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Surgical Considerations and Management Options in Premature and Very Low Birth Weight Infants With Complex Congenital Heart Disease

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Abstract

Purpose of Review The purpose of this review is to provide a concise discussion regarding surgical management of infants born pre-term and/or of low birth weight with congenital heart disease (CHD). The following provides a summary of current available experiential data and treatment paradigms that remain in evolution for this high-risk subset of infants. The composite of these findings supports center- and patient-specific decision-making to define the optimal timing and technique utilized for the palliation and definitive surgical treatment of CHD across a spectrum of severity.

Recent Findings The following establishes that infants born both pre-term and of low birth weight represent a high-risk surgical cohort with CHD. Despite this increased risk of both morbidity and mortality following surgical palliation or definitive anatomic correction, advancements in prenatal diagnostics, in postnatal resuscitation, and in the conduct of complex neonatal surgery and cardiopulmonary bypass now enable early intervention with improved outcomes and favorable long-term risk of need for re-intervention.

Summary Infants of low birth weight and those born pre-term represent a high-risk subset of patients with CHD. Advancements in both surgical technique and the advent of interventional therapies have introduced important considerations that have enabled earlier treatment in a subset of carefully selected patients. Further prospective, well-controlled data are needed to better define the multi-system effects of early surgical intervention in this high-risk patient population.

Introduction

Congenital heart disease in low birth weight (LBW) infants presents a unique set of challenges for neonatologists, cardiologists, and congenital cardiac surgeons. Rates of pre-term deliveries are on the rise internationally. Approximately 15 million infants are born pre-term each year and comprise 11% of all deliveries [1]. One of the most important factors impacting survival for pre-term infants is the significant threat of congenital heart disease. A population-based study has demonstrated that pre-term infants have a nearly twofold higher incidence of cardiovascular malformations as infants born at term and comprise 16% of all infants with congenital heart disease [2]. Furthermore, pre-term infants born at less than 32 weeks have an overall in-hospital mortality of 26.3%, and a 7.5-fold increased adjusted odds of death compared with infants born at term [3].

Infants with congenital heart disease are also thought to be more likely to have LBW for gestational age, with patients carrying diagnoses of endocardial cushion defect, hypoplastic left heart syndrome, pulmonary stenosis, coarctation of the aorta, and ventricular septal defect having significant birth weight deficits [4]. The etiology for this association remains unclear, yet has been traditionally thought to predispose infants of LBW to increased mortality [5, 6].

The advent and advancement of prenatal imaging has improved early diagnosis of severe congenital heart disease and has decreased associated morbidity and mortality by aiding resuscitative preparations and surgical plans prior to birth; however, prenatal diagnosis of congenital heart disease has been associated with earlier delivery [7, 8]. In addition to delivery planning and perinatal management, prenatal diagnosis enables early genetic counseling and parental education.

Risk of serious perinatal pulmonary morbidity is significantly increased with pre-term delivery [9]. These findings have been corroborated by a study on 971 neonates with critical congenital heart disease, demonstrating that infants delivered before 39 weeks had increased morbidity and mortality [10]. Furthermore, neurodevelopmental outcomes at 4 years of age have been shown to be inferior for pre-term infants with congenital heart disease compared with term infants [11]. As a result of these data, guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommend elective delivery at 39 weeks or greater, and retrospective data support the safety of vaginal delivery for infants with congenital heart disease [12, 13].

Preoperative considerations

Critical to the management of both pre-term and LBW infants is an understanding of early organ maturation to guide resuscitative efforts and to define optimal timing for surgical correction of structural cardiac defects. First, the myocardium contains fewer contractile elements and an underdeveloped sarcoplasmic reticulum, making the neonatal myocardium extremely sensitive to changes in extracellular calcium levels [14, 15•]. Furthermore, ventricular compliance is poor and cardiac output is defined primarily by heart rate given the fixed stroke

volume. Hemodynamic and perfusion monitoring are critical in these neonates to ensure adequacy of oxygen delivery and diastolic coronary perfusion to prevent subtle changes in cardiac output that may result in life-threatening myocardial ischemia [16]. In addition, serum glucose and calcium levels must be monitored and aggressively replaced, as stores of both calcium and glycogen are diminished [17].

The respiratory system in LBW infants with congenital heart disease is often underdeveloped. Their lungs lack surfactant and demonstrate a lack of alveolarization with poor arborization of the pulmonary vasculature [18]. As a result, respiratory distress syndrome and bronchopulmonary dysplasia can complicate preoperative resuscitation and postoperative recovery [19]. Treatment considerations include surfactant administration [20], lower oxygenation goals [21], positive pressure ventilation [22], and caffeine to treat infant apnea [23]. Aminophylline, while not specifically studied in premature infants, has also been demonstrated as a plausible agent to treat apnea while infants are supported on prostaglandin therapy [24].

Brain development is also delayed in pre-term infants with congenital heart disease. It is proposed that cardiac malformations result in altered cerebral blood flow in utero, resulting in maturational delays, particularly in the white matter of the brain [25–27]. Furthermore, the risk of necrotizing enterocolitis (NEC) is significant, secondary to diastolic runoff associated with structural heart lesions or shunts [28]. Management strategies include early enteral feeding and close monitoring for feeding intolerance so that appropriate management can be employed. Reduced glomerular filtration rate, impaired renal electrolyte concentrating abilities [29], and an increased susceptibility to jaundice as a result of liver immaturity [30] can also complicate management of pre-term infants with congenital heart disease. In addition, LBW infants also have deficiencies of potassium, iron, and bicarbonate and are susceptible to hypothermia, anemia, polycythemia (CHD), thyroid hormone insufficiency, and polypharmacy.

Timing

Successful management of pre-term and LBW infants requires careful consideration of the risks of waiting for an operation weighed against the risks of the operation itself. Infants with congenital heart disease have inherent physiologic derangements that may result in significant long-term consequence should surgical palliation or correction be delayed. The three most common scenarios are volume overload, pressure overload, and/or cyanosis from poor pulmonary circulation [31•, 32]. Ductal-dependent circulation in these critically ill neonates is maintained by treatment with prostaglandin E1. Side effects include low blood pressure, apnea, fever, intraventricular hemorrhage, and electrolyte imbalance. Despite these side effects, even with long-term therapy, prostaglandin therapy is well tolerated [33].

Historically, pre-term and LBW infants were allowed to grow to a size at which surgical repair would be considered more technically feasible, resulting in more palliative operations being performed. Common palliative approaches to cyanotic or mixing lesions include pulmonary shunting to augment pulmonary blood flow, pulmonary banding for overcirculation, and surgical

septectomy or balloon septostomy [34]. While these surgical procedures are seemingly less technically demanding, each carry significant early postoperative mortality risk while also creating anatomical challenges for later definitive repair.

Prior retrospective studies have demonstrated disparate outcomes following definitive repair in LBW and pre-term infants [5, 35, 36, 37•, 38, 39]. Despite these earlier findings and treatment approaches, the paradigm is shifting toward earlier intervention on smaller neonates. Kalfa et al. analyzed outcomes of neonates weighing less than 2.5 kg at the time of surgery. They compared this group of 146 patients with a group ($n = 30$) weighing 2.5 to 4.5 kg undergoing cardiac repair. They found a higher in-hospital mortality (10.9% vs. 4.8%) in the lower weight group. Outcomes were not dependent on timing, but a lower gestational age at birth was a risk factor for in-hospital mortality [40]. Furthermore, Hickey et al. analyzed 1618 admissions for CHD at one institution. LBW below 2.0 kg and prematurity were associated with poor outcomes. They then compared the infants in this group and split them into a "usual" group (24 patients) and a "delayed" group (46 patients). Survival was identical in both groups. Other factors seemed to account for survival differences, including lesion type, associated noncardiac congenital defects, and antenatal diagnosis [41]. Another review of 450 infants compared outcomes among infants less than 1.5 kg with those weighing 1.5–2.5 kg. The authors did not find that weight was an independent predictor of mortality [42]. Diagnosis may, in fact, be more important than birth weight with regard to outcomes for LBW infants undergoing cardiac surgery [43]. Several studies have found that acceptable survival can be achieved among pre-term and LBW infants, yet discernment is warranted in this high-risk cohort to determine the optimal surgical plan and timing [44–47]. Supporting this approach, delayed management has been demonstrated to offer acceptable outcomes in select patients [48], while hybrid approaches are emerging as a potential strategy for the palliation of complex neonatal conditions in infants with lower birth weight [49•, 50–52]. Thus, the decision algorithm for these neonates remains challenging as well-controlled, multi-center studies are lacking. The following encompasses common neonatal conditions along a spectrum of severity that are often encountered in the pre-term and LBW infant patient population and provide diagnosis-specific considerations to optimize individualized, patient-centered care.

Operations/outcomes

Coarctation

Debate persists regarding the optimal timing for surgical correction of severe aortic coarctation in infants of VLBW and prematurity. Severe coarctation of the aorta occurs in 4.4 per 10,000 live births and represents one of the most common defects diagnosed in infants of VLBW with an estimated incidence of 11% in this population [6, 53]. While a retrospective review in limited series has demonstrated an extrapolated 5-year estimated survival of 80% for VLBW infants following surgical repair, other series have demonstrated mortality rates as high as 50% for infants less than 1 kg at birth following surgical correction [54]. Critical to the interpretation of these findings is the importance of prompt postnatal diagnosis and institution of resuscitative measures including

prostaglandin therapy for normalization of acid-base balance and end-organ perfusion/function prior to surgical repair.

Following medical stabilization and assessment of associated neurologic and genetic factors that may preclude early surgical repair, determination of surgical candidacy must also be dictated by concomitant cardiac anatomic abnormalities and individualized arch anatomy. Specifically, dedicated imaging must determine the optimal strategy for arch reconstruction while also assessing the adequacy of the mitral valve, left ventricle, and aortic valve for the maintenance of systemic cardiac output and laminar arch flow that is maintained with somatic growth. Prior multivariable models have intuitively demonstrated that Shone's complex and concomitant hypoplasia of the aortic arch are risk factors for mortality in VLBW infants undergoing coarctation repair, representing the severe end of the coarctation spectrum of pathology and validating the need for precise preoperative imaging and left ventricular volumetric analysis if indicated [55]. Echocardiography, computed tomographic imaging with angiography, and magnetic resonance imaging each have established roles in the determination of the optimal surgical strategy for reconstruction and multidisciplinary management of complex obstructive lesions within VLBW infants.

In addition to an associated increase in postoperative mortality, residual or recurrent coarctation is common in VLBW infants following surgical repair, with 44% of VLBW infants needing catheter-based or surgical re-interventions [55]. Though several series have demonstrated feasibility for surgical repair of coarctation in VLBW infants, the advent of transcatheter-based therapies has introduced salient considerations for staged palliation prior to surgical repair in patients with end-organ hypoperfusion, left ventricular dysfunction, pulmonary insufficiency, or severe hypertension. Limited retrospective series have demonstrated successful palliation in infants weighing 680–1380 g utilizing 3–5 mm coronary stents until definitive surgical correction at a median age of 200 days and weight of 5500 g with no needed re-interventions at 2.8 years follow-up [56, 57]. Furthermore, prolonged prostaglandin infusion has been performed up to 7 weeks in an infant weighing 560 g prior to surgical correction for relaxation of the juxta-ductal constriction [58]. With the advancement of transcatheter technologies and diagnostic imaging modalities, treatment paradigms for VLBW will remain in evolution to define both the optimal timing and strategy for reconstruction or staged palliation to limit the associated increases in morbidity and mortality for this high-risk patient population.

Multiple aortopulmonary collateral arteries/tetralogy of Fallot

Multiple systemic to pulmonary collateral arteries (MAPCAs) have been demonstrated to have an incidence of 66% in very low birth weight infants and have been postulated to be the result of increased time of positive pressure ventilation and length of hospital stay [59]. It is important to delineate this pathophysiology from that of native congenital heart disease. Tetralogy of Fallot represents a spectrum of maldevelopment that in the most severe form may manifest as pulmonary valve atresia with MAPCAs (PA/VSD/MAPCA). Preoperative evaluation of collateral vessel caliber, sixth arch vessel continuity and dominance, pulmonary arborization patterns, and lobar dominance will guide unifocalization strategy and timing for complete repair in this high-risk subset

of patients [60]. Cardiac catheterization and computed tomographic imaging have established roles in the early evaluation of sixth arch vessel continuity and distal arborization patterning. In addition, cardiac catheterization provides a diagnostic and therapeutic modality for the evaluation of MAPCA stenosis that should be addressed at the time of unifocalization. Limited reports of staged repair exist in VLBW infants given the associated morbidity and mortality of this diagnosis and practice patterns vary significantly even for non-VLBW infants. For non-VLBW infants, the authors favor early unifocalization, reserving creation of an aortopulmonary arterial window for infants having predominately dual-supply MAPCAs (≥ 15 lung segments with dual supply from native PAs and MAPCAs) and cyanotic infants with confluent yet hypoplastic pulmonary arteries with normal arborization patterns [61, 62]. The Stanford group has elegantly outlined the adoption of an intra-operative flow study at the index unifocalization procedure utilizing a central pulmonary artery catheter to achieve a flow rate of 3 L/min/m^2 with a maximum pulmonary artery pressure of 25 mmHg. Adopting this approach, central shunt placement is employed in infants that fail the flow hemodynamic assessment to achieve a postoperative right ventricle to aortic pressure ratio less than 0.50 [61, 63]. While this experience encompassed 307 patients with PA/VSD/MAPCAs, weights ranged from 2.1 to 41.8 kg at a median age at operation of 4.5 months (range 0.1 to 11.5 years) [61]. While this strategy and the optimal weight for operative intervention have yet to be validated for infants of VLBW, considerations for operative candidacy should involve intensive assessment of the pulmonary arterial/MAPCA anatomy to support consideration for early surgical repair with unifocalization when medically stable.

For infants of low birth weight and pre-term birth with tetralogy of Fallot and either pulmonary stenosis or ventricular septal defect physiology, early repair is favored once medical management fails given the low risk for cardiopulmonary bypass and need for re-intervention. Despite this strategy, infants of LBW and pre-term infancy represent a higher risk cohort for survival to hospital discharge [64, 65].

Hypoplastic left heart syndrome

Hypoplastic left heart syndrome (HLHS) represents a spectrum of underdevelopment involving the critical left heart structures that is universally fatal if untreated. In total, 16% of infants with HLHS are classified as LBW (< 2.5 kg) and 15% are pre-term (< 37 weeks gestational age) with each being established risk factors for mortality after stage I Norwood palliation [66–68]. Review of LBW infants undergoing stage I palliation at a median birth weight of 2.14 kg and gestational age of 36 weeks demonstrated an in-hospital mortality of 51% for this patient subset, with comparable survival statistics following stage 2 (91%) and 3 (94%) palliations [69]. This study importantly identified an overall post-Fontan survival of 36% for LBW infants, with the highest mortality being assumed following the first stage of palliation [69].

With the understanding and acceptance of increased risk in infants with LBW and pre-term birth, treatment paradigms for this high-risk population remain in evolution. Extended applications of hybrid procedures involving branch pulmonary artery band placement and ductal stenting within lower volume centers and in higher risk neonates have been proposed as an effective approach to

address the early mortality effect of either low-volume center experience or LBW [70]. Despite initial enthusiasm for widespread application, resource utilization and highly specialized demands have tailored application of hybrid strategies to be most effective in achieving comparable survival to surgery in infants with high-risk features including LBW, aortic atresia, and obstructed pulmonary venous return [71].

Despite selective application, the optimal follow-up surgical strategy has yet to be defined for this high-risk patient population. A dedicated study of staged palliation has demonstrated that following hybrid procedure with branch PA banding, neither Stage I Norwood nor comprehensive Stage II palliation (Bi-directional Glenn + arch reconstruction/Damus-Kaye-Stansel) mitigates the mortality risk associated with LBW and aortic atresia [72]. Although these findings demonstrate a persistence of mortality risk for LBW infants despite palliation strategy, multivariable analysis has identified interstage weight gain as a primary predictor of transplant-free interstage survival [73]. Taken together, multidisciplinary assessment must account for the individualized risk profile to optimize balanced pulmonary:systemic (Qp:Qs) blood flow while supporting weight gain for the most effective palliation of single ventricle anatomy in LBW infants. Further prospective study and subgroup analyses of the single ventricle reconstruction (SVR) trial are needed to define timing and palliation strategy for this high-risk group of infants with concomitant LBW and single ventricle anatomy.

Complete congenital heart block

Complete congenital heart block has an estimated incidence of 1 in 20,000 live births and has been associated with maternal autoimmune and connective tissue disorders [74, 75]. Infants with a heart rate of < 50–55beats/min may require expeditious pacemaker placement shortly after birth [76]. VLBW infants present a particularly difficult patient population for both pacemaker placement and management given the small size of the umbilical vein for potential transvenous temporary lead placement and the friable nature of the myocardium for epicardial lead placement. With this consideration, the optimal strategy for initial palliation involves placement of a multifilament temporary pacing lead through a lower sternotomy and onto the epicardium of the right ventricle [77]. The skin may be used as the positive electrode and two epicardial leads are favored on the right ventricle due to the anticipated increase in impedance. This strategy will serve as an effective palliation until weight gain is achieved to the point that permanent pacemaker placement may be pursued by median sternotomy and generator placement within the preperitoneal, retro-rectus abdominus muscular space.

Cardiopulmonary bypass

Early reports of cardiac surgery in LBW infants (< 2.5 kg) demonstrated an associated hospital mortality of 10–16.5% across a spectrum of pathologic severity. Within this study, multivariable analysis associated this increased risk to the presence of preoperative metabolic acidosis, univentricular versus biventricular repair, and duration of cardiopulmonary bypass [78, 79]. Importantly, a retrospective study has identified the presence of associated non-cardiac malformations or syndromes in 30% of LBW infants needing cardiac

surgery [79]. This statistic highlights the importance of multidisciplinary involvement to define associated neurologic and end-organ risks of cardiopulmonary bypass and early corrective repair in both LBW and VLBW infants. Reddy et al. have championed early repair for a spectrum of cardiac anomalies adopting minor technical modifications to the conduct of cardiopulmonary bypass and employing cooling with low-flow and circulatory arrest to avoid the potential deleterious effects of small venous vessel cannulation in the repair of intracardiac defects in this patient population [79]. This study demonstrated no significant neurologic sequalae occurring in a series of 102 LBW and VLBW infants undergoing complete repair, indicating that extrapolation of neurologic risks from published ECMO experiences (up to 50% of infants with MRI-identifiable parenchymal injury) to that of shorter run cardiopulmonary bypass with cooling may not be appropriate [80]. Despite the early promising results from these published studies, few have replicated these data in a controlled, prospective manner, indicating that multidisciplinary assessment of risk and associated anomalies is critical to the risk management and determination of optimal timing for complete surgical correction in infants of VLBW.

Summary

VLBW infants constitute 1.4% of all births within the USA yet comprise greater than 50% of infant deaths [81, 82]. Despite surgical advancements and adoption of early strategies for complete repair, outcome reporting remains desperate with acknowledged increased risks of morbidity and mortality across a spectrum of cardiac pathologies.

Important to the interpretation of these findings and with the advent of early surgical repair, a rigorous and well-controlled review of outcomes is needed to define the optimal timing, place, and technique for surgical correction. Two strategies that have been proposed for improving outcomes in VLBW infants are the collaborative approach and the evidence-based selective referral approach [82]. The collaborative approach identifies "best practices" utilized in high-performing hospitals and encourages the adoption of these practices in all hospitals, while the evidence-based selective referral approach is a competitive-based model that seeks to improve outcomes through selection rather than improvement of an individual hospital's performance [82]. Complicating the assessment of these administrative strategies for outcome improvements has been an absence of a widely accepted metric for quality as prior studies have failed to establish center volume-based referrals as the optimal strategy for improving outcomes in VLBW infants. Data from the Vermont Oxford Network from 1994 to 2000 have demonstrated that selective-referral strategies based upon volume are less likely to have an effect on mortality among VLBW infants in comparison with outcomes data [82]. Referral strategies that moved the lowest ranked 20% into the best 20% would result in a total reduction in mortality of 34.2% using mortality statistics compared with 4.2% utilizing volume statistics alone [82]. These figures support the current era of public and institutional reporting to define both national and regional practice patterns for the postnatal resuscitation and surgical correction of infants of VLBW.

Inherent to the interpretation and reconciliation of desperate outcomes for LBW and VLBW infants is the need for improved prenatal diagnosis and access

to care for underserved populations. A dedicated study has demonstrated that racial disparities exist in the incidences of premature birth and prevalence of VLBW, with Black infants being more likely than White infants to be of VLBW [82]. Demographic and access-to-care variables are beyond the scope of this chapter yet present potentially modifiable factors to decrease incidences of high-risk VLBW births and the associated risks should cardiac surgical correction be indicated. Furthermore, early postnatal access to high-quality care is essential to avoid the exponentiated risk of surgical correction that is assumed with multisystem organ failure preoperatively. As we embark on an era of surgical advancement and early surgical correction, a standardized, well-controlled, and prospective study is needed to guide both treatment and referral patterns for this high-risk group of infants with congenital heart disease.

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