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Review

The hidden world of anti-phospholipid antibodies and female infertility: A literature appraisal

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ABSTRACT

Even though the association of anti-phospholipid antibodies (aPL) with infertility is debated, infertile women are commonly screened for aPL. To review evidence, a systematic PubMed search was conducted to retrieve papers addressing (i) the association between aPL and infertility, (ii) the positivity rate of criteria and non-criteria aPL in women with infertility, (iii) the association between aPL and assisted reproduction technologies (ART) outcome, (iv) the efficacy of medical treatments on ART outcome, and (v) the effects of ART on thrombotic risk. A total of 46 papers were considered; several limitations emerged: (i) wide heterogeneity in study populations, (ii) non-prospective design in 90% of studies, and (iii) aPL cutoffs not conforming to international guidelines in more than 75% of studies; aPL positivity not confirmed in 89% of studies. Most studies evinced an association between infertility and anti-β2GPI antibodies and almost all non-criteria aPL. The association rate with infertility was below 50% for lupus anti-coagulant, anti-cardiolipin antibodies (aCL), and anti-phosphatidic acid antibodies. According to our estimates, overall positivity rates of criteria and non-criteria aPL tests are 6% and 3% among infertile women, 1% and 2% among controls, respectively. A significant difference in the positivity rate of patients versus controls emerged for aCL only. Five of 18 studies reported a detrimental effect of aPL on ART outcome. Only one of the six studies assessing the effects of treatment on ART outcome among aPL-positive infertile women reported a benefit. All relevant studies reported no increase in the rate of thrombosis among aPL-positive women undergoing ART.

Contents

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1. Introduction

Anti-phospholipid antibodies (aPL) are the serological markers of the anti-phospholipid syndrome (APS), a systemic autoimmune condition characterized by vascular thrombosis and/or pregnancy morbidity. Three tests are considered in the updated criteria for APS classification: two solid-phase assays detecting antibodies against cardiolipin (aCL) and beta-2 glycoprotein I (anti-β2GPI antibodies) plus the functional test for lupus anticoagulant (LA) [1]. aPL do not provide merely serum APS biomarkers but rather exert a direct pathogenic role in mediating both vascular and obstetric events. Given the deleterious effects played by aPL on gestation, it has been postulated that these autoantibodies might be involved in infertility [2]. Infertility is defined as the inability of a sexually active, non-contracepting couple to conceive over a twelve-month period. Infertility is a common condition; it has been estimated to affect 8–12% of couples with a woman in childbearing age. Female and male infertility are equally prevalent, therefore both partners should be investigated with an exhaustive routine work-up. Men should undergo two semen analyses; assessment of female fertility should include the measurement of serum progesterone in the mid-luteal phase to rule out ovulatory dysfunction, the screening for chlamydia antigen, and a hysterosalpingogram to evaluate tubal patency. As second-line investigation, a diagnostic laparoscopy with dye transit should be performed to evaluate the pelvis in case of strong suspicion of endometriosis, tubal occlusive disease, or adnexal adhesions. Despite a full diagnostic evaluation, approximately 20% of infertility cases remain unexplained [3,4].

Reproductive problems exert a considerable psychological stress, making it easy to understand why novel potential causes of infertility are so attractive. Many physicians devoted to infertility routinely screen for aPL and treat infertile women with aPL positivity whilst they are undergoing assisted reproduction technologies (ART) [5]. This approach is pursued despite the recommendations of the American Society for Reproductive Medicine—in a critical review published in 2008, the society concluded that aPL positivity is not associated with a reduced success of assisted reproduction, thus not justifying aPL screening nor treatment of infertile subjects [6].

In order to update the evidence about the clinical impact of aPL positivity on female fertility, we analyzed currently available papers assessing (i) the association between aPL and infertility, (ii) the positivity rate of criteria and non-criteria aPL in women with infertility, (iii) the association between aPL and ART outcome, (iv) the efficacy of medical treatments on ART outcome, and (v) the effects of ART on thrombotic risk.

2. aPL pathogenic effects on pregnancy

aPL provide the most frequent acquired risk factor for pregnancy complications [7]. Such an association is clearly supported by experimental animal models showing that the infusion of aPL IgG induces fetal loss and growth retardation in pregnant naive mice. Since the first histopathological report of APS placentas by De Wolf and colleagues in 1982, aPL were thought to induce spiral artery thrombosis leading to placental infarction [8]. The resulting impairment of the maternal–fetal blood exchange interferes with pregnancy physiology. Indeed, aPL can induce a procoagulant state by disrupting the anticoagulant annexin A5 shield on trophoblast and endothelial cell monolayers. Consistently, a reduced distribution of annexin A5 covering the intervillous surfaces was observed in placentas of aPL-positive women. However, it is now acknowledged that different mechanisms might also be implicated in APS-associated pregnancy complications, including non-thrombotic etiologies [8,9]. aPL interact with Toll-like receptor (TLR) 4 at placental sites, resulting in the activation of monocytes and endothelial cells, with neutrophil infiltration. aPL-mediated activation of TLR4 elicits a pro-inflammatory response, with up-regulation of pro-inflammatory mediators such as tumour necrosis factor (TNF), interleukin (IL)-1β, and IL-8. In addition, aPL activate the classical pathway of the complement cascade, with increased deposition of the component C4d. The key role played by the complement system in obstetric APS etiopathogenesis is further suggested by the evidence from an in vivo model that animals deficient in complement components are protected from aPL-mediated pregnancy complications. aPL display also a direct effect on trophoblast, with a down-regulation of chorionic gonadotropin and an abnormal expression of integrins and cadherins resulting in a reduced trophoblast proliferation, syncytialization, and invasion [10]. Given the above-cited effects on placentation, it can be envisaged that aPL might affect implantation interfering with early stages of uterine decidualization, thus resulting in female infertility [8,9]. However, no in vivo evidence has been to date raised in support of such hypothesis.

3. Assisted reproduction: a brief overview

ART include three different phases: (a) ovulation induction (OI), (b) in vitro fertilization (IVF) and subsequent embryo transfer to the uterus, and (c) therapy with progesterone or exogenous human chorionic gonadotropin (hCG).

OI might be induced through administration of several different compounds:

- Anti-estrogens, such as clomiphene citrate, an oral non-steroidal estrogen. Clomiphene acts on the hypothalamus as an anti-estrogen to block negative feedback, resulting in a surge of endogenous follicle stimulating hormone (FSH) and luteinizing hormone (LH) and subsequent follicular maturation.
- Gonadotropin-releasing hormone (GnRH), such as leuprolide. When given continuously, GnRH induces a 3-day stimulation followed by rapid suppression of endogenous hormone secretion, allowing a precisely timed ovulation.
- Human menotropic gonadotropin (hMG), such as FSH and LH administered via subcutaneous or intramuscular injections [11].

Ovarian hyperstimulation syndrome provides the most serious complication of regimens, including GnRH or hMG; this is a relatively rare condition characterized by ovarian edema, electrolyte imbalance, and diffuse capillary leak ultimately leading to pleural effusions and ascites, and even hypotension, phlebothrombosis, and hydrothorax [12]. Ovarian hyperstimulation syndrome is thought to result from the elevated serum 17β-estradiol E2 (17β-E2) concentrations achieved during stimulation. The levels of circulating 17β-E2 in women with hyperstimulation can exceed 2000 pg/ml. In controlled OI, plasma estradiol levels reach 1500 pg/ml, which is ten times the average concentration in non-pregnant women but less than one-tenth that at the end of pregnancy (20,000 pg/ml) [11]. Noteworthy, a hypercoagulable state has

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