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Research Article

Are Infertile Women with Endometriosis More Prone for Thyroid Autoimmunity? A Systematic Review -

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ABSTRACT

Hypothyroidism, often caused by anti-thyroid antibodies (TAI), is associated with both adverse maternal and foetal outcome. Studies have indicated that the risk of TAI is higher in infertile women suffering from endometriosis. By reviewing the literature, this study aimed to clarify whether women with infertility due to endometriosis, seeking fertility treatment were more prone to have TAI than women with other causes of infertility.

PubMed, Embase, SveMed, Cochrane and Cinahl were searched for studies on the presence of antithyroid antibodies in infertile women with endometriosis.

Three studies qualified and were included. The prevalence of TAI among infertile women with endometriosis varied from 20 to 29% vs. 14 to 22% among women with other causes of infertility, but only one study found a significantly higher prevalence of thyroid autoimmunity in infertile women with endometriosis.

Due to the sparse literature and small study groups, no firm conclusion could be drawn. As the consequences of missing subclinical hypothyroidism may be severe, this urgently calls for large studies on TAI in infertile women to elucidate the cost effectiveness in screening all infertile women.

Keywords: Thyroid autoimmunity; Hypothyroidism; Infertility; Endometriosis; Screening

INTRODUCTION

Thyroid dysfunction is associated with adverse maternal and fetal outcome, but screening for thyroid dysfunction in women of childbearing age is widely debated [1-3]. American Thyroid Association (ATA), Endocrine Society (ES), and European Thyroid Association (ETA) all advocate a case finding strategy in high-risk women. It is however shown that this strategy misses 30 % of women developing subclinical hypothyroidism during pregnancy[4]. Assisted Reproductive Technologies (ART) and pregnancy put a strain on the pituitary-thyroid-axis with the risk of thyroid hypofunction at a critical period of fertilisation and gestation. This is in particularly pronounced in women with Thyroid Auto Immunity (TAI), which is characterized by formation of anti-thyroid antibodies, including anti-thyroperoxidase (TPO-Abs) and anti-thymoglobulin antibodies (TG-Abs), often causing hypothyroidism. Currently, screening for TAI is not recommended as part of infertility work-up.

Two prospective studies [5,6] have shown that 20 % of prenatally euthyroid women with TAI develop Sub Clinical Hypothyroidism (SCH) during pregnancy. In TAI positive women, a single thyroid test prenatally might thus prove insufficient. Therefore identifying women at risk is crucial.

Autoimmune thyroid disease is frequent in women of childbearing age [7]. Studies of the prevalence of TAI among women with infertility are diverging, and a possible increased prevalence of TAI may depend on the underlying cause of infertility[8].

Endometriosis affects up to 10% of women in their reproductive years and as many as 50 % of women with infertility have endometriosis [9]. Endometriosis fulfils many of the criteria for autoimmune disease and is associated with such [10]. Some studies indicate that the risk of TAI is higher among women with infertility caused by endometriosis as compared to other causes [11,12]. Reports on the topic however are diverging [13].

Therefore we undertook this study to systematically review the litterature to determine if women with endometriosis were more prone for thyroid autoimmunity.

MATERIAL AND METHODS

This review is based on the PRISMA statement [14].

PubMed, Embase, SveMed, Cochrane, and Cinahl were searched for studies made on the presence of antithyroid antibodies in infertile women with endometriosis, published between 1990 and 2015.

The terms 'infertility' OR 'endometriosis' were combined with thyroid AND autoimmune thyroiditis OR TPO antibodies OR Thyroid microsomal antibodies OR autoantibodies OR thyroglobulin.

The search was performed in June 2015 and was made independently by two of the authors HFB and DGL.

The reference lists of the included studies were examined to identify additional articles relevant to this review.

Titles and abstracts of the retrieved studies were screened for study design, type of exposure, and outcome.

Papers were reviewed by two of the authors and all data were extracted in a data extraction form covering eligibility, population and setting, methods, participants, outcomes, results, and applicability. Where disagreements were found all the authors examined the papers.

Articles considered relevant or potentially relevant was critically read in full length.

Studies had to be published as full-length articles in English.

In general, studies had to encompass a study group of infertile women and causes of infertility should be accounted for.

The prevalence of TAI between groups was compared.

For validity assessments on the quality of the included studies, we used the Newcastle-Ottawa Scale, which scores the selection, comparability, and the ascertainment of outcome or exposure.

RESULTS AND DISCUSSION

A flow diagram of the systematic search is shown in (Figure 1).

A total of 503 papers were identified in our database searches. After duplicates were removed, 270 did not meet the inclusion criteria.

18 papers were critically read in full and evaluated. Fifteen papers were excluded, because they had other endpoints or did not differentiate between the various causes of infertility ($n = 10$), could not be retrieved in full-length articles ($n = 1$), or elaboration was

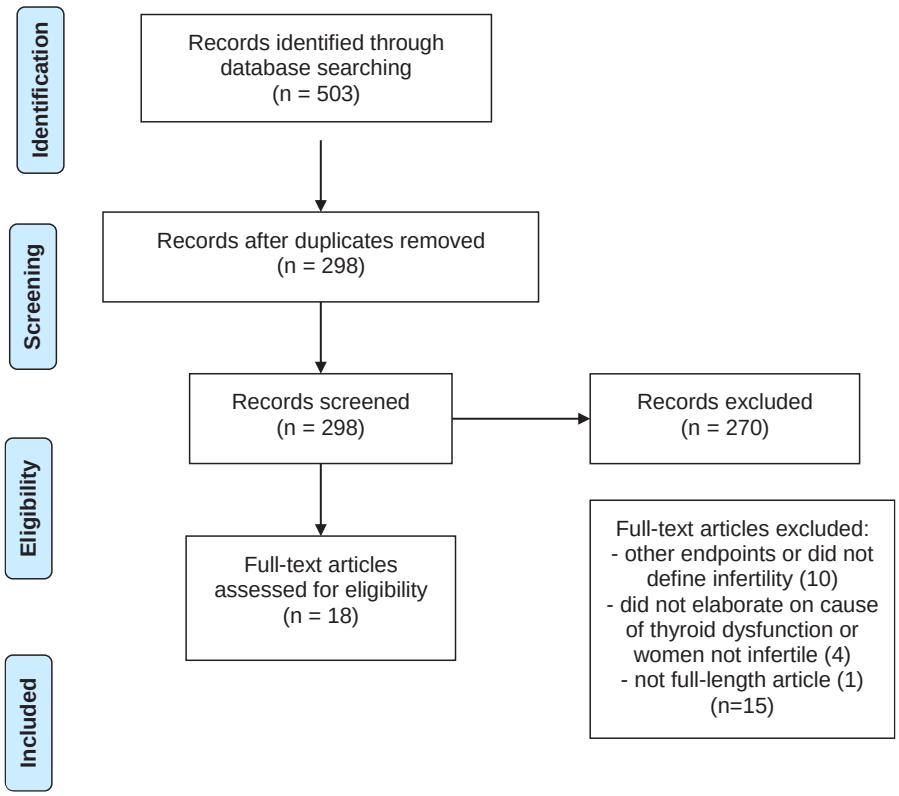

Figure 1: PRISMA flow diagram describing the systematic search and selection.

Table 1: Summary and quality scores of the included studies.

	Poppe et al. 2002 (12)	**Abalovich et al. 2007** (15)	**Unuane et al. 2013** (16)
Study population	Cases (n=438) women with various causes of infertility, female infertility in 197, idiopathic infertility in 73. Male infertility in 168 Controls (n=100) age matched healthy parous women	Cases (n= 244) consulting on infertility. Control (n=155) healthy fertile women.	Cross-sectional analysis. Cases, infertile women (n= 451), fertile controls (n =458)
N	270	244	451
Endometriosis in total infertile	21/270=8%	16/244 = 7%	65/451=14 %
TAI in total infertile	40/270=15%	62/244=26%	81/451 = 18%
TAI in infertile women with endometriosis	6/21=29%	4/16=25%	13/65 =20 %
TAI in infertile women without endometriosis	34/249=14%	58/228=22%	68/386=18%
TAI in fertile controls	8/100= 8%	Not reported	60/458 = 13 %
Outcome Measures	Presence of TPO abs, serum TSH, and free T4.	Levels of TSH and TPO. Diagnose of SH and pregnancy rate in hypothyroid women in L4 treatment.	Thyroid dysfunction (serum TSH and T4) and prescence of TAI (TPO and Tg- abs)
Evidence level	III	III	III
Results	Significantly higher prevalence of TPO abs in women with endometriosis (p=0.016). Significantly higher prevalence in women with female infertility (all causes except idiopathic included) compared to controls (p=0.024)	TAI found in 25% of women with endometriosis. Although not significant, more women with female infertility were found to have TAI compared to controls.	TAI (both TPO and/or Tg) in 13 women with endometriosis. Significantly higher prevalence in women with female infertility (all causes except idiopathic included) compared to controls (p=0.047)
NOS score	5	4	4
Association	Strong	Weak	Weak

not made on whether the thyroid dysfunction was due to thyroid autoimmunity, or none of the women with endometriosis were reported infertile (*n=4*).

Three articles were found relevant for our review on the prevalence of TAI in infertile women with endometriosis.

An overview of the papers can be found in table 1 and below.

Poppe and Abalovich [12-15] reported TPO-Abs whereas Unuane [16] reported measures of both TG-Abs and TPO-Abs.

Poppet et al. [12] studied women with various causes of infertility and healthy controls to evaluate the prevalence of autoimmune thyroid disease. The women were consulting the Center for Reproductive Medicine in Brussels, Belgium.

There were 21 patients with endometriosis among the study group of 270 infertile women. Among infertile patients with endometriosis, prevalence of TAI was significantly higher compared to the remaining infertile women (29 % vs.14 %). The prevalence of TAI among the fertile control group was 8 %.

Abalovich et al. [15] determined the prevalence of TAI as well as different grades of subclinical hypothyroidism in a population of infertile women presenting at the Reproductive Section of the Endocrinology Division at the Hospital Carlos Durand, Buenos Aires.

Endometriosis was the cause of infertility in 16 of the 244 infertile women and TAI was observed in 25 % of these women. This prevalence was not significantly different from the prevalence of TAI among the remaining infertile women. The prevalence of TAI measured in a subgroup of the fertile controls was 15 %.

In women consulting for fertility treatment, Unuane et al. [16] reviewed the question of the potential added value of thyroglobulin antibodies in the detection of thyroid autoimmunity. In line with previous studies, the women were consulting a tertiary referral; Center for Reproductive Medicine, at the Universitair Ziekenhuis in Brussel, Belgium. Of the 451 infertile women, 65 had endometriosis.

The authors found that 20% of the women with endometriosis were TAI positive. Of these women 77% were positive for both types of antibodies, 15% had isolated TPO-Abs, and 8% had isolated TG-Abs.

In the group of infertile women without endometriosis, the prevalence of TAI was 19%. Among the fertile controls the prevalence was 13 %.

To screen or not to screen thyroid function in fertile women is being debated widely. A thyroid function test (thyrotropin) is recommended by endocrine societies as part of infertility work-up. However, there is no recommendation on screening for TAI.

Adverse fetal cognitive consequences of maternal hypothyroidism is well documented, and recent studies indicate a risk of abortion, reduced psycomotoric performance[17-19] and risk of preterm delivery in offspring of mothers with even Sub Clinical Hypothyroidism (SCH) and low-normal thyroid function[20]. Pregnancy puts a strain on the pituitary-thyroid-axis and it is accepted that presence of TAI increases risk of developing SCH or hypothyroidism during pregnancy. Despite reluctance to screen for TAI, guidelines from ATA, ETA and ES are unanimous considering the recommendation to take action on TAI in pregnant women; that is in TAI positive women to do regular thyroid function tests and in selected cases initiate levothyroxine treatment during pregnancy.

Studies have indicated that ART may burden thyroid function as well with the risk of thyroid hypofunction at a critical period of fertilisation and gestation. Presence of TAI negatively affects ovarian stimulation [21], and all together, this might call for a special attention towards the presence of TAI in infertile women seeking fertility treatment. Sharing similarities with autoimmune disease, endometriosis may be a condition of special concern in this regard.

Reviewing the literature we found only three studies on this topic. Prevalence of TAI among the fertile controls varied from 8 to 14 %. Prevalence of TAI among infertile without endometriosis varied from 14 to 22%, while the prevalence of TAI among infertile women with endometriosis varied from 20 to 29%. However, only one of these three studies found that the prevalence of TAI was significantly higher among the infertile patients with endometriosis.

CONCLUSION

Due to the sparse literature on the topic and small study groups, we were not able to draw any firm conclusions. However, the studies did demonstrate a high occurrence of TAI among infertile patients in general and especially in infertile women with endometriosis.

This might call for a special attention towards detecting TAI in infertile women, in case of which repeated measurements of thyroid function may be warranted.

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