OPINION

The immunological ‘Wars of the Roses’: disagreements amongst reproductive immunologists

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The relevance of abnormal autoimmune function to reproductive function in the female has over recent years become an increasingly controversial and contentious issue. Opposing views have led to a polarization of opinions which, at times, resulted in publications of rather vocal opinions by individuals as well as societal committees. This communication is an attempt to reconcile these, at times diametrically opposing opinions, in a concept of (auto)immune-driven reproduction failure, which could explain and unify these opposing opinions and, thus, hopefully end the ongoing ‘immunological wars of the roses’.

Key words: antiphospholipid antibodies/autoimmune function/fertility/IVF

It is only ~20 years since the creation of the American Society for Reproductive Immunology (ASRM) and the recognition that there probably was a speciality area of research within reproductive medicine, called reproductive immunology. Disagreements amongst investigators were, as expected, not uncommon, but they were played out in traditional settings of oral discussions at annual scientific meetings and in published scientific studies. Most importantly, the discourse was collegial and fact-based.

All of this started to change when the field drifted towards clinical applicability of basic research. Differences of opinion became more personal and the volume and quality of discourse underwent a dramatic change. These developments reached a peak as some investigators chose to link their careers and personal fortunes to the practice of clinical reproductive immunology and, by so doing, opened themselves up to conflict of interest charges. The consequence was ‘Wars of the Roses’ amongst reproductive immunologists, so well documented in recent issues of Fertility and Sterility, though by no means restricted to the pages of that publication.

Based on most recent communications, it appears that the majority of recent conflicts primarily centre around the question whether antiphospholipid antibodies (APAs) affect fertility and, secondarily, IVF. These are, therefore, the principal issues which, in view of all these conflicting opinions, now need to be clarified in an attempt to return scientific discourse to a more collegial level, where it belongs.

The recent barrage of publications started with a meta-analysis by Hornstein et al. in which the authors concluded that the measurement of APAs is not warranted in patients undergoing IVF (Hornstein et al., 2000). Hill and Scott followed with an editorial which in its title ‘Immunology tests and IVF: please, enough already’ was clearly indicative of the authors’ opinions (Hill and Scott, 2000). Then, Coulam, on behalf of (a paradoxically anonymous) American Society for Reproductive Immunology (ASRI) Antiphospholipid Antibody Committee (and apparently not the ASRI itself), submitted a rebuttal to an ASRM Practice Committee Report, published in late 1999 (ASRM Practice Committee Report, 1999; ASRI Antiphospholipid Antibody Committee, 2000). In her rebuttal Coulam argued vehemently for continuous APA testing, while, of course, the ASRM Committee had concluded otherwise. Coulam’s rebuttal was followed by opposing contributions of Hornstein, Hill and Scott, basically reiterating their previously published opinions (Hill, 2000; Hornstein, 2000; Scott, 2000).

This amount of radically opposing opinions is unprecedented. However, what appears even more unprecedented is the fact that both sides to the conflict may, at the same time, be correct and incorrect in their respective conclusions.

Background

Over the last decades many, previously poorly understood, medical conditions have been recognized as ‘autoimmune’ in nature. As such, we recognize the fact that the immune system in all of these conditions erroneously attacks tissue components of ‘self’, which a normally functioning immune system during embryonic life supposedly learns to avoid. Why our immune system suddenly breaches the concept of immunological tolerance has remained an enigma and has been subject of innumerable studies in a large variety of autoimmune conditions.
In a riveting keynote address at the last Annual Meeting of the ASRM in San Diego, California, Faustman noted that all autoimmune conditions may, in fact, represent one and the same (genotypically defined) condition, just phenotypically expressed differently when manifesting as different autoimmune diseases (Faustman, 2000).

This is a potentially important concept because it creates a general framework for addressing the relevance of abnormal autoimmune function with regards to reproductive success. For example, if evidence can be found that abnormal autoimmune function, in principle, can affect reproductive success, then the question of whether APAs do or don't by themselves (which is the basis for the here reviewed dispute) becomes almost irrelevant.

As individual autoimmune diseases may just reflect different phenotypical expressions of one underlying pathophysiology, so would APAs have to be seen as only one amongst many phenotypical markers; maybe a hint, but certainly not confirmation of autoimmune disease.

Does abnormal autoimmune function affect fertility?
In his rebuttal to the position paper from the ASRI, Hill incorrectly (and with no reference) states that, ‘Women with systemic lupus erythematosus (SLE) do not have difficulty with implantation, rather, these women have difficulty in carrying their pregnancies to viable term delivery’ (Hill, 2000). In fact, while SLE in the past was believed to be associated with normal fertility and increased risk of pregnancy loss as well as intrauterine demise, recent studies suggest a significant fertility deficit in SLE patients (Gleicher, 1999; Hardy et al., 1999). Moreover, SLE is not the only autoimmune disease with decreased fertility: Rheumatoid arthritis (RA), one of the classical autoimmune diseases, preferentially affecting females, has also been demonstrated to cause a decrease in fertility and does so even before the disease manifests itself clinically (Nelson et al., 1993). The same applies to scleroderma, another autoimmune condition with female preponderance, which recently has become a most interesting study model for the autoimmune condition with female preponderance, which has now been reported by innumerable investigators, using different laboratories. The highest incidence of such autoimmune abnormalities in comparison with normal controls. Further autoimmune diseases historically associated with decreased fertility: Rheumatoid arthritis (RA), should anyhow not be based exclusively on one test alone. Abnormal autoimmune function is principally a polyclonal event. APAs may be present or they may not. The question is not whether APAs are present or not. The real question is, does the patient demonstrate signs of a polyclonal activation of her immune system or not? Such signs may or may not include APA-positivity.

Medical practice uses many test results on a daily basis which have only a relative or conditional diagnostic value. For example, in 1997 the Food and Drug Administration and the American College of Obstetricians and Gynecologists alerted physicians to false positive results in immunoglobulin (Ig)M anti-toxoplasmosis antibody testing. The test is still in wide use (Foler, 2000). Interestingly, embryotoxicity testing, developed in Hill's own laboratory and known to have far larger variability than APA testing, according to Hill and Scott, should only then not be used clinically, if Hill's own suggested laboratory control criteria are not followed (Hill and Scott, 2000). In other words, properly performed, his test is clinically valid. Why then should the same argument not apply to properly performed APA testing?

The principal problem does not lie, as suggested by opponents of APA-testing, with the quality of APA testing (though laboratory quality should, of course, be maximized). Instead, the real problem lies in the interpretation of APA test results, since their relevance (in isolation) has been over-interpreted by proponents of APA-testing and incorrectly dismissed by opponents.

What does the presence of APAs really mean?
Infertile women demonstrate a very significant increase in autoimmune abnormalities in comparison with normal controls. These abnormalities include, but are not limited to, APAs and have now been reported by innumerable investigators, using different laboratories. The highest incidence of such autoantibody abnormalities will be found in infertile women reaching IVF (Gleicher et al., 1993; Geva et al., 1997). These findings have never been disputed, but have been largely ignored by the Practice Committee of the ASRM, by Hill, Hornstein, Scott, and largely even the proponents of...
APA-testing (ASRM Practice Committee Report, 1999; ASRI Antiphospholipid Antibody Committee, 2000; Hill, 2000; Hornstein, 2000; Scott, 2000). What then does the presence of these antibodies really mean?

We were the first to suggest that APAs may have an adverse impact on IVF (El-Roeiy et al., 1987). Then, however, we followed up with a fully blinded study and were, therefore, also the first to disprove our own assumptions (Gleicher et al., 1994).

The fact that APAs do not affect IVF outcome, however, does not disprove the confirmed observation that abnormal autoimmune function, in general, does have an adverse effect on fertility. As we know from the preceding paragraphs, the supportive evidence for such a conclusion is strong. As one would expect, in full analogy to other autoimmune diseases, APAs alone are only one marker (amongst many) of an activated immune system, and may or may not be present in the presence of an abnormal autoimmune state.

To assume that APAs alone can predict infertility and/or poor IVF outcome would be equal to saying that the diagnosis of SLE can only be made in the presence of APA-positivity. Both are, of course, nonsensical.

A conclusion like this then raises the question of how abnormal autoimmune function should be tested for. The answer is not simple since there is no one test, or grouping of tests, that define an activated immune system.

In our practice it means a broadly based evaluation of immune function which includes an APA panel, involving IgG, IgM and IgA isotypes of seven phospholipid antibodies, a broadly based screen of multiple antinuclear antibodies, inclusive of histones, thyroid antibodies, total immunoglobulin levels for IgG, IgA and IgM and, finally, an immunophenotype in order not only to define natural killer cell activity but also basic B-lymphocyte numbers which, after all, are the cells responsible for autoantibody production.

It would exceed the framework of this communication to provide in these pages the detailed rational for why we have chosen all of these tests to 'detect' immune activation. For this purpose the reader is referred to Gleicher et al. (Gleicher et al., 1993). Published data, summarized in this reference, strongly suggest that broadness, rather than specificity of immune activation, is predictive of reproductive failure. In other words, it is quantity and not necessarily quality of the immune response that appears important in predicting reproductive failure. Each of the tests described above, by itself, has been statistically associated in the literature with reproductive failure, if abnormal and reproductive failure, due to infertility as well as pregnancy loss, has been reported in association with abnormalities in these tests (Gleicher et al., 1993).

The more one tests, the more abnormal results will, of course, be obtained. It is exactly for this reason that the emphasis needs to be placed on quantity: one test can be expected to be positive here or there if a large number of tests are performed. But four out of six positive antiphospholipid antibodies, in IgG isotype, will practically always be statistically significant.

This concept is currently being increasingly utilized in clinical immunity, as immunologists associate so-called Th-1 and Th-2 responses with specific clinical conditions (Choudhury and Knapp, 2000). In order to define these two mutually inhibitory immune responses, a variety of immune parameters have to be assessed, with many, in fact, being common to both and yet, all of them together being representative of the immune system’s status in general (Gleicher, 2002). Such studies in humans have suggested that Th-1 preponderance is associated with various forms of reproductive failure, thus also making the point that immunologically induced reproductive failure is an immune system-wide process and not a single event (Raghupathy et al., 2001).

This does not suggest, however, that other immunological test panels than the one we have chosen will demonstrate lower specificity. They may be equally good or bad, better or worse. The weakness of all of this, of course, lies in the fact that nobody yet knows for sure what the specificities and sensitivities for various test panels are. But why should reproductive (auto)immune failure be any different from SLE or other autoimmune diseases, where multiple laboratory tests and clinical symptoms are required to reach a diagnosis and, still, patients often cannot be specifically designated to one autoimmune disease or another.

Conclusions

Proponents and opponents of APA testing are, therefore, equally right and equally wrong in their interpretation of the literature and in missing the forest for the trees. APA testing (alone) should not be expected to be able to define autoimmune-associated infertility and should, therefore, neither be proposed nor used for that purpose. To expect that APA positivity alone would predict IVF outcome is, therefore, immunologically, naive since APA positivity in isolation does not denote abnormal autoimmune function. On the other hand, to disqualify APA testing as a tool (amongst many) in searching for abnormal autoimmune function is equally wrong.

Newcomers to reproductive immunology cannot be blamed for looking at a question like this in isolation. Reproductive immunologists and professional societies, like ASRM and ASRI, should, however, know better and call upon a broader circle of experts before publishing narrow and misleading clinical opinions.

The worldwide community of reproductive immunologists has for years been split into feuding camps, with different factions accusing each other of poor science, bad will and most recently, even unethical behaviour.

Potential conflicts of interest, unfortunately, nowadays abound. While it is our responsibility to avoid such conflicts wherever possible, we also owe our colleagues the benefit of the doubt when such suspicions arise.

Hill, who in his comments has probably been the most outspoken, extensively quotes the opinions of various esteemed editors on conflict of interest rules (Hill, 2000). Korn recently summarized this important issue well by concluding that, ‘Conflicts of interest are ubiquitous and inevitable in academic life, indeed, in all professional life’ (Korn, 2000). At the same time, as Korn also notes in his excellent piece, there is an
absolute need for transparency to preclude even the appearance of potential conflict of interest situations if we want to maintain the trust of the public and of colleagues.

In the USA, ~8.5 million people currently suffer from autoimmune diseases. Amongst those, 85% are women and many are trying to conceive and to carry a pregnancy to term as we speak (McCarthy, 2000). If we want to make progress in our ability to help them, we had better stop shouting at each other and start talking again.

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**References**


