

What Is Superimposed Preeclampsia (and Does It Actually Exist)?



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In 1905, the text of a lecture entitled “On the albuminuria of pregnancy and the kidney of pregnancy” by F.G. Blacker appeared in *The Lancet*.¹ I highly recommend reading it, not only for the elegance of the writing and the keen clinical descriptions and remarkable medical intelligence it contains, but principally because the conclusions still hold true today, making us reflect on the lasting power of the clinical assessment of patients, now called “deep phenotyping.”

In the article, Blacker¹ described 4 different cases, exemplifying the various scenarios that can be present with albuminuria in pregnancy: a 42-year-old multiparous woman with blurred vision and increasing proteinuria who developed oliguria, which finally resolved after the delivery of a neonate who was dead and small for gestational age; a 23-year-old primipara who died from “early” eclampsia, after the induced delivery of 2 dead twins; a young

woman with chronic kidney disease (CKD), who ultimately died of “acute uremia”; and a 24-year-old woman with “chronic” Bright’s disease, who survived pregnancy, but died in uremic status a few months later. The author speculates on how the kidney of pregnancy differs from those of patients with Bright’s disease, which leads him to question what a differential diagnosis between preeclampsia (PE) and CKD can be based on. He discusses the toxemic theory, according to which a circulating factor produced in pregnancy affects the kidneys, anticipating the era of circulating biomarkers, and focuses attention on the question of why in some cases this pregnancy-related disease principally affects the kidneys and in others the liver. He concludes that it should be considered probable “that this toxic condition of the mother’s blood is one of the causes of the development of the kidney of pregnancy and of the occurrence of albumin in the urine (...) Whether the poisons act on the central nervous system, on the vessels of the kidney, or on the renal epithelium we cannot say, but probably they act in one or more of these ways (...).”¹ He also

hypothesizes that there are predisposing factors, and that these factors may be related both to preexistent Bright’s disease, at the time a sort of eponym of CKD, and also to subclinical kidney damage, thus anticipating the issue of superimposed preeclampsia, and also discusses the relationship between subclinical kidney damage and predisposition to what we now call PE.

Among Blacker’s concluding remarks, one merits particular attention: “The diagnosis of the so-called kidney of pregnancy from acute nephritis or acute Bright’s disease is much more difficult and may be impossible. No doubt that one condition frequently merges into the other.”¹ More than a century later, we are still struggling with these unsolved questions.

The history of the definitions of PE parallels the history of obstetric nephrology: once held to be a transient kidney disease ultimately cured by delivery, PE is no longer considered transient, and attention on its long-term consequences is changing its profile, making a clinical distinction even more important, whatever the outcome of the pregnancy, for both the mother and the fetus.^{2,3} Is PE the harbinger, the epiphenomenon of an undiagnosed kidney disease, or is it the first indication of kidney damage that could become clinically evident over time? The cause-effect relationship remains unclear, and the lack of long-term longitudinal studies impairs our ability to foresee the clinical evolution of some patients with PE toward CKD.⁴

The article by Wiles and coworkers⁵ deals with this difficult diagnosis. It focuses on 15 women who were diagnosed with

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superimposed PE, and presents an analysis based on a comparison of the study group with other groups of patients, encompassing 45 patients with CKD without PE and 18 patients with PE without CKD. Twenty controls without CKD and PE complete the series, used to test some of the classic biomarkers, as well as several new ones. The authors suggest that plasma hyaluronan and vascular adhesion molecule, markers of endothelial glycocalyx dysfunction, can serve to discriminate between women with CKD who develop superimposed PE and those who do not, and their findings show that the pathogenesis of superimposed PE is due to endothelial dysfunction, in keeping with what is currently held for PE, and rule out a major role for complement or renin system activation. In this series, the presence of kidney damage does not appear to be relevant.

The article's major merit is its underlining of the importance of the relationship between CKD and PE; however, as the authors themselves state, the article's limit is that it is based on a definition that is not fully clear.⁵ An increase in antihypertensive treatment is quite common in the second half of pregnancy in patients with CKD, and quantifying it is often difficult; the importance of doubling of proteinuria can differ, depending on the severity of the initial level, and both mild and severe proteinuria can be modulated by dietary habits.^{6,7}

Within the limits of the small series studied, the authors suggest that the outcomes and the biochemical phenotype of patients with superimposed PE and with PE without CKD are similar.

If the devil hides in the details, here the details are probably hidden in definitions. The effect on fetal growth is a crucial issue: in this series, the infants from

pregnancies with superimposed PE were more likely to be both small for gestational age and preterm, and the prevalence was the same as in PE. Interestingly, in other series, patients with CKD often display a picture of "late" PE, in which late-preterm delivery is dissociated from growth restriction. It is interesting that the finding of "late PE," which has either a minimal effect or no effect at all on fetal growth, is consistent in different kidney diseases, from IgA nephropathy to reflux nephropathy, and is also observed in kidney donors, the prototype of "healthy" reduction of the kidney parenchyma.⁸

The relationship between early delivery and being small for gestational age is modulated by obstetric policy and by the decision to induce delivery in the presence of a flattening of the growth curve or of pathologic Doppler flows, whose threshold levels often vary from center to center. Balancing the risk of prematurity (inducing delivery at initial flattening of the growth curve) and the risk of fetal ischemia (trying to prolong pregnancy as long as possible) is one of the most difficult decisions made in maternal-fetal medicine, in part because demonstrating the validity of the choice made would require long-term follow-up of children.^{3,9} In this context, based on the delivery data, the series described is characterized by a remarkably high prevalence of early PE (and of early superimposed PE), because the identification of these cases occurred at an average of 33 weeks, with quite a narrow confidence interval. This should be kept in mind, because it is currently considered that early PE (usually, but not universally, defined as PE becoming clinically evident before 34 gestational weeks) represents only

approximately 10% of pregnancies worldwide. These early forms of PE are associated with the highest maternal and fetal risks, and the authors' decision to focus on them is praiseworthy.

The study, therefore, has the merit of being informative on the most clinically relevant forms of PE, which are also the most typical ones, but tends to be less informative on the most common forms, those that are usually recognized at a more advanced gestational age, and whose clinical presentation may be more nuanced. This observation also indirectly suggests that it is much easier to correctly identify PE when it occurs in the earlier pregnancy phases than in the late ones, and offers an explanation of the discrepancies between the outcomes of superimposed PE reported in the literature.

In this regard, this article can be read as a demonstration of the fact that early PE does not significantly differ in patients with and without CKD. In other words, the article suggests that a "clinically relevant" increase in proteinuria and hypertension in the context of CKD, especially when defined by skilled clinicians and occurring before 34 gestational weeks, is a "true" PE, and that early and carefully diagnosed PE and superimposed PE are indistinguishable in terms of the profile of their clinical and biomarkers. Although early-onset PE in CKD exists, and behaves like any other form of PE is an important message, we probably still need more data on other, less severe situations in which hypertension and proteinuria worsen or develop in patients with CKD in late pregnancy.

Nephrologists are among the most curious physicians, and every insight into the pathogenesis of diseases that are still as elusive

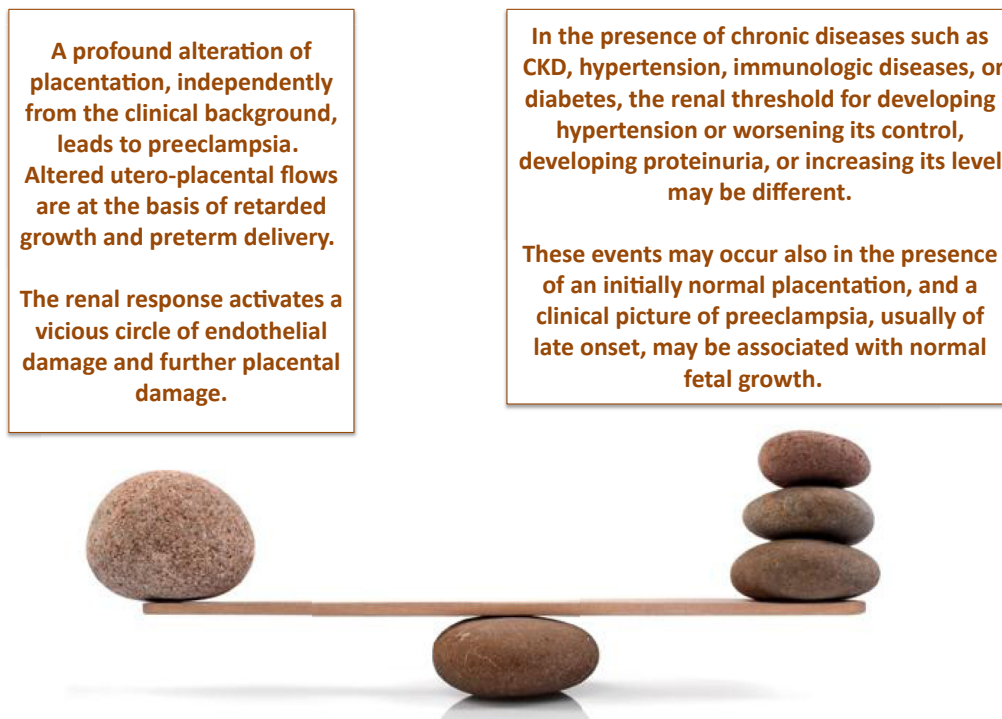


Figure 1. Preeclampsia and the renal response to pregnancy in the presence of clinical (chronic kidney disease [CKD]) or subclinical (diabetes hypertension) kidney damage: a hypothesis.

as PE is welcome. However, it is legitimate to question what the assessment of biomarkers adds to the clinical management of our patients, if their major merit is that they are in keeping with carefully assessed clinical definitions.

The authors correctly emphasize that the biomarker approach may contribute to the differential diagnosis between CKD and PE, suggesting that this could lead to different clinical choices in pregnancy. Although this is logical, we are not in full agreement with their view, as the decision on whether or not to induce delivery has to be based on the well-being of both the fetus and the mother: Doppler flows and fetal well-being, on the one hand, and the presence of uncontrolled hypertension or impending life-threatening complications in the mother, on the other. These decisions are not modulated by the presence of a diagnosis of either PE or CKD or both; in such a setting, the tenet that, for example, CKD is less

ominous in pregnancy may even be misleading.

This article suggests that at least in its early severe forms, PE is always PE, even when it occurs in patients with CKD. The logical outcome of this thesis is to question whether superimposed PE really exists, or whether we are dealing with 2 different situations: PE, whose clinical threshold may be lower in patients with CKD, and a modulation of CKD parameters (namely hypertension and proteinuria) induced by pregnancy; the same alterations can be discovered or occur *de novo* in pregnancy. It is in these latter cases that the biomarkers can help us understand what is not PE, and possibly avoid an overly aggressive attitude toward pregnancy termination (Figure 1).

In summary, this interesting series, which questions the existence of superimposed PE as a distinct entity, suggests that our interest should shift from the identification of what PE is, to the

identification of cases that “smell and taste” like PE, but are actually CKD, preexistent or enhanced by the stress of pregnancy. Although we sincerely hold that all patients with PE should be followed up after pregnancy, we are aware that this may be overambitious.⁹ Identifying cases that are not PE could help limit the amount of work and resources required by allowing us to select those patients who must be given follow-up after delivery, to ensure that the problems that occurred in pregnancy are associated with better long-term health perspectives for the mother.

DISCLOSURE

The author declared no competing interests.

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