PREGNANCY, THE Puerperium, AND PULMONARY EMBOLISM

Normal pregnancy is characterized by adaptive hemodynamic changes that promote the blood supply and physiologic development of the uteroplacental unit and the fetus it nourishes. These adaptive changes include increased plasma volume, blood volume, heart rate, and cardiac output, along with systemic and regional vasodilatation. Such a hyperdynamic, hyperperfused, vasodilated state, however, carries the risk of marked hemorrhage if blood vessels are breached for whatever reason, or when such a circulatory breach is due to a pregnancy-specific cause, such as the separation of the placenta from the uterus during normal delivery, or prematurely during a miscarriage in pregnancy. Normal pregnancy is also characterized by the tipping of the hemostatic balance to a decidedly prothrombotic state, a change teleologically explained by the need to minimize hemorrhage that may occur during the antepartum, intrapartum, and postpartum phases of pregnancy. The prothrombotic state of pregnancy is multifactorial in origin, arising from, among other mechanisms, increased levels of fibrinogen, certain clotting factors, and von Willebrand factor, in conjunction with decreased fibrinolytic mechanisms. Other components of the Virchow triad that underlie a prothrombotic state also exist in pregnancy including venous pooling in the lower extremities and vascular injury as occurs during delivery in any pregnancy and, specifically, the more generalized vascular injury that attends hypertensive disorders of pregnancy. This prothrombotic phenotype of pregnancy raises the possibility that the risk of deep vein thrombosis (DVT) is increased in pregnancy, and, as confirmed by numerous studies, this risk is increased many-fold in pregnancy and the puerperium.

But what about acute pulmonary embolism (PE), the major complication of DVT? This issue is addressed by Elgendy et al in the current issue of Mayo Clinic Proceedings. Using the National Inpatient Sample to glean and examine pregnancy-related hospitalizations in the United States between the years 2007 and 2015, these authors report that acute PE is relatively uncommon in pregnancy and the puerperium, occurring in 1 in every 5925 hospitalizations. The occurrence of acute PE imposes striking mortality, the latter increased approximately 200-fold and remaining essentially unchanged over the time frame of the analysis by Elgendy et al. Acute PE was associated with such risk factors as older maternal age (35 years or older), Black race, obesity, hypertension, diabetes mellitus, preeclampsia/eclampsia, heart failure, and thrombophilia. An intriguing finding is that the prevalence of such risk factors for acute PE generally increased between 2007 and 2015, but the prevalence of acute PE remained largely unchanged. This raises the question whether an increased propensity to acute PE imposed by the increased prevalence of these risk factors is offset by improvements, generally, in the care of patients during pregnancy and...
the puerperium over this time frame. A fundamental challenge that remains is the extremely high and unchanged mortality caused by acute PE in pregnancy and the puerperium. Insights into the basis for such strikingly increased mortality caused by acute PE in pregnancy and the puerperium are needed, and, as also emphasized by Elgendy et al, the need for novel approaches in preventing, diagnosing, and managing acute PE in these settings.


WHY ARE ACEIs/ARBs UNDERPRESCRIBED IN PROTEINURIC CHRONIC KIDNEY DISEASE?

Chronic kidney disease (CKD) tends to be a progressive process and may culminate in endstage kidney disease (ESKD). The onset of ESKD increases the morbidity and mortality of patients with CKD, compromises their lifestyle, and necessitates either dialysis or transplantation. Management of CKD includes three main objectives: 1) targeting the cause of CKD by disease-specific therapies; 2) reducing the adverse consequences of CKD; and 3) retarding the loss of kidney function with the intent of delaying or avoiding ESKD. A major strategy that delays the progression of proteinuric CKD is the use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), both of which are effective anti-hypertensive and anti-proteinuric agents. Through such effects as well as their reductive effect on intraglomerular hydrostatic pressure and their suppressive effect on renal inflammation and fibrosis, these agents are widely recommended in patients with proteinuric CKD. However, such use of these agents is not as common as recommended by current guidelines. In the present issue of Mayo Clinic Proceedings, McCoy et al examine the basis for this disparity between their recommended and actual use. Employing a single-payer database with patient-level administrative and demographic data, these authors examined current ACEI/ARB prescriptions on a given date (April 15, 2017) and prior ACEI/ARB use in more than 40,000 adults with proteinuric CKD. The data demonstrate that less than one half of the patient population (49%) had an active prescription on the index date, whereas the majority (87%) were prescribed these agents at some time prior to this date. Curtailing the use of ACEIs/ARBs were four main factors: a previous history of acute kidney injury (AKI) or hyperkalemia, advanced CKD (stages 4 and 5), and failure to receive nephrology-based care. ACEIs/ARBs may cause a minor increase in serum creatinine because they decrease efferent arteriolar resistance, thereby leading to a fall in intraglomerular pressure, and, accordingly, in glomerular filtration. A modest increase in serum creatinine is generally acceptable (<30%), but an increase above this, which is more likely to occur when there is concomitant renal hypoperfusion for whatever reason, may be considered “AKI.” However, this ceiling for a permissible rise in serum creatinine has been questioned by some experts as too conservative. ACEI/ARB-induced hyperkalemia reflects diminished levels of aldosterone or decreased levels/effects of angiotensin II, the latter representing a major stimulus to aldosterone production by the adrenal cortex. These adverse effects of ACEIs/ARBs are more pronounced in advanced CKD. McCoy et al demonstrate that the observed low usage of these agents reflects their discontinuation because of these adverse effects, and not because of the failure to initiate them. Against this backdrop McCoy et al appropriately emphasize the efficacy of these agents in retarding the progression of proteinuric CKD and that attempts should be made in enabling their continued use without imposing risks to the patient. In this regard, and in some instances, as classified by McCoy et al, these 4 barriers may be considered either modifiable (hyperkalemia can be mitigated by a number of approaches/therapies; nephrology-based care should be introduced) or inappropriate (a modest rise in serum creatinine is permissible; these...
agents may be used in stage 4/5 CKD with careful monitoring to avoid the risk of hyperkalemia or AKI). Resolving any problem usually starts with identifying its causes. McCoy et al are to be commended for their identification of the barriers that limit the use of ACEIs/ARBs in proteinuric CKD, for their delineation of strategies that may circumvent these barriers, and for underscoring that the progression of proteinuric CKD may be retarded by the discerning and judicious use of ACEIs/ARBs with appropriate monitoring and medical management such that patient safety is always ensured.


**Noncardiac Surgery and the Reduction of Cardiac Complications**

In the present issue of *Mayo Clinic Proceedings*, and as part of the ongoing series of Thematic Reviews on Perioperative Medicine started in the April 2020 issue, Ganesh et al provide a comprehensive review on perioperative cardiac risk reduction in patients undergoing noncardiac surgery. In the perioperative period surrounding noncardiac surgery, a number of stressors are imposed on the cardiovascular system, and patients with pre-existing cardiovascular conditions are at an increased risk for myocardial injury and postoperative major adverse cardiac events. Ganesh et al begin by broadly discussing strategic approaches in patients with ischemic heart disease (IHD), emphasizing the differences in management of patients with either one of its major subtypes, namely, an acute coronary syndrome or chronic IHD. They then discuss the timing of noncardiac surgery in patients with a recent myocardial infarction or revascularization, and if revascularization was undertaken, how approaches are specifically geared to either coronary artery bypass graft or percutaneous coronary intervention. The article addresses strategies that reduce the risk for myocardial injury after noncardiac surgery; the management of patients with heart failure, either with reduced or preserved ejection fraction, that aims to reduce the risk for cardiovascular morbidity and mortality; and concepts and approaches in managing hypertension and arrhythmias in the perioperative period. The final section of the review discusses perioperative cardiovascular medication management, including such medications as agents with antiplatelet activity, nonsteroidal anti-inflammatory drugs, aspirin, P2Y12 inhibitors, beta blockers, HMG-CoA reductase inhibitors, ACE inhibitors and angiotensin receptor blockers, alpha-2 agonists, calcium channel blockers, and diuretics; a helpful table summarizes key aspects of management of the medicines in the perioperative period. This review by Ganesh et al has many strengths including the following: the synthesis in one readily accessible article salient management issues and recommendations pertaining to this topic; clearly enunciated recommendations that incorporate published guidelines from prominent societies that address this topic; the upgrading of these recommendations, where relevant, based on new evidence that is now available since these society guidelines were published several years ago; the provision of reasoned and prudent recommendations where these societies provide guidelines that substantively differ; and the delineation of areas of uncertainty in this field that are very much in need of further study.


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