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KEY POINTS

- Survival after abdominal organ transplantation continues to improve.
- The imbalance between organ supply and demand is increasing as new indications emerge and transplantation is offered to growing numbers of older candidates.
- To increase the supply of organs, living donors and extended criteria deceased donors are being used more frequently.
- Evolving organ preservation techniques employing graft perfusion offer the promise of improved outcomes with marginal organs, potentially enlarging the organ supply.
- Knowledge of the pathophysiologic changes associated with end-stage disease is required to provide optimal care for patients undergoing transplant surgery.
- The kidney is the most frequently transplanted organ.
- Kidney transplant recipients are older and are more likely to have chronic illnesses than in the past.
- The perioperative and long-term risk of cardiovascular disease is increased in patients with end-stage renal disease.
- Maintenance of renal perfusion pressure in the perioperative period is critical for kidney graft function.
- Liver transplant recipients are older in age and have more comorbidities than in the past.
- The Model for End-stage Liver Disease (MELD) score prioritizes candidates for organ allocation in the United States.
- The pathophysiologic changes associated with liver disease affect nearly every organ system.
- Intraoperative care of liver transplantation recipients requires preparation for massive transfusion, management of coagulation abnormalities, and hemodynamic instability.
- Pancreatic transplantation is definitive treatment for diabetes mellitus.
- Pancreatic transplants are performed simultaneously with kidney transplantation (SPK), after kidney transplantation (PAK), or alone (PTA).
- Patients under 50 years with diabetes and end-stage renal disease benefit from SPK; however, more patients over age 50 and those with type 2 diabetes are now undergoing pancreas transplantation.
- In pancreatic transplant recipients, frequent monitoring of blood glucose concentrations is required during the perioperative period.
- Diabetic patients are at significant risk for cardiovascular disease.

Solid organ transplantation continues to grow worldwide. The success of transplantation over the past decades corresponds to improved survival for recipients. Increasingly, indications for transplantation have broadened. Patients with conditions previously considered contraindications, such as advanced age and some types of cardiopulmonary disease, are no longer precluded from transplantation.

Based on global data, 126,670 organs were transplanted in 2015, with a steady increase in yearly transplant activity over the past 5 years (Fig. 60.1).¹ In the United States there were 33,610 organ transplants performed in 2016; transplant volumes have increased annually in the United States as well.² In the United States and worldwide, the kidney

is the most transplanted organ followed by the liver (Figs. 60.2 and 60.3).

Despite an encouraging trend in transplant volume, the number of patients who could benefit from transplantation far exceeds those who receive an organ. The imbalance between graft supply and demand is the major factor limiting organ transplantation in all countries. Solutions to organ shortage include living donor transplantation, which is used more commonly for kidney than liver transplantation. Other strategies include the use of extended criteria donors, including grafts from marginal donors declared brain dead (donation after brain death) and from donors dying from cardiac arrest (donation after cardiac death). These are discussed in detail elsewhere.

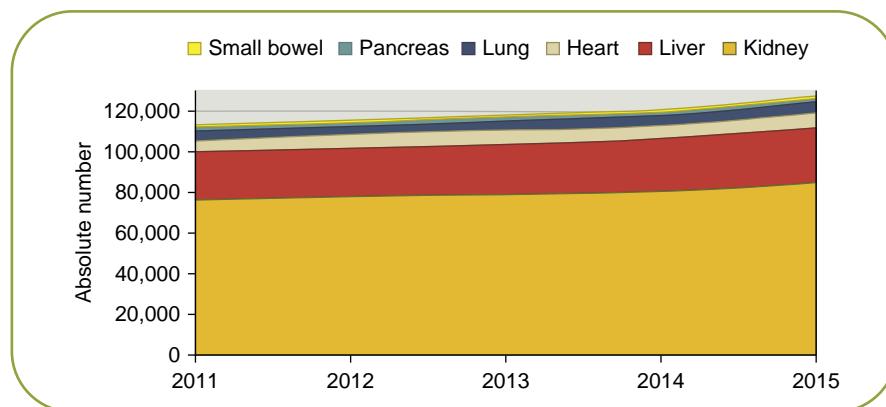


Fig. 60.1 Global transplant activity by organ, 2011–2015. (From <http://www.transplant-observatory.org/organ-donation-transplantation-activities-2015-report-2/>. Accessed June 25, 2018.)

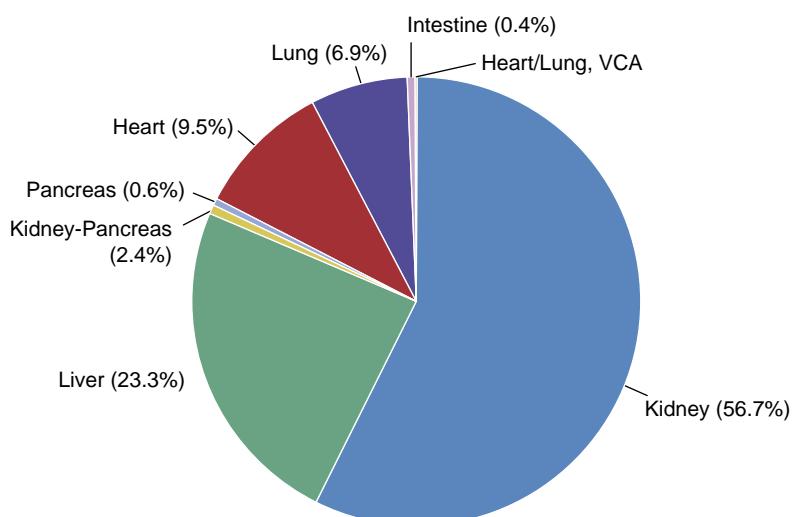


Fig. 60.2 U.S. transplants by organ, 2016. (From <https://unos.org/about/annual-report/2016-annual-report/>. Accessed June 25, 2018.)

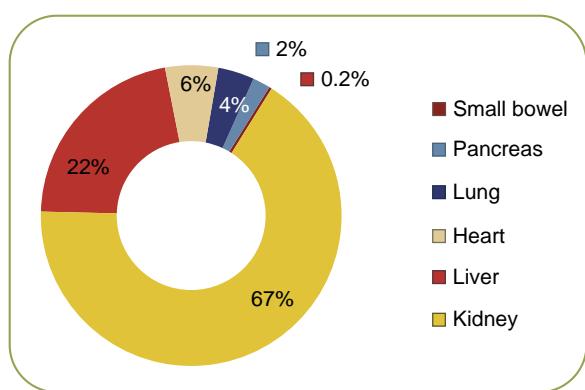


Fig. 60.3 Global transplants by organ, 2015. (From <http://www.transplant-observatory.org/organ-donation-transplantation-activities-2015-report-2/>. Accessed June 25, 2018.)

The evaluation of patients for transplantation varies among transplant centers, but the goals are similar. These include ascertaining that: (1) transplantation is indicated for the management of the prospective recipient, (2) comorbidities do not preclude transplantation, and (3) emotional and social resources permit a major surgery and

its associated rehabilitation, including compliance with long-term immunosuppression therapy. The center's transplant selection committee typically consists of physicians (nephrologist and hepatologist for kidney and liver transplantation, respectively), transplant surgeon, psychiatrist, dietitian, social worker, and additional consultants as indicated. Anesthesiologists consult on high-risk candidates as agreed by local protocol. These include those with significant cardiovascular or respiratory comorbidities, poor nutritional or functional status, multiorgan failure, limited vascular access, or known anesthetic risks.

Reasons to deny transplantation vary among transplant centers, although in liver transplantation American Association for the Study of Liver Diseases guidelines and international consensus would mandate predicted 5-year survival greater than 40% to 60%. Critically ill patients receiving life support, vasopressors, or dialysis have decreased posttransplant survival.³ Additional comorbidities can exacerbate the risk to a level that may be unacceptable to some centers. These may include significant coronary artery disease (CAD), moderate or severe pulmonary hypertension, metastatic disease, uncontrolled intracranial hypertension, and untreated sepsis. Psychosocial contraindications include

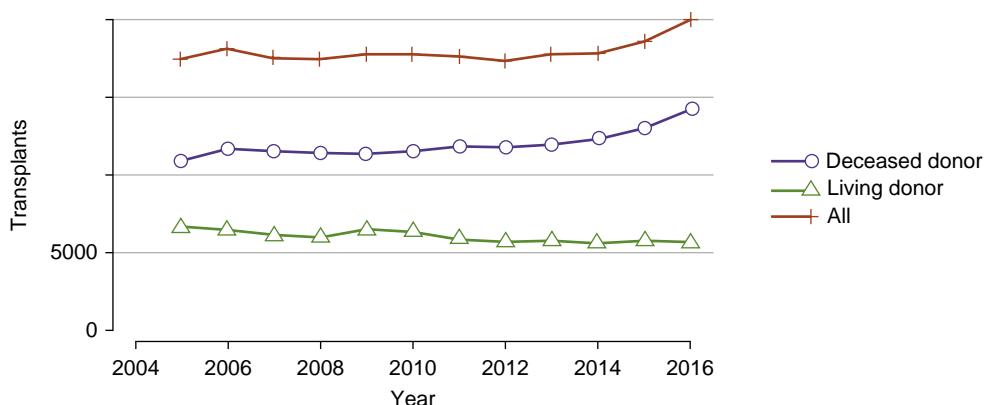


Fig. 60.4 U.S. kidney transplantation trends, 2004–2016. (From Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2016 Annual Data Report: Kidney. *Am J Transplant.* 2018;Suppl 1:18–113.)

alcohol or recreational drug use, and the lack of social support, which might preclude compliance with immunosuppression regimens, follow-up care, or both. Age alone is generally not a contraindication unless associated with a low actuarial life expectancy (median survival), such as in the case of liver transplant, under 5 years posttransplant. More often a combination of age and comorbidities will exclude transplant in the older patient.

The success of organ transplantation relies heavily on a highly specialized team approach that includes the organ procurement organization, transplant coordinators, nurses, physicians, and allied healthcare providers. With the exception of kidney transplantation, most abdominal organ transplants are performed at tertiary medical centers with extensive resources available to support the program. Many of these centers have specialized anesthesia teams, particularly for liver and multivisceral transplantation.

This chapter reviews the anesthetic considerations for kidney, liver, pancreas, and intestinal transplantation in adults. The overall care of pediatric patients is described elsewhere in this text, as is the management of heart and lung transplantation.

Kidney Transplantation

Early attempts at human kidney transplantation date to the 1930s, however long-term success was not demonstrated until the 1950s. Kidney transplantation remained an experimental treatment for renal failure with isolated cases from various centers demonstrating varying success until breakthroughs in tissue typing and immunosuppression led to improved graft survival.

Today, kidney transplantation is the most common organ transplant surgery performed. Kidney transplant rates continue to rise on an international scale with growth of kidney transplant programs throughout Europe, North America, and Asia, as well as in many developing countries. Worldwide, there are substantial differences in the distribution of living versus cadaveric donor organs determined by cultural barriers to deceased donation or lack of organ procurement facilities. Many countries in Africa and Asia rely exclusively on living donation, whereas some countries in Europe perform mainly cadaveric renal

transplants.⁴ However, many developing countries have implemented national deceased donor kidney transplant distribution systems that have steadily increased access to transplantation.^{5,6} Despite this effort, obstacles remain for renal transplant programs in many developing countries including patient access to care, costs, infrastructure, and cultural barriers.⁷ Regardless of location, the lack of donors in the setting of increasing rates of end-stage renal disease (ESRD) affects all countries equally.

The demographics of kidney transplant patients in the United States have changed over the past 2 decades for many reasons, including an aging population and higher prevalence of diabetes and hypertension. Diabetes and hypertension are the two most common etiologies of ESRD in adults in the United States. Although it is not known how many patients with chronic kidney disease (CKD) progress to ESRD, the prevalence of ESRD in the United States has continued to increase. There were 703,243 documented cases of ESRD in the United States at the end of 2015, a 3.4% increase from the prior year.⁸ ESRD also continued to increase on an international level; all countries that reported data in 2015 showed increased prevalence from the year before.⁹ Although the prevalence of ESRD in the United States has continued to increase, this observation may reflect longer survival of patients with the diagnosis of ESRD. Encouragingly, 30% of all ESRD cases reported in the United States at the end of 2015 had a functioning kidney transplant.⁸

In the United States, the national kidney transplant waitlist steadily increased up to the year 2014, reflecting an increased incidence of CKD in older populations due to hypertension and diabetes. However, in 2016, the waitlist for kidney transplant decreased for the second year in a row; 30,869 patients were added to the United States waitlist while 33,291 patients were removed.¹⁰ In concordance, the total number of kidney transplants performed in the United States increased in 2016 for the second year in a row as well; a total of 19,060 were performed. This increase in kidney transplant activity was directly due to an increase in deceased donor transplants, as living donor transplants remained stable (Fig. 60.4).¹⁰ A new kidney allocation system implemented in the United States at the end of 2014 was likely responsible for this observed increase in deceased donor kidney transplants. This system was designed to

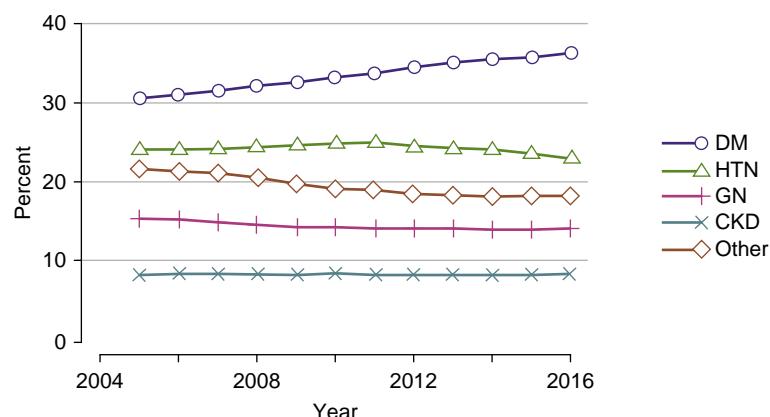


Fig. 60.5 Distribution of adults awaiting kidney transplant in U.S. 2004–2016 by diagnosis. CKD, Cystic kidney disease; DM, diabetes; GN, glomerulonephritis; HTN, hypertension. (From Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2015 Annual Data Report: Kidney. *Am J Transplant*. 2018;Suppl 1:18–113.)

improve transplant equity by increasing access to deceased donor kidney transplants for a number of candidate subgroups including racial/ethnic minorities, B blood type candidates, highly sensitized candidates, and those with a history of prolonged dialysis prior to listing.¹¹ Analysis of the results of this new allocation policy demonstrated a 7% increase in kidney transplants performed in the first 18 months after implementation with observed increases in transplant rates in many of the prioritized subgroups.¹² Despite these recent successes, more patients were removed from the transplant list in 2016 than in previous years because of being too ill for transplant.¹⁰ This trend reflects a kidney transplant population that is older and more likely to suffer from chronic diseases, which also has significant implications regarding perioperative risk during kidney transplant. Nevertheless, continued improvements in both short- and long-term living and deceased donor graft outcomes were reported in 2016.¹⁰ One-year deceased donor graft survival rates remain over 90% in the United States, Europe, Canada, and Australia/New Zealand. Five-year deceased donor survival rates are slightly better in Europe, Canada, and Australia/New Zealand compared to the United States for reasons that are not completely defined.¹³

Despite an observed graft survival advantage for living kidney transplants over deceased donor transplants, the rates of living donor transplants have remained static over the past 10 years in the United States at approximately 5000 per year for reasons that are not fully understood.^{10,13} Paired donation, consisting of two incompatible donor-recipient pairs exchanging kidneys to create two compatible pairs, is a strategy to increase access to living donors. Paired donation has increased in both the United States and internationally. With the development of donor chain transplants and establishment of organized allocation systems for paired donation, these techniques are expected to increase the future rate of living donor kidney transplants.¹⁴

INDICATIONS FOR KIDNEY TRANSPLANTATION

Kidney transplantation is indicated in patients with ESRD caused by any one of a variety of underlying conditions. Glomerular disease, congenital diseases, and polycystic

kidney disease are common indications in younger patients. Nephropathies associated with hypertension and diabetes are the most common indications for kidney transplantation in the United States. Diabetes is the leading cause of ESRD in the United States, representing 36% of all wait-listed candidates in 2016 (Fig. 60.5).¹⁰ Renal graft failure is an increasingly common indication for transplantation as well. In 2015, 16% of all waitlisted candidates in the United States were awaiting retransplantation and higher percentages have been reported in other countries.^{15,16}

PATHOPHYSIOLOGY OF END-STAGE RENAL DISEASE

ESRD refers to the final progression of CKD, when renal function is irreversibly impaired and the development of uremia is imminent. Essential functions of the kidney include regulation of the ionic composition of the plasma, maintenance of fluid volumes, elimination of nitrogenous wastes and drugs, synthesis of erythropoietin, and adjustment of plasma pH. Significant declines in glomerular filtration rate (GFR) and urine production occur when these critical functions are damaged, resulting in the clinical manifestations of uremia. After the development of ESRD, renal replacement therapy is required. ESRD has an effect on nearly every organ system, and it has a major impact on patient mortality despite chronic therapy including hemodialysis.

ESRD results in abnormalities of fluid balance and electrolytes. With the onset of uremia and oliguria, expansion of the extracellular fluid volume ensues, presenting with edema, hypertension, and signs and symptoms of volume overload. Disorders of sodium, calcium, magnesium, and phosphate can result in chronic changes in bone metabolism, hyperparathyroidism, and vascular calcifications. The development of hyperkalemia, with its effects on the myocardium, is the most critical electrolyte abnormality. Failure of the renal elimination of organic acids results in the development of an anion-gap metabolic acidosis.

ESRD has a significant effect on the cardiovascular system. Cardiovascular disease is the most common cause of morbidity and mortality in patients with ESRD, accounting for 35% to 40% of all deaths in patients receiving

hemodialysis.¹⁷ As GFR decreases, the risk of cardiac mortality increases.¹⁸ ESRD increases the development of atherosclerosis and is a major risk factor for the development of ischemic vascular disease, which can affect the coronary, cerebrovascular, and peripheral vascular systems. The likelihood of CAD, which can present as angina, myocardial infarction, arrhythmia, or sudden cardiac death, may be even greater in patients with hypertension and diabetes. Hypertension may be the etiology of ESRD in nearly 30% of patients, or conversely, hypertension may result from hyperreninemia, hypervolemia, and renal vasculature changes associated with ESRD. Concentric left ventricular hypertrophy and diastolic dysfunction occur in the early stages of CKD, and are the two most common echocardiographic abnormalities in patients with ESRD.¹⁹ Patients with ESRD are at particular risk for diastolic congestive heart failure, especially in the setting of excessive intravascular volume. Heart failure owing to dilated cardiomyopathy with decreased systolic function can occur in patients with ESRD as well. The cardiorenal syndrome is defined by an interconnection between the renal and cardiac systems, where the decline of one organ influences the decline of the other. There is evidence that correction of renal function by renal transplantation can improve systolic dysfunction and reverse left ventricular dilation and hypertrophy.^{20,21} A variety of arrhythmias can occur in ESRD because of progression of cardiac disease, myocardial ischemia, or electrolyte disturbances. Atrial fibrillation occurs in up to 27% of patients on hemodialysis and is associated with an increased risk of stroke, heart failure, and hemodynamic disturbance. Stroke is of significant concern in ESRD patients with atrial fibrillation, as patients with ESRD have nearly a 50% increased risk of stroke compared to the general population.²² Clinical dilemmas are common regarding anticoagulation in patients with atrial fibrillation and ESRD. Pericardial disease is common in patients with uremia, manifesting as pericarditis or pericardial effusion.

Characteristic hematologic and hemostatic abnormalities occur with ESRD. Normochromic, normocytic anemia secondary to lack of erythropoietin is common and may be exacerbated by iron deficiency, chronic inflammation, and bone marrow fibrosis. Anemia decreases quality of life in ESRD and is associated with adverse cardiac outcomes. Erythropoiesis-stimulating drugs and iron are commonly prescribed for the treatment of uremic anemia, and hemoglobin levels of 11 to 12 gm/dL are typically achieved.²³ ESRD is associated with abnormal hemostasis because of a broad spectrum of platelet function abnormalities including decreases in platelet activity, aggregation, and adhesiveness. Production of von Willebrand factor and factor VIII is decreased. Historically, renal failure patients were considered to be at an increased risk for bleeding. However, ESRD is also associated with a hypercoagulable state owing to a variety of complex hemostatic changes including increased fibrinogen levels, reduced antithrombin levels, acquired thrombophilic factors, and endothelial alterations. Clinically, the risk of venous thromboembolism appears to increase as renal function decreases; manifestations may include deep venous thrombosis/pulmonary embolism and thrombosis of arteriovenous fistulas and vascular access catheters.²⁴

Many of the hematologic changes of hypercoagulability have been shown to resolve in patients with ESRD after kidney transplantation.²⁵

Gastrointestinal signs and symptoms of ESRD include nausea, vomiting, and abdominal pain. Patients with ESRD may have delayed gastric emptying, regardless of the timing of their last oral intake. Dyspepsia occurs in 50% to 70% of patients on hemodialysis; ESRD patients with symptomatic dyspepsia have been shown to have particularly prolonged gastric emptying times.²⁶ The presence of diabetes and obesity may further impair gastric emptying.

Central nervous system and neuromuscular abnormalities can occur in ESRD secondary to retained nitrogenous molecules. These abnormalities range from mild changes in memory or attention to signs and symptoms of neuromuscular irritability. Severe neurologic manifestations of uremia with asterixis, seizures, and decreased mental status are rare with regular dialysis. Peripheral neuropathy is the most common neurologic manifestation of ESRD and is documented in up to 90% of dialysis patients. Autonomic dysfunction is also common, documented in up to 50% of dialysis patients. Autonomic neuropathy is implicated in ESRD patients with orthostatic hypotension, cardiac arrhythmias, and gastric dysmotility. Kidney transplantation is the most effective treatment for the neurologic manifestations of ESRD.²⁷

ANESTHESIA FOR KIDNEY TRANSPLANTATION: PREOPERATIVE EVALUATION

Before kidney transplantation, patients typically undergo a prolonged pretransplant evaluation by a multidisciplinary transplant committee to determine their fitness for transplantation and to assess for the likelihood of long-term survival following transplantation. In general, the preoperative evaluation of patients for kidney transplant should focus on the multiorgan manifestations of ESRD, with the goals of risk stratification and optimization of the medical status of the patient before transplant. Cadaveric kidney transplantation is an urgent procedure, because harvested organs tolerate a finite duration of cold ischemia of approximately 24 hours. Living donor kidney transplants are scheduled well in advance, allowing for a thorough preoperative assessment before surgery.

As discussed previously, the current demographic of kidney transplant patients has a frequent association with cardiac disease, which has a major effect on posttransplant outcome. As a result, preoperative cardiac evaluation is of critical importance in this patient group. Compared with the routine preoperative evaluation of surgery patients without cardiac disease, the renal transplant patient should be assessed to consider both short- and long-term cardiac outcomes. The goal of the preoperative cardiac evaluation is ultimately to decrease the morbidity and mortality associated with cardiovascular disease in kidney transplant candidates. Although decisions regarding candidacy in high-risk patients are usually made well before surgery, the anesthesiologist should be involved in the routine cardiac risk assessment of the kidney transplant patient before surgery. The major focus of the preoperative cardiovascular assessment in kidney transplant patients is to identify occult ischemic heart disease.

The 2014 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery recommends a preoperative algorithm designed to assist in the risk stratification of surgical patients. The stepwise algorithm includes identification of known CAD or CAD risk factors, estimation of the perioperative risk for major adverse cardiac events based on combined clinical and surgical risk factors, and determination of functional capacity. The decision to proceed with surgery or to undergo further noninvasive ischemia testing is contingent on functional capacity, scored by metabolic equivalent tasks (METS). No further testing is recommended when functional status is considered moderate or good (more than 4-10 METS) or excellent (more than 10 METS). If functional status is less than 4 METS or cannot be assessed, further ischemia testing may be considered.²⁸ The utility of published guidelines to detect patients with ischemic heart disease has been called into question in the kidney transplant population and, in contrast to the 2014 more general guidelines, in 2012, the AHA and the American College of Cardiology Foundation issued a scientific statement stating that the cardiac evaluation and management among kidney and liver transplantation patients should form the basis of the long-term evaluation of the transplant patient.²⁹ Silent myocardial ischemia may occur more frequently in patients with ESRD than in the general population, making the detection of unstable coronary syndromes more difficult. One study reported that chest pain presenting at the time of acute myocardial infarction was less common in patients with ESRD requiring dialysis compared with patients not using dialysis (44% vs. 68%).³⁰ Decreased functional status might not be a specific or sensitive indicator of cardiovascular risk in kidney transplant candidates, and many ESRD patients are unable to exercise secondary to deconditioning. One study of kidney transplant candidates examined the effectiveness of various guidelines to detect asymptomatic CAD. The authors determined that if the 2014 ACC/AHA guidelines had been strictly applied to this group of patients, only a small proportion of the candidates with documented myocardial ischemia on noninvasive testing would have been detected.³¹ Finally, renal insufficiency is itself a CAD risk factor. The unique characteristics of ESRD patients, along with discrepancies among published guidelines, has called into question the applicability of available recommendations regarding cardiac testing in the kidney transplant population.²⁹

Noninvasive testing methods for CAD have been well studied in the kidney transplant population, although most investigations consisted of small study populations. In studies that compared either dobutamine stress echocardiography (DSE) or myocardial perfusion imaging with angiography in patients with renal failure, both methods demonstrated decreased accuracy compared to their accuracy in nonrenal failure patients.^{29,32} The response to coronary vasodilators appears to be decreased in ESRD patients with diabetes; this may contribute to false negative myocardial perfusion testing results.³³ Chronotropic incompetence may diminish the maximum heart rate response to dobutamine in patients with ESRD and left ventricular hypertrophy may limit detection of reversible wall motion abnormalities during echocardiographic stress testing.³⁴

Although noninvasive testing appears to be less reliable in kidney transplant patients compared to the general population, ischemia detected on noninvasive testing correlates with adverse cardiac events and mortality in patients with ESRD and in kidney transplant patients.^{35,36} One meta-analysis that analyzed studies using either DSE or myocardial perfusion studies in patients with ESRD demonstrated that patients with inducible ischemia or fixed defects had a significantly increased risk of cardiac death compared with patients with normal tests.³⁷

Although many guidelines and consensus-based recommendations regarding preoperative cardiac risk assessment in kidney transplant candidates have been published, there is no validated standardized approach.^{29,38} A stepwise process including a comprehensive cardiovascular history and evaluation of signs and symptoms of advanced cardiac disease, assessment of functional status, and identification of risk factors should be reviewed.

A baseline electrocardiogram (ECG) is an appropriate initial screening test in most kidney transplant patients, especially in patients older than 40 years. ECG abnormalities associated with cardiac disease are common in patients with ESRD. A preoperative ECG should be obtained in patients with known CAD, peripheral vascular disease, and cardiac symptoms.²⁹ Noninvasive testing may be considered in asymptomatic patients with multiple risk factors for CAD. The most recent consensus document published in 2012 by the ACC/AHA provides recommendations for preoperative cardiac testing in kidney transplant candidates.²⁹ Noninvasive ischemia testing should be considered in candidates with three or more of the following risk factors: known cardiovascular disease, diabetes, dialysis for more than 1 year, age over 60 years, tobacco use, left ventricular hypertrophy, dyslipidemia, and hypertension. The authors also recommend that the decision to proceed with noninvasive testing based on the presence of the above risk factors should be made regardless of functional status in kidney transplant candidates.²⁹

Preoperative assessment of left and right ventricular function by echocardiography is an appropriate test in most kidney transplant candidates.²⁹ The likelihood of structural cardiac abnormalities and the potential for left ventricular dysfunction in ESRD is significant, and transthoracic echocardiography provides detailed information regarding resting cardiac function and structure with minimal testing risk.

An increased prevalence of occult pulmonary hypertension, up to 40% reported in one series, occurs in patients receiving dialysis. The mechanism involves both uremia-induced pulmonary vasoconstriction and increased cardiac output secondary to an arteriovenous fistula. Pulmonary hypertension may be reversible after kidney transplantation. The identification of pulmonary hypertension is important because its presence in patients with ESRD is associated with decreased survival.³⁹ Right heart catheterization may be indicated in patients with evidence of significant pulmonary hypertension by echocardiography.

Patients with cardiac conditions may remain on transplant lists for many years before undergoing transplantation. During this time, cardiac disease can progress. Although routine periodic noninvasive screening in asymptomatic patients awaiting transplant is not warranted,

patients with known cardiac disease should undergo regular repeat cardiac assessments although the frequency of assessments has not been defined.²⁹

Cardiovascular medications should be reviewed during the preoperative evaluation in kidney transplant candidates, and the patient advised on which medications should be taken before surgery. Most patients with ESRD receive multiple medications for the chronic treatment of hypertension; however, the ideal combination of drugs is not clear. Strategies for the perioperative administration of antihypertensive blood pressure medications are important; however, the urgency of deceased-donor kidney transplantation often allows only the immediate preoperative administration of antihypertensive medications. The risks and benefits of initiating or maintaining perioperative medical therapy in surgical patients have been extensively reviewed in the most recent ACC/AHA guideline; β -blockers, statins, α -2 agonists, calcium channel blockers, and angiotensin-converting enzyme inhibitors were included.²⁸ There is limited information regarding perioperative antihypertensive therapy and its impact on survival in kidney transplant patients. In general, it is reasonable to apply current ACC/AHA recommendations regarding perioperative antihypertensive therapy in kidney transplant candidates.

As mentioned previously, there is an increasingly high prevalence of diabetes in the kidney transplant population. Perioperative hyperglycemia is associated with adverse outcomes in both diabetic and nondiabetic populations.⁴⁰ Perioperative glycemic therapy should be initiated in patients with diabetes who are undergoing kidney transplant, yet a benefit from strict blood glucose control in the kidney transplant population has not been demonstrated. Studies demonstrating the risks of hypoglycemic episodes in protocols employing "tight" glucose control in surgical and intensive care unit (ICU) patients suggest that conventional glycemic targets may be safer during the perioperative period.^{41,42} Most medical society organizational guidelines recommend targeting blood glucose levels between 110 to 160 mg/dL and initiating insulin therapy for blood glucose levels over 180 mg/dL during the perioperative period.⁴⁰

Day of Surgery

Prior to surgery, patients receiving hemodialysis should be maintained on their regular dialysis schedules. If possible, dialysis should be performed immediately prior to surgery. Preoperative laboratory assessment of electrolytes, complete blood count, and platelet count is necessary in all kidney transplant patients on the day of surgery. Documentation of an increased potassium level, especially with ECG changes consistent with hyperkalemia, should prompt consideration for the delay of surgery and for immediate dialysis to correct potassium levels. Preoperative vital signs should be closely assessed, especially heart rate and arterial blood pressure trends in hospitalized patients. Preoperative intravascular volume status should be assessed. Comparing the patient's current weight to their known euvolemic weight, or "dry weight," may be helpful. Orthostatic assessments and the presence of resting hypotension and increased heart rate may identify significant hypovolemia. Patients who have preoperative body weights heavier than their euvolemic weight may have an excessive

intravascular volume and may be at risk for congestive heart failure during the perioperative period. A thorough cardiopulmonary examination is indicated in all patients, and findings of significant excessive intravascular volume may be an indication for immediate preoperative dialysis. On the day of surgery blood glucose levels should be measured; insulin therapy may be initiated in patients before surgery for significant hyperglycemia, with appropriate serial blood glucose measurements during the perioperative period. As in all types of surgery, orally administered antihyperglycemic medications should be withheld in patients with non-insulin-dependent diabetes. A type and screen or crossmatch for packed red blood cells should be obtained. Although major blood loss during routine kidney transplantation is not common, the surgery involves major vascular structures and catastrophic rapid bleeding can occur. Finally, in patients with known cardiac disease or in those with changes in cardiac symptoms, bedside ultrasound examination of cardiac structures may be indicated, particularly to assess for changes in ventricular function, valvular pathology, or pericardial disease.

ANESTHESIA FOR KIDNEY TRANSPLANT: INTRAOPERATIVE MANAGEMENT

General anesthesia with endotracheal intubation is the preferred anesthetic method for kidney transplantation in most institutions. The goals of anesthesia are to facilitate an adequate depth of anesthesia while maintaining hemodynamic stability and to provide appropriate muscle relaxation to facilitate surgical conditions. As mentioned previously, patients with ESRD are considered at risk for aspiration of gastric contents secondary to the presence of uremic gastropathy and other conditions, such as obesity and diabetes. An oral nonparticulate antacid and intravenous administration of an H-2 blocker may be considered before induction of anesthesia. A rapid-sequence induction of anesthesia is the preferred method of induction for general anesthesia. Succinylcholine can be used safely in standard doses in patients with ESRD when potassium levels are within normal limits (usually < 5.5 mEq/L). Potassium transiently increases 0.5 to 1.0 mEq/L for 10 to 15 minutes before returning to baseline levels in patients with ESRD and those with normal renal function.⁴³ A modified rapid-sequence induction using rocuronium 0.8 to 1.2 mg/kg intravenously may be a substitute for succinylcholine when hyperkalemia or other contraindications to succinylcholine exist. Rocuronium should be used in ESRD with caution as the duration of action is prolonged. A meta-analysis of 26 studies that compared the intubating conditions produced by succinylcholine and rocuronium found that intubation conditions were clinically similar when propofol was used as the induction anesthetic.⁴⁴ The hemodynamic response to laryngoscopy may be accelerated in patients with ESRD with underlying chronic hypertension. Tachycardia and hypertension can be attenuated with supplemental short-acting agents or opioids titrated to effect. Following the stress of tracheal intubation, kidney transplant patients may develop hypotension before surgical incision, especially in patients who have been rendered hypovolemic from recent dialysis or in patients receiving renin-angiotensin blocking drugs.

Intraoperative monitoring may be limited to standard noninvasive monitors in younger, healthier transplant recipients and in select living donor recipients. Intraarterial blood pressure monitoring can be beneficial, especially in patients with uncontrolled hypertension, CAD, or heart failure. A radial arterial catheter, if used, is placed contralateral to a preexisting arteriovenous fistula and the femoral artery is typically avoided. Femoral access on the side selected for implantation is contraindicated due to the risk of hematoma or thrombosis adversely affecting the implanted graft. It is important to assess the risk versus benefit of arterial access in ESRD patients, as upper extremity arterial lines may jeopardize future arteriovenous access for dialysis. Pulmonary artery (PA) catheter or transesophageal echocardiographic monitoring may be considered in patients with advanced CAD, left or right ventricular dysfunction, and pulmonary hypertension but is rarely indicated otherwise. Central venous pressure monitoring may be employed in some centers; however, central venous pressure is not a reliable monitor of fluid status or responsiveness.⁴⁵ The insertion of a central line provides reliable venous access for intravascular fluid resuscitation and transfusion, easy blood sampling, and access for administration of immunosuppression drugs and vasoactive infusions. In patients without a pre-existing arteriovenous fistula or dialysis catheter, a central line allows urgent postoperative dialysis, if required. Many centers find central line insertion unnecessary; the risks and benefits of central line placement should be considered. Large-bore venous access is necessary for appropriate intravascular volume administration. Intravenous access can be challenging in some kidney transplant patients, as intravenous sites may be limited by the presence of an upper extremity arteriovenous fistula. Conversely, central venous access may be difficult to accomplish in patients with ESRD who have undergone multiple previous central venous dialysis catheter placements, especially if central venous thrombosis has been documented.

Maintenance of anesthesia is typically performed using a combination of intravenous and inhaled anesthetics. Volatile inhaled anesthetics are titrated to the level of surgical stimulation. Desflurane and isoflurane are not associated with nephrotoxicity. Although sevoflurane has potential nephrotoxic effects from the metabolites compound A and fluoride ion, detrimental effects on renal function have not been demonstrated in patients with renal insufficiency.^{46,47} Although large prospective studies are lacking in kidney transplant patients, the use of sevoflurane during kidney transplantation appears to be a reasonable anesthetic choice.

Analgesia during the intraoperative period can be provided with the synthetic opioids fentanyl, sufentanil, alfentanil, and remifentanil because their pharmacokinetics and pharmacodynamics are not affected by renal insufficiency. Morphine, oxycodone, and meperidine should be used sparingly in patients with renal failure because these drugs have active metabolites that accumulate in these patients.

Appropriate neuromuscular blockade during kidney transplantation may facilitate optimal surgical conditions; however, recovery from neuromuscular blockade may be variable in patients with ESRD regardless of the drug used.⁴⁸ Vecuronium and rocuronium have prolonged durations of action in renal failure patients, because their clearances

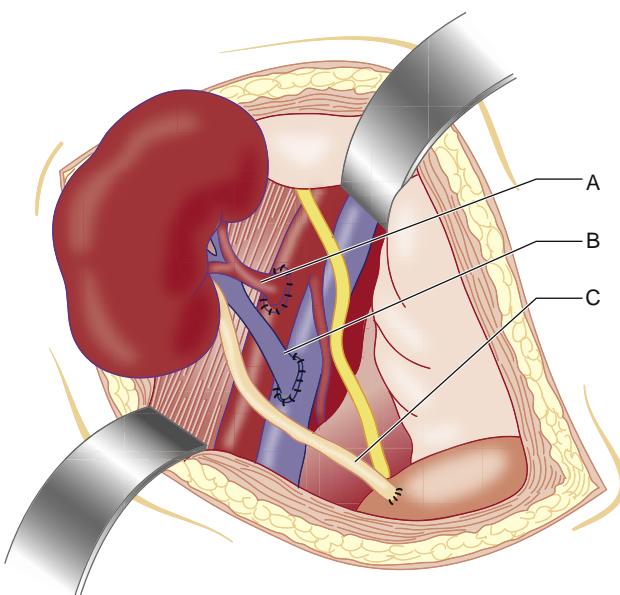


Fig. 60.6 Renal transplantation. A, Renal artery anastomosis performed end-to-side to the external iliac artery. B, Renal vein anastomosis performed end-to-side to the external iliac vein. C, Ureteral anastomosis to the bladder mucosa. (From Hardy JD. *Hardy's Textbook of Surgery*. 2nd ed. Philadelphia: JB Lippincott; 1988.)

rely both on renal and hepatic metabolism. Cisatracurium is likely the muscle relaxant of choice in patients with ESRD, because it undergoes organ-independent clearance. Pancuronium is primarily eliminated by the kidneys, and probably should be avoided in patients with renal failure. For patients with ESRD who are undergoing kidney transplantation, judicious use of neuromuscular blocking drugs is a necessity. Titration to surgical conditions and close monitoring of the level of neuromuscular blockade are crucial.

The surgical procedure involves placement of the renal allograft in the left or right extraperitoneal fossa, although the right side is usually preferred (Fig. 60.6). A vertical curvilinear incision 20 to 25 cm long is typically made, extending from the pubis symphysis to above the anterior superior iliac spine. The abdominal musculature is divided, and the peritoneum is entered and retracted. During the initial incision and dissection, surgical stimulation is increased and hemodynamic responses may be exaggerated in some patients. Adequate analgesia, depth of anesthesia, and muscle relaxation should be appropriately titrated to effect. The external iliac vein and artery are identified and mobilized. Occasionally, different vascular structures are chosen for the renal anastomoses. Heparin may be administered before clamping of the vessels. The external iliac vein is clamped first, and the renal vein anastomosis is performed. Next, the external iliac artery is clamped and the renal artery anastomosis is performed. During the anastomoses of the renal vessels, expansion of intravascular volume with balanced salt solutions should be initiated. Furosemide and mannitol are administered before reperfusion to stimulate diuresis. Mannitol, along with adequate intravascular volume resuscitation, decreases the likelihood of acute tubular necrosis in renal transplantation.⁴⁹ Adequate intravascular volume expansion with crystalloid or colloid increases renal blood flow, which improves immediate graft function.⁴⁸ At the time of removal of the vascular

clamps, additional intravascular volume expansion may be required to stabilize hemodynamics. On rare occasions, removal of vascular clamps may be associated with acute bleeding requiring further resuscitation and transfusion. Hypotension following reperfusion will result in hypoperfusion of the graft. Hypotension may precipitate renal injury owing to ischemia and can contribute to vascular thrombosis of the graft. Appropriate decreases in the depth of volatile anesthetic and volume expansion will maintain adequate renal perfusion pressures in most patients. In the event of hypotension, adrenergic vasoconstrictors are typically avoided because of renal vasoconstrictive effects. Hypotension unresponsive to volume expansion may require interventions to increase cardiac output, especially in high-risk patients. Invasive hemodynamic monitoring is invaluable in this situation. Inotropic agents may be necessary to maintain renal perfusion pressure; there is no consensus regarding which agent is preferred in kidney transplant patients. After completion of the vascular anastomoses, the donor graft ureter is implanted into the recipient bladder. The bladder is filled with antibiotic saline irrigation solution by way of a three-way Foley catheter, allowing for implantation of the donor ureter. A temporary ureteral stent may be placed as well. After completion of the bladder anastomosis, the wound is closed in layers. Neuromuscular blockade should be maintained until the fascial layer has been closed to prevent straining or coughing that could potentially disrupt the graft position or vascular connections. During emergence, exaggerated hemodynamic responses are common, especially in patients with poorly controlled hypertension. Appropriate titration of short-acting drugs to attenuate these responses upon emergence is helpful, especially in patients at risk for CAD. Careful neuromuscular blockade monitoring and appropriate administration of reversal agents are central to avoiding postoperative pulmonary complications. Sugammadex, a binding agent specific for rocuronium, forms an inactive complex that is primarily cleared by the kidneys. Clearance of this complex is reduced in ESRD patients, although removal of this complex using dialysis has been demonstrated.⁵⁰ Sugammadex has been shown to be clinically effective in ESRD patients, however its safety has not yet been demonstrated in kidney transplant populations.⁵¹ ESRD patients may demonstrate delayed emergence from anesthesia and have exaggerated responses to opioids and sedative-hypnotics. Extubation of the trachea should occur after the patient demonstrates the ability to protect the airway, because kidney transplant patients are still considered a risk for aspiration of gastric contents at the completion of surgery.

ANESTHESIA FOR KIDNEY TRANSPLANT: POSTOPERATIVE MANAGEMENT

After extubation of the trachea, the kidney transplant recipient requires careful monitoring in the postanesthesia care unit. Close monitoring of urine output in the initial postoperative period is important. Acute decreases in urine output should initiate a rapid evaluation of the etiology and appropriate treatment. A prerenal etiology should be treated with aggressive intravascular volume resuscitation. In some patients, additional invasive hemodynamic monitoring may be required. Postrenal etiologies owing

to technical problems with the ureteral anastomosis may require early surgical re-exploration. Postoperative surgical complications include vascular thromboses, wound hematomas, and infection. Nonsurgical cardiovascular, pulmonary, and gastrointestinal postoperative complications are not unusual after kidney transplant; one institution reported a 90-day severe postoperative complication rate of 15%.⁵² High-risk patients with advanced cardiac and pulmonary disease may require further postoperative monitoring in the intensive care setting. In general, postoperative intensive care admissions for kidney transplant recipients are much less common than for liver and kidney-pancreas transplant recipients. One single-center study found a 6% rate of ICU admission following kidney transplant. The mortality rate in kidney transplant patients that required intensive care admission was higher than in nontransplant ICU patients.⁵³

Postoperative pain control is usually provided with synthetic opioid analgesics without active metabolites. Pain after kidney transplant is highly variable; in some patients, pain may be severe and challenging to treat effectively. Renal failure alters the pharmacology of most opioid medications; dose reductions are generally required in renal failure patients. In addition, chronic underlying pain conditions and opioid dependence may impact postoperative pain following kidney transplant; chronic pain conditions occur in 40% to 60% of dialysis patients.⁵⁴ Patient-controlled opioid analgesia is commonly initiated in the postanesthesia care unit and continued for 24 to 48 hours. Regional anesthesia for kidney transplantation is controversial. One report demonstrated effective postoperative analgesia in kidney transplant recipients with epidural analgesia, however concerns for uremic coagulopathy and hypotension have limited its widespread use in kidney transplant patients.⁵⁵ Although transversus abdominis plane block has been advocated for postoperative analgesia in kidney transplant patients, results from randomized controlled trials have been inconsistent.⁵⁶⁻⁵⁸

ORGAN MATCHING AND ALLOCATION

Organ matching for kidney transplantation involves several steps to determine compatibility between donor and recipient. Initially, matching of the major ABO blood group is determined for all donors and recipients. Before the transplant surgery, a crossmatch is performed by mixing recipient blood with donor blood cells. This crossmatch is performed to identify any recipient antibodies that are reactive against donor antigens. Histocompatibility matching is an important part of the matching process, in which the human lymphocyte antigen (HLA) profile of the recipient is determined and compared with the HLA profile of the donor. Organ rejection by the recipient's immune system is mediated by the recognition of mismatched (non-self) HLAs located on the surface of donor cells. Many standard HLAs are compared between potential donors and recipients before transplantation. In general, graft survival rates are worse with HLA-mismatched grafts. Although better immunosuppression has improved the overall survival rates for kidney transplants during the past 3 decades, the graft loss rate for HLA-mismatched kidneys has remained higher than HLA-matched grafts.⁵⁹ For all potential

recipients awaiting a deceased donor, their HLA profile is compared to the donor profile, and an appropriate donor-recipient pairing is made based on the best match. For living donors, HLA matching is performed well in advance of the surgery. The U.S. kidney allocation system implemented in 2014 prioritizes deceased donor transplantation for highly sensitized candidates, a group of candidates that have previously endured prolonged waitlist times before receiving organ offers. One-year analysis of the new kidney allocation system demonstrated a fourfold increase in the transplant rate for highly sensitized candidates with an overall 6-month graft survival rate that matched the years prior.¹¹

ANESTHESIA FOR PATIENTS AFTER KIDNEY TRANSPLANTATION

After successful kidney transplantation, most patients are classified as having National Kidney Foundation stage 2 or 3 CKD with usual GFRs more than 30 mL/min. GFR typically deteriorates by 1.4 to 2.4 mL/min/year in renal transplant recipients.⁶⁰ Posttransplant mortality increases as renal graft function deteriorates. Renal function is followed closely within the first few years after transplant to assess for rejection, which is identified by worsening organ function. In post-kidney transplant patients undergoing nontransplant surgery, renal function should be assessed before surgery. Most patients will be under the care of a nephrologist within the first years of a kidney transplant; assessment of the patient's medical records or renal function tests should be obtained preoperatively. Rejection should be ruled out before nontransplant surgery, as surgery during an episode of rejection can increase morbidity.⁶¹

Although successful kidney transplantation decreases overall cardiovascular risk in ESRD patients, cardiovascular disease is more prevalent in kidney transplant recipients compared to the general population and remains the most common cause of death in kidney transplant patients.⁶² As described previously, cardiovascular disease is involved in the pathogenesis of renal failure and is a consequence of kidney disease as well. Ischemic heart disease, cerebrovascular disease, and peripheral vascular disease significantly affect the survival of kidney transplant patients. Progression of preexisting CAD can occur in the posttransplant patient, as immunosuppression contributes to the development of de novo hyperlipidemia, hypertension, and diabetes. The incidences of hypertension (92%), hyperlipidemia (66%), diabetes (41%), and obesity (38%) are increased in kidney transplant recipients.⁶³ Known CAD in kidney transplant recipients has been documented in 10 centers worldwide and 20% of selected populations, but the prevalence of CAD likely increases in the years following transplant.^{63,64} Because long-term studies on cardiac outcomes following nontransplant surgery in kidney transplant recipients are lacking, there are no specific recommendations for cardiovascular evaluations in kidney transplant recipients. For previous kidney transplant patients undergoing nontransplant surgery, the ACC/AHA guideline for perioperative cardiovascular evaluation for noncardiac surgery should be used to guide preoperative cardiovascular testing.²⁸

Other disease processes related to kidney disease and immunosuppression should be sought. Kidney transplant patients are at increased risk for posttransplant malignancies, anemia, and osteodystrophy. Infection is a constant concern in kidney transplant recipients, because they are at risk for both opportunistic and community-acquired infections. Cytomegalovirus (CMV) infection is the most common infection in kidney transplant patients, and it is rarely acquired by transfusion. CMV-negative blood should be used when transfusions are required in patients who are CMV negative.

Anesthesia for nontransplant surgery can be accomplished safely with general, regional, and local sedation techniques. Most anesthetic drugs are safe in posttransplant patients, assuming the presence of adequate hepatic and renal function.⁶¹ Although preoperative creatinine may be near normal in kidney transplant recipients, GFR in these patients is usually reduced, resulting in prolongation of the activity of drugs cleared by the kidneys. Obviously, drugs that cause nephrotoxicity should be avoided.

Pancreas Transplantation

Surgical treatment for diabetes includes pancreas transplant alone (PTA) and, in patients with diabetes and ESRD, pancreas after kidney transplant (PAK) and simultaneous pancreas-kidney transplant (SPK). Usually, a whole pancreas is transplanted from deceased donors. Less commonly, the distal pancreas is transplanted from a living donor. Islet cell transplant from a cadaveric donor is a new, nonsurgical option offering less effective glycemic control. This involves infusion of β cells into the portal vein, typically done under sedation in an imaging unit.⁶⁵

The first successful pancreas transplant was performed in 1966. Due to improvements in surgical technique, donor-recipient matching, graft surveillance, and immunosuppression, pancreas transplant graft survival has improved and now matches graft survival rates of kidney and liver transplant.⁶⁶ In 2016, the United States reported rates of 90-day graft survival were 92% for PAK, 91% for PTA, and 92% for SPK, all improved from 10 years prior.⁶⁷ Worldwide, pancreas transplant rates increased during the 1990s as outcomes improved. Despite these improvements, the rates of pancreas transplants in the United States peaked in the early 2000s and declined steadily thereafter.⁶⁶ However, in 2016 there was a total of 1013 pancreas transplants in the United States, the majority SPKs. This represented a 7% increase in total pancreas transplants from the year prior, the first yearly increase in more than 10 years. This increase was likely a result of changes made to the U.S. pancreas allocation system that were implemented in 2014.⁶⁷ These changes included creation of a distinct SPK waitlist separate from the kidney waitlist, allowing the pancreas candidate access to the kidney from the same pancreas donor. Additionally, all pancreas transplant candidates are placed on a single waitlist and given equal priority to pancreas donors, regardless of the type of pancreas transplant they are to receive.⁶⁶ Despite this increase in total transplants, the U.S. pancreas transplant waitlist continues to increase with 957 new candidates added in 2016.⁶⁷

INDICATIONS FOR PANCREAS AND KIDNEY-PANCREAS TRANSPLANTATION

Pancreas transplantation provides patients with insulin-dependent diabetes mellitus a permanent source of endogenous insulin, thus restoring normoglycemia. SPK and PAK transplants are indicated in patients with diabetes and ESRD who are deemed appropriate candidates for kidney transplantation or who have already undergone kidney transplantation. PTA is indicated in patients with diabetes without indications for kidney transplantation and who have a history of severe frequent metabolic complications, including hypoglycemia unawareness, or who have a history of problems maintaining insulin therapy that result in intractable diabetic complications.^{65,68} Most patients who undergo pancreas transplant have type 1 diabetes mellitus. Rare indications for pancreas transplant include select cases of type 2 diabetes mellitus, chronic pancreatitis that has developed endocrine deficiency, cystic fibrosis with endocrine deficiency, and prior total pancreatectomy.

Previously pancreas transplant was reserved for younger patients, traditionally under age 40. For patients with diabetes and ESRD, older data found that SPK patients younger than 50 years had better reported survival rates than older patients.⁶⁹ Recently, pancreas transplant has been considered for candidates over age 50, corresponding with population trends toward more aging diabetic patients. Recent single-center studies have demonstrated similar results in pancreas transplant recipients over age 50 compared to younger patients.^{70,71} These results suggest a future role for pancreas transplant expanded to older populations, a trend that has been observed in other solid organ transplant populations.⁶⁶ Regardless of patient age, survival benefits in SPK are likely due to long-term decrease in CAD complications.⁷²

For patients with normal renal function who undergo PTA, long-term survival is the same as in patients receiving chronic insulin therapy.⁷³ Pancreas transplant appears to have a favorable effect on the progression of retinopathy as well. The progression of retinopathy is decreased or reversed in a significant percentage of PTA patients compared to diabetic patients treated with conventional insulin therapy.⁷⁴

PATHOPHYSIOLOGY OF PANCREATIC INSUFFICIENCY

Type 1 diabetes mellitus occurs secondary to destruction of pancreatic islet cells resulting in a permanent functional loss of the endogenous production of insulin, necessitating life-long exogenous insulin therapy. The underlying cause of type 1 diabetes mellitus remains unknown. Type 2 diabetes mellitus results from peripheral resistance to the effects of insulin. Both diseases produce chronic increases of blood glucose concentrations resulting in the multiorgan manifestations of diabetes.

The chronic complications of diabetes that have the greatest effect on patient morbidity and survival are those that affect the cardiovascular system. CAD, cerebrovascular disease, and peripheral vascular disease occur in patients with diabetes owing to acceleration of atherosclerosis. Both macrovascular and microvascular disease occurs. Patients with diabetes develop CAD earlier, are more likely to have

atypical symptoms, and have a higher mortality rate from myocardial infarction than nondiabetics.⁷⁵ Peripheral and autonomic neuropathies develop in diabetes, resulting in gastroparesis, lower extremity paresthesia, ulcerations, orthostatic hypotension, and labile heart rate and arterial blood pressure. Patients with diabetes have a high cumulative prevalence of blindness (16%), renal failure (22%), lower extremity amputation (12%), myocardial infarction (21%), and stroke (10%).⁷⁶

Acute complications of type 1 diabetes mellitus typically involve conditions associated with severe hyperglycemia, such as diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic coma. Hypoglycemia is a direct result of exogenous insulin administration. Patients with type 1 diabetes are prone to large fluctuations in blood glucose levels. Hypoglycemic episodes contribute to acute morbidity and mortality in diabetic patients. Hypoglycemia unawareness in particular can have a marked impact on quality of life and is a frequent indication for pancreas transplant.

ANESTHESIA FOR PANCREAS TRANSPLANTATION: PREOPERATIVE EVALUATION

The preoperative evaluation for the patient undergoing pancreas transplantation involves an assessment of all of the potential acute and chronic complications of type 1 diabetes. Pancreas transplant centers pursue a comprehensive, multidisciplinary evaluation and selection process before listing candidates. The evaluation should address the organ systems most affected by long-standing diabetes, including the cardiovascular, renal, and neurologic systems. Assessment for the presence and severity of CAD should be undertaken in all candidates, including noninvasive ischemia testing, evaluation of ventricular function, and coronary angiography in select patients. Previously, patients considered for pancreas transplantation were younger than 50 years and had a lower risk for the cardiac and vascular sequelae of diabetes. Older patients are now considered for pancreas transplantation, but have a significantly higher risk for CAD and vascular disease.⁷⁷ Strategies to reduce cardiac complications, such as maintenance of β -adrenergic blockade and continuation of drugs that decrease blood lipid concentrations during the perioperative period, should be applied when appropriate.²⁸

In most cases, pancreas transplantation involves a deceased-donor organ with a 24-hour maximum cold ischemia time; therefore, pancreas transplantation is considered an urgent procedure. Preoperative evaluation by the anesthesiologist should focus on any acute changes in the patient's medical status, especially those involving acute diabetic complications such as ketoacidosis and hypoglycemia. Blood glucose measurements should be assessed closely before surgery and recent insulin administration should be noted. Most patients will have a preoperative variable-rate intravenous infusion of insulin with maintenance glucose during a period of fasting. Evaluation of renal function in all candidates is important before surgery. Most patients with diabetes listed for pancreas transplant have ESRD as well and will undergo SPK. A full evaluation of electrolytes, including creatinine and potassium, should

be obtained before surgery. Serial trends in heart rates and arterial blood pressures in hospitalized patients should be assessed, as most patients will have a history of hypertension requiring multiple medications, especially patients with renal failure. Preoperative assessment of intravascular volume status is especially important in patients with ESRD on hemodialysis. Finally, a directed physical examination focusing on the airway and cardiopulmonary system should be performed. The incidence of difficult tracheal intubations in patients with long-standing diabetes was thought to be more frequent because of anatomic changes of the upper airway; however recent data does not demonstrate this.^{78,79} Nevertheless, attention to anatomic signs of a potentially difficult airway is important in patients with diabetes, especially those with cervical arthritis and significant obesity.

ANESTHESIA FOR PANCREAS TRANSPLANTATION: INTRAOPERATIVE MANAGEMENT

General anesthesia with endotracheal intubation is performed for all types of pancreas transplantation except islet cell transplant, which is usually done under sedation in an interventional radiology setting. The surgical procedure is typically prolonged, and an adequate depth of anesthesia and muscle relaxation is required for optimal surgical conditions. Diabetic patients and those with ESRD have a high likelihood of gastropathy and may have an increased risk for aspiration of gastric contents. Administration of an oral nonparticulate antacid preoperatively should be considered. A rapid-sequence induction of anesthesia is the safest approach to securing the airway. Patients with diabetes, ESRD, cardiovascular disease, and autonomic neuropathy may be prone to wide fluctuations in heart rate and arterial blood pressure during induction and intubation. Vital signs should be closely monitored and maintenance of hemodynamic stability should be a primary anesthetic goal, especially during and immediately following anesthetic induction. Invasive monitoring is standard for pancreas transplantation. Arterial monitoring allows for beat-to-beat arterial blood pressure measurements, as well as access for analysis of arterial blood gases and blood glucose monitoring. Central venous access may be indicated for central administration of vasoactive infusions and immunosuppression drugs. Large-bore venous access is essential, and a temporary dialysis catheter may be useful for both resuscitation and postoperative dialysis if preexisting dialysis access is absent.

Central venous pressure monitoring is used in some centers; however, the usefulness of this practice has been questioned, as central venous pressure might not be a reliable indicator of intravascular fluid responsiveness.⁴⁵ Arterial line placement before induction of anesthesia may be considered, especially in patients with severe hypertension or CAD. Anesthesia is typically maintained with a balanced technique using volatile anesthetics, opioids, and muscle relaxants. In patients with renal failure, medications should be chosen that are not dependent on the kidneys for elimination. All the caveats for the anesthetic management of patients undergoing kidney transplantation should be applied for patients undergoing SPK.

A midline surgical incision is made for both pancreas and kidney-pancreas transplant surgeries. Extensive retraction necessitates adequate muscle relaxation. Prolonged exposure of the abdominal viscera results in significant third-space losses; adequate volume expansion with crystalloid or colloids is often required. The pancreas graft is usually placed in the iliac fossa. The arterial vascular supply to the pancreas graft is usually provided by an anastomosis to the iliac artery. Usually the venous outflow from the pancreas is delivered to the iliac vein, which is associated with a lower rate of venous thrombosis. Alternatively, venous outflow may be directed to the native portal vein, which is the physiologically normal pattern of pancreatic venous efflux. There appears to be no significant advantage to portal venous drainage over systemic venous drainage for pancreas transplantation.⁷²

Pancreatic exocrine drainage can be delivered to either the bladder or the intestine (Fig. 60.7). Although enteric pancreatic drainage is physiologically normal, this method is associated with surgical complications that can result in graft dysfunction, thrombosis, and early rejection. Exocrine drainage to the bladder allows for measurement of urinary amylase levels, which can be used to diagnose early rejection episodes before blood glucose levels are affected. Exocrine bladder drainage is associated with urologic complications and metabolic acidosis. Currently, most pancreas transplants utilize enteric drainage as there is no difference in graft or patient survival compared to bladder drainage.⁸⁰

Prior to completion of the vascular anastomoses during pancreas transplantation, blood glucose levels should be assessed at least hourly as levels frequently fluctuate in brittle diabetic patients. Blood glucose should be maintained at less than 200 mg/dL, using intravenous insulin and dextrose infusions if necessary. Sliding scale insulin infusion protocols may be applied. Dextrose prevents the development of ketoacidosis during the early stages of the procedure. However, some centers stop insulin infusion when the pancreas comes out of ice, re-starting after reperfusion only if hyperglycemia is observed. Before unclamping of the vascular anastomoses, adequate volume resuscitation should be initiated. Adequate cardiac preload and normal arterial blood pressures should be the hemodynamic goals before unclamping.

After unclamping of the vascular connections, heavy bleeding can occur. This is typically from retroperitoneal and mesocolonic collaterals that are missed during cold dissection on the back table. Maintenance of adequate graft perfusion pressure is critical. Hypotension should be corrected rapidly, and intravascular volume status should be optimized. If hypotension occurs because of myocardial dysfunction, intracardiac pressure monitoring or transesophageal echocardiography can assist in the diagnosis and may help to guide therapy. Blood transfusions, colloids, and vasoactive medications may be required for the treatment of hypotension after reperfusion of the pancreatic graft. Therapy should also be guided by frequent arterial blood gas analyses with assessment of electrolytes and hemoglobin.

One of the most important intraoperative care points for pancreas transplantation is the management of blood glucose following pancreas reperfusion. After unclamping, the pancreas may release insulin into the circulation within several minutes. Blood glucose should be measured

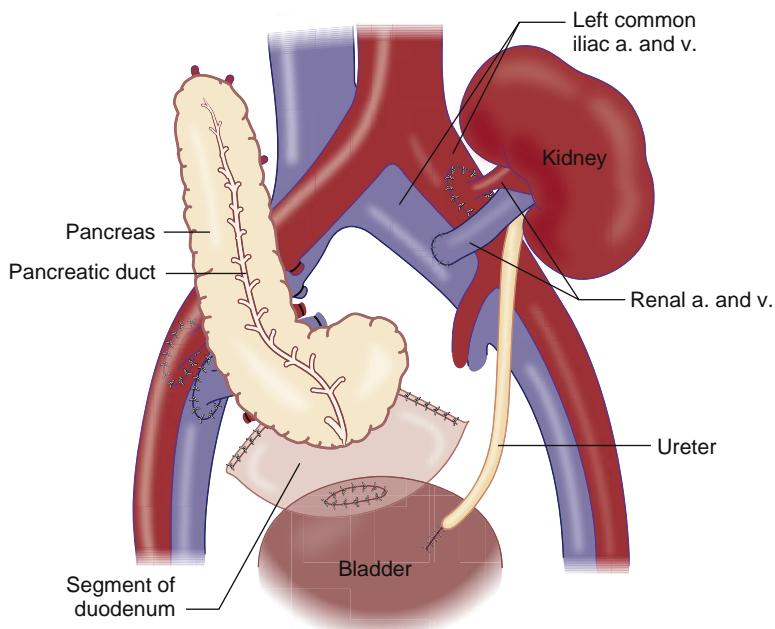


Fig. 60.7 Pancreas transplantation. Bladder drainage is through a pancreatic duodenocystostomy. A renal transplant is shown with the common iliac vessels used for vascular anastomoses. (Modified from Moody FG, ed. *Surgical Treatment of Digestive Diseases*. 2nd ed. St Louis: Mosby-Yearbook; 1990.)

approximately every 30 minutes for the remainder of the procedure. After successful transplantation, insulin requirements rapidly decline, and patients may be at risk for hypoglycemia. Delayed graft function can be identified by the presence of hyperglycemia. In this event, insulin infusion should be titrated to maintain blood glucose levels less than 200 mg/dL.⁷⁶

ANESTHETIC MANAGEMENT OF PANCREAS TRANSPLANTATION: POSTOPERATIVE MANAGEMENT

After the completion of surgery, full reversal of neuromuscular blockade, hemodynamic stability, normothermia, and the ability of the patient to protect the airway will facilitate tracheal extubation. Pancreas transplant patients should be monitored closely in the postanesthesia care unit and ICU. Regular blood glucose measurements should be continued in the postoperative period to avoid hypoglycemia. Electrolytes, complete blood count, and analysis of arterial blood gas should be obtained immediately postoperatively, because acid-base disturbances, anemia, and electrolyte imbalances are common. Euvolemia should be maintained. Depending on the patient's age and underlying risk for CAD, serial troponins and ECG may be assessed for the presence of myocardial ischemia or infarction, because cardiac symptoms may be lacking in this population. Postoperative pain can be severe, given the extensive surgical wound and duration of surgery. Postoperative pain usually is managed with opioids in the perioperative period with transition to patient-controlled analgesia in the early postoperative period. Epidural analgesia may be appropriate for pancreas transplant recipients, although the risks of hypotension,

dilutional coagulopathy, and spinal cord hypoperfusion in patients who may have severe microvascular disease have not been quantified. For SPK, the usual postoperative strategies for kidney transplant patients including close monitoring of urine output should be applied.

Surgical complications occur in 7% to 9% of all pancreas transplants and usually require reoperation. Technical complications are associated with the potential for graft loss and patient morbidity.⁸¹ Unlike kidney transplantation, technical complications are the most common cause of pancreas transplant graft failure in the first year after surgery. Graft thrombosis is the most important early complication and requires emergent surgical exploration. Intraabdominal bleeding can occur secondary to coagulopathy induced by anticoagulation for the treatment of graft thrombosis. Late complications include bladder or enteric leaks, intraabdominal sepsis, and rejection. Rejection is the most common cause of long-term graft loss after 1 year and occurs in 15% to 21% of pancreas transplant recipients within 1 year of surgery.⁸²

ORGAN MATCHING AND ALLOCATION

The organ matching process for pancreas transplantation is similar to that for kidney transplant organ matching. Blood group and HLA matching are initially performed to match the donor and recipient, followed by a crossmatch at the time of surgery. Most organs allocated for pancreas transplantation are for diabetic recipients younger than 40 years. However, over the past decade, the average transplant recipient's age has increased because of the allocation of more organs for patients with type 2 diabetes.⁷⁷ In 2016, the number of pancreas transplants performed in patients

over age 50 increased to 240 from 185 the year prior, corresponding with an increase in type 2 diabetics undergoing pancreas transplants.⁶⁷

ANESTHESIA FOR PATIENTS AFTER PANCREAS TRANSPLANTATION

After successful pancreas transplantation, long-term normoglycemia is expected. For patients with a history of previous pancreas transplant presenting for surgery, a comprehensive posttransplant history of any episodes of surgical complications and episodes of rejection should be obtained. Blood glucose concentrations should be measured on the day of surgery. A detailed history and review of medical records focusing on CAD, renal disease, and vascular disease is critical. Although the end-organ progression of diabetes is favorably impacted by pancreas transplant, pancreas transplant patients have a high prevalence of these conditions compared to the general population. Disease progression can occur despite successful pancreas transplantation. Therefore, the preoperative cardiac evaluation for the post-pancreas transplant patient undergoing surgery should be guided by ACC/AHA Guideline.²⁸

Liver Transplantation

In 1963, shortly after the effectiveness of azathioprine and prednisone was established for renal transplantation, Dr. Thomas Starzl performed the first human liver transplant.⁸³ The recipient, a 3-year-old child with biliary atresia, died in the operating room from massive hemorrhage caused by venous collaterals and uncontrollable coagulopathy. Four years later, Starzl performed the first successful transplant in an 18-month-old infant with hepatocellular carcinoma. The advent of cyclosporine in 1979, followed by the 1983 pronouncement of the National Institutes of Health Consensus Conference that liver transplantation was no longer experimental, ushered in the era of liver transplantation. Over the ensuing decades, liver transplantation centers were established around the world, and the field matured following continued improvements in surgical technique, immunosuppression, and the management of coagulopathy and infections.

The number of disciplines that have contributed to the advances in liver transplantation illustrates the team approach involved in the care of the liver transplant recipient. Hepatologists, surgeons, nephrologists, specialists in critical care medicine and infectious disease, anesthesiologists, pediatricians, radiologists, and pathologists have important roles. Key team members extend beyond physicians and include transplant coordinators, nurses, blood bank personnel, and procurement organizations.

Liver transplantation is unique among abdominal organ transplants in that a dedicated team is typically involved because of the unique challenges encountered during liver transplant surgery. The United Network of Organ Sharing (UNOS), which manages the U.S. organ transplant system under contract with the U.S. Department of Health and Human Services, recognizes the important role of anesthesiologists in the perioperative care of liver transplant candidates. In 2011, UNOS instituted a

requirement that U.S. liver transplant programs designate a Director of Liver Transplant Anesthesia who meets qualifications based on experience and training. These qualifications parallel similar requirements for the transplant surgeon and physician (hepatologist). In addition, UNOS delineated the clinical responsibilities of the Director of Liver Transplant Anesthesia, which include preoperative assessment of transplant candidates, participation in candidate selection, intraoperative management, postoperative visits, and participation in mortality and morbidity conferences.⁸⁴ Lastly, the director is expected to maintain current knowledge in the field of transplant anesthesia by participating in continuing medical education activities related to transplantation.

INDICATIONS FOR LIVER TRANSPLANTATION

Liver transplantation is the only definitive treatment for decompensated cirrhosis secondary to hepatitis C virus (HCV) and alcoholic liver disease, unresectable primary hepatic malignancies, acute liver failure (ALF), and metabolic disease including non-alcoholic fatty liver disease (NAFLD). Of these indications, the category other, which includes patients with NAFLD, accounted for nearly a third (31%) of adult liver transplants performed in the United States in 2016, followed by alcoholic liver disease (24%), HCV (18%), hepatocellular carcinoma (14%), cholestatic disease (9%), and ALF (3%) (Fig. 60.8).

Chronic liver disease and cirrhosis is the fourth leading cause of death in the United States for individuals aged 45 to 64 years, accounting for 4.2% of deaths in this age group. It is surpassed only by cancer, heart disease, and accidents (unintentional injury). Among all age groups, liver disease accounted for more than 29,000 deaths in 2015, making it the 12th leading cause of death.⁸⁵

TRENDS IN LIVER TRANSPLANTATION

The number of adult liver transplants in the United States increased to over 7800 in 2016, a 10% increase from the prior year and a doubling since 1998. European transplant centers perform a similar number of transplants per year (approximately 7000 in 2013) for similar indications.⁸⁶ The increase in transplants is attributable to an increased number of deceased donors. In 2016, graft survival continued to improve, with a 1-year failure rate of 10%. Five-year patient survival reported in 2016 was 86% in the United States, which represents an improvement from 74% reported in 2015.^{87,88}

Advances in the treatment of chronic liver disease, particularly antiviral therapy, led to a declining number of transplants for hepatitis C, which as of 2016 was no longer the most common indication for liver transplantation.⁸⁷ Over the past decade, the proportion of transplants performed for obesity-related fatty liver (NAFLD) is increasing. With the sharp reduction in transplants for HCV, NAFLD has overtaken HCV as the most frequent indication for transplantation. However, despite these advances, when life-threatening complications of liver failure such as encephalopathy, ascites, gastrointestinal bleeding, or uremia develop, survival is significantly improved by liver transplantation (90% 1-year survival) compared with

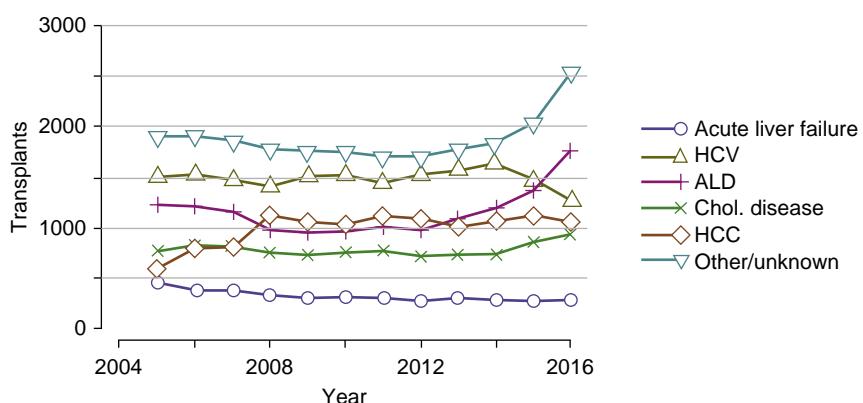


Fig. 60.8 U.S. total liver transplants by diagnosis, 2004–2016. ALD, Alcoholic liver disease; Chol disease, cholestatic disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus. (From Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2016 Annual Data Report: Liver. *Am J Transplant*. 2018;18:172–253.)

TABLE 60.1 Prognosis: Complications of Cirrhosis

Event	Survival
Variceal bleeding	65%–70% at 1 year*
Ascites	48%–60% at 1 year†
Hepatorenal syndrome	50% at 3 months‡
Encephalopathy (grade 2/3)	40%–50% at 1 year§

Survival after complications is poor compared with 90% patient survival at 1 year after liver transplantation.

*Thomopoulos K, Theocaris G, Mimidis K, et al. Improved survival of patients presenting with acute variceal bleeding. Prognostic indicators of short- and long-term mortality. *Dig Liver Dis*. 2006;38:899–904.

†Fernández J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology*. 2007;133:818–824.

‡Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology*. 2005;41:1282–1289.

§Stewart C, Malinchoc M, Kim W, et al. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. *Liver Transplant*. 2007;13:1366–1371.

medical therapy (Table 60.1). Referral for liver transplantation is appropriate in the presence of an index complication of cirrhosis.

During the past decade, the number of patients (adult and pediatric) living with a functioning liver transplant more than doubled, from 30,000 in 2001 to nearly 80,000 in 2015.^{88,89}

The median time to transplant in the United States for the period ending in 2015 was 11.3 months, the shortest waiting time in recent history.⁸⁷

Over the past decade, the proportion of recipients aged 65 years or older continued to increase. This age group received over 20% of liver transplants performed in the United States in 2015.⁸⁷

Despite an increase in organs available, the number of waitlisted candidates has exceeded 13,000 for each of the last 3 years. Waitlist mortality remains a concern with 10% to 12% mortality over the same period.⁸⁷ Responses to these concerns have resulted in the use of expanded-criteria donors, including grafts donated after cardiac death, which increased from less than 2% of liver transplants in 2001 to 6% in 2011, where it remained in 2015.⁸⁷ Living donation has decreased over the past 10 years, particularly for adult

recipients. In 2001, more than 400 living donor grafts were transplanted into adult recipients. In 2015, fewer than 300 adults received living donor grafts. This change highlights the concern over postoperative complications in living donors, particularly those providing a larger liver mass, as is the case with right lobe donation. Two living donor deaths were reported in 2010, further illustrating the risk to living donors.

The number of pediatric liver transplants in the United States has been stable at 500 to 600 per year over the past several years (2002–2015). During the same period, approximately 10% to 15% of pediatric recipients in the United States received grafts from living donors, down from 20% to 25% in the prior decade.⁸⁹ The most common indication for transplant in pediatric recipients is cholestatic disease (43%), followed by metabolic disease (15%), ALF (4%), and hepatoblastoma (2%).⁸⁷ The European Liver Transplant Registry reports similar numbers of pediatric recipients, approximately 10% of the total number of liver recipients.⁹⁰

PATHOPHYSIOLOGY AND EVALUATION FOR LISTING

Cirrhosis is the end product of chronic parenchymal inflammation and necrosis, which results in fibrosis and disruption of hepatic architecture. Resistance to blood flow leads to portal hypertension and the formation of vascular shunts between portal and systemic veins.⁹¹ When the pressure gradient between the portal and hepatic veins exceeds 10 to 12 mm Hg, portal hypertension is severe, and complications such as ascites, esophageal variceal bleeding, encephalopathy, and hepatorenal syndrome (HRS) occur. Decompensated cirrhosis affects nearly every other organ system.⁹² The preoperative assessment of liver transplant candidates requires a knowledge of the pathophysiologic changes associated with decompensated cirrhosis.

Cardiovascular Complications

Hyperdynamic circulation—characterized by a high cardiac output, low arterial blood pressure, and low systemic vascular resistance—is the hallmark of end-stage liver disease. Patients appear well perfused despite systolic arterial pressures less than 100 mm Hg. Pulmonary arterial pressures may be mildly elevated because of increased flow;

however, the pulmonary vascular resistance (PVR) is usually within the normal range. These patients have an elevated intravascular volume that is sequestered into a dilated splanchnic vascular bed. The effective circulating volume is typically reduced.

Hyperdynamic circulation is the result of portal hypertension-induced production of vasodilators such as natriuretic peptides, vasoactive intestinal peptide, endotoxin, glucagon, and particularly nitric oxide.⁹³ Elevated production of nitric oxide has been observed to precede the formation of the hyperdynamic circulation in cirrhosis. The overproduction of vasodilators is responsible for reduced circulatory responsiveness to sympathetic stimulation.⁹⁴ Clinically, this frequently results in a need for increased doses of vasopressors.

In addition, patients with cirrhosis can have other cardiac functional abnormalities that are not immediately apparent in the baseline state. These abnormalities define a condition termed *cirrhotic cardiomyopathy* and include systolic and diastolic dysfunction, cardiac resistance to β -adrenergic stimulation, and electrophysiologic abnormalities. Systolic incompetence is revealed by physiologic or pharmacologic stress and is manifested by an inability to increase cardiac output in response to exercise, and an inability to increase ejection fraction despite an increase in end-diastolic volume. The severity of cardiac dysfunction seems to be correlated directly with the severity of liver disease.⁹⁵ Diastolic dysfunction has been described in patients with cirrhosis as well, on the basis of diagnostic echocardiographic findings of abnormalities in transmural flow during diastole. These abnormalities consist of a decrement or reversal of the E/A wave ratio and prolongation of E wave deceleration time, reflecting ventricular resistance to diastolic filling. Diastolic dysfunction manifests as sensitivity to changes in cardiac filling and results in vulnerability to heart failure.

Autonomic dysfunction is present in a significant proportion of cirrhotic patients. It presents as chronotropic and hemodynamic incompetence in response to hemodynamic challenges. Prolonged QTc interval is also observed in patients with cirrhosis, and care should be taken when treating these patients with drugs known to prolong the QT interval.⁹⁶

Risk factors for CAD in patients with cirrhosis are similar to those of other patient populations: hypertension, dyslipidemia, age, gender, and obesity. However, NAFLD has been recognized as an increasingly important cause for transplantation and carries with it the risks of obesity, diabetes, and chronic inflammatory state. The optimal test for identifying cirrhotic patients with significant CAD is unclear. Because many of these patients cannot exercise, pharmacologic stress testing is most commonly used. Unfortunately, studies investigating the predictive value of noninvasive functional testing, particularly DSE, have generally shown poor sensitivity and varying negative predictive value (75%-89%).⁹⁷ Thus, among liver transplantation candidates, consideration should be given to proceeding with coronary angiography if the patient is judged to have a high likelihood of CAD.⁹⁸ For less complex surgeries, however, this may not be warranted. There is evidence that patients with treated CAD have posttransplant survival similar to patients without angiographic evidence of CAD.⁹⁹

Pulmonary Complications

As many as 50% to 70% of patients with chronic liver disease complain of shortness of breath.¹⁰⁰ The differential diagnosis includes ventilation-perfusion abnormalities associated with underlying obstructive airways disease, fluid retention, pleural effusion, and decreased lung capacities secondary to large volume ascites. α -1 antitrypsin deficiency has both lung and liver manifestations, as does cystic fibrosis. In addition, there are two types of vascular abnormalities unique to the setting of portal hypertension, and they have significant morbidity and mortality. These abnormalities, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN), are unique entities that have discrete implications on liver transplant candidacy.

HPS is present in up to 20% of patients who present for liver transplantation.¹⁰¹ The diagnostic criteria for HPS include portal hypertension, PaO_2 less than 70 mm Hg on room air (or alveolar-arterial oxygen gradient greater than 15 mm Hg), and evidence of intrapulmonary vascular dilation (IPVD).^{102,103} Demonstration of IPVD can be made by contrast-enhanced echocardiography or by perfusion lung scanning using technetium-labeled macroaggregated albumin. In the absence of HPS, microbubbles and albumin macroaggregates injected into the venous circulation are trapped by the pulmonary capillary bed. The delayed (more than three cardiac cycles) appearance of microbubbles in the left atrium (on echocardiography) or increased (>5%) extrapulmonary uptake of technetium-labeled macroaggregated albumin suggests the presence of IPVD, which results in a massive increase in pulmonary capillary diameter, from between 8 to 15 μm and 50 to 500 μm . This increase, together with the usually hyperdynamic circulation of the cirrhotic patient, allows insufficient time for oxygen diffusion through the entire stream of capillary blood. As a result, the central stream of poorly oxygenated blood is functionally shunted. This lesion is typically correctable with the administration of oxygen. Because IPVDs predominate in the bases of the lungs, standing worsens hypoxemia compared with the supine position (orthodeoxia).

The natural history of HPS is usually one of progressive hypoxemia. Liver transplantation can be expected to correct hypoxemia in greater than 85% of patients, although it may take up to 1 year to do so.¹⁰⁴ In patients with HPS, survival with transplantation is considerably more frequent than without transplantation. Previously, $\text{PaO}_2 \leq 50$ mm Hg was considered a predictor of increased mortality with or without transplantation. However, in the largest single-center series of liver transplantation for HPS, the overall 5-year survival was 76%, comparable to transplantation in patients without HPS.¹⁰⁵ These findings suggest that timely transplantation in patients with HPS results in positive outcomes. Accordingly, allocation exception points have been assigned to patients with HPS and room air $\text{PaO}_2 < 60$ mm Hg.¹⁰⁶

PPHTN is defined as pulmonary hypertension in the presence of portal hypertension in a patient without other predisposing factors. The European Respiratory Society Task Force on Hepatopulmonary Disease diagnostic criteria are: (1) clinical evidence of portal hypertension with or without hepatic disease; (2) mean PA pressure of 25 mm Hg at rest or 30 mm Hg during exercise; (3) mean PA occlusion pressure less than 15 mm Hg or transpulmonary gradient

TABLE 60.2 Right Heart Catheterization Data From Four Representative Patients With Cirrhosis and Similar Elevations in Mean Pulmonary Artery Pressure

Patient	Mean PA Pressure (mm Hg)	Pulmonary Capillary Wedge Pressure (mm Hg)	Cardiac Output (L/m)	Pulmonary Vascular Resistance (dyn s cm ⁻⁵)	Diagnosis
1	35	15	5	320	Primary pulmonary hypertension
2	35	15	10	160	Hyperdynamic circulation
3	35	25	5	160	Fluid overload
4	35	25	10	80	Fluid overload in a patient w/ hyperdynamic circulation

Note that only the first patient has primary pulmonary hypertension, as evidenced by elevated pulmonary vascular resistance. PA, Pulmonary artery.

(mean PA pressure minus wedge pressure) greater than 12 mm Hg; and (4) PVR greater than 240 dyn·s·cm⁻⁵ or 3 Wood Units.¹⁰⁷

The requirement for calculation of the PVR is a reflection of the fact that many patients with cirrhosis have mildly elevated mean pulmonary arterial pressure based simply on an elevated cardiac output (Table 60.2). Mild, moderate, and severe PPHTN are defined by mean PA pressure less than 35 mm Hg, 35 to 50 mm Hg, and greater than 50 mm Hg, respectively.

The prevalence of PPHTN is 2% in a population of patients with known portal hypertension,¹⁰⁸ as compared with 0.13% in an unselected population.¹⁰⁹ The prevalence is 4% to 6% among liver transplant candidates.¹¹⁰ The occurrence of PPHTN is unrelated to the severity of the underlying liver disease. Similar to HPS, the symptoms of PPHTN are nonspecific, commonly consisting of dyspnea, generalized weakness, and decreased exercise tolerance.

The single best screening study for PPHTN is two-dimensional transthoracic echocardiography, which estimates right ventricular systolic pressure using the velocity of the tricuspid regurgitant jet. In the absence of pulmonary valvular stenosis, right ventricular systolic pressure is a good estimate of pulmonary arterial systolic pressure. Transthoracic echocardiography screening has a sensitivity of 97% and a specificity of 77% in diagnosing moderate to severe PPHTN in patients undergoing pretransplantation workup.¹¹¹ Right-sided cardiac catheterization is necessary, however, to confirm elevated pressures and to measure PVR.

Moderate and severe PPHTN are associated with increased mortality during liver transplantation. In a multicenter study of 36 patients with PPHTN who underwent liver transplantation, more than one-third of the patients died during the hospitalization (within 3 weeks of surgery). Nonsurvivors (12 of 13 patients) had mean PA pressures greater than 35 mm Hg.¹¹² In addition to elevated mortality, the effect of successful liver transplantation on the natural course of PPHTN is unpredictable. Some patients experience a resolution with transplant, some continue to require medical therapy, and in some cases PPHTN worsens. This suggests that patients with moderate or severe PPHTN should undergo treatment for PPHTN before liver transplantation.

Vasodilator therapy consists of prostaglandins (epoprostenol), phosphodiesterase inhibitors (sildenafil), and endothelin antagonists (bosentan). Calcium channel blockers,

often used in noncirrhotic patients with pulmonary hypertension, are contraindicated in patients with cirrhosis because the associated mesenteric vasodilation worsens portal hypertension. Patients who respond to treatment sufficiently to reduce their mean PA pressure below 35 mm Hg and PVR below 400 dyn·s·cm⁻⁵ should be considered suitable transplant candidates.^{112,113}

Renal Dysfunction

Renal dysfunction in patients with cirrhosis is the result of renal hypoperfusion and avid retention of sodium. HRS is a prerenal abnormality caused by circulatory derangements of advanced cirrhosis. It is considered a functional disorder, based on successful transplantation of kidneys from patients with HRS.¹¹⁴ Renal function is an important risk factor for mortality, a fact that is emphasized by its presence as one of only three variables used in calculating the Model for End-Stage Liver Disease (MELD) score.

In addition to HRS, patients with cirrhosis are also at risk for other causes of renal dysfunction, such as parenchymal renal disease, sepsis, nephrotoxicity, and hypovolemia. HRS is a diagnosis of exclusion, and other treatable causes must be ruled out. HRS accounts for only about one-fourth of the cases of acute kidney injury in hospitalized cirrhotic patients.¹¹⁵ In patients with cirrhosis and ascites, the incidence of HRS is nearly 40% at 5 years.¹¹⁶

HRS is caused by the local production of vasodilators, particularly nitric oxide, in patients with portal hypertension. Splanchnic vasodilation leads to a decrease in the effective circulating blood volume and a decrease in arterial blood pressure, which activates the sympathetic, renin-angiotensin-aldosterone, and vasopressin systems. The net result is a severe reduction in renal perfusion and glomerular filtration.

Type I HRS is characterized by rapidly progressive renal failure and a doubling of serum creatinine over 2 weeks after a precipitating cause such as spontaneous bacterial peritonitis, sepsis, gastrointestinal bleeding, or surgical stress. Patients with type I HRS have a median survival of 2 to 4 weeks without therapy.^{117,118} Patients with type II HRS have a median survival of about 6 months.¹¹⁹

Although renal vasoconstriction is the proximate cause of HRS, therapy aimed at directly increasing renal perfusion by the use of prostaglandins, dopamine agonists, or endothelin antagonists has not proven to be successful. Vasoconstrictor therapy targeting the underlying splanchnic vasodilation is more effective.¹²⁰

These therapies include arginine vasopressin, somatostatin, and α -agonists such as norepinephrine and midodrine, combined with volume expansion. Terlipressin, the most studied vasopressor for HRS, is in phase 3 trials in the United States.¹²¹⁻¹²³

Placement of a transjugular intrahepatic portosystemic shunt (TIPS) lowers portal pressures and can decompress the splanchnic circulation. Pilot studies have shown that a TIPS is capable of reversing both types of HRS, but because of extensive exclusionary criteria in trials and the risk of worsening hepatic encephalopathy (HE), a TIPS might not be suitable for all patients with HRS.¹²⁴

Liver transplantation is the definitive therapy for HRS. For patients with HRS who are transplant candidates, renal replacement therapy is the typical bridge to transplantation. Although renal recovery is anticipated, 35% of patients with pretransplant HRS will continue to require support in the immediate postoperative period, compared with 5% of patients without pretransplant HRS.¹²⁵ During the First International Liver Transplantation Society Expert Panel Consensus on Renal Insufficiency in Liver Transplantation, it was recommended that patients who received dialysis at least twice weekly for more than 6 weeks before liver transplantation be considered for combined liver-kidney transplantation.¹²⁶

Hepatic Encephalopathy

HE is a serious, albeit reversible neuropsychiatric complication that is a feature of both chronic and acute liver disease. Manifestations range from subtle, subclinical abnormalities to overt neurologic and behavioral derangements that are readily apparent at the bedside.

HE has been attributed to hyperammonemia, but the severity of HE does not necessarily correlate with ammonia levels. A number of other factors and mechanisms also contribute to HE, including other gut-derived neurotoxins, γ -aminobutyric acid (GABA) and other endogenous GABA-receptor agonists, oxidative stress, inflammatory mediators, hyponatremia, and abnormal serotonin and histamine neurotransmission.^{127,128}

The initial step in evaluating the patient with liver disease who presents with encephalopathy is to rule out causes other than HE. The differential diagnosis includes other metabolic causes such as uremia, sepsis, glucose and electrolyte abnormalities, and endocrinopathies. Structural and vascular central nervous system lesions or infections should also be considered. Because cirrhotic patients are exquisitely sensitive to sedative medications and have impaired hepatic (and often renal) metabolism, a careful search for possible drug-related encephalopathy should be undertaken. Once other potential causes have been eliminated, the next step should be a systematic search for an underlying cause or precipitating factor, such as infections (e.g., spontaneous bacterial peritonitis, sepsis) or gastrointestinal bleeding.

Therapy to reduce ammonia levels consists of the nonabsorbable disaccharide lactulose and nonabsorbable antibiotics such as neomycin, metronidazole, and rifaximin. Nonabsorbable antibiotics appear to be equally effective to nonabsorbable disaccharides but concerns about toxicity associated with long-term administration limit their use.

Ascites

Ascites is the most common complication of cirrhosis leading to hospitalization.¹²⁹ Patients who have ascites should be referred for liver transplantation evaluation in the absence of contraindications. Nonhepatic causes account for 15% of ascites and include malignancy, cardiac failure, renal disease, pancreatitis, and tuberculosis. Paracentesis is an important aid in diagnosis.¹³⁰ A serum-ascites albumin gradient greater than 1.1 mg/dL indicates portal hypertension with 97% accuracy.¹³¹ Rapid correction of hyponatremia is undesirable because patients with cirrhosis are at risk for central pontine myelinolysis, a potentially devastating neurologic complication. Observations in liver transplant recipients suggest limiting correction to less than 16 mEq/L during the intraoperative period.¹³⁰

Once ascites becomes refractory to maximum standard medical therapy, therapeutic options are limited and include serial paracentesis, liver transplantation, TIPS placement, and peritoneovenous shunt.

Risk factors for development of spontaneous bacterial peritonitis include a prior episode of this acute infection, gastrointestinal bleeding, and an ascites albumin level of less than 1.5 g/dL. Long-term antibiotic prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole is recommended for patients who have survived an episode of spontaneous bacterial peritonitis.¹²⁹

Varices

Cirrhosis increases portal pressure as a result of chronic inflammation. Fibrosis and regenerative nodules cause resistance to splanchnic flow and lead to formation of portosystemic collaterals. Progression of portal hypertension leads to increased local production of nitric oxide and exacerbates splanchnic vasodilation. Rupture of the high-pressure collaterals that are formed is a highly lethal and feared complication of portal hypertension.

Portal hypertension is diagnosed by measurement of the wedged hepatic venous pressure (WHVP). Although this is not a direct measure of portal pressure, WHVP has been demonstrated to correlate well with portal pressure.¹³² This measurement is taken by advancing a catheter into a hepatic vein to the wedge position. To correct for the contribution of increased intraabdominal pressure from ascites, a free hepatic venous pressure or an inferior vena cava (IVC) pressure should be subtracted from the measured WHVP to give the hepatic venous pressure gradient (HVPG). A normal HVPG is 3 to 5 mm Hg. Patients with varices have HVPGs of 10 to 12 mm Hg or greater.

Esophagogastroduodenoscopy is the gold-standard procedure for diagnosing varices. Risk for variceal bleeding correlates with size of varices, presence of red wale marks, and variceal pressure (i.e., HVPG). Therapeutic decisions are based on these observations and measurements. Nonselective β -adrenergic blockers reduce portal pressure by two mechanisms: a decrease in cardiac output (β_1) and splanchnic vasoconstriction (β_2). For patients who cannot tolerate β -adrenergic blockers or in whom they are contraindicated, another option for primary prophylaxis of variceal bleeding is endoscopic ligation. The TIPS procedure had been considered a backup procedure for variceal bleeding, but recently has been advocated for early treatment in select patients.¹³³ However, TIPS is associated with a higher incidence of

encephalopathy; despite this, TIPS may decrease mortality in select patients.¹³³

Acute variceal bleeding should be managed with a combination of intravascular volume resuscitation, correction of severe coagulopathy, pharmacologic manipulation of portal pressure, and endoscopic variceal ligation. Aggressive intravascular volume replacement can lead to resistant or recurrent bleeding because bleeding is a pressure-related phenomenon.^{134,135} Elective intubation of the trachea for airway protection is often warranted. Medications to reduce portal pressure include vasopressin and somatostatin. Although β -adrenergic blockers can reduce portal pressures, their effect on systemic pressures makes them undesirable in this setting. Early endoscopic variceal ligation in combination with pharmacotherapy is the preferred treatment for acute variceal bleeding. Balloon tamponade can be effective for resistant variceal bleeding, but is associated with significant complications, including esophageal rupture and aspiration. It is recommended as a bridge to more definitive therapy such as surgical shunt, TIPS, or liver transplantation.

Hemostasis

Hemostasis is a dynamic process that is the product of interaction between coagulation, platelets, and fibrinolysis, resulting in the formation and revision of clot. Liver disease affects all of these components, both quantitatively and qualitatively. The liver is the site of synthesis for all procoagulant and anticoagulant factors, with the exception of tissue thromboplastin (III), calcium (IV), and von Willebrand factor (VIII). It is also the site for clearance of activated factors.

Patients with cirrhosis are customarily considered to have a bleeding diathesis based on abnormal results in conventional tests of coagulation, such as prothrombin time (PT) and partial thromboplastin time (PTT). However, such tests reflect the activity of only a portion of the procoagulant factors, and do not consider the concomitant decrease in anticoagulant factors, which are not assessed. It is the balance of procoagulant and anticoagulant forces, not the isolated measurement of either portion of the coagulation system, that indicates the effective generation of thrombin. Not surprisingly, PT and PTT abnormalities correlate poorly with bleeding complications following invasive procedures, such as liver biopsy.¹³⁶ There is evidence that decreased levels of protein C in cirrhotic patients balance the decreased levels of procoagulants, which can leave thrombin generation in vivo unaltered.¹³⁷

If procoagulants predominate because of disproportionate reductions of anticoagulants (protein S and C, antithrombin III), accompanied by an increase in procoagulants (FVIII), a hypercoagulable state results.^{138,139} This possibility is supported by studies reporting venous thromboembolism associated with cirrhotic and noncirrhotic liver disease.^{140,141}

Thrombocytopenia is a well-known feature of cirrhosis. The primary cause is splenic sequestration in the setting of portal hypertension. Elevated levels of von Willebrand factor compensate for decreased platelet counts, augmenting the platelet–endothelial cell interaction on vessel walls.

The fibrinolytic system in cirrhotic patients has many abnormalities, which may account for accelerated fibrinolysis. The liver is the site of tissue plasminogen activator

clearance, and elevated tissue plasminogen activator levels have been noted in patients with cirrhosis.¹⁴² The liver is also the site of synthesis for plasmin inhibitors, such as plasmin activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor. A balance of factors that promote and inhibit fibrinolysis is desired. Commonly used studies for assessing the presence and severity of accelerated fibrinolysis include euglobulin clot lysis time and thromboelastography (TEG).

Disseminated intravascular coagulation (DIC) is primarily a thrombotic diathesis, followed by widespread secondary fibrinolysis. As factors are consumed, DIC becomes a bleeding diathesis of factor and platelet deficiency. Whether or not DIC is a feature of stable chronic liver disease is controversial. Standard laboratory tests cannot distinguish between consumption and decreased synthesis, and so have little utility. Instead, assays to assess for excessive thrombin production are used. These assays include the cleaved by-products of coagulation factor activation such as prothrombin fragment F1+2, fibrinopeptide A, and thrombin-antithrombin complexes. These assays suggest that overt DIC is not a feature of stable chronic liver disease¹⁴³; however, accelerated intravascular coagulation and fibrinolysis has been described, which is a low-grade consumptive process.¹⁴⁴ Patients who exhibit accelerated intravascular coagulation and fibrinolysis are at increased risk of DIC in the presence of a known stimulus, such as sepsis or spontaneous bacterial peritonitis.

OBESITY AND SARCOPENIA

Liver disease is associated with altered protein, carbohydrate, and lipid metabolism. Protein calorie malnutrition is present in over 50% of decompensated cirrhotics.¹⁴⁵ A standardized battery of questions and physical exam findings can be used to evaluate nutritional status. Among the available tools is the Subjective Global Assessment and Royal Free Hospital Global Assessment,^{146,147} which uses a composite of several variables. Muscle wasting and fat depletion are highly correlated with scores based upon these tools. Triceps skinfold thickness, a marker of fat reserve, is associated with malnutrition. A value of less than the fifth percentile is diagnostic of severe malnutrition.¹⁴⁸ In addition, computed tomography has been evaluated as an assessment method for sarcopenia (muscle loss), which correlates with pretransplant mortality.¹⁴⁹

NAFLD refers to the presence of hepatic steatosis in the absence of known causes for hepatic fat deposition. It is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH); the latter is distinguished from the former by the presence of inflammation identical to that of alcoholic steatohepatitis. Factors associated with disease progression include body mass index, diabetes, and increasing age. As the most common indication for liver transplantation is now NAFLD, the body mass index of transplant recipients has risen in parallel.⁸⁷

SURGICAL PROCEDURE

Preoperative Considerations

In 2015, the median time to transplant in the United States was 11 months (interquartile range, <1 month to <1 year).⁸⁷ As a result, a transplant candidate can be months

removed from their initial evaluation when a suitable donor graft is identified. Therefore, the prospective recipient's evaluation should be reviewed while arrangements are made for donation. Candidates undergo an extensive preoperative assessment by multiple teams that typically include the surgical team, hepatologists, cardiologists, pulmonologists, psychiatrists, and social workers. In the event of unique comorbidities, additional consultants are involved as needed. Of particular interest to the anesthesiologist are interim changes in health status, hospitalizations (the possibility of infection should be considered with new-onset encephalopathy, variceal bleed, ascites, or hemodynamic deterioration), details of the initial and any subsequent cardiopulmonary evaluation (assess for the presence of coronary disease, heart failure, pulmonary hypertension, or arrhythmia), and renal status (acute kidney injury).

Unlike chronic liver disease, ALF is associated with increased intracranial pressure (ICP); preoperative evaluation and treatment focuses on the prevention of irreversible neurological injury. See section on "Acute Liver Failure" later.

Futility. The allocation policy in the United States, adopted by many programs worldwide, uses MELD scores to prioritize allocation of grafts to the sickest patients. Modifications to this MELD score have been proposed in efforts to improve the score's predictive ability.^{150,151} This policy, however, is in tension with saving as many patients as possible, since outcomes in high-MELD patients are, in general, inferior. Attempts to define futility have led to multiple definitions, such as 90-day mortality¹⁵² and less than 50% survival at 5 years. However, these definitions are subjective, as they require projections based upon age, coexisting disease, and physical frailty, factors not captured by the MELD score. A recent review provides an in-depth discussion of futility.¹⁵³ The concept of futility is likely to evolve, and hopefully 1 day provide objective criteria that can be reliably implemented.

Patients predicted to have decreased survival 1 year after transplant represent a high-risk group and include patients undergoing retransplantation or those supported by mechanical ventilation, infusions of vasopressors, and renal replacement therapy.³ Patients dependent on renal replacement therapy will benefit from preoperative dialysis; patients with oliguria, hyperkalemia, or acidemia, may benefit from intraoperative renal replacement therapy.^{154,155} Intraoperative renal replacement is not without risk; intraoperative fluctuations in clotting was associated with filter circuit clotting in 40% of patients in one series.¹⁵⁴ In our experience, circuit clots may suggest a hypercoagulable state associated with cardiac thromboembolic events.

A protocol should be in place to notify the blood bank of the pending transplant, which results in the setup of red blood cells and plasma in a volume according to institutional protocol. If any delay is anticipated in the availability of blood products, for instance in the event of antibodies, the blood bank personnel should notify the transplant coordinator and anesthesiologist. In the presence of red cell antibodies, our institutional policy is to set up compatible red cells for the start and completion of the transplant, and to use compatibility-unknown red cells in the event of large transfusion requirements.

The surgical procedure is divided into three distinct stages. During the preanhepatic or dissection stage, the liver is mobilized and vascular structures (suprahepatic and infrahepatic vena cava, portal vein, and hepatic artery) are identified. The anhepatic phase begins with clamping of these vessels and hepatectomy of the native liver and continues during the implantation of graft. Reperfusion, usually via the portal vein, starts the neohepatic phase, which continues through completion of the remaining vascular anastomosis (usually the hepatic artery), anastomosis of the bile duct, hemostasis, and abdominal closure.

Intraoperative Management

The intraoperative course of liver transplantation may be complex and prolonged; anesthesia teams are crucial to the success of programs. Intraoperative personnel and monitoring vary among liver transplant services based on institutional practice, caseload, and resources. Most centers allocate two anesthesia providers for liver transplants; however, the qualifications of these providers vary. A typical arrangement in an academic setting consists of an attending anesthesiologist experienced in liver transplantation and a senior resident. In private practice settings the second provider may be a second anesthesiologist, a certified nurse anesthetist, a licensed healthcare provider such as a perfusionist, or some combination of these. In general, most centers employ dedicated liver transplant anesthesia groups. Members of these groups are highly trained and experienced in the management of liver transplantation and often focus research and academic efforts toward liver transplant anesthesia. Liver transplant anesthesia fellowships dedicated to training physicians for careers in liver transplant anesthesia have been established in many centers. There is evidence that the experience of the anesthesia provider affects outcome; one series demonstrated that postoperative mortality was increased when the anesthesiologist had performed fewer than six liver transplant anesthetics.¹⁵⁶

Anesthesia typically begins with a rapid-sequence induction. Liver transplant patients are considered at high risk for aspiration of gastric contents because of the emergent nature of the surgery, preoperative administration of oral immunosuppressants/bowel decontamination antibiotics, and the presence of ascites. An arterial catheter is placed either before induction of anesthesia or immediately thereafter, depending on the hemodynamic stability of the patient prior to induction. Some centers routinely place femoral arterial lines because of the concern that radial arterial monitoring may underestimate central arterial pressure during episodes of intense vasodilation or in patients receiving high-dose vasopressors. However, there are no clear data in liver transplant patients to definitively recommend the use of central arterial pressure monitoring over radial monitoring.¹⁵⁷ Large-bore intravenous access is necessary as rapid blood loss, large fluid shifts, and hemodynamic instability are frequent. Most centers place large single- or double-lumen introducers centrally, or in the event of significant concern for blood loss (as is the case for retransplantation or in patients with extensive prior abdominal surgery) two introducers may be placed in a central vein. Sites designated for venovenous bypass (VVB) are avoided, if possible. There are differences between institutions regarding the routine use of PA catheters. In

patients with a history of PPHTN or in those with echocardiographic evidence of elevated PA pressures, PA catheter placement may be necessary to calculate PVR prior to incision; the results may impact the patient's candidacy for transplant.¹⁵⁸ In the patient with elevated PA pressures or borderline PVR, a PA catheter may help guide therapy during the perioperative period. However, if the recipient has had a recent negative evaluation for pulmonary arterial hypertension, a PA catheter may not be deemed necessary by some practitioners. Transesophageal echocardiography is increasingly used during liver transplant as it provides continuous cardiac imaging and may facilitate the rapid diagnosis of critical events such as ventricular failure, myocardial ischemia or infarction, pericardial tamponade, and intracardiac thrombosis. A recent survey demonstrated that transesophageal echocardiography is utilized widely in U.S. liver transplant centers.¹⁵⁹ Transesophageal echocardiography appears to be associated with a low likelihood of hemorrhagic complications, even in the presence of esophageal varices.¹⁶⁰ Some liver transplant centers avoid PA catheter insertion in the event that transesophageal echocardiography is used. New technologies, including arterial pressure waveform analysis and three-dimensional echocardiography, do not correlate with thermodilution-derived parameters and are not currently advocated for routine use intraoperatively.^{161,162}

A rapid infusion system capable of high transfusion flow rates (>500 mL/min) is typically used. Such systems incorporate a reservoir, pump, filters, heat exchanger, and safety features designed to avoid and monitor for the presence of blood or air embolism, hypothermia, and line occlusion. Rapid infusion systems are important for volume replacement, transfusion management, and maintenance of normothermia.

The effects of the anesthetic technique on patient outcome are unknown. At many centers a balanced anesthetic is used; this typically consists of a volatile anesthetic in low to moderate concentrations (0.5-1.0 minimum alveolar concentration [MAC]) to ensure unconsciousness, whereas a synthetic opioid, often fentanyl, is chosen to blunt the sympathetic response to stimulation and to provide a smooth transition for postoperative analgesia. In recipients with fulminant hepatic failure and cerebral edema, volatile anesthetics are avoided or used cautiously in low concentrations, in many cases with ICP monitoring (see later). In either case, periods of hypotension during the surgery may require temporary decreases of volatile anesthetic concentrations. Midazolam, with minimal hemodynamic effects, can be used for its amnestic effects during these hypotensive periods. Historically, the volatile anesthetic of choice has been isoflurane, which preserves splanchnic blood flow better than previously used volatile drugs.¹⁶³ Studies in healthy humans have demonstrated the vasodilatory effects of isoflurane on the hepatic circulation.¹⁶⁴ This beneficial effect on hepatic oxygen supply may be advantageous to the newly reperfused graft. The effects of desflurane on hepatic blood flow have been evaluated with conflicting results. In animals, desflurane decreased total hepatic blood flow in a dose-dependent fashion at concentrations up to 1.0 MAC; however, in a human study that excluded patients with liver disease, liver blood flow was slightly more rapid with desflurane than with

isoflurane, although this effect was not statistically significant.¹⁶⁵ Another study compared the effects of sevoflurane and desflurane on hepatic blood flow and hepatocellular integrity in older patients.¹⁶⁶ Both anesthetics resulted in decreases in gastric mucosal pH and increases in cytosolic liver enzymes. The authors conclude that hepatocyte function is well preserved, although their results suggest that splanchnic perfusion and oxygen delivery to the liver are transiently decreased. Whether the increased metabolism of sevoflurane (100-fold that of desflurane) is detrimental to the liver is unknown, but it seems unlikely that the metabolites of sevoflurane cause liver damage.¹⁶⁷ Compound A, a breakdown product of sevoflurane found to be nephrotoxic in animals, has not been shown to cause renal toxicities in humans, even during low-flow sevoflurane administration.¹⁶⁸

Cisatracurium is an attractive choice for neuromuscular blockade in patients undergoing liver transplantation because of its organ-independent elimination and diminished histamine release.¹⁶⁹ In patients with end-stage liver disease, the volume of distribution of cisatracurium is larger than that in healthy control patients. Hepatic clearance is also increased in patients with liver disease; this results in similar elimination half times and similar duration of action. Other reports have suggested the use of rocuronium during liver transplantation, because the duration of the neuromuscular block appears to be a useful predictor of primary allograft function. All patients whose recovery time was longer than 150 minutes experienced primary graft dysfunction.¹⁷⁰

Preanhepatic Stage

The preanhepatic stage begins with surgical incision and ends with vascular exclusion and hepatectomy of the native liver. Using conventional caval interposition technique, vascular exclusion of the liver is accomplished by cross-clamping the portal vein, the suprahepatic IVC, the infrahepatic IVC, and the hepatic artery (Fig. 60.9). If a piggyback technique is used, the native retrohepatic vena cava is preserved (Fig. 60.10).

The preanhepatic phase involves dissection and mobilization of the liver and identification of the porta hepatis. With abdominal incision and drainage of ascites, hypovolemia can occur. This should be treated in an anticipatory fashion with colloid-containing fluid to minimize changes in preload. In addition, the dissection phase may be complicated by significant bleeding necessitating massive transfusion and management of hemostasis (see later). Bleeding during this phase of surgery is related to the degree of preexisting coagulopathy, the presence and severity of portal hypertension, and the duration and complexity of the surgical procedure, which is adversely affected by prior abdominal surgery and adhesions.^{171,172} The use of vasoactive infusions to maintain end-organ perfusion pressure is common, especially in critically ill patients with underlying cirrhotic cardiomyopathy. Occasionally during the preanhepatic stage, patients may exhibit hostile abdominal anatomy that impedes hepatic resection or may develop severe cardiovascular and metabolic instability that render them inoperable; discussion between the anesthesia and surgical teams to determine if the transplant should be aborted is crucial to prevent futile care in these situations.

In addition to massive transfusion and coagulopathy, the preanhepatic stage may be associated with significant metabolic and acid-base disturbances that require close monitoring and active management. Abnormalities of sodium are not unusual in liver transplant patients; hyponatremia

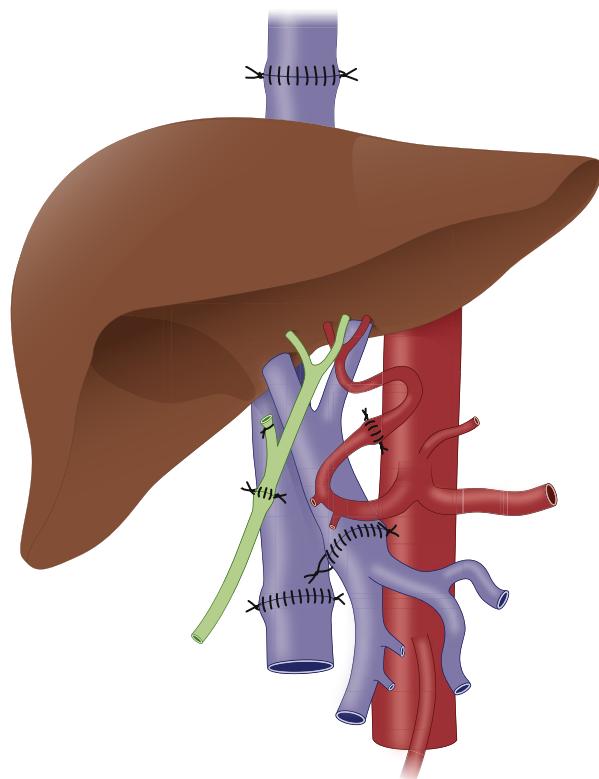


Fig. 60.9 Liver transplantation. Classic caval interposition technique illustrating anastomoses of the suprahepatic and infrahepatic inferior vena cava, the portal vein, the hepatic artery, and the bile duct. (From Molmenti E, Klintmalm G. *Atlas of Liver Transplantation*. Philadelphia: Saunders; 2002.)

should not be corrected rapidly. A perioperative increase of 21 to 32 mEq/L in the serum sodium level was associated with central pontine myelinolysis in one report, whereas an increase of less than 16 mEq/L was not.^{130,173} Citrate intoxication (ionized hypocalcemia resulting from the infusion of citrate-rich blood products in the absence of hepatic function) is avoided by the administration of calcium chloride. Ionized hypomagnesemia also results from citrate infusion, but values of ionized magnesium gradually return to normal after graft reperfusion.¹⁷⁴ The clinical significance of this remains speculative, but cardiovascular function may be affected. Aggressive treatment of hypokalemia is best avoided, particularly in preparation for reperfusion and the associated increase in serum potassium. Hyperkalemia should be avoided by the administration of diuretics and insulin accompanied by glucose or, in the event these are ineffective, by intraoperative dialysis. In the absence of insulin administration, supplemental glucose is usually not required except in pediatric patients or those with severe disease, such as fulminant hepatic failure. Hyperglycemia should be avoided, because glucose levels greater than 180 mg/dL are associated with an increase in surgical site infections in liver transplant recipients.¹⁷⁵ Blood gases, electrolytes, glucose, ionized calcium, and hemoglobin levels should be assessed regularly, and as frequently as hourly in the event of massive blood loss or preexisting abnormalities. Point-of-care testing facilitates rapid turnaround times for laboratory values. Coagulation studies are typically assessed at the beginning of the surgery, after correction of specific deficiencies, after reperfusion, and in the presence of microvascular bleeding.

The maintenance of urine output is desirable; however, the use of low-dose dopamine for this reason is unproven.^{176,177} Hypothermia should be avoided. Core temperature control can be aided with heated VVB during the anhepatic phase. Regardless of whether bypass is used, forced-air warming blankets should be positioned beneath the patient and over the lower and upper body.

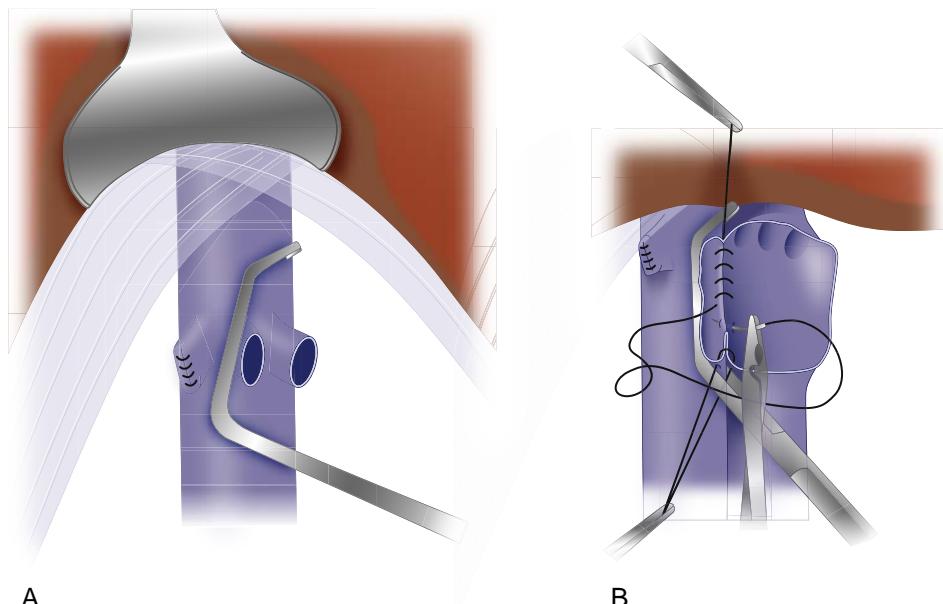


Fig. 60.10 Liver transplantation. (A) Piggyback technique illustrating partial vena caval clamping and an oversewn native right hepatic vein. (B) Preservation of the native retrohepatic vena cava and hepatic venous cuff anastomosis. (From Molmenti E, Klintmalm G. *Atlas of Liver Transplantation*. Philadelphia: Saunders; 2002.)

Anhepatic Stage

The anhepatic stage begins with the occlusion of vascular inflow to the liver, and it ends with graft reperfusion. Cross-clamping of the suprahepatic and infrahepatic IVC decreases venous return by as much as 50%. VVB diverts IVC and portal venous flow to the superior vena cava via the axillary vein, attenuates the decrease in preload, improves renal perfusion pressure, lessens splanchnic congestion, and can delay the development of metabolic acidosis.¹⁷⁸ However, the use of VVB is not without risk. Air embolism, thromboembolism, and inadvertent decannulation can be fatal or result in significant morbidity.¹⁷⁹ VVB is not uniformly used at all centers. A meta-analysis of three trials failed to reveal any difference in the incidence of renal failure or blood transfusion requirements between patients randomized to VVB compared with patients in whom the technique was not used.¹⁸⁰ The use of the “piggyback” technique, with IVC preservation, decreases the need for VVB.¹⁸¹

Hepatectomy is followed by hemostasis and vascular anastomoses of the suprahepatic and infrahepatic IVC and the portal vein. Despite the absence of hepatic clotting factor production during the anhepatic stage, blood loss is usually limited by vascular clamping of the inflow vessels to the liver. However, fibrinolysis may begin during this stage because of an absence of liver-produced plasminogen activator inhibitor, which results in the unopposed action of tissue plasminogen activator. The use of antifibrinolytics varies among centers (discussed later).

Neohepatic Stage

Reperfusion of the graft through the portal vein begins the neohepatic stage. Reperfusion is associated with abrupt increases in potassium and hydrogen ion concentrations, an increase in preload, and a decrease in systemic vascular resistance and blood pressure. Hypothermia, monitored through a centrally placed catheter, is a marker for the presence of graft outflow into the central circulation. Life-threatening hyperkalemia, clinically detectable by changes in the EKG, requires prompt treatment. Calcium chloride and sodium bicarbonate are the drugs of choice for the acute treatment of hyperkalemia. If time permits, albuterol and insulin are also effective. Intraoperative dialysis should be considered early in the procedure for patients with oliguria and elevated potassium levels.

The hallmark of the postreperfusion syndrome (PRS) is systemic hypotension and pulmonary hypertension occurring within the first 5 minutes after reperfusion of the graft. Approximately one in three patients undergoing orthotopic liver transplantation (OLT) have profound hypotension after reperfusion. The cause is uncertain, but a number of factors have been implicated, such as hyperkalemia, acidosis, hypothermia, emboli (air or thrombotic), and vasoactive substances. Risk factors for hyperkalemia in the early postreperfusion period are elevated preanhepatic potassium levels and the use of donated-after-cardiac-death donor organs.¹⁸² One study identified suboptimal grafts (higher degree of steatosis) and graft cold ischemia time as risk factors for PRS.¹⁸³ In this study all cases of PRS, defined as mean blood pressure less than 60 mm Hg, occurred in suboptimal donors with graft cold ischemia times longer than 6 hours. The PRS group had higher postreperfusion K⁺ levels

and lower postreperfusion temperature than in the group without PRS.

In addition, other critical events such as severe, acute bleeding resulting in hemodynamic compromise and necessitating massive transfusion can occur at any point during the surgery. Arrhythmias and intracardiac thromboembolism can also occur at any time intraoperatively, but are more likely after reperfusion.^{184,185}

Hepatic arterial anastomosis and biliary reconstruction are generally performed after venous reperfusion, although in pediatric patients the arterial anastomosis may be completed before reperfusion. Signs of graft function that might be observed in the operating room and early postoperative period include decreased calcium requirements, improvement in acidosis, increased urine output, a rise in core temperature, and bile output from the graft.¹⁸⁶

Management of Transfusion, Hemostasis, and Coagulation

As previously described, end-stage liver disease produces a complex disorder of coagulation that affects both procoagulant and anticoagulant systems, resulting in a fragile state that can lead to either bleeding or thrombosis depending on the clinical conditions of the patient. During liver transplantation, the preexisting coagulopathy of end-stage liver disease may be further impacted by massive transfusion, dilutional coagulopathy, the loss of hepatic synthetic function, a heparin-like coagulopathy following graft reperfusion, and fibrinolysis.¹⁸⁷ The management of coagulopathy and transfusion is crucial in the care of liver transplant patients.

Starting in the preanhepatic phase, drainage of ascites and surgical blood loss necessitate volume resuscitation. In the presence of coagulopathy, fresh frozen plasma may be indicated soon after incision, although some authors have challenged the need for fresh frozen plasma during OLT.^{188,189} Prothrombin complex concentrates (PCCs), which contain vitamin K-dependent factors, may be considered as an alternative to plasma transfusion to avoid the risk of transfusion-related acute lung injury and transfusion-associated circulatory overload.^{190,191} Several PCCs, containing therapeutic levels of factor II, VII, IX, and X in addition to varying amounts of protein C and S, are available for clinical use.¹⁹² The primary concern related to PCC administration is thromboembolic complications, which vary according to the patient's underlying disease, dosing, and the constituents in each of the commercially available PCC products.¹⁹³ Although the reported risk of thrombosis was low (1.4%) in a large study that investigated PCC for the reversal of warfarin in non-liver transplant populations, there are no published randomized controlled trials that have assessed the safety of PCC in liver transplant patients.¹⁹⁴ Another product, recombinant activated factor VII (rFVIIa), was evaluated during liver transplantation and was found to improve coagulation study results, but did not result in a decrease in transfusion requirements.^{195,196} rFVIIa has been linked to an increased risk of arterial, but not venous, thromboembolic events.¹⁹⁷ Fibrinogen levels may decrease during liver transplant due to massive bleeding, dilution, and consumptive processes. Fibrinogen-rich components such as cryoprecipitate and fibrinogen concentrates may be indicated for coagulopathic bleeding with documented hypofibrinogenemia. Cryoprecipitate

is available in North America and the United Kingdom, while fibrinogen concentrates are employed in Europe.¹⁹² Thrombocytopenia is common in the liver transplant patient, however prophylactic platelet transfusion during liver transplant appears to have limited efficacy for improving coagulation parameters in liver transplant patients.¹⁹² In addition, adverse effects from intraoperative platelet transfusions have been demonstrated in liver transplant patients, including increased rates of acute lung injury as well as increased 1-year graft failure and mortality.^{198,199} In general, administration of blood products and/or factor concentrates in liver transplant patients should be for clinically significant bleeding; prophylactic administration is not recommended.²⁰⁰

TEG or standard laboratory tests (PT, fibrinogen, and platelet count) are used to guide the correction of coagulopathy.^{190,201} Viscoelastic-guided coagulation management has been extensively studied in cardiac surgery patients and has been shown to decrease blood transfusions.²⁰² Although viscoelastic-guided protocols have been described in liver transplant cohorts, there is less evidence to show that they significantly impact transfusion requirements. In one single-center study of liver transplant patients, a viscoelastic-guided protocol was employed for intraoperative hemostatic management that included the use of PCC and fibrinogen concentrate. The median red blood cell transfusion requirement was low (two units); 29% of patients received platelets and 15% received plasma.²⁰³ However, another single-center comparative study in liver transplant patients showed that a viscoelastic-guided algorithm did not decrease blood transfusions compared to a standard transfusion protocol.²⁰⁴ Considerable institutional variation exists in transfusion practices for OLT, as do variations in patient acuity as evidenced by MELD scores. Intraoperative blood transfusion has been shown to be a predictor for posttransplant survival in single-center studies, although the reported transfusion thresholds that affected outcome vary.²⁰⁵⁻²⁰⁷ Transfusion requirements for liver transplant patients appear to be multifactorial; many donor, recipient, and procedural factors have been shown to impact intraoperative transfusion.²⁰⁰ Fibrinolysis may contribute to bleeding necessitating targeted therapy during liver transplant. Fibrinolysis is most severe after reperfusion and is caused by abrupt increases in tissue plasminogen activator from graft endothelial cell release. Antifibrinolytic drugs and cryoprecipitate may be required. Since the removal of aprotinin from the world market in 2008, the lysine analogues epsilon-aminocaproic acid and tranexamic acid are typically employed for the treatment of coagulopathic bleeding due to fibrinolysis, although optimal dosages in liver transplant patients have not been determined.²⁰⁰ Antifibrinolytic therapies have been studied in liver transplant patients to assess their impact on blood transfusion. Three recent studies demonstrated that prophylactic administration of lysine analogues decreased transfusion requirements, although one study showed that antifibrinolytic therapy was associated with a higher risk of deep venous thromboses.²⁰⁸⁻²¹⁰ Although there is no clear evidence that antifibrinolytic therapy produces a hypercoagulable state during liver transplant, major thrombotic complications have been well reported in liver transplant patients.²⁰⁰ In general, antifibrinolytic therapy should be employed in

the setting of significant bleeding with suspected or documented hyperfibrinolysis.²⁰⁰

Postoperative Care

The goals of the immediate postoperative period are to ensure a smooth transition from anesthesia and surgery (maintain hemodynamic stability, metabolic homeostasis, adequate analgesia), monitor graft function (transaminase levels, PT, bilirubin levels, bile and urine output, acid-base status), and maintain surveillance for known complications (bleeding, bile leaks, vascular thrombosis, primary nonfunction). The use of steroids leads to hyperglycemia, which can require insulin infusion.

The lack of bile output, accompanied by hemodynamic instability, suggests primary nonfunction of the graft, which may require urgent retransplantation. Conversely, a functioning liver graft facilitates early neurologic recovery, cardiovascular stability, and improved renal function, signs that can occur within hours of the completion of surgery.

Hepatic artery thrombosis can lead to graft necrosis, necessitating retransplantation. Within the first 2 to 3 postoperative days, markedly abnormal transaminase levels are common because of graft ischemia or injury during procurement, preservation, and reperfusion. After this period, hepatic enzyme and bilirubin levels that do not trend downward suggest the possibility of hepatic artery thrombosis, which should lead to prompt evaluation with Doppler ultrasonography.

Postoperative pain control is generally achieved with opioids, including patient-controlled analgesia. Analgesic requirements may be decreased compared with other major abdominal surgery.^{211,212} Epidural analgesia is contraindicated because of coagulopathy, which usually preexists, or develops during the perioperative period.

The timing of tracheal extubation and termination of postoperative mechanical ventilation is not clear.^{213,214} Early extubation of the trachea, including endotracheal tube removal in the operating room, is feasible in select patients. However, the benefits of immediate extubation appear limited to the potential of decreased resource utilization, which might not be fully realized in centers that direct posttransplant patients to ICUs regardless of their need for ventilatory support. As a result, many centers prefer to see clear signs of graft function before extubation.

ACUTE LIVER FAILURE

ALF (previously termed *fulminant hepatic failure*) is defined as the appearance of encephalopathy together with coagulopathy (international normalized ratio [INR] ≥ 1.5) in a patient without previous liver disease who has an illness of less than 26 weeks in duration. ALF is a rare entity with an estimated incidence of approximately 2000 cases per year in the United States and a reported incidence of 1 to 8 per million population in the United Kingdom.²¹⁵ Drug-related toxicity, primarily acetaminophen, accounts for the majority of the cases of ALF in the United States and Europe while viral infections are the most common etiologies in many Asian and developing countries.²¹⁶ Other causes include idiopathic, autoimmune, and ischemic. Etiology has a significant bearing on outcome; patients with acetaminophen toxicity, ischemic injury, or hepatitis A have

the most favorable prognosis, whereas those with non-acetaminophen drug-induced liver injury, acute hepatitis B, Wilson disease, or autoimmune hepatitis have poor prognoses in the absence of transplantation.²¹⁷ Outcomes in patients with ALF have significantly improved over the past 40 years due to both transplantation and advances in medical management; over 70% of ALF patients now survive their illness.^{218,219} Overall, ALF is a rare indication for liver transplant. In a study of ALF patients listed for transplant in the United States over a 13-year period, only 64% of patients underwent liver transplant. Of those that did not undergo transplant, more than half survived with medical management.²¹⁹ In the United States there has been a slight decrease in both waitlist registrations and transplant rates for adult patients with ALF over the last 12 years.⁸⁷ In Europe, approximately 7% of liver transplants were performed yearly for ALF.²²⁰ One-year liver transplant survival rates for patients with ALF are between 74% to 84%; both early and late outcomes are generally inferior compared to chronic liver failure patients.²²¹ There are also significant differences in liver transplant outcomes based on etiology of ALF; outcomes are better in patients with acetaminophen toxicity and acute viral hepatitis compared to other indications.²¹⁵ The severity of preexisting multiorgan failure including neurologic involvement in critically ill patients with ALF likely impacts posttransplant outcomes.

Evidence of portal hypertension and cirrhosis is absent in ALF because of the rapid progression of disease. Acute decompensation of chronic liver disease, termed acute-on-chronic liver disease, is a separate condition with different etiologies, therapy, and prognostic indicators. Although various etiologies of ALF exist, there are manifestations that are common to all patients with massive hepatic necrosis. The most serious, and lethal, is acute cerebral edema and intracranial hypertension. Effects on other organ systems include coagulopathy, circulatory dysfunction and hypotension, acute kidney injury, and metabolic derangements.

General measures to reduce cerebral edema include maintaining the patient in a 30-degree, head-up position, and making sure the head is in neutral position so as not to impede venous return. Supportive care includes maintenance of normovolemia, vasopressor therapy for blood pressure support, prevention of sepsis, and intubation for airway protection and control of ventilation. Sedation and muscle relaxants should be considered to minimize increases in ICP from coughing, bucking, and shivering. Mannitol can be used to induce an osmotic diuresis but may have limited utility in the patient with compromised renal function. Early use of renal replacement therapy may be indicated for control of ammonia levels and to optimize electrolyte and acid-base status. Hypertonic saline, ideally targeting a serum sodium of 145 to 155 mEq/L, may be indicated. Current recommendations are to maintain normocarbia and to reserve hyperventilation for response to acute increases in ICP. Barbiturates can be used to decrease cerebral metabolism; however, their use may be limited by hypotension.

Monitoring techniques for cerebral edema and intracranial hypertension are controversial. Serial head computed tomography images are not sensitive indicators of intracranial hypertension. Computed tomography can, however, provide information on structural abnormalities such as

intracranial hemorrhage. Although many centers place an ICP monitor to guide therapy in patients with stage III-IV coma, there are no randomized controlled studies to support this practice. Furthermore, ICP monitor placement is not a benign procedure, frequently entailing aggressive correction of coagulopathy and transport to and from the operating room for a critically ill, fragile patient. Nonetheless, ICP monitors are invaluable for guiding acute therapy, and for helping to determine who might no longer be a viable candidate for transplantation. In addition to measuring ICP, these monitors allow calculation of cerebral perfusion pressure (CPP = mean arterial pressure [MAP] – intracranial pressure [ICP]), which should be kept between 50 and 80 mm Hg. An effective protocol for managing intracranial hypertension in patients with stage III or IV encephalopathy has been described and resulted in a 95% response to treatment in episodes of ICP greater than 20 mm Hg. Furthermore, in this prospective series, ICP was monitored in all patients, and no patients died of isolated cerebral edema. The authors used a protocol that included rFVIIa to correct coagulopathy before ICP placement. Significant bleeding complications from ICP monitoring were not encountered.²²²

The decision regarding which patients should receive a transplant, based on who might recover spontaneously or who is unlikely to benefit from transplantation, is one of the most difficult decisions encountered during the management of patients with liver disease. The two most widely used prognostic models are the Clichy or Paul Brousse Hospital criteria and the King's College Hospital criteria. The Clichy criteria recommend transplantation for patients in stage III or IV coma, based on age and factor V levels.²²³ There is no distinction made for etiology of ALF, which is considered a weakness of these criteria. The King's College Hospital criteria are superior for predicting outcomes in patients with ALF based on acetaminophen toxicity. However, the negative predictive value is less than 50% in patients who have not used acetaminophen.²²⁴ Thus, patients who fail to fulfill these criteria include a number of patients who will die without proper consideration for transplantation. Recently, dynamic models have been used to predict outcomes in acute ALF patients.²²⁵

In patients with ALF who are undergoing an invasive procedure, correction of thrombocytopenia to 50,000 platelets/mm³ or greater and INR to 1.5 or less is suggested.^{217,226} Prophylactic therapy may be initiated for severe abnormalities (e.g., platelet count \leq 10,000/mm³, INR $>$ 7, and fibrinogen $<$ 100 mg/dL).²¹⁷ Viscoelastic testing may be useful for guiding therapy. Use of rFVIIa is reserved for rapid correction in patients who cannot tolerate a large volume of plasma. This agent may carry a thrombotic risk and is contraindicated in hypercoagulable states. The prophylactic use of rFVIIa is generally not recommended unless an invasive procedure is planned.²²⁷ PCC may also have a role in this setting.

Hypotensive patients with ALF should undergo intravascular volume status and cardiac function assessment before consideration of inotropes or vasopressors. MAP should be raised to provide adequate CPP. Vasopressors can be used to treat either systemic hypotension or to maintain an adequate CPP. Based on recommendations for septic patients, norepinephrine should be used. The use of vasopressin is

TABLE 60.3 Pugh's Modification of the Child-Turcotte Classification

Variable	POINTS		
	1	2	3
Encephalopathy	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Prothrombin time (sec prolonged)	<4	4-6	>6
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dL)	<2	2-3	>3

Child-Pugh class A, 5-6; class B, 7-9; class C, 10-15.

Modified from Wiesner RH, McDarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. *Liver Transplant*. 2001;7(7):567-580.

controversial because there is evidence that its use is associated with increases in ICP.²²⁸ However, another study in which terlipressin was used did not reveal similar increases in ICP.²²⁹

LIVING DONOR LIVER TRANSPLANTATION

See [Chapter 61](#) (Anesthesia for Organ Procurement).

PEDIATRIC LIVER TRANSPLANTATION

See [Chapter 77](#) (Pediatric Anesthesia) and [Chapter 78](#) (Anesthesia for Pediatric Cardiac Surgery).

ORGAN MATCHING AND ALLOCATION

The primary criteria used to match donor liver grafts with recipients are ABO blood type and graft size. ABO-incompatible liver transplantation (ILT) is generally limited to emergent situations, and as many as half of the adult recipients in early reports required retransplantation. Subsequent reports have identified patient populations with more favorable outcomes after ILT. Recipients with blood type O and pediatric patients tolerate ILT better than others.²³⁰ Nonetheless, ILT remains a technique reserved for emergent situations.

In the United States, a national registry maintained by UNOS allocates organs to transplant candidates. In Europe, there are a number of regional or national organ allocation bodies that distribute organs within their respective country or region based on different allocation criteria. UNOS considers only disease severity, and no longer uses waiting time, when allocating deceased-donor liver grafts. Older systems used the Child-Turcotte-Pugh (CTP) score to determine disease severity ([Table 60.3](#)). Beginning in 2002, the MELD score replaced the CTP score. The MELD score is a mathematical formula that incorporates the serum bilirubin, creatinine level, and INR. It is considered more objective because there is no reliance on subjective physical examination to determine the presence and severity of findings, such as ascites or encephalopathy. The MELD score is a continuous scale, rather than categorical (found in the CTP score), which provides more discriminatory ability since

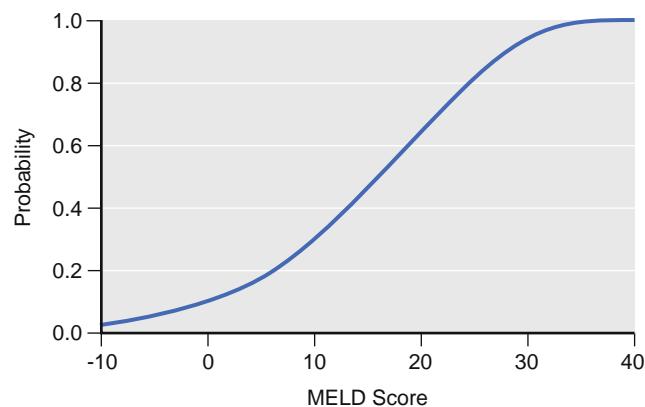


Fig. 60.11 Relationship between Model for End-Stage Liver Disease (MELD) score and 3-month mortality in hospitalized (pretransplant) patients with cirrhosis. (From Wiesner RH, McDarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. *Liver Transplant*. 2001;7:567-580.)

disparate risks are not grouped within a single category. In addition, the inclusion of the creatinine level (not found in the CTP score) reflects the prognostic importance of renal dysfunction on advanced liver disease. The MELD score is an excellent predictor of 90-day pretransplant (waitlist) mortality ([Fig. 60.11](#)).

The MELD allocation system is regarded as a major advance in liver organ allocation. However, adjustments to the MELD system based on updated information and addition of MELD exception points for specific subsets of patients have been implemented to optimize allocation. For instance, based on observations that hyponatremia is a predictor for mortality in patients with cirrhosis, sodium was added to the calculation for organ allocation (MELD-Na score) in 2016.²³¹ Hepatocellular carcinoma can progress to inoperable status before manifesting changes in the MELD score, which disadvantages patients with HCC. As a result, UNOS policy grants exception points to patients with HCC to allocate organs equitably to patients with this condition; this exception policy has undergone multiple changes since 2002.²³² Other patient subsets including those with PPHTN, HPS, amyloid, and hilar cholangiocarcinoma also receive MELD exception points. Regional disparities in candidate access to transplantation have been addressed with the Regional Share 35/National Share 15 policy.²³³ Candidates with MELD scores less than 15 have better survival without transplantation.²³⁴ However, when the qualities of the donor graft are taken into account using the donor risk index, candidates with MELD scores of 12 to 14 benefit from liver transplant in the event that a favorable (low donor risk index) graft is transplanted.²³⁵

ANESTHESIA FOR PATIENTS AFTER LIVER TRANSPLANTATION

There are nearly 8000 patients living with liver transplant grafts in the United States; these patients may present for all types of nontransplant surgeries.⁸⁷ Liver transplant recipients with functioning grafts typically metabolize drugs in a normal fashion, but graft function must be assessed rather than assumed. The PT (or INR) is an excellent marker of synthetic function. In patients with grafts with impaired

synthetic function, clotting abnormalities can be corrected with vitamin K or fresh frozen plasma; ascites managed with diuretics, albumin administration, or paracentesis; and the risk of encephalopathy minimized with lactulose administration and careful use of sedatives.

Careful adherence to sterile technique is required to prevent infectious complications in this immunosuppressed population. A stress dose of corticosteroids is required for patients receiving chronic supplementation. Renal function should be assessed and managed carefully to avoid an exacerbation of immunosuppressant-associated renal impairment. Hypertension is a common finding in patients whose condition is managed with calcineurin inhibitors such as cyclosporine. Drugs known to decrease hepatic blood flow, such as propranolol, should be avoided. Regional anesthesia is an option in patients with acceptable clotting status.

INTESTINAL, LIVER-INTESTINAL, AND MULTIVISCERAL TRANSPLANT

Background

Intestinal, liver-intestinal, and multivisceral transplants have been performed since the mid-1980s, but results were poor until the introduction of tacrolimus and antilymphocyte monoclonal antibodies in the 1990s, which allowed adequate control of rejection. Over the past 2 decades, further refinements in immunosuppression, donor-recipient matching, surgical technique, and perioperative care have steadily improved outcomes. These procedures now have an established role in the treatment of intestinal failure from a wide range of causes. The Intestinal Transplant Registry collected international data from 82 programs transplanting 2699 patients between 1985 and 2013 and reported pooled patient survival of 76%, 56%, and 43% at 1, 5, and 10 years, respectively.²³⁶ Results are continuing to improve, but survival and cost-effectiveness still lag behind those achieved with other organ transplants.²³⁷⁻²³⁹ Intestinal transplantation requires a highly specialized multidisciplinary team who must also provide long-term posttransplant care. Small numbers favor management in regional or national units in which experience is concentrated.

Definitions of intestinal transplant procedures are debated but the most widely used are as follows: Small intestine transplant: intestine without the liver or stomach; liver-intestine transplant: small intestine and liver but no stomach; modified multivisceral transplant: stomach and intestine without liver; multivisceral transplant: intestine plus liver and stomach. The pancreas is often included in a composite graft, usually for technical simplicity but sometimes also to treat pancreatic insufficiency. A segment of colon may also be included.

Indications for intestinal transplant in children include short bowel syndrome from gastroschisis, necrotizing enterocolitis and volvulus, and microvillous inclusion disease. Adults are offered transplantation for thrombotic and traumatic intestinal infarction, desmoid tumor, Crohn-related short bowel syndrome and gut motility disorders. In most of these conditions transplantation has been offered because of life-threatening complications of parenteral nutrition, including progressive cholestasis and liver

failure, venous thrombosis leading to loss of two central sites for vascular access, and recurrent catheter-related sepsis. In others, transplant is indicated because of a high risk of death related to the underlying condition, as in congenital mucosal disorders, desmoid tumor, and ultrashort bowel syndrome. In some patients, transplant is considered in the context of frequent debilitating hospitalizations, often for dehydration from stomal losses. While improvements in PN lipid formulations in recent years have significantly reduced PN-associated liver disease, potential new indications have emerged.²³⁹ These include portomesenteric thrombosis in patients with end-stage liver disease, chronic abdominal fistula and sepsis, and patients' unwillingness to accept life-long PN. Outcome data on these has yet to be reported.

Surgical Procedures

Organs transplanted depend on the indication, recipient liver function, and surgical conditions following previous procedures. Isolated small bowel or small bowel-stomach-duodenum transplant is usual in short bowel syndrome, motility disorders, and desmoid tumor. In this procedure, a donor-to-recipient superior mesenteric artery (SMA) anastomosis supplies arterial inflow; the donor portal vein to recipient IVC or portal vein provides venous outflow (Fig. 60.12).

Liver-intestine transplant, with or without stomach, duodenum, and pancreas, is indicated when PN-related liver disease is significant. Inclusion of pancreas avoids the risk of hilar injury associated with its removal on the back-table and reduces the risk of kinking of adjacent vessels (superior mesenteric vessels, portal vein, middle colonic artery) in the implanted graft. It also avoids the need for Roux loop biliary drainage and is beneficial if the recipient is diabetic. Inflow is typically via aorta-to-SMA anastomosis or conduit, and outflow via donor hepatic veins to IVC or side-to-side anastomosis of donor to recipient retrohepatic IVC (piggyback technique). Pretransplant renal dysfunction from obstructive uropathy, renal vein thrombosis, or recurrent severe dehydration may require implantation of a kidney graft as part of the same procedure.

Once the graft complex is reperfused, a proximal intestinal, gastric, or gastroesophageal anastomosis, is performed for upper gut continuity. This may be followed by end-to-side anastomosis of recipient colon to donor ileum to complete lower gut continuity. The distal end of the transplanted small intestine is then brought out as a temporary stoma. Alternatively, to preserve the recipient ileocecal valve, the donor ileum can be anastomosed to the recipient's distal ileum, which is then used to form the ileostomy. The ileostomy ensures that the graft is not distended postoperatively and allows endoscopic monitoring for rejection. Preservation of the colon is not essential but improves fluid and electrolyte absorption and is naturally preferred by the patient. After completion of the bowel anastomoses, the abdominal wall is closed. This may be difficult, sometimes requiring delayed primary closure, use of reinforcing mesh, a muscle flap, or even grafting of the donor abdominal wall.

Preoperative Assessment

Multivisceral transplant, and to a lesser extent non-liver intestinal transplant, is usually associated with major

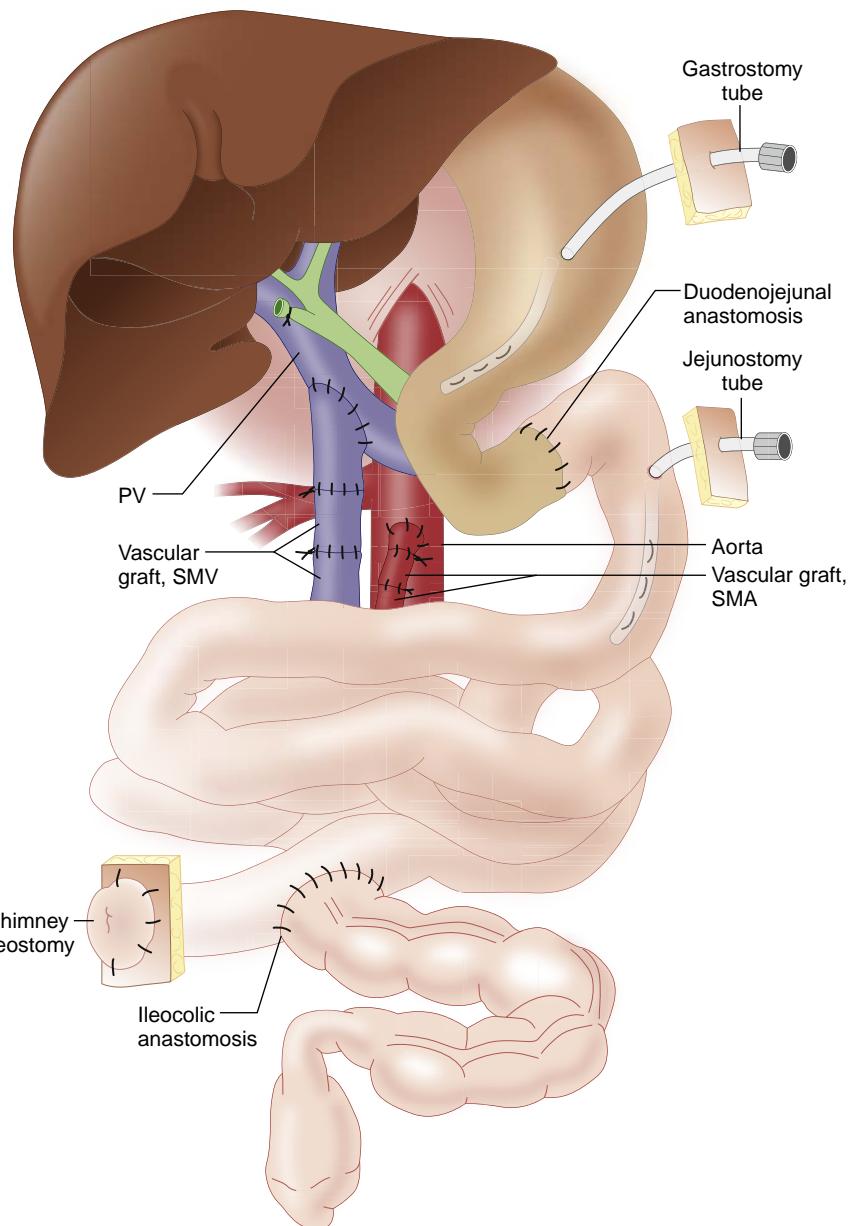


Fig. 60.12 Intestinal transplantation. The implanted donor intestine is illustrated. PV, Portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein. (Modified from Abu-Elmagd K, Fung J, Bueno J, et al. Logistics and technique for procurement of intestinal, pancreatic and hepatic graft from the same donor. *Ann Surg.* 2002;232:680–687.)

operative hemorrhage, hemodynamic instability, electrolyte imbalance, and metabolic acidosis. Adequate nutritional reserve and cardiorespiratory fitness are paramount. Preoperative assessment mirrors that for liver transplant (described earlier) with additional caveats as follows.

Central venous access is often compromised by previous catheter-related infection or thrombosis. Partial or complete obstruction of the innominate veins or superior vena cava is sometimes encountered, even presenting as facial swelling with fluid overload or with exercise, which may contraindicate any graft incorporating a liver. All central vessels must be assessed for patency by ultrasound and, if any doubt, by magnetic resonance angiography. Access above the diaphragm is critical in patients receiving a liver

because of the surgical requirement for partial or complete occlusion of the IVC intraoperatively. This is not essential in intestine-only recipients, but patency of both femoral veins must be confirmed. Access should be planned before wait listing, including provision for involvement of an interventional radiologist if necessary.

Coagulation assessment should include rotational TEG and thrombophilia screen. Most multivisceral candidates are prothrombotic on viscoelastic testing, even in the presence of liver dysfunction, and confirmation of this can influence intraoperative management. Chronic abdominal pain associated with opiate use is also present in many intestinal transplant candidates, and specialist pain service assessment and advice are important, since postoperative and longer-term follow-up are often needed.

In candidates with liver disease, PPHTN and HPS should be excluded as routinely done in prospective liver recipients. Given the greater physiological and metabolic demands of a multivisceral procedure compared to liver transplant alone, both of these conditions may contraindicate multivisceral transplant. Important comorbidities include sarcopenia, ischemic heart disease, and diabetes, especially in candidates over 60 years old, and may also indicate prohibitive risk.

Intraoperative Management

To date, literature on the perioperative anesthetic management of intestinal and multivisceral transplant recipients is largely anecdotal. Anesthetic technique, vascular access, and monitoring modalities are mainly as described in the setting of liver transplantation, although the pathophysiological changes of end-stage liver disease are only present in liver-intestine and multivisceral candidates. A description of the differences between liver-intestine and liver-only transplantation follows.²⁴⁰⁻²⁴²

Some liver-intestine procedures take 24 hours or longer. Most require the presence of two highly experienced anesthesiologists and specialist ancillary staff, including nurses or technicians to help manage hemofiltration, VVB, cell salvage, rapid infusion devices, and point-of-care testing.

Most recipients have had extensive previous abdominal surgery, so they will have varying degrees of peritoneal sclerosis. Those with portomesenteric venous thrombosis or PN-associated liver disease may also have severe portal hypertension. Dissection and removal of recipient viscera can therefore be prolonged and associated with severe surgical bleeding. In some cases of full multivisceral transplant, on-table angiography and SMA/celiac embolization are performed immediately before surgery to reduce operative hemorrhage. In others, blood loss may be reduced by avoiding left upper quadrant dissection and splenectomy, providing there is enough space for the graft. In all cases, loss of multiple blood volumes should be anticipated. An agreed upon massive transfusion protocol with the hospital blood bank is essential.

Difficult dissection also increases the risk of long ischemia times and harm to the graft. The need to minimize ischemic time requires close coordination between donor and recipient teams, and the recipient anesthetic is started as soon as the organs are judged to be usable, sometimes even before donor explant.

In some transplant centers, in adult patients for liver-intestine transplant with portal hypertension and expected major blood loss, VVB is used from early in the dissection phase to decompress the portal circulation and support cardiac output. This depends on adequate access for femoral and/or portal outflow and internal jugular vein, SCV, or brachial inflow. A heat exchanger is incorporated in the bypass circuit to maintain normothermia during a long period of partial extracorporeal circulation. Since acidosis and hyperkalemia are also common complications in these massively transfused patients, some centers employ preemptive intraoperative hemofiltration, requiring placement of a dual-lumen dialysis catheter in another central vein, ideally separate from any multi-lumen catheter used for vasoactive drugs. Separate cannulae for rapid infusion of blood products and (in adults) a PA catheter are also

needed, and one or both may be placed alongside bypass return cannulae and a quadruple-lumen catheter in the right internal jugular vein. Ultrasound guidance during cannulation is indispensable. If right internal jugular vein cannulation is known to be not possible, alternative sites should be planned at the time of assessment. These may involve interventional radiology or surgical access at other supradiaphragmatic sites.

Monitoring for liver-intestine transplant mirrors that in liver transplantation. An added advantage of transesophageal monitoring is the immediate detection of air and thrombus in the heart, both of which are hazards of VVB. The risk of spontaneous thromboembolism, potentially life-threatening, also appears to be higher than in liver-alone implantation, given the hypercoagulability often seen on baseline thromboelastogram and unpredictable changes in coagulation during rapid administration of large volumes of blood products. Cell salvage may be used during dissection, but only as long as bowel or bowel fistulae are not breached and the surgical field remains uncontaminated. In practice, this is often brief. However, when hemofiltration is not used, the cell saver may be used to wash bank blood before infusion, reducing the risk of hyperkalemia.

Coagulation is managed as in liver transplantation, guided by the appearance of the surgical field and by TEG. Tranexamic acid is avoided if there is a clinical history of thrombosis or hypercoagulability on TEG. However, if major bleeding supervenes with a clinical coagulopathy and fibrinolysis on TEG, tranexamic acid can be considered. Open communication with a specialist in transfusion medicine is essential. This will help maintain a supportive relationship between blood bank and the transplant team despite exceptional demands on this service, and also facilitates timely use of prothrombin and fibrinogen concentrates when requested.

Reperfusion of an intestine-only graft is typically uneventful, but inclusion of liver in a composite graft usually produces hyperkalemia and at least transient hypotension, since reperfusion involves a large mass of tissue and occurs via hepatic arterial and portal venous routes in close succession. Management is as for liver transplant, with cautious administration of volume and vasopressor as required to maintain MAP. A marked fall in temperature is also seen. Although this is temporary if VVB with a heat exchanger is in use, it can otherwise be slow to correct, especially if continuous venovenous hemodiafiltration is running. Although the latter may be helpful in the prevention of hyperkalemia and severe acidosis, its benefits are unproven. Its use is often interrupted by clot formation in the filter or warming unit, and some consider it a significant distraction in an already complicated environment.

Postoperative Care

Postoperative management involves a variable period of continued mechanical ventilation, and maintenance of intravascular volume, which is diminished by tissue translocation that can persist for 1 to 3 days. Perioperative administration of prophylactic antimicrobials and intensive multi-agent induction of immunosuppression are also essential, as is monitoring of graft perfusion by Doppler ultrasound and stoma endoscopy. Abdominal wall (rectus sheath and subcostal transversus abdominis plane

blockade) infusions aid analgesia after extubation, but patient-controlled analgesia is often used at high doses and an ongoing opiate requirement is common. Opiate use often continues beyond discharge despite specialist pain service input and may require long-term psychological support. Postoperative surgical complications are frequent but graft loss is now rare.

Conclusion

Numbers treated in this challenging field are fortunately small, but 20 years of experience is yielding better results, and better outcomes are bringing more and earlier referrals. Further progress will depend on concentrating experience in national or regional centers, and close collaboration among these centers in defining indications and refining clinical care.

POSTABDOMINAL TRANSPLANTATION COMPLICATIONS

Surgical Complications

Early postoperative surgical complications include postoperative bleeding, drainage leaks (bile, urine, pancreatic secretions), and vascular thrombosis. The risk of bleeding and thrombosis is lessened when a balance is maintained between procoagulants and anticoagulants (proteins S and C, antithrombin). Because standard laboratory tests monitor only coagulation, this balance may be difficult to assess in the absence of viscoelastic tests, which evaluate whole blood clotting.

Complications vary based on donor graft qualities and recipient characteristics. For instance, hepatic artery thrombosis is more common in pediatric recipients because of the small caliber of the vessel, and bile leaks are more common after liver transplantation using grafts from cardiac death donors.²⁴³

Infection

After the immediate postoperative period, infection is the primary cause of death. Immunosuppressive medications, used to prevent rejection, are largely responsible for this risk. Bacterial infections predominate during the early postoperative period. Surgical site infections, intraabdominal abscesses, and infected hematomas are common. In this immunosuppressed population, multidrug-resistant organisms are common. In liver transplant recipients, bacterial translocation or bile leaks can result in peritonitis, cholangitis, and perihepatic abscesses. In one study of liver transplant recipients, 47% of ICU patients had bloodstream infections, 35% had intraabdominal abscesses, and 17% had ventilator-associated pneumonia.²⁴⁴ Prompt diagnosis and treatment with minimally invasive drainage techniques should be considered over early laparotomy. When this approach fails, laparotomy is indicated.

Prolonged endotracheal intubation and indwelling central venous and urinary catheters are a common source of infection. These devices should be removed as early as possible in the postoperative period. In the meantime, strict aseptic technique is required when accessing indwelling catheters and tubes.

Comorbidities, such as diabetes and renal dysfunction, can increase the risk of infection. Viral and fungal infections

are more likely after the first postoperative week. Risk factors for fungal infection in liver transplant patients include preexisting viral hepatitis, diabetes mellitus, multiple organ system failure, prolonged parenteral nutrition, long-term mechanical ventilation, and increased antibiotic use.²⁴⁵ Common sites of fungal infection include oral, esophageal, pulmonary, and intracerebral. Invasive fungal infections, despite prolonged treatment with amphotericin or itraconazole, are associated with a poor prognosis.

Immunosuppression

Acute cellular rejection (ACR) is an important cause of graft dysfunction within the first year of transplant. ACR rates have decreased with improvements in immunosuppression; ACR occurs in 15% to 25% of liver transplant patients and in less than 10% of kidney recipients.^{10,246} Generally, ACR responds well to therapy, however, chronic rejection is a significant cause of graft loss for all organs. The goals of immunosuppression are to prevent graft loss and to avoid the adverse consequences of antirejection regimens.²⁴⁷ Immunosuppression for solid organ transplant is divided into initial (induction) and maintenance phases. Calcineurin inhibitors cyclosporine and tacrolimus (formerly FK506) are the foundation for the majority of induction and maintenance regimens. Both agents inhibit transcription of interleukin (IL)-2 and other cytokines, primarily in helper T lymphocytes. Both manifest renal toxicity, which is caused by afferent arteriolar vasoconstriction and a reduction in GFR. The resulting azotemia is reversible with a reduction of dosage. Hypertension is due to vasoconstriction and sodium retention, and typically appears within the first weeks of treatment. Neurologic toxicity includes tremors, headaches, seizures, and even focal neurologic abnormalities. Mycophenolate mofetil therapy is a beneficial adjunct by allowing a reduction in the doses of calcineurin inhibitors.

In addition to tacrolimus, the most widely used drug, there are many other drugs available.²⁴⁸ Sirolimus, an inhibitor of the protein mTOR, is used for calcineurin-sparing effects and in patients transplanted for hepatocellular carcinoma to reduce recurrence.²⁴⁹ Basiliximab, a monoclonal antibody to CD25, has been used as an alternative to steroids for the induction of immunosuppression in liver transplantation.²⁵⁰

New immunosuppressive drugs are typically introduced for use in renal transplantation before they are applied in liver transplantation. Of note, recipients of liver grafts require less immunosuppression than do recipients of other organs, and liver grafts confer protection on other organs transplanted from the same donor. This effect is an example of the privileged immune status of the liver.²⁴⁷

The diagnosis of rejection requires a biopsy. The threshold for performing a biopsy should be low, albeit with an awareness that other conditions can mimic the histologic changes seen with rejection. For instance, diffuse lymphocytic infiltration of the kidney can be seen with rejection or lymphoproliferative disorder, and recurrent hepatitis C in the liver can resemble rejection.

Malignancy

Immunosuppressant drugs increase the susceptibility of transplant recipients to malignancy.²⁵¹ This effect is

primarily related to the level of immunosuppression, but production of transforming growth factor- β may also be responsible. The spectrum of malignancy is wide ranging and includes cancers seen with HIV-infection, a condition also associated with immunosuppression. Lymphoma regression occurs if the immunosuppressive agent is discontinued early.

In a retrospective study of more than 250,000 solid organ transplant recipients, Hodgkin lymphoma risk factors included male sex, young age, and Epstein-Barr virus (EBV) seronegativity at the time of transplant.²⁵² In a study of 175,000 solid organ recipients (primarily kidney and liver recipients), malignancy was identified in more than 10,000 patients, a standardized incidence ratio (SIR) of greater than 2 compared with the general population.²⁵³ The cancer sites with the highest relative risk included Kaposi sarcoma (SIR = 61), lip (SIR = 17), skin, nonmelanoma (SIR = 14), liver (SIR = 12), vulva (SIR = 8), and non-Hodgkin lymphoma (SIR = 8).

Posttransplant lymphoproliferative disorder (PTLD) is associated with a proliferation of B cells after transplantation in response to infection with EBV. Clinical presentation varies from a mononucleosis-like syndrome to malignant lymphoma. Pediatric patients are at increased risk due to a lower likelihood of prior exposure to EBV. Diagnosis is made by biopsy of the affected area, which can include the graft. Treatment consists of a reduction of immunosuppression levels and antiviral therapy against EBV, primarily ganciclovir. Individuals at high risk, such as patients who are seronegative for EBV or who receive a graft from a seropositive donor, should be maintained on antiviral prophylaxis.

The mean latency period for all cancers is 3 to 5 years after transplant, although specific malignancies exhibited unique time intervals. Cancer sites vary depending on the organ transplanted; for example, renal transplant recipients have a 100-fold greater than expected risk of developing carcinoma in the native kidney.²⁵⁴ The reasons are unclear, but prolonged dialysis before transplantation may be a risk factor.²⁵⁵ The use of specific immunosuppressive drugs also affects the relative risk of various cancers. For example, OKT3, which contains antibodies directed against T lymphocytes, is associated with an increased incidence of PTLD. Antibodies directed against B lymphocytes (rituximab) can reduce the incidence of PTLD. Sirolimus is not associated with cancer risk, and in fact may have antitumor effects.

Long-Term Survival

Long-term survival is affected by common diseases such as hypertension, hyperlipidemia, and diabetes mellitus.²⁵⁶ The leading long-term causes of death after liver transplant are hepatic processes (disease recurrence or organ rejection), malignancy, and cardiovascular disease.²⁵⁷

Conclusions

Abdominal organ transplantation has matured over the past 50 years. From its beginning as an experimental procedure, it has become the best hope for survival in the case of liver transplantation, and the best option for an independent life without morbidity in the case of renal and pancreatic

transplantation. Challenges for the future include a solution to the organ shortage, methods to minimize the likelihood of disease recurrence, and pharmacologic advances aimed at limiting the side effects of immunosuppression.

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KEY POINTS

- The shortage of organs available for transplantation is a worldwide problem.
- The discrepancy between the number of patients waiting for organ transplantation and the available organs remains significant, but has narrowed since 2013.
- Most organs in the United States are donated after neurologic death, with a small portion donated after circulatory death and from living organ donors.
- Neurologic-death donors have physiologic alterations that must be actively managed to ensure that the organs are suitable for transplantation.
- Determining neurologic death and circulatory death should follow national guidelines and local institutional protocols.
- The anesthesiologist must have an awareness of the ethical and legal issues related to the declaration of death that precedes organ donation.
- Expansion of the donor pool through the inclusion of extended criteria, such as high-risk donors, addresses the organ shortage and decreases waiting-list mortality.
- The use of extended criteria high-risk organs significantly impacts recipient outcomes and presents challenges to perioperative management.
- Ischemia-reperfusion injury in organ transplantation is unavoidable; however, management strategies can lessen the likelihood of postoperative graft failure.
- Goal-directed donor management can improve the number of organs transplanted per donor.
- Living organ donor kidney transplantation remains an important donor source in the United States, whereas the use of living donors for liver transplantation varies by country.
- New technologies, including machine perfusion after procurement, are promising as a means to mitigate the effects of prolonged preservation time, to increase the donor pool, and to improve transplant recipient outcomes.

Introduction

Organ transplantation requires the donation and successful procurement of a human organ. The success of organ transplantation relies on a functioning donor graft. The majority of organs used for transplantation in the United States are from donors after the declaration of neurologic death (donation after neurologic death, DND). Organs from donation after circulatory (cardiac) death (DCD) and living organ donation are in the minority, however, they remain an important source of donors.¹ Organs procured from these sources have different characteristics and present varying challenges in management. For instance, DND donors often have significant physiologic alterations and hemodynamic instability that is associated with neurologic death. These alterations and instability, if not treated, will lead to organ deterioration and may prevent the organ from being suitable for transplantation. In contrast, DCD donors have an obligatory period of hypotension of varying duration before cardiac arrest. The resulting compromise in perfusion can exacerbate reperfusion injury and lead to an increased incidence of posttransplant biliary dysfunction.

The shortage of organs is a worldwide problem and is the most important obstacle in organ transplantation. The

gap between the number of patients waiting for transplant and the available organs has widened (Fig. 61.1). In 2015, more than 119,000 transplant candidates were wait-listed in the United States through the United Network for Organ Sharing. Of these, 33,000 candidates underwent transplant surgery.² The majority of candidates were awaiting kidney grafts, with a smaller number awaiting liver, heart, and lung grafts. Many strategies were implemented to decrease the gap between the demand and supply, including public awareness campaigns and updates to the organ allocation system. Organ donation rates and the number of organs transplanted per donor vary substantially across geographic regions. Per 100 eligible deaths in the United States in 2016, the organ donation rate was 72.3, ranging from 52.9 to a high of 93.3 (Israni OPTN 2016 Annual Data Report).³ To increase the number of organs for transplant, many programs have expanded the donor pool by using extended criteria donors (ECDs). Not surprisingly, the number of organs transplanted per donor varies according to donor category: ECD, DCD, or standard criteria donor (SCD). The number of organs transplanted from DCD donors is similar to ECDs, primarily attributable to the ability of the kidney to tolerate the longer periods of ischemia associated with organ procurement after DCD. The use of

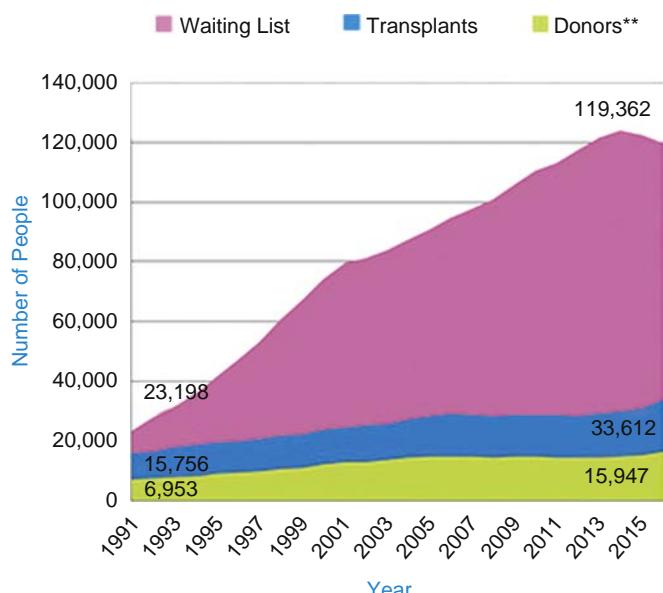


Fig. 61.1 The gap in the United States between the number of donors, patients transplanted, and patients on the waitlist by year, 1991 to 2015. The gap has declined since 2013. **Donors can be deceased and living. <http://www.organdonor.gov/statistics-stories/statistics.html>.

living-related and living-unrelated donors is widespread in countries with moral or legal objections to neurologic death and is an important worldwide donor source. Many policies have been proposed to promote the best practices in organ donation.^{3,4} There are several areas that have the potential to expand the donor pool, which include deaths that are not referred to the organ sharing agencies and organs that have been procured, but unused for transplant.

Organ transplantation is a complex process that requires close coordination among many specialized teams. Procurement organizations, transplant coordinators, social workers, nurses, surgeons, internists, intensivists, and anesthesiologists are involved in the process. To maximize the number of organs transplanted and to preserve the best possible function of donated organs, anesthesiologists need to understand the pathophysiologic derangements associated with donation and ischemia-reperfusion injury. In addition, anesthesiologists must be aware of the ethical and legal issues related to the declaration of death and organ donation.

Management of Organ Donors After Declaration of Neurologic Death

DND (also called after declaration of brain death) provides the majority of donated organs in the United States.³ Organ procurement from DND donors can only occur after the declaration of death. The concept of neurologic death emerged in the 1950s. In 1968, a Harvard Ad Hoc Committee on Irreversible Coma established a set of criteria that has been widely used for the determination of neurologic death.⁵ In the United States, the Uniform Determination of Death Act

TABLE 61.1 Pathophysiologic Changes Associated With Neurologic Death

Signs and Symptoms	Pathophysiologic Changes	Incidence (%)
Hypertension	Catecholamine storm	80-90
Hypotension	Vasoplegia, hypovolemia, reduced coronary blood flow, myocardial dysfunction	80-90
Bradycardia and other arrhythmias	Catecholamine storm, myocardial damage, reduced coronary blood flow	25-30
Pulmonary edema	Acute blood volume diversion, capillary damage	10-20
Diabetes insipidus	Posterior pituitary damage	45-80
Disseminated intravascular coagulation	Tissue factor release, coagulopathy	30-55
Hypothermia	Hypothalamic damage, reduced metabolic rate, vasodilation, and heat loss	Varied
Hyperglycemia	Decreased insulin concentration, increased insulin resistance	Common

was approved in 1981 by the National Conference of Commissioners on Uniform State Laws, in cooperation with the American Medical Association, the American Bar Association, and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Although the criteria for the declaration of neurologic death were based on ethical principles established several decades ago, the criteria remain valid today.⁶

Although the concept of neurologic death has been widely accepted in Western cultures, minor variations in definition and implementation exist in different countries. Despite these differences, the clinical criteria are similar.⁷ A larger difference exists among different cultures in accepting and implementing the neurologic death criteria. In fact, neurologic death has not reached a legal status in some countries, such as China.

PATHOPHYSIOLOGIC CHANGES WITH NEUROLOGIC DEATH

A variety of pathophysiologic changes are associated with neurologic death. The pathophysiologic mechanisms of neurologic death have profound effects at the molecular, cellular, and tissue levels. The clinical presentations associated with neurologic death may be complex and vary from patient to patient. They can be further complicated by prior pathologic abnormalities, disease, and therapy. The typical pathophysiologic changes associated with neurologic death are further described in Table 61.1.

CARDIOVASCULAR RESPONSES TO NEUROLOGIC DEATH

The cardiovascular system is closely regulated by the central neural system. Cardiovascular responses to neurologic death usually consist of two phases. The first phase is characterized by sympathetic discharge (catecholamine

storm), which causes intense vasoconstriction or elevated systemic vascular resistance (hypertensive crisis), tachycardia, and a redistribution of blood volume with visceral ischemia. Acute myocardial injury can occur in neurologic-dead donors without a history of coronary artery disease.⁸ Echocardiographic evidence of myocardial dysfunction is observed in 40% of neurologic-dead donors under consideration for heart donation.⁹ At times, parasympathetic activation can result in bradycardia. After the sympathetic discharge of the first phase, the loss of sympathetic tone, decreased cardiac output, blunted hemostatic responses, and severe peripheral vasodilatation (vasoplegia) characterize the second phase. In addition to neurohormonal disturbances, other contributing factors include blood loss, intravascular depletion attributable to capillary leakage, osmotic therapy for rising intracranial pressure (ICP), and diabetes insipidus.

The first phase is correlated with ischemia in various parts of the brain and is attributable to an increase of ICP, and the second phase is caused by cerebral herniation and spinal cord ischemia. Although the first hypertensive phase generally represents a transient period in the progression to neurologic death, the second hypotensive phase is profound and sustained. Failure to correct these cardiovascular derangements results in poor organ perfusion and inadequate tissue oxygenation, which will threaten the viability of the donated organs.

RESPIRATORY RESPONSES TO NEUROLOGIC DEATH

An increase in systemic vascular resistance after neurologic death results in blood shifting from the systemic circulation to the more compliant pulmonary circulation. The resulting increase in hydrostatic pressure in the pulmonary circulation causes pulmonary capillary leakage and pulmonary edema. Sympathetic activity triggers a sterile systemic inflammatory response, initiating infiltration of neutrophils and increasing pulmonary endothelial permeability, which further contributes to lung injury. Proinflammatory cytokines are released at the alveoli and are associated with early graft failure and mortality after lung transplantation. The inflammatory response in neurologic-dead donors is associated with the deterioration in cardiac function and a shift to anaerobic metabolism. Hormonal instability can reduce alveolar fluid clearance, resulting in significant accumulation of extravascular lung water. If ventilation is not supported, then respiratory arrhythmia progresses to apnea and cardiac arrest.^{10,11}

ENDOCRINE, METABOLIC, AND STRESS RESPONSES TO NEUROLOGIC DEATH

Neurologic death is frequently associated with pituitary failure and disturbances of cortisol, thyroid hormones, antidiuretic hormone, and insulin. Posterior pituitary function in neurologic-dead donors is frequently lost. The development of central diabetes insipidus results in severe fluid and electrolyte derangements and can be observed in up to 90% of neurologic-dead donors.¹⁰ Anterior pituitary function in neurologic death can also be affected, resulting in a deficiency in triiodothyronine (T_3) and thyroxine

(T_4), adrenocorticotrophic hormone, thyroid-stimulating hormone, and human growth hormone. Thyroid hormonal deficiency may be similar to the euthyroid sick syndrome commonly observed in the non-neurologic injured patient with multisystem organ failure. Hyperglycemia is commonly encountered in neurologic-dead donors because of decreased insulin concentrations and increased insulin resistance. Hypothalamic function and control of body temperature are lost. Although hyperpyrexia may initially occur, hypothermia follows, which is caused by a reduction in metabolic rate and muscle activity, in combination with peripheral vasodilation. Disseminated intravascular coagulation is present in up to one-third of isolated patients with head injuries and is believed to be caused by the release of tissue thromboplastin from brain tissue.¹¹

Donation After Circulatory (Cardiac) Death

Before the acceptance of neurologic death, all organs procured were from donors who suffered a cardiac demise (DCD, previously known as donation from a non-heart-beating donor). After the establishment of the Harvard criteria for neurologic death, DND quickly became the principal source of organ donation. However, an interest in the use of DCD organs has been renewed in recent years, driven by the persistent shortage of DND donors and the lack of acceptance of neurologic death in some countries. Policies and protocols developed by healthcare organizations now encourage DCD organs, and their use is increasing in the United States and other countries. In the United States, the number of DCD donors continues to increase, and accounted for over 17% of donors in 2016 (Fig. 61.2).³ During the same period, the number of living donors dropped slightly from 7000 to 6600. Kidney grafts accounted for over 95% of the organs transplanted from living donors during this period. The American Society of Anesthesiologists established a Sample Policy for Organ Donation after Circulatory Death, with the recommendation that its members actively participate in the development of institutional DCD protocols.

DCD donors are divided into five categories: I, patients who are dead on arrival at the hospital; II, unsuccessfully resuscitated patients; III, patients in whom cardiac arrest is imminent; IV, cardiac arrest in neurologic-dead donors; V, unexpected arrest in the intensive care unit (ICU). Categories III and IV are considered as controlled DCDs, whereas the remaining categories are considered uncontrolled DCDs. Controlled DCD implies that life-support withdrawal can be planned and the transplant team is awaiting the cardiac arrest and is ready for rapid organ recovery. In contrast, uncontrolled DCD implies the patient has experienced an unanticipated cardiac arrest, and organ donation is considered only after an unsuccessful resuscitation. Warm ischemia time is significantly longer in uncontrolled DCDs. Currently, most DCD donors for organ transplantation are controlled DCD donors. Successful use of the uncontrolled DCD grafts has been reported in several studies.¹²

DCD donors usually suffer from irreversible brain or spinal injury but do not meet the neurologic death criteria. The prognosis for a meaningful quality of life is poor. Withdrawal of therapy must be based on a clinical decision of

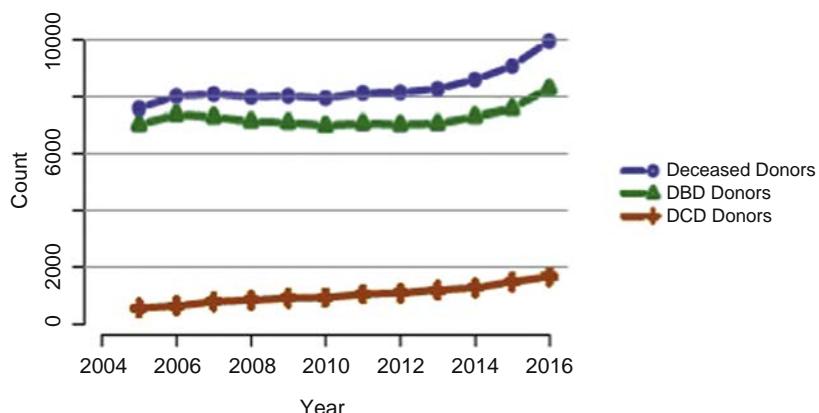


Fig. 61.2 Total number of organ donors in the United States by year, 2005 to 2016. DBD, Donation after brain death; DCD, donation after cardiac death. (Redrawn from Israni AK, Zaun D, Rosendale JD, et al. OPTN / SRTR 2016 Annual Data Report: Deceased organ donation. *Am J Transplant*. 2018;18:434–463.)

futility and conform to the wishes of the patient and family. The consideration of the withdrawal of life-sustaining therapies must be independent from any discussion related to transplantation. The transplantation team cannot be involved in this decision. Drugs can be used to relieve pain and anxiety and to provide comfort for the patient during withdrawal. Therapies designed to improve graft quality, but without benefit to the patient, are controversial; however, therapies with minimal impact on the patient that improve organ survival are allowed in some protocols.

Declaration of circulatory death should follow procedures proposed by national organizations and policies adopted by the local institution.^{13,14} After a decision has been made to withdraw support, the trachea is extubated and life support is stopped. A physician who is not involved with organ transplantation declares cessation of cardiac function. Declaration of circulatory death is not different from clinical practice, which requires a clinical examination to confirm pulselessness or the absence of an arterial waveform. The duration between cessation of cardiovascular activities and the declaration of circulatory death is usually 2 to 5 minutes to ensure irreversibility. Organ procurement starts after death is declared.

Although organs procured from DCD donors are not exposed to the physiologic derangements of neurologic death, they are at greater risk for ischemia-reperfusion injury than organs from DND donors. This results from hypoxemia and ischemia in a warm environment, which is unique during DCD procurement. The time elapsed from extubation to circulatory death is an important factor for determining the suitability of organ donation. If spontaneous breathing and/or heart function continues for a prolonged period after life support withdrawal, then the organs may not be suitable for transplantation, particularly in donors with comorbidities. To assist physicians in predicting how long a patient will sustain life after the withdrawal of life support, a 6-variable score was developed by the University of Wisconsin (UW) (Table 61.2). A low score (8–12) means that breathing and/or cardiac function will continue for some time. A high score (19–24) means that apnea and cardiac arrest are imminent.¹⁵

The two separate definitions and procedures used for DND and DCD have led to a new debate about the definition and determination of death. A uniform concept of death, which combines all previous criteria for death, is emerging.

TABLE 61.2 University of Wisconsin Criteria for Donation After Circulatory Death: An Evaluation Tool

Variables	Points
SPONTANEOUS RESPIRATION AFTER 10 MIN	
Respiratory rate > 12 breaths/min	1
Respiratory rate < 12 breaths/min	3
Tidal volume > 200 mL	1
Tidal volume < 200 mL	3
Negative inspiratory force > 20 cm H ₂ O	1
Negative inspiratory force < 20 cm H ₂ O	3
No spontaneous respiration	9
BODY MASS INDEX (KG/M²)	
<25	1
25–29	2
≥30	3
VASOPRESSORS	
None	1
1 pressor	2
≥2 pressors	3
PATIENT AGE (YEARS)	
0–30	1
31–50	2
>50	3
INTUBATION	
Endotracheal tube	3
Tracheostomy	1
OXYGENATION AFTER 10 MIN	
O ₂ saturation > 90%	1
O ₂ saturation 80%–90%	2
O ₂ saturation < 80%	3

University of Wisconsin score: 8–12, high probability; 13–18, moderate probability; and 19–24, low probability for continuing to breathe after extubation. (From Lewis J, Peltier J, Nelson H, et al. Development of the University of Wisconsin Donation After Circulatory Death Evaluation Tool. *Prog Transplant*. 2003;13:265–273.)

A growing consensus is that all criteria used to diagnose human death rely on the demonstration of the irreversible loss of the capacity to breath, combined with the irreversible loss of the capacity for consciousness. The irreversible loss of these two functions equates to human death.¹⁶

Category III (impending cardiac arrest) DCD is the ideal source for organ transplant. Kidneys from DCD donors are frequently used. Several studies have shown that, despite a

higher incidence of delayed graft function (DGF), kidneys from DCD donors have comparable short- and long-term graft survival.¹² Livers from DCD donors have a higher likelihood of postoperative biliary complications such as diffuse ischemic cholangiopathy with intrahepatic biliary stricture and may also have a higher incidence of primary graft nonfunction and DGF compared to grafts from DND donors.¹⁷ Ischemic cholangiopathy occurs more frequently if the donor is older, is overweight, and has a prolonged ischemic period. Heart and lungs are susceptible to ischemia and only a few cases of the successful use of such grafts from DCD donors have been reported.¹⁵

Extended Criteria Donor

Traditionally, DND organ donors are young and otherwise healthy until stricken by an isolated cerebral event or head injury (SCDs). As the numbers of patients waiting for transplant increase, many centers have extended donor criteria to minimize waiting-list mortality. Many terms, including suboptimal donor, marginal donor, inferior donor, nonstandard donor, and high-risk donor, have been used.¹⁸ The criteria that make up the ECD group are more elusive and evolving. Donor characteristics of ECDs vary from organ to organ but generally include advanced age, prolonged cold ischemia time, inferior organ function, and other comorbidities.^{18,19} However, donor risk is a relative term and should be described as a continuum, not a dichotomy of SCD and ECD. Therefore, donor risk index (DRI) has been developed for donors.

The kidney DRI has been developed using 10 donor characteristics (Box 61.1).²⁰ The kidney DRI can be converted into the kidney donor profile index (scale 1%-100%). A higher kidney donor profile index indicates a higher graft failure rate. The DRI has been defined for liver grafts. DRI is a quantitative assessment of the risk of graft failure associated with the donor. Liver DRI is calculated from eight donor characteristics (Box 61.2).²¹ Despite an increased risk of graft failure, moderate-to-high acuity transplant candidates who receive a high DRI graft have a survival benefit compared with those remaining on the wait list.²² Calculation of the DRI can help physicians make a decision to accept or reject a donor offer; however, the calculation requires a projected cold ischemia time.

The use of ECD or high-risk DRI grafts has implications on intraoperative management. In a study of liver transplantation, several donor characteristics are associated with a high incidence of intraoperative hyperkalemia in adults: DCD grafts, prolonged ischemia time, and prolonged donor hospital stay before procurements.²³ ECD liver grafts are also associated with postreperfusion syndrome, intraoperative bleeding, and postoperative reoperation.²⁴

Management of Organ Donors Before Procurement

As previously discussed, various physiologic derangements are common in DND donors. If not treated, these derangements can lead to graft deterioration, resulting in organs unsuitable for transplantation. A discussion of treatment strategies follows.

BOX 61.1 Kidney Donor Profile Index

The following donor characteristics are used to calculate the kidney donor profile index

- Age
- Height
- Weight
- Ethnicity
- History of hypertension
- History of diabetes
- Cause of death
- Serum creatinine
- Hepatitis C Virus status
- Donation after circulatory death status

From <https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator>.

BOX 61.2 Liver Donor Risk Index

Age (four categories): >40, >50, >60, >70 years
 Cause of death (two categories): cerebrovascular accident (lower risk) versus other
 Race: African American (higher risk) versus other
 Donation after circulatory death: yes or no
 Partial or split graft: yes or no
 Height: increasing risk as height decreases below 170 cm
 Regional or national share: yes or no
 Cold ischemia time

CARDIOVASCULAR MANAGEMENT

Although both hypertension and hypotension are associated with neurologic death and can result in poor perfusion to the organs, hypotension is more profound and difficult to treat. Maintaining adequate intravascular volume is probably the most effective therapy for vasoplegia. No evidence demonstrates that a specific crystalloid solution is superior to another. Adequate resuscitation, as evidenced by a mean arterial pressure of 60 to 100 mm Hg, may decrease cytokine levels and increase the number of organs available for transplantation.²⁵ Large doses of starch-based colloids should be avoided because they may be associated with DGF.²⁶

When hemodynamic stabilization is not achieved with fluid resuscitation, vasoactive drugs should be considered. Dopamine is most commonly used in this setting. If a large dose of dopamine is required, then a second vasoactive agent can be added. Dopamine and other catecholamines have beneficial antiinflammatory and immunomodulatory effects. Vasopressin is recommended as the initial therapy of choice for potential heart donors by the American College of Cardiology.²⁷ Vasopressin reduces catecholamine requirements and is an effective treatment for diabetes insipidus.

For a potential heart donor, cardiac function should be assessed, with early interventions to improve the donor procurement rate. Echocardiography is useful since it can identify both functional and structural abnormalities. Functional abnormalities identified in the early stage can be managed before heart transplantation, whereas structural abnormalities may preclude transplantation. Coronary angiography is useful in older donors with suspected or

known coronary artery disease. Myocardial damage caused by catecholamine storm may be prevented or attenuated by controlling cardiovascular responses, which may increase the number of heart transplants.¹¹ However, large doses of norepinephrine are associated with increased cardiac graft dysfunction and increased recipient mortality.²⁸

Excessive intravascular fluid therapy may have detrimental effects and should be avoided in lung donors. Fluid restriction increases the number of lung grafts available for transplantation.¹⁰ Because this practice creates a conflict of interest on the basis of which organs will be procured, particularly between the lungs and kidneys, fluid management should be balanced to optimize overall donation potential.¹⁰ The goal is to maintain a euvolemic state and to maintain arterial blood pressure and cardiac output with the least amount of vasoactive support possible. Invasive hemodynamic monitoring may be used to guide intravascular fluid therapy.

PULMONARY MANAGEMENT

The lungs are vulnerable to injury and, consequently, are one of the most difficult organs to preserve. Only 15% to 25% of donated lungs are used in transplantation. Current pulmonary management for potential lung donors favors small tidal volume ventilation. The focus of pulmonary management is to recruit and retain lung units while limiting tidal volume and inspiratory pressure. This strategy is extrapolated from studies in acute respiratory distress syndrome. Specific approaches to ventilator management for the donor are variable, but a common approach is a low tidal volume (6-8 mL/kg), low fraction of inspired oxygen concentration (FiO_2), and relatively high positive end-expiratory pressure (PEEP).²⁹ Pulmonary recruitment maneuvers, using pressure-controlled ventilation and high PEEP (15 cm water), followed by a return to conventional volume-controlled ventilation with a lower PEEP, are recommended by others. The administration of aerosolized terbutaline increases alveolar fluid clearance via β -adrenergic stimulation.³⁰ As previously discussed, a large amount of intravascular fluid and/or large-dose vasopressors are associated with impaired graft function in potential lung donors.¹⁰

Adequate gas exchange and good oxygenation are the most important indicators of the functional quality of the lung. However, an initial $\text{PaO}_2/\text{FiO}_2$ ratio less than 300 mm Hg should not be used as grounds for exclusion. Reversible processes such as secretions, pulmonary edema, and atelectasis can affect the $\text{PaO}_2/\text{FiO}_2$ ratio. Bronchoscopy is generally performed to remove mucous plugs that are present.

TEMPERATURE

Since hypothalamic function and regulation of body temperature are lost, DND donors usually have initial hyperpyrexia followed by hypothermia. Donor hypothermia is also contributed by reduced metabolic rate and peripheral vasodilatation. Normothermia has been traditionally recommended before and during procurement by using active warming devices. A recent report from a prospective trial challenges this traditional temperature management before procurement. In this trial, organ donors were randomized

into two targeted temperature groups: mild hypothermia (34°C-35°C) or normothermia (36.5°C-37.5°C). The hypothermia group is associated with a significantly lower rate of DGF after kidney transplantation.³¹ In a retrospective study, mild hypothermia is confirmed to reduce DGF, but not graft survival in kidney transplantation.³²

HORMONES, STEROIDS, ELECTROLYTES, AND GLYCEMIC CONTROL

Hormonal deficiency is common in neurologic-dead donors and hormonal replacement is beneficial.^{8,10} Exogenous replacement of antidiuretic hormone in neurologic-dead donors improves graft function in kidney, liver, and cardiac recipients.¹⁰ Thyroid hormone replacement improves the number of organs transplanted per donor and cardiac recipient survival.^{25,33} However, most studies showing advantages to hormone supplement are retrospective; adequately powered randomized trials are lacking.

The systemic inflammatory response associated with neurologic death leads to pulmonary infiltration of neutrophils and the elevation of interleukins. The systemic inflammatory response of the donor is associated with graft failure and recipient mortality. Methylprednisolone administration can moderate the inflammatory response and may improve oxygenation, reduce lung water, and increase lung yield. Methylprednisolone administration can also decrease inflammation in the liver, heart, and kidney.

Intravascular volume replacement is essential in the donor management. An isotonic crystalloid (lactated Ringer solution or 0.9% saline) is the preferred choice. However, 0.9% saline may not be the best choice due to the development of hyperchloremic metabolic acidosis. Colloid solutions are appropriate for rapid intravascular volume expansion. Routine use of hydroxyethyl starch is not recommended since it is associated with potential acute kidney injury, and coagulopathy. After administering initial fluid to correct hypovolemia, hypernatremia should be treated by giving a hypotonic solution.¹⁰ Studies have demonstrated that donor hypernatremia ($>155 \text{ mmol/L}$) is associated with poor post-liver transplant outcomes.³⁴ Analysis of heart donors in Europe showed increased recipient mortality when donor sodium was less than 130 or greater than 170 mmol/L.³⁵ Correction of severe hypernatremia before organ procurement appears to attenuate post-transplant liver dysfunction.¹⁰ Hyperglycemia in the donor is common and exacerbated by steroid therapy. Poor glucose control adversely affects donor renal function.³⁶ Insulin management should target a glucose level between 120 and 180 mg/dL. Routine use of IV fluid containing dextrose is not recommended.³³

DONOR MANAGEMENT GOALS

Current recommendations stress the use of standardized donor management with specific preprocurement goals. The objective of donor management goals (DMGs) is to maintain cardiovascular, pulmonary, renal, and endocrine homeostasis. The primary hemodynamic goal is to maximize perfusion for organ preservation by ensuring adequate intravascular volume and cardiac output.³³ Table 61.3 summarizes common goals reported by various

TABLE 61.3 Donor Management Goals, as Reported by Various Authors

Preset Clinical End Points	Six DMGs*	Eight DMGs†	Ten DMGs‡
Mean arterial pressure (mm Hg)	≥60	60–120	60–100
Central venous pressure (mm Hg)	≤10 (or serum osmolality 285–295 mmol/L)	4–12	4–10
Final sodium (mmol/L)	≤155	≤155	135–160
Pressors	≤1 (1 plus vasopressin to treat DI is acceptable)	≤1 or low dose	≤1 and low dose
PaO ₂ (mm Hg) or PaO ₂ /FiO ₂ ratio	PaO ₂ ≥ 300 while on 100% oxygen (or PaCO ₂ /FiO ₂ ratio > 3)	Final PaO ₂ > 100	PaO ₂ /FiO ₂ ratio: >300 on PEEP = 5 cm H ₂ O
Arterial blood gas: pH	7.25–7.50	7.30–7.50	7.30–7.45
Glucose (mg/dL)		≤150	<150
Urine output (mL/kg/h) in 4 h before procurement		0.5–3.0	1–3
Ejection fraction of left ventricle			>50%
Hemoglobin (mg/dL)			>10

DI, Diabetes insipidus; FiO₂, fraction of inspired oxygen concentration; PaCO₂, partial arterial pressure of carbon dioxide; PaO₂, partial arterial pressure of oxygen; PEEP, positive end-expiratory pressure.

*Hagan ME, McClean D, Falcone CA, et al. Attaining specific donor management goals increases number of organs transplanted per donor: a quality improvement project. *Prog Transplant*. 2009;19(3):227–231.

†Franklin GA, Santos AP, Smith JW, et al. Optimization of donor management goals yields increased organ use. *Am Surg*. 2010;76(6):587–594.

‡Malinoski DJ, Daly MC, Patel MS, et al. Achieving donor management goals before deceased donor procurement is associated with more organs transplanted per donor. *J Trauma*. 2011;71(4):990–995, discussion: 996.

studies and recommended by some committees. Studies have shown that compliance with predetermined goals significantly improves the number of organs procured and transplanted.^{25,37} Early achievement of DMGs is important. Donors with four or more organs transplanted per donor have significantly more individual DMGs met at the time of consent. Efforts should focus on early management in patients with catastrophic neurologic injury until the intent to donate is known.³⁸ One study showed that only 15% of donors met DMGs at the time of consent, although the rate was higher immediately before organ procurement.

Management of Donors After Circulatory Death

The majority of DCD donors are patients awaiting cardiac arrest in the ICU (category III). To minimize warm ischemia time, life support is usually withdrawn in the surgical unit. However, the family's desire to be present has led some institutions to withdraw life support in other nearby locations. The procurement team should not take part in patient management before a determination of irreversible death, which includes the period during which withdrawal of support and declaration of death occur. The administration of pharmacologic drugs for the purpose of maximizing donation potential, particularly therapies capable of hastening death, is controversial. However, narcotics and benzodiazepines are commonly continued and can be titrated to blunt sympathetic responses. Premortem administration of heparin can facilitate organ procurement but, because of the bleeding risk, is omitted in some institutional policies. Most protocols require specific consent for premortem donor therapy.

Invasive premortem techniques for reducing warm ischemia time have been described. These include cannulation of the femoral artery and vein before the withdrawal of life support, which allows rapid infusion of cold preservation solution after the declaration of death. These cannulas can also be used for extracorporeal membrane oxygenation (ECMO) after death. However, the postmortem use of ECMO to restore the blood flow to vital organs generates vigorous debate, which highlights the ongoing ethical questions in donor management—the need to protect the best interest of the dying patient, while facilitating his or her wish to donate.³⁹

Management of Organ Donor During Procurement Surgery

Anesthesia care for organ procurement is required only in the case of neurologic-dead donors. The majority of organ procurement occurs at community hospitals, not tertiary medical centers. As a result, the logistics of organ procurement, the social circumstances, and the unusual sequence of intraoperative events may seem intimidating to the anesthesiologist.

Surgical techniques may vary, depending on whether single or multiple organs are procured. Generally, wide exposure of the surgical field is established via a midline laparotomy extended by sternotomy. A cannula is placed in the aorta to flush the organs with the cold preservation solution. Ice is applied to the surgical field to further protect the organs. The organs are removed with their vascular structures after isolation in an order according to their susceptibility to ischemia, with the heart first and the kidney last.

Most donors arrive in the surgical unit with an endotracheal tube in place, and supported by the intravenous administration of vasoactive drugs. During procurement surgery, patients can have movements resulting from spinal reflexes; therefore, neuromuscular blockers are desirable. Spontaneous spinal reflex or surgical stimulation can cause catecholamine release and hypertension. Hypertension can be managed by a number of drugs including vasodilators, opioids, and anesthetics; however, volatile anesthetics are commonly preferred. As previously mentioned, volatile anesthetics may provide additional benefits that include ischemic preconditioning and the reduction of ischemia-reperfusion injury.⁴⁰

The intravascular administration of fluids and vasoactive drugs can treat blood loss and cardiovascular instability caused by surgical manipulation. Maintaining hemodynamic stability allows surgeons to procure the organs without further damage to the organs. Vasodilators such as phentolamine or alprostadil (for lung recovery) may be administered during cross-clamping with the goal of decreasing systemic vascular resistance and allowing an even distribution of the preservation solution. Clinically significant bradycardia in neurologic-dead donors does not respond to atropine; therefore, a direct-acting chronotrope such as isoproterenol should be readily available. Heparin is usually administered before cross-clamping the aorta. If recovery of the heart or lung is anticipated, then pulmonary artery catheters and/or CVP catheters need to be withdrawn before cross-clamping. If lung recovery is anticipated, then the lungs are ventilated well beyond cross-clamping. Communication between the surgical team and the anesthesiologist is crucial to ensure optimal organ quality. As soon as the organs are perfused with the cold solution, mechanical ventilation and anesthesia care can be stopped.

Management of Living Organ Donors

Living donor organ transplantation has been successfully used as an alternative to deceased donor transplantation. In the United States the number of living donor organ transplants has remained flat since 2011.³ In some Asian countries such as Japan and Korea, living donor transplantation is a standard procedure since DND is unusual because of cultural beliefs in these countries. Living donor organ transplantation has some advantages. The procedure can be scheduled as elective surgery at the same facility, which allows donor and recipient surgeries to be coordinated and the cold ischemia time to be minimized. Additionally, the graft is not exposed to the physiologic alterations associated with DND or DCD donors. Living donors direct their donation to a specific recipient; therefore, the timing of the transplant can be optimized for the recipient, and prolonged waiting times associated with deceased donor transplantation are typically avoided. As a result, the recipient is generally in better overall condition. Although living organ transplantation has its advantages, it exposes healthy donors to medical risks. Additional concerns are potential decreased quality of life and an adverse financial impact after donation. The ethical aspect of living organ donation, particularly liver donation, continues to be vigorously scrutinized.^{41,42}

Living donation should be preceded by a thorough medical, psychologic, and social evaluation that confirms the absence of contraindications and the lack of coercion. The informed consent includes full disclosure of possible complications and is facilitated by a patient advocate in many institutions with no relationship to the recipient. In the past, donors were typically related to the prospective recipient. Now, living unrelated donors make up a greater proportion of living kidney transplant in the United States.¹ Paired or chain donation allows two or more recipients with incompatible living donors to exchange donors, improving the graft match for both recipients. Similar to the expansion of deceased donor criteria, living donor criteria have been extended to include donors of advanced age and those with obesity.⁴³ Living multi-organ donation from a single donor, either simultaneously or sequentially, although rare, has been reported. Careful selection of such donors, disclosure of risks, and close follow-up are needed.⁴⁴

LIVING KIDNEY DONOR

Because the kidney is a paired organ, it is a natural choice for living donation. The first successful kidney transplant was a living organ transplant performed between identical twins in 1954. Now, living donors account for approximately 29% of kidney transplants in the United States.^{1,45} Living donor kidney transplantation provides the optimized timing for transplant and can avoid pretransplant dialysis, which is associated with improved survival.⁴⁶ In addition, living donor grafts provide better function and last longer than grafts from deceased donors.⁴⁷ A wide range of medical and nonmedical factors need to be considered to ensure donor safety. To ensure a sufficient reserve after donation, many transplant centers use a glomerular filtration rate (GFR) greater than 80 mL/min/1.73 m² as a cutoff for donation. GFR is typically estimated by the measurement of urine creatinine clearance. If the estimated GFR is marginal, then radioactive and nonradioactive tracers can provide additional information.⁴⁸ Some centers allow a lower GFR.⁴⁹

Traditionally, living kidney donor surgery was performed via open nephrectomy via a subcostal lateral incision. Now, it is commonly performed via laparoscopy. With this approach, donors experience less postoperative pain, a faster recovery, and a shorter hospital stay.⁴⁹ Either the left or the right kidney can be used for transplant; however, the left kidney is usually preferred because of the easier surgical exposure and longer vascular supply. The right kidney has a short vein, and its artery courses posterior to the inferior vena cava.

The patient is placed in a lateral position with the table flexed and the kidney rest elevated. The surgical procedure begins with mobilization of the kidney with subsequent identification and dissection of the ureter, renal vein, and artery, and separation of the adrenal vein. When the right donor nephrectomy is performed, additional steps include duodenal mobilization and separation of the kidney from the liver. After mobilization of the kidney and clamping of the vascular structures, the kidney is retrieved through a small incision by either a hand-assisted or non-hand-assisted technique. Donor nephrectomy can be performed via a transabdominal route but is increasingly accomplished via

a retroperitoneal approach using minimally invasive techniques. The advantage of a retroperitoneal approach is less manipulation of intraabdominal viscera. Single-incision donor nephrectomy has been described using uniquely designed devices. Recently, robotic-assisted laparoscopic living donor nephrectomy has been reported.^{49,50} This technique may further decrease the trauma and discomfort to the donor.

Anesthetic management of elective laparoscopic donor surgery on a healthy patient is similar to that used for elective laparoscopic nephrectomy. Standard noninvasive monitors are usually sufficient. One or two large-bore peripheral intravenous lines are usually placed. Transfusion of red blood cells is rare; however, type and screen, or type and cross for 1 to 2 units of blood, is routine practice in some centers in case of injury to major vessels. General anesthesia is required for laparoscopic nephrectomy and general anesthesia combined with epidural anesthesia is often used if open nephrectomy is planned.

Although laparoscopic nephrectomy on a healthy patient may be routine, some concerns in addition to potential blood loss exist. High intraabdominal pressure reduces venous return and has been associated with postoperative renal dysfunction. Lower insufflation pressure may prevent compression of the renal veins and parenchyma.⁵¹ Adequate intravascular fluid administration appears to be the best strategy to preserve kidney function. Some advocate liberal fluid administration (10-20 mL/kg/h), although laparoscopic nephrectomy is typically associated with minimal blood loss. Others use urinary output as an indicator for fluid management. To ensure that the urinary output is greater than 2 mL/kg/h, fluid is usually given in excess of the physiologic need throughout the procedure. The surgeon may request the administration of furosemide and/or mannitol during the surgery for the purpose of increasing urine output. The preferred type of fluid for intravascular volume expansion during donor nephrectomy is not known. In the absence of evidence, most centers use an isotonic crystalloid solution. Nitrous oxide is best avoided because of a concern over bowel distention and poor surgical exposure. Intravenous heparin (3000-5000 international units [IU]) is often administered immediately before the renal vessels are clamped. Protocols may vary among institutions, and close communication with the transplant surgeon is essential. If hypotension occurs after adequate fluid replacement, then dopamine and ephedrine are preferable to direct-acting vasopressors to minimize vasoconstriction in the graft. After the kidney is retrieved, anesthesiologists should be prepared for a quick closure and ensure that neuromuscular blockade is reversed.

Mild or moderate pain after laparoscopic nephrectomy originates from the port insertion, the abdominal incision, pelvic organ manipulation, diaphragmatic irritation, and/or ureteral colic. Postoperative pain can be easily managed in most patients with supplemental intravenous opioids in the early postoperative period and later with oral opioids and acetaminophen. Nonsteroidal antiinflammatory drugs should be used with caution because of their potential prostaglandin-mediated adverse renal effects. Pain after open nephrectomy with subcostal lateral incision is severe and can last several days, which can limit the patient's efforts to breathe, cough, and move, leading to atelectasis and

postoperative infection. Postoperative epidural analgesia should be considered for pain relief in these patients.

Post-donation complications reported to the Organ Procurement and Transplantation Network within 6 weeks of surgery include the need for blood transfusion (0.4%), readmission (2.1%), interventional procedures (0.9%), and reoperation (0.5%).⁴⁵ A study of more than 80,000 living kidney donors showed a 90-day mortality of 3.1 per 10,000 donors (0.03%) and remains unchanged in the last 15 years.⁵² Pulmonary embolism occurred in 0.1% of donors and is the main cause of mortality.⁴⁵ Kidney donors are at moderate risk for developing venous thromboembolism; therefore, intermittent pneumatic compression devices and prophylactic heparinization are recommended until ambulation. A decrease of approximately 30% in GFR can be expected after donation, and most donors will maintain a GFR greater than 60 mL/minute at 3 months.⁴⁹ Donor nephrectomy does not appear to increase long-term mortality or end-stage renal disease. Within the donor population, the likelihood of postdonation chronic kidney disease, hypertension, and diabetes is relatively higher among certain subgroups, such as African-American and obese donors, but the impact of unilateral nephrectomy on the lifetime risks of adverse events in these subgroups is unknown because the risks without nephrectomy have not been defined.⁴⁵ It should be noted that all studies on post-donation complications are retrospective without long-term follow-ups and matched controls.

LIVING LIVER DONOR

Living donor liver transplantation (LDLT) was first introduced in 1988 for pediatric recipients⁵³ and later expanded to adult recipients. Although LDLT is commonly performed in some Asian countries, it only consists of a small portion (<5%) of overall liver transplants performed in the United States.³ The primary concern, that of harm to a healthy, altruistic donor, is greater in LDLT, compared with kidney donation.

The liver's remarkable reserve, coupled with its unique capacity to regenerate, forms the basis for LDLT. After resection of as much as two-thirds of the liver, the donor's liver regains its original size in 2 to 3 weeks.⁵⁴ A portion of the adult liver (typically the left lobe or left lateral segment) transplanted to a pediatric recipient will grow with the recipient. Most LDLTs are electively performed in patients with chronic liver disease. Emergent LDLT is uncommon but is occasionally performed for acute liver failure. LDLT performed in patients with very advanced disease generates considerable debate.

The determination of donor liver volume and anticipated graft size is unique to LDLT. Formulas using demographics, including body weight, height, age, and sex, have been developed. Methods using radiologic or ultrasonic measurements also have been proposed.⁵⁵ Accurate estimation of donor liver volume and intended liver graft volume is critical to avoid small-for-size syndrome in the recipient and to preserve adequate remnant liver volume in the donor.⁵⁶ For pediatric LDLTs, the left lateral segment (segments II and III) or a total left hepatic lobectomy (segments II, III, and IV) is generally enough to provide sufficient liver mass (Fig. 61.3). From a surgical point of view,

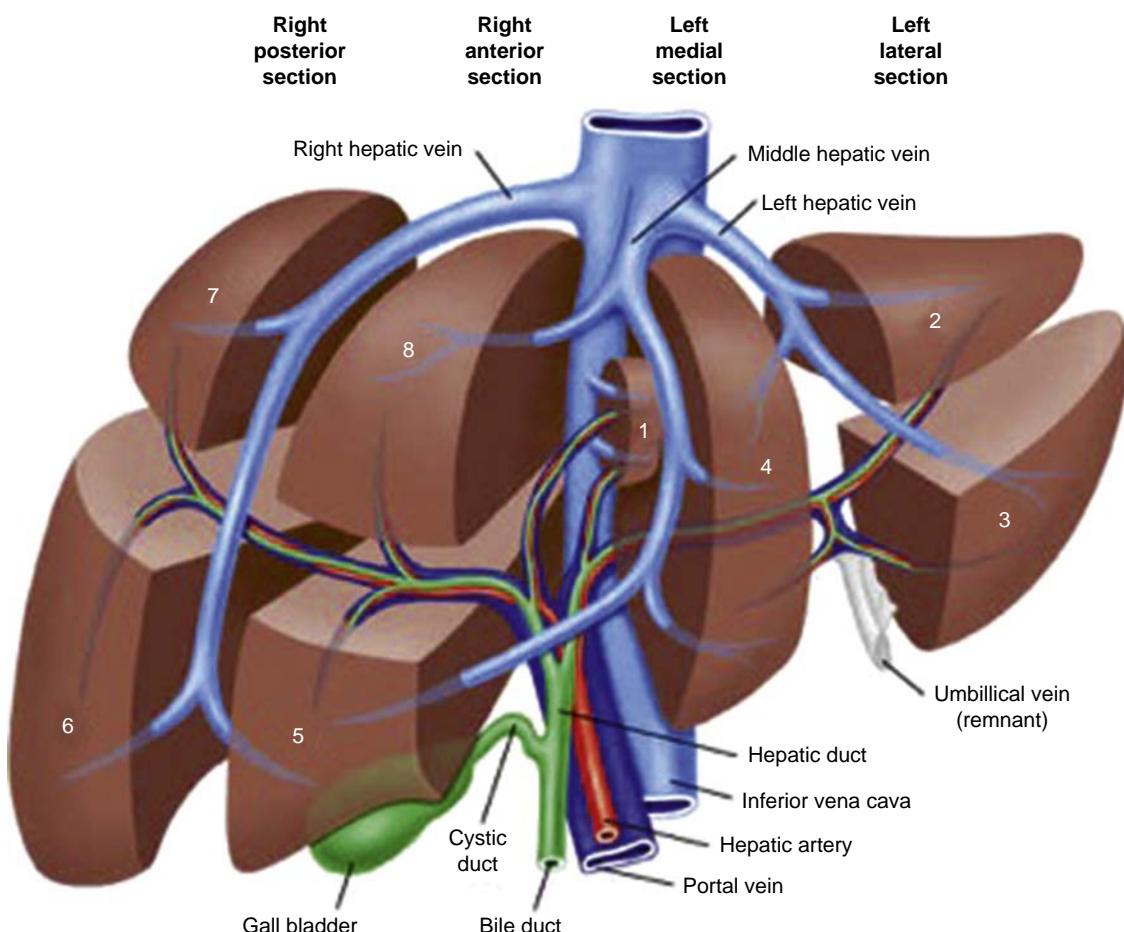


Fig. 61.3 Segmental liver anatomy illustrates the segments resected during various partial hepatectomies. (Redrawn from Steadman RH, Braunfeld M, Park H. Liver and gastrointestinal physiology. In: Hemmings HC, Egan T, eds. *Pharmacology and Physiology in Anesthesia: Foundations and Clinical Applications*. Philadelphia: Saunders; 2013:475–486.)

a left hepatectomy is less complex, and the duration of surgery is shorter. Since the first report in 2002, more living donor left lobectomies are performed using laparoscopy.⁵⁷ For adult-to-adult LDLT, right hepatic lobectomy is usually required. The surgical technique for right hepatectomy involves separation of the right hepatic lobes (segments V, VI, VII, and VIII) from the left. Compared with left hepatectomy, right hepatectomy is technically more challenging and associated with more perioperative risk. Right hepatectomy results in a graft weighing 500 to 1000 g, which leaves the donor with approximately one-third of the original liver mass. If one donor cannot provide sufficient liver mass, then a technique using two donors to one recipient has been reported.⁵⁸ For a small recipient, the left lobe of a large donor organ may suffice.

Anesthetic management starts with a preoperative discussion with the donor patient and family that addresses the risks and concerns associated with the procedure. Most transplant programs provide extensive educational materials, discussion, and support, beginning well before the day of surgery. General anesthesia with neuromuscular blockade is required for living liver donation surgery. The patient is placed in a supine position and intraoperatively uses the reverse Trendelenburg position to facilitate the exposure of the liver. Two large-bore intravenous catheters are placed. Standard noninvasive monitors and arterial blood pressure

monitoring are typically used. A nasogastric tube is placed for decompression of the stomach and surgical exposure.

An L-shaped or standard bilateral subcostal incision with a midline extension is frequently used in living donor surgery. During mobilization of the liver and its vasculature, manipulation of the liver occasionally results in decreased venous return to the heart with episodes of hypotension. The return of the liver to its orthotopic position will relieve the venous obstruction; alternatively, administering short-acting vasoactive agents and/or a fluid bolus will generally treat the problem. Most blood loss occurs during transection of the liver parenchyma. With surgical devices specifically designed for hepatectomy, blood loss during living donor hepatectomy is significantly reduced. After the vasculature of the donor lobe is clamped and divided, the graft is removed, and the vasculature and bile duct are oversewn. The abdomen is closed after hemostasis is achieved.

Blood loss during hepatectomy is a major concern and is associated with adverse outcomes. Placement of the CVP catheter and the use of low CVP (<5 cm H₂O) technique are advocated in some centers to reduce blood loss and transfusion requirements.⁵⁹ Low CVP reduces blood loss by increasing venous drainage from the hepatic sinusoids and decreasing blood backflow.⁵⁹ In addition, low CVP may reduce graft edema and improve postoperative graft function.⁵¹ Low CVP is most often achieved by intravascular

fluid restriction and sometimes by drugs, including diuretics and vasodilators.⁵⁹ Others consider the placement of a CVP catheter and low CVP technique unnecessary during hepatic resection surgery because of the inability to demonstrate a relationship between CVP and blood loss.⁶⁰ Other factors, including steatosis, body weight, and sex, may be more important than CVP in influencing blood loss during living donor hepatectomy.⁶¹ Potential drawbacks of the low CVP technique are the risk of CVP catheter placement and difficulty reversing hemodynamic disturbances in the event of massive bleeding. Others point out that the use of low CVP originates from early experience with hepatectomy several decades ago, when blood loss was significant. With improved surgical techniques and equipment, blood loss during hepatectomy has been dramatically reduced, making CVP placement and monitoring unnecessary.^{60,61} At the authors' institution, CVP placement is rarely used. Peripheral venous pressure measurements in the arm may be measured as an alternative to conventional CVP measurements.⁶²

Several other blood-saving strategies have been used in living donor hepatectomy. These include cell salvage techniques and preoperative donation of 1 to 2 units of autologous blood, which reduces the chance of allogeneic blood transfusion. Intraoperative isovolemic hemodilution with retrieval of 1 to 2 units of blood in the surgical unit can minimize the likelihood of blood transfusion.⁶³ The application of one or more of the blood-saving strategies previously listed is usually sufficient in the vast majority of patients.⁶⁰ After the graft is removed, excessive intravascular volume should be avoided because it may impede venous return and result in congestion of the remnant liver.⁵¹

Most living liver donors can be extubated at the end of the procedure in the surgical unit and transferred to the postoperative care unit. Discontinuation of mechanical ventilation reduces intrathoracic pressure, which reduces congestion in the remnant liver. Admission to the ICU is generally unnecessary but preferred in some institutions. Caution is required with the use of intravenous analgesics and opioids in the immediate postoperative period. The remnant liver is assumed to have some degree of insufficiency, although this assumption has not been thoroughly investigated.⁵¹ Optimal perfusion of the remnant liver is achieved by the maintenance of adequate cardiac output and an avoidance of hypovolemia, anemia, and hypothermia-induced coagulopathy.⁵¹

The use of epidural anesthesia for postoperative pain control in living donor surgery remains controversial. Similar to other upper abdominal surgery, postoperative epidural analgesia provides excellent pain control with less sedation, compared with intravenous patient-controlled analgesia.⁶⁴ By facilitating pulmonary toilet, epidural analgesia reduces the risk of respiratory infections. Despite these advantages, preoperative placement of a thoracic epidural catheter is routinely performed in some transplant centers and is entirely avoided in others. The difference of practice originates from the development of postoperative coagulopathy in patients after donor hepatectomy. Postoperatively, thrombocytopenia occurs while the prothrombin and activated partial thrombin times are prolonged. These changes peak on postoperative day 2 to 3, followed by a steady trend toward normalization in the following days.⁶⁵ Thus,

concern over the potential development of an epidural hematoma is the basis for avoiding epidural catheter placement. Several studies examining the use of the epidural catheter in this population report no adverse effects. In a study of 755 donors who received an epidural catheter for postoperative pain management, no complications associated with the epidural catheter were reported.⁶⁶ Another study including 242 living liver donors also showed that epidural analgesia seems to be a safe option when carefully used.⁶⁵ Another piece of evidence supporting epidural placement is that hypercoagulability, not hypocoagulability measured by thromboelastography, can develop in the majority of patients after hepatectomy.^{67,68} Despite the low overall incidence of epidural hematoma, these studies are criticized for a lack of power to assess the risk of this rare event. If the epidural catheter is placed, then the catheter should not be removed until satisfactory coagulation parameters have been retained, which usually takes 3 to 5 days.⁵¹ If the epidural catheter is not placed, then patient-controlled analgesia is used. The choice of pain-control strategy is influenced by the patient's expectations, surgical preferences, institutional consensus, postoperative monitoring capabilities, and nursing staff familiarity with the various techniques.

Worldwide, a number of LDLT-related donor complications, including mortality, have been reported.^{69,70} A multicenter observational study of 760 adult-to-adult LDLTs with up to 12 years of follow-up revealed that 40% of donors had complications (Table 61.4).⁶⁹ A total of 19% of donors had more than one complication. Although most of the complications were not associated with residual disability, some were severe. Infection is the most common complication and biliary complications such as bile leaks or stricture can be difficult to treat and can lead to prolonged hospital stays with the possibility of further surgery. Higher preoperative creatinine levels, intraoperative hypotension, and intraoperative transfusion are associated with donor complications. Increased institutional experience is not associated with decreased complications.⁶⁹ Another recent study involving 5202 living donor hepatectomies found that 12% of donors developed at least one complication, of which 3.8% were major events, which doubled after right hepatectomy.⁷¹

LIVING LUNG DONOR

Living lung transplantation is an alternative to deceased lung transplantation. Typically, two donors are used for one recipient in living lung transplantation, although the use of a single living donor has been reported.⁷² If two donors are involved, then careful coordination and timing of the anesthetic induction of the two donors and recipient are required. The right lower lobe of one donor and the left lower lobe of the second donor are implanted in the recipient in place of the whole right and left lungs. Donor lobectomy requires sufficient bronchial, arterial, and vein cuffs to permit successful anastomoses. A bronchial air leak can result in a prolonged need for chest tube drainage, which lengthens hospital stay.

After the induction of general anesthesia, a single-lumen endotracheal tube is usually placed initially to facilitate fiberoptic bronchoscopic examination before incision. Once

TABLE 61.4 Type and Frequency of Complications of Living Liver Donors of 760 Donor Procedures, ~40% (296 Donors) Suffered 557 Complications; 20 Procedures Were Aborted

Complications	Frequency (% of 760 procedures)
Infections	13.2
Pleural effusion	11.0
Bile leak or biloma	8.1
Incisional hernia	6.6
Psychologic difficulty	5.6
Neuropraxia	3.4
Ascites	2.8
Unplanned reexploration	2.7
Pulmonary edema	2.1
Bowel obstruction	1.6
Intraabdominal abscesses	1.2
Pulmonary embolism	1.0
Pneumothorax	0.8
Deep vein thrombosis	0.8
Biliary stricture	0.7
Portal vein thrombosis	0.5
Inferior vena cava thrombosis	0.4

Modified from Abecassis MM, Fisher RA, Olthoff KM, et al. Complications of living donor hepatic lobectomy—a comprehensive report. *Am J Transplant*. 2012;12:1208–1217.

a decision is made to proceed, a left-sided double-lumen endotracheal tube later replaces the single-lumen endotracheal tube. Standard noninvasive monitors, intraarterial blood pressure monitoring, and capnography may be sufficient. After placing the donor in the lateral decubitus position and rechecking the double-lumen tube position by fiberoptic bronchoscope, a thoracotomy is performed. Intraoperative cardiorespiratory and metabolic homeostasis minimizes the risk of postoperative complications. Prostaglandin E₁ is usually intravenously administered to dilate the pulmonary vessels with titration according to systemic blood pressure (hypotension needs to be avoided). After mobilization is complete, the lung is reinflated for 5 to 10 minutes, followed by the administration of heparin and a steroid. Transection of the lung is performed after the lung is recollapsed.

Thoracic epidural analgesia is a useful adjunct for perioperative care. The epidural catheter may be placed hours before surgery.⁵¹ Although this approach may be questionable in patients undergoing heparinization, the superiority of postoperative analgesia and the avoidance of atelectasis and infection appear to justify the risk of donor epidural catheterization.⁷³

ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion injury of transplanted grafts is unavoidable if blood supply is interrupted. An interruption of the blood supply during the ischemic period results

in metabolic and pathophysiologic changes. Restoration of blood flow and reoxygenation can also cause tissue injury, as well as profound immune and inflammatory responses.⁷⁴

Ischemia-reperfusion injury results from a wide range of pathologic processes. During ischemia, a lack of oxygen supply leads to a depletion of adenosine triphosphate (ATP) and glycogen. Without ATP, sodium-potassium (Na-K) pumps cannot maintain ion gradients across the cellular membrane. As a result, extracellular sodium ions move into cells, causing swelling. Vascular permeability is increased since intracellular cyclic adenosine monophosphate levels and adenylyl cyclase activity is decreased.^{74,75} The restoration of the blood supply causes a series of pathophysiologic changes that lead to tissue injury. Reperfusion-related injuries include necrosis, apoptosis (programmed death), and autophagy-associated cell death. Reperfusion also activates autoimmune responses including natural antibody recognition of neoantigens, activation of the complement system, activation of innate and adaptive immune responses, and cell migration to the affected area.

Organ Preservation and Management After Procurement

After procurement, preservation of organs in a cold (4°C) solution until reperfusion remains a mainstream management after procurement. Although static cold preservation slows the metabolic rate, energy consumption is not completely stopped. Accumulation of metabolites and intracellular calcium limit the maximum time for static cold storage.⁷⁶ Various cold-storage solutions are used worldwide with the UW solution one of the most widely used. The UW solution contains high potassium and adenosine to supply ATP during cold storage. Histidine-tryptophan-ketoglutarate (HTK) solution, originally developed for cardioplegia and subsequently applied to organ preservation in Europe, has gained popularity.⁷⁷ The potential for hyperkalemia during organ reperfusion (particularly with the liver) increases when the UW solution is used, compared with the HTK solution. However, the graft is typically flushed with colloid before reperfusion, regardless of the solution used, which decreases the likelihood of severe hyperkalemia. Recent data suggest that the HTK solution may be associated with poor graft function in abdominal organ transplantation.^{78,79} Organ-specific solutions, such as Perfadex solution (manufactured by Vitrolife in Göteborg, Sweden) for the lung and Celsior solution (manufactured by Genzyme in Cambridge, MA) for the heart, are available. Although ischemia time should be kept minimal, a longer storage time allows transportation of the graft to the highest acuity patient for a long distance. Generally accepted cold ischemia times during static cold preservation are 24 hours for the kidney, 12 hours for the liver, 6 hours for the heart, and 4 hours for the lung.

In addition to static cold preservation, machine perfusion can be used to preserve procured organs. The driving force for recent renewed interest in machine perfusion is to expand the donor pool.⁷⁹ The potential advantage for machine perfusion techniques include a longer storage time, ability to assess the viability of organ, and potential therapeutic interventions during preservation. Temperature during

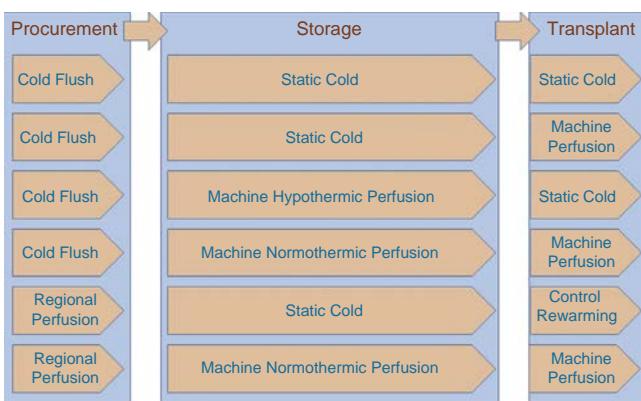


Fig. 61.4 Various techniques and combination of techniques can be used to improve donor function and recipient outcome during procurement, preservation, and transplant.

machine perfusion can be hypothermic (4°C-10°C), subnormothermic (12°C-30°C), and normothermic (35°C-37°C). Different temperatures have different advantages and disadvantages.⁷⁶ When normothermia is used, oxygen needs to be added. Combination of different techniques and temperatures may be used in different situations (Fig. 61.4).⁷⁹ Clinical trials and metaanalysis suggest machine perfusion improves short-term outcomes including a reduction in DGF and primary nonfunction. These effects are more obvious in high-risk donors.^{76,80-82} Changes of biomarkers in perfusate reflect damage of preserved organs and may be used to predict posttransplant outcome. Tests using metabolomics, proteomics, and genomics approaches may provide useful information in the future.⁸³ Several pharmacologic and biologic agents have been tested in animal models and preclinical trials; some, including recombinant agents that block leukocyte adhesion, have shown promise.^{84,85} Preconditioning with volatile anesthetics has been shown to protect tissue from ischemia-reperfusion injury in animal models.⁸⁶ In human trials, volatile anesthetics have some beneficial effects in the setting of myocardial infarction, minimizing ischemia-reperfusion injury, although the data remain inconclusive.⁸⁷

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KEY POINTS

- The normal physiologic changes of pregnancy begin in the first trimester, affect all organ systems, and alter pharmacokinetic and pharmacodynamic responses to many drugs commonly used in anesthesia.
- Maternal-fetal exchange of most drugs and other substances occurs primarily by diffusion. The rate of diffusion and peak levels in the fetus depend on maternal-to-fetal concentration gradients, maternal protein binding, molecular weight of the substance, lipid solubility, and the degree of ionization of that substance.
- All women in labor are considered to have a full stomach and an increased risk for pulmonary aspiration of gastric contents during induction of anesthesia and aspiration prophylaxis should be considered before all surgical procedures during pregnancy.
- Uterine blood flow increases progressively during pregnancy from approximately 100 mL/min in the nonpregnant state to between 700 and 900 mL/min (~10% of cardiac output) at term gestation. Consequently, hemorrhage during pregnancy carries significant morbidity and is a leading cause of maternal death worldwide. Early recognition with timely intervention, optimal team performance, and appropriate blood product transfusions are essential to patient outcomes.
- Uterine and placental blood flow depend on maternal cardiac output and are directly related to uterine perfusion pressure and inversely related to uterine vascular resistance. Decreased perfusion pressure can result from maternal hypotension secondary to hypovolemia, aortocaval compression, sympathetic blockade, and decreased systemic resistance from either general or neuraxial anesthesia. Prophylactic or therapeutic phenylephrine in boluses or as an infusion reduces the incidence and severity of hypotension from spinal anesthesia for cesarean delivery. In comparison to ephedrine, phenylephrine results in less fetal acidosis.
- During pregnancy, the maternal oxyhemoglobin dissociation curve shifts to the right with pregnancy while the fetal oxyhemoglobin dissociation curve lies to the left. This facilitates oxygen transfer from maternal to fetal hemoglobin. Fetal O₂ saturation does not exceed 60% even with 100% O₂ delivery to the mother. Maternal PaCO₂ decreases from 40 mm Hg to approximately 30 mm Hg during the first trimester. This reduction facilitates carbon dioxide transfer across the placenta, which is primarily limited by blood flow and not diffusion.
- Labor is a continuous process separated into first, second, and third stages. The first stage of labor includes the change of the uterine cervix from a thick closed tube to an opening of approximately 10 cm through which the fetus can be expelled. This stage is further divided into latent and active phases.
- Neuraxial analgesia is the most reliable and effective method of reducing pain during labor. Adequate analgesia is achieved with blockade of T10 to L1 during the first stage of labor and requires extension to include S2 to S4 during the second stage of labor.
- Neuraxial analgesia in comparison to unmedicated birth or intravenous opioid analgesia may prolong the second stage of labor but does not increase the risk for cesarean delivery. Epidural analgesia inserted *early* compared to *late* in labor does not increase the risk for cesarean delivery or prolong the first stage of labor.
- Remifentanil patient-controlled analgesia (PCA) may offer superior pain relief and less fetal effects than other intravenous opioid analgesics but its analgesic effects are inferior to epidural labor analgesia and it requires careful maternal oxygenation and ventilation monitoring.
- Hypertensive disorders of pregnancy complicate 5% to 10% of worldwide pregnancies and can cause maternal and fetal mortality. Patients with preeclampsia are at increased risk for cerebral hemorrhage, pulmonary edema, and coagulopathy. Systolic and diastolic blood pressure higher than 160/110 mm Hg should be treated to prevent intracerebral hemorrhage.
- Sepsis is a leading cause of maternal morbidity and mortality in the UK and United States. Early identification and treatment has been shown to improve outcomes.

Physiologic Changes During Pregnancy and Delivery

During pregnancy and the peripartum period, substantial changes in maternal anatomy and physiology occur secondary to (1) changes in hormone activity, (2) mechanical effects of an enlarging uterus, and (3) increased maternal metabolic demands and biochemical alterations induced by the fetoplacental unit. These changes have a significant impact on anesthetic pharmacology and physiology resulting in unique anesthesia management requirements during pregnancy. Pregnant women with comorbid conditions require even greater anesthetic modifications.

CARDIOVASCULAR CHANGES

Changes in the cardiovascular system occur throughout gestation and include (1) anatomic changes, (2) an increase in intravascular volumes, (3) an increase in cardiac output, (4) a decrease in vascular resistance, and (5) the presence of supine hypotension. Table 62.1 and the following sections detail these changes.

Physical Examination and Cardiac Studies

The cardiovascular changes of a normal pregnancy are significant. In cardiac auscultation an accentuated first heart sound (S_1) can be heard, with an increased splitting noted from dissociated closure of the tricuspid and mitral valves. A third heart sound (S_3) is often heard in the final trimester, and a fourth heart sound (S_4) can also be heard in some pregnant patients as a result of increased volume and turbulent flow. Neither the S_3 nor S_4 heart sounds have clinical significance. In addition, a benign grade 2/6 systolic ejection murmur is typically heard over the left sternal border and is secondary to mild regurgitation at the tricuspid valve from the annular dilation associated with the increased cardiac volume. Table 62.1 details the effects of pregnancy on the electrocardiogram and echocardiography. The elevation of the diaphragm by the growing uterus shifts the heart anteriorly and to the left. Left axis deviation as well as left ventricular hypertrophy are common findings in normal pregnancy. Women who present with chest pain, syncope, high-grade flow murmurs, arrhythmias, or heart failure symptoms such as hypoxia or clinically significant shortness of breath should undergo appropriate diagnostic investigation and referral.

Intravascular Volume

Maternal intravascular fluid volume begins to increase in the first trimester secondary to changes in the renin-angiotensin-aldosterone system promoting sodium absorption and water retention. These changes are likely induced by rising progesterone from the gestational sac. Plasma protein concentrations accordingly decrease with a 25% decrease in albumin and 10% decrease in total protein at term compared with nonpregnant levels.¹ Consequently, colloid osmotic pressure decreases from 27 to 22 mm Hg over the time of gestation.² At term, the plasma volume is 50% to 55% above the nonpregnant level. It is thought that the increase in blood volume prepares the parturient for delivery blood loss. Blood volume returns to prepregnancy values approximately 6 to 9 weeks postpartum.

TABLE 62.1 Changes in the Cardiovascular System During Pregnancy

Cardiovascular Parameter	Value at Term Compared With Nonpregnant Value
Intravascular fluid volume	Increased 35%-45%
Plasma volume	Increased 45%-55%
Erythrocyte volume	Increased 20%-30%
Cardiac output	Increased 40%-50%
Stroke volume	Increased 25%-30%
Heart rate	Increased 15%-25%
Vascular Pressures and Resistances	
Systemic vascular resistance	Decreased 20%
Pulmonary vascular resistance	Decreased 35%
Central venous pressure	No change
Pulmonary capillary wedge pressure	No change
Femoral venous pressure	Increased 15%
Clinical Studies	
Electrocardiography	Heart rate dependent decrease in PR and QT intervals Small QRS axis shift to right (first TM) or left (third TM) ST depression (1 mm) in left precordial and limb leads Isoelectric T-waves in left precordial and limb leads Small Q-wave and inverted T-wave in lead III
Echocardiography	Heart is displaced anteriorly and leftward Right-sided chambers increase in size by 20% Left-sided chambers increase in size by 10%-12% Left ventricular eccentric hypertrophy Ejection fraction increases Mitral, tricuspid, and pulmonic valve annuli increase Aortic annulus not dilated Tricuspid and pulmonic valve regurgitation common Occasional mitral regurgitation (27%) Small insignificant pericardial effusions may be present

TM, Trimester.

Data from references Bucklin BA, Fuller AJ. Physiologic Changes of Pregnancy. In: Sures MS, Segal BS, Preston RL, Fernando R, Mason CL, eds. *Shnider and Levinson's Anesthesia for Obstetrics*. 5th ed. Philadelphia: Lippincott Williams & Wilkins 2013; Kron J, Conti JB. Arrhythmias in the pregnant patient: current concepts in evaluation and management. *J Interv Card Electrophysiol*. 2007;19:95-107; and Conklin KA. Maternal physiologic adaptations during gestation, labor, and puerperium. *Semin Anesth*. 1991;10:221-234.

Cardiac Output

By the end of the first trimester, maternal cardiac output typically increases approximately 35% to 40% above pre-pregnancy values and continues to increase 40% to 50% by the end of the second trimester.³⁻⁵ Cardiac output remains

stable throughout the third trimester. This increased cardiac output is secondary to increases in both stroke volume (25%-30%) and heart rate (15%-25%).^{6,7} Labor further increases cardiac output, which fluctuates with each uterine contraction. Increases above prelabor values of 10% to 25% occur during the first stage and 40% in the second stage. The largest increase in cardiac output occurs immediately after delivery, when cardiac output can increase by 80% to 100% more than prelabor values.⁸ This abrupt increase is secondary to the autotransfusion of uteroplacental blood as the evacuated uterus contracts, reduced maternal vascular capacitance from loss of the intervillous space, and diminished lower extremity venous pressure from release of the aortocaval compression. This large fluctuation in cardiac output presents a unique postpartum risk for patients with cardiac disease, especially those whose heart cannot accommodate an increase in cardiac output such as those with fixed valvular stenosis or pulmonary vascular hypertension. Cardiac output returns toward prelabor values within 24 hours postpartum depending on the mode of delivery and degree of blood loss.⁹ Cardiac output decreases substantially toward prepregnant values by 2 weeks postpartum, with complete return to nonpregnant levels between 12 and 24 weeks after delivery.¹⁰

Systemic Vascular Resistance

Although cardiac output and plasma volume increase, systemic blood pressure decreases in an uncomplicated pregnancy secondary to a reduction in systemic vascular resistance. Systemic vascular resistance decreases as a result of the vasodilatory effects of progesterone and prostaglandins as well as the low resistance of the uteroplacental vascular bed.¹¹ Although affected by positioning and parity, systolic, diastolic, and mean blood pressure may all decrease 5% to 20% by 20 weeks gestational age and then gradually increase toward nonpregnant values by term.¹²⁻¹⁴ Diastolic arterial blood pressure decreases more than systolic arterial blood pressure resulting in a slight increase in pulse pressure. Central venous and pulmonary capillary wedge pressures do not change during pregnancy,⁶ despite the increased plasma volume, because venous capacitance increases.

Aortocaval Compression

Aortocaval compression by the gravid uterus as a result of supine positioning is associated with a decrease in systemic blood pressure. Although the inferior vena cava is compressed in nearly all term parturients,¹⁵ supine hypotension syndrome (also known as aortocaval compression syndrome) is experienced by only 8% to 10% of women.¹⁶ Supine hypotension syndrome is defined as a decrease in mean arterial pressure of more than 15 mm Hg with an increase in heart rate of more than 20 beats/min and is often associated with diaphoresis, nausea, vomiting, and changes in mentation. At term, the inferior vena cava can be almost completely occluded in the supine position with the return of blood from the lower extremities through the epidural, azygous, and vertebral veins that become engorged (Fig. 62.1A). Also, significant aortoiliac artery compression occurs in 15% to 20% of pregnant women. Inferior vena caval compression in the supine position causes a decrease in both stroke volume and cardiac output of 10% to 20%

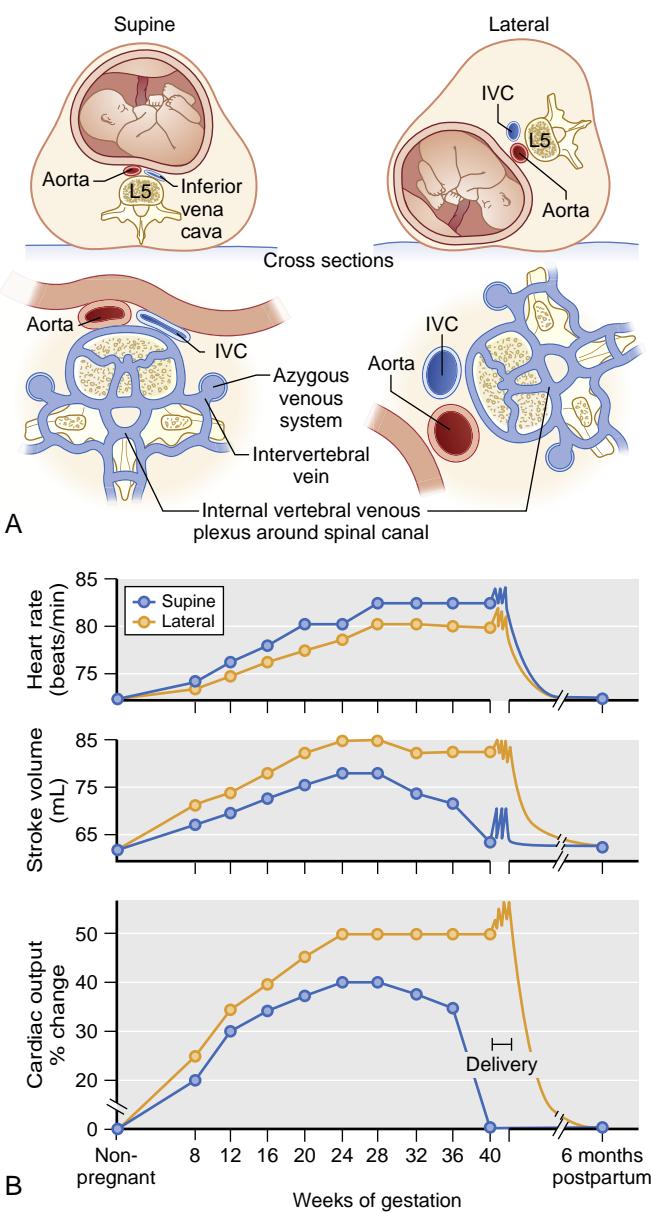


Fig. 62.1 Aortocaval compression. (A) Cross-sectional views of aortocaval compression from the gravid uterus in the supine position with loss of compression in the lateral position. (B) Alterations in heart rate, stroke volume, and cardiac output for both supine and lateral positioning with increasing gestation of pregnancy. IVC, Inferior vena cava. (Reprinted with permission from Bonica JJ, ed. *Obstetric Analgesia and Anesthesia*. Amsterdam: World Federation of Societies of Anaesthesiologists; 1980.)

in comparison to the upright position (see Fig. 62.1B), and may exacerbate venous stasis in the legs and thereby result in ankle edema, varices, and increased risk for lower extremity deep venous thrombosis.

Most pregnant women have compensatory adaptations that reduce supine hypotension symptoms despite aortocaval compression. One compensatory response is a reflexive increase in peripheral sympathetic nervous system activity. This increase in sympathetic activity results in increased systemic vascular resistance and permits arterial blood pressure to be maintained despite the reduced cardiac output. Consequently, the reduced sympathetic tone from

neuraxial or general anesthetic techniques impairs the compensatory increase in vascular resistance and exacerbates the impact of hypotension from supine positioning.

Therefore in general, supine positioning is avoided during use of neuraxial techniques for labor analgesia and cesarean deliveries. Reducing the compression of the inferior vena cava and abdominal aorta with left tilt may mitigate the degree of hypotension and help maintain uterine and fetal blood flow. This is accomplished by positioning the patient laterally or by elevating the right hip 10 to 15 cm (with a historical goal of 15 degree left-tilt) with a blanket, wedge, or table tilt.

The practice of left uterine displacement has been challenged recently. In a magnetic resonance imaging (MRI) study of healthy pregnant volunteers, the volume of the inferior vena cava did not differ significantly between the supine position and the 15 degree left-tilt position but when the patients were tilted to the 30 degree left-tilt position, the inferior vena cava volume did increase.¹⁵ Additionally, healthy women undergoing elective cesarean delivery under spinal anesthesia and a phenylephrine infusion were randomized to supine or 15 degree left-tilt position and no difference was found on neonatal acid-base status; however, the supine patients had lower cardiac output and required more phenylephrine.¹⁷ Further studies are needed to investigate who benefits from left uterine displacement and the amount required to achieve the greatest benefit without hindering the surgical procedure. In the meantime, left uterine displacement should continue to be utilized during induction of neuraxial analgesia/anesthesia and during episodes of maternal hypotension or fetal compromise.

RESPIRATORY SYSTEM CHANGES

Pregnancy results in significant alterations in (1) the upper airway, (2) lung volumes and ventilation, and (3) O₂ consumption and metabolic rate (Table 62.2).

The Upper Airway

Capillary engorgement with increased tissue friability and edema of the mucosal lining of the oropharynx, larynx, and trachea begins early in the first trimester. As a result, an increased risk for bleeding exists during manipulation of the upper airway, in addition to an increased risk of difficult mask ventilation and intubation of the trachea. Suctioning of the airway and placement of devices should be performed gently to prevent bleeding and nasal instrumentation should be avoided. Furthermore, there is increased risk for airway obstruction during mask ventilation and both laryngoscopy and tracheal intubation are more difficult. Also, after extubation, the airway may be compromised as a result of edema, with subsequent risk for airway obstruction in the immediate recovery period.

Consequently, attempts at laryngoscopy should be minimized and experts recommend a cuffed endotracheal tube with a smaller diameter (6.0-7.0 mm internal diameter)^{18,19} should be placed to minimize the chances of difficult placement secondary to airway edema. Airway edema can be more severe in patients with coexisting preeclampsia, in upper respiratory tract infections, and after active pushing as a result of associated increased venous pressure.²⁰ In addition, pregnancy-associated weight gain and

TABLE 62.2 Changes in the Respiratory System at Term

Pulmonary Parameter	Value Near Term Compared With Nonpregnant Value
Minute ventilation	Increased 45%-50%
Respiratory rate	Increased 0%-15%
Tidal volume	Increased 40%-45%
LUNG VOLUMES	
Inspiratory reserve volume	Increased 0%-5%
Tidal volume	Increased 40%-45%
Expiratory reserve volume	Decreased 20%-25%
Residual volume	Decreased 15%-20%
LUNG CAPACITIES	
Vital capacity	No change
Inspiratory capacity	Increased 5%-15%
Functional residual capacity	Decreased 20%
Total lung capacity	Decreased 0%-5%
OXYGEN CONSUMPTION	
Term	Increased 20%-35%
Labor (first stage)	Increased 40% above prelabor value
Labor (second stage)	Increased 75% above prelabor value
RESPIRATORY MEASURES	
FEV ₁	No change
FEV ₁ /FVC	No change
Closing capacity	No change

Data from Conklin KA. Maternal physiologic adaptations during gestation, labor, and puerperium. *Semin Anesth*. 1991;10:221-234.

increase in breast tissue, particularly in women of short stature or with coexisting obesity, can make insertion of a laryngoscope difficult. A patient's position should always be optimized and back-up airway instrumentation available before attempts are made at intubation of the trachea. The Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed intubation in obstetrics recommends a videolaryngoscope should be immediately available for all obstetric general anesthetics.²¹

Ventilation and Oxygenation

The increased O₂ demand and carbon dioxide production of the growing placenta and fetus cause minute ventilation to be elevated 45% to 50% more than nonpregnant values in the first trimester and for the remainder of the pregnancy. This larger minute ventilation is attained primarily as a result of a larger tidal volume and a slight increase in respiratory frequency. Maternal PaCO₂ decreases from 40 mm Hg to approximately 30 mm Hg during the first trimester as a reflection of the increased minute ventilation. Arterial pH, however, remains only mildly alkalotic (typically 7.42-7.44) because of metabolic compensation with increased renal excretion of bicarbonate ions (HCO₃⁻ is typically 20 or 21 mEq/L at term). Early in gestation, maternal room air PaO₂ is more than 100 mm Hg because of the presence

TABLE 62.3 Arterial Blood Gas Measurements in Pregnancy

Blood Gas Values	Pregnant	Nonpregnant
PaCO ₂	30	40
PaO ₂	103	100
HCO ₃	20	24
pH	7.44	7.4
P50	30	27

of hyperventilation and the associated decrease in alveolar CO₂. Later, PaO₂ becomes normal or even slightly decreased in the supine position, most likely reflecting small airway closure with normal tidal volume ventilation and intrapulmonary shunt. Arterial oxygenation can be significantly improved by moving the patient from the supine to the lateral position. With pregnancy, the maternal oxyhemoglobin dissociation curve shifts to the right, with the P50 (partial pressure of O₂ at which hemoglobin is 50% saturated with oxygen) increasing from 27 to approximately 30 mm Hg at term.²² The higher P50 in the mother and lower P50 in the fetus means that the fetal blood has higher affinity for O₂ and offloading of O₂ across the placenta is facilitated. A comparison of arterial blood gas measurements in pregnant versus nonpregnant patients is summarized in Table 62.3.

At term, O₂ consumption is increased by 20% to 35%. During the first stage of labor, O₂ consumption increases above prelabor values by 40% and during the second stage it is increased by 75%. The pain of labor can result in severe hyperventilation causing PaCO₂ to occasionally decrease below 20 mm Hg.

Lung Volumes

During pregnancy, tidal volume increases 20% during the first trimester and increases up to 45% above nonpregnant values at term. The expanding uterus forces the diaphragm cephalad and creates a 20% decrease in functional residual capacity (FRC) by term (see Table 62.2).²³ This reduction is comprised of nearly equal reductions in both the expiratory reserve volume (ERV) and residual volume (RV). However, closing capacity (CC) remains unchanged and creates a reduced FRC/CC ratio. This results in more rapid small airway closure with reduced lung volumes, and in the supine position FRC can be less than CC for many small airways, giving rise to atelectasis. Vital capacity does not change with pregnancy. The combination of increased minute ventilation and decreased FRC results in a more rapid rate at which changes in the alveolar concentration of inhaled anesthetics can be achieved. Spirometric measurements of bronchial flow are unchanged in pregnancy.

During induction of general anesthesia, desaturation and subsequent hypoxemia occur more rapidly than in a nonpregnant patient because of decreased O₂ reserve (secondary to decreased FRC) combined with increased O₂ uptake (resulting from increased metabolic rate). Preoxygenation before general anesthesia is critical for patient safety to mitigate these physiologic changes and increase apnea time. Preoxygenation with inhalation of 100% O₂ with a goal of end-tidal oxygen fraction greater than 0.9 is recommended

(can usually be obtained with 2-3 minutes of preoxygenation before induction of anesthesia) (see Chapter 44). Although the use of high-flow humidified nasal oxygen has been shown to be as effective as conventional preoxygenation in nonpregnant patients, it has not been shown to achieve acceptable preoxygenation levels in term pregnant women.²⁴ The increased airway edema makes both ventilation and tracheal intubation more difficult and further increases the potential for complications and morbidity of general anesthesia in pregnancy.

GASTROINTESTINAL CHANGES

After midgestation, the induction of general anesthesia places pregnant women at increased risk for regurgitation, aspiration of gastric contents, and development of acid pneumonitis. The stomach and pylorus are moved cephalad by the gravid uterus, which repositions the intraabdominal portion of the esophagus intrathoracically and decreases the competence of the lower esophageal sphincter muscle. Higher progesterone and estrogen levels of pregnancy further reduce lower esophageal sphincter tone. Gastrin, secreted by the placenta, increases gastric hydrogen ion secretion and lowers the gastric pH in pregnant women. These changes in combination with the increased gastric pressure from the enlarged uterus increase the risk for acid reflux in pregnancy. Maternal gastric reflux with subsequent esophagitis (heartburn) is common in pregnant women and increases with increased gestational age.²⁵ Gastric emptying is not prolonged in pregnancy.²⁶ Conversely, gastric emptying is decreased with the onset of labor, pain, anxiety, or administration of opioids. Increased gastric contents can further increase the risk for aspiration. Epidural analgesia using local anesthetics alone does not further delay gastric emptying; however, epidural boluses of fentanyl can cause gastric emptying delay.²⁷

All women in labor are considered to have a full stomach and an increased risk for pulmonary aspiration of gastric contents during induction of anesthesia. To reduce this risk, a nonparticulate antacid, a rapid sequence induction of anesthesia technique including cricoid pressure, and endotracheal intubation are considered routine parts of general anesthesia in a pregnant woman past midgestation.

HEPATIC AND BILIARY CHANGES

Blood flow to the liver does not change significantly with pregnancy. The markers of liver function, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin, increase to the upper limits of normal with pregnancy. Alkaline phosphatase levels more than double secondary to placental production. Plasma protein concentrations are reduced during pregnancy, and the decreased serum albumin levels can result in elevated free blood levels of highly protein-bound drugs. Plasma cholinesterase (pseudocholinesterase) activity is decreased approximately 25% to 30% from the 10th week of gestation up to 6 weeks postpartum.²⁸⁻³⁰ Although neuromuscular transmission should be analyzed before extubation, the clinical consequence of the reduced cholinesterase activity is unlikely to be associated with marked prolongation of the neuromuscular block resulting from succinylcholine.

The risk for gallbladder disease is increased during pregnancy with incomplete gallbladder emptying and changes in bile composition. Acute cholecystitis is the second most common cause of acute abdomen in pregnancy and occurs between 1 in 1600 to 1 in 10,000 pregnancies.³¹

RENAL CHANGES

Renal blood flow and the glomerular filtration rate (GFR) increase during pregnancy. Renal blood flow rises 60% to 80% by midpregnancy and in the third trimester is 50% greater than nonpregnant values. GFR is increased 50% above baseline by the third month of pregnancy and remains elevated until 3 months postpartum.³² Therefore the clearance of creatinine, urea, and uric acid are increased in pregnancy, and the upper laboratory limits for blood urea nitrogen and serum creatinine concentrations are decreased approximately 50% in pregnant women. Levels of urine protein and glucose are commonly increased as a result of decreased renal tubular resorption capacity. The upper limits of normal in pregnancy in a 24-hour urine collection are 300 mg protein.

HEMATOLOGIC CHANGES

As previously discussed, blood volume increases during pregnancy. At term, the plasma volume has increased approximately 50% above prepregnancy values and the red cell volume has increased only approximately 25%. The greater increase in plasma volume creates a physiologic anemia of pregnancy with a hemoglobin value normally around 11.6 g/dL. Hemoglobin values less than this at any time during pregnancy are concerning for anemia. Overall oxygen delivery is not reduced by the normal physiologic anemia of pregnancy because of the subsequent increase in cardiac output. The additional intravascular fluid volume of approximately 1000 to 1500 mL at term helps compensate for the estimated blood loss of 300 to 500 mL typically associated with vaginal delivery and the estimated blood loss of 800 to 1000 mL that accompanies a standard cesarean delivery. After delivery, contraction of the evacuated uterus creates an autotransfusion of blood often in excess of 500 mL that offsets the blood loss from delivery.

Leukocytosis is common in pregnancy and is unrelated to infection. Leukocytosis is defined as a white blood cell (WBC) count greater than 10,000 WBCs/mm³ of blood. In pregnancy, the normal range can extend to 13,000 WBCs/mm³. WBC count may rise in labor with the degree of increase related to the duration of elapsed labor.³³ The WBC count may decrease over the first week postpartum but may take weeks or months to return to nonpregnant values.³⁴

Coagulation

Pregnancy is characterized by a hypercoagulable state with a marked increase in factor I (fibrinogen) and factor VII and lesser increases in other coagulation factors (Table 62.4). Factors XI and XIII are decreased, and factors II and V typically remain unchanged. Antithrombin III and protein S are decreased during pregnancy and protein C levels remain unchanged.³⁵ These changes result in an approximately 20% decrease in prothrombin time (PT) and partial thromboplastin time (PTT) in normal pregnancy. Platelet count

TABLE 62.4 Changes in Coagulation System at Term

PRO-COAGULANT FACTORS	
Increased	I, VII, VIII, IX, X, XII von Willebrand factor
Decreased	XI, XIII
Unchanged	II, V
ANTI-COAGULANT FACTORS	
Increased	None
Decreased	Antithrombin III, Protein S
Unchanged	Protein C
Platelets	Decreased 0%-10%

may remain normal or slightly decreased (10%) at term as a result of dilution. However, 8% of otherwise healthy women have a platelet count less than 150,000/mm³.³⁶ In the absence of other hematologic abnormalities, the cause is usually gestational thrombocytopenia, from which the platelet count does not usually decrease to less than 70,000/mm³. This syndrome is not associated with abnormal bleeding. Gestational thrombocytopenia is due to a combination of hemodilution and more rapid platelet turnover and is a diagnosis of exclusion. Other more consequential diagnoses such as idiopathic thrombocytopenic purpura and hemolysis, elevated liver enzyme, and low platelet count (HELLP) syndrome must be excluded (see section on maternal comorbidities, coagulopathies).

Thromboelastography (TEG) is a hemostatic assay that measures the kinetics of clot formation and breakdown. It can provide information about clotting variables, including platelet function as well as the function of other coagulation factors (see also Chapter 50). At term gestation, TEG analysis reflects a hypercoagulable state with decreased time to start of clot formation (R), decreased time to specified clot strength (K), increased rate of clot formation (α), and increased clot strength (MA).³⁷ Although the timing and degree of change in TEG analysis varies with each parameter, many of the changes begin to occur within the first trimester.³⁸

NEUROLOGIC CHANGES

Pregnant patients are considered more sensitive to both inhaled and local anesthetics. They have a reduced minimum alveolar concentration (MAC) for inhaled anesthetics. The MAC of a volatile anesthetic is reduced by 40% in animals^{39,40} and 28% in humans during the first trimester of pregnancy.⁴¹ However, it appears the decrease in MAC (i.e., immobility in response to volatile anesthetics among 50% of patients) occurs at the level of the spinal cord based on an electroencephalographic study suggesting that anesthetic effects of sevoflurane on the brain are similar in the pregnant and nonpregnant state.⁴² The underlying mechanism of reduced MAC in pregnancy remains unclear; it is likely multifactorial, and many postulate progesterone may have a role.

Pregnant women are more sensitive to local anesthetics and neuraxial anesthetic requirements are decreased by 40% by term. At term, the epidural veins are distended and

the volume of epidural fat increases, which decreases the size of the epidural space and volume of cerebrospinal fluid (CSF) in the subarachnoid space. Although the decreased volume of these spaces facilitates the spread of local anesthetics, the local anesthetic dose requirement is decreased for neuraxial block as early as the first trimester, before significant aortocaval compression or other mechanical or pressure-related changes occur.⁴³ Consequently, the increased nerve sensitivity and decrease in local anesthetic dose requirements are likely biochemical in origin.

Uteroplacental Physiology

The placenta is a remarkable organ that undergoes vast changes from a fertilized ovum's initial implantation into the uterine wall until birth. The placenta is composed of both maternal and fetal tissues and is the interface of maternal and fetal circulation systems. It provides a substrate for physiologic exchange between the two systems. The placenta is made up of a basal and a chorionic plate that are separated by the intervillous space. Maternal blood is delivered to the placenta by the uterine arteries and enters the intervillous space via the spiral arteries. It travels toward the chorionic plate, passing fetal villi where exchange takes place, and then drains back to veins in the basal plate and then ultimately away from the uterus via the uterine veins. The fetal blood arrives at the placenta via two umbilical arteries that form umbilical capillaries that cross the chorionic villi. After placental exchange, oxygen-rich, nutrient-rich, and waste-free blood is returned from the placenta to the fetus through a single umbilical vein.

UTERINE BLOOD FLOW

An understanding of uteroplacental blood flow is critical for appropriate clinical care. Uterine blood flow increases progressively during pregnancy from about 100 mL/min in the nonpregnant state to 700 to 900 mL/min (~10% of cardiac output) at term gestation.^{44,45} Approximately 80% of the uterine blood flow perfuses the intervillous space (placenta) and the remainder perfuses the myometrium. Uterine blood flow has minimal autoregulation, and the vasculature remains essentially fully dilated during pregnancy. Uterine and placental blood flow depend upon maternal cardiac output and are directly related to uterine perfusion pressure and inversely related to uterine vascular resistance. Decreased perfusion pressure can result from maternal hypotension secondary to multiple causes including hypovolemia from blood loss or dehydration, decreased systemic resistance from general or neuraxial anesthesia, or aortocaval compression. Increased uterine venous pressure from aortocaval compression, frequent or prolonged uterine contractions, or prolonged abdominal musculature contraction with bearing down (Valsalva) during second-stage pushing can decrease uterine perfusion. Additionally, extreme hypocapnia ($\text{PaCO}_2 < 20 \text{ mm Hg}$) occasionally associated with hyperventilation secondary to severe labor pain can reduce uterine blood flow with resultant fetal hypoxemia and acidosis. Neuraxial blockade does not alter uterine blood flow as long as maternal hypotension is avoided but decreases in maternal blood pressure during neuraxial or general anesthesia should be immediately corrected.

Endogenous maternal catecholamines and exogenous vasopressors may cause increasing uterine arterial resistance and decreasing uterine blood flow depending on the class and amount given. In a pregnant ewe model, use of α -adrenergic vasopressors—methoxamine and metaraminol—increased uterine vascular resistance and decreased uterine blood flow, whereas administration of ephedrine did not reduce uterine blood flow despite drug-induced increases in maternal arterial blood pressure.⁴⁶ As a result, ephedrine was previously considered the vasopressor of choice for the treatment of hypotension caused by the administration of neuraxial anesthesia to pregnant women. In complete contrast, more recent human trials demonstrate the use of phenylephrine (α -adrenergic agonist) for prophylaxis or treatment of neuraxial-induced hypotension is not only effective in preventing hypotension, but also is associated with less fetal acidosis and base deficit than the use of ephedrine.⁴⁷⁻⁵⁰ Other methods to reduce maternal hypotension with induction of regional or general anesthesia are discussed in the section on anesthesia for cesarean delivery.

PLACENTAL EXCHANGE

Oxygen Transfer

The delivery of O_2 from the mother to the fetus depends on a variety of factors, including the ratio of maternal to fetal placental blood flow, the O_2 partial pressure gradient between the two circulations, the diffusion capacity of the placenta, the respective maternal and fetal hemoglobin concentrations and O_2 affinities, and the acid-base status of the fetal and maternal blood (Bohr effect). O_2 delivery to the fetus is facilitated primarily because the fetal oxyhemoglobin dissociation curve is to the left (greater O_2 affinity) of the maternal oxyhemoglobin dissociation curve (decreased O_2 affinity). Fetal hemoglobin has a higher O_2 affinity and lower partial pressure at which it is 50% saturated (P50: 18 mm Hg) compared to maternal hemoglobin (P50: 27 mm Hg). Fetal PaO_2 is normally 40 mm Hg and never more than 60 mm Hg, even if the mother is breathing 100% O_2 .⁵¹ Animal studies note that in the face of decreased O_2 delivery, fetal O_2 consumption can be maintained with increased O_2 extraction until the maternal O_2 delivery is approximately 50% of its normal state.^{52,53} CO_2 easily crosses the placenta and its transfer from the fetus to the mother is limited by blood flow and not diffusion.

Drug Transfer

Maternal-fetal exchange across the placenta occurs by one of four mechanisms: passive diffusion, facilitated diffusion, transporter-mediated mechanisms, and vesicular transport.⁵⁴ Most drugs have molecular weights less than 1000 Daltons and, therefore, cross the placenta by diffusion if the drug is not ionized. The rate of diffusion and peak levels in the fetus depend on maternal-to-fetal concentration gradients, maternal protein binding, molecular weight, lipid solubility, and the degree of drug ionization. The maternal blood concentration of a drug is typically the primary determinant of how much drug will ultimately reach the fetus. Nondepolarizing neuromuscular blocking drugs are ionized, have a high molecular weight, and poor lipid solubility resulting in minimal placental transfer. Succinylcholine has a low molecular weight but is highly ionized and

therefore does not readily cross the placenta unless given in large nonclinical doses. Thus during administration of a general anesthetic for cesarean delivery, the fetus or neonate is not paralyzed. Both heparin and glycopyrrolate have minimal placental transfer because they are highly charged. In contrast, placental transfer of volatile anesthetics, benzodiazepines, local anesthetics, and opioids is facilitated by the relatively low molecular weights of these drugs. Dexmedetomidine may cross the placental barrier but is stored within the placenta and transfer to the fetus is reduced.⁵⁵ As a general consideration, drugs that readily cross the blood-brain barrier also readily cross the placenta. Therefore most centrally acting general anesthetics cross the placenta and affect the fetus. There is a paucity of evidence on the placental transfer of newer drugs such as liposomal bupivacaine and sugammadex at this time.

Fetal blood is more acidic than maternal blood, and the lower pH creates an environment in which weakly basic drugs, such as local anesthetics and opioids, cross the placenta as nonionized molecules and become ionized in the fetal circulation. Because this newly ionized molecule has more resistance to diffusion back across the placenta, the drug may accumulate in the fetal circulation and reach levels higher than the maternal blood. This process is referred to as "ion trapping." During fetal distress (fetal acidemia), higher concentrations of these weakly basic drugs can be trapped.⁵⁶ High concentrations of local anesthetics in the fetal circulation decrease neonatal neuromuscular tone. Extremely high levels, such as those associated with unintended maternal intravascular local anesthetic injection, result in a variety of fetal effects, including bradycardia, ventricular arrhythmias, acidosis, and severe cardiac depression. Placental transfer and fetal uptake of specific analgesic and anesthetic drugs are detailed later in the sections that discuss methods of labor analgesia and anesthesia for cesarean delivery.

FETAL CIRCULATION AND PHYSIOLOGY

Fetal blood volume increases throughout gestation. Approximately one-third of the fetal-placental blood volume is contained within the placenta.⁵⁷ During the second and third trimester, the fetal blood volume is estimated to be approximately 120 to 160 mL/kg of fetal body weight.⁵⁸ Thus the total blood volume of a term normal fetus is approximately 0.5 L. Although fetal liver function is not yet mature, coagulation factors are synthesized independent of the maternal circulation. The serum concentrations of these factors increase with gestational age and do not cross the placenta. However, fetal clot formation in response to tissue injury is decreased in comparison to that in adults.

The anatomy of the fetal circulation helps decrease fetal exposure to potentially high concentrations of drugs in umbilical venous blood. Approximately 75% of umbilical venous blood initially passes through the fetal liver, which may result in significant drug metabolism before the drug reaches the fetal heart and brain (first-pass metabolism). Fetal and neonatal enzymatic drug metabolism activities are lower than those of adults, but most drugs can be metabolized. In addition, drugs entering the fetal inferior vena cava via the ductus venosus, thus bypassing

the portal circulation and the liver, are initially diluted by drug-free blood returning from the fetal lower extremities and pelvic viscera. These anatomic characteristics of the fetal circulation add to the complexity of maternal-fetal pharmacokinetics.

Labor Progress

Labor begins with the onset of repetitive uterine contractions that result in the dilation of the cervix, thus permitting passage of the fetus from the uterus through the birth canal. In reality, however, preparation for labor may begin several hours or days before active labor with an inflammatory process mediated by cellular infiltration and release of local cytokines that result in softening of the cervix. The signals that orchestrate the onset of spontaneous labor are not precisely known. However, "labor" is the onset of organized, regular uterine contractions that result in progressive cervical dilation and effacement. When spontaneous labor does not occur at an appropriate time, labor may be induced for fetal or maternal indications with various pharmacologic and physical methods.⁵⁹

Labor is a continuous process separated into first, second, and third stages. The first stage of labor begins with regular, painful uterine contractions and includes the change of the uterine cervix from a thick, closed tube to an opening of approximately 10 cm through which the fetus can be expelled. This stage is further divided into a latent phase and an active phase. The second stage of labor begins when the cervix is fully dilated and ends with the birth of the newborn. The third stage of labor is the delivery of the placenta. The time course of the first stage of labor was first studied by Emanuel Friedman who described a sigmoidal relationship between cervical dilation and time (Fig. 62.2A). The sigmoidal nature of the relationship has since been challenged in that little evidence exists for a deceleration phase as the cervix approaches complete dilation (10 cm). However, the separation of the first stage of labor into an early slow phase termed *latent labor* and a more rapid phase of active labor has stood the test of time and advances in modeling techniques.^{60,61} To account for the contemporary obstetric population including an older maternal age and increased maternal and fetal body sizes, a new labor curve has been proposed after analysis of 62,415 parturients.^{62,63} The main difference of the newly proposed curve is when latent labor is considered to transition to active labor. Traditionally, this transition point was 4-cm dilation. However, the new curve proposes active labor beginning at 6-cm dilation in both multiparous and nulliparous parturients (Fig. 62.2B).

Labor may be referred to as "abnormal" on the basis of having abnormally slow latent labor, arrest in the active phase, or arrest of descent (failure of stage 2). Dystocia, or abnormal labor, may be a result of inadequate uterine contractions, mismatch of fetal and pelvic size, or abnormal fetal position. The diagnosis of dystocia is based on deviation from normal values derived from populations; however, significant variability exists among individual laboring women. Various demographic and genetic factors contribute to the variability in labor progress.^{60,61,64-67} Multiparity is associated with

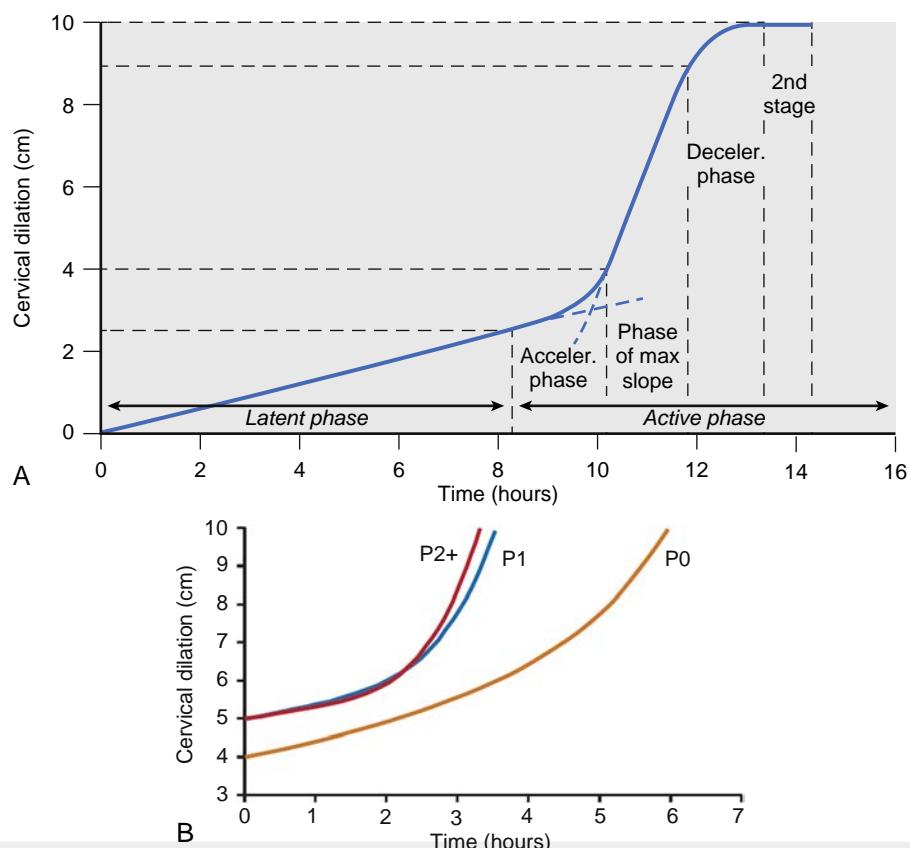


Fig. 62.2 Cervical dilation. (A) Friedman's original sigmoid model of the progress of cervical dilation over time based on an analysis of 500 nulliparas at term. (B) The modern labor curve, which eliminates the deceleration (Deceler.) phase and changes the threshold for the active phase from 4 to 6 cm. Acceler, Acceleration; P0, nulliparous women; P1, women of parity 1; P2+, women of parity 2 or higher. (B) (Legend from Zhang, Fig. 2) Average labor curves by parity in singleton term pregnancies with spontaneous onset of labor, vaginal delivery, and normal neonatal outcomes. (Reproduced with permission from [A] Friedman E. Primigravid labor: a graphicostatistical analysis. *Obstet Gynecol*. 1955;6:567–589; and [B] Zhang J, Landy HJ, Brand DW, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. *Obstet Gynecol*. 2010;116:1281–1287. doi: 10.1097/AOG.0b013e318fdef6e.)

faster labor. Greater maternal weight, older age, and larger fetal size have been associated with slower labor.^{60,65,68} Evidence also indicates a hereditary role in labor progress from epidemiologic studies.⁶⁹ Specifically, β_2 -adrenergic and oxytocin receptor polymorphisms have been implicated in mediating variability in labor progress.^{64–66} An abnormally poor response to intrinsic or extrinsic oxytocin may result in abnormal contractility, as would an abnormally strong response to β_2 -adrenergic agonists (either exogenous or endogenous) which inhibit contractility.

LABOR AND FETAL MONITORING

Intrapartum fetal monitoring was created to evaluate fetal well-being and detect fetal distress earlier in labor to allow intervention prior to permanent fetal injury. Electronic fetal monitoring (EFM) combines interpretation of fetal heart rate (FHR) monitoring and uterine contraction monitoring. FHR monitoring was developed in the 1960s and its use has been increasing since.⁷⁰ There is high interobserver and intraobserver variability of FHR tracing interpretation.^{71,72} A meta-analysis comparing EFM to intermittent FHR auscultation noted the use of EFM reduced the risk for neonatal seizures (relative risk [RR]: 0.50), but not the

risks for perinatal mortality or cerebral palsy.⁷³ The use of this monitoring has been shown to increase the rate of both operative and cesarean deliveries.^{73,74}

The nomenclature, interpretation, and management principles for FHR monitoring were updated in 2009 by the American Congress of Obstetricians and Gynecologists (ACOG).⁷⁴ These current guidelines are detailed later, and related terminology is presented in **Box 62.1**. An understanding of the specific uterine contraction and FHR monitoring terminology as well as the clinical implications is critical for optimal communication during emergent situations among anesthesiologists, obstetricians, midwives, and labor nurses.

CONTRACTION MONITORING

Uterine contractions can be monitored externally with a tocodynamometer or internally with an intrauterine pressure transducer. External monitors only allow determination of contraction frequency, whereas internal monitors also allow quantitative measurement of intrauterine pressure. The Montevideo unit is traditionally used by obstetricians to assess the adequacy of uterine contractions. The Montevideo unit is defined as the intensity of contractions

BOX 62.1 Fetal Heart Rate Monitoring Pattern Definitions

Baseline

- The mean FHR rounded to increments of 5 bpm during a 10-min segment, excluding:
 - Periodic or episodic changes
 - Periods of marked FHR variability
 - Segments of baseline that differ by more than 25 bpm
- The baseline must be for a minimum of 2 min in any 10-min segment, or the baseline for that period is indeterminate. In this case, one may refer to the prior 10-min window for determination of baseline.
- Normal FHR baseline: Rate is 110–160 bpm.
- Tachycardia: FHR baseline is greater than 160 bpm.
- Bradycardia: FHR baseline is less than 110 bpm.

Baseline Variability

- Fluctuations occur in the baseline FHR that are irregular in amplitude and frequency.
- Variability is visually quantitated as the amplitude of peak-to-trough in beats per minute.
 - Absent: Amplitude range is undetectable.
 - Minimal: Amplitude range is detectable but 5 bpm or fewer.
 - Moderate (normal): Amplitude range is 6–25 bpm.
 - Marked: Amplitude range is greater than 25 bpm.

Acceleration

- A visually apparent abrupt increase (onset to peak in <30 s) occurs in the FHR.
- At 32 weeks' gestation and beyond, an acceleration has a peak of 15 or more bpm above baseline, with a duration of 15 s or more but less than 2 min from onset to return.
- Before 32 weeks' gestation, an acceleration has a peak of 10 or more bpm above baseline, with a duration of 10 s or more but less than 2 min from onset to return.
- Prolonged acceleration lasts 2 min or more but less than 10 min.
- If an acceleration lasts 10 min or longer, it is a baseline change.

Sinusoidal Pattern

- Visually apparent, smooth, sine wave–like, undulating pattern occurring in FHR baseline, with a cycle frequency of 3–5 cycles/min that persists for 20 min or longer.

bpm, Beats per minute; FHR, fetal heart rate.

Data from Macones GA, Hankins GD, Spong CY, et al. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol*. 2008;112:661–666.

(in millimeters of mercury, as measured with an intrauterine pressure catheter) multiplied by the number of contractions that occur in 10 minutes.

Uterine contractions are quantified over a 10-minute window that is averaged over a 30-minute window with guidelines provided by the ACOG.⁷⁴ Normal contractions are defined as five or fewer contractions in 10 minutes, averaged over a 30-minute window. Tachysystole is defined as uterine activity greater than five contractions in 10 minutes, averaged over a 30-minute window. Tachysystole applies to both spontaneous and augmented labor and should always be qualified as to the presence or absence of associated FHR decelerations. Treatment of tachysystole during labor may differ depending on the clinical situation

but may include sublingual or intravenous nitroglycerin⁷⁵ to briefly relax the uterus, as well as the use of β_2 -adrenergic drugs such as terbutaline.

FETAL HEART RATE TRACING

FHR monitoring is most commonly accomplished with a surface Doppler ultrasound transducer (external monitoring), but it may be necessary to apply a fetal scalp electrode to obtain accurate continuous FHR monitoring (internal monitoring). For internal monitoring, a peak or threshold voltage of the fetal R wave from the scalp electrode is used to measure FHR. Of note, a fetal scalp electrode can be placed only if the cervix is minimally dilated and the membranes are ruptured. The FHR pattern changes in response to fetal asphyxia from activation of peripheral and central chemoreceptors and baroreceptors.⁷⁶ It also shows changes as a result of various fetal brain metabolic changes that occur with asphyxia.⁷⁶ These changes in the FHR produce specific patterns and characteristics that provide an evaluation of the fetal state.

The FHR tracing is used as a nonspecific reflection of fetal acidosis. It should be interpreted over a time course in relation to the clinical context and other known maternal and fetal comorbidities, because multiple factors other than fetal acidosis can influence the FHR tracing. Box 62.1 defines FHR baseline, variability, and accelerations. A normal baseline FHR ranges from 110 to 160 bpm. FHR variability are fluctuations in the baseline FHR that are irregular in frequency and amplitude. Normal FHR variability predicts early neonatal health and a fetal central nervous system that is normally interacting with the fetal heart. Accelerations are abrupt changes in the FHR above baseline and are defined by gestational age of the fetus.

Fig. 62.3 details FHR tracing deceleration characteristics. Late decelerations are a result of uteroplacental insufficiency causing relative fetal brain hypoxia during a contraction. The resulting sympathetic outflow elevates the fetal blood pressure and activates the fetal baroreceptors and an associated slowing in the FHR. A second type of late deceleration is from myocardial depression in the presence of increasing hypoxia.⁷⁷ Therefore late decelerations are considered worrisome. On the other hand, early decelerations are considered benign and tend to mirror the uterine contraction and are believed to be in response to vagal stimuli, which are often the result of fetal head compression. Variable decelerations are associated with umbilical cord compression. A sinusoidal FHR pattern is associated with fetal anemia and is considered ominous.⁷⁸ In general, minimal-to-undetectable FHR variability in the presence of variable or late decelerations is associated with fetal acidosis.⁷⁹ Prolonged decelerations (<70 beats/min for >60 seconds) are associated with fetal acidemia and are extremely ominous, particularly with the absence of variability.⁸⁰

FETAL HEART RATE CATEGORIES

A three-tiered FHR category classification system is currently recommended for fetal assessment with the specific criteria for each category outlined in Box 62.2.^{74,78} This

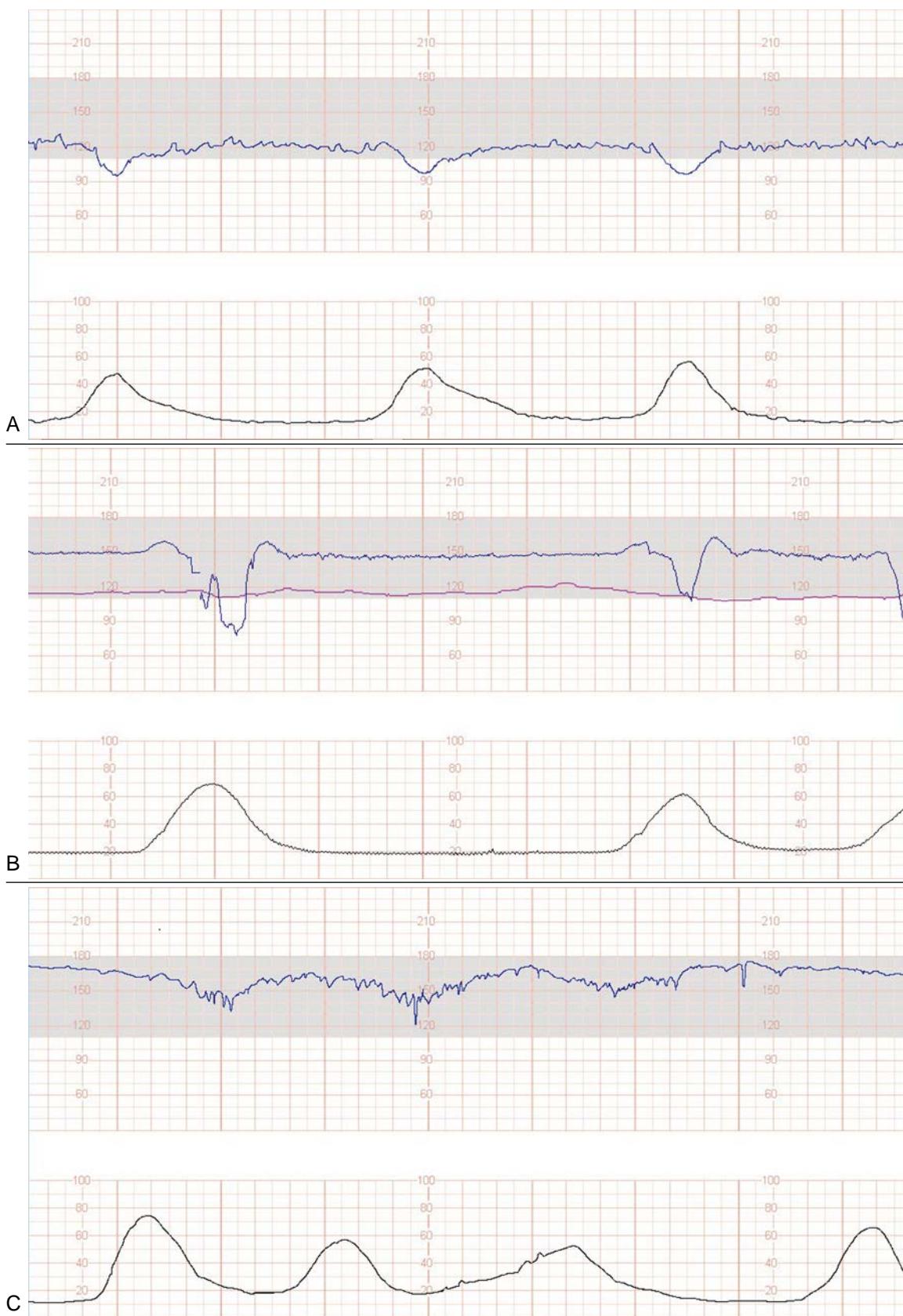


Fig. 62.3 Fetal heart rate deceleration. (A) Early deceleration: visually apparent, usually symmetric gradual decrease and return of the fetal heart rate (FHR) with the nadir of the deceleration occurring at the same time as the peak of the contraction. (B) Variable decelerations: visually apparent, abrupt decrease in FHR ≥ 15 seconds and < 2 minutes. The relationship of the onset of the deceleration compared to the contraction is variable as is the depth and duration. (C) Late FHR decelerations: visually apparent, usually symmetric gradual decrease and return of the FHR during which the nadir of the deceleration occurs after the peak of the contraction.

BOX 62.2 Three-Tier Fetal Heart Rate Interpretation System

Category I

Category I FHR tracings include all of the following:

- Baseline rate of 110–160 beats/min
- Moderate baseline FHR variability
- Late or variable decelerations are absent
- Accelerations and early decelerations may be present or absent

Category II

Category II FHR tracings include all FHR tracings not categorized as Category I or III. Category II FHR tracings may include any of the following:

- Baseline rate:
 - Bradycardia not accompanied by absent baseline variability
 - Tachycardia
- Baseline FHR variability
 - Minimal baseline variability
 - Absent baseline variability with no recurrent decelerations
 - Marked baseline variability
- Accelerations
 - Absence of induced accelerations after fetal stimulation
- Periodic or episodic decelerations
 - Recurrent variable decelerations accompanied by minimal or moderate baseline variability
 - Prolonged deceleration ≥ 2 min but < 10 min
 - Recurrent late decelerations with moderate baseline variability
 - Variable decelerations with slow return to baseline, “overshoots,” or “shoulders”

Category III

Category III FHR tracings include either:

- Absent baseline FHR variability plus any of the following:
 - Recurrent late decelerations
 - Recurrent variable decelerations
 - Bradycardia
- Sinusoidal pattern

FHR, Fetal heart rate.

Data from Macones GA, Hankins GD, Spong CY, et al. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol*. 2008;112:661–666.

system evaluates the fetus for the given moment of the assessment. The fetal condition may move back and forth among the categories over time. Specific terminology used for categorization is defined in [Box 62.1](#).

Category I FHR tracings are considered normal and are predictive of a normal fetal acid-base state at the time of observation, and no specific management is required.

Category II FHR tracings are considered indeterminate and include all tracings not in categories I or III. Category II tracings are not predictive of abnormal fetal acid-base status and require continued monitoring and reevaluation with consideration for the entire clinical picture. In some cases, additional tests may be obtained or intrauterine resuscitative measures taken to improve the fetal condition.

Category III FHR tracings are considered abnormal and are associated with an abnormal fetal acid-base state at the time of observation. These tracings require prompt patient evaluation and efforts to improve the fetal

condition. These interventions may include intrauterine resuscitation with change in maternal position, discontinuation of labor augmentation, treatment of maternal hypotension with fluids and/or vasopressor administration, use of supplemental O₂, and/or administration of a tocolytic agent such as terbutaline. If the FHR tracing does not improve, expeditious delivery should occur which may involve an assisted vaginal (forceps or vacuum) delivery or a cesarean delivery.

Labor Analgesia

Childbirth is a pinnacle event in a family's life that is surrounded by many beliefs and traditions, some of which are founded in science and others more historical, cultural, personal, or even spiritual. In this context, several non-pharmacologic techniques have been used to relieve the pain of childbirth throughout history, including acupuncture,⁸¹ massage,^{82,83} and hypnosis.⁸⁴ Drugs were not used in Western medicine to relieve pain in childbirth until the mid-1800s, most famously when the English Queen Victoria chose to inhale chloroform for analgesia during the birth of Prince Leopold.⁸⁵

For most women, labor is intensely painful. However, the time course of pain intensity is highly variable, dynamic, and unpredictable. Some women will experience severe pain only just before and during the second stage of labor, whereas others will report severe pain from their first contraction. Rarely do women experience a pain-free labor and give birth unexpectedly under inopportune conditions.⁸⁶ The source of these differences in labor pain is not completely known but may be in part genetic. In one study, Asian women reported more pain in labor than women of other ethnic backgrounds.⁶⁰ This association was also found with a single nucleotide polymorphism in the β_2 -adrenergic gene.⁶⁵ Other factors may include parity; maternal pelvic size and shape; fetal size and presentation; maternal anxiety, pain tolerance, and other psychological variables; the presence of maternal social and psychological support during labor; induction of labor; and whether contractions are augmented.

NONPHARMACOLOGIC LABOR PAIN MANAGEMENT

Many patients prefer to use nonpharmacologic methods of pain management during all or part of labor. Acupuncture can be effective in treating postoperative pain after cesarean delivery,⁸⁷ but it is not as effective for analgesia during labor. A systematic review and meta-analysis of acupuncture for pain relief in labor involving 10 randomized controlled trials ($n = 2038$) found that acupuncture was not superior to sham acupuncture (superficial needling lateral to an actual acupuncture point) at 1 and 2 hours.⁸⁸ Unfortunately, most of the trials were not properly blinded, increasing the likelihood of bias.

Several trials have found a reduction in pain and anxiety during the first stage of labor with the use of massage. A Cochrane review on massage in labor identified seven randomized trials of massage, six of which were judged to have low or unclear risk for bias.⁸³ During the first stage of labor,

pain was reduced in the massage group by -0.98 (confidence interval [CI], 1.17-0.47) on a 10-point pain scale. No difference was found in the use of pharmacologic pain relief between groups or in pain reported during the second and third stages of labor. Of note, one study of 60 women found that massage decreased anxiety.⁸⁹

Hypnosis has been used both as a relaxation technique and for management of pain during labor. When hypnosis was compared with standard care, no evidence was found that pain was less with the use of hypnosis, nor was evidence found for a difference in satisfaction with pain relief.⁸³ A Cochrane review of 9 trials randomizing 2954 women found women in the hypnosis group were less likely to use pharmacologic pain relief compared to those in the control groups. There were no clear differences for satisfaction, spontaneous vaginal birth, and postpartum depression between the two groups.⁹⁰

Other nonpharmacologic techniques include the breathing techniques described by Lamaze, the LeBoyer technique, the Bradley method, transcutaneous nerve stimulation, hydrotherapy, presence of a support person, intradermal water injections, and biofeedback. A retrospective national survey of women's childbearing experiences in the United States found that although neuraxial methods of pain relief were considered the most helpful and effective, nonpharmacologic methods of hydrotherapy and massage were rated more or equally helpful in relieving pain compared with the use of intravenous opioids.⁹¹ Although many nonpharmacologic techniques seem to reduce the perception of labor pain, most published studies lack the rigorous scientific methodology for useful comparison of these techniques to pharmacologic methods.

CONSIDERATIONS FOR PHARMACOLOGIC TREATMENT OF PAIN IN LABOR

Preprocedural assessment by an anesthesia provider should be performed for any candidate for neuraxial labor analgesia. Clinical assessment should be considered for all patients admitted to a labor and delivery floor not only to discuss labor analgesia options prior to excruciating pain, but also to assess the patient for comorbid conditions that could complicate labor, obstetric procedures, or anesthesia. The obstetric anesthesia team should be prepared to care for all admitted patients in the event of an obstetric emergency. In otherwise healthy women, laboratory testing is not required during a routine preprocedural obstetric assessment.⁹²

Although any laboring woman has the potential to require cesarean delivery, labor takes many hours and requires adequate nutrition and hydration. While balancing these two considerations, the ASA has recommended that moderate amounts of clear liquids be allowed during the administration of neuraxial analgesia and throughout labor. A period of abstention from solids before the placement of neuraxial analgesia is not required. However, the ASA does recommend the ingestion of solid foods be avoided in laboring patients.⁹²

SYSTEMIC MEDICATIONS

Opioids can be used for labor analgesia. They are inexpensive, widely available, and can be administered intramuscularly

without the need for intravenous access. Although there are differences among opioids, they all cross the placenta and can have fetal effects including dose-related respiratory depression and decreased FHR variability.

Although meperidine was once the most commonly used long-acting opioid in obstetric practice,⁹³ it is the most likely to result in side effects. Meperidine is typically administered intravenously in doses of up to 50 mg or intramuscularly in doses ranging from 50 to 100 mg. Maternal half-life of meperidine is 2.5 to 3 hours whereas the half-life for its active metabolite normeperidine is 13 to 23 hours. The half-life of both is up to three times longer in the fetus and newborn. Normeperidine can accumulate with repeated doses and can be neurotoxic. With increased dosing and shorter intervals between doses and delivery, risk to the newborn is increased, including lower Apgar scores and prolonged time to sustained neonatal respiration.⁹⁴

Morphine is rarely used for labor pain. Like meperidine it has an active metabolite (morphine-6-glucuronide) with a half-life that is longer in neonates than in adults, and it produces significant maternal sedation. Obstetricians may use intramuscular morphine for analgesia, sedation, and rest. This produces analgesia with an onset of 10 to 20 minutes and is used most commonly in latent labor. Maternal side effects may include respiratory depression and histamine release resulting in pruritus and rash.

Mixed agonist-antagonist opioid analgesics such as nalbuphine and butorphanol are utilized to treat labor pain. Nalbuphine has similar analgesic potency as morphine. It is given either intravenously, intramuscularly, or by subcutaneous injection at doses of 10 to 20 mg every 4 to 6 hours. Butorphanol is five times as potent as morphine and 40 times more potent than meperidine. A dose of 1 to 2 mg intravenously or intramuscularly is commonly used for labor analgesia. Both medications are often well tolerated by the parturient.

Fentanyl and, more recently, remifentanil have become popular systemic opioid analgesics over the past two decades. Fentanyl is a synthetic opioid that is highly lipid-soluble and has a short duration and no active metabolites. When given in small IV doses of 50 to 100 μ g/h, no significant differences are seen in neonatal Apgar scores and respiratory effort compared with those in newborns of mothers not receiving fentanyl.⁹⁵ Fentanyl is also commonly used in patient-controlled analgesia (PCA) during labor. Common doses utilized for fentanyl PCA include a bolus dose of 10 to 25 μ g with a lockout interval of 5 to 12 minutes. High doses of systemic fentanyl, especially immediately prior to birth, could result in neonatal depression.

Remifentanil PCA may offer superior pain relief and lesser fetal effects than other intravenous opioid analgesics but its analgesic effects are inferior to epidural labor analgesia and it requires careful maternal oxygenation and ventilation monitoring. The metabolism of remifentanil depends completely on tissue and plasma esterases, which are fully mature in the fetus. Further, it is more rapidly metabolized in the placenta (by placental esterases) than in the maternal plasma and thus the fetal-to-maternal ratio is small. In the pregnant ewe model, the maternal-to-fetal ratio of remifentanil is approximately tenfold,⁹⁶ and the ratio was similar in human studies.⁹⁷ Because of these characteristics, more remifentanil can be administered to the mother at times close to delivery than would be considered safe for

longer-acting opioids that rely on slower metabolism by the liver. Remifentanil is more effective than long-acting opioids⁹³; however, the improvement in pain relief may be because comparatively larger doses of remifentanil were given.⁹⁸

Although remifentanil may be superior to longer acting systemic opioids, it is inferior to epidural labor analgesia. A meta-analysis of randomized controlled trials comparing remifentanil PCA and epidural analgesia found that parturients with remifentanil PCA had higher pain scores at one hour than those who received epidural analgesia.⁹⁹ The incidence of pruritus, nausea, and vomiting were not statistically different between the two groups; however, the confidence intervals were wide. A subsequent meta-analysis confirmed that women were less satisfied when receiving remifentanil PCA compared to women in the epidural group but more satisfied than women receiving other parenteral opioids.¹⁰⁰ The major risk of remifentanil in labor is maternal respiratory depression. Careful surveillance is required to ensure adequate oxygenation and ventilation throughout treatment and for this reason, some practices choose not to offer remifentanil PCA labor analgesia.

INHALED ANALGESIA

While volatile anesthetics are no longer used for labor analgesia, nitrous oxide (N₂O) is commonly used worldwide. Typically, it is blended with O₂ in a 50:50 ratio for patient-inhaled self-administration just before and during contractions. A systematic review evaluating N₂O for labor analgesia found that epidural analgesia provided more effective pain relief than N₂O but most studies were of poor quality.^{101,102} Some studies have demonstrated moderate analgesia in response to inhaled N₂O (pain scores of 8 in 10 reduced to 6 in 10),¹⁰³ whereas others have shown no difference in visual analogue pain scores.¹⁰⁴ Paradoxically, in this negative study, many women wished to continue using nitrous labor analgesia after the study period. Overall, although patients are *less likely* to report excellent pain control with N₂O, they were *as likely* to express satisfaction with their anesthesia care.¹⁰² Therefore although it is less efficacious than neuraxial analgesia, it provides an alternative to patients who desire a less invasive analgesic approach as well as those who have a contraindication for neuraxial analgesia. Without the coadministration of opioids, the use of 50% N₂O in O₂ is safe and does not result in hypoxia or unconsciousness.¹⁰⁵

NEURAXIAL ANALGESIA

Neuraxial analgesia is the most reliable and effective method of reducing pain during labor.⁹¹ A large meta-analysis found epidural analgesia offered better pain relief compared with placebo (median pain scale reduction 3.4 in 10, 95% CI, 1.3-5.4) and reduced the need for additional pain medication.¹⁰⁶ Analgesia is given most commonly by epidural, spinal, combined spinal-epidural (CSE), or dural puncture epidural (DPE). These techniques provide superior analgesia to alternative approaches and are safe.

Neuraxial Analgesia and Progress of Labor

Considerable controversy has been generated regarding the effects of neuraxial analgesia on the progress of labor. Observational studies have suggested that epidural analgesia is associated with slower labor progress as well as higher cesarean delivery rates.^{65,107} Confounding variables are likely responsible for this association. For example, patients who have dysfunctional labor (which are at higher risk to proceed to cesarean delivery) would have more exposure to severe pain, would be more likely to request epidural analgesia, and more likely to request it earlier. Before-and-after studies and multiple prospective, randomized controlled trials have found no association between epidural labor analgesia and cesarean delivery. In fact, a 2011 Cochrane review of 38 studies involving 9658 women comparing epidural versus non-epidural analgesia in labor found no difference in the risk for cesarean delivery.¹⁰¹ Large prospective studies in which patients were randomly assigned to early or late neuraxial anesthesia have invariably concluded that earlier neuraxial labor analgesia does not affect the length of the first stage of labor or increase the risk for cesarean delivery.¹⁰⁸⁻¹¹² In contrast, several prospective trials and a meta-analysis suggest that neuraxial anesthesia may cause a modest prolongation of the second stage of labor by approximately 15 minutes.^{106,113,114} Increase in the duration of the second stage may occur because dense motor blockade could impede coordinated pushing. Local anesthetic dosing is sometimes reduced in the second stage if the blockade is too dense to allow for coordinated expulsion efforts. However, a recent double-blind trial randomized 400 women with an epidural to either saline or local anesthetic at the onset of the second stage of labor and found no difference in length.¹¹⁵

Epidural labor analgesia may offer maternal benefits during the second stage. When labor is comfortable, tolerance for a longer second stage may allow uterine contractions to lower the fetal station before active pushing efforts begin, a technique sometimes called “laboring down.”¹¹⁶ A large randomized clinical trial of term nulliparous women receiving neuraxial analgesia found no difference in the rate of spontaneous vaginal delivery if they delayed pushing or immediately started pushing at the onset of the second stage.¹¹⁷ This technique may allow women a less strenuous delivery and can be employed for women with significant comorbid cardiac or vascular conditions to limit the hemodynamic effects of repetitive Valsalva maneuvers. Further, epidural labor analgesia may protect the perineum from injury during delivery by allowing a more controlled expulsion of the fetus that allows for stretching (instead of tearing) of tissues.¹¹⁸

Timing of Placement

The optimal timing for the placement of a neuraxial anesthetic has been extensively studied. In 2011, a meta-analysis including prospective, randomized trials was conducted to test if the placement of neuraxial analgesia during the early first stage of labor was associated with a prolonged first stage of labor.¹¹⁹ Six studies of 15,399 parturients compared placement of neuraxial analgesia at 3-cm cervical dilation or less to placement in active labor.

No increase in the incidence of cesarean delivery was found in the early epidural group nor was the first stage of labor prolonged. Thus if a parturient chooses neuraxial analgesia, there is no point during the first stage of labor that is “too early” to initiate epidural analgesia. Current ASA guidelines note that maternal request for labor pain relief is sufficient justification for epidural initiation and the timing should not depend on an arbitrary cervical dilation.⁹²

Epidural Analgesia

Lumbar epidural analgesia offers a safe and effective method of pain relief during labor and is the mainstay of labor analgesia. Epidural analgesia is most commonly initiated after placement of a catheter into the epidural space between L2-3 and L4-5 (see [Chapter 45](#)). The analgesia technique is versatile and the block may be made denser and prolonged if operative delivery is required. Typically, a combination of low-dose local anesthetic and opioid are administered to provide continuous sensory block during labor. Benefits of epidural analgesia include decreased maternal catecholamines, effective pain relief, increased patient satisfaction, and the ability to quickly achieve surgical anesthesia for an emergency cesarean delivery.

Prevention of accidental intravascular or intrathecal local anesthetic administration is paramount in the safety of epidural techniques. Initial dosing of local anesthetic through the needle within the epidural space is not recommended because of potential unintended intravascular or intrathecal placement that would result in local anesthetic systemic toxicity or total spinal. Further, most anesthesia providers “test dose” the epidural catheter after placement to assess for intravascular or intrathecal placement.¹²⁰ A test dose may consist of a small dose of local anesthetic that would induce an altered sensorium (dizziness, buzzing in the ears, or numbness in the lips) if injected intravascularly but would not cause harm. Likewise, if this small dose were injected into the intrathecal space, it would cause numbness and motor block in the lower extremities but not a high spinal block. Some clinicians favor inclusion of a small dose of epinephrine in the test dose so that if the placement were intravascular, a slight tachycardic and/or hypertensive response would ensue. Overall, even with test dosing, unidentified intravascular or intrathecal catheter placement is possible. This risk can be mitigated by dosing slowly, aspirating the catheter intermittently throughout the injection process, watching for CSF or blood return in the aspirated catheter, and vigilance for rapid and unexpected changes in vital signs, central nervous system (CNS) symptoms, or motor block throughout the dosing process.

Spinal Analgesia

Intrathecal analgesia for labor can be administered as a single dose or as a continuous infusion. A single injection of opioid combined with a small dose of local anesthetic in the subarachnoid space is quick to perform, provides rapid analgesia, and dissipates when no longer needed. A single spinal injection for labor analgesia can be utilized in a parturient who is unable to hold still to facilitate placement of an epidural but is usually reserved for when the duration of labor can be reasonably estimated, such as in

multiparous parturients with advanced dilation or in the second stage of labor. Continuous spinal analgesia with a spinal catheter can be considered in the case of accidental dural puncture or in the high-risk parturient. The high incidence of postdural puncture headache (PDPH) precludes the elective placement of spinal catheters through epidural needles in most patients. A catheter-over-needle system provides the option for a 23-gauge intrathecal catheter placed over a 27-gauge pencil-point spinal needle. Although theoretically this should decrease the rate of PDPH, a recent series of five cases reported two cases of PDPH.¹²¹ When utilized, continuous spinal analgesia provides excellent analgesia and can be quickly converted to surgical anesthesia if necessary.

Combined Spinal-Epidural Analgesia

The CSE has become increasingly popular in obstetric anesthesia practice. It provides effective, rapid onset of analgesia with minimal motor blockade. It is most commonly placed utilizing the “needle-through-needle” technique, which involves identification of the epidural space through a loss-of-resistance technique followed by insertion of a long, pencil-point spinal needle (25-27 gauge) into the intrathecal space. After free-flow of CSF is confirmed, an opioid, local anesthetic, or both, is injected. The spinal needle is removed and a catheter is threaded into the epidural space. A large systematic review of 27 trials involving 3275 women found CSE had a faster onset of analgesia and was less likely to need additional epidural boluses. There was no difference between CSE and traditional epidural in terms of incidence of PDPH or rate of cesarean delivery.¹²² In one large retrospective review, the incidences of overall failure, inadequate analgesia, and catheter placement were lower in parturients receiving CSE compared to epidural.¹²³ Disadvantages of CSE include the inability to assess the effectiveness of the epidural catheter until the spinal medication has subsided; however, one study not only found that CSE had lower epidural catheter failures (6.6% vs. 1.6%; $P = .001$) but more failed catheters with CSE (48.4%) than with an epidural (30.6%) were recognized within 30 minutes of placement ($P = .009$).¹²⁴

Dural Puncture Epidural

An emerging technique in labor analgesia is the DPE. After the epidural space is located with the epidural needle, a pencil-point spinal needle is inserted utilizing the “needle-through-needle” technique and the dura is punctured. A 25- or 26-gauge spinal needle is usually used because a DPE placed by a 27-gauge needle was shown to offer no benefit in a single study.¹²⁵ No medication is directly introduced into the intrathecal space but the dural puncture may facilitate the intrathecal migration of medication administered into the epidural space. DPE has been associated with a decreased median time to adequate analgesia after block placement.¹²⁶ One study found improved block quality (measured by the number of physician administered *top-up* boluses) and a lesser incidence of asymmetric block in the DPE compared to the epidural group,¹²⁷ while another study did not observe this difference.¹²⁶ More studies are needed to fully understand the role of the DPE in the neuraxial labor analgesia armamentarium.

Neuraxial Analgesic Medications

Any preservative-free local anesthetic can be used in an epidural catheter. A perfect labor analgesic recipe provides excellent analgesia without motor blockade or other maternal or fetal effects. Low concentrations of local anesthetics (alone or in combination with opioids) are used to maximize sensory blockade and minimize motor blockade and maternal hypotension from sympathetic blockade. Most commonly, bupivacaine (0.0625%-0.125%) and ropivacaine (0.0625%-0.2%) are used because the ratio of sensory to motor blockade is greater than that for lidocaine or 2-chloroprocaine. Ropivacaine and levobupivacaine were synthesized to reduce cardiotoxicity that occurs with inadvertent intravascular bolus doses of bupivacaine. However, with the dilute concentrations of local anesthetic currently used for labor analgesia, cardiotoxicity is uncommon.

The addition of fentanyl to bupivacaine has been shown to reduce local anesthetic requirements while still providing similar pain relief.^{128,129} Therefore lipid-soluble opioids, fentanyl 1 to 3 µg/mL, or sufentanil 0.1 to 0.5 µg/mL, are typically added to local anesthetic labor epidural mixtures to reduce total local anesthetic administration and thereby reduce motor blockade while preserving analgesia and enhancing maternal satisfaction.¹³⁰ Of note, opioid-only epidural regimens do not provide adequate analgesia without unacceptable side effects. The most troublesome complication that limits the dose of epidural fentanyl and sufentanil is pruritus.

The search for the perfect labor epidural drug combination has led to the use of other adjuvant drugs that can reduce the dose of required local anesthetic. Most of these drugs act through activation of adrenergic receptors. Epinephrine is a nonselective adrenergic agonist activating α_1 -, α_2 -, β_1 -, and β_2 -adrenergic receptors. Activation of α_1 -receptors in the epidural vasculature causes vasoconstriction that delays the vascular uptake of local anesthetic and opioid.¹³¹ Additional analgesia is likely provided by epinephrine through activation of α_2 -adrenergic receptors.¹³² The dose of epidural epinephrine in labor epidural mixtures is typically dilute (1:400,000-1:800,000) secondary to concerns for uterine artery vasoconstriction by the systemic effects of higher doses. Intrathecal or epidural neostigmine produces analgesia by increasing acetylcholine stimulation of spinal muscarinic and nicotinic receptors.¹³³⁻¹³⁵ Intrathecal neostigmine, however, caused an unacceptable incidence of nausea and vomiting and continued clinical development was abandoned.¹³³ However, epidural neostigmine has been shown to reduce local anesthetic requirements without nausea and vomiting. A randomized controlled trial compared bupivacaine use in laboring patients when neostigmine versus fentanyl was added and found no difference in bupivacaine requirements.¹³⁶

Clonidine is a relatively selective α_2 -adrenergic antagonist that when added to dilute local anesthetic solution provides adjuvant analgesia.^{137,138} Although clearly effective for labor analgesia, within the United States epidural clonidine carries a US Food and Drug Administration (FDA) warning that states it is "not recommended for obstetrical, postpartum, or perioperative pain management as the risk of hemodynamic instability (e.g., hypotension, bradycardia) may be unacceptable in this

population." Monitoring recommendations related to this statement declare that in "a rare obstetrical, postpartum, or perioperative patient, potential benefits may outweigh possible risks." Dexmedetomidine is a highly selective α_2 -adrenergic receptor agonist that is not approved for neuraxial use in the United States.¹³⁹ However, when used in combination with epidural bupivacaine or ropivacaine it has been found to be an efficacious adjunct for labor analgesia.^{140,141}

Administration Techniques

Epidural analgesia can be administered by continuous infusion, patient-controlled epidural analgesia (PCEA), or programmed intermittent epidural bolus (PIEB). The continuous infusion is commonly utilized because it allows the maintenance of a steady anesthesia level without frequent, time-consuming manual boluses by the anesthesia provider. PCEA allows the patient to self-deliver a dose through the epidural catheter with the use of a pump that limits the maximum drug dose per hour to prevent toxicity. PCEA can be used alone or in combination with a continuous infusion or PIEB. PCEA results in reduced local anesthetic use and decreased motor blockade.¹⁴² PIEB utilizes a pump that gives automated boluses at a fast rate at set intervals instead of a slow continuous infusion. Theoretically, the PIEB function allows for greater, more uniform spread of the epidural infusion thus reducing unilateral blocks, areas of block sparing, and total amounts of local anesthetic required for analgesia. Early studies indicate that this pump function may, in fact, offer such benefits.¹⁴³⁻¹⁴⁵

Contraindications of Neuraxial Anesthesia

Contraindications to the placement of a neuraxial procedure include patient refusal, coagulopathy, infection at the site of needle insertion, uncorrected hypovolemic shock, increased intracranial pressure from mass effect, and inadequate resources or expertise. Relative contraindications may include systemic infection, preexisting neurologic disease, severe cardiac valvular stenosis, and pharmacologic anticoagulation. The decision to place neuraxial anesthesia should be individualized for the patient and the risks and benefits should be considered.

OTHER REGIONAL NERVE BLOCKS

Local anesthetic nerve blocks have been used for many years to relieve labor pain, mostly by obstetricians.¹⁴⁶ For a paracervical block, local anesthetic is injected lateral to the cervix at 4 o'clock and 10 o'clock, taking care to avoid vascular structures. It controls pain of the first stage of labor only and is more effective than placebo or intramuscular meperidine.¹⁴⁷ No difference was found in pain relief comparing paracervical block to PCA with intravenous fentanyl.¹⁴⁸ Paracervical block can be complicated by injection of local anesthetic into the presenting fetal head, which can have devastating consequences. More commonly, side effects of transient fetal bradycardia and maternal local anesthetic toxicity have been reported.¹⁴⁹⁻¹⁵¹ Therefore for the delivery of a viable fetus, obstetricians in the United States avoid this procedure. The technique of paracervical block is still used in intrauterine fetal demise labor analgesia, dilation and curettage, and dilation and evacuation

procedures. It has become safer with more superficial injection ensured by a needle guide and more dilute solutions of local anesthetic.

The pudendal nerve is derived from sacral nerve roots (S2-S4) and can be blocked with local anesthetic using a transvaginal or transperitoneal approach to treat pain during the second stage of labor and for episiotomy repair. Although a pudendal nerve block provides some relief during second stage, it is not as effective as a subarachnoid block with fentanyl and bupivacaine.¹⁵² A pudendal block can impede the urge to push during the second stage of labor.¹⁵³ Other complications include a high rate of block failure; systemic local anesthetic toxicity; ischiorectal or vaginal hematoma; and, rarely, fetal injection of local anesthetic.

Anesthesia Considerations for Operative Delivery

Low-dose epidural analgesia can be inadequate for assisted vaginal delivery with forceps or vacuum. In this setting, a higher concentration local anesthetic can be administered through an indwelling epidural catheter. Supplementation of an indwelling epidural catheter with 5 to 10 mL of 1% to 2% lidocaine or 2% to 3% 2-chloroprocaine is usually adequate, depending on whether vacuum or forceps are being used. Pudendal nerve block also can be considered for operative delivery. Consideration could be given to a CSE approach instead of a single injection “second stage spinal” in the event that the operative vaginal delivery fails and cesarean delivery is subsequently required.

Anesthesia for Cesarean Delivery

MATERNAL RISKS AND CONSIDERATIONS

Cesarean delivery rates in the United States increased by 50% between 1998 and 2016, rising from 22% to 32% of all births.^{154,155} Common indications for cesarean delivery include fetal malpresentation, nonreassuring fetal status, labor dystocia, and prior cesarean delivery. Although maternal mortality substantially decreased during the first half of the twentieth century, the maternal mortality ratio has not declined in over 25 years and appears to have recently been increasing in the United States.¹⁵⁶ Of interest, the incidence of maternal mortality is 10 times higher in women who underwent cesarean delivery versus vaginal delivery, based on a retrospective study of 1.5 million deliveries between 2000 and 2006.¹⁵⁷

Pregnant women who undergo general anesthesia for cesarean delivery are at increased risk of pulmonary aspiration of gastric contents, failed intubation of the trachea, or inadequate postoperative ventilation compared with those under neuraxial blockade, particularly in emergent situations. However, it appears that the risks associated with general anesthesia have decreased significantly over time to the point where it is difficult to say that avoiding general anesthesia prevents maternal mortality. Data in the United States from 1979 to 1990 noted a risk ratio of 16.7 for mortality with general anesthesia for cesarean delivery compared with neuraxial blockade,¹⁵⁸ whereas between 1997

to 2002, the risk ratio was not significantly greater with general versus neuraxial anesthesia (RR 1.7; CI, 0.6-4.6, $P = .2$).¹⁵⁹ This reduction in the risk ratio may be because of advanced airway techniques (e.g., supraglottic airways and video laryngoscopy) and safer airway practices (e.g., difficult airway algorithms).

Use of neuraxial anesthesia for cesarean delivery minimizes exposure of the neonate to maternal anesthetic medications, avoids airway manipulation, improves postoperative pain, and allows the mother to see the child almost immediately after birth. All pregnant women should undergo a preoperative evaluation, regardless of planned delivery mode or type of anesthetic technique, with appropriate risk and benefit counseling. The current status of the fetus and obstetric management plan also should be taken into consideration when formulating the anesthetic plan. In addition, appropriate equipment and medications should always remain readily available to safely provide general anesthesia for an emergent or unanticipated situation.

Although the rates of significant maternal aspiration of gastric contents with induction of general anesthesia are difficult to determine, the mortality from such an event is estimated at 5% to 15% based on retrospective data.^{160,161} ASA guidelines recommend aspiration prophylaxis with the administration of nonparticulate antacids, H₂ receptor antagonists, and/or metoclopramide before obstetric surgical procedures.⁹² The decision to use general anesthesia or neuraxial block for cesarean delivery is determined by a variety of factors that include the fetal condition and urgency of delivery, maternal comorbidities, presence of a previously placed epidural for labor analgesia, surgical considerations, and maternal wishes. At present, most cesarean deliveries in developed countries are performed with neuraxial techniques.

SPINAL ANESTHESIA

If an epidural catheter is not already placed, spinal anesthesia is typically used for nonemergent cesarean deliveries. Compared with an epidural, a single injection spinal is often faster and technically easier to perform, allows adequate operating conditions in a shorter time, provides a denser block, is more cost effective, and is less likely to fail (failure rate <1%).^{162,163} Spinal anesthesia is most often administered through a small (24 gauge or smaller), pencil-point needle. On occasion, a continuous spinal catheter may be used for anesthesia for cesarean delivery. As previously discussed, a spinal catheter may be placed in the case of an inadvertent dural puncture but can be placed intentionally for cesarean delivery in high-risk obstetric patients.

The chance of significant maternal hypotension is greater with spinal anesthesia than with epidural anesthesia. Left uterine displacement with appropriate administration of fluids and use of vasopressor medications can minimize the associated hypotension. Intravenous administration of crystalloid or colloid can reduce the degree of hypotension after spinal anesthesia for cesarean delivery.¹⁶⁴ A Cochrane review assessed 11 trials with 698 women comparing colloid versus crystalloid and found significantly fewer women became hypotensive after colloids (RR 0.68; 95% CI, 0.52-0.89).¹⁶⁵ However, concern exists regarding the safety of synthetic colloids as part of intraoperative and critical

care resuscitation. Of note, fluid co-loading is thought to have limited efficacy in consistently preventing postspinal hypotension and is typically utilized in combination with a vasopressor.

Historically, ephedrine was considered the vasopressor of choice to manage hypotension caused by neuraxial anesthesia in pregnancy; however, prophylactic or therapeutic phenylephrine in boluses or as an infusion is not only effective in reducing hypotension but also has less transfer to the fetus and results in less fetal acidosis than ephedrine.^{62,90,166} Phenylephrine is now considered the vasopressor of choice for the treatment of spinal hypotension, and there is accumulating evidence that administration by prophylactic infusion is most effective in preventing hypotension. A systematic review found prophylactic phenylephrine infusions compared to placebo significantly reduced the risk of hypotension (RR 0.36; 95% CI, 0.18-0.73) and nausea and vomiting (RR 0.39; 95% CI, 0.17-0.91).¹⁶⁷ Phenylephrine is an α -adrenergic receptor agonist and is often associated with reflexive slowing of maternal heart rate and a decrease in cardiac output. There is increasing interest in norepinephrine as an alternative vasopressor for treating spinal hypotension. Compared to phenylephrine, norepinephrine had similar efficacy for maintaining arterial blood pressure during spinal anesthesia for cesarean delivery and was associated with a greater heart rate and cardiac output.¹⁶⁸ Further work needs to be done to assess the safety and efficacy of norepinephrine as the vasopressor of choice to prevent and treat postspinal hypotension.

Although various local anesthetics can be used for spinal blockade, hyperbaric bupivacaine 10 to 12 mg is frequently used to achieve an adequate (T4) level block. Neither patient height nor weight affect block extension,¹⁶⁹ although dosing may require adjustment at extremes of the height spectrum. Lipid soluble opioids (such as fentanyl or sufentanil) may be added to enhance neuraxial blockade by reducing local anesthetic dose and decreasing stimulation from surgical traction of the viscera. Epinephrine (0.1-0.2 mg), may be added to improve the quality and duration of the block.¹⁷⁰ Clonidine can also prolong the duration of the block and improve intraoperative analgesia but can increase sedation and is considered off-label for this use.¹⁷¹ Preservative-free morphine 0.1 to 0.2 mg or hydromorphone 0.75 mg is frequently administered with the spinal to reduce postoperative pain for 18 to 24 hours after the anesthetic has dissipated.^{172,173}

EPIDURAL ANESTHESIA

If an epidural catheter has already been inserted for labor analgesia, it provides an excellent method to provide surgical anesthesia for cesarean delivery. A catheter-based technique allows for the ability to titrate the local anesthetic to the proper block height and provide additional local anesthetic administration during the case. For patients who do not already have a catheter in place, this technique may be chosen if the procedure is anticipated to take additional time, or if maternal comorbidities would favor a more gradual, controlled onset of epidural anesthesia. Achieving surgical block conditions takes longer with an epidural than spinal technique but can be rapid enough for use in many urgent situations if already in place and used for maternal analgesia.

Although use of a rapid-onset local anesthetic such as 3% 2-chloroprocaine to attain a T4 level in a newly placed catheter may take 10 minutes,¹⁷⁴ extension of a T10 *anesthetic* level to a *surgical anesthetic* T4 level can be obtained in approximately 5 minutes using 3% 2-chloroprocaine or alkalinized 2% lidocaine.¹⁷⁵ Bupivacaine 0.5% may be used if rapid onset is not needed, but is often avoided because of the increased risk of local anesthetic systemic toxicity. Typical epidural local anesthetic volumes required for cesarean delivery range between 10 and 20 mL, depending on whether the epidural is already in use. The administration of epidural local anesthetic should occur in divided doses to ensure that the catheter has not migrated into the intravascular or intrathecal space. Block quality can be improved with addition of epinephrine 1:200,000, fentanyl 50 to 100 μ g, or sufentanil 10 to 20 μ g. Epidural clonidine 50 to 100 μ g can be useful in patients with preexisting chronic pain or severe hypertension if the benefit is judged to outweigh the risk for hypotension, bradycardia, and sedation. Epidural morphine 2 to 5 mg is frequently administered to improve postoperative pain.¹⁷⁶

COMBINED SPINAL-EPIDURAL ANESTHESIA

Use of a CSE for cesarean delivery may be optimal in some situations as it combines the benefits of the spinal and epidural techniques. This technique allows for the rapid onset of a dense reliable block while allowing the block time or height to be extended with use of the epidural catheter. A low-dose sequential CSE, a technique where a small intrathecal dose of local anesthetic is given followed by administration of epidural medications, can be used in patients with cardiac disease or patients with short stature.¹⁷⁷ Possible disadvantages of a CSE for surgical anesthesia include the presence of an untested catheter and the possibility of a misplaced or nonfunctioning epidural. More details regarding the CSE neuraxial block are discussed in the previous section on labor analgesia.

GENERAL ANESTHESIA

Although neuraxial anesthesia is typically preferred, in certain emergent situations (e.g., fetal bradycardia, maternal hemorrhage or coagulopathy, uterine rupture, maternal trauma) general anesthesia may be needed for cesarean delivery because of its rapid onset. In addition, it allows for a controlled airway, controlled ventilation, and in some scenarios such as massive hemorrhage, improved hemodynamic control and perhaps decreased maternal psychological stress in comparison to neuraxial anesthesia.

Appropriate equipment preparation, knowledge of patient comorbidities, airway examination, and familiarity with the difficult airway algorithm are necessary preparation for delivering a safe general anesthetic. The ASA difficult airway algorithm¹⁷⁸ has been modified slightly by some authors for use in the setting of cesarean delivery, and a previously published example is provided in Fig. 62.4. Clear, concise communication among all members of the perioperative team is especially critical in urgent or emergent situations to maximize patient safety and minimize procedural complications. Open lines of communication are

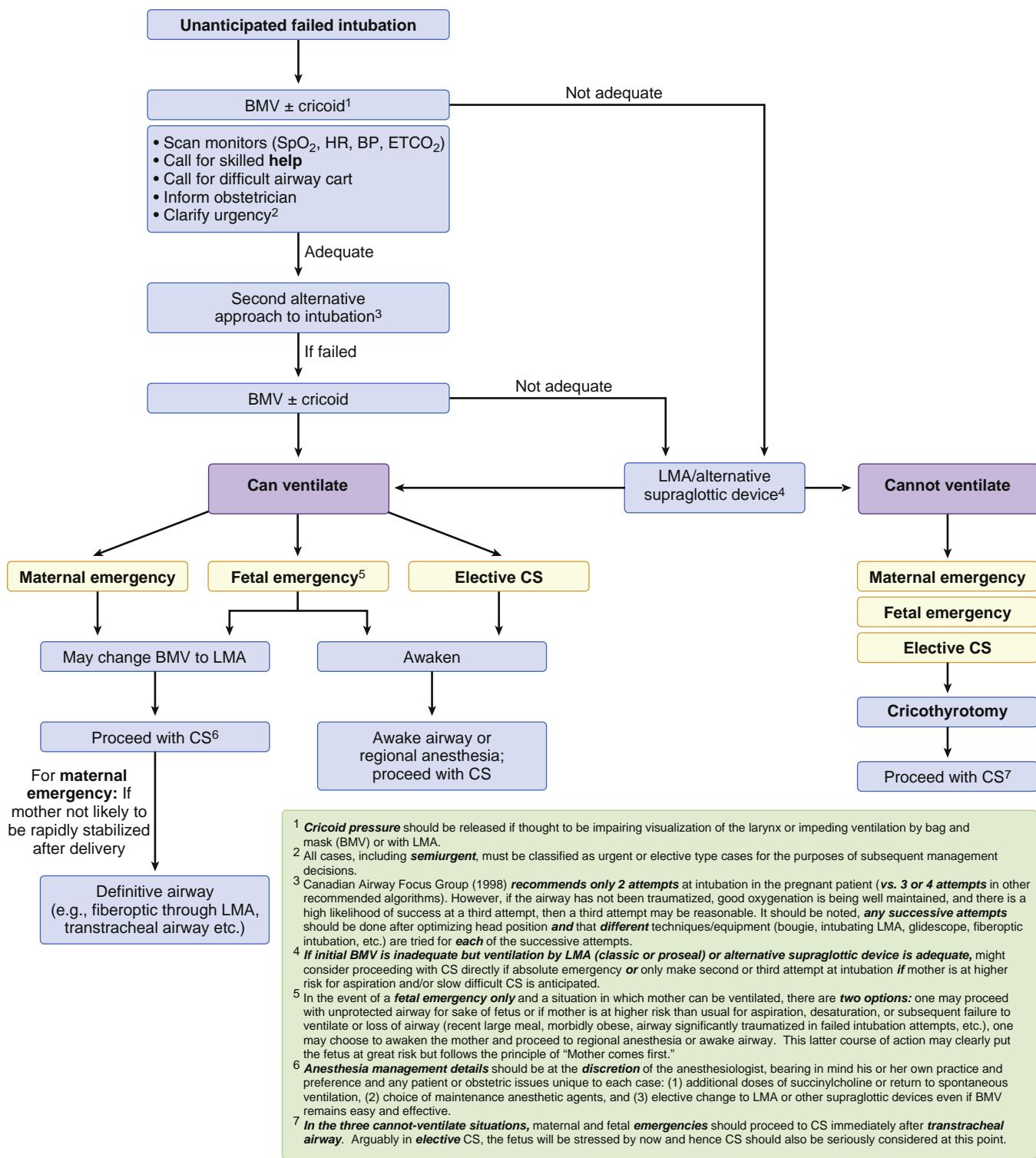


Fig. 62.4 Algorithm for management of unanticipated difficult airway in obstetric patients. BMV, Bag-mask ventilation; BP, blood pressure; CS, cesarean section; ETCO₂, end-tidal carbon dioxide; HR, heart rate; LMA, laryngeal mask airway; SpO₂, oxygen saturation. (Redrawn from Balki M, Cooke M, Dunering S, et al. Unanticipated difficult airway in obstetric patients: development of a new algorithm for formative assessment in high-fidelity simulation. *Anesthesiology*. 2012;117:883–897, with permission.)

essential around the time of induction of anesthesia, airway management, and surgical incision.

A rapid-sequence induction commences with preoxygenation, followed by the application of cricoid pressure and the administration of an intravenous induction drug (typically propofol) and a neuromuscular-blocking drug

(typically succinylcholine or rocuronium). If endotracheal intubation fails, consider placement of a supraglottic airway device, such as a laryngeal mask airway (LMA), or ventilation with mask and cricoid pressure.⁹² The LMA has a high success rate for placement in obstetric patients; however, it does not protect against aspiration of gastric

contents and should be used primarily for rescue of a failed intubation. Of note, the LMA has been used without observed aspiration or presence of hypoxia in a prospective study of over 1000 lean, low-risk patients undergoing elective cesarean delivery.^{179,180}

Complications as a result of general anesthesia for cesarean delivery can be more common than general anesthesia for other procedures. For example, although the overall risk of intraoperative awareness is estimated to be 1:19,000 general anesthetics, the awareness risk for cesarean delivery is estimated at 1:670 (1:380-1:1300).¹⁸¹ Anesthesia-related mortality from airway difficulties may occur during emergence and in the recovery period,¹⁸² as well as during induction. Improper monitoring, provider inexperience, emergent situations, and patient obesity all increase patient risk.¹⁸³ Emergent cesarean delivery requiring general anesthesia is an uncommon but predictable emergency that can be practiced by teams using simulation to improve performance.

Induction of Anesthesia: Intravenously Administered Drugs

Premedication with lidocaine or fentanyl is typically avoided in cesarean delivery to limit fetal exposure. In scenarios in which hemodynamic stability is prioritized, such as preeclampsia or heart disease, remifentanil 1 to 2 μ g/kg or fast-acting antihypertensives such as esmolol or labetalol can be used.

Propofol is most commonly used for induction of general anesthesia for cesarean delivery and is able to induce unconsciousness in approximately 45 seconds. Sodium thiopental 4 to 6 mg/kg intravenously is still used in many countries for induction of anesthesia. Propofol can result in significant hypotension and has an umbilical artery (UA) to umbilical vein (UV) ratio of 0.7.¹⁸⁴ Propofol administration does not affect neonatal Apgar scores with typical intravenous induction doses (2-2.5 mg/kg), but repeated or larger cumulative doses (9 mg/kg) are associated with significant newborn depression.¹⁸⁵

Etomidate is quick acting and its rapid hydrolysis results in a relatively short duration of action. Unlike propofol and thiopental, etomidate has minimal direct effects on maternal hemodynamics and significant hypertension can occur when etomidate is used without adjuvant premedication in the healthy parturient. Etomidate has higher rates of nausea and vomiting and can increase risk for seizures in patients with decreased seizure threshold. At typical induction doses (0.3 mg/kg), decreased neonatal cortisol production for less than 6 hours was noted with unclear clinical significance.¹⁸⁶

Ketamine inhibits the *N*-methyl-D-aspartate receptor and has analgesic, amnestic, and hypnotic properties with minimal respiratory depression effects. At typical induction doses (1-1.5 mg/kg), ketamine causes central stimulation of the sympathetic nervous system and inhibits the reuptake of norepinephrine. This helps maintain arterial pressure, heart rate, and cardiac output but could result in hypertension in the preeclamptic patient. It is an ideal choice for a pregnant woman in hemodynamic compromise resulting from bleeding. No neonatal depression is observed with standard induction dosing.¹⁸⁷ Larger doses can increase uterine tone, reduce uterine arterial

perfusion, and lower maternal seizure threshold. In certain situations, ketamine may be used in smaller intravenous doses (<0.25 mg/kg) as a profound analgesic, but often causes unwanted hallucinations, which can be reduced with coadministration of benzodiazepines. Care should be taken if used for analgesia and conscious sedation so that repeated dosing does not result in loss of consciousness with an unprotected airway increasing the risk for pulmonary aspiration.

Muscle Relaxants

Uterine muscle tone is not affected by skeletal muscle relaxants, and in standard doses all classes of muscle relaxants are poorly transferred to the fetus. Succinylcholine 1 to 1.5 mg/kg intravenously has rapid onset (30-45 seconds) and short duration of action. After administration, it is hydrolyzed in the plasma by pseudocholinesterase and only small amounts cross to the fetus because it is highly ionized and poorly lipid soluble. It is undetectable in umbilical cord samples unless larger maternal doses are administered (2-3 mg/kg), and exceedingly high maternal doses (10 mg/kg) are needed to inadvertently create neonatal neuromuscular blockade.¹⁸⁸ After succinylcholine administration, maternal muscle strength should always be monitored because prolonged weakness can occur if the hydrolytic enzyme has a reduced plasma concentration or an atypical form (such as in pseudocholinesterase deficiency) or if muscle weakness is exacerbated by prior administration of magnesium sulfate.

Rocuronium may be considered as an alternative to succinylcholine for muscle relaxation. It allows adequate relaxation for endotracheal intubation in less than 60 seconds at intravenous doses of 0.9 to 1.2 mg/kg.^{189,190} This is an attractive alternative to succinylcholine because even after an intravenous intubating dose of 0.9 to 1.2 mg/kg body weight, the neuromuscular blocking effect can rapidly be reversed by a large intravenous dose of sugammadex (12-16 mg/kg body weight), which makes the total duration of action shorter than after an equipotent dose of succinylcholine. Like succinylcholine, nondepolarizing muscle relaxants do not cross to the fetal circulation in amounts that would cause neonatal weakness.¹⁹¹ However, if large doses of nondepolarizing neuromuscular blockers are given over long periods, neonatal neuromuscular weakness can occur. Although cholinesterase inhibitors may be administered to the neonate, treatment is primarily respiratory support until the drug is eliminated. Neonatal elimination of muscle relaxants may take significantly longer than adult elimination.

In the case of administration of magnesium sulfate, a distinct potentiation of the effect of any nondepolarizing agents occurs, with subsequently prolonged recovery time. The choice and dosing of neuromuscular blocking drugs should therefore take into account the interaction with magnesium sulfate and the potential risk for muscle weakness resulting from residual neuromuscular block in the recovery room or postanesthesia care unit. As a consequence, neuromuscular monitoring based on an objective monitoring technique should be used to assess neuromuscular function in these patients.

Maintenance of General Anesthesia

After induction, general anesthesia is most frequently maintained with a volatile anesthetic agent with or without N₂O. Volatile anesthetics help reduce the incidence of maternal recall. Although the MAC to prevent movement in response to a painful stimulus is reduced in pregnancy, electroencephalographic evidence suggests that anesthetic effects of a halogenated agent on the brain are similar in the pregnant and nonpregnant state.⁴² Volatile anesthetics are highly lipid soluble, have a low molecular weight, and are readily transferred to the fetus. Fetal concentrations depend on both the maternal plasma concentrations and duration of the anesthetic before delivery. After delivery, opioids, propofol, benzodiazepines, N₂O, or a combination are administered and the halogenated anesthetic is typically reduced to 0.5 MAC. These additional intravenous drugs are administered only after the cord is clamped to prevent any transfer to the neonate and associated respiratory depression. Use of only volatile anesthetics at higher concentrations is associated with increased blood loss secondary to uterine atony because all volatile anesthetics negatively impact uterine muscle contraction.¹⁹²

General anesthesia for cesarean delivery is frequently used in cases of fetal distress because it is rapid and reliable. Clearly, a fetus depressed before delivery often becomes a depressed neonate. A Cochrane systematic review of uncomplicated cesarean deliveries comparing regional and general anesthesia concluded that “No significant difference was seen in terms of neonatal Apgar scores of six or less and of four or less at one and five minutes,” and the need for neonatal resuscitation with oxygen was not different between the two groups.¹⁹³ The review noted neither method of anesthesia was superior for neonatal outcome.

If large concentrations of volatile anesthetics are administered for a prolonged time, neonatal flaccidity, cardiorespiratory depression, and decreased tone may be anticipated. If neonatal depression is due to volatile anesthetics, the infant should respond to assisted ventilation to facilitate exhalation of the anesthetics. Consequently, physicians able to assist with neonatal ventilation should be present at all cesarean deliveries performed under general anesthesia. In addition, communication to all perioperative physicians is critical if extended anesthetic time is anticipated before delivery. A prolonged time under general anesthesia prior to delivery can be anticipated by obstetricians in some patients such as those with significant scar tissue from prior surgeries or extreme obesity. Neonates may experience greater benefit from regional anesthesia in these scenarios.

Postcesarean Pain Control and Recovery

Pain after cesarean delivery is variable in intensity among patients. Excellent pain control after cesarean delivery can lead to improved maternal functional ability, enhanced recovery, decreased persistent opioid use, decreased incidence of chronic pain, and improved maternal-infant bonding.^{194,195} Postoperative pain control can be achieved with multimodal therapy. A typical strategy consists of neuraxial opioids, scheduled nonsteroidal

antiinflammatory drugs, scheduled acetaminophen, and limited systemic opioids. Neuraxial opioids are considered the “gold standard” for effective postoperative pain control and have been shown to be superior to systemic opioids¹⁹⁶ and transversus abdominis plane (TAP) block.¹⁹⁷ Pruritus, nausea and vomiting, and respiratory depression are opioid-related side effects.

Alternative modes of analgesia are available and can be utilized if neuraxial opioids are contraindicated or general anesthesia is utilized. Peripheral nerve blocks include TAP, quadratus lumborum, and ilioinguinal-iliohypogastric blocks (see Chapter 46). A meta-analysis demonstrated TAP blocks significantly reduced postoperative pain intensity and decreased opioid consumption in women who did not receive intrathecal morphine.¹⁹⁷ Quadratus lumborum blocks are gaining popularity in cesarean deliveries and may have advantages over TAP blocks. A randomized controlled trial comparing quadratus lumborum with TAP blocks found a reduction in morphine use in the quadratus lumborum group.¹⁹⁸ Continuous wound infiltration with local anesthetics may also be beneficial for patients having general anesthesia.¹⁹⁹

Complications of Regional Anesthesia

In addition to the neuraxial drug-related complications noted previously, administration of neuraxial anesthesia can result in complications including PDPH, epidural or spinal hematoma, neurologic injury, or total spinal anesthesia (see also Chapter 45).

POSTDURAL PUNCTURE HEADACHE

The earliest experiments with spinal cocaine resulted in severe PDPH. Leakage of spinal fluid is thought to result in vascular hyperemia, migraine physiology, and traction on pain-sensitive fibers. The headache associated with PDPH is postural in that it is worsened by standing and relieved by lying down. The incidence, severity, and duration of PDPH are related to the size of the needle and the shape of the tip. Spinal needles used for CSE technique range from 25 to 29 gauge and result in an incidence of PDPH of less than 1%.^{200,201} Epidural catheters are most commonly placed through a 17- or 18-gauge blunt-tipped needle. The incidence of unintentional dural puncture during labor epidural placement is 1% to 1.5%.^{202,203} The incidence of headache after an unintentional dural puncture with an epidural needle is reported at 30% to 80%.²⁰⁰

In the setting of an unintended dural puncture with an epidural needle, an intrathecal catheter may be threaded, or the epidural needle may be removed and replaced at a different interspace. If an intrathecal catheter is placed, unintentional injection of an epidural anesthetic dose must be carefully avoided. Placement of the intrathecal catheter can provide labor analgesia and alleviates the need for multiple repeat epidural attempts with the potential of a second accidental dural puncture.²⁰⁴

When diagnosing a PDPH, it is important to consider other causes of headache in the postpartum period. Assessing the patient for fever and nuchal rigidity is important

because postdural-puncture meningitis can initially present with a headache. Early treatment of meningitis is important to prevent morbidity and mortality. Likewise, assessing the patient for hypertension is important to detect postpartum preeclampsia, which can present with a headache and requires rapid treatment to prevent maternal stroke. A thorough neurologic exam should also be performed because cerebral venous thrombosis, cranial subdural hematoma, and ischemic or hemorrhagic stroke can present as a postpartum headache. Benign headaches from tension, dehydration, sleep deprivation, caffeine withdrawal, or migraine should be considered prior to treating a PDPH.

PDPH is often initially treated conservatively. Given the similarity of symptoms to those of migraine headache, PDPHs have been treated with drugs that are useful in migraine with variable success. Caffeine can be minimally effective to treat the pain of a PDPH in the short-term likely because of its vasoconstrictive effects.²⁰⁵

If the symptoms are severe enough to limit a patient's activity then an epidural blood patch (EBP) should be considered. If there is evidence of cranial nerve involvement such as diplopia, then an EBP should be performed immediately. Note that the symptom of muffled hearing is common with PDPH and thought not to be a result of cranial nerve involvement, but instead, a decrease in middle ear pressure because the middle ear fluid is connected to the cranial CSF via the cochlear aqueduct. In one retrospective review of an EBP database, all parturients with PDPH experience relief after the EBP but 16.8% required two and 1.5% required three EBPs.²⁰³ Controversy exists over the optimum volume of blood to be injected during an EBP but studies support an attempt to administer 20 mL of autologous blood during the procedure.^{203,206}

EPIDURAL HEMATOMA

The epidural space is highly vascular, and vessels can be punctured during neuraxial needle placement or catheter threading. However, with normal platelets and coagulation factors, epidural hematoma is extremely uncommon. The Serious Complication Repository (SCORE) Project reported the incidence of epidural hematoma to be 1 in 251,463 (95% CI, 1:46,090-1:10,142,861)²⁰⁷ and another large study found no cases of hematoma out of 79,837 obstetric epidural placements with an estimated upper limit of 1 in 4.6×10^{-5} .²⁰⁸ Although rare, back pain and persistent motor blockade are potential signs of epidural hematoma and should be thoroughly evaluated. Patients should be followed postpartum until complete resolution of the epidural blockade. Patients are at increased risk for developing a hematoma in the setting of coagulopathy and anticoagulation use. Following the guidelines of the American Society of Regional Anesthesia (ASRA) with consideration for the Society for Obstetric Anesthesia and Perinatology (SOAP) Consensus Statement (Fig. 62.5) regarding anticoagulation therapy and neuraxial anesthesia in the obstetric patient is recommended.^{209,210} If an epidural hematoma is suspected, imaging should occur immediately with the goal of prompt epidural hematoma evacuation to avoid permanent neurologic injury.

NEUROLOGIC INJURY

Direct spinal cord damage from an epidural or spinal needle placed for labor is exceedingly rare because obstetric neuraxial anesthesia procedures are typically performed below the level of the conus medullaris. It has, however, been described with spinal anesthesia attempts performed at unintentionally high levels resulting in spinal cord syrinx formation with injection. In a series of seven such cases, all of the patients who experienced this complication described pain on injection.²¹¹ Therefore if a patient complains of pain on injection of neuraxial medication, the proceduralist should stop injecting *immediately*.

Overall, damage attributed to direct neurologic injury has been estimated at 0.6 in 100,000 with epidural and 3 in 100,000 with spinal analgesia.²¹²⁻²¹⁴ Data from the SCORE project show an incidence of serious neurologic injury in the postpartum period to be 1 in 11,389 (95% CI, 1:7,828-1:17,281) but only 1:35,923 (95% CI, 1:17,805-1:91,244) are thought to be related to anesthesia.²⁰⁷

Evaluating postpartum lumbosacral neuropathies is a common part of an obstetric anesthesia practice. A large prospective study showed that 0.92% of women experienced postpartum lumbosacral or lower extremity nerve injury, the incidence of which was associated with nulliparity and prolonged second stage of labor, but not epidural analgesia use.²¹⁵ Femoral and lateral femoral cutaneous neuropathies were the most common, likely from women in extreme hip flexion in the semi-Fowler position. Encouraging women to straighten their legs between pushes can restore blood flow to the nerves of the lumbar plexus. Most of these peripheral neuropathies heal with time but outpatient follow up with a neurologist to follow the course and rule out other causes should be considered.

LOCAL ANESTHETIC SYSTEMIC TOXICITY

The accidental injection of intravascular local anesthetic could result in the development of local anesthetic systemic toxicity (LAST). The development of LAST is rare in obstetrics secondary to the dilute local anesthetic solutions utilized for epidural analgesia and the use of lidocaine and 2-chloroprocaine for operative delivery. The SCORE project reported one maternal cardiac arrest from LAST after a TAP block.²⁰⁷ LAST as a result of TAP blocks in obstetrics has been reported multiple times and the use of no greater than 0.25% concentration of bupivacaine, adding 1:200,000 epinephrine, administering no greater than a 20 mL volume on each side, placement under ultrasound to be sure the injection is not intraperitoneal, and careful, slow, injection with intermittent aspiration is recommended.²¹⁶ The treatment of LAST includes the administration of lipid emulsion in addition to basic and advanced cardiac life support.²¹⁷

TOTAL SPINAL BLOCK

A total spinal block is a rare and life-threatening complication that occurs after excessive cephalic spread of local anesthetic in the CSF resulting in severe respiratory and cardiac compromise. It can occur after a single spinal injection or as a result of inadvertent intrathecal spread of epidural

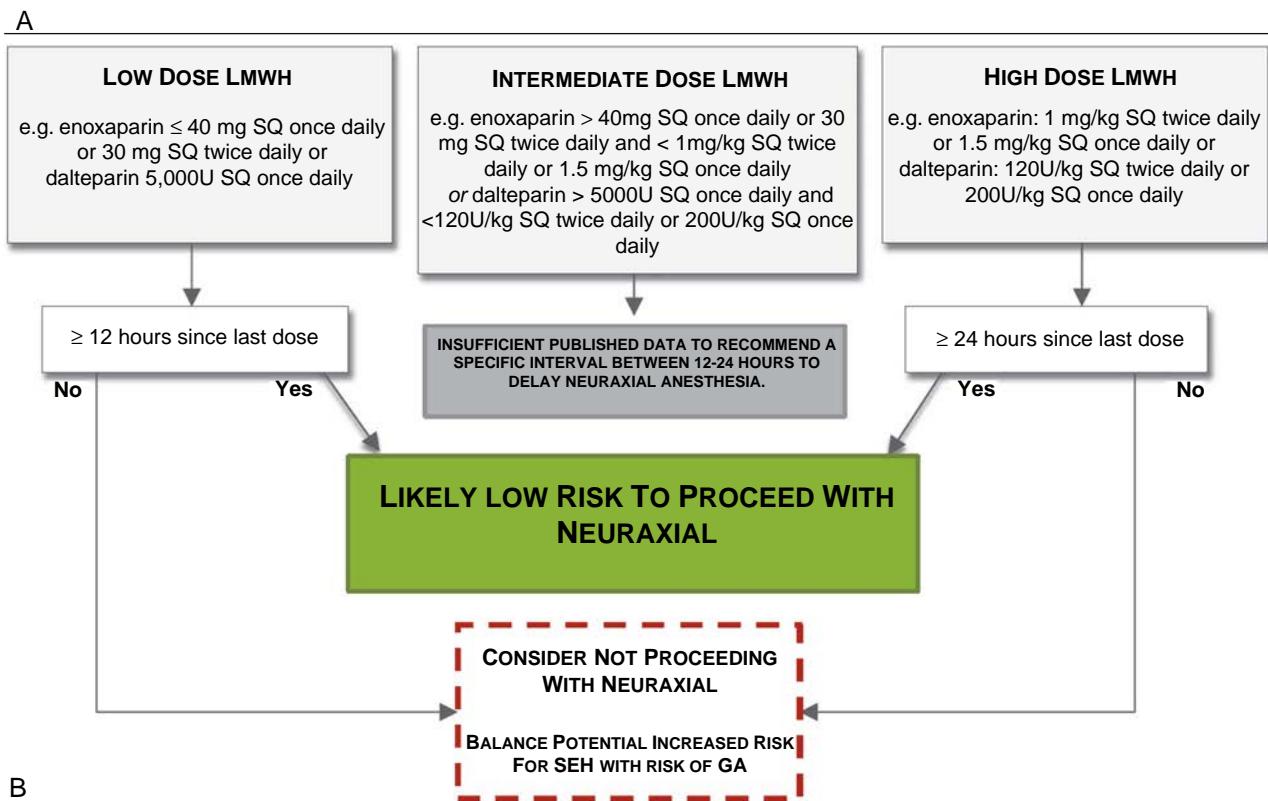
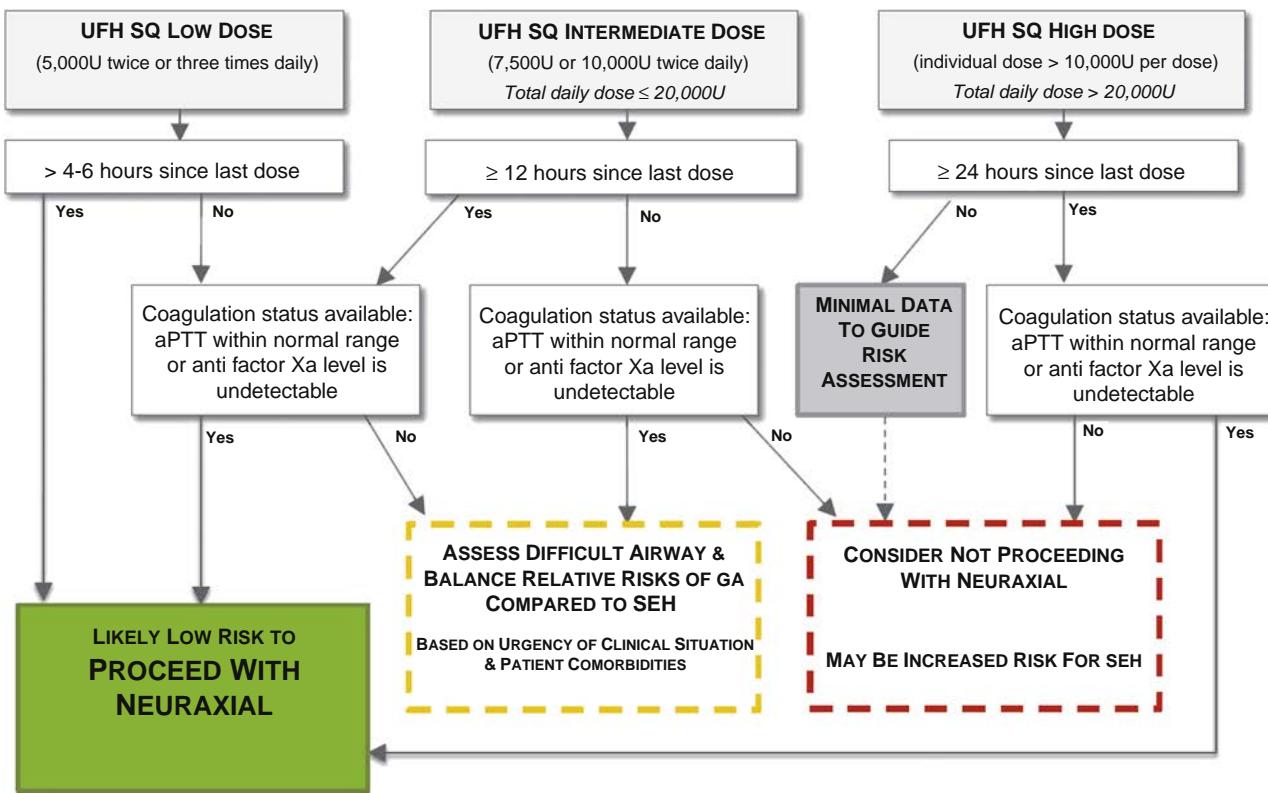


Fig. 62.5 (A) Decision aid for urgent or emergent neuraxial procedures in the obstetric patient receiving unfractionated heparin. (B) Decision aid for urgent or emergent neuraxial procedures in the obstetric patient receiving LMWH. *aPTT*, activated partial thromboplastin time; *GA*, general anesthesia; *LMWH*, low-molecular-weight heparin; *SEH*, spinal epidural hematoma; *SQ*, subcutaneous; *UFH*, unfractionated heparin. (Reproduced with permission from Leffert L, Butwick A, Carvalho B, et al. The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants. *Anesth Analg*. 2018;126:928-944.)

medication. Risk factors associated with high neuraxial blockade include obesity, spinal technique after failed epidural anesthesia, short stature, epidural after an accidental dural puncture, and spinal deformity.²⁰⁷

OTHER COMPLICATIONS

When strict aseptic technique is used, infection is uncommon with spinal and epidural anesthesia.^{218,219} Nonetheless, postdural puncture meningitis and epidural abscess has been described²²⁰ and the ASA and ASRA recommend the following aseptic techniques during placement of neuraxial needles and catheter: removal of jewelry, hand washing, wearing of caps, wearing of masks covering both mouth and nose, use of sterile gloves, use of an antiseptic solution (e.g., chlorhexidine with alcohol), and sterile draping of the patient.^{221,222}

Postpartum back pain is common after childbirth regardless of whether neuraxial analgesia has been used. However, no evidence indicates that back pain is more common when neuraxial analgesia is used for labor. Several trials have identified an association between increased maternal temperature and epidural use as a secondary outcome.²²³ Attribution of causality is difficult in this setting and the etiology is not well understood but likely involves noninfectious inflammation.^{223,224}

Maternal Comorbidities

HYPERTENSIVE DISORDERS

Hypertensive disorders of pregnancy are among the most common causes of maternal morbidity and are associated with more frequent rates of maternal and fetal mortality.²²⁵ Hypertensive disorders of pregnancy complicate 5% to 10% of pregnancies worldwide and preeclampsia is diagnosed in 3% of pregnancies.²²⁵ The World Health Organization (WHO) has identified hypertension as the second most common cause of maternal death, accounting for 14% of mortality associated with pregnancy.²²⁶ Chronic hypertension may precede pregnancy and may or may not be complicated by superimposed preeclampsia.

Although some variations exist in hypertensive definitions worldwide, the following are used in the United States by the ACOG based on a working group in 2013.²²⁷ Gestational hypertension is defined as the onset of hypertension (systolic blood pressure [SBP] >140 mm Hg or diastolic blood pressure [DBP] >90 mm Hg) after 20 weeks' gestation in a previously normotensive parturient without proteinuria. Preeclampsia is defined as hypertension (SBP >140 mm Hg or DBP >90 mm Hg) after 20 weeks' gestation associated with proteinuria. Preeclampsia is diagnosed when urine protein excretion is greater than 300 mg in a 24 hour period or, alternatively, there is a protein/creatinine ratio of at least 0.3. In 2013, massive proteinuria (>5 g in 24 hours) and fetal growth restriction were eliminated as considerations of severe preeclampsia. In addition, the term *mild preeclampsia* is no longer used. Now only *preeclampsia* or *preeclampsia with severe features* are defined. Severe features of preeclampsia include an SBP of 160 mm Hg or greater or DBP of 110 mm Hg or greater on two

separate occasions at least 4 hours apart while on bed rest; thrombocytopenia (platelet count less than 100,000/ μ L); impaired liver function with twice normal concentrations of liver enzymes; right upper quadrant pain; progressive renal insufficiency with serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine without other known renal disease; pulmonary edema; and new onset cerebral or visual abnormalities. In the absence of proteinuria, preeclampsia can be diagnosed with new onset hypertension (as previously defined) and the presence of a severe feature.²²⁷

The combination of hemolysis, elevated liver enzyme, and low platelet count (HELLP) is considered preeclampsia with HELLP syndrome. Eclampsia is preeclampsia complicated by seizure activity. The incidence of preeclampsia has increased likely as a result of increases in maternal age and obesity, whereas the risk for eclampsia has decreased because of improved prenatal care and the use of prophylactic intravenous magnesium.^{225,228} The cause of preeclampsia is not known, but it is generally thought that placental insufficiency through a cascade of antiangiogenic factors (e.g., s-Flt) eventually leads to maternal generalized endothelial dysfunction. The cause of the placental insufficiency is likely variable and could include maternal or paternal genetics and/or environmental factors. Patients with preeclampsia have an elevated risk for cerebral hemorrhage, pulmonary edema, and coagulopathy. Current guidelines recommend treating SBP more than 160 mm Hg for prevention of intracerebral hemorrhage.²²⁷ Initial treatment typically includes intravenous labetalol, hydralazine, and/or oral nifedipine.²²⁹ Other considerations are increased airway edema with associated difficulty of intubation and increased rates of postpartum atony related to the use of magnesium sulfate. Methylergonovine (Methergine) should be used cautiously in patients with preeclampsia because it may lead to hypertensive crisis. Women with preeclampsia can be sensitive to both endogenous and exogenous catecholamines. Therefore careful administration of adrenergic agents is recommended.

Women with a diagnosis of preeclampsia should have their platelet count checked before initiation of regional anesthesia or removal of an epidural catheter. Coagulopathy is a contraindication to regional anesthesia. Although the risk for spinal hematoma is lower in pregnant women than in the elderly,²¹³ one study found 68% of patients who had spinal hematomas after neuraxial blockade had pre-existing coagulopathy.²³⁰ Lastly, despite the concerns for hypotension, spinal anesthesia is safe to administer in preeclamptic patients.^{231,332}

COAGULOPATHIES

Thrombocytopenia complicates 10% of pregnancies as a result of several etiologic factors.^{233,234} Thrombocytopenia may be preexisting or can develop as a result of the pregnancy. As discussed earlier, thrombocytopenia that develops after 20 weeks' gestation may be a sign of preeclampsia with HELLP syndrome. However, most thrombocytopenia that develops in pregnancy is benign, gestational thrombocytopenia. The platelet count is expected to decrease by approximately 10% in a normal pregnancy.²³⁵

Autoimmune thrombocytopenia, antiphospholipid syndrome, and liver disease are less common.²³⁴ Glucocorticoids and IV immunoglobulin can be used to elevate platelet counts in certain types of severe disease but require several days to be effective.²³⁶ No platelet count is universally accepted as safe for epidural placement. Most anesthesiologists agree that placement of an epidural in the setting of a platelet count greater than 100,000/mm³ is safe and recent literature suggests lower thresholds may be safe. A retrospective observational study of cases from 14 diverse institutions combined with a systematic review evaluated 1524 parturients with a platelet count of less than 100,000/mm³ and found the upper bound of the 95% CI for the risk of epidural hematoma for a platelet count of 0 to 49,000/mm³ is 11%, 50,000 to 69,000/mm³ is 3%, and 70,000 to 100,000/mm³ is 0.2%.²³⁷ Of note, no cases of epidural hematomas requiring surgical decompression were identified in this cohort.

Women with von Willebrand disease are at increased risk for bleeding intrapartum and postpartum.²³⁸ Prophylactic treatment is recommended for women with von Willebrand factor (vWF) less than 50 international units/dL. Because of the multiple types and subtypes of von Willebrand disease that have different responses to therapy, it is imperative that hematologic studies be part of the management to help guide the most appropriate therapy. In type I von Willebrand disease, a partial reduction in the quantity of vWF is seen. Women with type I von Willebrand disease usually do not need prophylactic treatment because their vWF typically rises in the third trimester of pregnancy to greater than 50 international units/dL. Desmopressin can be used in women with type 1 von Willebrand disease to release vWF. Type 2 von Willebrand disease is characterized by a defect in the function of vWF, and facilitation of release is not helpful. Parturients with type 3 von Willebrand disease almost always require replacement of vWF before delivery, because they have almost no intrinsic vWF. Although concern should be elevated for epidural hematoma, women with normal factor levels can have regional anesthesia in the setting of a normal platelet count.²³⁹

Deep venous thrombosis (DVT) and pulmonary embolism are more common in pregnancy as a result of hormonal changes. Significant risk factors are factor V Leiden, prothrombin G20210A, protein S, protein C and antithrombin deficiency, and antiphospholipid antibodies.²⁴⁰ Patients diagnosed with DVT or pulmonary embolism in pregnancy will need prolonged anticoagulation and will require delivery planning with a brief anticoagulation hiatus for regional anesthesia and delivery. Factor V Leiden is an abnormal variant of factor V that acts as a cofactor that allows activation of thrombin by factor Xa. The factor V Leiden variant cannot be easily degraded by activated protein C and thus leads to hypercoagulability. Patients with a factor V Leiden abnormality may be maintained on anticoagulants for prophylaxis or treatment of DVT and appropriate cessation of anticoagulants must occur prior to placement of neuraxial blockade.^{210,241}

OBESITY

Maternal obesity (prepregnancy body mass index ≥ 30 kg/m²) and metabolic syndrome cause gestational diabetes,

newborn hyperglycemia, larger babies, prolonged labor, and cesarean delivery.^{68,242} Cesarean delivery for obese women holds greater risk of mortality.^{243,244} Sleep apnea is more common in obese parturients and is a risk factor for hypoventilation after treatment with systemic opioids and difficult tracheal intubation when general anesthesia is required. Morbidly obese parturients are at increased risk of longer first stage of labor and operative delivery.²⁴⁵ Epidural anesthesia placement in obese parturients is more difficult and takes longer and they are more likely to require a repeat procedure due to inadequate pain control or failure to achieve bilateral sensory blockade.^{245,246} An early anesthesia consultation is advised for morbidly obese women regardless of planned delivery mode.

CARDIAC DISEASE

The leading cause of maternal mortality in the United States is cardiac disease.¹⁵⁶ In planning an anesthetic for a delivery in a woman with congenital or acquired heart disease, the anesthesia provider must take into consideration the patient's cardiac lesion or disease state; the normal physiologic changes of pregnancy, labor, and delivery; and the hemodynamic changes of the anesthetic itself. During pregnancy, labor, and delivery, regurgitant valvular lesions are generally tolerated better than stenotic valvular lesions.²⁴⁷ Pulmonary hypertension, severe left ventricular outflow tract obstruction, moderate to severe mitral stenosis, and cyanotic congenital heart disease all carry significant risk for maternal morbidity and mortality. Multiple risk factors have been identified as increasing a woman's likelihood of major morbidity and mortality including prior stroke, low ejection fraction, aortopathy, and heart failure symptoms. The American Heart Association, the American College of Cardiology, and the European Society of Cardiology have classified certain conditions or cardiac lesions as high maternal or fetal risk.²⁴⁸⁻²⁵¹ In comparison to other risk stratification systems,^{251,252} the modified WHO risk stratification system appears to perform best in predicting maternal morbidity or mortality during pregnancy and delivery.²⁵³ Such risk stratification informs the obstetric and anesthesia team as to what resources a parturient with heart disease may require, and thereby whether they need to transfer to a tertiary care facility for delivery.

Increased monitoring including 5-lead ECG or intra-arterial blood pressure monitoring may be necessary for labor, especially in women who have a history of tachyarrhythmia or are hemodynamically tenuous. Epidural labor analgesia is recommended for women with heart disease to decrease catecholamine release and eliminate the increased cardiac output and tachycardia attributable to labor pain. The afterload reduction that occurs with epidural analgesia should be followed closely and may need to be countered with a carefully titrated α -adrenergic agonist to prevent tachycardia and ischemia. When cesarean delivery is indicated, it is important to tailor the anesthetic technique to each individual patient. Regional anesthesia is not necessarily contraindicated and should be considered for most patients.

ANTICOAGULATION

Anticoagulation is often required for women with artificial heart valves, certain types of congenital heart disease, pulmonary hypertension, and cardiomyopathy. It is necessary to carefully time stopping anticoagulation to allow for epidural placement and birth while restarting before a clot can form. For this reason, women are usually maintained on heparin at the end of pregnancy, pending delivery, because of its quick offset. If IV unfractionated heparin was used, it should be stopped 4 to 6 hours before the procedure and normal coagulation status (PTT or activated clotting time [ACT]) documented before neuraxial instrumentation or removal of an epidural catheter.^{209,210} If a parturient is maintained on subcutaneous unfractionated heparin, the time interval required to stop prior to a neuraxial procedure corresponds to the dose and activated partial thromboplastin time (aPTT) that can be measured (see Fig. 62.5A). If conversion to intravenous heparin cannot take place before labor, warfarin should be stopped and neuraxial analgesia deferred until the PT is within normal limits and the INR is documented at less than 1.5. Low-molecular-weight heparin (LMWH) has been used frequently for prophylaxis of DVT in pregnancy. Unlike unfractionated heparin, the anticoagulant effects of LMWH cannot be reliably measured, and it is not reversible with protamine. It is recommended to wait a prespecified time interval prior to performing a neuraxial procedure, rather than ordering laboratory testing. The decision to place or remove a neuraxial block in a patient on LMWH should correspond to the individual dose and total daily dose (see Fig. 62.5B).²¹⁰ Nonsteroidal antiinflammatory drugs do not in themselves increase risk for spinal hematoma, but can increase risk in combination with other anticoagulants.²⁰⁹ If labor begins before neuraxial analgesia can safely be given, intravenous remifentanil and N₂O are alternatives in some settings.^{254,255}

PULMONARY DISEASE

As previously detailed in the section on pulmonary changes, adaptations in the respiratory system are required to meet the metabolic demands of the mother and fetus with increases in minute ventilation, decreased O₂ reserve, and increased airway edema most notable.

Asthma is characterized by reversible airway obstruction, airway hyperresponsiveness, and airway inflammation. It is the most common respiratory disease in pregnancy with considerable maternal morbidity. A prospective trial of 1739 pregnant asthmatic patients found those with mild asthma had an exacerbation rate of 12.6% and a hospitalization rate of 2.3%, those with moderate asthma had an exacerbation rate of 25.7% and a hospitalization rate of 6.8%, and those with severe asthma had an exacerbation rate of 51.9% and a hospitalization rate of 26.9%.²⁵⁶ Bronchodilators and antiinflammatory drugs are generally safe for the fetus and should be used in pregnancy to control asthma. A meta-analysis found that maternal asthma was associated with increased risk of maternal and placental complications including cesarean delivery, gestational diabetes, abruption, and hemorrhage.²⁵⁷

Community-acquired pneumonia is the most common nonobstetric infectious complication that results in maternal death.²⁵⁸ During the 2009 H1N1 influenza epidemic, pregnant women were disproportionately affected. Pregnant women were at increased risk for hospitalization, ICU admission, and death.²⁵⁹ Preterm delivery is a significant complication of pneumonia even in the setting of antibiotic therapy. Aspiration of gastric contents is also more common during endotracheal intubation in pregnant than in nonpregnant patients because of laxity of the gastroesophageal junction combined with anatomic changes from the expanding uterus.²⁶⁰ Strict fasting recommendations, rapid-sequence tracheal intubation, and antacids are used before general anesthesia in pregnancy.

Cystic fibrosis is a common autosomal-dominant disorder in women of northern European origin. With improved medical care, women with cystic fibrosis are living to reproductive years and beyond. Pregnancy is uncommon in women with cystic fibrosis (216 pregnancies in 24,000 women), but when it occurs, careful multidisciplinary care is required.²⁶¹ The disease is caused by a mutation in the cystic fibrous membrane conductance regulator in epithelial cells, which causes abnormalities in the lungs, pancreas, intestines, and hepatobiliary systems. The major issues in pregnancy are restrictive lung disease and diabetes.

NEUROLOGIC DISORDERS

Multiple sclerosis is a neuroinflammatory disorder that disproportionately affects young women. Pregnancy is associated with a decrease in the incidence of relapse, although the rate of relapse during the first 3 months postpartum is increased in comparison with the year before pregnancy.²⁶² Multiple sclerosis is a disease of demyelination, and thus theoretic concern exists that local anesthetic toxicity may be enhanced. Cases of worsening symptoms after regional anesthesia have been reported; however, it is hard to impute causality in a relapsing and remitting disease. Nevertheless, the lowest effective concentration possible should be given and vasoconstrictive agents should be avoided. Some recommend epidural instead of intrathecal local anesthetic administration when possible.²⁶³

Neurofibromatosis is an autosomal-dominant disorder that occurs in 1 in 3000 individuals, with variable manifestations. It is characterized by café-au-lait lesions on the skin, cutaneous neurofibromas, Lisch nodules of the iris, bone abnormalities, and tumors of the spinal cord and cranial nerves.²⁶¹ Neurofibromas often grow in pregnancy. Disagreement exists as to whether neuraxial anesthesia is contraindicated in women with neurofibromatosis because of the incidence of vascular spinal tumors. Epidural hematoma has been reported in a woman with neurofibromatosis in the setting of a spinal tumor.²⁶⁴ The hormonal changes of pregnancy may cause tumor growth, and a knowledge of lesion location and current clinical symptoms is needed to avoid instrumentation of tumors and safely deliver neuraxial anesthesia.²⁶⁵

OPIOID DEPENDENCE

Opioid use is increasing in the United States and opioid abuse is now epidemic. Opioids are commonly prescribed to women during pregnancy and one study found 14% of American women were prescribed opioids at least once during pregnancy.²⁶⁶ Of concern, opioid abuse or dependence during pregnancy is associated with obstetrical morbidity and mortality including abruption, increased hospital length of stay, oligohydramnios, and maternal death.²⁶⁷ In addition, extended opioid use or dependence can result in neonatal abstinence syndrome (NAS) in the neonate, which often requires medication and extended hospital stay. NAS is characterized by hyperirritability of the central nervous system and dysfunction of the autonomic nervous system, gastrointestinal system, and respiratory system. Methadone is often utilized for treatment of opioid dependence during pregnancy but is associated with NAS. Buprenorphine is increasingly utilized in pregnancy and although it is associated with NAS, the symptoms may be milder in buprenorphine-exposed neonates.²⁶⁸ Peripartum pain management can be challenging in patients with opioid dependence and multimodal therapy is recommended for both vaginal and cesarean delivery.

Anesthesia for Malpresentation and External Cephalic Version

Breech presentation occurs when the fetal buttocks or lower extremities are the presenting part in the pelvis and is the most common abnormal presentation in pregnancy. Approximately onequarter of pregnancies are in a breech presentation before 28 weeks but most change to vertex by 34 weeks' gestation. Approximately 3% to 4% of fetuses are breech presentation at term.²⁶⁹ Breech presentations can sometimes be converted to vertex by an external cephalic version. Neuralgic anesthesia is associated with a higher success rate for external cephalic version.²⁷⁰ Anesthetic rather than analgesic concentrations allow for relaxation of abdominal wall musculature, which may help the obstetrician²⁷¹; however, a recent randomized, double-blind trial found escalating doses of bupivacaine (2.5, 5, 7.5, and 10 mg) did not change the success rate of external cephalic version.²⁷² External cephalic version has an overall success rate (all gestational ages) of approximately 60%, with risks for abruption, fetal bradycardia, rupture of membranes, and need for emergent delivery. For these reasons, an anesthesiologist should be immediately available when external cephalic version is performed in the event an emergent delivery is needed.

Higher order multiple births are frequently delivered by cesarean delivery because of the likelihood of cord entanglement and possibility of head entrapment. Twin pregnancy can be delivered vaginally but may present difficulties at delivery. If the second twin is not in the vertex position, an epidural can provide abdominal muscle relaxation and analgesia to allow for version or manual extraction.²⁷³⁻²⁷⁵ In addition, it provides analgesia and perineal relaxation for instrumented delivery if needed, and the ability for conversion to cesarean delivery if the second twin becomes

distressed or is unable to be delivered vaginally. The same considerations apply for external cephalic version of a singleton breech presentation.

Obstetric Emergencies

A variety of emergent conditions may manifest during the care of obstetric patients. These urgent situations frequently involve maternal hemorrhage, fetal distress, or both. To optimize the clinical outcome, prior preparation and excellent communication among all members of the peripartum care team are essential.

MATERNAL MORTALITY

An estimated 303,000 maternal deaths occurred worldwide in 2015.²⁷⁶ Developing regions account for approximately 99% of the global maternal deaths. Accurate measurement of maternal mortality is challenging and many deaths go uncounted. Hemorrhage, hypertensive disorders of pregnancy, and sepsis are the leading causes of maternal deaths worldwide.²²⁶ Although globally the maternal mortality ratio is declining, it is increasing in the United States^{156,226} for reasons that have not been completely understood. However, it is likely the incidence of maternal death is increasing as a result of an increase in maternal age, obesity, births by cesarean delivery, and prepregnancy comorbid conditions.

A study examined pregnancy-related deaths from 2006 to 2010 in the United States using data from the Pregnancy Mortality Surveillance System and found the number one cause of death to be cardiovascular conditions (14.6%). Other causes of pregnancy-related death included infection (13.6%), noncardiovascular medical conditions (12.7%), cardiomyopathy (11.8%), hemorrhage (11.4%), thrombotic pulmonary or other embolism (9.6%), and hypertensive disorders of pregnancy (9.4%). Of concern, non-Hispanic black women have the highest risk of dying from pregnancy complications.¹⁵⁶ This study also found deaths due to cardiovascular conditions and infection have increased while deaths from hemorrhage, hypertensive diseases of pregnancy, embolism, and anesthetic complications declined compared to previous time periods examined.¹⁵⁶

The UK Confidential Enquiry into Maternal Deaths and Morbidity found from 2014 to 2016, Asian women had a twofold and black women had a fivefold difference in maternal mortality compared to white women.²⁷⁷ During this time period, the leading causes of direct maternal deaths included thromboembolisms, obstetric hemorrhage, and suicide. The majority (57%) of maternal deaths in the UK are related to indirect causes with cardiac disease being the largest single contributor. Sepsis is also a leading cause of maternal morbidity and mortality in the UK and United States.

To improve maternal patient safety, organizations and patient safety bundles have been created to prevent morbidity and mortality associated with postpartum hemorrhage, maternal venous thromboembolism, and severe hypertension in pregnancy.²⁷⁸ When a comprehensive obstetric hemorrhage patient safety bundle was implemented, women with hemorrhage experienced a 20.8% reduction

in severe maternal morbidity compared to a 1.2% reduction ($P < .0001$) in hospitals without bundle implementation.²⁷⁹ As peripartum physicians, anesthesiologists can contribute to improved outcomes by implementing these patient safety bundle elements.

OBSTETRIC HEMORRHAGE

Hemorrhage during pregnancy carries significant morbidity and is a leading cause of maternal death worldwide.^{226,280} In addition, the need for blood transfusion is the most common indicator of severe maternal morbidity based on 2008 to 2009 US peripartum hospitalization data.²⁸¹ Most of these hemorrhage-related deaths are preventable, and appropriate training, simulation, team communication, and education are all essential elements needed to improve patient outcome.^{282,283} Common difficulties with hemorrhage management include inaccurate determination of blood loss, unrecognized hemorrhage risk factors, delayed intervention, and improper or inadequate transfusion of blood products. Various causes of peripartum hemorrhage and management of obstetric hemorrhage are discussed in greater detail in the following section.

Placenta Previa and Accreta

Placenta previa is diagnosed when the placenta is located low in the uterus and in front of the presenting fetus, either covering or encroaching on the cervical os. The incidence is approximately 0.5% of all pregnancies. Associated risk factors include advanced maternal age, assisted pregnancy, multiparity, prior placenta previa, and uterine scarring from infection or prior surgery. Placenta previa normally manifests as painless vaginal bleeding, with the first occurrence being self-limited. The diagnosis is confirmed or determined by ultrasonography. Cesarean delivery is required with placenta previa unless the placenta significantly changes position during gestation away from the cervical os before the time of delivery.

The term *placenta accreta* is often used to include the three subtypes of accreta vera, increta, and percreta. Placenta accreta vera is an abnormal adherence to the myometrium with an absent decidua line of separation. Placenta increta is abnormal implantation and growth of the placenta into the myometrium, and placenta percreta is growth of the placenta through the uterine wall with placental implantation onto surrounding tissue that might include bladder, bowel, ovaries, or other organs surrounding the uterus. Presence of accreta occurs in approximately 0.04% of pregnancies in developed countries; however, the rate is increasing and appears to affect from 0.17 to 0.34% of deliveries.^{284,285} In a multi-institutional cohort study, the sensitivity for detecting placenta accreta using ultrasound or magnetic resonance imaging was 93% and 80% with specificities of 71% and 65%, respectively.²⁸⁶ Rates of accreta are significantly affected by the presence of placenta previa and the number of prior hysterotomies. In patients with a known placenta previa, the rates of accreta are 3%, 11%, 40%, and more than 60% with zero, one, two, and three or more prior uterine incisions, respectively.²⁸⁷ Unfortunately, the diagnosis of accreta is not certain until the time of hysterotomy, and in patients with significant risk factors, massive hemorrhage

could occur, regardless of imaging study result.^{92,283} If the diagnosis of placenta accreta or percreta is made before delivery, preoperative interventions such as bilateral common iliac artery balloon catheter insertion or selective embolization of uterine vessels near the time of delivery could be considered, but efficacy remains unclear.²⁸⁸⁻²⁹⁰

Vasa Previa

Vasa previa is a rare condition in which velamentous insertion of umbilical vessels occurs so that these fetal vessels traverse the fetal membranes and are positioned over the cervical os.^{291,292} The incidence is between 0.04% and 0.02% of pregnancies and carries significant fetal morbidity and mortality if not diagnosed antenatally. In a study of 155 women, neonatal survival was 97% with antenatal diagnosis and only 44% without diagnosis before delivery.²⁹³ If undiagnosed, vaginal bleeding may be noted at the time of membrane rupture and represents fetal blood loss rather than maternal. Previously undiagnosed vasa previa represents an obstetric emergency requiring immediate cesarean delivery, typically done under general anesthesia because of its rapidity. In cases in which the diagnosis is known antenatally, cesarean delivery is performed before labor. The optimal gestational age for delivery is not definitively established, but delivery by cesarean at approximately 36 weeks of gestation is suggested with consideration for administration of steroids for fetal lung maturity and consideration of maternal hospitalization between 28 and 32 weeks' gestation in the case of the need for urgent preterm delivery.^{291,292}

Placental Abruption

Placental abruption is defined as partial or complete separation of the placenta from the uterine wall after 20 weeks' gestation but before delivery. The incidence is approximately 1% of pregnancies, and risk factors include advanced maternal age, chorioamnionitis, cocaine use, excessive alcohol use, hypertension, premature rupture of membranes, history of abruption, smoking, and trauma. Abruption often manifests with vaginal bleeding and uterine tenderness with examination. However, a significant volume of blood can be trapped behind the placenta and remain in the uterus. As for any situation with massive bleeding in pregnancy, coagulopathy resulting from massive blood loss can frequently occur. Patients with placental abruption (versus those without) were 54 times more likely to have a coagulopathy and 11 times more likely to have a fetal demise.²⁹⁴ Appropriate laboratory panels should be obtained and preparation for massive transfusion and administration of additional coagulation factors initiated, taking into account the need for close collaboration with transfusion medicine or blood bank expertise (see later discussion of management of massive obstetric hemorrhage).

Uterine Rupture

Uterine rupture can be a life-threatening emergency for both the mother and the fetus. The occurrence rate for women undergoing a trial of labor after cesarean delivery ranges between 0.4% and 1% and includes a range of pathologic processes from cases of scar dehiscence to complete uterine wall rupture.²⁹⁵ Other risk factors for uterine

rupture include fetal malposition, instrumented delivery, macrosomia, excessive oxytocin administration, rapid delivery, trauma, and tumor. Typical clinical presentation includes fetal bradycardia, cessation of uterine contractions, abdominal pain, vaginal bleeding, and loss of station. A nonreassuring FHR tracing is the most reliable and sensitive clinical sign, and breakthrough pain may be present in only a minority of patients and unrelated to epidural use.²⁹⁶⁻²⁹⁸ If trial of labor after cesarean delivery is the planned method of delivery, the American College of Gynecology recommends that an obstetrician, anesthesiologist, and nursing staff be immediately available to the laboring patient so that an emergent cesarean delivery and possible hemorrhage management can be started immediately if a rupture occurs.²⁹⁹

Uterine Atony

Postpartum uterine atony is the most common cause of severe postpartum hemorrhage. The associated hemorrhage is the leading cause of maternal death worldwide and is increasing in incidence.^{226,300,301} Risk factors include chorioamnionitis; oxytocin use during labor, high parity, macrosomia, multiple births, prolonged labor, retained products of conception, and use of volatile anesthetics, magnesium sulfate, or terbutaline. After bimanual massage, oxytocin should be administered as the initial treatment and prophylactic drug for uterine atony. Specific dosing of oxytocin varies across institutions and countries.³⁰² Although the WHO recommends 20 international units of oxytocin administered in 1 L of crystalloid after uncomplicated cesarean delivery, less is likely needed in most situations.³⁰³ There are advocates for more controlled modes of oxytocin administration including small doses immediately after delivery (3 international units administered over 30 seconds) and the use of an infusion pump. Although a dilute oxytocin solution administered over a long time has minimal hemodynamic effects and is typically well tolerated, larger doses and bolus infusion can result in significant hypotension, tachycardia, nausea, and headache. If oxytocin is not sufficient in controlling postpartum hemorrhage, methylergonovine 0.2 mg intramuscularly, carboprost (which is prostaglandin F_{2α} [PGF_{2α}]) 0.25 mg intramuscularly, or misoprostol (which is a prostaglandin E₁ analog [PGE₁]) 600 to 800 µg orally, sublingually, vaginally, or rectally should be considered. These drugs can have a variety of side effects.³⁰⁴ Side effects of methylergonovine, an ergot derivative, include nausea, hypertension (systemic and pulmonary), and coronary artery spasm, and it is relatively contraindicated in patients with preeclampsia and those with cardiac disease. PGF_{2α} is associated with pulmonary hypertension, bronchospasm, desaturation, nausea, and tachycardia, and is contraindicated in patients with asthma. PGE₁ does not have significant cardiovascular effects but may result in mild hyperthermia. If postpartum hemorrhage is not controlled with drugs, invasive and surgical techniques described in the following section should be considered.

Management of Massive Obstetric Hemorrhage

Successful management of a massive obstetric hemorrhage requires excellent communication and coordination

of all perioperative disciplines, including anesthesiologists, obstetricians, labor and operating room nurses, neonatologists, interventional radiologists, gynecologic surgeons, and blood bank staff. Early diagnosis of hemorrhage and timely intervention are key to minimizing patient morbidity and mortality. Although few studies regarding hemorrhage in obstetrics exist, many studies have been published from the military and trauma hospitals regarding transfusion ratios and transfusion triggers. The development of a massive transfusion protocol has been beneficial in massive obstetric hemorrhage. Specific ratios of fresh frozen plasma (FFP) to packed red blood cells (PRBCs) for management of massive obstetric hemorrhage originate from nonobstetric settings and have been questioned by experts in obstetric hemorrhage in recent years.^{305,306} Although frequent laboratory studies with use of point-of-care testing if available is optimal, transfusion of blood products should initially be guided by the clinical situation and patient assessment rather than waiting for laboratory values to return. Cryoprecipitate or fibrinogen concentrate should be considered if decreased fibrinogen is present or likely. TEG and rotational thromboelastometry (ROTEM) can be used as tools for both diagnosis and treatment of hemorrhage-related coagulopathy. Recombinant activated factor VII is not universally recommended as multiple adverse events have been reported to the FDA with the off-label use of treating massive hemorrhage with factor VIIa.³⁰⁷⁻³⁰⁹

Tranexamic acid is an antifibrinolytic that is used in trauma, cardiac surgery, and multiple surgical populations to decrease blood loss. It is a lysine analogue that binds to receptors on plasminogen and plasmin, which results in inhibition of plasmin-mediated fibrin degradation. A large randomized, double-blind, placebo-controlled trial randomized 20,060 women to receive either tranexamic acid or placebo at the time postpartum hemorrhage was diagnosed. The authors found a reduction in death due to bleeding in women with postpartum hemorrhage if given within 3 hours (RR 0.69; 95% CI, 0.52-0.91; $P = .008$).³¹⁰ There was no difference between the two groups in terms of thromboembolic event or other side effects. In its most recent practice bulletin on postpartum hemorrhage, ACOG recommends that tranexamic acid should be considered when initial medical therapy for postpartum hemorrhage fails.³¹¹ Tranexamic acid can cross the placenta and into breastmilk and it is recommended to wait until the cord is clamped to administer the drug. Evidence about the effectiveness of prophylactic administration of tranexamic acid to prevent postpartum hemorrhage is still lacking. A multi-center, double-blind, randomized, controlled trial randomized 4079 women to receive prophylactic tranexamic acid or placebo, in addition to oxytocin, after a vaginal delivery and found the use of tranexamic acid did not reduce risk of postpartum hemorrhage compared to placebo.^{312,313} Tranexamic acid is contraindicated in patients with active venous thromboembolism, significant renal disease, and subarachnoid hemorrhage.

Cell salvage has been used successfully in numerous published cases of obstetric hemorrhage despite the theoretic concern of amniotic fluid embolism.^{314,315} The use of a salvage device with a leukocyte reduction filter has been

demonstrated to remove tissue factor, α -fetoprotein, fetal squamous cells, bacteria, and other undesirable contaminants.^{316,317} Cell salvage can be especially helpful if the supply of autologous blood is limited for a patient or in the event a patient refuses blood products. Even when these scenarios do not exist, cell salvage has been shown to be cost-effective in cases of massive obstetric hemorrhage.³¹⁷ In parturients who are Rh negative, anti-D immunoglobulin should be used as soon as possible in coordination with Kleihauer-Betke testing to prevent alloimmunization because variable amounts of fetal RBCs will be transfused to the mother with use of cell salvage.

When standard resuscitation methods are not adequate to control the obstetric hemorrhage, the peripartum obstetric team should consider use of invasive options, including uterine balloon tamponade, compression sutures, ligation of uterine vessels, and use of interventional radiology for arterial embolization if the patient is stable for transport. Based on a systematic review of the literature, no single invasive option is significantly better than another, and all have success rates of approximately 85% to 90%.³¹⁸ If these options fail or are not feasible, a hysterectomy should be performed.

AMNIOTIC FLUID EMBOLISM

The incidence of amniotic fluid embolism (AFE) is difficult to estimate because the diagnosis is difficult to establish. The incidence varies between 1.7 and 7.7 per 100,000 deliveries.³¹⁹⁻³²¹ Signs and symptoms of AFE include hypotension, respiratory distress, hypoxia, disseminated intravascular coagulation (DIC), altered mental status, and hemodynamic collapse. This constellation of clinical features must be differentiated from other more common conditions that mimic AFE (i.e., venous air embolism, pulmonary embolism, cardiac dysfunction, massive hemorrhage, and pulmonary aspiration). The mechanism of AFE remains unclear, but it is no longer believed to be embolic, but rather an anaphylactoid reaction.^{319,322} Previously, AFE was diagnosed based on the presence of fetal squamous cells in the maternal pulmonary circulation at autopsy, but the presence of these cells is frequently noted in the pulmonary circulation of healthy pregnant women around the time of labor and delivery. Consequently, determining the occurrence of an AFE is a clinical diagnosis of exclusion and no diagnostic laboratory test for AFE currently exists, even postmortem. Early recognition and aggressive resuscitation may improve outcomes in both the mother and fetus. The priorities of resuscitation include oxygenation, hemodynamic support, and correction of coagulopathy.³²³

SHOULDER DYSTOCIA

Shoulder dystocia occurs when after the delivery of the head, the shoulders cannot be delivered secondary to impaction on the maternal pelvis. This is an obstetric emergency. It is associated with prolonged gestation, labor induction, obesity, high fetal weight, prolonged dilation from 8 to 10 cm, and epidural analgesia.^{324,325} Prolonged gestation and slow difficult delivery make epidural analgesia more desirable, so the association between epidural analgesia and

shoulder dystocia is not causal. However, epidural analgesia provides superior conditions for rescue of the infant in the case of shoulder dystocia. Recommended procedures for the management of shoulder dystocia include the McRoberts maneuver, in which the mother's legs are flexed and pushed tightly to her abdomen with application of suprapubic pressure.³²⁶ The muscle relaxation and pain relief offered by epidural analgesia facilitate this process. However, the Gaskin maneuver requires placing the mother on her hands and knees, which may not be possible to sustain with the use of higher dose epidural local anesthetic because of inadequate motor strength. If these maneuvers are unsuccessful, pushing the fetus back into the pelvis and emergent cesarean delivery may be required. Deliveries with shoulder dystocia have an increased risk for postpartum hemorrhage and fourth-degree lacerations.³²⁷

OTHER OBSTETRIC EMERGENCIES

Certain urgent situations may occur around the time of labor and delivery that require tailored anesthetic care to optimize both the maternal and fetal outcome. Cord prolapse through the cervical os can result in abrupt fetal bradycardia. Rates of umbilical cord prolapse range between 0.1% and 0.6%.³²⁸ The risk is significantly increased with the presence of transverse lie, breech presentation, multiple gestations, and an abnormally long umbilical cord. In addition, cord prolapse may occur around the time the membranes are ruptured if an abnormal fetal presentation is present or the mother has polyhydramnios. Diagnosis is confirmed with visualization or palpation of the cord in the vaginal canal below the presenting fetal part. Intervention typically consists of elevating the compressing fetal part back into the pelvis off of the cord until an urgent cesarean delivery can be performed. Use of an in situ epidural catheter or spinal technique can be considered as long as the FHR tracing is reassuring, but general anesthesia is frequently used in the event of fetal compromise.

Uterine inversion occurs in approximately 0.04% of deliveries³²⁹ and is usually associated with hypotension, pain, and severe postpartum hemorrhage. Risk factors include excessive cord traction before placental separation, uterine atony, location of the placenta at the fundus, and the presence of placenta accreta. Treatment goals include relaxation of the uterus to aid replacement back through the cervix, maternal fluid resuscitation, and increased uterine tone after replacement to reduce postpartum hemorrhage. Initially, all uterotonic drugs should be immediately discontinued. Uterine relaxation can be quickly and reliably achieved using either intravenous nitroglycerin or volatile anesthetics.³³⁰⁻³³² The mother's hemodynamic condition may guide the choice of therapy. If the initial uterine intervention and replacement is not successful with nitroglycerin because of lack of relaxation, maternal pain, hemodynamic instability, or other logistics, transfer to the operating room should occur. A rapid sequence intubation with standard obstetric precautions followed by volatile anesthetic administration will allow needed uterine relaxation, pain control, and procedural conditions for uterine replacement. Only on rare occasions are vaginal maneuvers unsuccessful and laparotomy required. After uterine replacement, the uterine cavity should be explored for perforation, laceration,

or retained products. After the uterus has been replaced, uterotonic drugs can be started.

Lacerations of the vagina, cervix, and perineum are the most common injuries associated with vaginal birth. Significant bleeding can be concealed in hematomas, and maternal hypotension and tachycardia may be the first signs of the injury. Retroperitoneal hematomas are rare but can represent substantial life-threatening blood loss that requires exploratory surgery. Anesthetic management to allow surgical repair or exploration depends on the hemodynamic state of the mother and can include use of local anesthetic at the site, neuraxial blockade, or—in severe hemodynamic compromise—use of general anesthesia. Equally important is the hemodynamic assessment and initiation of resuscitation efforts for the mother. Even small unrecognized lacerations can result in significant blood loss.

ADVANCED CARDIAC LIFE SUPPORT IN PREGNANCY

Cardiac arrest in pregnancy involves the simultaneous care of two patients, the mother and fetus. The protocol for advanced cardiac life support (ACLS) in pregnancy is similar to that recommended for other adult cardiac arrest situations; however, compression of the maternal great vessels by the pregnant uterus greatly impedes the success of external cardiac massage. First responders should utilize strategies to oxygenate the patient while laryngoscopy should be performed by providers with advanced airway management experience. Although pregnant women are at increased risk of aspiration, oxygenation and ventilation should remain primary objectives and take precedence over aspiration prevention strategies. Intravenous access should be placed above the diaphragm and the patient should be supine with manual displacement of the uterus. If there is no return of spontaneous circulation after 4 minutes of resuscitative efforts, consider performing immediate cesarean delivery at the site of cardiac arrest with an aim

for delivery within 5 minutes of maternal cardiac arrest.¹⁹ Although potentially beneficial for the fetus if viable, hysterotomy and delivery improves ACLS effectiveness.³³³ If the maternal cardiac arrest may have been caused by local anesthetic toxicity, lipid rescue should be initiated.³³⁴

Nonobstetric Surgery During Pregnancy

PERIOPERATIVE CONSIDERATIONS

Although elective surgery is not performed during pregnancy, ACOG recommends that pregnant women should not be denied a medically indicated procedure. Between 0.75% and 2% of pregnant women will require nonobstetric surgery. The most common indications for surgery include acute appendicitis and cholecystitis, maternal trauma, and cancer.³³⁵ Box 62.3 provides a summary of the anesthetic considerations for the pregnant patient.

ANESTHETIC TOXICITY

All general anesthetic drugs cross the placenta; however, when standard dosing is used, current anesthetic drugs have not been shown to be teratogenic in humans. Although no clear evidence exists for toxicity of specific anesthetic drugs in humans, data in rodents and primates suggest that exposure to general anesthetic drugs, including volatile anesthetics, propofol, and ketamine, induce inappropriate neuronal apoptosis that is associated with long-lasting behavioral abnormalities.³³⁶⁻³³⁸ These preclinical results are concerning, but whether these drugs cause toxicity in humans is not known. The critical period of rapid synaptic development is extended in humans from the prenatal period through 2 years of postnatal life.³³⁹ Analyses of existing human data have found conflicting evidence and the results of these studies are difficult to interpret because the reason for anesthesia cannot be separated from the impact of anesthesia (see Chapter 77). Studies reveal no association between surgery and major birth defects, but there may be a small increase in the risk for preterm delivery or miscarriage, especially with abdominal surgeries.³⁴⁰⁻³⁴² In general, the second trimester is preferred for surgical intervention because this is a period after organogenesis but the risk for preterm labor is less than in the third trimester. In 2016, the FDA issued a warning that repeated or lengthy use of general anesthetic drugs during surgery in children less than 3 years of age or in pregnant women in the third trimester may affect the development of children's brains. There is concern that the warning could delay necessary surgeries or procedures and result in adverse outcomes for these patients especially as there is lack of data regarding adverse consequences of human fetal exposure to anesthesia.³⁴³

Monitoring for contractions is recommended, and in some situations suppression with tocolysis may be appropriate. Because the long-term impact of general anesthesia on the fetus is unknown, regional anesthesia is favored when possible for the surgical procedure but should not be undertaken unless both the anesthesiologist and surgeon are experienced in using the technique for a given procedure, and the mother is comfortable being awake.

BOX 62.3 Anesthetic Considerations for Nonobstetric Surgery in the Pregnant Patient

- Postpone elective surgeries until after delivery.
- Regional anesthesia should be utilized when possible.
- Consider aspiration prophylaxis.
- Left uterine displacement to relieve aortocaval compression after 20 weeks' gestational age
- Consider intraoperative fetal monitoring.
- Regional anesthesia
 - Reduced local anesthetic requirements in pregnancy
- General anesthesia
 - Maximize preoxygenation
 - Rapid sequence induction
 - Avoid hypoxia and hypotension
 - Goal ETCO₂ 28-32 mm Hg. Avoid hyperventilation as hypocarbia can decrease placental blood flow secondary to uterine vasoconstriction.
 - Extubate when awake
- Fetal heart rate and uterine tone should be monitored postoperatively.
- Provide appropriate postoperative analgesia.

PERIOPERATIVE FETAL HEART RATE MONITORING

Fetal well-being should be monitored in the perioperative period. ACOG recommends in a previable pregnancy, fetal heart rate measurement by Doppler before and after the procedure. In a viable fetus, minimum recommendations include electronic FHR monitoring and contraction monitoring before and after the procedure. Continuous intraoperative fetal monitoring is often used and FHR variability is a reliable sign of fetal well-being. Under general anesthesia, loss of FHR variability is expected while fetal bradycardia is more concerning and can be affected by hypothermia, maternal acidosis, or the maternal administration of drugs such as particular β -blockers that can cross the placenta and reduce FHR. The type of fetal monitoring is a decision that should be made in consultation with an obstetrician and should be based on an assessment of the individual patient and gestational age, procedure, and facilities available.³⁴⁴

ANESTHETIC MANAGEMENT

To minimize fetal exposure to anesthesia, regional anesthesia is preferred when possible to general anesthesia for nonobstetric surgery in pregnancy. Preoxygenation followed by a rapid sequence induction and endotracheal tube placement are recommended for general anesthesia. Starting in the second trimester, the increase in peripheral blood flow induced by pregnancy results in airway edema and friability. Pregnant women are at increased risk of difficult intubation and advanced airway equipment should be readily available prior to intubation. Equally important to anesthetic technique is avoidance of decreased uterine blood flow and oxygen delivery to the fetus as uterine blood flow is not autoregulated. Considerations similar to those discussed in the section on anesthesia for cesarean delivery should be undertaken for any nonobstetric surgery during pregnancy. The anesthetic plan should optimize both the maternal and fetal condition. Perioperative team planning should include consultation with an obstetrician regarding plans for unexpected events, including need for emergent cesarean delivery.

POSTOPERATIVE PAIN CONTROL

Maternal pain control after nonobstetric surgery is important to maternal well-being and could theoretically decrease the risk of preterm labor, especially after abdominal surgery. Multimodal analgesia is recommended. When intraoperative regional anesthesia with an epidural is used, it often can be continued for postoperative analgesia. Postoperative systemic opioids, including those used in patient-controlled analgesia, cross the placenta and may reduce FHR variability. If the fetus is born prematurely shortly after exposure to maternal systemic opioids, respiratory support may be necessary. Nonsteroidal antiinflammatory drugs, though useful adjuvant analgesics outside of pregnancy, are typically avoided in pregnancy. They are associated with an increased risk for miscarriage and fetal malformation when used early in pregnancy and premature closure of the ductus arteriosus and oligohydramnios when used after 30 weeks' gestation.³⁴⁵ Acetaminophen, oral or intravenous, is generally accepted as safe in pregnancy.

After surgery, both the FHR and uterine activity should be monitored. Preterm labor can be managed with appropriate tocolytic drugs. Distracting pain and postoperative pain relief medications may make it difficult for the patient to note early contractions and patient perception should not be considered a substitute for standard fetal and contraction monitoring postoperatively. In addition, thromboprophylaxis should be instituted unless surgically contraindicated.

SPECIFIC SURGICAL TECHNIQUES

Laparoscopy

Surgery for appendicitis and cholecystitis are common in pregnancy. These surgeries are typically performed with a laparoscopic technique outside of pregnancy and are increasingly more common in pregnancy because of reduced morbidity for the mother and potentially a decreased incidence of preterm labor as a result of reduced manipulation of the uterus.³⁴⁶ A recent meta-analysis of 20 studies involving 6210 pregnant women found open appendectomy may have a slightly less frequent rate of fetal mortality and prolonged gestation compared with laparoscopic appendectomy, although hospital length of stay and overall complications were more frequent.³⁴⁷ However, a study of over 2 million pregnancies in Sweden comparing laparoscopies and laparotomies found no difference in fetal outcome between the two techniques.³⁴⁸ Left uterine displacement should be maintained after the second trimester to facilitate uterine perfusion. With increased abdominal pressure from insufflation, maternal cardiac output and uteroplacental perfusion may decrease. Thus the smallest possible intraabdominal pressure should be used.

According to the guidelines issued by the Society of American Gastrointestinal Endoscopic Surgeons regarding laparoscopic surgery during pregnancy,³⁴⁹ whenever possible, surgery should be deferred to the second trimester and indications for the use of laparoscopic techniques are the same as in nonpregnant patients. Normocapnia should be maintained, and fetal and uterine status should be monitored. During laparoscopic surgery, gradients between end-tidal CO₂ and arterial CO₂ are typically less than 3 mm Hg, and although some anesthesia providers feel that arterial blood gas monitoring is not needed unless otherwise indicated,³⁵⁰ many may choose to follow PaCO₂ to be sure to avoid hypercapnia or hypcapnia. An open technique is preferred to enter the abdomen. Aortocaval compression should be avoided. Finally, low pneumoperitoneal pressure (15 mm Hg) should be used. A systematic review of laparoscopic surgery for appendicitis during pregnancy noted that trimester timing did not influence the complication rate, the need for conversion to open was less than 1%, and there was a lower rate of preterm delivery with laparoscopic in contrast to the open approach.³⁵¹

Trauma

The most common nonobstetric cause of maternal death in the United States is trauma. Initial primary and secondary survey should be directed toward maternal well-being, with consideration of the physiologic changes induced by pregnancy. Gestational age is an important variable in trauma evaluation. During the first trimester, the fetus is protected by the bony pelvis and damage is unlikely in the absence of

severe hypoperfusion. However, as pregnancy progresses, the uterus is not only exposed but also causes pressure on the maternal inferior vena cava and aorta, potentially compromising perfusion and resuscitation. After 20 weeks' gestation, left uterine displacement should be implemented as the initial step. Blunt trauma carries a risk for intrauterine fetal demise, fetal injury, placental abruption, and uterine rupture. These dangers should be evaluated with fetal heart monitoring, ultrasonography, computed tomography, or exploratory laparotomy when indicated.³⁵² The consequences for ACLS are discussed earlier in the chapter.

Cardiac Surgery

The hemodynamic changes of pregnancy can exacerbate the symptoms of some preexisting heart diseases. The increase in intravascular volume and cardiac output can result in heart failure and arrhythmias in patients with moderate to severe mitral or aortic valvular stenosis. These patients may require a cardiac intervention during pregnancy. Percutaneous balloon valvuloplasty may obviate open cardiac intervention in pregnancy and has been associated with reduced fetal and neonatal mortality.^{353,354} Cardiopulmonary bypass increases risk to the fetus as a result of nonpulsatile perfusion, low perfusion pressures, emboli to the uteroplacental unit, and maternal release of catecholamines.³⁵⁵ Higher pump flows (>2.5 L/min/m²) and perfusion pressures (>70 mm Hg) are recommended to support uteroplacental blood flow.^{356,357} Normothermic bypass and pulsatile flow may better preserve uteroplacental perfusion and improve fetal survival. Hypothermic (versus normothermic) bypass has been associated with greater fetal loss. Hypocapnia should be avoided because it causes uteroplacental vasoconstriction and decreased oxygen delivery to the fetus. Likewise, hypercapnia causes fetal acidosis.

Neurosurgery

Intracranial hemorrhage secondary to aneurysm rupture or arteriovenous malformation can be a neurosurgical emergency made more complex by pregnancy. The risk for intracranial hemorrhage is increased by hypertensive diseases of pregnancy. In patients who are not pregnant, usual anesthetic treatment might include controlled hypotension, hyperventilation, and osmotic diuresis. Such techniques need to be conducted with particular care in pregnancy. Reduction of mean arterial pressure below 70 mm Hg may significantly reduce uteroplacental perfusion and use of fetal monitoring should be considered as a guide to fetal well-being. Extreme hyperventilation can cause uterine artery vasoconstriction and reduce uterine perfusion. Hyperventilation also shifts the maternal oxyhemoglobin dissociation curve to the left, which decreases oxygen delivery to the fetus. Osmotic diuresis, used to reduce brain edema, could theoretically decrease amniotic fluid volume and cause negative fluid shifts in the fetus. In animal studies, mannitol may accumulate in the fetus, leading to hyperosmolarity, reduced renal blood flow, and increased plasma sodium concentration.³⁵⁸ A case report of a single dose of mannitol used for awake craniotomy in a pregnant patient revealed a reduction of intrauterine volume with subsequent volume recovery after 48 hours and no fetal adverse effects.³⁵⁹ Loop diuretics are an alternative

to osmotic diuretics but should be used with care and monitoring of amniotic fluid volume.

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