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Contemporary Outcomes of Patients with Isolated Bilateral Renal Agenesis with and without Fetal Intervention

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Abstract
Introduction: Bilateral renal agenesis (BRA) is a lethal diagnosis, specifically meaning that natural survival beyond birth is not expected secondary to pulmonary hypoplasia. Limited contemporary data are available about intervention and the impact of restoring amniotic fluid volume in relation to the risk for lethal pulmonary hypoplasia and other factors that might influence survival in cases of fetal BRA. ***Objective:*** We report the largest series of patients undergoing fetal intervention and postnatal care for BRA at a single comprehensive fetal center. ***Methods:*** All patients with fetal BRA were reviewed from January 2004 to November 2017. Maternal and neonatal data were collected in an institutional review board-approved retrospective review. ***Results:*** From 2014 to 2017, 20 singleton pregnancies with isolated fetal BRA were evaluated and 14 had amnioinfusion. Eight had serial infusions. Of those, there were 6 neonatal deaths. There were 2 neonatal survivors beyond 30 days; however, both died of sepsis on dialysis. One of these survivors received amnioinfusions by percutaneous approach and one via amnioport. There were no survivors to transplantation. ***Conclusion:*** Fetal intervention via amnioinfusion may promote pulmonary survivorship after birth, but postnatal survival remains poor. Future studies must place an emphasis on standardizing the postnatal approach to this patient population.

Introduction

Bilateral renal agenesis (BRA) is a rare condition occurring in approximately 3 per 10,000 live births, but may be present in up to 10 times the number of all pregnancies when considering rates of spontaneous abortion and fetal demise [1, 2]. It is universally published that BRA is a lethal diagnosis, specifically meaning that natural survival beyond birth is not expected secondary to pulmonary hypoplasia. Limited contemporary data are available about intervention and the impact of restoring amniotic fluid volume in relation to the risk for lethal pulmonary hypoplasia and other factors that might influence survival in cases of fetal BRA. The goal of fetal intervention is to promote adequate pulmonary development such that lethal

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pulmonary hypoplasia is averted. Biologic plausibility exists, largely derived from data from other models of oligohydramnios, such as preterm prolonged premature rupture of membranes [3, 4].

There is 1 published case report of survival after serial amnioinfusions with subsequent peritoneal dialysis and transplantation [5] and 1 recently published case report of survival to 4 years of age in an infant born with coincident duodenal atresia that helped to preserve a normal amniotic fluid volume [6]. There have been a series of reports of monoamniotic twins discordant for BRA who achieved pulmonary survival, likely due to fluid preservation by the co-twin [7–10]. To our knowledge, however, the previously cited case report is the only survivor of BRA that has achieved successful transplantation. Nevertheless, many questions remain regarding the safety, feasibility, and effectiveness of fetal intervention for BRA. Furthermore, with newborn survival, a complicated course of renal replacement therapy ensues which introduces a number of additional obstacles that must be overcome prior to receiving a kidney transplant. In this paper, we aim to provide the largest case series of isolated fetal BRA to date. We report outcomes on those with and without antepartum amnioinfusions.

Table 1. Characteristics of pregnancies in era of fetal intervention (n = 20)

Termination following evaluation	2 (10)
Fetal demise	4 (20)
Intervention prior to presentation[1]	1 (5)
Gestational age at rupture of membranes, weeks	32.5 (29–35)
Gestational age at delivery, weeks	33.5 (29–35)
Birth weight, g	1,685 (1,222–1,922)
Cesarean delivery	7 (35)
Delivery at Fetal Center facility	5 (25)
Intervention at Fetal Center	14 (70)
Single amnioinfusion	6 (30)
Serial amnioinfusion – percutaneous[2]	7 (35)
Serial amnioinfusion – amnioport[2]	2 (10)
Complications of fetal intervention (can be multiple)	
Unable to complete procedure	2
Chorioamniotic separation	7
PPROM <37 weeks	3
Chorioamnionitis	
Fetal bradycardia	1
Placental abruption	0
Delivery indication (can be multiple)	
Preterm labor	10
Placental abruption	1
Chorioamnionitis	3
Non-reassuring fetal status	3
Term	1
Placenta previa	1

Data are presented as n (%) or the median (IQR). PPROM, preterm premature rupture of membranes.

[1] Multiple percutaneous amnioinfusions.

[2] One patient received amnioinfusions via both serial percutaneous and amnioport.

Materials and Methods

A retrospective review of all cases referred to our tertiary center for evaluation of isolated fetal BRA from January 2004 to November 2017 was conducted. The data source utilized to identify patients were the Fetal Center database, for which patients give informed consent to maintain records. The electronic medical record was then queried to obtain complete data for each mother/infant dyad. The study was approved by the institutional review boards at each site.

Patients who met diagnostic criteria for isolated fetal BRA were included. The diagnosis was defined as ultrasonographic and/or MRI evidence of bilateral absence of renal tissue and no additional anomalies on prenatal imaging. Amnioinfusion prior to prenatal imaging was not universally performed. Patients received multidisciplinary consultation with a team of providers including representatives from pediatric and maternal specialties. Maternal Fetal Medicine, Neonatology, Pediatric/Fetal Surgery, Nephrology, Urology, Genetics, Palliative Care and Transplant Surgery all participate in the prenatal consultations. A medical ethicist provides oversight to the program along with our institutional Oversight Committee. Following extensive counseling and genetic diagnostic work up, patients are presented with pregnancy management options, including expectant management of the pregnancy or fetal interventions. Fetal intervention was offered in cases when the patients strongly desired intervention versus expectant management and had chosen not to electively terminate the pregnancy. Comprehensive medical, obstetrical, and social histories were collected. Physical examination and medical record reviews were performed. Genetic analysis included cell-free fetal DNA and/or amniocentesis for FISH, karyotype, or microarray. Three patients did not have genetic testing sent; all other patients had normal genetic testing at the time of fetal therapy evaluation. Data were extracted by chart review for patient demographics, gestational age at evaluation and intervention, intervention(s) performed, maternal and neonatal medical diagnoses, medical course, surgical interventions, imaging, disposition, and dates of follow-up visits/admissions.

Patients received extensive counseling and gave informed consent for fetal amnioinfusion. Serial amnioinfusions were performed at least once weekly and done either by percutaneous route or via amnioport from 18 until 34 weeks. Two patients received amnioinfusion with local care providers outside of the study institution at some point in the pregnancy. Their practices were not able to be reconciled for the purposes of this report.

Percutaneous Methods

A 20-G needle was inserted under ultrasound guidance through the abdomen into the amniotic space by an experienced fetal med-

Table 2. Infant characteristics and outcomes for those choosing fetal intervention (n = 8)

Female sex	3 (38)
Attempted resuscitation	7 (88)
Survival >7 days	3 (38)
Required intubation in delivery room	4 (50)
Required intubation in first 48 h	7 (88)
Pneumothorax	4 (50)
Pulmonary hypertension	1 (13)
Hypotension requiring vasopressors	3 (38)
Dialysis ever (could receive both)	3 (37.5)
Hemodialysis/aquapheresis	2 (66.7)
Peritoneal	3 (100)
Dialysis started, day of life	3±1.4
Complications of dialysis	3 (100)

Data are presented as n (%) or the mean ± SD.

icine specialist trained in invasive procedures. Proper placement was assured by ultrasound evidence of free-floating fluid with no evolving chorioamniotic separation. Subsequently, isotonic crystalloid solution was injected manually under continuous ultrasound monitoring. The required volume was calculated by multiplying the gestation in weeks by 10 mL and/or achieving a deepest vertical pocket between 5 and 7 cm. Following the procedure, the single deepest pocket was remeasured. Complications that occurred within 24 h of the procedure and through the remainder of the pregnancy were recorded.

A second method of amnioinfusion is via surgically placed amnioport [11]. This technique has been described elsewhere. Intravenous or intra-amniotic antibiotics were not routinely utilized at the time of amnioinfusion. Patients were followed weekly by ultrasound until delivery. Antenatal surveillance was started based on clinical discretion of fetal viability for dialysis feasibility (estimated fetal weight of 1,800–2,000 g). The timing of delivery was targeted at 37 weeks unless indicated earlier. All patients who chose an aggressive route of fetal intervention or neonatal care were delivered in a level III NICU setting. The mode of delivery was planned as spontaneous vaginal delivery unless cesarean section was indicated as per the obstetric standard.

Neonatal care proceeded following extensive prenatal counseling regarding resuscitation at delivery and goals of care. Weight-based criteria exist at our center for dialysis (>1,800 g), and additionally without coexisting anomalies that would require postnatal abdominal surgical intervention, thereby making peritoneal dialysis not feasible. Respiratory care was according to the discretion of the neonatal team, but included trial of intubation, mechanical ventilation with conventional or high-frequency oscillatory ventilation, surfactant if clinically appropriate, and evacuation of pneumothoraces. Cardiovascular, nutritional, and other care occurred by clinical discretion. Placement of peritoneal dialysis and/or hemodialysis catheters occurred once sufficient clinical stability had been achieved such that pulmonary survivorship was established. Data were collected on neonatal resuscitation, survival, early and late morbidities including hemodynamic instability, pulmonary hypertension, infection/sepsis, growth failure, dialysis feasibility, and complications. Autopsy results were reviewed in the few cases where available. For infants not cared for in our institution, review of their medical records occurred with HIPPA consent from the families to obtain these records. As there is no uniform clinical definition of pulmonary hypoplasia, for the purposes of this report, it was defined as either lethal or non-lethal based on survival past 7 days of life.

Statistical Analysis

Descriptive statistics consisted of counts and percentages for categorical variables, means and standard deviations (or medians and IQR when appropriate) for continuous variables utilizing STATA version 15 (StataCorp, College Station, TX, USA) to conduct analyses.

Results

Between 2004 and 2017, we evaluated 47 patients with fetal BRA. No amnioinfusions for the purpose of intervention were done until 2014, and no aggressive neonatal interventions were offered before that time. From 2014 to 2017, 20 patients with singleton pregnancies and isolated fetal BRA were evaluated (Table 1). Initial CFC evaluation occurred at a median of 21 weeks (IQR 21–24). Maternal characteristics included a median age of 25 years (IQR 22.5–32.5), median BMI of 29.2 (IQR 24.8–38.9), and 35% nulliparity (7/20). In the cohort of 20 patients from 2014 to 2017, 2 patients had termination following evaluation, 8 chose aggressive fetal intervention, and 10 patients chose expectant management. Among those 10 patients who elected expectant management, 6 had a single infusion for genetic testing and imaging (ultrasound and MRI) but pursued no further fetal intervention. The natural history of those who chose expectant management included a high intrauterine or intrapartum demise rate (40%), and the remaining 6 with early neonatal demise. Nine were delivered vaginally and at a median gestational age of 32.9 weeks.

Eight patients chose aggressive fetal management via serial infusions to promote lung maturation. Seven families chose to pursue aggressive neonatal interventions (Table 2) and one family chose comfort care due to extreme prematurity. Patients who chose serial amnioinfusion received between 3 and 26 infusions (median 11.4, IQR 7–14). Six patients had amnioinfusions via the percutaneous route, 1 via amnioport, and 1 via both amnioport and percutaneous routes. A total of 98 infusions were performed on these 8 patients. The most frequent obstetric complications seen were chorioamniotic separation and premature rupture of membranes; the maternal complications are described in Table 1. Initial amnioinfusion was

Table 3. Characteristics of maternal and neonatal patients undergoing serial amnioinfusion

Patient No.	GA at CCHMC evaluation, weeks	AI total, *n*	Route of AI	GA first AI[1], weeks	GA last AI, weeks	Duration of AI, weeks	Complications	Delivery indication	GA at delivery, weeks (delivery route)	Neonatal complications	Max. pulmonary support	Cause of death	Received dialysis	Age at death
1	26.0	8	Perc	25.9	Unk.		Single AI with fluid infused into SQ space	Placenta previa	36.9 (CS)	Sepsis	MV	Sepsis	PD	33 days
2	26.1	14	Both	26.0	33.3	7.3	CAS, migration of port tubing	Fetal distress, IUGR	36.3 (CS)	Severe SGA status, bilateral pneumothorax	HFOV	PH	No	<24 h
3	19.1	7	Perc	19.0	30.0	11	CAS, PPROM	Fetal distress	34.0 (CS)		DR demise	PH	No	<24 h
4	19.6	3	Perc	19.4	23.4	4	CAS, PTL, chorioamnionitis	Chorio, PTL	23.7 (SVD)	Comfort care due to extreme prematurity		Prematurity	No	<24 h
5	23.9	24	Port	24.9	32.7	7.8	PROM with resealing, PTL	PTL	33.4 (CS)	Bilateral pneumothorax, hypotension, PHTN, peritonitis, sepsis	MV	Sepsis	HD, PD	187 days
6	20.3	3	Perc	22.6	Unk.		CAS, single AI with fluid infused into SQ space, chorioamnionitis	Chorio, PTL	29.6 (CS)	Prematurity, pneumothorax, hypotension, PD catheter complication	MV	Dialysis complications	HD, PD	11 days
7	26.0	26	Perc	22	34.9	12.9	CAS, amniotic fluid culture positive	Presumed chorio	36.0 (SVD)	Hypotension	MV	Cardiovascular instability	No	<48 h
8	24.9	13	Perc	24.7	33.6	8.9	Fetal bradycardia	Fetal distress	33.6 (CS)		DR demise	PH	No	<24 h

CCHMC, Cincinnati Children's Hospital Medical Center; AI, amnioinfusion; GA, gestational age; Perc, percutaneous; Port, amnioport; Unk., unknown; CAS, chorioamniotic separation; PPROM, preterm premature rupture of membranes; PTL, preterm labor; IUGR, intrauterine growth restriction; CS, cesarean section; SVD, spontaneous vaginal delivery; SQ, subcutaneous; SGA, small for gestational age; HD, hemodialysis; PD, peritoneal dialysis; PH, pulmonary hypoplasia; PHTN, pulmonary hypertension; MV, mechanical ventilation; HFOV, high-frequency oscillatory ventilation; DR, delivery room.

[1] Some AI was performed at initial imaging or with initial provider.

performed at a median of 22 weeks gestation (IQR 21–24). The last amnioinfusion ranged from 23 to 34 weeks, with a median latency of 8.5 weeks from initiation. The volumes of fluid instilled varied based on imaging parameters with a median of 250 mL per infusion (IQR 200–320). Procedure complications included 63% chorioamniotic separation, 25% premature rupture of membranes, 37.5% chorioamnionitis, with displacement of amnioport tubing in 1 patient. All were delivered <37 weeks of gestation at a median of 33.8 weeks, 75% via cesarean section. The most common indications for delivery were preterm labor, chorioamnionitis, and a non-reassuring fetal status (Table 1).

Despite attempts at aggressive management in 7/8 cases, no neonates survived to hospital discharge. The neonatal and infant outcomes are summarized in Tables 2 and 3. The rate of early neonatal demise (<48 h) was 57% (4/7). These patients died within the first 48 h due to cardiopulmonary failure: 1 with intractable hypotension and non-lethal pulmonary hypoplasia, 2 with lethal pulmonary hypoplasia, and 1 with early death due to lethal pulmonary hypoplasia and weight below the threshold for dialysis feasibility.

Overall, 3/8 (38%) patients with aggressive intervention survived more than 48 h, and all survived longer than 7 days. In 3 of the neonates who had undergone serial amnioinfusions, lung disease was present but determined to be non-lethal; however, initiation or continuation of renal support was difficult or impossible due to an unstable hemodynamic status. These 3 patients achieved sufficient stability to undergo dialysis catheter placement. Two patients received some form of modified hemodialysis, while all 3 received peritoneal dialysis. One infant died following the withdrawal of support at 11 days of life after birth at 29 1/7 weeks secondary to a leaking PD catheter without surgical options. Two infants survived beyond 30 days, but both required prolonged mechanical ventilation for >30 days. Both patients died of sepsis following the initiation of peritoneal dialysis, at 33 and 187 days of life. Both had chosen serial amnioinfusions; 1 by a percutaneous approach and 1 via amnioport. Both patients surviving more than 30 days experienced complications associated with dialysis, which remains a significant limitation to successful bridge to transplantation.

Discussion

Despite advances in the field of fetal medicine, a fetal diagnosis of BRA nearly always leads to perinatal or early neonatal death. With improving neonatal renal replace-

ment technology and the ability to reduce the risk of lethal pulmonary hypoplasia in other analogous situations [12–14], it becomes an appealing prospect to offer fetal interventions based on a rational and ethical approach. We report a case series of BRA patients that underwent serial amnioinfusion in attempt to restore amniotic fluid. Despite its presumed benefit, this procedure was associated with significant obstetrical complications, prematurity, and limited neonatal survival due to cardiopulmonary failure, dialysis complications, and infection. Considering this limitation, interventions for BRA should be limited to prospective studies.

The maternal implications of any fetal intervention cannot be minimized. As in many fetal therapies, the mother takes on the entirety of risk with no medical benefit other than the psychological benefits that may result from a favorable outcome. The most frequent obstetric complications seen were chorioamniotic separation and premature rupture of membranes. Many women pursuing fetal intervention also required delivery via cesarean section, a risk to the index and future pregnancies. The number of complications related to amnioinfusion seen in our population are significant and require adequate counseling in regard to maternal safety. In this regard prospective research is needed to provide guidance to the optimal management, including the timing and frequency of infusions, as this has implications with respect to both maternal and fetal/neonatal risk.

An internationally recognized definition of pulmonary hypoplasia does not exist. Rather, a diagnosis is made by eliminating other possible causes of symptoms. Congenital pneumonia, neonatal respiratory distress syndrome, and pulmonary hypoplasia may occur simultaneously and have overlapping symptoms. While postmortem diagnosis is not uniform throughout the literature, the criteria are more objective than those for infants who survive. All of the patients described in our series experienced some degree of pulmonary hypoplasia, due to renal oligohydramnios and/or prematurity. Difficulty exists in the definition as contributions of prematurity and potential infection such as chorioamnionitis and congenital pneumonia cannot be clearly differentiated. We propose that the critical differentiation in these cases is whether this lung disease is lethal or not, hence our decision to categorize as such for the purpose of this report. Other goals for registries and prospective study would be creation of standardized definitions and criteria for diagnosis and treatment of pulmonary hypoplasia, as well as identification of imaging or biomarkers of severity of lung disease and patient survival. Because survival is so rare, it follows that there is no consideration to the other facets of supportive neonatal care, such as nutritional, cardiovascular, pulmonary, hematologic, and gastrointestinal. These programs also remain uninvestigated in large part. The growing interest in true investigation by the NICHD [15] and reputable perinatal centers is encouraging, and our hope is that it will be supported.

Our experience has shown us that even when pulmonary disease can be mitigated or improved, there remain barriers that limit long-term renal support and survival. Unfortunately, none of the current fetal therapies can impact the ability to achieve normal growth trajectories and abdominal capacity, which are limitations in dialysis and transplant. In our population, the most common neonatal morbidities in those deemed to be pulmonary survivors were complications of dialysis and cardiovascular instability. We have previously reported our experience with cardiorespiratory features that complicate the ability of these patients to survive the first days of life, including intractable hypotension [16]. Despite clinical investigation in a number of these cases, no clear etiology has been found. Speculation regarding relative adrenal insufficiency and abnormalities of the renin-angiotensin pathway remain unproven. Of great concern and interest based on our experience is the risk of infection for the infant receiving peritoneal dialysis, as well as the feasibility of dialysis when other abdominal surgery is necessary. Some authors counter the conventional wisdom concerning inability to perform peritoneal dialysis in the face of abdominal surgery for bowel abnormalities [6], but this is not yet the standard of care in our center. Large prospective registries currently follow outcomes of infants and children undergoing peritoneal dialysis, and the worst outcomes of survival and complications are seen in those starting dialysis within the first weeks of life [17]. The prospective studies and registries will potentially provide material for novel research.

A single report remains the only contemporary case of serial amnioinfusions for promotion of pulmonary development; however, very few details were provided regarding the complicated neonatal course that allowed the child to reach a point of stability and growth to allow for transplantation. A recent gathering of experts in the field provided opportunity for anecdotal reports of survival [18]. The conclusions of the symposium authors and others consider purposeful intervention in cases of BRA to be experimental, with performance occurring within the context of formal research studies [15, 18]. Currently, investigators in the North American Fetal Therapy Network collaborative have initiated a prospective study en-

rolling patients whose fetuses have BRA; however, this is specifically geared towards maternal safety of amnioinfusions and the ability to successfully perform neonatal dialysis. We believe that further efforts should focus on optimizing the neonatal approach to care with specific attention to hemodynamic management and the frequency of life-threatening infections in this population, and we support further study in a multicenter collaborative. At this time, due to the poor survival seen in our center's experience with BRA, fetal interventions have been suspended until we are better able to establish a comprehensive neonatal approach and more robust technology for neonatal dialysis.

Conclusion

Historically, a fetal diagnosis of BRA overwhelmingly resulted in no intervention for the affected fetus as there was no means to provide renal support needed from the time of birth. Our experience has not demonstrated a significant paradigm shift in this regard. There is some suggestion that serial amnioinfusions may promote pulmonary survivorship, though with no long-term survivors this is difficult to assess. While we agree that any further treatment of this population should only be performed with careful institutional review board and ethical oversight, any future studies should focus more on standardizing the approach to the neonatal care of these infants.

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Statement of Ethics

Our research complies with the guidelines for human studies and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the institution's committee on human research (IRB), approval 2017-0401. A waiver of informed consent was granted by the Cincinnati Children's Hospital IRB.

Disclosure Statement

Paul Kingma is a paid consultant for Airway Therapeutics Inc. No work related to Airway Therapeutics was included in the present study. The other authors have no conflicts of interest to declare.

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Author Contributions

S.R.: substantial contributions to the conception and design of the work, acquisition, analysis, and interpretation of data, drafting the work and critical revision. M.H. and S.T.: substantial contributions to the conception and design of the work, the analysis and interpretation of data, and made significant contributions to drafting the work and critical revision. F.Y.L. and P.K.: substantial contributions to the conception and design of the work, the interpretation of data, and made significant contributions to critically revising the work. M.M.: substantial contributions to the acquisition and interpretation of data for the work, revising it critically for important intellectual content. W.P.: substantial contributions to the conception and design of the work, the analysis and interpretation of data, revising it critically for important intellectual content. All authors approve of the version to be published and agree to be accountable for all aspects of the work.

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