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Antiphospholid antibodies and the risk of pregnancy complications

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ABSTRACT

Antiphospholipid antibodies (APLAbs) are generally considered as risk factors for foetal death, for premature birth ≤34 weeks due to severe pre-eclampsia or severe placental insufficiency and for recurrent consecutive spontaneous abortions <10 weeks. Among these three obstetrical morbidities, only the first one is however not regularly questioned. The coexistence of an inflammatory disease and/or of thrombotic manifestations increases the obstetrical risks. Among the three criteria APLAbs, i.e. lupus anticoagulant (LA), anticardiolipin (aCL) Abs, anti-β2 glycoprotein-I (aβ2GP1)Abs, LA seems the more widely associated to clinical risks, the clinical impact of aβ2GP1Abs is progressively defined and the pejorative impact of triple positivity is still discussed. High quality prospective multicentric epidemiological studies are still awaited. The identification of predictors of pregnancy outcome is necessary to streamline the design and use of new treatments acting on pathophysiological molecular targets.

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1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune entity defined by clinical and laboratory criteria. It is associated with thrombotic and/or obstetric morbidities. Consensus classification criteria for APS were first proposed in 1998 in Sapporo, Japan [1] and were revised in 2006 in Sydney, Australia [2]. Pregnancy-related clinical criteria include one or more unexplained deaths of a morphologically normal foetus ≥10 weeks' gestational age (foetal death FD, also including stillbirths: intrauterine foetal deaths occurring after 20 weeks, all being defined by a functional uteroplacental circulation), one or more premature births of a morphologically normal neonate ≤34 weeks for severe pre-eclampsia or severe placental insufficiency, or three or more unexplained, consecutive spontaneous abortions <10 weeks (recurrent pre-embryonic loss <6 weeks and embryonic loss <10weeks, in absence of any functional uteroplacental circulation, globally abbreviated under the REL acronym). In women, features at diagnosis can be a purely thrombotic, a purely obstetric or a mixed disease. Investigators are encouraged to stratify groups of women according to their previous pregnancy morbidities [2]. The widely used term "miscarriage", i.e. the death of an embryo or foetus before 20 weeks, is an unacceptable ambiguous term which mixes two different subtypes of pregnancy losses with heterogeneous circulation patterns: studies on recurrent miscarriages areconfusing, the underlying pathophysiological cellular targets and effects of aPLAbs being obviously suspected of heterogeneity. APS can develop in the context of a systemic inflammatory disease (secondary APS, the most emblematic one being SLE) which by itself can have some impact on the evolution of pregnancies. None of the three subgroups of pregnancy morbidities included into the APS diagnosis is still molecularly defined, which do not favour precision medicine and can lead to some false causal associations between antiphospholipid antibodies (APLAbs) and pregnancy morbidities.

2. APLAbs and the risk of recurrent pre-embryonic/embryonic loss REL

Human pregnancy is unique among species by its ineffectiveness. Early loss occurs in 12–14% of clinically recognised pregnancies and up to 30% of conceptions, 2% of women attempting pregnancy experience two consecutive pregnancy loss (PL), as far as 0.4%-1% experience three consecutive losses [3]. Recurrent clinical REL mainly occurs in superfertile women, with abnormaly efficient implantation rates [4]: in this casedecidualising endometrial stromal cells, which serve as sensors of embryo quality upon implantation [5], fail to detect abnormal embryos which are allowed to implant. This impaired natural embryo selection related to an impaired decidualisation causes early placental failure and PL [6]. The

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high rate of early PLs in human beings is the consequence of a complex and tightly regulated molecular process of embryo selection potentially submitted to numerous inborn or acquired errors. The high rate of cytogenetic abnormalities in specimens from couples with REL is thus not surprising (46% using conventional cytogenetic analysis: [7]). A familial predisposition to spontaneous abortion in families where REL occurs is suggested, with evidence of a genetic linkage [8,9], and women with idiopathic recurrent PL tend to have losses recur in the same gestational age period [10], underlying causes being thus at least partly inherited and specific of PL subtypes. All these points act as confounding factors in the association between APLAbs and REL.

The analysis of APLAbs in REL has yielded variable results, the frequency ranging from 5 to 20% [3]. This wide variation is due to the various definitions of pregnancy used (pregnancy test vs. clinical), the number of PLs required for inclusion (at least two vs. three), the variable exclusion of other cofactors for REL, types of APLAbs included in laboratory tests, threshold values for cut-off for APLAbs positivity and finally studies often performed on limited number of patients.

The meta-analysis on the association between APLAbs and REL at less than 13 weeks [11] computed a positive association (OR 3.56, 95% CI 1.48–8.59) between anticardiolipin (aCL) IgG antibodies – including low and moderate to high titers aCL IgG, with no data on lupus anticoagulant (LA) and aCL IgM antibodies, and non-significance on anti-β2 glycoprotein-I (aβ2GP1) antibodies, but only 2 studies could be included into the analysis. A review on studies published before July 2013 only found 4 studies on REL among the 44 on pregnancy morbidities, the overall frequency of criteria APLAbs being 2% (2–6%) [12], with strong general limitations of the literature on APLAbs frequency: 60% of the papers were published before 2000, all 3 criteria APLAb tests were performed in only 11% of the papers, 36% of papers used a low-titer aCL cutoff, aβ2GP1Abs cutoff was quite heterogeneous, APLAbs confirmation was performed in only one-fifth of papers, and the study design was retrospective in nearly half of the papers.. The results from the Salt Lake City group [13] in patients with 2 PLs before 10 weeks found 7 persistently tested positive women out of 338 (2.1%), 4 being positive for aCL IgM and 2 for aβ2GP1 IgM antibodies (no LA positivity): a low prevalence of APLAbs in women with an isolated chief complaint of REL. This is different in secondary APS and in non-purely obstetric APS women [13].

Published results from 2257 patients attending a high-risk pregnancy clinic supports data on the prevalence of LA: only 5 patients were tested positive and had experienced REL [14]. The same group evoking strong doubts on the widely described association between aCLAbs and REL, and on the high diagnosis frequency in medical practice [15], arguing that the current APS classification thresholds are too broad [16], and that patients with lower levels of APLAbs, no LA, and REL only should not be given the APS designation at all. Our recent observational study on REL women showed that purely obstetric APS women treated with the low-dose aspirin-low-molecular weight heparin association do not develop less PL <10 weeks gestation than non-treated women with normal thrombophilia screening tests, but develop less foetal losses: the causality of some positive APLAbs into REL can be questioned. Finally, cut off values for APLAbs are statistically defined (99th percentile of what is observable in a control population), are still non-medically defined, we currently have no idea of the APLAbs levels which can by itself induce pregnancy loss. Women with REL (3 embryo losses) must have suffered from a first then a second loss: we thus prospectively observed the second pregnancy of women with a previous embryonic loss, both with and without positive APLAbs. APLAb positive women were more prone to an embryonic loss recurrence (30.9% vs. 12.7%), the risk being associated with LA or aCL IgM positivity, not with aCL IgG or aβ2GP1 positivity, with a strong interaction between LA and aβ2GP1 IgG, LA being a risk factor only in aβ2GP1 IgG negative women [18].

Finally, the report from the 14th International Congress on Antiphospholipid Antibodies, 2013, Rio de Janeiro, Brazil, underlines that only few studies meet Sapporo/Sydney criteria but, despite limitations of the available studies, doesn't give up supportingthe association between APLAbs and REL [19]. Some of the participants even conclude that the association between REM and aPL remains inconclusive, the findings of the treatment trials being at best inconsistent and at worst misleading [20]. More convincing data are critically needed before establishing an evidence-based association.

3. APLAbs and the risk of foetal death FD

The review of published case-control, cohort and cross sectional studies before 2010 in untreated women without autoimmune diseases, 28 studies being finally included, mainly showed that LA was associated with late fetal loss in four case-control studies and only with late fetal loss amongst three cohort studies (OR 10.6, 95% CI 1.9–59.9); aCLAbs were also associated with late fetal loss amongst seven case-control studies and only late fetal loss (OR 8.9 95% CI 1.8–42.5) amongst five cohort studies; aβ2GP1 antibodies showed associations with late fetal loss (OR 23.5, 95% CI 1.2–455) in two cohort studies [21]. Many studies included a small number of patients, being thus underpowered. The timing of FD also varied greatly between studies, from 8 to 24 weeks, the association being however positive for both foetal deaths (>10 weeks) and stillbirths (>20 weeks). Only a few papers included the three criteria laboratory tests and checked for a persistent positivity.

A large multicenter, population-based multiethnic prospective case-control study of stillbirths and live births was conducted in United States in 582 cases of foetal death delivered between 2006 and 2008 beyond the 20th gestational week and 1,547 controls with term live births [22]. LA activity was not screened. Elevated levels of aCL IgG and of aβ2GP1 IgG were associated with a threefold to fivefold increased odds of stillbirth, thus supporting consideration of testing for solid-phase APLAbs in cases of otherwise unexplained stillbirth. Elevated levels of aβ2GP1 IgM gave non-significant results, aCL IgM being associated with stillbirths only in case of nonanomalous stillbirths without any obstetric complications.

Triple aPLAb positivity, i.e. LA plus aCL IgG/IgM plus ab2GP1 IgG/IgM positivity, was described to strongly indicate the risk of pregnancy failure, whereas APS patients diagnosed on the basis of a single positive test and/or history of pregnancy morbidity alone generally had successful pregnancies in an Italian multicentric case-control study [23]. LA was the primary predictor of a composite criterion of adverse pregnancy outcomes after 12 weeks' gestation, including FD, in the multicentric prospective observational PROMISSE study in the USA [24] and ACLAbs or ab2GP1Abs, if LA was not present, did not predict adverse pregnancy outcomes. The study of an independent group of PROMISSE women recently confirmed that LA, but not ACLAbs nor aβ2GP1Abs, is the main predictor of adverse pregnancy outcomes after 12 weeks [25]. In the subgroup of women with persistently positive aβ2GP1Abs, aβ2GP1 domain I IgG and ACLAbs seemed to be independently associated with the risk of previous FD [26].

A major point is that clinical symptoms and complications related to APLAbs positivity act as confounding factors. SLE or other autoimmune diseases, history of both thrombosis and pregnancy morbidity were described to precipitate pregnancy failure whereas APS patients diagnosed on the basis of pregnancy morbidity alone generally had favorable pregnancy outcomes [23,24].

The association between APLAbs and FD seems convincing, the clinical value of aPLAb titers and of aPLAb associations/profiles require clarifications, the one of aβ2GP1-dependent LA and of

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