New Drugs and Technologies

Current Status of Fetal Cardiac Intervention

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The potential benefits of fetal cardiac intervention (FCI) have been realized for many years. In 1975, Eibschitz et al.1 reported intrapartum treatment of fetal ventricular tachycardia by administering propranolol to the mother, and as early as 1986, in utero pacing was attempted for complete heart block in a human fetus.2 Recently, however, interest in tachycardia by administering propranolol to the mother, and FCI has accelerated.3–18 As with other fetal interventions, pharmacological therapy, most often for fetal arrhythmia or cardiomyopathy, is available orally by the mother with transplacental passage of cases.

This review will touch on all of these topics, with a focus on evidence regarding pharmacological and surgical FCI as well.

Pharmacological FCI

The first reported and most entrenched mode of FCI is pharmacological FCI. Over the years, most antiarrhythmic agents have come into more common use recently, including sotalol, amiodarone, and flecainide. Transplacental delivery of some drugs is impaired in the setting of hydrops, and supraventricular tachycardia may be refractory to other reasons as well. In such circumstances, intravascular administration and/or oral agents with better placental uptake kinetics may be indicated.25,27,28 Direct administration, usually by percutaneous umbilical venous injection, introduces the risks of cordocentesis and is reserved for high-acuity refractory cases.

Fetal Tachyarrhythmias

Pharmacological FCI was first described by Eibschitz et al.,1 who treated fetal tachycardia with propranolol in 1975. Maternal digoxin was first used to treat fetal supraventricular tachycardia several years later.23 Fetal supraventricular tachycardia, most often atrioventricular (AV) reentry or atrial flutter, probably remains the most common indication for pharmacological FCI. Over the years, most antiarrhythmic agents have been used to treat fetal supraventricular tachycardia.23–29 Digoxin has been a mainstay of therapy; other agents have come into more common use recently, including sotalol, amiodarone, and flecainide. Transplacental therapy with first-line agents is usually effective in nonhydropic fetuses, but outcomes remain suboptimal, with fetal death in ≈10% of cases overall and a higher percentage of fetuses with hydrops.27,28

The optimal therapeutic strategy for fetal supraventricular tachycardia has not been determined in a standardized trial, and practice varies. The indications for therapy may depend on fetal age and disease severity. When hydrops is present, pharmacological FCI may help as a bridge to delivery and postnatal treatment. In preterm fetuses, sustained tachycardia should probably be treated regardless of cardiac dysfunction or hydrops, because these sequelae can develop rapidly. For intermittent tachycardia, treatment is generally unnecessary, unless hydrops or cardiac dysfunction is evident. Transplacental delivery of some drugs is impaired in the setting of hydrops, and supraventricular tachycardia may be refractory for other reasons as well. In such circumstances, intravascular administration and/or oral agents with better placental uptake kinetics may be indicated.25,27,28 Direct administration, usually by percutaneous umbilical venous injection, introduces the risks of cordocentesis and is reserved for high-acuity refractory cases.

Fetal Bradycardia

Sustained fetal bradyarrhythmia may be caused by sinus node dysfunction, long-QT syndrome, AV block, or fetal distress with acidosis. The most common fetal bradycardia and the primary indication for FCI is high-grade AV block. The potential consequences of fetal AV block are cardiomyopathy...
and hydrops. AV block in the fetus generally occurs in association with either maternal autoimmune disease, malformation syndromes such as heterotaxy, or L-loop transposition of the great arteries.29–32

Autoimmune fetal AV block can be treated with maternal administration of dexamethasone and/or sympathomimetic agents.29–32 Several recent multicenter studies found that transplacental dexamethasone did not reverse high-grade block, although it may have prevented the progression of first-degree block to second- or third-degree block, and it was associated with a higher risk of premature birth and growth restriction.29,30 Other studies reported that dexamethasone, typically in association with β-adrenergic agonists when significant bradycardia was present, improved the overall prognosis in fetuses with autoimmune AV block.31,32 Sympathomimetic agents may increase the heart rate in fetuses with bradycardia due to AV block or sinus node dysfunction, but they do not restore AV synchrony.29–32 It is unclear whether in utero β-adrenergic stimulation improves outcome, because the postnatal management of AV block associated with complex congenital heart disease is challenging under any circumstances.

**Fetal Hydrops Due to Other Cardiac Causes**

Transplacental treatment with digoxin has also been described for fetal hydrops resulting from other conditions, including structural anomalies (eg, Ebstein’s anomaly, absent pulmonary valve syndrome), right heart dysfunction from left heart disease, premature closure of the ductus arteriosus, intrauterine myocardial infarction, cardiac tumor, cardiomyopathy, and others.24,33 These are uncommon conditions, with published reports limited to individual cases,24,33 so the efficacy of digoxin in their management is unknown.

**Maternal Hyperoxia**

Maternal hyperoxia, which affects fetal vascular function and hemodynamics, has been used to assess placental function and treat intrauterine growth retardation, but its benefits have not been established.34,35 Recently, Szwast et al36 reported using maternal hyperoxia to assess pulmonary vasoreactivity in fetuses with hypoplastic left heart syndrome (HLHS) and found diminution of the normal pulmonary arterial flow response to predict fetuses at high risk for critical atrial septal restriction after birth. Although not therapeutic, maternal hyperoxia in this application is a form of pharmacological transplacental FCI that may have implications for postnatal intervention and other methods of prenatal intervention.

**Experimental Fetal Cardiac Surgery**

Research on fetal cardiac surgery has been performed for more than 25 years.38 The major focus of investigation has been the pathophysiology of extracorporeal circulatory bypass, which is likely to be necessary for fetal cardiac surgery. In early studies, it was shown that a 1- to 1.5-kg lamb fetus could be placed on and separated from cardiac bypass reproducibly but that postbypass fetal demise was imminent.39 Further work in sheep, goats, and primates has furthered our knowledge of the pathophysiology of fetal cardiac bypass and the feasibility of fetal cardiac surgery.40–56 Survival to term can now be achieved in a high percentage of cases.50,56

**Cardiovascular and Placental Response to Extracorporeal Circulation**

The most significant response to fetal bypass when the placenta is incorporated as the oxygenator is severe placental dysfunction characterized by increased vascular resistance, reduced blood flow, and consequent impairment in fetal gas exchange, with fetal acidosis rapidly ensuing during and after bypass.59 The pathophysiology of postbypass placental dysfunction is multifactorial and includes bypass-induced production of prostanoids, endothelial dysfunction, leukocyte and complement activation, and other endogenous vasoactive and inflammatory pathways.40,45–48,51 Fetal cardiac bypass and surgery may also lead to changes on the maternal side of the placenta, with reduction in uterine arterial flow and consequent impairment of fetoplacental gas exchange.54
Fetal Cardiac Function and the Fetal Stress Response
Fetal cardiac bypass and surgery induce a significant stress response that has important effects on fetal hemodynamics independent of the placental dysfunction discussed above. The stress response stimulates a rise in endogenous fetal catecholamines, which increases total vascular resistance and cardiac afterload. Because the contractile apparatus of the fetal myocardium is immature, the heart tolerates increased afterload poorly. In ovine fetal bypass studies, survival to term was first achieved with spinal anesthesia to blunt the stress response and indomethacin to block prostaglandin synthesis. More recently, it was shown that fetal bypass leads to cardiac injury, reflected in troponin elevation and increased plasma natriuretic peptides. Calcium-handling properties of the fetal myocardium differ from the more mature state, and recent studies have started to define strategies for myocardial protection during fetal open heart surgery.

Technical Considerations for Fetal Cardiac Surgery
In experimental fetal cardiac bypass, surgical exposure, intervention, and cardiac bypass have proven technically feasible. Nevertheless, successful fetal bypass requires consideration of several technical adaptations.

Placental function during fetal bypass is altered by inclusion or exclusion of the placenta in the bypass circuit. Placental inclusion obviates the need for an extracorporeal oxygenator, which decreases contact activation of inflammatory and vasoactive mediators. On the other hand, inclusion of the high-capacitance, low-resistance placenta in the circuit requires high flow rates, which can be limited by cannula size. Placental perfusion during bypass also causes placental endothelial damage and dysfunction, although these effects may be mitigated when bypass is performed with pulsatile rather than continuous flow, possibly owing to preserved nitric oxide production during the former.

The systemic effects of postnatal cardiopulmonary bypass are known to result in part from blood contact with artificial surfaces in the bypass circuit. Thus, miniaturization of the fetal bypass circuit has been a technical priority. For example, in fetuses undergoing cardiac bypass with a modified bypass circuit that uses an in-line axial flow pump and no maternal blood prime, placental function was preserved relative to control fetuses in which a conventional circuit was used. Despite these difficulties, models of congenital heart disease created in utero confirm the feasibility of operating on the heart of the lamb fetus with survival to full term.

Fetoscopic and Adjunctive Forms of Closed FCI
Fetoscopic access has been investigated as an approach to FCI and fetal monitoring during cardiac and noncardiac interventions. Although the relative risks of percutaneous and fetoscopic access have not been assessed, port-access uterine entry for fetoscopic FCI may carry a higher risk of premature labor than percutaneous access.

Open FCI in Humans
The first reported open FCI procedure in a human fetus was pacemaker placement for complete AV block. Subsequently, animal models were developed to evaluate pacing for fetal AV block, but this has not become a clinically viable treatment strategy, isolated human cases notwithstanding. Human FCI aided by fetoscopy and cardioscopy has also been reported, with technical success and fetal survival in several cases. We are aware of 1 open heart surgery performed in a third-trimester human fetus with tricuspid valve dysplasia, severe tricuspid regurgitation, and hydrops by Dr Frank Hanley in 2003 (personal communication, June 6, 2009). Cardiopulmonary bypass was initiated and the tricuspid valve repaired successfully, but separation from bypass was prevented by anatomic pulmonary atresia (thought to be functional atresia before surgery), and the fetus died.

Closed Fetal Cardiac Intervention
In the present review, “closed FCI” indicates mechanical interventions in which the uterus is not opened or accessed with a port ≥3 mm in diameter. In practice, closed FCI consists primarily of percutaneous interventions in which an 18- to 19-gauge needle is used to gain uterine and fetal access. The first reported case of closed FCI was a balloon aortic valvuloplasty performed in 1989. Since then, FCI has been reported in human fetuses with aortic stenosis (AS), HLHS with atrial septal restriction, pulmonary atresia or stenosis, and AV block. In 2000, we began a program for FCI, initially to treat fetal AS with evolving HLHS, then expanding to include HLHS with an intact or highly restrictive atrial septum, pulmonary atresia with an intact ventricular septum (PA/IVS) and evolving hypoplastic right heart syndrome, and structural anomalies causing hydrops. Since our first procedure, we have attempted FCI in more than 120 fetuses.

Typically, we perform FCI using a percutaneous ultrasound-guided approach with maternal and fetal anesthesia; in a minority of cases, laparotomy without hysterotomy is used to facilitate fetal imaging or access. All of the procedures we perform consist of opening an atrietic or restrictive valve or septum, and instrumentation is limited and simple, with an access cannula, a guidewire, an angioplasty balloon and/or stent, and sometimes an additional needle to enter the heart or perforate an atrietic valve or septum. With the exception of an 18-gauge curved-tip cannula that was developed specifically for FCI (SHARC Access Needle Set, ATC Technologies, Wilmington, Mass), we use off-label equipment that was designed for other applications and may limit technical options and potentially procedural feasibility.

Fetal Aortic Valvuloplasty
The most common closed FCI procedure is aortic valvuloplasty, and the primary indication for fetal aortic valvuloplasty is to alter the in utero natural history of midgestation fetal AS with evolving HLHS. Some patients with HLHS are diagnosed during the second trimester with valvar AS and a normal-sized or dilated left ventricle (LV) and evolve to HLHS over the course of gestation. In other fetuses diagnosed with AS in midgestation, left heart growth and function will remain sufficient for a biventricular outcome. Several abnormal physiological features are associated with progression to HLHS: Retrograde flow in the transverse aortic arch, severe...
LV dysfunction, monophasic and short mitral valve inflow, and left-to-right flow across the foramen ovale. Thus, one can reliably predict which midgestation fetuses with AS will evolve to HLHS. The potential benefit of FCI for evolving HLHS is that decreasing LV afterload or promoting flow through the left heart may help prevent progressive left heart dysfunction and hypoplasia over the subsequent course of gestation and, in the process, prevent evolution to HLHS.

The first known fetal aortic valvuloplasty was performed in 1989. Kohl et al. reviewed the published experience with this procedure in 2000. From 1989 to 1997, 12 cases were performed in third-trimester fetuses with AS or atresia (not midgestation AS with evolving HLHS) at 6 centers. A balloon was passed across the valve and expanded in 7 of the 12 fetuses, but only 1 of these 7 survived beyond the newborn period. This early experience highlighted several important issues, including the technical feasibility of third-trimester closed FCI, the importance of delivering the valvuloplasty balloon through an access cannula without a sharp edge, and the risk and potential consequences of fetal bradycardia.

We reported our initial experience with aortic valvuloplasty for fetal AS in 2004 and recently updated this experience. After an initial learning curve, technical success has been achieved consistently in 75% to 80% of procedures. When the valve is dilated, there is immediate improvement in flow across the aortic valve, and there may be an obvious decrease in LV size. Moderate or severe postdilation aortic regurgitation (AR) occurs in nearly 40% of technically successful procedures. As with postnatal aortic valvuloplasty, the larger the balloon–annulus diameter ratio, the higher the likelihood of significant AR, but in contrast to neonatal aortic valvuloplasty, the target ratio is 1.1 to 1.2 instead of 0.9.

After successful fetal aortic valvuloplasty, in utero aortic and mitral valve growth are improved relative to control fetuses, but there is no difference in LV short- or long-axis growth velocity. In contrast to the modest changes in left heart growth, there are clear beneficial changes in left heart physiology after fetal aortic valvuloplasty, as reported previously and updated in Table 2. Namely, after successful FCI, the left heart physiological parameters reported by Makikallio et al. to predict progression to HLHS were improved in a large majority of successfully treated fetuses but not in controls that were similar before intervention. In summary, there is solid evidence that balloon dilation of the aortic valve in fetuses with AS and evolving HLHS improves left heart physiology and leads to improved growth of the aortic and mitral valves but has no apparent effect on LV growth per se.

Ultimately, the goal of FCI for AS with evolving HLHS is to alter left heart physiology and growth sufficiently to allow postnatal survival with a healthy biventricular circulation. In our recently published experience, just over 30% of patients who underwent technically successful FCI for this indication had a biventricular circulation from birth, and another 8% were converted to a biventricular circulation after initial univentricular palliation. Patients with larger LV size and higher LV pressure at the time of intervention were more likely to have a biventricular outcome. Using multivariable analysis, we identified a cohort of patients with essentially no chance of biventricular outcome and modified our selection criteria to exclude patients who fall below a defined threshold score (Table 3). It has become clear that prenatal intervention is not a stand-alone intervention. In all cases that have gone on to biventricular outcome postnatally, postnatal interventions have been required, including repeat aortic valvuloplasty in most cases, temporary left atrial decompression, and frequently surgical intervention such as coarctation repair, resection of endocardial fibroelastosis, and mitral valvuloplasty.

Almost half of fetuses undergoing prenatal aortic valvuloplasty experience a combination of bradycardia and right ventricular dysfunction of variable severity. Fetal hemodynamic instability occurs almost exclusively in fetuses undergoing ventricular puncture (as opposed to atrial access) and may become evident either before the balloon is introduced into the ventricle, during dilation, or even after removal of equipment from the fetal heart. In our early experience, we treated this with intramuscular or intracardiac epinephrine, but we currently use a prophylactic approach, introducing epinephrine and bicarbonate through the balloon catheter at the time of intervention, regardless of whether bradycardia and right ventricular dysfunction have been identified.
subsequent treatment is necessary, intracardiac or intramuscular medication is given as well. In addition to fetal hemodynamic instability, hemopericardium is also common and may be accompanied by bradycardia. The hemopericardium is frequently small (less than ~1 to 2 mm) but may be substantially larger, in which case percutaneous drainage is attempted, usually with successful removal of fluid. In fetuses that develop hemodynamic instability or hemopericardium, treatment generally results in restoration of an adequate circulation. The pathophysiology and inciting factors for hemodynamic instability are not entirely clear but are likely the result of some combination of fetal hypoxemia and autonomic or direct response to ventricular compression and puncture.7

Despite the frequency of these hemodynamics changes, there has been only 1 death due to inability to resuscitate the fetus during the procedure and <10% fetal loss within 72 hours. Another 3 fetuses were delivered prematurely at <30 weeks’ gestation. We consider all of these deaths and premature deliveries to be related to FCI, although the mechanism of death (a large hemopericardium) was confirmed in only 1 case. There have been no maternal complications from FCI in this cohort.

The foundation for FCI in fetuses with AS and evolving HLHS is the belief that a biventricular circulation is superior to a univentricular circulation. Of course, this is not a simple dichotomous calculus, because all univentricular or biventricular circulations are not of equal functional quality.65,66 Although this determination is central to the debate about the practice of FCI, the details are beyond the scope of this review. Another potential benefit of FCI for AS, in the event that a biventricular circulation is not achieved, is a greater contribution of the left side of the heart to the functionally univentricular circulation, which may improve its efficiency and/or durability.

The risks of fetal aortic valvuloplasty for AS with evolving HLHS have not been defined completely. As noted above, we have experienced no maternal morbidity and a 10% rate of fetal death or premature delivery. Although we have seen no obvious evidence of end-organ disease or dysfunction, the potential collateral effects of FCI are unknown. We have yet to perform concerted postnatal evaluation to determine whether there are adverse neurological consequences of FCI, but a recent study found no evidence that prenatal aortic valvuloplasty significantly affected cerebral arterial flow parameters.67 All of the patients in our experience have required postnatal cardiovascular interventions, and although postnatal survival after FCI has been very good, the prenatal and postnatal risks of mortality must be considered additive regardless of whether the outcome is univentricular or biventricular.

In the final analysis, the risk-benefit analysis of FCI for evolving HLHS depends to a large extent on individual opinions about the importance of biventricular versus univentricular physiology, and it must take into account both the chronic morbidity and mortality risks of a functionally univentricular circulation and the unknown longer-term risks of a biventricular circulation after FCI. The robustness and health of a biventricular circulation can vary, and the presence of multilevel left heart disease may significantly impact the health of a biventricular circulation. Thus, any risk-benefit analysis before FCI is necessarily speculative and based on the limited available data, as well as being situated in the context of evolving management options and outcomes in patients with both univentricular and biventricular heart disease.

**Fetal HLHS With Intact or Highly Restrictive Atrial Septum**

Although neonatal survival in infants with HLHS continues to improve, outcomes among certain subsets of patients remain poor; one of the strongest risk factors for early mortality is an intact or highly restrictive atrial septum.68,69 Although limited pulmonary venous egress may be well tolerated in utero, neonates with major septal restriction are at substantially higher risk of death than those without.67,68 There are 2 primary problems associated with this condition: (1) Profound hypoxemia after birth due to restricted outflow from the pulmonary veins, which results in little effective pulmonary blood flow, and (2) chronic pulmonary venous hypertension in utero due to restriction to left atrial outflow, which results in pulmonary venous thickening68 and perioperative morbidity and mortality. Thus, even if postnatal opening of the atrial septum is rapid and effective, damage to the pulmonary vasculature may contribute to further mortality in the first few weeks or months of life.

In fetuses with HLHS and an intact atrial septum, FCI may improve both of the major problems posed by the restriction of pulmonary venous outflow. If the left atrium can be decompressed before birth, the profound perinatal hypoxemia and acidosis and their associated morbidities may be prevented. If left atrial decompression can be achieved sufficiently early in gestation, adverse pulmonary venous remodeling may also be prevented. Physiologically, the earliest possible treatment of left atrial hypertension on diagnosis of atrial septal restriction should maximize the benefit of normalizing the developmental conditions for the pulmonary vasculature. In our experience, however, there are technical limitations to creating a large interatrial defect in the second trimester. Thus, for logistical reasons, we have focused on creating a large atrial communication. Given the currently available technological options, this can be pursued more aggressively in older and larger fetuses, and we thus tend to wait until the early-to-mid third trimester to perform this procedure. At the same time, we continue to search for technical and technological innovations that will allow earlier effective atrial septal opening.

We recently reported our experience with FCI in 21 fetuses with HLHS and an intact or highly restrictive atrial septum.9 Prenatal atrial septostomy for this condition has also been reported by others with various monitoring and interventional approaches.10,11 In our experience, the atrial septum was crossed and an interatrial communication created in all cases, either with balloon dilation or placement of a stent. Fetal demise occurred in 2 cases; in both of these, a significant hemopericardium was noted at the conclusion of the procedure. Among neonates delivered after FCI for HLHS with significant atrial septal restriction, surgical survival remains
quite poor (58%); however, in utero creation of an atrial septal defect does appear to have some benefit in terms of preoperative management, because neonates with an interatrial defect ≥3 mm after FCI had higher oxygen saturation at birth and were less likely to need urgent postnatal left atrial decompression. Although assessment of any postnatal survival benefit of FCI in patients with HLHS and an intact atrial septum will require more extensive experience, the potential to avert immediate postnatal deterioration has been demonstrated, and we consider FCI indicated for the comprehensive management of these high-risk fetuses.

**Fetal Pulmonary Atresia With Evolving Hypoplastic Right Heart**

PA/IVS occurs as a spectrum of hypoplastic right heart disease, with cases at the mild end of the spectrum amenable to biventricular repair and those with more severe right heart hypoplasia managed with univentricular palliation or transplantation. In newborns with PA/IVS, the likelihood of a biventricular outcome can be estimated from the Z-score of the tricuspid valve annulus, with a Z-score above −3 associated with biventricular outcome and below −3 with univentricular palliation. Prior work from our center found that the tricuspid valve Z-score in fetuses with PA/IVS can also be used to assess ultimate anatomic suitability for a biventricular outcome.

The potential role of FCI in fetuses with PA/IVS is to promote right heart growth and functional development and increase the chance of a biventricular circulation after birth. Identification of potential candidates for FCI for PA/IVS should be based on the risk of progression to a functionally univentricular circulation postnatally without FCI and the possibility of altering that progression prenatally. There is limited information about predictors of postnatal outcomes in fetuses with PA/IVS. Both anatomic and physiological characteristics are likely to be important, but many patients are in the middle of the severity spectrum, and postnatal management strategy plays an important role in the ultimate outcome.

Cases of third-trimester fetal pulmonary valvuloplasty have been reported by other groups. Since 2002, we have offered FCI for selected midgestation fetuses with PA/IVS and evolving hypoplastic right heart. Our preliminary experience included 11 cases. The first 4 procedures were technically unsuccessful, but the subsequent 7 were successful. There were no fetal deaths or major complications, aside from bradycardia that resolved with treatment, and no maternal complications. On the basis of this limited experience, it appears that prenatal pulmonary valve perforation and dilation may be performed successfully in midgestation fetuses, with maintenance of valvar patency throughout gestation and apparently improved growth of right heart structures. The effects of this strategy on right heart functional development and postnatal outcome remain to be determined. Because postnatal outcomes for the majority of patients with PA/IVS are usually favorable, it may be more of a challenge to appropriately select patients and demonstrate effectiveness than for the previously discussed anomalies.

**Future Directions**

There is much that remains to be learned about the benefits and potential adverse effects of FCI. Although pharmacological FCI is well established in the management of fetal arrhythmias and heart block, there is room for improvement nonetheless. In addition, novel pharmacological strategies, such as maternal hyperoxia, and the prospect of other agents for other conditions will inevitably emerge. On the basis of the experimental evidence, open FCI appears feasible, although the indications for and establishment of open FCI in humans must be explored critically. There are severe congenital cardiac anomalies for which more complex interventions may be beneficial, such as severe Ebstein’s malformation with fetal hydrops.

Since our first procedure in 2000, referrals for closed FCI have grown steadily, with more than 90% of prospective and actual patients coming from outside our usual geographic catchment. Ultimately, the utility of FCI will depend on a variety of clinical and technological factors, including more frequent, earlier diagnosis of congenital heart disease in utero, characterization of prognostic features in fetuses with congenital heart disease, better understanding of the capacity and optimal gestational windows for cardiovascular remodeling after FCI, and improved and focused technology. Advances in imaging and instrumentation should facilitate greater precision and effectiveness of intervention and may open the door to procedures for more complex indications. More sophisticated image-guided or robotic interventional approaches to closed FCI are being explored and may help improve precision and success, potentially shifting the gestational horizon to allow safe intervention in younger fetuses. At the same time, as experience with FCI accumulates, risk profiles can be expected to improve, which may facilitate FCI for less severe conditions if such procedures can be expected to improve outcomes.

**Disclosures**

Dr Lock holds a patent on the SHARC access needle set.

**References**


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