Aiming to Coordinate Care, ACO Proposed Rule Falls Short

By Rachel Shaffer and Daniel Kochis

In January 2012, the Centers for Medicare and Medicaid Services (CMS) will launch a new congressionally mandated initiative designed to help improve the quality of patient care. In the initiative currently proposed, accountable care organizations (ACOs) may not be well positioned to appropriately care for patients on dialysis or who have a recent kidney transplant. Despite this concern, the ASN ACO task force believes that ACOs may offer significant benefits to the chronic kidney disease patient population; however, significant modifications to the existing proposal would be necessary. ACOs are envisioned by Congress as a new, coordinated approach to care delivery and reimbursement that will drive down costs while ensuring quality. While ACOs were mandated by the Affordable Care Act (ACA) of 2010, CMS must issue regulations that specify how ACOs will function. In March, CMS issued an ACO Proposed Rule outlining its vision for the program and solicited public comment. The ASN ACO Task Force, chaired by Lee Hamm, MD, conducted a comprehensive review of the 427-page proposed rule and drafted a comment letter to CMS detailing ASN’s recommendations and concerns. According to Hamm, “Overall, while the Task Force recognized the potential ACOs hold for advancing care and driving down costs, we were very concerned that the proposal, as written, could do more harm than good for patients on dialysis or with a recent kidney transplant.” (See Q and A on p. 2).

According to the ACA, an ACO is a network of providers, hospitals, and other health care organizations that agree to assume responsibility for providing care to

Vascular Access and Dialysis Modality

Catheter Use, Health Differences Influence Morbidity in Hemodialysis vs. Peritoneal Dialysis

By Doug Kaufman

End stage renal disease (ESRD) patients receiving peritoneal dialysis (PD) usually have lower morbidity than hemodialysis (HD) patients, but other factors play a role as well. The difference in morbidity could be partly due to the higher risk of early death among patients undergoing HD with central venous catheters (CVCs), according to a study in the June Journal of the American Society of Nephrology. In addition, “it may reflect the patients selected more than the process itself,” said lead author Jeffrey Perl, MD, a nephrologist at St. Michael’s Hospital and the University of Toronto School of Medicine, both in Toronto, Ontario. Health differences among patients in past comparisons of PD and HD success rates make it difficult to declare one treatment better than the other, Perl said.

In this study, Perl looked at more than 38,500 Canadians starting dialysis between 2001 and 2008. The study took into account the various factors that come into play when the most effective type of dialysis

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Dan Weiner, MD, and Amy Williams, MD, were among the 12 ASN members who served on the ASN Accountable Care Organization (ACO) Task Force, which was chaired by Lee Hamm, MD, Here, the task force members discuss the ACO proposed rule and their perspectives on some of the complex issues the rule raised related to care of patients with kidney disease.

What is your overall impression of the ACO concept?

Dan Weiner (DW): In concept, the ACO model has the potential to better integrate medical care across the spectrum of health and disease, particularly when it comes to fairly healthy Medicare beneficiaries and those with less severe chronic illnesses.

Lee Hamm (LH): In practice, it is uncertain how ACOs will deal with high-cost patients with severe chronic diseases as well as those with severe acute illnesses. It is very uncertain whether physicians will have the flexibility to appropriately individualize care for the entire range of patients, including those seen by nephrologists.

Amy Williams (AW): Overall, the proposed ACO structure, governance, and required quality metric monitoring and reporting are too complex and rigid, reducing the flexibility to best manage highly complex patients needing subspecialty care.

The comment letter stated that ACOs may not be well positioned to care for patients on dialysis. Can you elaborate on how the Task Force came to that decision?

DW: The ACO proposed rule focuses on the primary care providers (PCPs) and patients who receive most of their medical care from PCPs. It emphasizes primary and secondary prevention to maintain wellness. Dialysis patients require a very different model of care from the general population. Besides being among the most costly of all Medicare beneficiaries, dialysis patients also have very different disease frameworks.

LH: Many of the care recommendations and proposed ACO quality measures cannot be extrapolated to dialysis recipients. For example, should blood pressure targets for dialysis patients uniformly be below 140 mm Hg systolic? Should dialysis patients with fractures have bone density scans and prescriptions for drugs to treat or prevent osteoporosis? Should chronic disease screening guidelines, such as mammography and colonoscopy, be the same for dialysis patients? These proposed ACO "quality performance measures" often may not be applicable to dialysis patients and, in some cases, could actually prove harmful and unnecessarily expensive to dialysis patients.

AW: In addition, the performance metrics required for the ACOs are very different from those required for the dialysis expanded bundled and quality incentive program (QIP). These differences may lead to confusion and decreased coordination of care. Finally, many dialysis patients receive the majority of their medical care from nephrologists and other dialysis-affiliated professionals; this frequently includes primary care as well as cardiovascular disease and diabetes management. As proposed, ACOs make no allowance for this fact.

What do you see as the potential benefits of ACOs for patients with CKD?

DW: First, most evidence-based medicine recommendations for the general population likely also apply to people with CKD stage 3 and 4. So improving these elements of care for all patients should also lead to similar improvements for patients with CKD.

LH: Second, we have failed to date in timely preparation and education of patients with advanced CKD for their future, be it dialysis, transplantation, or conservative care. The framework for ACOs, by incentivizing preventive care, could improve integration of planning for kidney failure. We would hope that future iterations of ACOs would address this aspect of care.

AW: ASN would gladly partner with CMS to define best practices and expectations for managing advanced CKD in the context of an ACO.

Some in the nephrology community have discussed the possibility of a “renal-specific” ACO. Why did the Task Force believe it was not necessary to discuss a specialty ACO in the comment letter?

LH: There were several reasons. First, the proposed rule from CMS was very clear that the current ACO model was focused on primary care and was not focused on specialist care. Accordingly, while there may ultimately be a role for more renal-specific care models, we felt it was important to deal directly with the issues raised by the current proposed rule.

DW: Second, given the rapidly changing dialysis provider environment, formation of renal-specific ACOs could have further major implications on provider consolidation that need to be considered in greater detail. Finally, dialysis in the United States, under the expanded bundle and Quality Incentive Program (QIP), already incorporates many of the major features of ACOs, with the major difference that hospital care and physician fees, even if related to dialysis, are not included. However, the QIP is tailored to dialysis patients, with dialysis-specific technical expert panels charged with refining dialysis metrics.

AW: Given the recent implementation of the expanded bundle and forthcoming QIP, we felt that it was important to explore the successes and failures of this “limited” ACO model in dialysis before considering substantial expansions. We do support the option to have multiple demonstration projects to further explore the concept of a “renal-specific” ACO.

What did the Task Force think about the 65 proposed quality measures as they might affect patients with kidney disease?

DW: The list of quality measures really reinforced for us that the ACO proposed rule was not meant for dialysis patients. Many of the systems and care coordination measures, if relevant, are already discussed in the Conditions for Coverage, while the vast majority of the patient “evidence-based” measures to promote wellness have no evidence to support their use in dialysis patients and some may actually lead to harm and increased costs.

What were the difficult decisions the group faced?

DW: There were several very difficult decisions. We were fairly certain that dialysis patients did not belong in an ACO as proposed, but remained concerned that excluding them could create a disincentive for ACOs to provide appropriate pre-dialysis care. For example, there would be no financial incentive for an ACO to cover placement of an AV fistula prior to initiation of dialysis if the ACO would not receive the downstream benefit.

LH: We proposed that CMS could solve this dilemma by establishing a quality measure for patients with late stage CKD for timely implementation of a kidney replacement model. This measure would include creation of hemodialysis access if hemodialysis were the primary planned kidney replacement modality.

AW: Clearly, provision of vascular access remains an important issue that will require collaboration between CMS and CKD providers. We stated in the comment letter that ASN stands ready to work with CMS to develop a standard approach to late stage CKD patient care, and that quality measures based on these recommendations should be included in an ACO’s expectations.

DW: The second difficult decision was what to say about transplant recipients, and we in fact consulted with the ASN Transplant Advisory Group to develop a nuanced position on this issue. Many of the reasons why we felt that dialysis patients were inappropriate for ACOs are also applicable to transplant recipients, particularly those who are in the immediate peri-transplant period. However, ACOs, if successful, could provide substantial benefits to stable transplant recipients. This led the workgroup to call for exclusion of recent transplant recipients from ACOs, and to offer to work with CMS to develop criteria defining a “recent” transplant recipient versus a recipient who has been living stably and could potentially benefit from being in an ACO.

Moving forward, how do you see kidney patients and nephrologists interacting with an ACO?

DW: For the immediate future (if the ACO rules are finalized as proposed), I suspect the program will be very much like the HMO model, with a shift toward primary care doctors providing most medical care for CKD patients until late stage CKD is present. Ultimately I hope that nephrologists, particularly those who provide a lot of primary care to their patients, will be able to participate in an ACO model if they so choose.

AW: The ability of a nephrologist or nephrology group to contract with an ACO is critical to coordinate the care of patients needing subspecialty care. As the relationship between nephrologists and ACO providers evolves, it may become apparent that there are cost savings and improved quality of care when a nephrologist provides primary care to their complicated subspecialty patients. To demonstrate these advantages, and document and report quality metrics, a shared medical record is a necessity.
A specific group of at least 5000 Medicare beneficiaries. If an ACO meets certain quality standards for patient care and reduces the cost of that care to below what CMS expects it would otherwise have cost, the ACO will get to keep some of the savings. This sets the ACO model apart from the traditional fee-for-service payment system, in which providers are not held to any quality benchmarks and generally receive greater reimbursement for administering more tests and procedures.

As reported from this basic framework, Congress gave CMS significant discretion in determining the specifics of which provider types can participate in ACOs, how ACOs are structured, and the quality standards ACOs must meet. The proposed rule constitutes CMS’s first effort at tackling these details.

For the nephrology community, perhaps the most important detail in the proposal was CMS’s crystal-clear statement that it envisions ACOs as organizations centered exclusively on primary care. The only providers who may have patients assigned to them to form an ACO are primary care providers (internal medicine, general medicine, family practice, and geriatric medicine) who provide a predefined set of primary care services. Although nephrologists and renal care providers may provide services to patients who are assigned to ACOs, CMS proposes that no specialists may form an ACO. Discussion of a potential option for a “renal-specific” ACO had been suggested by some in the kidney community, but CMS has strongly indicated that specialty-specific ACOs are not on the table at this time.

In the proposed rule, CMS recommended a number of approaches to improve the quality and reduce the cost of patient care, including promoting evidence-based medicine best practices, patient and provider education, reporting on cost and quality measures, coordination of care, and individualized care plans. While these approaches are all valuable steps to improving the quality of care, many of these key ACO care processes are already routinely undertaken in dialysis units in an ESRD-specific format and setting, as implemented by the Medicare ESRD Program. It is unclear how dialysis care would fit into an ACO model.

ASN articulated concern that aligning the complex existing dialysis care system with a primary care-oriented ACO that uses quality metrics designed for the general population would be an extraordinarily complex task for dialysis units, the ACO, and nephrologists without adding value to individual kidney patients’ care. Subjecting dialysis patients to multiple sets of care providers would not only change the ACO and the dialysis unit—could have an unintended negative influence on quality of care, leading to dual processes, conflicting care mandates, duplication of resources, and fragmented patient care.

CMS laid out 65 proposed quality metrics that ACOs must achieve to be eligible for shared savings. While potentially of great value to the general population receiving care in an ACO, many of the proposed quality metrics may not be appropriate for kidney patients. Yet CMS did not indicate that the quality measures might apply differently to dialysis or transplant patients. Nor did CMS provide any detail regarding case-mix adjustment of the quality measures to account for variation in patient populations. ASN commented that these omissions are problematic, and could create perverse incentives for an ACO to provide care appropriate only for the general population in order to meet the standards necessary to be eligible for shared savings—to the detriment of complex patients with kidney disease. According to Amy Williams, a member of the task force, “patients on dialysis simply have different care needs from the general patient population, and it was unclear based on CMS’s proposals that it would differentiate between the two groups. It is imminently possible that ACOs could be penalized for providing appropriate care to a patient on dialysis if that care led to an outcome divergent from the standards set for the general population.”

CMS proposes to assign beneficiaries to an ACO based on the primary care provider (PCP) from whom they receive a plurality (exact percent unspecified) of their primary care services (Table 1). ASN emphasized to CMS that many nephrologists serve as PCPs for their kidney patients, particularly those in late-stage CKD, those maintained on dialysis, and those who have received a recent transplant. To preserve this vital patient-nephrologist relationship, and to prevent any unintended consequences for specialized patients in a primary care ACO, ASN recommended that dialysis patients and transplant recipients—populations who often receive the plurality of their care from a nephrologist—should not be attributed to an ACO.

This arrangement would permit patients with earlier stages of kidney disease to remain in the ACO and benefit from the coordinated care processes it facilitates, but, as indicated by their disease progression, eventually allow them to receive the specialized care they need: be it dialysis or transplantation—without affecting the ACO’s overall performance on the quality metrics.

Because care of patients with CKD, especially those with more advanced CKD, is extremely complex and requires close, multidisciplinary collaboration between the patient’s PCP and nephrologist as well as other physician and nonphysician providers in order to limit complications of the disease, including progression to kidney failure, ASN commented that ACOs may offer significant benefits for CKD patients, with some key modifications.

Processes that an ACO would facilitate—such as electronic patient data collection and sharing, quality monitoring, and individualized care plans, may lead to better outcomes and more patient-centered care for CKD patients. However, these outcomes will be dependent on whether the care processes and quality standards ACOs select are appropriate for CKD patients’ unique health status. ASN strongly supports efforts to improve outcomes for CKD patients within the context of ACOs. For instance, vascular access planning could be streamlined in an ACO model through improved and timely communication between PCPs and specialists, as well as through incentives for vascular access to be placed prior to the start of dialysis, when appropriate. ASN suggested that CMS establish timely creation of a dialysis access as a quality measure for patients with late stage CKD, creating an incentive for ACOs to establish a dialysis access in their patients.

ASN was one among many hundreds of organizations and individuals to submit comments to CMS regarding the ACO Proposed Rule. Many commentators—including those who were among the ACO program’s strongest proponents prior to release of the proposed rule—expressed concerns. The 65 quality measures have been widely panned as overly “burdensome” and “prescriptive,” and commentators have also expressed concern that ACOs will not know which patients it is responsible for until years after care has been provided (under CMS’s proposal patients will be retroactively attributed to ACO by CMS. Patients are free to seek care outside of the ACO from other providers).

To read ASN’s comments to CMS on the ACO proposed rule, please visit the ASN Public Policy web page.

Providing helpful feedback to CMS on the proposed ACO rule, the ASN ACO Task Force will continue to follow CMS’s ACO activities closely leading up to implementation of the program, and stand ready to help CMS further assess the effects of ACOs on the kidney patient population or to offer any additional guidance.

For those interested in reviewing the feedback and anticipated to alter its proposal, CMS will likely then issue either a final rule (which would not be open for comment) or an interim final rule (upon which CMS could solicit comment). ASN and the ACO Task Force will continue to follow CMS’s ACO activities closely leading up to implementation of the program, and stand ready to help CMS further assess the effects of ACOs on the kidney patient population or to offer any additional guidance.

Table 1. Key features of the ACO Proposed Rule

<table>
<thead>
<tr>
<th>Feature</th>
<th>Detail</th>
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<tbody>
<tr>
<td>Primary care focus</td>
<td>Only primary care providers (internal medicine, general medicine, family practice, and geriatric medicine) who provide the “plurality” of a specific set of primary care services may have patients assigned to the ACO in which they participate.</td>
</tr>
<tr>
<td>Retrospective beneficiary assignment</td>
<td>Beneficiary assignment will occur after the end of the performance year, based on utilization data. ACOs might have to wait for up to 9 months after the end of the fiscal year to know who was actually “assigned” to their ACO.</td>
</tr>
<tr>
<td>Quality measures</td>
<td>ACOs will report on 65 quality measures, in five domains, beginning in the first performance year of the program.</td>
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<tr>
<td>Evidence-based medicine</td>
<td>The ACOs are required to implement evidence-based medicine or clinical practice guidelines and processes. All ACO participants and suppliers/providers must agree to abide by these guidelines and processes, and must be evaluated for their compliance.</td>
</tr>
<tr>
<td>ACO risk models: one sided model</td>
<td>Participants would be eligible to share in any cost savings associated with the program and would not be liable for any cost overruns. In the third year of participation, ACOs would undergo mandatory transition to the two-sided model.</td>
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<tr>
<td>ACO risk models: two-sided model</td>
<td>Participating ACOs would be receive a higher percentage of savings than participants in the one-sided model, however, ACOs in the two-sided model could be held responsible for costs that exceed certain benchmarks and could end up owing Medicare money.</td>
</tr>
<tr>
<td>Patient choice</td>
<td>ACOs must notify patients that they are receiving care from providers that participate in an ACO. However, patients (and providers) will not know for sure whether the patient will be retroactively attributed to that ACO by CMS. Patients are free to seek care outside of the ACO from other providers.</td>
</tr>
<tr>
<td>Electronic health records</td>
<td>At least 50 percent of the ACO participants must have Electronic Health Records and be “meaningful users,” by the start of the second year of participation in the ACO program.</td>
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Vascular Access and Dialysis Modality

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In the 7-year study, 63 percent of the patients started HD with a central catheter inserted into one of the large veins. Anoth-
er 17 percent began HD with an arterio-
venous fistula (AVF) or arteriovenous graft (AVG). The remaining 19 percent started with PD at home, with education in ad-

vance about treatment options.

In the first year of the study, the risk of
death for patients starting HD with a CVC
was 80 percent higher than for patients who
began with PD. The first-year death risk for
patients with an AVF or AVG was similar
to that in the PD group. In the 5 years after
dialysis was begun, the death risk was still
20 percent greater in the patients receiving
HD with a CVC compared with the PD
group. The survival rate for patients receiv-
ing HD with an AVF or AVG remained similar
to that in the PD patients.

All the previous studies tried to com-
pare hemodialysis versus peritoneal dialy-
sis in terms of patient survival,” Perl said.
“Ideally, the best way to study this question of
which therapy is associated with better
survival is to do a randomized controlled
trial. That’s not going to be feasible when
so much of why patients choose one ther-
apy over another is lifestyle-based. It’s really
difficult to do studies that are randomized
terminated trials in this area.”

The next best thing researchers can
do is look at very large databases that
have tracked the outcomes in patients who
have chosen HD versus patients receiving
PD, and examine the outcomes in those
patients after accounting for things like
diabetes, age, and comorbidities that may
make comparison more difficult.

“They studies have traditionally dem-
"strated that peritoneal dialysis was as-
sociated with better outcomes in the first
1 to 2 years compared to hemodialysis,”
Perl said. The main criticism of such stud-
is that the average PD patient tends to
be younger, with fewer comorbidities, and
generally healthy enough to handle the
home therapy: “The results of those studies
may speak more toward the type of patient
selected for peritoneal versus PD, rather
than the actual effect of the therapy itself,”
Perl said.

In designing this study, Perl said he
hoped to delineate an HD patient who
chose HD, was able to start electively, and
had predialysis care—just like a PD pa-
tient. One indication would be if a patient
on HD had a surgical access—a planned
way of creating a connection between the
artery and the vein—which can take
months to establish.

“That would be a marker of someone
who’s been exposed to nephrology care for
a long period of time, and had to obviously
get predialysis care and education, enough
to have this access created and ready to
use during their first treatment,” Perl said.
HD patients who start with a fistula might
be much more similar to a PD patient.
By contrast HD patients who start with
a catheter, which can be inserted within
hours after the decision that a patient needs
dialysis, generally need to begin dialysis
more urgently.

“In the Perl study, the survival compari-
sion was between those using a fistula or
graft and those on peritoneal dialysis with
exclusion of patients starting with a cath-
eter. This removed some of the bias associ-
ated with starting dialysis with a catheter
and compared a more homogeneous pop-
ulation, those who attended nephrologi-
cal care, were able to make decisions and
who were considered ‘eligible’ for PD and
HD with a fistula or graft,” said coauthor
Louise Moist, MD, of the University of
Western Ontario. “This allows us to truly
compare the dialysis modalities without
as much influence from differences in the
population that we are not able to control
for. This study has addressed an impor-
tant question. The two modalities, HD and
PD, have similar outcomes once the
playing field is leveled. Now the decisions
should be based on patient preference and
health-related quality of life.”

Per Perl: “When you separate the he-
modialysis patients into those two groups,
you realize that, really, it’s not that PD is
associated with an early survival advantage; it’s
that hemodialysis patients tend to be sicker,
and those who start dialysis with a catheter
actually have worse survival in the first 1 to
2 years. But those who start, optimally with
a fistula or graft, have quite similar survival
[rates] to peritoneal dialysis patients.”

Catheters have a greater risk of infec-
tion. “There’s no doubt about it. When
you compare catheters to fistulas and
grafts, there’s a higher rate of infection
[with catheters], and there’s a higher rate
of mortality,” Perl said. But the catheter
does not necessarily cause all the problems. “It’s
difficult to tease out how much of the im-

pact of catheters is the effect of infection
on mortality, and how much is based on
the type of patient who uses a catheter," he said. "We're never going to randomize patients to a catheter or a fistula or graft. That would be unethical, based on the evidence we have right now; to suggest that catheters are associated with a much higher risk of death. But it's a difficult question."

The study's other "take-home point," Perl said, concerns the importance of planning and education. "To get a fistula or a graft takes quite a bit of time," he said. "You need to see patients months in advance." Not all patients, even with the best intentions of the nephrologist and the treatment team, will be ideal candidates for a fistula or a graft. For patients who are diagnosed late, or who may be ineligible for a fistula or a graft, or who have a high likelihood of experiencing fistula or graft failure and having to start HD with a catheter, it would be good to have another option.

In spite of the risks, HD with a CVC may be the best option in some instances. "Every dialysis modality decision is a patient-by-patient analysis of the risks and benefits of each therapy," Perl said. "Not all patients are ideal candidates for peritoneal dialysis. It requires an intact abdominal cavity. So, for example, if someone has had multiple surgeries on their abdomen and bowel surgeries, they may not be an ideal candidate for peritoneal dialysis. Similarly, not all patients are candidates for fistula or graft. It requires relatively preserved blood vessels to facilitate being able to create, and then undergo a surgery to connect the artery to the vein."

So, while most nephrologists would consider HD with a CVC "the least favorable option," Perl said, "in many cases it is the only option." It can be the only option, for instance, in emergency situations where the kidney failure is identified in a hospital and dialysis must be started immediately. Also, some patients who have received predialysis care and education and are qualified candidates for fistula or graft or PD still make a conscious decision to have HD with a catheter. "This study couldn't really tease out those two types of patients. Getting around that would be very helpful," Perl said.

One of the study's shortcomings may be that comments about residual renal function and why the relative risk of PD versus HD changes over time may not be entirely correct said John Burkart, MD, professor of nephrology at Wake Forest Baptist Medical Center. "The effect of residual kidney function (RKF) was not examined. One hypothesis based on these observations and the knowledge that RKF tends to decrease over time is that PD had an early survival advantage because of preservation of RKF or starting patients on PD who have F/U and RKF, I think disproved by this observation," Burkart said. “[For example], for the population as a whole HD starts out bad—due to CVC usage—however, we still do not know why. Relative risk changes over time and starts to favor HD. It may be that over time, as the RKF ‘buffer’ decreases, PD does not do as well because the MDs have typically not had the infrastructure or knowledge of how to adjust prescriptions and individualize the prescription. This is not shown or investigated in this data.”

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Renal and Reproductive Functions: Inextricably Linked

By Phyllis August

Healthy kidneys—healthy pregnancy

A healthy pregnancy—a baby born at term, with minimal untoward physical consequences to the mother—is the ideal outcome and indeed, when it occurs, is nothing short of a miracle. That the maternal kidneys are such important players in this process is perhaps not news to the seasoned nephrologist, but it is a concept that bears emphasizing, particularly when a woman with kidney disease or even hypertension contemplates pregnancy. Why this should be so is likely a result of the critical role of the kidneys in adapting the circulation to the increasing demands of the conceptus, and accommodating the alterations in blood flow that are necessary for the rapidly enlarging uterus, the growing placenta, and of course the fetus.

Renal-hemodynamic adjustments to pregnancy

The most dramatic renal accommodations to pregnancy include marked vasodilation, increase in glomerular filtration rate (GFR) of 50 percent, and increase in renal blood flow up to 80 percent above baseline. Despite increased GFR and lower blood pressure, there is a cumulative retention of sodium of about 900 mEq, which is a critical step in the generation of the increased plasma volume necessary for perfusion of the growing fetus as well as all other vital organs. These normal physiologic adjustments to pregnancy are barely noticed by the pregnant woman.

There are, however, subtle signs that may be detected on physical and laboratory examination even early in pregnancy. The most noticeable is the early decrease in blood pressure, which in normotensive women results in decrements of about 5–10 mm Hg systolic and 2–5 mm Hg diastolic in comparison with prepregnancy blood pressures. This early pregnancy vasodilation, which becomes even more noticeable in midgestation, is often more apparent in the woman with pre-existing hypertension, in whom decreases in systolic and diastolic blood pressure may be significant enough to permit cessation of antihypertensive therapy during pregnancy.

The mediator(s) of this fairly dramatic phenomenon are not clearly known. “Candidate” vasoconstrictors of pregnancy include estradiol, relaxin, and nitric oxide. Additional consequences are increased cardiac output and increased heart rate secondary to decreased afterload, as well as marked stimulation of all components of the renin-angiotensin-aldosterone system. Without this latter adjustment, women might find it difficult to remain standing for any length of time while pregnant; indeed, a few are prone to syncope.

We demonstrated the importance of the stimulated renin-angiotensin system (RAS) in pregnancy for maintaining normal blood pressure by administering a single dose of captopril to first- and second-trimester normotensive women and observing their blood pressure and renin responses after 1 hour. In comparison with age-matched nonpregnant women, acute blockade of the RAS system in early pregnancy resulted in significantly greater decreases in blood pressure and compensatory increases in plasma renin activity, suggesting that the stimulated RAS was playing a critical role in supporting blood pressure (1). The increases in GFR and renal blood flow are largely mediated by vasodilation and increased renal plasma flow (2). The results of clinical studies using clearance techniques (inulin, p-aminohippuric acid, and neutral dextrans) suggest that additional factors, such as decreased oncotic pressure and an increased glomerular ultrafiltration coefficient, are also important. Renal blood flow increases more than GFR in early and midpregnancy, and filtration fraction decreases; however, in late gestation, there is an increase in filtration fraction. Thus, there is little evidence for increased intraglomerular pressure and therefore little risk that the hyperfiltration associated with gestation is associated with additional strain on the kidneys (3).

Nonhemodynamic alterations in renal function in normal pregnancy

During pregnancy, there are increases in respiratory rate, tidal volume, and alveolar ventilation, resulting in reduced arterial PCO₂. This has been attributed to increased progesterone, which stimulates the medullary respiratory center. The partly compensated respiratory alkalosis is detectable by a reduction in hydrogen ion concentration, PCO₂, and serum bicarbonate. Water metabolism is also altered. There is a decreased osmotic threshold for thirst and arginine vasopressin release during pregnancy, with a decrease in plasma osmolality and serum sodium (4). Levels of 1,25-dihydroxyvitamin D are increased in pregnancy, parathyroid hormone is decreased, and urinary excretion of calcium is decreased (5).

There are other physiologic adjustments in pregnancy that are less well characterized but that may be relevant in women with underlying kidney disease. These include adjustments in inflammation and immunity. The alterations in immunity are in part related to the immunologically privileged status of the fetus. There is also specific maternal tolerance to fetal antigens at the maternal–fetal interface and alterations in circulating immune cell populations and antibodies that may downregulate the maternal immune response (6). Pregnancy has also been characterized as a state of enhanced inflammation, which may be mediated by trophoblast-derived microparticles that are released into the maternal circulation and stimulate the maternal systemic inflammatory response. The subtle increases in leukocyte count, C-reactive protein, and erythrocyte sedimentation rate in pregnant women may be interpreted as signs of increased inflammation (7).

Familiarity with these changes is critical to the accurate interpretation of laboratory results in the pregnant woman, in whom BUN, creatinine, serum sodium, and bicarbonate are usually slightly lower than in normal pregnant women (8).

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Evidence supporting a relationship between underlying renal histologic features and pregnancy outcome is lacking. There are, however, a few generalities worth making. Women with diabetic nephropathy should be counseled to plan pregnancy before they develop macroalbuminuria, given that pregnancy outcomes are significantly better when GFR is preserved and microalbuminuria rather than macroalbuminuria is present. Women with lupus should be in remission for 6 months before conception, and even then, flares of disease are not uncommon during pregnancy. High titers of antiphospholipid antibodies, and/or presence of the lupus anticoagulant, greatly increase the risk of adverse outcomes, and strong consideration should be given to prophylactic anticoagulation in this setting. Mycophenolate mofetil is a teratogen, and this drug should be withdrawn and women treated with other agents (e.g., azathioprine, cyclosporine, prednisone) well before conception. Cyclophosphamide is also contraindicated in pregnancy. Finally, blockers of the RAS, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and renin inhibitors, should be discontinued before pregnancy, and nephrologists should be aware that cessation of these drugs, as well as the hemodynamic changes of pregnancy, may be partly if not totally responsible for significant increases in proteinuria that are noted early in gestation. Finally, if the cause of the underlying renal disease is unknown, renal biopsy may be helpful if performed early in pregnancy, particularly in the setting of nephrotic syndrome or reduced renal function, and especially if therapeutic interventions are contemplated.

In summary, the renal adaptation to pregnancy is critical to ensure appropriate volume expansion and increased perfusion to meet the needs of the developing fetus and placenta. Vasodilation, lower blood pressure, and increased cardiac output are the most obvious consequences of this process. Women with kidney disease have diminished capacity to adapt to pregnancy, and the degree to which pregnancy is compromised is related to the degree of renal functional impairment and the degree of hypertension. The treatment of pregnant women with kidney disease is a team effort and involves close monitoring, appropriate blood pressure control, and carefully timed delivery.

References
Acute Kidney Injury in Pregnancy

By Richard Lafayette

During pregnancy, the development of acute renal failure is especially daunting because two lives are involved and at risk. The outcomes of acute kidney injury (AKI), as in other settings, can be quite poor, with significant morbidity and mortality rates of 20–30 percent.

Variable definitions of AKI have been used for pregnancy. The normal baseline serum creatinine during pregnancy is approximately 0.5 mg/dL; thus, a rise over 48 hours to values greater than 1.0 mg/dL, or an increase from a baseline of more than 0.5 mg/dL in 48 hours, should trigger further evaluation for AKI. It has been suggested that the RIFLE criteria be used, focusing on the percent change in creatinine or the development of oliguria to define AKI in pregnancy (1), but validation is needed. Regardless, there is clear evidence that the incidence of AKI in pregnancy has fallen over the past several decades, likely because of improved access to prenatal care and emergency services for the care of obstetric complications in developing countries and among disadvantaged populations. Still, in some less developed nations, the rates of AKI related to septic abortion and other infectious and hemorrhagic complications remain high (2).

Presently, the incidence of AKI in pregnancy has fallen to approximately 1 in 15,000 pregnancies (3), but the outcomes have not significantly improved (3, 4).

Causes of AKI in pregnancy

Pregnant women are subject to many of the non–pregnancy-specific causes of AKI, and a general approach that considers pre-pregnancy, intrarenal, and obstructive causes is best. However, some specific issues are more common in pregnancy. One approach would be to evaluate AKI on the basis of its timing (Table 1).

Early pregnancy

From the first trimester to about 20 weeks, AKI is quite rare; the major contributor is hyperemesis gravidum, which is generally easily supported with increased fluids and vigilance. Complications of tubal pregnancies and septic abortions also contribute to the prevalence of AKI (4). Some 1 in 10,000 pregnancies results in ectopic pregnancy, and tubal pregnancies have a high risk of recurrent tubal pregnancy (5).

Thrombotic microangiopathy, possibly related to immune depletion of ADAMTS 13 antibodies, who have a high risk of recurrent tubal pregnancy, accounts for some of these cases. Thrombotic microangiopathy is an important cause, as a consequence of dilution of the urinary tract and the effects of uterine size (7).

Management

Acute kidney injury profoundly risks the outcome of pregnancy. Mortality rates and other complication rates remain high. It is key to make an appropriate diagnosis and to treat the underlying disorder. Volume and electrolyte support should be optimally controlled, and medical interventions should be adjusted to estimated levels of renal function. General measures such as maintaining nutrition and physical conditioning may also be important. The immediate indications for dialysis are the same as for the nonpregnant patient in terms of fluids and electrolyte control and preventing complications of uremia. However, there is some controversy regarding the best time to begin prophylactic dialysis. Registries, at least for chronic kidney disease, suggest that aggressive control of azotemia results in better fetal and maternal outcomes. Experts suggest starting dialysis when the urea levels are only modestly elevated and maintaining them at less than 60 mg/dL (3). No controlled trial is available, to our knowledge, but the physician should likely be prepared to start dialysis early and maintain effective doses when pregnancy continues (4). For postpartum patients, there is no evidence to support dosing their dialysis differently than for other patients with AKI.

Late pregnancy

After 20 weeks, AKI is more common and is more likely to be related to the classic complications of pregnancy. Complications of uterine infection remain rare but are easily assessed. Obstructive uropathy is an rare cause, as a consequence of dilution of the urinary tract and the effects of uterine size (7).

Systemic lupus erythematosus, which may be available in the future to stabilize endoglin, may be available in the future to stabilize endoglin, may be available in the future to stabilize endoglin, may be available in the future to stabilize endoglin, may be available in the future to stabilize endoglin. Screen for soluble angiogenic factors, such as trophoblast growth factor, hCG, and angiopoietin, which are elevated in pregnant women with significant chronic kidney disease (8). This syndrome, renal failure is not uncommon (up to 10 percent of the time) and is associated with markers of coagulopathy (10).

The treatment of severe renal failure typically presents as abdominal discomfort, mental status changes, and a rapid rise in bilirubin out of proportion to elevated liver enzymes. The incidence of acute fatty liver of pregnancy appears to be on the rise (more than 1 in 10,000 pregnancies (10)). Renal involvement is common, with AKI reported in at least 30–35 percent of patients. Features of the hepatorenal syndrome are usually present, although acute tubular necrosis also occurs. Definitive diagnosis requires liver biopsy showing microvesiculation, but clinical diagnosis generally prevails, and treatment, again, is early delivery and supportive care. Most patients recover well over time, but liver transplant has been necessary in some cases.

A metabolic acute renal syndrome usually occurs in the early postpartum period and is marked, of course, by thrombocytopenia, microangiopathic anemia, and renal failure (13). This can occur before delivery and is easily confused with pre-eclampsia. Plasma exchange, avoiding plasminogen transfusions, and more conservative treatments (e.g., steroids, antiplat red agent) are available to treat this syndrome.

Pre-eclampsia AKI is generally related to sepsis, shock, hemorrhage, or antithrombotic emboli. Complications related to placental calciphylaxis or uterine hemorrhage can commonly lead to acute tubular necrosis, and pregnant women are almost uniquely vulnerable to acute cortical necrosis (14), which is likely to leave the patient dependent on renal replacement therapy, or occasionally with substantial CKD.

References


Table 1. Differential of acute kidney injury in pregnancy based on physiology and timing

<table>
<thead>
<tr>
<th>Physiological Stage</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EARLY</strong></td>
<td><strong>Prexrenal</strong></td>
</tr>
<tr>
<td>Hyperemesis gravidum</td>
<td>Postrenal</td>
</tr>
<tr>
<td>Rare</td>
<td>Infrarenal</td>
</tr>
<tr>
<td>Chronic kidney disease progression</td>
<td>Hypertensive disease, glomerulonephritis</td>
</tr>
<tr>
<td>Complications of hemorrhage, sepsis, urinary tract infection, etc.</td>
<td>Familial hemolytic uremic syndrome/TTP</td>
</tr>
</tbody>
</table>

| LATE | **Prexrenal** |
| Bleeding | Acute fatty liver of pregnancy |

| **Postxrenal** | **Bleeding** |
| Obstruction from stones | Postrenal |

| **Infrarenal** | **Obstruction from uterus** |
| Chronic kidney disease progression | Severe pre-eclampsia/hemolysis, elevated liver enzymes, low platelets |

| **Late** | **Acute fatty liver of pregnancy** |
| Hemolytic uremic syndrome/TTP | Postrenal |
| Acute tubular necrosis from sepsis, hemorrhage |
Antiangiogenic Factors and Pre-eclampsia

By Sharon E. Maynard

Pre-eclampsia is a systemic syndrome occurring in the second half of pregnancy, with cardinal manifestations of hypertension and proteinuria. Pre-eclampsia is one of the most common glomerular diseases in the world, affecting approximately 3–5 percent of all pregnancies. Although careful obstetric management—including antihypertensive medications and seizure prophylaxis with intravenous magnesium—is important for the treatment of pre-eclampsia, delivery of the neonate and placenta remains the only definitive treatment. Thus, pre-eclampsia remains a leading cause of maternal mortality, preterm birth, and consequent neonatal morbidity and mortality. In developing countries, where access to safe, emergent delivery is not readily available, pre-eclampsia claims the lives of over 60,000 mothers every year (1).

Maternal endothelial dysfunction

Our understanding of the pathogenesis of pre-eclampsia has evolved remarkably over the past decade and is summarized in a simplified way in Figure 1. Pre-eclampsia appears to originate in the placenta, where abnormal vascular development precedes the clinical syndrome by weeks to months. The target “organ” is the maternal vascular endothelium. The clinical manifestations of pre-eclampsia—hypertension, proteinuria, and glomerular endotheliosis (2) (which is characterized by abnormal pericyte and smooth muscle cell proliferations) and other features such as edema, headache, and seizures—reflect widespread endothelial dysfunction, with vasoconstriction and end-organ ischemia. Mounting evidence over the past several years has implicated antangiogenic proteins, produced by the placenta and secreted into the maternal circulation, as the pathogenic link between placental dysfunction and maternal endothelial damage.

Pre-eclampsia is a final common pathway of maternal vascular dysfunction with diverse and multifactorial origins, many of which remain obscure. The development of pre-eclampsia in any individual woman results from a combination of placental dysfunction (leading to aberrant production of antangiogenic proteins and other factors) and maternal susceptibility. Genetic predisposition probably contributes to risk at both those levels. Most cases of pre-eclampsia occur in otherwise healthy primiparous pregnant women, and in those cases excessive placental production of angiogenic factors is probably the key factor. However, in women with underlying endothelial disease (diabetes mellitus or chronic hypertension, for example), maternal susceptibility to placental angiogenic factors is probably responsible for an increased risk of pre-eclampsia.

Soluble fms-like tyrosine kinase 1: a circulating antagonist to transforming growth factor β

Angiogenesis is defined as the formation of new blood vessels. Soluble fms-like tyrosine kinase 1 (sFlt1) is often referred to as an antangiogenic protein because, when secreted into the circulation, it binds and inactivates the proangiogenic vascular endothelial growth factor (VEGF) and placental growth factor (PIGF).

Although essential for angiogenesis, VEGF is also critical for the maintenance of the health of mature endothelial beds, especially the renal glomerular endothelium, a major target in pre-eclampsia. Placental expression of sFlt1 is increased in pre-eclampsia and is associated with a marked rise in the levels of maternal circulating sFlt1 (2). Increased circulating sFlt1 binds and antagonizes VEGF and PIGF in the maternal circulation, leading to endothelial dysfunction and pre-eclampsia. Animal models support this theory: sFlt administered to pregnant rats results in a syndrome resembling human pre-eclampsia, including hypertension, proteinuria, and glomerular endotheliosis (2). Circulating levels of sFlt1 and PIGF are altered several weeks before the onset of clinical disease and are correlated with the severity of disease (3–5). The levels of sFlt1 normalize within several days after delivery, coinciding with improvement in proteinuria and hypertension.

Soluble endoglin: a circulating antagonist to transforming growth factor β

Soluble endoglin (sEng), another antangiogenic biomarker that is upregulated in pre-eclampsia in a pattern similar to that of sFlt1, is a truncated form of endoglin (CD105), a cell surface receptor for transforming growth factor-β (TGF-β). sEng amplifies the vascular damage mediated by sFlt1 in pregnant rats, inducing a severe pre-eclampsia–like syndrome with features of the HELLP syndrome (6). As with sFlt1, circulating sEng levels are elevated weeks before the onset of pre-eclampsia (7), and increased sEng levels are observed in the rat model of pre-eclampsia induced by uterine ischemia (8). The similarity in the gestational patterns of circulating sFlt1 and sEng suggest that they may be regulated by a common upstream signaling pathway.

Insights from pre-eclampsia risk factors

Higher sFlt1 levels have been noted in first versus second pregnancies (9), twin versus singleton pregnancies (10, 11), diabetes mellitus (12, 13), and women with fetuses having trisomy 13 (14). All of these conditions are established risk factors for pre-eclampsia. Conversely, decreased levels of sFlt1 in pregnant smokers (15, 16) may explain the protective effect of smoking in pre-eclampsia.

Screening and prediction

Effective preventive and therapeutic strategies for pre-eclampsia have remained elusive. Nevertheless, early detection, monitoring, and supportive care are considered beneficial in improving outcomes for both mother and neonate. Reliable prediction of pre-eclampsia would allow closer prenatal monitoring, early diagnosis, and timely intervention—with steroids to enhance fetal lung maturity, magnesium for seizure prophylaxis, antihypertensive medications, bed rest, and expedited delivery when indicated.

Results from dozens of studies have confirmed that maternal serum levels of PIGF, sFlt1, and/or sEng are significantly altered before the onset of pre-eclampsia. Whether these changes are marked enough to constitute an effective screening or early diagnostic test remains to be seen. Changes in PIGF are seen by the first or early second trimester, and reproducible alterations in sFlt1 and sEng are noted in the middle to late second trimester onward.

The discrimination of sFlt1 for pre-eclampsia has been reported as high as 96 percent (17), although sensitivity and specificity appear to be much lower for late-onset pre-eclampsia, especially when sFlt1 is sampled early in pregnancy. Maternal sFlt1 levels are particularly elevated in severe pre-eclampsia, early-onset pre-eclampsia, and pre-eclampsia with intrauterine growth restriction (3, 18). Urinary PIGF is lower in women with pre-eclampsia before the onset of symptoms (19), especially in early-onset and severe disease (20).

The timing, source (i.e., serum versus urine), and combination of biomarkers and other tests that will prove most predictive of pre-eclampsia and its complications are now being explored. For example, the combination of ultrasonographic changes and angiogenic biomarkers in the second trimester may be more predictive of pre-eclampsia than angiogenic markers alone (21). Combining biomarkers into a single angiogenic index appears to be more predictive than any single marker, and some of these combinations meet the likelihood ratios and other criteria required for a prediction test to be clinically useful (7, 22–26).

Diagnosis and risk stratification

Antiangiogenic proteins may prove useful in establishing the diagnosis of pre-eclampsia in challenging, ambiguous, or atypical cases. For example, angiogenic biomarkers may distinguish pre-eclampsia from other causes of hypertension in pregnancy in patients with pre-existing renal disease (27) and from other causes of gestational thrombocytopenia such as idiopathic thrombocytopenic purpura (28); they may also identify pre-eclampsia in cases of gestational hypertension or proteinuria before 20 weeks gestation (29). The observation that derangements in circulating angiogenic biomarkers appear to correlate with the severity of pre-eclampsia and complications such as placental abruption and intrauterine growth restriction has suggested that they might be useful for risk stratification. In 2009, angiogenic factor testing was approved as a diagnostic test for pre-eclampsia in the European Union (PIGF and sFlt1 immunosassay, Roche Diagnostics), and a similar assay is being prepared for approval in the United States. Larger studies are in progress that probe the utility of angiogenic biomarkers in the clinical arena.

Novel treatment strategies

The identification of sFlt1 and sEng as key links between placental pathology and maternal endothelial dysfunction suggests that the biomarkers may be useful for risk stratification. Potential therapies would be directed at restoring normal angiogenic balance in the maternal circulation—that is, the biologic activity of proangiogenic factors such as VEGF, PIGF, and TGF-β relative to antangiogenic factors such as sFlt1 and sEng. For example, both VEGF (30) and PIGF (31) diminish hypertension and ameliorate proteinuria in rodent models of pre-eclampsia, while apparent harm to the fetus. Direct administration of VEGF and/or PIGF in humans would be burdensome because it would require continuous intravenous infusion, so agents that enhance endogenous VEGF, PIGF, or TGF-β production are also being explored. For example, pravastatin induces endogenous PIGF production and ameliorates hypertension and proteinuria in a mouse model of sFlt1-induced pre-eclampsia (32). An effective treatment for pre-eclampsia could have an enormous impact. In cases of extremely early-onset pre-eclampsia (22–28 weeks), for example, a treatment that allowed delivery to be safely postponed for just days to weeks could markedly improve neonatal outcomes. Unfortunately, clinical research involving novel treatments in pregnant women has ethical, medicolegal, and logistic challenges in addition to the usual scientific challenges. These issues have slowed progress from bench to bedside for this promising breakthrough in our understanding of the disease.

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Pregnancy and the Kidney

References


Long-Term Consequences of Placental Disease

By Michelle Hladunewich

A bout 5 percent of pregnancies suf-
fer complications from abnormal
placental development. The process of
placentalization begins when blastocysts ad-
here to the uterine endometrium, forming a
lineage of epithelial cells termed the invasive
extravillous cytotrophoblast, which then in-
vades the uterine wall to create the decidua,
transforming the spiral arteries into low-
resistance uteroplacental circulation.

Impaired development of the uteroplac-
cental vasculature, therefore, has its origins
in the first trimester as a result of an ab-
normal interaction between the invading
extravillous cytotrophoblast and the mater-
nal immune system, resulting in decidual
vasculopathy, with small, poorly developed
spiral arteries. As these pregnancies progress,
placental ischemia and infarction may result
in a decidual vasculopathy, a term used for
placental ischemia, placental abruption, and/or the en-
suming adverse perinatal outcomes, including
fetal growth restriction and stillbirth.

It was previously thought that the con-
sequences of maternal placental disease re-
solved quickly and completely after delivery
of the placenta. More recently, however, it has
become clear that placental disease, as a major basis of the maternal placental syn-
drome, is a marker of future vascular disease,
forecasting a vastly different health trajectory
than that of a woman who has had normal
placental function and a healthy pregnancy.

Epidemiology

The first study to describe the relationship
between pre-eclampsia and cardiovascu-
lar disease used the Norwegian Medical
Birth Registry (1). Although this study did not
show an increased risk of death among women with pre-eclampsia who were de-
livered before 37 weeks, it did show an eight-
fold increased risk of death and an eightfold
increased risk of cardiovascular death in
women who were delivered before 37 weeks,
interpreted as a surrogate marker for more
severe disease.

An increased risk of cardiovascular death was
also noted among women with preemergent
delivery but without clinical pre-eclampsia.
This highlights a key component to un-
derstanding which women are at risk for future vascular disease, inasmuch as a third of preterm deliveries are caused by placental
implantation abnormalities. These findings
have been confirmed and expanded by other
studies in which, in addition to an increased
risk of cardiovascular disease, an increased
risk of cerebrovascular disease, peripheral
vascular disease, and end stage renal disease
was also noted (2, 3).

In the Canchave Health After Maternal
Placental Syndromes study, the importance of placental vascular disease in long-term maternal outcome was again
highlighted; inasmuch as the worst survival
was noted in women with pre-eclampsia ac-
 companied by fetal death (2). The societal
effect of this increased vascular risk, however,
is best demonstrated by the Child Health
Development Cohort. Data from over
14,000 women with an average of 30 years of
follow-up noted the median age for car-
diovascular events to be 56 years, with a cu-
mulative survival of 86 percent for women
with early-onset pre-eclampsia compared
with 98 percent for those with late-onset
pre-eclampsia and 99 percent for those with
healthy pregnancies (4).

Pathophysiology

Whether damage to the vascular endothe-
lum secondary to maternal placental syn-
drome results in an increased risk of future
vascular disease, or whether vascular factors underlie both the predisposition to
placental disease and the later development of
vascular disease, is unknown. Studies,
however, are noting common genetic and
physiologic links and, therefore, shared risk
factors between pre-eclampsia and cardiovas-
cular disease.

There are several examples of common
gene pathways. Catechol-O-methyltrans-
ferase (COMT) is responsible for the degra-
dation of both estrogens and catecholamines.
Mice deficient in COMT, and hence 2-
methoxyestradiol (2ME), have abnor-
mal placentation and develop a phenotype
that resembles human pre-eclampsia (5).
In a mouse model of cardiovascular disease,
2ME treatment can decrease atherosclerosis
by 52 percent and cholesterol by 19 percent (6).
Human data have also emerged for this
shared genetic factor. A nested case-control
study assessed the three common haplo-
types of the central region of the COMT
gene wherein the haplotype translates into
COMT activity. The haplotype associated
with low COMT activity was noted in 7 per-
cent of the population and was associated
with a three-fold increased risk of pre-eclampsia (7).

In other studies attempting to determine a
relationship of haplotype to coronary artery
disease, low COMT activity was associated
with worse coronary outcomes, interacting
with higher homocysteine levels (8). The
T235 allele, an angiotensin gene poly-
morphism, has been noted in women with
abnormal spiral artery modeling (9). The
ACCO2 gene polymorphism was studied in
the decidua basalis tissue of women with
pre-eclampsia and was noted to be downreg-
ulated and inversely correlated to triglycer-
ide levels (10). Finally, homoygotes for the
nitric oxide synthetase gene polymorphism
ASPA298 had significantly lower flow medi-
ated vasodilation than those homozygous
for the GLU298 polymorphism at 12 weeks
gestation, and this may prove important in
the vascular adaptation to pregnancy (11).
Such genetic polymorphisms have been not-
ed to also contribute to hypertension, coro-
nary artery disease, and even chronic kidney
disease in other populations.

Examples also exist of shared physiologic
processes. There is significant evidence to
suggest that alterations in the renin-angio-
tensin system (RAS) play a significant role
in the pathogenesis of pre-eclampsia. In
normal pregnancy, the RAS regulates blood
pressure and volume status. Because the pla-
centa has no autonomic innervation, it relies
on angiotensin to regulate vascular resistance.
Although components of RAS have been
demonstrated to be upregulated in normal
pregnancy, vascular insensitivity to angio-
tensin II (AngII) infusions has been dem-
onstrated in healthy pregnant women, and
AngII sensitivity is a demonstrated predictor
for the development of pre-eclampsia (12).
A potential mechanism for enhanced sen-
sitivity is the presence of an immunoglobu-
lin G autoantibody to the AT1 receptor
identified in the serum of women with
pre-eclampsia (13). Alternatively, upregula-
tion of the AT1 receptor on the decidual, or
maternal, side of the placenta has also been
demonstrated (14). Such a maternal abnor-
mality could result in abnormal placentca-
 tion as well as future cardiovascular disease.
Furthermore, abnormalities in angiotensin
sensitivity have been shown to remain into
the postpartum period. In a recent study,
women with a history of pre-eclampsia
were noted to have salt-sensitive hyperten-
sion, and in the salt-deprived state—a state
wherein the RAS is maximally stimulated—
there was evidence of increased angiotensin
sensitivity with respect to both aldosterone
release and blood pressure response to AngII
infusions (15).

There seems little doubt that the vascular
endothelial cell is the primary target of ma-
ternal placental and is intimately
involved in the future pathogenesis of va-
cular disease. Flow-mediated vasodilation
(FMD) is a well accepted physiologic meas-
uring of endothelial dysfunction that has been
demonstrated to be associated with long-
term adverse vascular consequences. En-
dotheil-dependent vasodilation is impaired
in women with pre-eclampsia compared with
healthy gravid control individuals. Fur-
thermore, there appears to be an association
with uterine artery Doppler assessment, giv-
en that the highest rates of impaired FMD
were noted in patients who also had abnor-
mal uterine artery flow (16).

Recent studies have also demonstrated
impaired endothelial-dependent, but not
endothelial-independent, vasodilation in the
forearm vasculature months after delivery in
women with a history of maternal placental
disease that cannot be explained by adjust-
ment for traditional cardiovascular risk fac-
tors. In a recent study wherein the maternal
phenotype was carefully classified, endothe-
ilial dysfunction, as determined by impaired
FMD, was observed in 93 percent and 89
percent of women with early-onset pre-
elampsia (54 weeks gestation) and isolated
intravenous growth rate (fetal growth below
the fifth centile without evidence of mater-
nal factors) respectively, compared with
22 percent of women with late-onset pre-
elampsia—a value that did not differ sig-
nificantly from that in a control population
(17). Moreover, the findings appeared to be
driven by fetal growth restriction, paralleling
the epidemiologic literature and highlight-
ing the importance of assessing future va-
cular risk on the basis of placental pathology.

The recent discovery of endothelial pro-
genitor cells (EPCs) suggests that vascular
repair and angiogenesis constitute a dynamic
process that extends well beyond the embry-
thonic phase, modulated by numerous identi-
fied and as yet undiscovered cardiovascular
risk factors. Endothelial progenitor cells
may mediate the noted differences in endothelial
dysfunction between women with or with-
out pre-eclampsia, and they are established
in the cardiovascular literature as biomarkers
of vascular disease. In women with maternal
placental syndrome manifest as pre-eclamps-
ia, EPCs are decreased, with increased rates
of cellular senescence (18). As measured by
standard flow cytometry, EPCs have been
demonstrated to be significantly decreased
in a small group of women with pre-eclampsia
as compared with healthy control individu-
als in the third trimester (19).

With both shared genetic and physiologic
paths between maternal placental and cardiovas-
cular disease, one might also expect to
shared risk factors. A recent study that com-
bined data from two large population-based
studies with medical birth registry data iden-
tified 3225 singleton births with a prepreg-
nancy cardiovascular risk assessment (20).
When adjustment was made for traditional
vascular risk factors, including body mass
index, blood pressure, and cholesterol in the
women who developed pre-eclampsia during
pregnancy, much of the risk for fu-
ture vascular disease could be accounted for,
suggesting that women programmed to
develop vascular disease also get placental
vascular disease and that both cardiometabolic
and endothelial dysfunction likely predate
and persist after pregnancy.

Summary Statements

Maternal placental disease is now regarded as
a female-specific risk factor for future mor-
bidity and mortality caused by vascular dis-
 ease. Future studies will continue to identify
common pathways and potential treatment
targets. In the interim, it is critical that we
recognize the vulnerability of this patient
population, particularly women with severe
manifestations of placental vascular disease.
Women with severe early-onset disease and
fetal growth restriction require regular va-
cular risk assessments, and placental disease
should be ascertained in our patients’ histo-
ries to assist with risk stratification. Cardio-
vascular risk factors should be aggressively
targeted with lifestyle modifications and, if
necessary, pharmacologic therapy.

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Health Sciences Centre.

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mothers and fathers after pre-eclampsia:


The accurate diagnosis of pre-eclampsia is difficult in transplant recipients because surrogate markers occur frequently in patients with impaired renal function. Transplant patients often are hypertensive, have proteinuria, and have increased urea acid levels (because of calcineurin inhibitors). Pregnancy may be associated with worsening proteinuria, hypertension, and hyper tension, thereby mimicking pre-eclampsia. Furthermore, small changes in serum creatinine levels may hide more serious changes in GFR because of the natural hyperfiltration of pregnancy. Newer markers of pre-eclampsia, such as s-flt and soluble endoglin, have not been validated in the renal transplant population (23, 24).

There are many other medical considerations in the maternal transplant recipient, including gestational diabetes, anemia, and infections such as urinary tract infections (23–27). It is recommended that maternal kidney transplant recipients be screened every trimester for gestational diabetes (28). Other comorbidities, such as urinary tract infections, are quite common in renal transplant patients, and therefore frequent screening is mandatory (25, 28). Several other infections need to be considered in the maternal transplant recipient; the reader is referred to an earlier review for details (14).

Many infants are delivered by caesarean section (29). However, the presence of the transplanted kidney in the false pelvis does not interfere with vaginal delivery (28, 30). Thus, unless there is an obstetric reason to indicate caesarean delivery, vaginal delivery is preferred (10).

**Fetal risks of pregnancy in transplant recipients**

There are potential risks to the developing fetus that should be discussed with the maternal transplant recipient and her partner. We believe that a frank discussion of these concerns should be conducted long before pregnancy occurs so that the future parents are prepared for the possibility of adverse outcomes, including premature delivery, intrauterine growth retardation (IUGR), and long-term developmental problems.

Data from all three registries have documented an extremely high risk for premature delivery (2). Premature delivery is defined as any delivery occurring earlier than 37 weeks. Premature delivery has been documented in recipients of all solid organs but occurs in about 50 percent of renal transplant pregnancies (2). Among the consequences of premature delivery are increased risk of learning disabilities and neurocognitive deficits (31). There is also a very high risk for IUGR, suggesting a primary pathologic process involving the placenta. IUGR occurs in approximately 20 percent of deliveries and is associated with comorbidities including hypertension, diabetes mellitus, neurologic abnormalities, and developmental delay (14).
Interestingly, gross congenital abnormalities are not common in infants exposed in utero to immunosuppressive medications, with the exception of mycophenolate mofetil (2, 32–34). Recent data have shown a pattern of congenital abnormalities in infants exposed in utero to mycophenolate mofetil, and the Food and Drug Administration has established labeling category D. It is therefore recommended that women considering pregnancy cease taking any mycophenolate drug (CellCept or Myfortic) at least 6 weeks before attempting pregnancy (14). Whether to add azathioprine to the patient’s drug regimen is something to consider doing this at our institution, and it is recommended that women be aware of the possibility of breast-feeding their infants after immunosuppressive exposure. Azathioprine levels in breast milk vary widely, and the pharmacokinetics and pharmacodynamics of mycophenolate monophosphate secreted in breast milk have not been defined (36–58). Large controlled studies that evaluate breast milk concentrations of immunosuppressants in solid organ recipients have not been performed, to our knowledge. The mother should be informed that it is unknown whether the risks of further exposure of her infant to immunosuppressive outweigh the benefits of breast-feeding.

Conclusion

The first woman to become pregnant after a kidney transplant died this year at the age of 76. Fifty-three years since the report of her first pregnancy and many thousands of pregnancies later, it is clear that pregnancies in transplant patients can occur successfully if kidney function is good and proteinuria is minimal, without a negative impact on the allograft. These pregnancies are high risk. Pregnancy in renal transplant recipients must be approached with counseling both before and after transplantation, and with close follow-up, for the prevention and management of medical and obstetric complications.

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References

Let’s start by reviewing the physiologic changes in the kidneys and the urinary tract during pregnancy.

During pregnancy, the kidney undergoes both anatomic and physiologic changes. The size of the kidneys increases by about 1 to 1.5 cm, and there is dilatation of the ureters, accompanied by decreased motility. There is greater dilatation of the right collecting system than of the left. The increase in size reverts to normal during the first week postpartum. The dilatation of the ureters may persist as long as 12 weeks postpartum.

Glomerular filtration rate and renal plasma flow increase by 30 to 50 percent with a detectable increase as early as 4 weeks gestation. The increased GFR peaks at 9 to 11 weeks and is maintained until near term. Renal plasma flow increases by 35 to 50 percent. Pregnant women become volume expanded by 6 to 8 liters, with 75 percent of the expanded volume extracellular. Plasma volume expands by 40 to 50 percent, and there is a net retention of about 900 mEq of sodium. Urinary protein excretion may increase but it remains below 300 mg/24 h in normal pregnancy and urinary albumin remains less than 30 mg/24 h.

Other changes include a respiratory alkalosis, which results in the serum bicarbonate dropping to 18 to 22 mEq/L. There is a reset osmostat, which results in lower osmolality, primarily through a drop in serum sodium to about 134 mEq/L. Uric acid levels drop because of a combination of increased filtration and decreased tubular reabsorption so that levels are normally 2.5 to 4 mg/dL.

There is a decrease in systolic blood pressure of about 9 mm Hg and in diastolic blood pressure of 17 mm Hg brought about by systemic vasodilatation. The lowest blood pressure is seen between 16 and 20 weeks gestation, and the blood pressure gradually increases toward term. There is an eightfold increase in plasma renin, a fourfold increase in angiotensin, and a 10- to 20-fold increase in aldosterone.

Pre-eclampsia remains the most common and among the most important hypertensive disorders in the pregnant population. Based on the latest research and evidence, it appears that we understand more and more about this disease. Can you tell us what we currently know and what advances we have learned about the pathophysiology of pre-eclampsia?

Pre-eclampsia is a multisystem disease characterized by endothelial dysfunction and vasocostriction. It results in end organ disease, which can affect the kidney, liver, brain, and hematologic system. Although clinical manifestations are only apparent after 20 weeks gestation, the problem begins with abnormal placentation development. There is a failure of fetal cells to transform uterine spiral arteries from small constricted vessels to dilated high-flow vessels, resulting in placental ischemia. In pre-eclampsia, the placenta releases excessive amounts of the antiangiogenic factors soluble fms-like tyrosine kinase 1 (sFlt1) and endogly. When present in high quantities, these bind to vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). VEGF and PIGF are necessary for preserving the ability of the endothelium to produce vasodilatory proteins such as nitric oxide and prostacyclin. The recognition of the role of antiangiogenic factors may lead the way to treatment of pre-eclampsia other than delivery of the baby.

What is the significance of ‘podo-cyturia’? What are the pros and cons?

The finding of viable glomerular epithelial cells has been proposed as a test for the diagnosis of pre-eclampsia. At this point, there is not enough experience with it to justify routine use.

The use of angiotensin converting enzyme (ACE) inhibitor therapy in the first trimester remains controversial. What about angiotensin receptor blockers (ARBs)?

ACE inhibitors (and ARBs) are contraindicated in the second and third trimester because they are associated with renal dysplasia and pulmonary hypoplasia, resulting in contractures, abnormal calcification of the fetal skull, acute or chronic renal failure, and death from respiratory failure. They were thought to be safe in the first trimester until a 2006 report in the “New England Journal of Medicine” noted congenital anomalies in 7.1 percent of infants born to women exposed to ACE inhibitors compared to 2.6 percent of infants who were not exposed to any antihypertensive drugs. There were 209 infants exposed to ACE inhibitors and 29,096 controls. Congenital anomalies were predominantly cardiac malformations.

Several studies with comparable numbers of exposed infants have not confirmed these findings, and the association is still in doubt. It makes sense to stop ACE inhibitors in women planning pregnancy who are expected to conceive quickly. I don’t think there is enough evidence to avoid ACE inhibitors in all women of childbearing age. Counseling about the need to plan pregnancies and to stop the drug when pregnancy is attempted should be enough. A small group of women have renal disease and markedly decreased fertility. For them, stopping the drug when pregnancy is planned may mean years without the drug. I have continued ACE inhibitors in such women. There is less experience with ARBs but most people assume that ARBs will carry the same risk.

Does underlying CKD have any effect on fertility? On pregnancy?

Fertility is decreased once the creatinine is about 2 mg/dL. Because we don’t know the denominator of women trying to become pregnant with different degrees of CKD, the estimate of fertility can’t be precise. CKD increases the risk of hypertension/pre-eclampsia, and premature birth. In women with serum creatinine greater than 1.4 mg/dL, pregnancy will cause an acceleration of renal disease in 30 to 50 percent.

How reliable is the MDRD GFR formula in estimating renal function in pregnant patients?

The MDRD formula hasn’t been validated in pregnancy.

Is it possible for dialysis patients to become pregnant? What are the complication rates compared to the general population?

In surveys of women of childbearing age treated with dialysis, the likelihood of pregnancy ranges from 0.3 percent per year in Belgium to 1 percent per year in Saudi Arabia. There is a group of nocturnal dialysis patients in Toronto who dialyze 36 h/week, who have had a 15 percent conception rate. Only about half of pregnancies in dialysis pa-
Patients result in surviving infants, and premature delivery is the rule (80 percent). Maternal complications include hypertension and anemia.

If a patient on dialysis happens to become pregnant, are there any adjustments in the dialysis prescription that need to be made? Are there any unique complications that need to be monitored?

Dialysis time should be increased to 24 h/week. The likelihood of a surviving infant increases to 75–80 percent with more than 20 h/week of dialysis. A 24 h/week prescription allows for access failure and snowstorms. Hypophosphatemia, hypokalemia, and metabolic alkalosis are complications of increased dialysis. Premature labor and fetal distress with hypotension during dialysis are problems unique to pregnant dialysis patients.

Please tell us about the use of ESAs in pregnant patients.

Most dialysis patients have been on ESAs for weeks before pregnancy is diagnosed and it does not appear to be associated with congenital anomalies. Erythropoietin probably does not cross the placenta, but it is not known whether darbepoietin does.

During pregnancy, a higher dose may be needed to achieve the same target hemoglobin. Most of the complications seen in pregnant dialysis patients were seen before ESAs were available. Patients with renal insufficiency not on dialysis may become more anemic during pregnancy. Since ESAs may increase the risk of hypertension, I would not start them until the hemoglobin reaches 8 g/dL.

Knowing from published studies that successful kidney transplant recipients may have improved fertility rates, what are the potential issues (especially with regard to use of immunosuppressive therapy) that need to be addressed if a kidney transplant recipient becomes pregnant?

Mycophenolate is teratogenic and should be discontinued or switched to another drug. There is very little experience with sirolimus and everolimus. Doses of calcineurin inhibitors may need to be changed because of the change in space of distribution.

Women are usually advised to wait 1 to 2 years after transplant to become pregnant. Blood pressure and blood sugar should be well controlled and creatinine less than 2 mg/dL (preferably 1.4 mg/dL or less). Opportunistic infections such as cytomegalovirus, toxoplasmosis, listeria, and herpes are problematic during pregnancy.

There has been a lot of research involving lupus nephritis. Please tell us what we have learned from these studies with regard to lupus nephritis and pregnancy.

Lupus nephritis has a high risk of relapse during pregnancy even if it is in remission at the time of conception. There may be rapid progression of renal insufficiency even in women who start pregnancy with a normal serum creatinine. Some of the most difficult problems come from extrarenal lupus such as cerebritis or pericarditis.

Lupus flares can be treated with high dose steroids in the first trimester. Cyclophosphamide has been used later in pregnancy. Antibodies associated with lupus are IgG and cross the placenta. Anti SSA is associated with congenital heart block. Other antibodies may give rise to rashes and thrombocytopenia in the newborn.

What is your experience with regard to performing percutaneous renal biopsies in pregnant patients? Indications? Complication rates?

Indications include new onset lupus, unexplained renal failure, and nephritic syndrome severe enough that steroid treatment is being considered. In experienced hands, complications from renal biopsy during pregnancy are similar to complications from biopsies in women who aren’t pregnant, but most people have too little experience to be able to calculate complication rates.
FDA Changes its Thinking on Medication Guide Distribution for ESAs

By Rachel Shaffer

Responding to concerns voiced by ASN and others in the nephrology community, the Food and Drug Administration (FDA) announced on June 2 that it has changed its plan to issue a Medication Guide to dialysis patients every time they receive an erythropoiesis stimulating agent (ESA). The FDA will now require that dialysis patients receive the Medication Guide—the primary component of the Risk Evaluation and Mitigation Strategy (REMS)—for ESAs at initiation of therapy and again if the guide is “materially revised or updated.”

In 2005, Renal Care Group submitted false claims for equipment provided to patients who were receiving dialysis in the home setting. Fresenius Medical Care set up a sham billing company directing buyers to certain dialysis supplies and equipment. Renal Care Group submitted claims to Medicare that were false, and the companies Renal Care Group, Renal Care Group Supply Company, and Fresenius Medical Holdings, were found liable for recklessly disregarding federal law when they billed Medicare for home dialysis supplies and equipment.

As part of the decision, the government claimed that Renal Care set up a sham billing company directing buyers to certain Renal Care Group supplies and limited choice, according to Courthouse News Service. The companies, Renal Care Group, Renal Care Group Supply Company, and Fresenius Medical Holdings, were found liable for recklessly disregarding federal law when they billed Medicare for home dialysis supplies and equipment.

Milk-Related Antibodies Linked to Childhood Membranous Nephropathy

At least some cases of idiopathic membranous nephropathy in young children are associated with antibodies to bovine serum albumin, suggests a study in the New England Journal of Medicine.

A sample of 50 patients with membranous nephropathy, the investigators found high levels of circulating anti-bovine serum albumin antibodies in 11 patients. This included four of nine children studied (age range 5–28 months). The antibodies were of both IgG1 and IgG4 subclasses. All patients with antibodies also had elevated levels of circulating bovine serum albumin, with no increase in circulating immune complex levels and no evidence of cow’s milk allergy.

Bovine serum albumin immunopurified from the serum of children with membranous nephropathy migrated in the basic range of pH, whereas bovine serum albumin from adult patients migrated in neutral regions as native bovine serum albumin. Bovine serum albumin was found in subepithelial immune deposits only in children with high levels of cationic circulating bovine serum albumin and bovine serum albumin—specific antibodies. These immune deposits colocalized with IgG, in the absence of M-type phospholipase A2 receptor. Eluted IgG from the subepithelial immune deposits showed specific anti-bovine serum albumin activity.

Membranous nephropathy is a rare cause of nephrotic syndrome in children. In recent studies, phospholipase A2 receptor was implicated as an antigen in 70 percent of cases of idiopathic membranous nephropathy. The antigens involved in other idiopathic and membranous nephropathies remain undefined.

This study demonstrated circulating cationic bovine serum albumin and anti-bovine serum albumin antibodies in some patients with idiopathic membranous nephropathy, including young children. These children might benefit from dietary elimination of bovine serum albumin. Future research may identify other food antigens as contributors to membranous nephropathy [Debiec H, et al. Early-childhood membranous nephropathy due to cationic bovine serum albumin. N Engl J Med 2011; 364:2101–2110].

Policy Update

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Since 2008, if FDA believes a drug’s risks may outweigh its benefits, or that the drug potentially poses serious risks to patients, it mandates that the manufacturer develop a REMS. Roughly 100 REMS exist, but the components of the REMS (such as Medication Guides or monitoring programs) vary by drug. FDA instated the REMS for ESAs in February 2010. As part of the REMS for ESAs, physicians would have had to provide a five-page Medication Guide about ESAs to all patients receiving the medication—including patients with kidney disease—when an ESA is dispensed.

Shortly after the policy was put in place, many in the nephrology community, including ASN, began to raise concerns that the REMS requirements were burdensome, and could pose a barrier for some patients to access needed drugs. ASN Public Policy Board Chair Thomas Hostetter, MD, FASN, testified on three panels at an FDA hearing on the REMS program on behalf of ASN in July 2010. Leading up to this FDA decision, ASN Public Policy Board member Wolfgang Winkelmayr, MD, Scd, FASN, also presented testimony about the currently available evidence regarding the safety and efficacy of ESAs at an October 2010 meeting. Recent FDA scrutiny of ESAs has been corollary to CMS’ National Coverage Decision (NCD) investigation into ESAs, which culminated in June 2011.

In his testimony, Hostetter raised concerns about the Medication Guide’s content, balance and sensitivity level. He conveyed apprehension that detailed review of the risks of ESAs (with scant information on their benefits), along with the frequency of distribution, could frighten patients away from a medication that is crucial to preserving their vitality and quality of life.

“I am extremely pleased by the FDA’s decision to limit distribution of the Medication Guide. It makes sense for patients and providers,” Hostetter said. “This was a very good outcome from ASN’s visit to the FDA last summer.”
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