OBSTETRICS

Why much of the pathophysiology of preeclampsia-eclampsia must be of an autoimmune nature

Norbert Gleicher, MD

> Research is to see what everybody else has seen, and to think what nobody else has thought.
>
> —*Albert Szent-Györgyi*

Preeclampsia-eclampsia (PE-E) is a poorly understood condition of human pregnancy, which can affect multiple organs and is a leading cause of maternal deaths worldwide. The etiology and pathophysiology remain enigmas, however, which hampers progress in prevention, diagnosis, and treatment of this condition. PE-E is characterized by many features typically seen in autoimmune diseases, or in association with autoimmune reactions. Although this does not mean that PE-E should be considered an autoimmune condition, it does suggest that abnormal autoimmune processes play an important part in the clinical presentation of PE-E. In that regard, PE-E mimics autoimmune responses also observed in situations of allograft rejection and graft-versus-host disease (GVHD). Indeed, PE-E shares many other clinical and laboratory characteristics with allograft rejection and GVHD. Recognizing PE-E as a clinical condition that is characterized by autoimmune abnormalities may facilitate earlier and more specific diagnosis, along with preventive and more specific therapies for women at risk.

Key words: allograft, allograft rejection, autoantibodies, autoimmunity, disease exacerbation, eclampsia, graft-versus-host disease (GVHD), microchimerism, preeclampsia, pregnancy

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The syndrome of preeclampsia-eclampsia (PE-E) has remained one of the enigmas of modern medicine. Despite decades of intensive research, the etiology, and much of the pathophysiology of this human, pregnancy-specific, condition are still not understood.[1-4] It is estimated that approximately 50,000 women die annually, worldwide, from PE-E.[5] A better understanding of etiology and pathophysiology is, therefore, essential if these deaths are to be circumvented by early prevention, more specific diagnosis, and better treatments.

Although autoimmune phenomena have been described in association with PE-E for decades, their potential pathophysiologic significance has been largely ignored. The investigators who have come closest to recognizing such an association have proposed that the syndrome reflects an excessive maternal inflammatory response to pregnancy.[2] A better interpretation of the syndrome may, however, be found in analogies to organ rejection after allograft transplantation and in graft-versus-host disease (GVHD); like PE-E, these are characterized by a multitude of systemic symptoms, inclusive of many autoimmune phenomena.

This article presents a description of PE-E as a multiorgan condition, characterized by autoimmune phenomena. Although it is tempting to speculate that the etiology of PE-E may, indeed, lie in a subclinical rejection of the fetal graft by the maternal immune system, such speculation is not the primary purpose of this paper. Instead, we wish to point out that the recognition of PE-E as characterized by autoimmune phenomena, may lead to better clinical approaches to this syndrome and thereby also to better diagnosis and treatments.

Abnormal autoimmune function

The clinical relationship between autoimmune diseases and pregnancy is unique. No other diseases are characterized by an exacerbation pattern, associated with the gestational period, that is particularly pronounced in the peripartum and postpartum periods.[6,7] Indeed, peripartal exacerbations are so typical for autoimmune diseases that one can practically assume an autoimmune etiology for any condition that exhibits such a flare pattern. A good example is peripartum cardiomyopathy, which until a few years ago, was considered a condition of unknown etiology, but in recent years has been widely recognized as, most likely, autoimmune in nature.[8] Peri- and postpartal disease flares can, therefore, be seen as a fairly diagnostic sign of an underlying autoimmune etiology and have been reported at any time, from late pregnancy up to approximately 3 months postpartum.[6]

PE-E is, of course, also characterized by a peripartal exacerbation pattern. A large majority of cases develop after 36 weeks gestation,[9] although more severe cases can occur at any time after 20 weeks[10] and in the postpartum period.[11] It is, indeed, remarkable how closely the flare pattern of PE-E mimics the timing of peripartum cardiomyopathy.[12]

From the Center for Human Reproduction (CHR), New York, NY, and the Foundation for Reproductive Medicine, Chicago, IL. Dr. Gleicher is a Visiting Professor at the Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT.

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Reprints: N. Gleicher, MD, CHR, 21 East 69 St, New York, NY 10021; ngleicher@thechr.com.

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TABLE
Selected autoantibody abnormalities reported in PE-E

Autoantibody against	References
Oxidized low-density lipoprotein	Ware Branch et al[19]
Vascular endothelium	Rappaport et al[15]
Platelets	Burrows et al[48]
Thyroid	
Phospholipids	Milliez et al[17]
Phospholipids	Yamamoto et al[18]
Phospholipids	Dekker et al[20]
Nuclear antigens	
Phospholipids	El-Roeiy et al[16]

Autoimmune conditions are often characterized by a combination of organ-specific and nonorgan-specific autoimmune responses, sometimes as part of a so-called polyclonal B cell activation. This means that, among humoral (and cellular) immune abnormalities (characteristic for abnormal autoimmunity), various autoantibody abnormalities can be detected; these can be nonspecific at some times and at other times, diagnostic.[13]

Such autoantibody abnormalities, in combination with typical cellular abnormalities,[14] have, indeed, also been reported in association with PE-E.[15-20] Moreover, as in classical autoimmune diseases, more severe PE-E appears to result in more autoantibody abnormalities, and of the more pathogenic IgG isotype.[15,16] Although other studies have disputed such associations,[21,22] a preponderance of evidence, nevertheless, suggests that classical, nonorgan-specific autoantibodies, and primarily antiphospholipid antibodies, are characteristic of PE-E, and especially in its more severe clinical expression.[16-18,20] Dekker et al, therefore, recommended active laboratory surveillance for patients at risk.[20] Table 1 summarizes reported autoantibody abnormalities in PE-E.

The most convincing evidence for humoral autoimmune responses has been reported in the most dangerous form of PE-E, what is known as the HELLP syndrome. Here, in addition to hypertension, the condition is accompanied by elevated liver enzymes and low platelet counts.[23] Cytopenias, including thrombocytopenia, and abnormalities in liver function, are characteristically reported in organ transplant rejection and GVHD and are generally considered autoimmune in nature because the removal of autoantibodies from the circulation improves the clinical situation.[24-26]

Both GVHD-related and classical autoimmune conditions often lend themselves to treatments that have been found successful also in the HELLP syndrome. Three classical examples are the treatment with corticosteroids, removal of autoantibody abnormalities via plasmapheresis,[25] and the competitive binding of autoantibodies with intravenous immunoglobulin[27] in GVHD and in the HELLP syndrome.[28-30] Donor lymphocyte infusion has been used experimentally for presumed alloimmunologic repeated pregnancy loss[31] but has not (except for one case[32]) been used in severe PE-E—even though it has been applied successfully in GVHD.[33] The evidence that blood transfusions decrease the prevalence of PE-E is decades old[34] and provides yet another analogy to successful organ transplantation.[35]

What characterizes abnormal autoimmunity?

There is consensus in the literature that the immune system's ability to differentiate between *self* and *nonself* represents its most essential feature. It allows for the protection of self and, without damaging the host, for an attack on nonself. Abnormal autoimmunity develops when this innate ability of the human immune system is disturbed, loses tolerance against self, and turns against the body's own antigenicity.[13,36]

Both in pregnancy and in organ transplantation, however, circumstances may be somewhat different and more complicated. Indeed, at least in GVHD, the autoimmune response is not necessarily as one would expect, the result of an autologous lymphocyte response against autoantigens. Indeed, it is generally believed that chronic GVHD is the consequence of an immune (antibody) response by donor lymphocytes (ie, lymphocytes from the donor organ) against the recipient. However, it now also appears that, to achieve transplant tolerance, a mixed microchimerism between donor organ and recipient has to be established, with donor cells entering the recipient and recipient immune cells entering the donor organ, at times resulting in GVHD, characterized by the formation of autoantibodies in the host.[37] Animal experiments suggest that chronic GVHD may be mediated primarily by the donor's T cells, which respond to antigens shared by donor and host.[38-39]

This model appears particularly relevant to pregnancy. Considering the significant degree of bidirectional cell traffic during pregnancy, one can speculate that, in analogy to GVHD, the autoimmune phenomena, seen in association with PE-E, may be immune responses by fetal lymphocytes to epitopes which mother and fetus share. As with so-called molecular mimicry in autoimmune conditions, induced by infectious agents, the resultant alloantibodies may show cross-reactivity with the mother's antigens and, therefore, in the final analysis, have to be considered autoimmune in their pathophysiologic effects on the maternal host.[40,41]

Alternatively, the autoimmune response in PE-E could, of course, be distinct from that in GVHD, and purely autoimmune in nature. This would then represent an immune response solely against maternal self-epitopes on fetal cells that have entered the maternal circulation, which the mother's immune system may not have been exposed to be-

fore. Such a circumstance has also been observed in association with autoimmune conditions, induced by infectious agents, and has been called the *bystander effect*.[42,43]

Whether antibodies in PE-E are generated by allo- or autoimmune responses, therefore, does not matter, as long as these antibodies, in their pathophysiologic effects cause autoimmune damage to the maternal host. In the organ transplantation literature they are, therefore, considered autoimmune in nature,[37] and it would seem appropriate to consider them as such also when in association with pregnancy.

That fetal-maternal cell traffic can affect maternal immune responses has been well demonstrated in Rh-disease[44] and in rheumatoid arthritis.[45] Indeed, in women with rheumatoid arthritis, where the maternal flare pattern depends on the paternal antigenic contribution to the fetus (ie, a potential allogeneic response),[45] the ultimate effect is on the maternal autoimmune response (ie, disease exacerbation). There need be no doubt left that the fetus can, indeed, affect maternal autoimmune responsiveness.

It is important at this point to reemphasize that none of these facts suggests that PE-E represents an autoimmune disease. Such a claim would be unsustainable, considering current evidence. What all of these facts suggest is only that, in analogy to GVHD, PE-E is characterized by immunologic abnormalities which affect the maternal host in an autoimmune fashion.

Abnormal autoimmune function can be characterized by a large variety of clinical findings. Amongst those, we previously noted the presence of autoantibodies, a frequent finding in association with PE-E (Table 1).[15-20] Autoantibody abnormalities, alone, however, are by no means diagnostic for the presence of abnormal autoimmune function. Autoantibody abnormalities have, for example, been also reported in association with HIV/AIDS[46] and malignancies.[47] When such antibodies bind to host-epitopes, and by doing so cause clinically apparent autoimmune effects, they have, however, to be considered suggestive of abnormal autoimmune function.[13,36]

The HELLP syndrome, as previously mentioned, provides clear evidence for such autoimmune effects.[16-18,20] Further evidence for the autoimmune nature of these processes comes from the success of directed therapies. As noted earlier, classical treatment modalities, proven effective in the amelioration of abnormal autoimmune function, have also been proven effective in PE-E.[25,27-29]

Autoantibody abnormalities in PE-E appear broad and, therefore, characteristic of the polyclonal B lymphocyte activation frequently seen with abnormal autoimmune function. As Table 1 shows, they involve both nonorgan-specific antibodies, such as antinuclear and antiphospholipid antibodies,[16] and tissue-specific antibodies, such as antiplatelet[48] and antithyroid antibodies.[17]

One, of course, has to be cautious in comparing the circumstances of pregnancy with those of GVHD because the latter usually occur within a general context of pharmacologic immunosuppression. This is not the case in pregnancy, though, in somewhat of an analogy, certain components of the immune system, indeed, may be suppressed during pregnancy (though others may be activated), as the immune system of the pregnant woman switches from a Th1 to an antibody-driven Th2 response.[49] Interestingly, such Th2 responses are also characteristic of some autoimmune diseases.[50]

Although it thus appears more likely that pregnancy-induced changes in the maternal immune response are responsible for the induction of PE-E, available data do not preclude that the observed changes in immune parameters in women with PE-E are secondary epiphenomena. To prove that autoimmune abnormalities do, indeed, precede PE-E (and, therefore, probably cause the condition) would be important if PE-E were to be defined as an autoimmune condition. For the present thesis that PE-E is associated with autoimmune phenomena, such proof does not appear to be essential.

GENETICS

Abnormal autoimmune function is highly familial and approximately 30% to 50% of the risk toward abnormal autoimmunity has been suggested to be genetic in nature.[13,36] The phenotypic expression of this genetic risk requires, however, environmental cofactors[13] and, therefore, even identical twins do not carry the same risk of developing disease.[51] Some autoimmune diseases are linked to specific class I or class II histocompatibility (HLA) molecules.[52] Familial occurrence and the risk toward multiple autoimmune conditions in genetically predisposed individuals have, therefore, to be considered additional characteristics of abnormal autoimmune function.[13]

Once again, PE-E shows considerable similarities.[3] For example, based on HLA-DRB1 genotype studies in a Japanese population, Takakuwa et al demonstrated differences in immunogenetic background between women with severe preeclampsia with, and without, antiphospholipid antibodies.[53] Others have suggested that maternal susceptibility to PE-E is most likely under the influence of a dominant major gene, with moderately low penetrance, but may be inherited in a multifactorial fashion.[54] Moreover, both men and women who are themselves the product of a PE-E pregnancy are more likely to have children who will be the product of a PE-E pregnancy.[55] Like autoimmune diseases, therefore, PE-E demonstrates a clear familial occurrence pattern.

It also demonstrates the genetic predilection for multiple autoimmune conditions in genetically predisposed individuals, as women with autoimmune diseases have been reported to demonstrate a statistically significant, approximately 4-fold, increase in PE-E.[56,57] Whether women with a history of PE-E carry an increased risk toward the development of autoimmune diseases has not been investigated but such a finding would not be surprising.

CLINICAL AND SUBCLINICAL DISEASE

Autoimmune diseases are characterized by varying levels of phenotypical expression. Practically all autoimmune condi-

tions pass through preclinical (or subclinical) stages before they become clinically overt. Indeed, many individuals with abnormal autoimmune function will never reach a stage of clinical overtness.[13]

The same can also be stated about PE-E. The syndrome, of course, may present with only insidious signs, may be moderate to severe, or may be life threatening.[1,3,4] This characteristic of PE-E potentially lends itself to earlier diagnosis and treatment.

PREECLAMPSIA-ECLAMPSIA

Fetus as allograft and autograft

Why the fetus, in half of its antigenicity a paternal allograft, is not rejected by the maternal immune system is still not well understood. It is clear, however, that the female immune system undergoes considerable changes to allow for the immunologic survival of the fetus during 9 months of pregnancy.[2,6,49,58]

Organ transplantation[59] and pregnancy[60] have been identified as clinical situations where donor organ and fetal cell microchimerism, respectively, in the host stand as likely prerequisites of allograft tolerance. Such microchimerism, if persistent within the host organism, in turn, has been associated with the occurrence of autoimmune abnormalities[37] and outright autoimmune diseases.[61]

Women with PE-E demonstrate a 5-fold increase in circulating fetal DNA in comparison to controls, suggesting either increased fetal-maternal cell traffic or a defect in maternal antigen clearance.[62] Like removal of a transplanted organ ends rejection and GVHD, removal of the products of conception accelerates immediate recovery from PE-E.[63]

The risk of PE-E appears inversely related to exposure to paternal semen.[64] Exposure to semen can, therefore, be viewed as nature's way to expose the maternal immune system, ahead of pregnancy, to at least temporary microchimerism with allogeneic cells of paternal origin. A number of "experiments of nature" are strongly supportive of such an assumption. Women who conceive through in vitro fertilization (IVF), using surgically obtained semen from initially azoospermic males (these women, of course have not been previously exposed to their partners' semen), demonstrate a 3-fold increase in PE-E.[65] Women who conceive twins through IVF show twice the normal PE-E prevalence.[66] Finally, IVF cycles involving donated gametes also demonstrate a significantly elevated rate of PE-E,[67] and this, interestingly, is true for donated semen, as well as donated oocytes[67,68] and, therefore, suggests that PE-E may very well represent an allo-, as well as autoimmune response.

The immune adjustments of pregnancy have been assumed to be primarily geared at the allogeneic components of the fetus. That the paternal genotype is important in that regard can be deducted from a number of observations; for example, some investigators have suggested that, the more similar the paternal histocompatibility complex is to that of the mother, the more likely a miscarriage will occur.[69] Similarly, the closer antigenically wife and husband are, the more likely mothers with rheumatoid arthritis will flare in pregnancy.[45] These observations, as already noted, quite obviously suggest that the fetus, based on its antigenic composition, can affect the mother's immune responses. They also point toward the need for aggressive antigenic stimulation of the female immune system to activate immune processes that allow for tolerance of the allograft component of the fetus.

The fetus is, of course, not only an allograft but also an autograft.[6] Because one half of the fetus is maternally derived in its antigenicity, the (primarily by the allograft) activated maternal immune system, faces, in parallel, an unprecedented autoimmune load, and with it, yet another rather unprecedented immune challenge. At no other time period in life has the female immune system to be ready for autoimmune challenges of this magnitude. The immune system's adjustment to pregnancy, therefore, does not only involve tolerance of the paternal allogenic, but also of the maternal autoimmunogenic, components of the fetus. Abnormalities in autoimmune responsiveness should, therefore, not surprise.

PE-E and pregancy loss

Autoimmune phenomena are principally seen in 2 periods of pregnancy: early conception and the peripartum period. In early conception, abnormal immune activation can lead to hyperemesis gravidarum[70] and pregnancy loss[71]; later stage activation appears to be associated with PE-E (nausea, as seen in hyperemesis is, of course, also a classical symptom of GVHD[72]). Indeed, women with early autoimmune activation, who (with treatment) do not miscarry, demonstrate a greatly increased risk for PE-E.[6] This observation, alone, is supportive of a common alloimmune or autoimmune etiology and pathophysiology for both of these conditions.

These are, of course, also the 2 periods of pregnancy when adjustments of the immune system to the fetal allo- and autografts are induced and reversed, respectively. Both of them, therefore, represent transitions for the female immune system. Consequently, these are the time periods of pregnancy when most malfunctions can be expected.

It, therefore, appears that a vigorous maternal immune response is required to process the allo- and autoantigenic stimuli of the fetal graft normally. During the 2 adjustment periods, at the beginning and upon conclusion of pregnancy, malfunctions in this immune response can occur.

This concept is further supported by the fascinating observation that immunocompromised, HIV-1 positive women demonstrate a significantly decreased prevalence of PE-E, which reverts back to normal once the immune system has been reconstituted through successful antiretroviral therapy.[73] In these women, a compromised immune system appears unable to mount the vigorous, normal immune response of pregnancy. Such a malfunction will result in less of a deviation from baseline and, therefore, fewer chances for PE-E to develop. Because the immunologic impairment with HIV/AIDS is mostly of cellular nature, these observations also point out the importance of the cellular immune response in pregnancy. Though there is no comparable

data reported on pregnancy loss, one could, based on these PE-E data, speculate that HIV-based immunosuppression should also decrease the risk of immunologically induced early pregnancy loss.

The concept of hyperplacentosis

Antigenic load matters. The larger the quantity of stimulating antigens, the earlier, and the more severe, an immune response can be expected. Therefore, one would expect a more intense immune response with larger infants and placenta, such as in diabetic pregnancies, fetal hydrops, and multiple pregnancies (ie, with so-called conditions of hyperplacentosis).[1,3-5]

Elkayam et al, indeed, recently reported that the prevalence of (autoimmune) peripartum cardiomyopathy was significantly increased with multiple births and that the condition occurred earlier in pregnancy if patients carried multiple gestations.[12] We are unaware of other investigations of autoimmune conditions in their association to conditions of hyperplacentosis. Unreduced triplet pregnancies after IVF experience show, however, as expected, a higher prevalence of PE-E than those that are reduced to twins.[74]

The statistical association of PE-E with all conditions of hyperplacentosis has, of course, been well documented. Indeed, this association is considered a clinical hallmark of PE-E.[1,3-5]

Consequences

Accepting the concept that PE-E is characterized by autoimmune phenomena can have major consequences for the field of obstetrics. First and foremost, it would open new research avenues into etiology and pathophysiology. One can, however, also conceive of quick benefits for better diagnosis and treatment. For example, as already noted earlier, autoimmune phenomena usually go through pre- or subclinical stages before they become clinically overt. At those early stages laboratory markers are often already detectable.[13,36] If the autoimmune phenomena of PE-E were to follow a similar pattern, earlier diagnosis and treatment should become feasible.

The diagnosis of organ rejection and GVHD, however, does not only rely on abnormal laboratory results, detectable in peripheral blood. Indeed, to diagnose early rejection, the transplanted organ (and other organs) are frequently biopsied for histological evidence of early transplant rejection and/or GVHD.[75] The diagnosis of PE-E could be pursued in similar ways. Histologically typical lesions for PE-E have been known for decades.[76] It is, however, the laboratory abnormalities and histological lesions of pre- or subclinical stages of PE-E that remain to be established.

Once better, and earlier, diagnosis becomes feasible one can expect innovative treatments to follow. Ideas that already now come to mind are: immunization with (paternal) antigens (in analogy to immunization with organ donor lymphocytes in transplantation immunology) and repeated pregnancy loss,[31,33] and stem cell therapy, which is increasingly used in the treatment of GVHD and autoimmune diseases.[77,78] More traditional treatments may also proof useful. As already noted, in analogy to GVHD, immunosuppression with corticosteroids, while maybe still somewhat controversial, has been proven successful in even the worst (HELLP) cases of PE-E[28] and may be ready for clinical trials in more moderate cases, as has immunomodulation with plasmapheresis[25] and intravenous gamma globulin.[27]

CONCLUSION

We do not mean to suggest that PE-E is an autoimmune disease. The here described observations, however, strongly suggest that PE-E, in analogy to acute organ rejection, and GVHD, on a temporary basis, is characterized by autoimmune responses to a variety of autoantigens.

Indeed, the similarities with acute organ rejection, and GVHD, do not end here: if a 100% allograft can elicit autoimmune responses during organ transplantation, one should not be surprised that a 50:50 autograft-allograft can do the same.

The recognition that PE-E is characterized by classical autoimmune responses is potentially very important: it may allow for a better understanding of clinical symptoms and their pathophysiology. It may, however, also point toward potential tools for early diagnosis because subclinical autoimmune abnormalities can be expected to be detectable at early pre- or subclinical stages of the condition. Most importantly, however, it may allow for the development of early preventive treatments of PE-E. Because PE-E remains a major cause of maternal, and perinatal, morbidity, and mortality, these developments could have a major impact on public health. ■

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