances of embryo implantation, and lower live birth rates [13]. Additionally, TAI-positive patients have a lower rate of insemination, fewer high-quality embryos, and a higher rate of preterm birth [17, 22, 28]. This may be owing to the in vitro phase of the ART procedure, during which ovarian stimulation is performed to collect as many oocytes as possible. A diminished thyroid response to human chorionic gonadotropin (hCG), coupled with the rapid increase in estradiol and thyroxin-binding globulin concentrations soon after controlled ovarian stimulation, may result in a decrease in the availability of free thyroid hormone [64, 81]. The thyroid hormone-dependent and -independent immunological effects of TAI on the ovary, uterus, and fetoplacental unit have been implicated. Additionally, TAI could

serve as a peripheral marker of a general immune imbalance that affects fertilization, implantation, and pregnancy maintenance [82–84]. Therefore, in 2021, the ETA recommended that women of subfertile couples should be systematically screened for serum TAI before undergoing an ART procedure [80]. In non-ART studies, TAI-positivity rates ranged from 10 to 39% in patients with infertility [34, 62]. Some researchers have recommended TAI screening for such patients [32]. In the present study, nine non-ART studies were included, and a meta-analysis revealed a TAI-positivity rate of 18%, which is similar to the prevalence of TAI in patients with infertility undergoing ART.

This means that the prevalence of TAI in patients with infertility is high, whether they receive ART therapy or not, and that routine TAI screening is important clinically for patients with infertility.

The non-simple euthyroid group in this systematic review included patients with hyperthyroidism and (sub-) hypothyroidism. The TAI-positivity rates in the euthyroid and non-simple euthyroid groups were 20% and 19%, respectively, with similar incidence rates. A previous study showed that the TAI-positivity rate was high in patients with thyroid dysfunction, often used as the key object of TAI screening [51].

In this study, the euthyroid group had a similar TAI-positivity rate, indicating that patients with infertility and euthyroidism should not be excluded from TAI screening. Routine TAI screening in all patients with infertility helps in the early detection and management of potential thyroid autoimmune problems.

In most cited studies, TAI was defined by the presence of TPOAb. TPOAb is widely recognized as a sensitive marker of TAI, which is associated with an increased risk of hypothyroidism [85]. Consequently, most studies have explored the impact of TPOAb or TPOAb and TgAb, with only a few studies investigating the effect of isolated TgAb. A prospective cohort study involving 436 women attending a fertility center found positivity rates of 10% for TPOAb and 9.2% for TgAb, with an overlap of 4.6% [49]. This suggests that up to 5% of patients with TAI positivity may be overlooked if only TPOAb levels are measured. Similar to TPOAb, TgAb interferes with the thyroidal response to hCG stimulation [86]. Moreover, TgAbs are associated with an increased risk of premature rupture of fetal membranes and low birth weight [87]. Additionally, TgAbs may significantly impact TSH concentrations [88]. In its 2017 guidelines, the American Thyroid Association stated the need for further research on the significance of isolated TgAb positivity [89]. As research advances, there is growing emphasis on the detection of both TPOAb and TGAb.

As of February 5, 2024, 37 studies on TPOAb-positivity, 27 on TGAb-positivity, and 18 on TPOAb and TGAb double-positivity were reported in this systematic review. The positivity rates for each antibody subtype were 12%, 7%, and 7%, respectively.

In the subgroup analysis by region, the positivity rates of single TPOAb and single TGAb among patients with infertility in Asia were higher than those in the other two continents; however, only the difference in the single TGAb-positive groups was statistically significant. Although TPOAb is commonly found in populations with infertility, simultaneous screening for both TPOAb and TGAb should be emphasized.

Pooled prevalence of thyroid autoantibody positivity among patients with infertility compared with that in healthy controls

In 11 studies comparing patients with infertility and healthy individuals, the RR of TAI positivity rate in patients with infertility was 1.51 (95% CI, 1.29–1.77), significantly higher than that in healthy controls. However, this is lower than the RR of 1.68 (95% CI, 0.78–3.65) reported by Poppe et al. [20] and of 2.1 (95% CI, 1.7–2.6) reported in a meta-analysis published by the same authors in 2007 [90].

The difference in TAI positivity rates in patients with infertility compared to RR values in the control group observed in different studies may be due to methodological differences. This study only focused on the detection of TPOAb, while other studies included literature that tested for both TPOAb and TgAb positivity, which may have resulted in a higher TAI positivity rate. If the control group comprised a population that was not rigorously screened, some patients with undiagnosed thyroid dysfunction or TAI could have been included, leading to a reduced difference in prevalence between the two groups and thereby affecting the RR value. These methodological differences limit the comparability of the results of different studies. In conducting such prospective studies in the future, methodological consistency should be ensured to accurately assess the prevalence and risk of TAI in patients with infertility.

In addition, a subgroup analysis was conducted based on whether patients received ART, experienced recurrent abortion, or had normal thyroid function. All subgroups revealed a higher risk of TAI positivity than that in the healthy control group. The significantly increased prevalence of TAI in women with infertility in both the ART and non-ART groups compared with that in healthy controls had overall RRs of 1.37 and 3.06, respectively. The definition and selection criteria of healthy control groups were not uniform, which may have led to underestimation or overestimation of TAI-positive rates in the control groups, thus affecting the calculation and interpretation of RRs.

The non-ART group had a significantly higher prevalence than the ART group. This discrepancy was mainly because three studies in this group involved patients with RSA and one study involved patients with UI; these groups of patients have been reported to have higher TAI positivity rates [70, 91]. Therefore, the high prevalence in the non-ART group may primarily reflect the characteristics of these specific patient groups and not necessarily be representative of all women with infertility who do not receive ART. This uneven subgroup composition may have led to a bias in the results. In addition, RSA and UI patients themselves may have had other factors that affect TAI-positive rates, such as immune system abnormalities or other underlying conditions. These confounding factors were not adequately controlled in the analysis and may have affected the accuracy of the RR values. Failure to adjust for these confounding factors may overestimate the true risk of TAI-positive rates in the non-ART group. In addition, the small sample size may not be representative of the larger population of patients with infertility, limiting the extrapolation of the results.

In the RSA and non-RSA groups, the TAI positivity rates were significantly higher than that in the healthy control group, with RRs of 1.80 and 1.39, respectively. The RSA group also revealed a higher risk of TAI positivity. However, this can only show an association between RSA and TAI-positive rates and cannot determine causation. It is not clear whether TAI is the cause or effect of RSA, or whether both are caused by common factors.

In addition, this study found that the positivity rate of TAI in the euthyroid group was significantly higher than that in the control group, with an RR of 2.77, and the RR was significantly higher than that in the non-euthyroid group. Phenotypic and functional analyses of peripheral blood mononuclear cells from healthy donors and patients with TAI positivity revealed Th1-oriented changes in innate immunity, elevated natural killer (NK) and NKT-like cell ratios, and enhanced natural cytotoxicity in TAI-positive women with euthyroid [92, 93].

This phenomenon has been verified in clinical practice. In a 2016 meta-analysis by Thangaratinam et al. involving 12,126 women, the chance of miscarriage increased by 2.9 times and the chance of preterm birth significantly doubled when thyroid autoantibodies were present [14]. Patients with TAI with a normal thyroid function still have a higher rate of miscarriage and premature birth.

Previous studies have shown that the prevalence of TAI positivity is higher in women with anovulation (26%), idiopathic infertility, and mostly endometriosis (30%) compared to that in the unselected population [94, 95]. In a prospective study, the prevalence of TPOAb/TgAb or a hypoechoic pattern on thyroid ultrasonography was significantly higher in these women than in controls (26.9 vs. 8.3% and 42.3% vs. 6.5%, respectively) [94]. A meta-analysis pooling four studies found that TAI was more prevalent in women with euthyroid and idiopathic infertility, with an OR of 1.47 (95% CI, 1.06–2.02) [91]. However, other studies have reported no significant differences in TPOAb levels between 14.9% of women with endometriosis and 22.2% of those in the control group [96]. A study of 210 women with polycystic ovarian syndrome (PCOS) and 343 age-matched controls showed no differences in the prevalence of TPOAb and hypoechoic patterns on thyroid ultrasonography between patients and controls [97].

In the present study, a meta-analysis was conducted on the TAI-positivity rate of patients with infertility with different etiological types compared to healthy controls. The results revealed that patients with UI (six studies), endometriosis (three studies), ovulation disorders (three studies), and tubal factors (four studies) had significantly higher RRs for TAI positivity than the healthy controls.

Owing to the limited data on PCOS in patients with infertility included in the study, a meta-analysis could not be performed. However, in other patients with PCOS who did not have infertility, a meta-analysis confirmed that PCOS is associated with a higher TAI positivity rate [98].

Women with endometriosis in previous studies had the highest prevalence of thyroid autoantibodies (29%) [20]. Some scholars have suggested that immune system abnormalities may explain the origin of ectopic endometrial tissue, and an association between endometriosis and autoimmune disease has been proposed [99]. Of note, in one prospective study, the findings suggested a significant association between endometriosis diameter and TPOAb levels [100]. Increased chronic pelvic pain and disease scores have also been reported in patients with endometriosis and concurrent thyroid disease [101].

Presently, there is no direct evidence that thyroid autoantibodies directly affect fallopian tube function. However, some studies have suggested that thyroid autoimmunity may lead to chronic inflammatory states or immune system abnormalities, which may affect the function of female reproductive organs [102]. Endometriosis may lead to fallopian tube adhesion, obstruction, or fibrosis through inflammation or immune-mediated action, affecting the developmental ability of gametes and embryos and transportation of embryos via the fallopian tubes [103–105]. We speculate that underlying undiagnosed endometriosis may manifest through fallopian tube dysfunction, leading to infertility of tubal origin, which was more prevalent in the infertility group than in the control group.

However, the data extracted for the various etiological types were from patients with infertility. Moreover, the sample size was relatively small, increasing the possibility that the results were subject to random errors, which

could have led to undetected existing differences. In addition, the etiology of infertility is complex and diverse. As patients with infertility of different etiologies such as anovulation, idiopathic infertility, endometriosis, and PCOS, which have different pathological mechanisms, were in and different degrees of association with TAI.

Based on the results of this study, we recommend that screening for TAI be included in the routine evaluation of patients with infertility, especially in women with UI or at high risk of having factors that contribute to infertility, whether they eventually receive ART or not, to facilitate early detection and management of thyroid abnormalities. For antibody-positive patients, early intervention may help improve pregnancy outcomes and potentially improve their chances of a successful pregnancy.

The studies in this meta-analysis had some heterogeneity in design, sample size, study population, and measurement criteria, which may have biased the results. For thyroid antibody detection methods, some studies used enzyme-linked immunosorbent assay, while others used chemiluminescence immunoassay. Differences in detection methods may explain the variation in the positive rate of thyroid antibodies and may have affected the results of the combined analysis; this should be considered when interpreting our findings. On the other hand, some potentially relevant studies were not included in the analysis due to incomplete original data; therefore, our findings have limited representativeness. Different geographic locations have differences in publication years and antibody assay threshold levels, which may have influenced the overall findings. The heterogeneity and methodological differences of the included studies should be considered when interpreting the results.

Future studies should further explore the causal relationship between TAI and infertility and their potential mechanisms. Although studies have shown a high prevalence of TAI in patients with infertility, the methods through which TAI affects ovarian function, embryo implantation, and the specific path of pregnancy maintenance remain unclear. Therefore, more high-quality multi-center studies are needed in the future to validate our findings and clarify the pathological mechanism of TAI from basic studies, especially in different infertility subtypes such as UI, endometriosis, PCOS and tubal factor infertility. At the same time, the standardization of TAI screening in infertility should be strengthened, especially in women with UI or who have high risk factors for infertility, to establish a unified clinical practice guideline to help clinicians individualize management. Finally, research across different regions and populations still needs to be strengthened, especially in underrepresented regions (such as Africa), to improve knowledge on the impact of different ethnic and environmental factors on TAI and infertility.

Conclusions

To the best of our knowledge, this meta-analysis is the first to analyze the prevalence of thyroid autoantibody positivity in a large sample of patients with infertility worldwide and to compare it with healthy populations. The included studies were rigorously evaluated, and sensitivity analyses were performed. Although this was a one-arm, two-tiered meta-analysis, it provides a relatively comprehensive overview of the presence of thyroid antibodies in patients with infertility, which may help professionals in offering counselling and treatment services to women with infertility.

Abbreviations

ART	Assisted reproductive technology
CI	Confidence interval
ETA	European Thyroid Association
hCG	Human chorionic gonadotropin
NOS	Newcastle-Ottawa Scale
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Risk ratio
TAI	Thyroid autoimmunity
Tg	Thyroglobulin
TmAb	Anti-microparticle protein
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone
UI	Unexplained infertility

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-024-03473-6.

Supplementary Material 1

Acknowledgements

None.

Author contributions

YH, AQ, and ML conceived and designed the study. JL, FH, and QH contributed to data collection. BX, YJ, RQ, JY, and JL conducted the data analysis and interpretation. YH, BX, and JL drafted the initial manuscript. YH, AQ, and ML revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 8 October 2024 / Accepted: 18 November 2024

Published online: 27 November 2024

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