

Female Infertility and Serum Auto-antibodies: a Systematic Review

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Abstract On average, 10 % of infertile couples have unexplained infertility. Auto-immune disease (systemic lupus erythematosus, anti-phospholipid syndrome) accounts for a part of these cases. In the last 20 years, aspecific auto-immunity, defined as positivity of auto-antibodies in blood sample without clinical or biological criteria for defined diseases, has been evoked in a subpopulation of infertile women. A systematic review was performed (PUBMED) using the MESH search terms “infertility” and “auto-immunity” or “reproductive technique” or “assisted reproduction” or “in vitro fertilization” and “auto-immunity.” We retained clinical and physiopathological studies that were applicable to the clinician in assuming joint management of both infertility associated with serum auto-antibodies in women. Thyroid auto-immunity which affects thyroid function could be a cause of infertility; even in euthyroidia, the presence of anti-thyroperoxidase antibodies and/or thyroglobulin are related to infertility. The presence of anti-phospholipid (APL) and/or anti-nuclear (ANA) antibodies seems to be more frequent in the population of infertile women; serum auto-antibodies are associated with early ovarian failure, itself responsible for fertility disorders. However, there exist few publications on this topic. The methods of dosage, as well as the clinical

criteria of unexplained infertility deserve to be standardized to allow a precise response to the question of the role of serum auto-antibodies in these women. The direct pathogenesis of this auto-immunity is unknown, but therapeutic immunomodulators, prescribed on a case-by-case basis, could favor pregnancy even in cases of unexplained primary or secondary infertility.

Keywords Infertility · Assisted reproduction · Reproductive technique · Auto-immunity · Serum auto-antibodies · Anti-nuclear antibodies · Anti-phospholipid antibodies · Immunomodulator

Introduction

The fertility of a couple is defined as their ability to obtain a pregnancy. In humans, fertilizability (monthly probability of initiating a pregnancy) is difficult to estimate but is thought to be about 20 to 30 %. The 12-month rate of infertility (absence of pregnancy despite regular unprotected sexual intercourse) is estimated as 9 % worldwide, and among these couples, 56 % consult for this reason [1]. In Europe, 60-month infertility (WHO definition) had a prevalence of 1.5 % in 2010 [2]. The causes of infertility can be divided into three main categories for which the prevalence is variable [3, 4]: female causes (33 to 41 %), male causes (25 to 39 %), and mixed causes (9 to 39 %). Male infertility is due to low or abnormal sperm function, blockages that prevent the delivery of sperm, varicocele, infection, tumors, hormone imbalances, or anti-sperm antibodies. The main etiologies for female infertility are ovulation disorders (polycystic ovary syndrome, hypothalamic dysfunction, premature ovarian insufficiency, etc.), tubal infertility, endometriosis, and/or uterine and cervical causes (cervical stenosis, polyps, tumors, etc.). Depending on the

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studies and their inclusion criteria, 8 to 20 % are labeled “unexplained or idiopathic infertility” at the conclusion of an etiologic assessment. The contribution of serum auto-antibodies to infertility remains debated, but some data tend to show its role in infertilities classified as idiopathic. In the context of an identified auto-immune disease, and in particular for anti-phospholipid syndrome (APS) and systemic lupus erythematosus (SLE), the risk of infertility is now well described [5, 6]. In contrast, apart from these precise nosologic contexts, few data exist on serum auto-antibodies and its influence on female fertility. Aspecific auto-immunity was defined as positivity of auto-antibodies in blood sample, without clinical or biological criteria for defined diseases (SLE, Sjogren syndrome, APS, scleroderma, etc.). During implantation and pregnancy, plethora of tolerance measures is put into action by both the mother and the fetus. Pre-implantation immunological events are in place to best prepare the nidation of the fetus into the mother endometrium. For example, recent study has shown a Th1 to Th2 shift with increase interleukin (IL)-10 synthesis and a decrease response to pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6 during pregnancy [7]. Presence of a wide spectrum of auto-antibodies correlates with the parturient pathophysiological course; however, when an association between an antibody and a type of disease has been found, this does not necessarily mean that there is a causal infertility.

We thus propose a review of the literature to assist the management of this particular aspect by both internists and specialists in assisted procreation. Here, we did not consider the data from the literature concerning the iterative miscarriage and focused on aspecific auto-antibodies, out of a clinical entity context.

Methods

A review of data in the literature was performed (PUBMED), using the following MESH search terms: “infertility” and “auto-immunity” or “reproductive technique” or “in vitro fertilization” or “assisted reproduction” and “auto-immunity.” We retained clinical and physiopathological studies that were applicable to the clinician in assuming joint management of both infertility associated with serum auto-antibodies in women; meta-analysis and reviews were excluded to avoid duplicates. We described only data published in English, including all female patients and excluded patients younger than 18 years old. Studies were included if they were a cohort design, including prospective and retrospective, randomized or not, and controlled or not. Two reviewers independently selected eligible studies and extracted the relevant data. Data extraction included general characteristics of the study (study design, year of publication, sample size, type of tests used, control population if any), characteristics of the

study groups and outcomes. We excluded studies about patients with a defined auto-immune disease diagnostic and concerning auto-immunity with iterative miscarriage; study about male infertility was excluded.

Results

One hundred sixty-three manuscripts were identified and screened according to methods above; 85 were retrieved for detailed evaluation. Sixty were included in this review; exclusion's criteria are described in Fig. 1. Main data are summarized in Table 1.

Anti-phospholipid Antibodies

Anti-phospholipid syndrome (APLS) is diagnosed according to the criteria of Sapporo established in 1999, with recognition of an obstetric form of APLS, characterized by one out of three clinical conditions (at least three spontaneous miscarriages before 10 weeks of gestation or at least one unexplained fetal death after 10 weeks or premature delivery before 34 weeks of gestation related to a vasculo-placental pathology) associated with one immunological markers in two samples taken at an interval of at least 12 weeks (lupus anticoagulant or anti-cardiolipin antibodies or anti-beta2 glycoprotein-1 antibodies -beta2-GP1- measured by a standardized ELISA test) [8]. However, in the absence of these criteria, one cannot retain the diagnosis of obstetric APLS.

Nevertheless, in 2006, in a cohort of 69 infertile women compared with 120 fertile women [9], a significantly higher prevalence of anti-phospholipid antibodies (APL) was found, in particular of the anti-prothrombin antibodies (OR, 5.11, prevalence of 12 vs. 2 %, respectively; $p < 0.05$).

However, most of the studies concerned prevalence of APL in infertile women undergoing assisted medical procreation (AMP), especially in vitro fertilization (IVF); data found a strong association according to certain studies in infertility

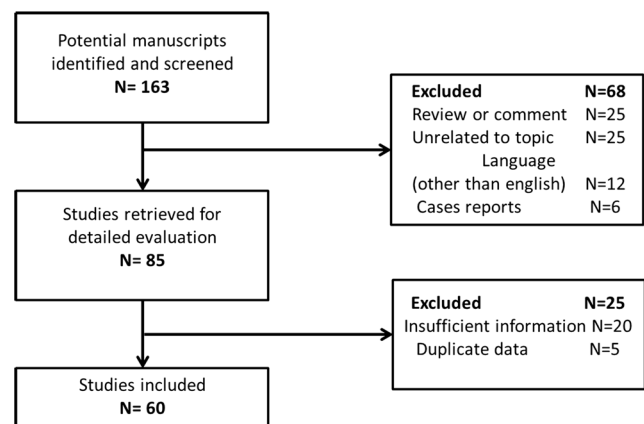


Fig. 1 Flow-chart of the study. *N* number of manuscript

Table 1 Summary of data available for serum auto-antibodies, in case of infertility, IVF or ICSI-IVF and treatment proposed

Antibodies	APL	ANA	Anti-tissue	Thyroid auto-immunity	Anti-ovarian	Others
Women infertility	Higher prevalence (anti-prothrombin) with OR 5.11 [9, 10, 22]. Weak influence of APL in fertility (rate, 0.58–4.72) [15]	Increased prevalence (20 vs. 3 % in infertile women [26]) and between 10–20 % [27, 28]	Higher prevalence of anti-smooth muscle antibodies (35 % infertile vs. 3 % in fertile women) [26, 28]	Higher prevalence [41, 42] for anti-TPO and anti-TG [43]	Higher prevalence [53–55]	Higher prevalence of ASCA [9] and of CD-associated auto-antibodies [62–65]
IVF	Higher prevalence of anti-beta2-GP1 level [13] and APL levels but no influence on the IVF results [10]. No association between APL and the results of IVF [12]	Lower rate of implantation [30, 32] and pregnancy [31, 32]. Positive correlation between ANA level and fertility rate [32]	n.a.	Lower rate of fertilization implantation and pregnancy [44]	Higher prevalence [53–55]	n.a.
ICSI-IVF	No association between APL and ICSI-IVF [11]	n.a.	n.a.	No incidence in the prognosis of FIV-ICSI [45–48]	n.a.	n.a.
Treatment	Aspirin 80 mg/day + prednisone 10 mg/day [21]. No efficacy for aspirin + heparin [22] but higher rate of pregnancy [23]	Cf Table 2	n.a.	n.a.	n.a.	n.a.

APL anti-phospholipid, TPO thyroperoxydase, TG thyroglobulin, ANA anti-nuclear antibodies, B2-GP1 beta2-glycoprotein-1, ASCA anti-*Saccharomyces cerevisiae* antibodies, CD celiac disease, IVF in vitro fertilization, ICSI-IVF intracytoplasmic sperm injection-IVF, n.a. not available

women [10] but nonexistent for others in IVF-ICSI [11]. A meta-analysis that included 2053 women undergoing IVF for infertility, of which 703 (34 %) showed at least an elevated level of APL (anti-cardiolipins or anti-beta2-GP1) did not find any association between APL and the results of in vitro fertilization [12]. In 2014, a French team [13] found an increased level of APL (20 %, $p < 0.0005$), primarily anti-beta2-GP1, in a population of infertile women requiring IVF compared with a group of fertile women. Nonetheless, there appears to be no difference in the success of embryonic implantation and the number of IVF necessary. Thus the role of APL is debatable in IVF, contrary to miscarriage [14]. In a review in 2008, Cervera et al. [15] reported the rate of pregnancy in patients presenting with APL to be between 0.58 and 4.72 over that of patients without APL, suggesting a weak influence of APL on fertility. It is now well established that APL recognize the surface antigens of the syncytiotrophoblast. They are at the origin of the damage leading to the dysfunction of this structure that is essential for the good progression of pregnancy, even in the absence of macroscopic thrombosis [16, 17]. The histological studies in mice presenting with the APS highlight vasculotrophoblastic lesions and atypical villary necrosis [18]. A recent study [19] showed an inflammatory response on gene expression analysis of decidual stromal cells treated with a β 2-GP1-

dependant APL monoclonal antibody, interfering with uterine decidualization and affecting the early stages of implantation. Treatment with immunomodulators could be an interesting approach to improve the fertility of these patients presenting with APL [20]. However, the available studies are underpowered. Treatment with aspirin (80 mg/day) and prednisone (10 mg/day) 2 weeks before the initiation of IVF in 15 patients presenting with APL or anti-nuclear antibodies (ANA) [21] produced a success rate of 47 % (seven patients). These encouraging but uncontrolled results were then explored in larger series. Kutteh et al. [22] found a prevalence of 18.8 % APL among 191 infertile patients. Of the 36 patients presenting with APL, the 19 treated with aspirin + heparin had a rate of pregnancy of 52.6 %, against 47 % for the 17 untreated patients (no significant difference). The largest therapeutic series [23] found a significantly higher rate of pregnancy after a treatment with subcutaneous heparin (5000 UI) twice a day associated with aspirin 80 mg/day (49 vs. 16 % among untreated women, $p < 0.05$).

By analogy with the treatment of APS in its obstetric forms according to the criteria of Sapporo [24], an association of low-dose aspirin and heparin would be the treatment of choice. In the same way, treatment with hydroxychloroquine ($6 \text{ mg kg}^{-1} \text{ day}^{-1}$) could constitute an effective and simple

therapy in the context of APS in infertile women, as shown by Mekinian et al. [25] in a different context of in utero fetal death and miscarriage. Physiopathology thus suggests a role of APL in the cause of infertility, despite the conflicting results of surveys of incidence. These problems are largely related to differences in the clinical criteria of infertility as well as to discrepancies in the laboratory tests used in research on APL. The inclusion criteria (antibody type, methods, and other auto-immune diseases) in studies assessing the incidence of APL in female infertility need to be standardized before being able to conclude. In the absence of randomized studies, the dosage of these auto-antibodies in the initial assessment of infertility is not recommended, except in cases of iterative miscarriage where the indication for dosage is irrefutable.

Nonspecific Anti-nuclear Antibodies

Nonspecific (or aspecific) serum anti-nuclear auto-antibodies was defined as immunofluorescent positivity for ANA, without any defined antigens in other techniques (ELISA, Blot) and without criteria for defined diseases (systemic erythematosus lupus, Sjogren syndrome, scleroderma, etc.).

A historical series in 1975 [26] found an increased prevalence of ANA in a group of women presenting early ovarian failure ($n = 77$) compared with a group of fertile women ($n = 75$), with a frequency of 20 and 3 % ($p < 0.05$), respectively. More recent studies confirm this increased prevalence (between 10 and 20 % in infertile patients against 3 to 4 % in fertile women) [27, 28]. The presence of ANA in patients presenting fertility disorders seems relevant following the results of a North-American study which showed that the prevalence of ANA was inversely associated with parity (OR, 2.0, $p = 0.001$) [29]. Estrogenic therapy (oral contraception) does not modify the prevalence of ANA [29].

In the context of IVF, a retrospective study [30] showed a lower rate of embryo implantation in women positive for ANA (14 vs. 32.4 %). Other studies reported a lower rate of pregnancy (28.1 vs. 46.4 %, $p < 0.05$) [31], and even a positive correlation between the level of serum ANA and fertility rate [32], not found in another contemporary study [33]. The more interesting study investigated 517 infertile women undergoing IVF treatment [34] between 2012 and 2014; the authors found higher level of serum ANA in the IVF group than in the control group (39.45 vs. 16.13 %, $p < 0.001$), lower level of implantation rate (16.09 vs. 27.03 %, $p < 0.001$) and clinical pregnancy ($p = 27.72$ vs. 45.03 %, $p < 0.001$) in the ANA-positive patients than in the ANA-negative patients, level dependent for ANA titer (1/100 vs. 1/320).

The multiple therapeutic studies [32, 35–38], although difficult to compare, are summarized in Table 2. Treatment with prednisone and aspirin does not decrease the level of ANA, and the modifications observed in this level during treatment do not correlate with the prognosis of the IVF

[32, 35]. While the corticoid posology is too low to reduce the antibody titer, its effect can be attributed to other mechanisms (anti-inflammatory action or reduction in endometrial natural killer cells). In the same way, the anti-thrombotic action of low-dose aspirin can reduce uterine and ovarian vascular resistance and improve the maturation of oocytes and the rate of implantation.

The mechanism leading to infertility attributed to ANA is only speculative. ANA are found in the follicular fluid and embryos of the patients showing a positive serum ANA levels with a negative correlation between the level and the number of good-quality embryos obtained [31]. These ANA levels could either be a reflection of an abnormally high dysimmunity in these patients or could have a direct detrimental effect. This direct detrimental effect was suggested by the work of Simerly et al. [39], which showed that in vivo injection of specific ANA (anti-centromeres) into mouse oocytes blocks their maturation at the pro-metaphase stage. In addition, the culture of embryos with ANA added to the culture medium led to the destruction of these embryos [31]; in 1999 [40], the authors showed a halt in murine embryonic development when the embryos were incubated with human auto-antibodies. These data suggest that it may be interesting to search for their presence in IVF in cases of persistent fertilization failures or in the event of repetitive precocious embryo fragmentation.

Anti-tissue Antibodies

The historical series of Wilson et al. in 1975 [26] found an elevated prevalence of anti-smooth muscle antibodies in infertile women without any particular clinical significance apart from infertility (35 vs. 3 % in fertile women, $p < 0.05$). This result was confirmed by a study in 2001 [28] showing a similar prevalence (respectively, 27.8 vs. 5.1 %, $p < 0.05$), with an anecdotic level of anti-gastric parietal cell antibodies and anti-mitochondrial antibodies in this series. However, despite the elevated prevalence, to our knowledge, no therapeutic study has been performed.

Thyroid Auto-immunity

Prevalence studies are in favor of an association between thyroid auto-immunity and infertility [41], but there were no evidence for a causal relationship. In women presenting auto-immune dysthyroidy [42], the prevalence of infertility reached 47 % (Grave's disease) and 52 % (Hashimoto disease) with persistence of infertility despite obtaining euthyroidy; however, this high rate of infertility were not confirmed by others [43] and methodological setup of this study was weak to investigate the prevalence of infertility. According to Unuane et al. [43], anti-thyroperoxidase (TPO) and anti-thyroglobulin (TG) antibodies are twice implicated (16 %

Table 2 Summary of therapeutic studies on ANA-positive infertile women

Reference	Population	Treatment	Duration	Efficacy
[32]	IVF-ICSI ANA+ ($n = 21$)	Prednisone 10 mg + aspirine 100 mg	Up to 3 months before IVF-ICSI	Increase in the number of suitable embryos (5.76 vs. 3.62), the rate of pregnancy (57.1 vs. 12.5 %) and of implantation (37.9 vs. 6.06 %)
[34]	IVF-ET ANA+ treated (number of cycles = 69) vs. untreated (350)	Prednisolone 10 mg + aspirine 81 mg	During the IVF cycle	Improvement in the rate of pregnancy (40.6 vs. 14.8 %) and of implantation (20.3 vs. 6.8 %)
[35]	IVF and ANA+ ($n = 51$) vs. ANA- ($n = 29$)	Prednisolone 5 mg or dexamethasone 0.5 mg	During the IVF cycle	Improvement in the rate of pregnancy (35.3 vs. 10.4 %) and of implantation (13.2 vs. 3.8 %)
[36]	IVF-ET ANA+ treated vs. ANA+ untreated	Prednisolone 15 to 60 mg/day	5 days	Improvement in the rate of implantation and pregnancy
[37]	IVF-ET ANA+ (52 women)	Prednisone 10 mg/day + aspirin 100 mg/day	4 weeks before induction of ovulation until IVF	Rate of pregnancy 32.7 %. No increase in the risk of gestational diabetes or arterial hypertension

IVF in vitro fertilization, ICSI intracytoplasmic spermatozoid injection, ET embryo transfer, ANA anti-nuclear antibodies

prevalence in an infertile population, with presence of isolated anti-TPO in 5 % of cases, anti-TG in 4 % of cases, and 8 % with double positivity).

These conclusions are debatable for the women undergoing IVF-ICSI. In a study in 2012 [44], 90 women presenting with anti-thyroid antibodies had a significantly lower rate of fertilization, implantation and pregnancy than women without these antibodies in a cohort of 676 infertile women, respectively 64.3 vs. 74.6, 17.8 vs. 27.1 %, and 33.3 vs. 46.7 %. On the contrary, Tan et al. [45] highlighted the absence of any significant difference in the prognosis of IVF-ICSI in the presence of anti-TPO or anti-TG among 835 women with normal thyroid function, as did Chai et al. [46] for the prognosis of IVF; it has been confirmed by a recent meta-analysis [47] from 5286 infertile women showed that clinical pregnancy rates were similar between euthyroid women with positive or without anti-thyroid antibodies. Thyroid auto-immunity seems not impair assisted reproductive treatment outcomes; ICSI may be the preferred assisted reproductive method in infertile women with thyroid auto-immunity instead of conventional IVF for Monteleone et al. [48] who described for the first time the presence of anti-thyroid antibodies in ovarian follicles.

Thus, if the thyroid hormones seem essential to the maturation of the oocytes and to the menstrual cycle [49], the discussion of the deleterious effect of the anti-thyroid antibodies remains outstanding. Several prevalence studies seem to favor of a clear role [9, 50] as well as a study in mice [51]. The presence of these auto-antibodies is greater in the context of early ovarian insufficiency, Addison's disease, endometriosis, or a syndrome of the poly-cystic ovaries syndrome [52].

Anti-ovarian and Adrenal Immunity

A readily detectable condition is early ovarian insufficiency, defined as a deficit in the pool of available oocytes before 40 years age. As well as infections or iatrogenic causes, an auto-immune etiology was proposed in the nineties, in particular by the description of anti-ovarian auto-antibodies and ovarian lymphocyte T CD4+ and CD8+, plasmocyte and macrophage infiltration in these women [53]. In this population, an increased prevalence of ANA (10.5 vs. 3.3 %) was observed [54], along with anti-thyroid antibodies and serum antibodies directed against the cell-producing steroid hormones (adrenal cortex, placenta, ovary, etc.) [55]. The anti-ovarian antibodies have several recognized targets, in particular the ooplasm, the zona pellucida (recognized in 5.6 % of women presenting early ovarian insufficiency [56]), the cells of the granulosa, and the 3beta-OH gonadotrophin dehydrogenase receptors, whose presence can be correlated to the prognosis of IVF [53–55]. Concerning Addison's disease (an auto-immune adrenal insufficiency), a study in 2004 [57] highlighted the presence of antibodies directed against a variety of steroid hormone producing cells in 60 % of women with early ovarian insufficiency. In the last few years, several publications have appeared on the characterization of new ovarian auto-antigens [58]. This could help towards understanding auto-immunity associated with ovarian infertility in the subgroup of women having infertility linked to primitive ovarian auto-immunity. The detection of these auto-antibodies is not still validate but could be interesting in particular in the context of thyroid, adrenal auto-immunity and for auto-immune polyendocrinopathies.

Auto-immunity Directed Against the Endometrium and the Trophoblast

A review from Berkkanoglu et al. [59] found a statistically significant association between endometriosis, a major cause of female infertility, and organ specific auto-immunity. For endometriosis, the target antigens implicated seems to be primarily endometrial, endothelial, or thyroid antigens and more often of laminine-1 type [60]. This protein intervenes in cellular differentiation and homeostasis and in the early stages of embryo implantation and in organogenesis. Interestingly, these data suggest an additional cause of infertility in women affected by endometriosis. For Seery [61], a reduction in the clearance of apoptotic endometrial cells in an inflammatory context could be at the origin of the production of auto-antibodies in women genetically predisposed to auto-immune diseases. However, at present, there exists no proof of the detrimental nature of these auto-antibodies.

Celiac-Disease-Associated Auto-antibodies

A recent meta-analysis [62] found a higher prevalence of celiac disease (CD) in patients with unexplained infertility than the general population (OR, 5.06, 2.13–11.35). Positive serology (IgA anti-transglutaminase or TG, endomysial antibody) without clinical and histology criteria of CD (called latent or subclinical CD) have been found in 10.3 % women with unexplained infertility by Machado et al. [63], in 5.65 % infertile women by Kumar et al. [64] (with a statistically difference from the control group which

seroprevalence were 1.30 %), and in 1.13 % infertile women (healthy blood donors, 0.45 %) by Vancikova et al. [65].

The pathogenesis of infertility could not only be linked to malabsorption and nutrient deficiency in CD [66] but also by auto-immune mechanisms. In vitro studies provided a pathogenic model of placental damage: direct binding of anti-TG antibodies to trophoblasts were able to reduce trophoblast invasiveness through apoptotic damage [67]; moreover, anti-TG antibodies on endothelial cells were shown to be detrimental to endometrial angiogenesis [68], which was confirmed in vivo in a murine model [68]. In vivo, TG is expressed in endometrial cells as well as in stromal and trophoblast placental cells [69] and may be a target of maternal auto-antibodies in CD.

Other Serum Auto-antibodies

Shoenfeld et al. [9] reported a prevalence study that found isolated and aspecific high levels of anti-*Saccharomyces cerevisiae* antibodies (ASCA), present in chronic inflammatory intestinal diseases, with OR of 3.9 in 269 infertile women. However, this observation has not been repeated since in the field of infertility.

Conclusion

The seroprevalence of certain auto-antibodies in women presenting with fertility disorders seems to be higher than in

Table 3 Simplified auto-immune tests proposed for infertile women at admission to an ART program

Pathology	Assays	Treatment
Auto-immune endocrinopathy	TSH, T3, T4, anti-TPO, and anti-TG plasma cortisol at 8 h <i>Anti-ovarian immunity?</i>	Replacement therapy <i>Corticotherapy</i>
Aspecific auto-immunity	ANA Anti-tissue antibodies <i>Complements (CH50, C3, C4)</i> <i>Serum protein electrophoresis</i>	Corticotherapy Low dose aspirin <i>Hydroxychloroquine?</i> <i>IVIg?</i>
Anti-phospholipid antibodies	Circulating anti-coagulants Anti-cardiolipines, anti-B2-GP1 <i>Blood platelet count</i> <i>Other: TPHA-VDRL, anti-prothrombin, anti-phosphatidylserine?</i>	Corticotherapy Low dose aspirin Anti-coagulants (heparin) <i>Hydroxychloroquine?</i> <i>IVIg?</i>
CD-associated antibodies	IgA and IgG anti-transglutaminase, IgA and IgG anti-endomysium	Gluten-free diet
Other	<i>ASCA?</i> <i>ANCA?</i>	?

The recommendations in italics have not been proven and have been proposed by the authors. *TSH* thyroid stimulating hormone, *TPO* thyroperoxydase, *TG* thyroglobulin, *ANA* anti-nuclear antibodies, *B2-GP1* beta2-glycoprotein-1, *CD* celiac disease, *ASCA* anti-*Saccharomyces cerevisiae* antibodies, *ANCA* anti-neutrophil cytoplasmic antibodies, *IVIg* intravenous immunoglobulins

fertile women. However, questions concerning the type of auto-antibody to explore and when tests should be performed remain unanswered. Essays used to measure antibodies (like APL, ANA, etc.) in the different studies and laboratories need to be homogenized to provide bias-free conclusion. The case-series studied are generally outdated, of small size, and with contradictory data. More preclinical and observational studies are needed, before a multicenter, prospective and randomized study, to conclude. In the current state of knowledge, it seems interesting to carry out an auto-immune assessment (Table 3), as already proposed by Zhu et al. in 2013 [33]. Women with unexplained infertility or acquired secondary infertility are subgroups of patients who should receive greater attention.

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Compliance with Ethical Standards

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interests The authors declare that they have no conflict of interests.

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