ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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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

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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 dialy-

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Inside

ASN Accountable Care Organization Task Force: Q & A

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 plan. 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.

ACOs

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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.

Aside 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' first effort at tackling the details.

For the nephrology community, perhaps the most important detail in the proposal was CMS' 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 engagement and surveying, 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 rules and processes—of both 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 patient 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' proposal 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 recent 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 with 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' proposal patients will be retroactively assigned to ACOs). Overall, CMS' highly anticipated proposal has been largely criticized by hospitals and physicians as too onerous with too little potential financial gain to justify the risks of participation.

Over the coming weeks, CMS will review the feedback and is 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' 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.

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

Having provided feedback to CMS on the proposed ACO rule, the ASN ACO Task Force will remain in place to address other aspects of new accountable care models. The task force is investigating the possibility of a potential CMS demonstration project on integrated care models for the CKD and ESRD populations. The task force will also continue to follow and respond to CMS' next steps related to the proposed ACO rule.

Table 1. Key features of the ACO Proposed Rule

Feature	Detail
Primary care focus	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.
Retrospective beneficiary assignment	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.
Quality measures	ACOs will report on 65 quality measures, in five domains, beginning in the first performance year of the program.
Evidence-based medicine	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.
ACO risk models: one sided model	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
ACO risk models: two-sided model	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.
Patient choice	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.
Electronic health records	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.

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Vascular Access and Dialysis Modality

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sis is determined.

In the 7-year study, 63 percent of the patients started HD with a central catheter inserted into one of the large veins. Another 17 percent began HD with an arteriovenous fistula (AVF) or arteriovenous graft (AVG). The remaining 19 percent started with PD at home, with education in advance 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 receiving HD with an AVF or AVG remained similar to that in the PD patients.

"All the previous studies tried to compare hemodialysis versus peritoneal dialysis 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 therapy over another is lifestyle-based. It's really difficult to do studies that are randomized controlled trials in this area."

The next best thing researchers can do is to 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.

"Those studies have traditionally demonstrated that peritoneal dialysis was associated with better outcomes in the first 1 to 2 years compared to hemodialysis," Perl said. The main criticism of such studies 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 hemo, 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 patient. 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 comparison was between those using a fistula or graft and those on peritoneal dialysis with exclusion of patients starting with a catheter. This removed some of the bias associated with starting dialysis with a catheter and compared a more homogeneous population, those who attended nephrological 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 important 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."

Said Perl: "When you separate the hemodialysis 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 infection. "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 impact 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."

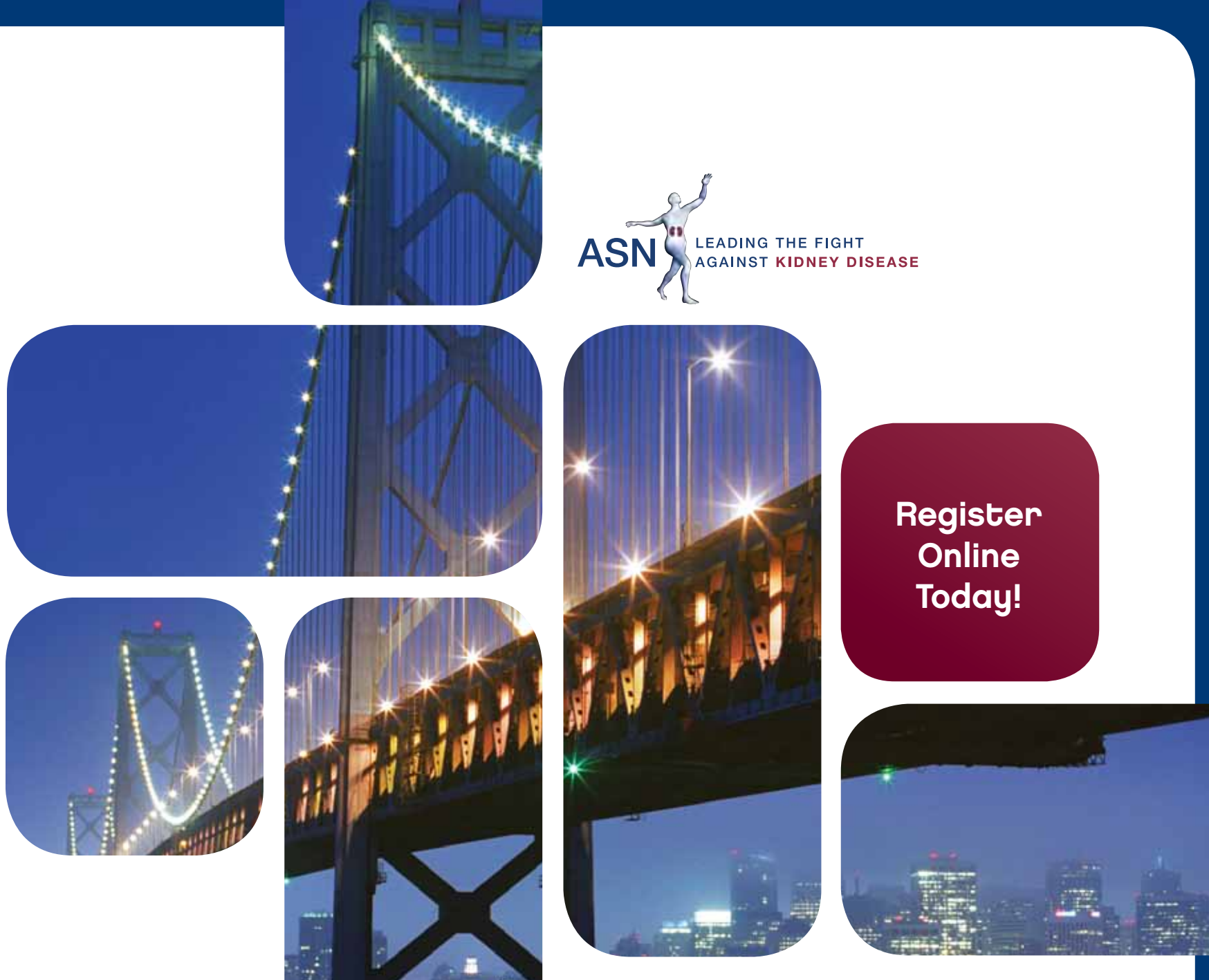
The study's other "take-home point," Perl said, concerns the importance of planning and education. "To get a fistula or a graft takes quite a bit of time," he said. "You need to see patients months in advance." Not all patients, even with the best intentions of the nephrologist and the treatment team, 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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Kidney News thanks Richard Lafayette, MD, for editing this special section.

Pregnancy and the Kidney

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" vasodilators 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 PCO_2. 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, PCO_2, 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).

Women with kidney disease in pregnancy

Given these profound hemodynamic, metabolic, and immunologic alterations that are features of normal healthy pregnancy, it is not surprising that women with kidney disease are at increased risk for pregnancy complications. Although data regarding pregnancy outcomes in women with renal disease are derived mainly from case series rather than from carefully conducted observational studies with control groups, there is consensus that the degree of renal functional impairment at the time of conception is the single most important determinant of both maternal and fetal outcomes.

One such landmark case series, reported in the *New England Journal of Medicine* 15 years ago by Jones and Hayslett, reported that 23 percent of women with a serum creatinine above 2.0 mg/dL at the beginning of pregnancy experienced progression to ESRD within 6 months after delivery (9). When hypertension is present early in pregnancy, the risks to both mother and fetus are considerably higher. Particularly striking is the impact of pre-existing hypertension in the setting of renal disease on the incidence of superimposed pre-eclampsia. The relationship between baseline proteinuria and pregnancy outcome is less clear, perhaps because increases in proteinuria during early pregnancy are usually related to the hemodynamic alterations in pregnancy rather than to progression or worsening of underlying renal histologic features.

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Renal and Reproductive Functions

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Specific renal diseases and pregnancy outcome

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.

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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 prerenal, 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, and in these areas, improved access to health care is extremely important in optimizing outcomes. From early in pregnancy, an increased incidence of urinary tract infection is demonstrable, but this only rarely causes AKI, with the development of bilateral pyelonephritis or systemic complications of sepsis. In women with significant chronic kidney disease (CKD) (creatinine >1.5–2.0 mg/dL), rapid progression of hypertension, proteinuria, and renal insufficiency can sometimes be seen early in pregnancy (5). Thrombotic microangiopathy can develop early in pregnancy, notably in women with anticardiolipin/antiphospholipid antibodies, who have a high risk of recurrent early fetal loss. Pregnancy-associated thrombocytopenic purpura (TIP) also occurs, related to immune depletion of ADAMTS 13 or caused by genetic deficiencies related to complement activation (6). Additionally, patients with autoimmune nephritis, especially systemic lupus erythematosus, sometimes experience a flare in early pregnancy, with active glomerular injury.

Late pregnancy

After 20 weeks, AKI is more common and is more likely to be related to the classic complications of pregnancy. Complications of urinary tract infection remain rare but are easily assessed. Obstructive uropathy is another rare cause, as a consequence of dilation of the urinary tract and the effects of uterine size (7). Kidney stones related to increased urinary calcium excretion, polyhydramnios, or underlying uterine fibroids can also contribute to obstruction in pregnancy. As in early pregnancy, women with systemic lupus erythematosus and autoimmune nephritis can experience a flare during this time; there are also many reports of postinfectious glomerulonephritis in late pregnancy as well (8). Women with significant CKD are more likely to experience progression late in pregnancy, and their course is usually marked by increasing blood pressure and proteinuria. Beyond this, there are several specific risks of pregnancy after 20 weeks to consider separately.

Pre-eclampsia is a common complication of pregnancy (3–5 percent of all pregnancies) and is generally seen in primigravidas or in women with multiple pregnancies (e.g., twins, triplets). It is defined by new-onset hypertension (>140/90 mm Hg) and proteinuria (≥2+), often with edema. Generally, pre-eclampsia is associated with a mild reduction in GFR, and the increase in creatinine does not meet the definition of AKI (9). However, severe pre-eclampsia can be associated with AKI, especially when complicated by systemic thrombotic microangiopathy, often in association with the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). In 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 pre-eclampsia focuses on preventing eclamptic seizures with magnesium, early delivery, and prevention/treatment of profound hypertension. It is often difficult to discern pre-eclampsia from disease progression in patients with CKD. Generally, pre-eclampsia is thought to progress more rapidly and may be associated with other laboratory and clinical changes. Screening for soluble angiogenic factors, such as soluble fms-like tyrosine kinase 1 and soluble endoglin, may be available in the future to help differentiate the causes of AKI (11).

Acute fatty liver of pregnancy 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 seems to be on the rise (more than 1 in 10,000 pregnancies) (12). 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 microsteatosis, 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.

Hemolytic uremic 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 platelet transfusions, and more controverisal treatments (e.g., steroids, antiplatelet agents) are available to treat this syndrome.

Postpartum AKI is generally related to sepsis, shock, hemorrhage, or amniotic fluid emboli. Complications related to placental catastrophes 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.

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 electrolytes should be optimally controlled, and medications 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.

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

EARLY	LATE	POSTPARTUM
Prerenal	**Prerenal**	**Prerenal**
Hyperemesis gravidum	Bleeding	Bleeding
Postrenal	Acute fatty liver of pregnancy	Medication side effects
Rare	**Postrenal**	**Postrenal**
Intrarenal	Obstruction from stones	Retained clots
Chronic kidney disease progression	Obstruction from uterus	**Intrarenal**
Autoimmune disease, glomerulonephritis	**Intrarenal**	Hemolytic uremic syndrome
Complications of hemorrhage, sepsis, urinary tract infection, stones	Chronic kidney disease progression	Severe pre-eclampsia
Familial hemolytic uremic syndrome/TTP	Severe pre-eclampsia/ hemolysis, elevated liver enzymes, low platelets syndrome	Chronic kidney disease progression
Anticardiolipin antibody syndrome	Acute fatty liver of pregnancy	Acute tubular necrosis from sepsis, hemorrhage
	Hemolytic uremic syndrome/TTP	
	Autoimmune glomerulonephritis, postinfectious glomerulonephritis	
	Pyelonephritis	

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; it affects 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 less 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 (signaling glomerular endothelial damage), liver injury (including the HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets), cerebral edema, and seizures—reflect widespread endothelial dysfunction, with vasoconstriction and end-organ ischemia. Mounting evidence over the past several years has implicated antiangiogenic 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 antiangiogenic 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 growth factors

Angiogenesis is defined as the formation of new blood vessels. Soluble fms-like tyrosine kinase 1 (sFlt1) is often referred to as an antiangiogenic protein because, when secreted into the circulation, it binds and inactivates the proangiogenic vascular endothelial growth factor (VEGF) and placental growth factor (P1GF).

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 PlGF 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 PlGF 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 antiangiogenic 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), hydatidiform mole (12, 13), and pregnancies with fetuses having trisomy 13 (14). All 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 expeditious delivery when indicated.

Results from dozens of studies have confirmed that maternal serum levels of PlGF, 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 PlGF 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 PlGF 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 urinary), 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

Angiogenic 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 (PlGF and sFlt1 immunoassay, 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 damage suggests that these biomarkers may also be effective therapeutic targets. 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, PlGF, and TGF-β relative to antiangiogenic factors such as sFlt1 and sEng. For example, both VEGF (30) and PlGF (31) diminish hypertension and ameliorate proteinuria in rodent models of sFlt1-induced pre-eclampsia, without apparent harm to the fetus. Direct administration of VEGF and/or PlGF in humans would be burdensome because it would require continuous intravenous infusion, so agents that enhance endogenous VEGF, PlGF, or TGF-β production are also being explored. For example, pravastatin induces endogenous PlGF 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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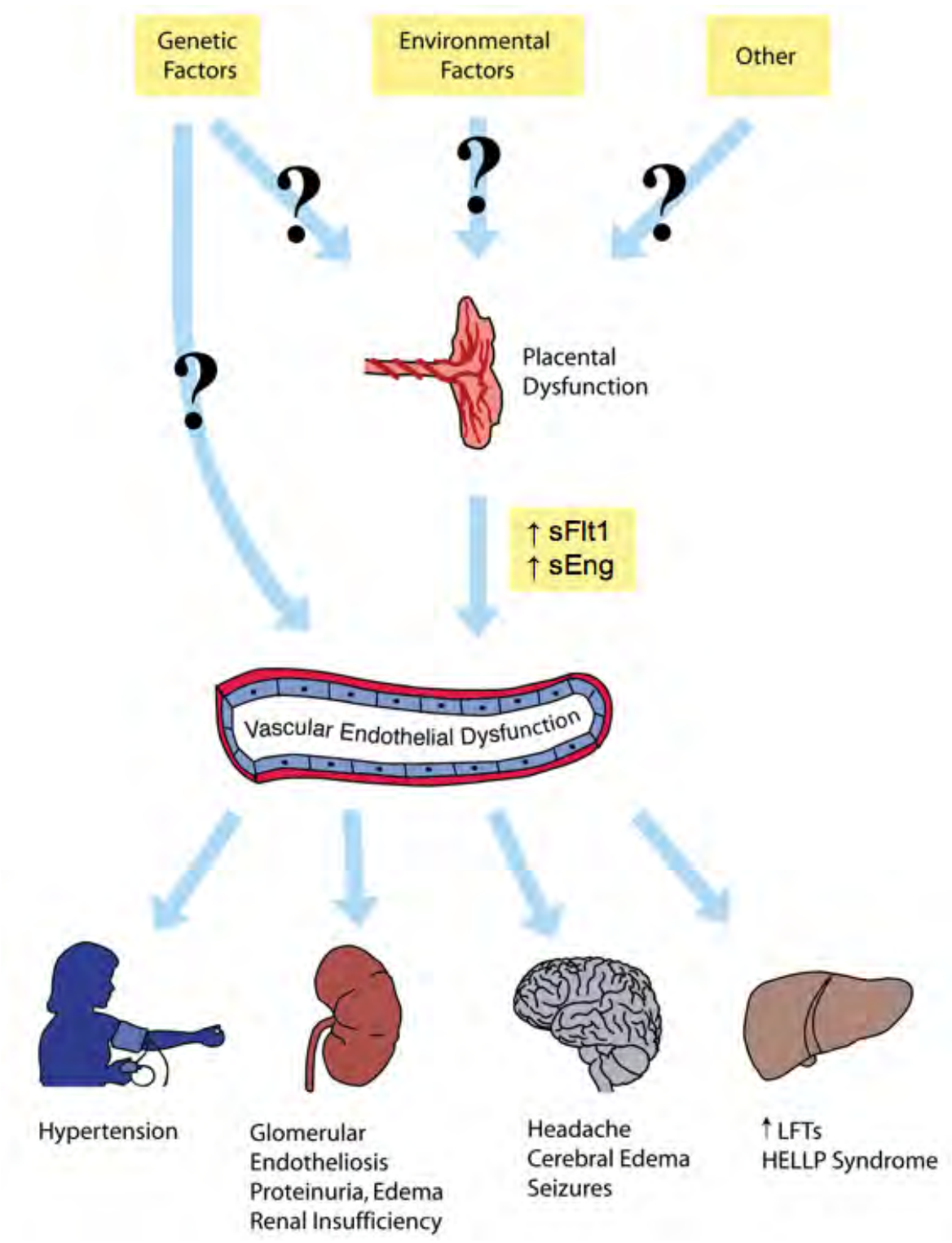
Figure 1



Source: Karumanchi SA, Maynard SE, Stillman IE, et al: Preecalmpsia: A renal perspective. *Kidney Int* 67:2101-2113, 2005.

Hypothetical framework for the pathogenesis of pre-eclampsia. Placental dysfunction triggered by poorly understood mechanisms—including genetic, immunologic, and environmental—plays an early and primary role in the development of pre-eclampsia. Placental dysfunction leads to aberrant production of antiangiogenic factors (soluble fms-like tyrosine kinase 1 and soluble endoglin), contributing to systemic endothelial cell dysfunction. Endothelial dysfunction, in turn, results in the systemic manifestations of pre-eclampsia.

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Long-Term Consequences of Placental Disease

By Michelle Hladunewich

About 5 percent of pregnancies suffer complications from abnormal placental development. The process of placentation begins when blastocysts adhere to the uterine endometrium, forming a lineage of epithelial cells termed the invasive extravillous cytotrophoblast, which then invades the uterine wall to create the decidua, transforming the spiral arteries into a low-resistance uteroplacental circulation.

Impaired development of the uteroplacental vasculature, therefore, has its origins in the first trimester as a result of an abnormal interaction between the invading extravillous cytotrophoblast and the maternal immune system, resulting in decidual vasculopathy, with small, poorly developed spiral arteries. As these pregnancies progress, placental ischemia and infarction may result in a maternal placental syndrome—pre-eclampsia, placental abruption, and/or the ensuing adverse perinatal outcomes, including fetal growth restriction and stillbirth.

It was previously thought that the consequences of maternal placental disease resolved 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 syndrome, 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 cardiovascular 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 delivered at term, it did show almost a three-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 preterm delivery but without clinical pre-eclampsia. This highlights a key component to understanding 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 Cardiovascular 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 accompanied by fetal death (2). The societal effect of this increased vascular risk, however, is best demonstrated by the Child Health and Development Cohort. Data from over 14,000 women with an average of 30 years of follow-up noted the median age for cardiovascular events to be 56 years, with a cumulative 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 endothelium secondary to maternal placental syndrome results in an increased risk of future vascular disease, or whether pre-existing 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 cardiovascular disease.

There are several examples of common genetic pathways. Catechol-*O*-methyltransferase (COMT) is responsible for the degradation of both estrogens and catecholamines. Mice deficient in COMT, and hence 2-methoxyestradiol (2ME), have abnormal 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 haplotypes 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 percent of the population and was associated with recurrent 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 angiotensinogen gene polymorphism, has been noted in women with abnormal spiral artery modeling (9). The ACOX2 gene polymorphism was studied in the decidua basalis tissue of women with pre-eclampsia and was noted to be downregulated and inversely correlated to triglyceride levels (10). Finally, homozygotes for the nitric oxide synthetase gene polymorphism ASP298 had significantly lower flow-mediated vasodilatation 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 noted to also contribute to hypertension, coronary 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-angiotensin 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 placenta 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 angiotensin II (AngII) infusions has been demonstrated in healthy pregnant women, and AngII sensitivity is a demonstrated predictor for the development of pre-eclampsia (12).

A potential mechanism for enhanced sensitivity is the presence of an immunoglobulin G autoantibody to the AT1 receptor identified in the serum of women with pre-eclampsia (13). Alternatively, upregulation of the AT1 receptor on the decidual, or maternal, side of the placenta has also been demonstrated (14). Such a maternal abnormality could result in abnormal placentation 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 hypertension, 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 infusion (15).

There seems little doubt that the vascular endothelial cell is the primary target of maternal placental syndromes and is intimately involved in the future pathogenesis of vascular disease. Flow-mediated vasodilation (FMD) is a well accepted physiologic measure of endothelial dysfunction that has been demonstrated to be associated with long-term adverse vascular consequences. Endothelial-dependent vasodilation is impaired in women with pre-eclampsia compared with healthy gravid control individuals. Furthermore, there appears to be an association with uterine artery Doppler assessment, given that the highest rates of impaired FMD were noted in patients who also had abnormal 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 adjustment for traditional cardiovascular risk factors. In a recent study wherein the maternal phenotype was carefully classified, endothelial dysfunction, as determined by impaired FMD, was observed in 93 percent and 89 percent of women with early-onset pre-eclampsia (≤34 weeks gestation) and isolated intrauterine growth rate (fetal growth below the fifth centile without evidence of maternal disease), respectively, compared with 22 percent of women with late-onset pre-eclampsia—a value that did not differ significantly from that in a control population (17). Moreover, the findings appeared to be driven by fetal growth restriction, paralleling the epidemiologic literature and highlighting the importance of assessing future vascular risk on the basis of placental pathology.

The recent discovery of endothelial progenitor cells (EPCs) suggests that vascular repair and angiogenesis constitute a dynamic process that extends well beyond the embryonic phase, modulated by numerous identified and as yet undiscovered cardiovascular risk factors. Endothelial progenitor cells may mediate the noted differences in endothelial dysfunction between women with or without pre-eclampsia, and they are established in the cardiovascular literature as biomarkers of vascular disease. In women with maternal placental syndrome manifest as pre-eclampsia, 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 individuals in the third trimester (19).

With both shared genetic and physiologic pathways between maternal placental and cardiovascular disease, one might also expect shared risk factors. A recent study that combined data from two large population-based studies with medical birth registry data identified 3225 singleton births with a prepregnancy cardiovascular risk assessment (20). When adjustment was made for traditional cardiovascular risk factors, including body mass index, blood pressure, and cholesterol in the women who developed pre-eclampsia during pregnancy, much of the risk for future 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 morbidity and mortality caused by vascular disease. 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 vascular risk assessments, and placental disease should be ascertained in our patients' histories to assist with risk stratification. Cardiovascular risk factors should be aggressively targeted with lifestyle modifications and, if necessary, pharmacologic therapy.

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PREGNANCY OUTCOMES in Maternal Transplant Recipients

By Dianne B. McKay and Michelle A. Josephson

The Nobel Laureate Joseph Murray provided the first report of pregnancy in a transplant recipient (1). Since that time, over 16,000 pregnancies have been documented in the world literature (2). Many more pregnancies have clearly occurred, now that pregnancy after transplantation is commonplace and is rarely reported. The data about pregnancy in transplant recipients come from case reports and registry reports, but these sources underrepresent the population of transplant recipients who have become pregnant (2).

This review relies on data from registry reports in the United States, the United Kingdom, and Europe, but we caution that the derivation of guidelines from these reports must be considered in light of their relatively small numbers. Furthermore, it is important to realize that registry reports are generally based on voluntary patient reporting and that they do not reflect data from prospective or retrospective reviews of hospital records or laboratory testing. Many investigators suggest that large well-designed prospective analyses are needed to address many of the questions regarding the risks of pregnancy after transplantation for both mother and child.

Fertility and contraception

A major concern of patients is whether or not they can reproduce after receiving a transplanted organ. Several studies document the rapid return of fertility after transplantation (3). The hypothalamic-pituitary access is suppressed in patients with ESRD, but gonadal suppression appears to be reversible, with reports of pregnancy occurring within months of successful transplantation (4). It is not known whether fertility is restored to age-appropriate "normal" levels after transplantation, because only scattered reports are available (of assisted reproduction) in transplant recipients. Men with ESRD have several defects in spermatogenesis that may be reversible (5, 6), but isolated deficits in ovarian function have not been documented to our knowledge. Another concern is whether immunosuppressive medications impair fertility. At this time it does not appear that immunosuppressive medications directly impair female fertility, although sirolimus (rapamycin) (7) is clearly associated with male infertility, and men wishing to father a child should therefore not take sirolimus.

Given that fertility is rapidly restored after transplantation, the patient and her partner need to be counseled about pregnancy prevention early in the process of pretransplant workup. Optimal contraception is a decision to be made between the patient and her gynecologist, inasmuch as there are no contraindications to the use of any contraceptive method. The options to consider include sterilization of either the transplant recipient or her male partner, and whether the patient wishes to have irreversible contraception or reversible contraception. If the patient wishes to have reversible contraception, the choices include intrauterine devices (IUDs) (based on either copper or progestin), progesterone-containing systemic contraceptives such as depot medroxyprogesterone acetate, progestin implant, progestin-only pills, estrogen-containing contraceptives such as birth control pills, contraceptive patches, and a vaginal ring (8, 9). Generally it is not optimal to use barrier methods alone because of their risk for nonuse, although they may provide protection against transmissible diseases. Some methods previously considered to be ill-advised in women who have undergone transplantation are being reconsidered (8). IUDs had previously been thought to increase the risk of uterine infection and to not be as effective, because it was reasoned that their efficacy was dependent on an intact immune system. Newer types of IUDs appear to be more effective and not complicated by increased infection risk (8).

Timing of pregnancy

The first few months after transplantation are complicated by multiple medical challenges, including the frequent adjustment of immunosuppressive medications, the concomitant use of teratogenic medications (such as valganciclovir), and early rejection episodes. It has thus been recommended that women considering pregnancy wait until graft function and immunosuppression are stable; this usually occurs by a year after successful transplantation (10, 11). An earlier recommendation had been to wait 2 years, but now that the wait-list time for allografts is lengthy and women are reaching transplantation at older ages, this suggestion has been changed (12, 13). Recent reports suggest that if a woman has good stable allograft function, with no episodes of rejection for 6 months, and is not required to take fetotoxic medications, she could consider pregnancy earlier than a year after transplantation (14).

Risks of graft loss or rejection

Whether or not pregnancy will increase the risk of graft loss is a concern that must be discussed with potential transplant recipients. Registries in the United States, the United Kingdom, and Europe, as well as case reports from around the world, have confirmed that the risk of graft loss is probably low if the patient has good graft function at the onset of pregnancy (14). Creatinine level is a poor indicator of graft function, but unfortunately we are not aware of any studies of GFR changes after pregnancy in transplant recipients. Therefore, the definition of good graft function includes a stable creatinine level (≤1.5 mg/dL), the absence of significant proteinuria (≤500 mg/24 hours), and no graft rejection within 6 months (10). Given these parameters, the risk of graft loss associated with pregnancy is not different from that in the nonpregnant transplant recipient (15, 16). Likewise, the risk of rejection is probably low as well, as long as there has not been evidence of poorly suppressed immunoreactivity (e.g., recent graft rejection) (14).

Immunosuppressive medications and pregnancy

Adequate immunosuppression must be maintained during pregnancy because drug levels vary widely throughout gestation. The mother is not immunosuppressed by her pregnancy, contrary to some folk beliefs, and therefore requires maintenance of adequate immunosuppression (17). Blood levels of immunosuppressive drugs should be monitored frequently during the pregnancy (14). At our transplant centers we see the patient bimonthly, checking calcineurin inhibitor and creatinine blood levels at each visit, and we continue this frequency for at least 2 months after delivery. The frequency of monitoring requires that the patient be willing to comply with close follow-up, and this requirement should be discussed with the patient before she becomes pregnant.

Maternal risks associated with pregnancy

Other risks to consider for the maternal transplant recipient are worsening hypertension and pre-eclampsia. Hypertension is common in transplant recipients and often worsens during the pregnancy (18, 19). Generally, the recommendations are to keep the pregnant transplant recipient normotensive if possible, which differs from the advice given to pregnant patients with chronic kidney disease (20). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated because of their fetotoxic potential (21), and therefore maternal transplant recipients are generally prescribed methyldopa or labetalol for the treatment of hypertension (20). Other acceptable agents include nifedipine, hydralazine, and thiazide diuretics (20).

Pre-eclampsia is also commonly diagnosed in pregnant transplant recipients. In the registries, pre-eclampsia was diagnosed in over 30 percent of pregnancies, in contrast to a 5 percent occurrence of that diagnosis in the general population (14). Pre-eclampsia occurs more frequently in patients with chronic kidney disease than in the general population as well (20). It is not known whether there is an independent effect of immunosuppressive medications on the placenta that contributes to the high risk of pre-eclampsia, but data now show that pre-eclampsia is also common in recipients of heart, lung, and liver transplants, who presumably do not have significantly impaired renal function (22).

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 uric acid levels (because of calcineurin inhibitors). Pregnancy may be associated with worsening proteinuria, hyperuricemia, and hypertension, 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 (20).

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 demonstrated 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 changed its labeling to 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. We do this at our transplant centers to be sure that adequate immunosuppression is maintained. At this time there are insufficient data about the safety of sirolimus or everolimus, and therefore we have also recommended a change in these medications 6 weeks before pregnancy is attempted.

Although obvious congenital malformations are rare, whether less obvious abnormalities are induced by in utero exposure to immunosuppressive medications is not known. All immunosuppressive medications cross the maternal–fetal barrier, although there are important differences in the delivery of active metabolites to the developing fetus (14). For instance, prednisone easily crosses the placental circulation, the placenta metabolizes prednisone, and therefore the fetal dosing is diminished. Likewise, azathioprine crosses the maternal–fetal barrier, but active metabolites are not present in the fetus because of the lack of a fetal enzyme to metabolize 6-mercaptopurine.

Calcineurin inhibitors easily pass through the maternal–fetal interface, and active metabolites have been reported in the fetal circulation (14). In fact, serum levels of cyclosporine have been reported in newborns at levels bioequivalent to that of the mother. Therefore, it appears that the developing fetus is likely exposed to calcineurin inhibitors throughout gestation. There is substantial evidence from animal models that in utero exposure to cyclosporine and tacrolimus induces autoimmunity by interfering with the negative selection of autoreactive T cells in the developing thymus. Whether the same phenomena occur in human infants is not known.

There is limited information on the neurocognitive or immunologic development of the human fetus exposed to immunosuppressive medications, and well-designed studies are needed. The National Transplantation Pregnancy Registry has tried to follow up children after delivery to determine whether more subtle defects are associated with fetal exposure to immunosuppressive medications. In the data from the National Transplantation Pregnancy Registry there was noted to be a 27 percent incidence of learning disabilities in school-age children exposed to immunosuppressive medications. Recently another report has suggested that this was associated with premature birth (35).

Breastfeeding

Many patients inquire about the possibility of breastfeeding their infants. Unfortunately, there are few data from which to derive recommendations for or against breastfeeding. The immunosuppressive levels in breast milk vary widely, and the pharmacokinetics and pharmacodynamics of immunosuppressant secretion in breast milk have not been defined (36–38). Large controlled studies that evaluate breast milk concentrations of immunosuppressant medications 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 immunosuppression outweigh the benefits of breastfeeding.

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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Practice Pointers

In this month's issue,* ASN Kidney News *editorial board member Edgar Lerma interviewed Susan Hou, MD, of the division of nephrology at Loyola University Medical Center.

PREGNANCY: Kidney Changes and Patient Considerations

Susan Hou

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 vasoconstriction. 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 placental 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 endoglyn. When present in high quantities, these bind to vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). VEGF and PlGF 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 'podocyturia?' 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 than1.4 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-

tients 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.

Industry Spotlight

Dialysis Companies Hit with Large Payment in U.S. Fraud Case

In late spring, a federal judge in Tennessee awarded the United States government $82.6 million from three companies in a Medicare fraud case brought by whistleblowers.

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 government also claimed that between 1999 and 2005, Renal Care Group submitted false claims for equipment provided to patients who were receiving dialysis in the home setting.

Fresenius completed its acquisition of Renal Care Group in 2006, which according to the company placed Fresenius in the number one slot as the top provider of dialysis services and products, where it remains.

Courthouse News Service reported that the award would be divided, with $38,873,592 of the total award going toward treble damages and $43,769,000 to civil penalties.

United States District Judge William J. Haynes, Jr., wrote that the case covered the claims for payment of equipment for at least 3979 patients, many of whom have advanced or life-threatening renal disease.

Journal View

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*.

In 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

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 erythropoeisis 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."

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 Winkelmayer, 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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