The Glomerular Injury of Preeclampsia

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ABSTRACT

Preeclampsia is a pregnancy-specific disorder that complicates approximately 5% of all pregnancies, making it perhaps the most common glomerular disease in the world. It is characterized by new-onset hypertension and proteinuria, in association with a characteristic glomerular lesion, endotheliosis. "Glomerular endotheliosis" represents a specific variant of thrombotic microangiopathy that is characterized by glomerular endothelial swelling with loss of endothelial fenestrae and occlusion of the capillary lumens. Associated thrombosis is unusual. Recent evidence suggests that this unusual glomerular lesion is mediated by a soluble vascular endothelial growth factor receptor that deprivess glomerular endothelial cells of the vascular endothelial growth factor that they require, leading to cellular injury and disruption of the filtration apparatus with subsequent proteinuria. This review summarizes the histologic changes and the pathogenesis of the glomerular lesions of preeclampsia.


RENAL INJURY OF PREECLAMPSIA

Preeclampsia, the most frequently encountered renal complication of pregnancy, is characterized by new-onset hypertension, proteinuria, and edema, usually developing after 20 wk of gestation.1 When seizures develop, it is known as eclampsia, a disease familiar to the pre-Hippocratic ancients. The presence of a placenta, with or without a fetus (hydatidiform mole), is necessary for its development. Consequently, definitive treatment is by delivery of the placenta, which, depending on gestational age, can involve significant fetal morbidity and mortality. Preeclampsia complicates approximately 5% of all pregnancies and thus may be the most common glomerular disease in the world.

The development of preeclampsia is believed to be a two-stage process: The first, asymptomatic stage is marked by abnormal placentation, possibly related to ischemia. Placental elaboration of soluble factors that enter the maternal circulation follows, leading to endothelial dysfunction and the clinical syndrome(s). Recent work has identified circulating antiangiogenic substances, which seem to cause the disease by depriving the glomerular endothelium (and possibly other fenestrated endothelium) of essential growth factors.2 Although preeclampsia is a multisystem process that affects vasculature throughout the body, this article focuses on its hallmark: Glomerular injury.

There is a tendency among caregivers
to ascribe all new-onset renal disease in pregnancy to preeclampsia, in part because of reluctance to perform a biopsy. However, many studies have documented the inaccuracy of clinical diagnosis alone. One found that when diagnosed clinically, before 37 wk, 67% of women who underwent biopsy had a renal disease other than preeclampsia. Therefore, biopsy remains the most reliable way of making the diagnosis and is particularly helpful in multiparas or early in the pregnancy, to exclude other entities for which effective therapies are available.

The renal biopsy findings of preeclampsia are best appreciated in the context of the pathologic patterns seen in thrombotic microangiopathies (TMA). TMA is a term used to describe a group of clinically diverse entities, such as hemolytic uremic syndrome and malignant hypertension, among others, that are defined by a primary locus of injury—the endothelium—and the ensuing thrombosis and vascular injury. Their similar pathologic expression has led nephropathologists to adopt the term TMA to describe them all. The lesions of preeclampsia share some similarities with and intriguing differences from those of nonpreeclamptic TMA, likely owing to their differing pathogenesis.

**LIGHT MICROSCOPY**

Although the central role of the kidney was first recognized in 1918, it took several decades, in particular, the application of ultrastructural analysis to renal biopsy material, to elucidate the characteristic lesions, which are similar for both preeclampsia and eclampsia. Preeclampsia is associated with a distinctive glomerular appearance: “Glomerular endo-theliosis,” a term coined by Spargo et al. The glomeruli are enlarged and solidified (“bloodless”), as a result of narrowed or occluded capillary lumens that are the result of swelling of the native endothelial cells and, to a lesser extent, mesangial cells (Figure 1). Glomerular volume is increased and correlates with the severity of the disease. The degree of endotheliosis can vary between glomeruli, although most show at least some involvement. Glomerular cellularity is not significantly increased. It is interesting that the endothelial changes are limited to the glomerular capillaries; arterioles are typically unaffected. Thrombosis by light microscopy is decidedly unusual, although fibrin can be detected by immunofluorescence in glomeruli. In marked contrast, in nonpreeclamptic TMA, thrombosis of vessels and/or glomeruli is a central finding. Cases of severe preeclampsia with accompanying vascular thrombosis often have clinical signs suggesting a superimposed nonpreeclamptic TMA. Coexistent diseases that are associated with endothelial dysfunction, such as diabetes and antiphospholipid antibodies, are also known to increase the risk for preeclampsia. These observations underscore the variable and site-specific phenotype of endothelial cells and suggest multiple and possibly overlapping pathways leading to endothelial injury in both preeclampsia and nonpreeclamptic TMA. As detailed next, the acute endothelial swelling seen in preeclampsia is due to vascular endothelial growth factor (VEGF) deprivation. In contrast, the endothelial injury noted in nonpreeclamptic TMA, although poorly understood and probably multifactorial, is likely not related to impairment of VEGF signaling. Free VEGF levels are higher in patients with hemolytic uremic syndrome/thrombotic thrombocytopenic purpura.

In severe cases of preeclampsia, in particular as the lesions evolve/resolve, mesangial interposition can be seen, a finding shared with other entities resulting from chronic endothelial insult, such as “chronic” TMA or transplant glomerulopathy. Other changes, such as
prominent podocytes with protein re-
sorption droplets and endocapillary
foam cells, are probably secondary to the
proteinuria. The presence of arterioles-
rosis suggests a coexisting process, such as “essential” hypertension. Whether
preeclampsia leads to chronic vascular
injury over ensuing years is not yet clear.

**IMMUNOFLOUORESCENCE
MICROSCOPY**

The immunofluorescence findings are
somewhat variable with fibrin deposi-
tion often being a prominent feature.
The low-level glomerular Ig deposition
in severe preeclampsia, reported by
some, probably represents nonimmuno-
logic insudation. This conclusion is sup-
ported by the ultrastructural observation
that electron-dense deposits are incon-
spicuous. Its chief diagnostic role lies in
excluding an immune complex glomer-
ulonephritis, such as lupus nephritis,
which often flares during pregnancy. The
pathogenetic role that fibrin and its re-
lated products play has not been re-
solved. Although the degree of deposi-
tion has been reported to vary widely, it
seems to be more common in renal biop-
sies obtained from patients with prema-
ture and severe preeclampsia.

**ELECTRON MICROSCOPY**

Ultrastructural analysis is the definitive
way to demonstrate endotheliosis and, in
some cases, may be required to make the
diagnosis. Endothelial cells demonstrate
loss of fenestrations with cytoplasmic
swelling, owing to fluid and lipid accu-
mulation and capillary occlusion (Figure
1C).7 Mesangial cells may show similar
changes. In contrast to most other TMA,
electron lucent expansion of the suben-
thelia! zone, when present, is usually
not prominent. It is interesting that de-
spite significant proteinuria, podocytes
show limited foot process effacement, a
phenomenon that may also be seen with
other TMA, particularly in the acute
phase.9 Indeed, when quantified, the fil-
tration slit frequency is not significantly
reduced in preeclampsia below con-
trols.7 This finding has significant impli-
cations for the investigation of mecha-
nisms of proteinuria in general because it
suggests that nephrotic-range protein-
uria can occur without significant fusion
of podocyte foot processes.9

**SIGNIFICANCE OF
ENDOTHELIOSIS**

Endotheliosis seems to be responsible
for the decreased GFR noted in pre-
eclampsia, primarily through reduc-
tion in the ultrafiltration coefficient as
opposed to diminished plasma flow. When focal, endotheliosis can be diffi-
cult to identify, and its specificity for
preeclampsia may then be limited. Mild
forms have been seen in up to
30% of patients with pregnancy-in-
duced hypertension without protein-
uria.10,11 Furthermore, a recent study
found five of 12 control subjects (non-
hypertensive third-trimester women)
with trace endotheliosis.10,11 As noted
by its authors, this study suggests a
continuum between healthy pregnant
women and the extreme of preeclamp-
sia. Recent work, as discussed next,
provides a rationale for this phenomenon.
Limited endotheliosis has also been
reported occasionally in associa-
tion with other disorders.12 Neverthe-
less, when endotheliosis is present in a
diffuse manner, in the appropriate
clinical setting, it is virtually pathogno-
monic for preeclampsia.

**NATURAL HISTORY AND
PROGNOSIS**

After delivery, the glomerular changes
usually reverse rapidly, coinciding with
resolution of the hypertension and pro-
teinuria. However, the relationship
among preeclampsia, underlying renal
and other conditions, and future disease,
including hypertension, is complex and
controversial. For example, FSGS (a
nonspecific form of glomerular scarring
that can be seen in association with “es-
sential” hypertension, as well as in pri-
mary glomerular disease) is said to ac-
company endotheliosis in a significant
percentage of cases, but it is not neces-
arily predictive of current or future renal
failure, as might otherwise be expected.13
Indeed, there is evidence that the seg-
mental sclerosis of preeclampsia may be
reversible. Nevertheless, considerable ev-
idence suggests that preeclampsia pre-
disposes women to late cardiovascular
diseases.14 The increased risk for hyper-
tension is not seen in their siblings, sug-
gesting that it is related to preeclampsia
and pointing to the role of subtle endo-
thelial injury leading to the development
of chronic hypertension.15

**PREECLAMPSIA FACTOR AND
ANTIANGIOGENIC STATE**

The search for a circulating factor that
causes the hypertension and proteinuria
of preeclampsia has been an area of intense
investigation. It is believed that excess cir-
culating antiangiogenic substances such as
soluble fms-like tyrosine kinase (sFlt1, also
referred to as sVEGFR1) play a prominent
role in the development of preeclampsia.
VEGF, synthesized constitutively in the
glomerulus by podocytes, is a critical factor
for the maintenance of endothelial health,
including the induction of fenestrae. In-
deed, genetic glomerular VEGF deficiency
has been shown to result in endotheliosis
with loss of fenestrae.16 sFlt1 is a secreted
protein that lacks the transmembrane and
cytoplasmic domain of the membrane-
bound VEGF receptor and acts as an en-
dogenous inhibitor of VEGF signaling.
Circulating levels of sFlt1, made predomi-
nantly by the placenta, are greatly increased
in women with established preeclampsia,
even before onset of clinical symptoms.17
That study also found a steady increase in
serum sFlt1 levels in normotensive near-
term women, a finding that suggests that
preeclampsia represents an early and exag-
gerated form of normal pregnancy and
helps to explain the mild endotheliosis oc-
casionally seen in near-term normotensive
biopsies. When administered to rats, sFlt1
produces a clinical syndrome and glomer-
ular lesions resembling human preeclamp-
sia.2 Similar observations have been noted
when other VEGF inhibitors such as neutralizing antibodies have been used in rodents or humans.\textsuperscript{18–20}

How VEGF-deficient states such as preeclampsia produce proteinuria is still unknown. Some have suggested that loss of podocyte nephrin expression may be responsible.\textsuperscript{19,21} However, whether the diminished nephrin expression is the cause or the consequence of proteinuria is unknown. Others have suggested that all three layers of the glomerular wall—endothelium, basement membrane, and slit diaphragm—may jointly constitute the barrier against proteinuria. Deen et al.\textsuperscript{22} argued that proteinuria can occur with endothelial disruption alone, which may explain the significant proteinuria noted with endotheliosis. More recently, yet another antiangiogenic protein, soluble endoglin, was reported to play a pathogenic role in preeclampsia.\textsuperscript{23} It is interesting that animals that were exposed to high levels of soluble endoglin had focal endotheliosis without significant proteinuria, whereas those that were exposed to both soluble endoglin and sFlt1 developed massive proteinuria and severe endotheliosis. Future work is necessary to clarify the mechanisms of the endotheliosis and proteinuria mediated by these circulating antiangiogenic substances.

NOTE ADDED IN PROOF
Recent case reports describe the development of proteinuria and TMA in patients receiving anti-VEGF therapy for cancer.\textsuperscript{24,25}

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DISCLOSURES
S.A.K. is listed as a co-inventor on multiple patents filed by the Beth Israel Deaconess Medical Center for the use of angiogenic proteins for the diagnosis and therapy of preeclampsia and is a consultant to Johnson & Johnson, Beckman Coulter, and Abbott Diagnostics.

REFERENCES