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Neonatal Survival After Serial Amnioinfusions for Bilateral Renal Agenesis

The Renal Anhydramnios Fetal Therapy Trial

Jena L. Miller, MD, [1] Ahmet A. Baschat, MD, [1] Mara Rosner, MD, MPH, [1] Yair J. Blumenfeld, MD, [2] Julie S. Moldenhauer, MD, [3] Anthony Johnson, DO, [4] Mauro H. Schenone, MD, [5] Michael V. Zaretsky, MD, [6] Ramen H. Chmait, MD, [7] Juan M. Gonzalez, MD, MD, PhD, [8] Russell S. Miller, MD, [9] Anita J. Moon-Grady, MD, [10] Ellen Bendel-Stenzel, MD, [11] Amaris M. Keiser, MD, [12] Radhika Avadhani, DrPH, [13] Angie C. Jelin, MD, [14] Jonathan M. Davis, MD, [15] Daniel S. Warren, PhD, [16] Daniel F. Hanley, MD, [13] Joslynn A. Watkins, MPH, [17] Joshua Samuels, MD, MPH, [18] Jeremy Sugarman, MD, MPH, MA, [19] and Meredith A. Atkinson, MD, MHS[17]

[1]Center for Fetal Therapy, Department of Gynecology and Obstetrics, Johns Hopkins University, Baltimore, Maryland
[2]Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, California
[3]Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
[4]The Fetal Center, Department of Obstetrics and Gynecology, University of Texas Health Center, Houston
[5]Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota
[6]Colorado Fetal Care Center, Children's Hospital of Colorado, Aurora
[7]Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles
[8]Department of Obstetrics and Gynecology, University of California, San Francisco
[9]Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, New York
[10]Division of Cardiology, Department of Pediatrics, University of California, San Francisco
[11]Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota
[12]Division of Neonatology, Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland
[13]Division of Brain Injury Outcomes, Johns Hopkins University, Baltimore, Maryland
[14]Division of Maternal-Fetal Medicine, Department of Gynecology and Obstetrics, Johns Hopkins University, Baltimore, Maryland
[15]Tufts Clinical and Translational Science Institute, Division of Newborn Medicine, Tufts Children's Hospital, Tufts University, Boston, Massachusetts
[16]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland
[17]Division of Pediatric Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland
[18]Division of Pediatric Nephrology and Hypertension, McGovern School at the University of Texas Health Science Center, Houston
[19]Berman Institute of Bioethics, Johns Hopkins University School of Medicine, Baltimore, Maryland
Corresponding author.

Article Information

Corresponding Author: Meredith A. Atkinson, MD, MHS, Division of Pediatric Nephrology, Johns Hopkins University School of Medicine, 200 N Wolfe St, Room 3064, Baltimore, MD 21287 (matkins3@jhmi.edu).

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Drafting of the manuscript: J. Miller, Baschat, Blumenfeld, Schenone, Chmait, R. Miller, Keiser, Avadhani, Hanley, Watkins, Atkinson.

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Key Points

Question

In pregnancies complicated by anhydramnios due to fetal bilateral renal agenesis, do serial amnioinfusions instituted before 26 weeks' gestation mitigate lethal pulmonary hypoplasia in neonates?

Findings

In this nonrandomized clinical trial, 82% of live-born infants survived to 14 days of life or longer and placement of dialysis access, but longer-term neonatal survival was reduced. Serial amnioinfusions were not associated with severe maternal complications.

Meaning

Prenatal serial amnioinfusions can mitigate neonatal lethal pulmonary hypoplasia in neonates with bilateral renal agenesis, but infants face substantial morbidity independent of lung function.

Abstract

Importance

Early anhydramnios during pregnancy, resulting from fetal bilateral renal agenesis, causes lethal pulmonary hypoplasia in neonates. Restoring amniotic fluid via serial amnioinfusions may promote lung development, enabling survival.

Objective

To assess neonatal outcomes of serial amnioinfusions initiated before 26 weeks' gestation to mitigate lethal pulmonary hypoplasia.

Design, Setting, and Participants

Prospective, nonrandomized clinical trial conducted at 9 US fetal therapy centers between December 2018 and July 2022. Outcomes are reported for 21 maternal-fetal pairs with confirmed anhydramnios due to isolated fetal bilateral renal agenesis without other identified congenital anomalies.

Exposure

Enrolled participants initiated ultrasound-guided percutaneous amnioinfusions of isotonic fluid before 26 weeks' gestation, with frequency of infusions individualized to maintain normal amniotic fluid levels for gestational age.

Main Outcomes and Measures

The primary end point was postnatal infant survival to 14 days of life or longer with dialysis access placement.

Results

The trial was stopped early based on an interim analysis of 18 maternal-fetal pairs given concern about neonatal morbidity and mortality beyond the primary end point despite demonstration of the efficacy of the intervention. There were 17 live births (94%), with a median gestational age at delivery of 32 weeks, 4 days (IQR, 32-34 weeks). All participants delivered prior to 37 weeks' gestation. The primary outcome was achieved in 14 (82%) of 17 live-born infants (95% CI, 44%-99%). Factors associated with survival to the primary outcome included a higher number of amnioinfusions ($P = .01$), gestational age greater than 32 weeks ($P = .005$), and higher birth weight ($P = .03$). Only 6 (35%) of the 17 neonates born alive survived to hospital discharge while receiving peritoneal dialysis at a median age of 24 weeks of life (range, 12-32 weeks).

Conclusions and Relevance

Serial amnioinfusions mitigated lethal pulmonary hypoplasia but were associated with preterm delivery. The lower rate of survival to discharge highlights the additional mortality burden independent of lung function. Additional long-term data are needed to fully characterize the outcomes in surviving neonates and assess the morbidity and mortality burden.

Trial Registration

ClinicalTrials.gov Identifier: NCT03101891

This prospective, nonrandomized clinical trial assesses neonatal outcomes after serial amnioinfusions initiated before 26 weeks' gestation to mitigate lethal pulmonary hypoplasia in pregnancies complicated by bilateral renal agenesis.

Introduction

Bilateral renal agenesis is the most severe congenital anomaly of the fetal urinary tract, with a prevalence of approximately 1 in 3000 births. With this condition, fetal anuria leads to absence of amniotic fluid (anhydramnios) by the second trimester, when placental transudate is no longer sufficient to sustain amniotic fluid volume.[1] This early-onset anhydramnios causes depressurization of the fetal airways, impairing pulmonary development and resulting in uniformly lethal pulmonary hypoplasia at birth.[2]

Case observations in monoamniotic twins discordant for bilateral renal agenesis demonstrated that preservation of adequate amniotic fluid by the twin with normally functioning kidneys can result in adequate pulmonary development for both fetuses. This observation provided evidence that installation of intrauterine amniotic fluid as a fetal intervention might promote lung development, enabling postnatal respiratory survival in congenital bilateral renal agenesis.[2,3,4,5,6] In 1994, the first publication of serial amnioinfusions in a pregnancy complicated by fetal bilateral renal agenesis described survival without lethal pulmonary hypoplasia at birth. However, the neonate died at 23 days of life after unsuccessful dialysis.[7] In a subsequent report, amnioinfusions resulted in live birth without life-limiting pulmonary hypoplasia, thereby allowing successful institution of long-term dialysis and, eventually, kidney transplant.[8,9] Although these reports indicate that survival is possible with congenital bilateral renal agenesis after serial amnioinfusions, the safety, feasibility, and efficacy of serial amnioinfusions for this indication have not been established.[8]

In August 2016, the National Institute of Diabetes and Digestive and Kidney Diseases and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development sponsored a workshop to define knowledge gaps related to anhydramnios secondary to severe congenital anomalies of the kidneys and urinary tract, including bilateral renal agenesis, and proposed a research agenda.[10] In the absence of data to inform an evidence-based approach to prenatal management of anhydramnios, the workshop report concluded that hypotheses regarding the safety and efficacy of amnioinfusions should be tested in the setting of institutional review board (IRB)–approved research.[10] The Renal Anhydramnios Fetal Therapy (RAFT) trial aimed to assess neonatal outcomes after serial amnioinfusions and to test the hypothesis that neonatal pulmonary survival without lethal pulmonary hypoplasia is possible after serial amnioinfusions in pregnancies complicated by anhydramnios from fetal anuria. Herein, we report the outcomes for participants with fetal bilateral renal agenesis.

Methods

Trial Design and Participants

This nonrandomized, open-label, prospective clinical trial was conducted at 9 fetal intervention centers in the United States (a list of sites is provided in eAppendix 1 in Supplement 1). The other centers within the North American Fetal Therapy Network agreed not to perform serial amnioinfusions for potentially eligible participants while the trial was ongoing. The trial design was previously described,[11] and the protocol (see Supplement 2 and Supplement 3 for trial protocol and statistical analysis plan, respectively) was approved by the Johns Hopkins Medicine IRB, which acted as the central IRB for all sites under a reliance agreement.

The RAFT trial data and safety monitoring board (DSMB) consists of 3 maternal-fetal medicine specialists (2 from the United States and 1 from Canada), 1 biostatistician, and 1 ethicist (eAppendix 1 in Supplement 1). The DSMB is convened every 6 months to review both maternal safety and neonatal outcome data.

To participate, RAFT centers were required to have a maternal-fetal medicine specialist with experience performing amnioinfusion procedures for oligohydramnios or anhydramnios (minimum of 15 amnioinfusion procedures performed by the maternal-fetal surgeon), as well as neonatology, pediatric surgery, and nephrology expertise to place dialysis access and perform dialysis in small (<2 kg) neonates. RAFT was designed with 2 parallel, noncomparative trial groups: an intervention group for patients electing serial amnioinfusions and an expectant management group for those electing only observational data collection throughout pregnancy and after delivery (Figure). Within each group, patients were further categorized by the underlying cause of anhydramnios: (1) fetal bilateral renal agenesis (initial recruitment goal of 35 maternal-fetal pairs) or (2) other causes of fetal kidney failure, including multicystic dysplastic kidneys or severe lower urinary tract outflow obstruction (recruitment goal of 35 maternal-fetal pairs). As noted above, this report presents the outcomes in the bilateral renal agenesis cohort only.

Individuals interested in the trial were prescreened by telephone and, if potentially eligible, they were offered a screening visit at a RAFT site. The Figure details screening and enrollment for the trial. Inclusion criteria were a maternal age of at least 18 years, singleton gestation with bilateral renal agenesis and anhydramnios, completed multidisciplinary consultations, ability to begin amnioinfusions by 26 weeks' gestation, willingness to receive prenatal care and deliver at a RAFT center for those enrolled in the intervention group, and willingness to have postnatal infant care at a RAFT center until discharge home receiving long-term dialysis. Exclusion criteria were presence of any additional extrarenal congenital fetal anomalies, given the likelihood that they suggest a multisystem syndrome or could complicate neonatal dialysis provision; any significant pathogenic or likely significant pathogenic findings on karyotype or microarray; or obstetric contraindications to amnioinfusions (chorioamnionitis, placental abruption, preterm prelabor rupture of membranes [PPROM], cervical length <25 mm, severe maternal medical condition in pregnancy [including but not limited to uncontrolled diabetes, refractory hypertension, or other conditions known to increase risk of infection, poor placental function, or preterm delivery], maternal depression as assessed by a Beck Depression Inventory[12] score ≥17 refractory to treatment, or technical limitation precluding amnioinfusions).

In addition to counseling with a maternal-fetal medicine specialist, eligible parents received multidisciplinary counseling from a neonatologist, pediatric nephrologist, pediatric kidney transplant specialist, pediatric surgeon, licensed clinical social worker, and genetic counselor. Prenatal counseling is designed to inform potential participants, as much as possible, of the likely postnatal and lifetime clinical course of a newborn with end-stage kidney disease, and includes the potential limitation that a very small, premature, or ill neonate may not be a candidate for placement of dialysis access due to practical limitations.[13] The informed consent process may be conducted over several in-person visits to allow sufficient time for all questions to be addressed and verify voluntary participation. In accordance with US federal regulations regarding research involving a pregnant person and fetus and offering the prospect of direct benefit solely to the fetus, both parents were required to provide written informed consent to study participation. Participants could select the intervention group with serial amnioinfusions or the expectant management group. A preenrollment amnioinfusion was performed to exclude

rupture of membranes as an etiology for anhydramnios and to allow for a more detailed sonographic fetal evaluation. Pregnant individuals enrolling in the expectant management group had the option to waive the diagnostic amnioinfusion.

Study Procedures

Participants received ultrasound-guided percutaneous amnioinfusions of isotonic fluid (normal saline or lactated Ringer) with antibiotics every 2 to 12 days using a 20-gauge or 22-gauge needle with local anesthesia for comfort. The timing and volume of fluid instilled at each amnioinfusion ranged from 300 mL to 800 mL at the discretion of treating clinicians, with the goal of maintaining a normal amniotic fluid index for gestational age (eAppendix 2 in Supplement 1). The amnioinfusion interventions were conducted in the outpatient clinic or in the labor and delivery unit, with hospital admission only for specific indications such as prelabor rupture of membranes or preterm labor. Amnioinfusions were stopped if a participant experienced prelabor rupture of membranes. All participants had 2 fetal magnetic resonance imaging studies and 2 fetal echocardiograms during the study period: once during screening to identify any extrarenal anomalies not apparent on ultrasound, and the second at the 32-week assessment visit if the pregnancy was ongoing. The second magnetic resonance imaging was performed to assess the fetal brain as well as lung volumes, and the second echocardiogram was to assess fetal pulmonary vascular response to maternal hyperoxygenation for future exploratory analyses.

Delivery timing and mode were determined by obstetric indications. Newborns were admitted to the neonatal intensive care unit. Neonatal management, including initiation of kidney replacement therapy, was guided by local practice, individual patient needs, and shared decision-making with parents. For participants enrolled in the expectant management group, delivery could occur at the RAFT center or at a home hospital, if desired by the participant, and palliative neonatal care was provided according to the local protocol.

Outcome Measures

The primary outcome was a composite of neonatal survival to at least 14 days of life and placement of dialysis access. This was chosen as a surrogate for demonstrating both the absence of lethal pulmonary hypoplasia and the size and clinical stability required to allow initial management of end-stage kidney disease in a neonate. We report 3 of 5 prespecified secondary outcomes, 1 maternal and 2 neonatal/infant. Maternal pregnancy complications including PPROM and preterm labor were used to assess the safety and feasibility of the intervention. Neonatal/infant secondary outcomes included survival to hospital discharge receiving long-term dialysis and survival to kidney transplant. Exploratory outcomes included respiratory and dialysis support at 30, 60, and 90 days of life and neonatal survival at 30, 60, and 90 days of life, at hospital discharge, and at transplant. To understand infant morbidity associated with the intervention, specific aspects of infants' medical course were captured, including need for invasive respiratory support, mode and duration of dialysis, and medical complications encountered during the initial hospitalization and after discharge, if applicable.

Statistical Analysis

Sample size determination for the RAFT trial was based on the primary outcome of survival to at least 14 days of life and placement of dialysis access in the intervention group. For efficacy of serial amnioinfusions, we used exact methods to calculate 95% CIs around survival proportions from 0.2 to 0.8. A

sample size of 35 maternal-fetal pairs in the intervention group was sufficient to show that the proportion of infants surviving to at least 14 days of life with dialysis access was greater than 30% (assuming the observed rate in the study is ≥50%). Normally distributed continuous variables are summarized as means with SDs and nonnormally distributed variables as medians with IQRs. Binary or categorical variables are summarized as frequencies and percentages. For each analysis, neonates were grouped into 2 categories based on the primary outcome (survival and nonsurvival to ≥14 days of life). Demographic and clinical characteristics were compared between the 2 groups using univariate analysis with the *t* test or Wilcoxon rank sum test for continuous variables depending on the normality of distribution, and the χ^2 or Fisher exact test for binary or categorical variables. For safety events, maternal adverse events and serious adverse events were recorded. Overall frequency and percentage per variable are reported for both events and participants. Neonatal respiratory support and dialysis type are reported as frequencies and percentages for all time points.

In response to investigator observations of long-term mortality and morbidity among infants surviving past the short-term primary end point, an interim analysis was performed after accrual of half of the planned sample size and presented to the DSMB. The boundaries for early stopping of the trial due to efficacy were ±4.3326 (corresponding to an $\alpha = .00001473$). We report the 95% CI for survival at the primary outcome time of 14 days. For secondary outcomes, a 2-sided $P < .05$ was considered statistically significant.

Results

Trial Participants

From December 2018 to July 2022, a total of 321 individuals underwent prescreening, of which 122 (38%) progressed to a screening visit at a RAFT site and 49 (15%) were eligible for screening for the bilateral renal agenesis group (Figure). Twenty-one (43%) of the screened individuals met inclusion criteria for enrollment in the bilateral renal agenesis group and provided written informed consent to participate; 18 (86%) underwent serial amnioinfusions and 3 (14%) participated in the expectant management group (Table 1). On July 16, 2022, following the interim data analysis, the DSMB recommended suspending recruitment into the bilateral renal agenesis group due to the efficacy of the intervention based on the primary outcome variable, and concern that secondary infant outcomes including morbidity and mortality represented a high degree of burden. This report presents the results of the 21 maternal-fetal participant pairs.

Primary Outcome

In the expectant management group, all 3 pregnancies resulted in live birth and neonatal death within 12 hours due to severe pulmonary hypoplasia. In the amnioinfusion group, 17 pregnancies (94%) resulted in live birth at a median gestational age of 32 weeks, 4 days, and all participants delivered before 37 weeks' gestation. There was 1 fetal demise at 24 weeks that was associated with PPROM after the second amnioinfusion. A total of 14 of 17 (82%; 95% CI, 44%-99%) live-born neonates who had amnioinfusions survived to at least 14 days and had placement of dialysis access.

Because neonatal survival without the intervention was 0%, no direct survival comparisons were made between neonates born to participants in the intervention group and those in the expectant management group. Factors associated with survival to the primary outcome were a greater number of am-

nioinfusions, a longer interval between the first amnioinfusion and PPROM, gestational age at birth of 32 weeks or greater, and higher birth weight (Table 2).

Secondary Outcomes

No serious maternal adverse events occurred beyond hospitalization or needing to stop the intervention due to pregnancy complications. Maternal and pregnancy complications that were related to amnioinfusions included PPROM (61%), chorioamniotic membrane separation (28%), and vaginal bleeding (22%) (Table 1).

Six (35%) of 17 live-born infants survived to discharge home from the hospital receiving long-term dialysis at a median of 24 weeks of age (range, 13-32 weeks). Two subsequently died; 1 due to infectious complications of dialysis at 2 years of age and 1 following cardiac arrest at home at 4 months of age. Three (50%) had strokes, 2 of whom remain long-term survivors. Seizure was the most common clinical symptom associated with stroke, and the pattern and timing of stroke differed among affected individuals (Table 3). As of this report, no surviving individuals had undergone kidney transplant. Although all surviving individuals are transplant candidates, time and intensive nutritional support are required for growth to a size to allow surgical placement of donor kidney (minimum weight of approximately 10 kg). In addition, most infants with bilateral renal agenesis lack a lower urinary tract, which complicates planning for posttransplant urinary outflow management.

Exploratory Outcomes

Survival to 30 days of age was identical to survival to at least 14 days (82%) but decreased over time, with 52% (9/17) and 47% (8/17) of infants surviving at 60 and 90 days, respectively. Sepsis (n = 6) was cited as the most common contributing cause of death in the clinical records (Table 3). One infant had total intestinal aganglionosis identified postnatally and died at 6 months of age.

Table 3 summarizes the postnatal course, complications, and cause of death (if applicable) in infants with bilateral renal agenesis. All infants who had long-term dialysis access placed had peritoneal dialysis catheters placed, but multiple modes of kidney replacement therapy were listed for many. Reasons for exposure to multiple dialysis modes include infant size too small or clinical status too unstable to accommodate peritoneal dialysis catheter placement soon after birth, or peritoneal dialysis catheter malfunction. Available autopsy reports are included in Table 3.

The eTable in Supplement 1 describes respiratory and dialysis support for hospitalized infants at each survival time point. Because intubation status was recorded only on the day of assessment, information on infants who may have been extubated and reintubated between time points is not captured. Multiple dialysis modes were used over time, and at some time points more than 1 dialysis mode was used simultaneously.

Discussion

Assessing the relative safety and efficacy of an intervention with regard to both pregnant and neonatal participants adds an element of complexity to fetal intervention trials in general, as does the need to assess both short- and longer-term neonatal outcomes. In the present multicenter trial involving singleton pregnancies with bilateral renal agenesis, serial amnioinfusions initiated before 26 weeks' gestation mit-

igated lethal pulmonary hypoplasia in newborns and was associated with survival to at least 14 days of life and placement of dialysis access in 82% of neonates. However, survival beyond 14 days was lower, with only 35% of live-born infants surviving to hospital discharge receiving long-term dialysis, and none had undergone kidney transplant at the time of this report. Although the results demonstrate the efficacy of the intervention to allow lung development, a significant degree of uncertainty remains regarding the longer-term burden of morbidity and mortality in surviving neonates. Notable maternal complications included PPROM and preterm delivery. All pregnancies in the intervention group and 2 of 3 in the expectant management group delivered at less than 37 weeks' gestation. There were no severe maternal obstetric complications.

RAFT is a unique fetal intervention trial because of the involvement of 2 major organ systems. Neonates with bilateral renal agenesis who successfully survive from a pulmonary standpoint still lack functional kidneys and a lower urinary tract, may have disruption of renin-angiotensin-aldosterone pathways in the absence of kidney tissue, which may contribute to difficulty with blood pressure regulation, and require permanent life-sustaining kidney replacement therapy with dialysis and, eventually, kidney transplant. Reflecting this complexity, fewer than half (6/14) of infants who survived to the primary outcome were discharged home from the hospital. This survival rate is substantially lower than reported survival for infants receiving dialysis overall. Data from the US Renal Data System registry of infants starting peritoneal dialysis before 1 month of age from 2000 to 2014 reported 1- and 5-year survival as 86.1% and 74.6%, respectively, but these data do not account for infants who died before hospital discharge or prior to the initiation of long-term dialysis.[14] Claes et al[15] recently published neonatal survival data for a cohort of 213 infants who are perhaps more, but not completely, comparable with RAFT neonates; those born with kidney failure (not restricted to bilateral renal agenesis) at 52 US children's hospitals whose data were collected via the Children's Hospital Association Pediatric Health Information System database. In this study, mortality during the initial hospitalization was reported to be 23.9%. Mortality rates differed by birth weight, with 43.8% mortality among infants weighing less than 1800 g, 22.1% among those weighing 1800 to 2500 g, and 22.5% among those weighing more than 2500 g.[15] In the RAFT trial, 83% of newborns weighed less than 2500 g and similarly, lower birth weight was also associated with higher mortality. The higher mortality rate before hospital discharge suggests that infants born without kidneys experience life-limiting complications at a higher rate than infants with kidney failure from all causes.

Although this trial was not designed to evaluate secondary outcomes of neonatal morbidities, stroke was a notable complication observed in 2 of the 4 infants who remained long-term survivors at the time of this report, as well as in at least 2 neonates who died prior to hospital discharge (Table 3). Several pathophysiologic mechanisms predispose patients with end-stage kidney failure to stroke, including acid-base imbalance, impaired cerebral autoregulation, and endothelial and platelet dysfunction,[16] but no data for neonatal stroke incidence and characteristics after initiation of dialysis exist for comparison. This observation was cited by the DSMB in their recommendation to stop recruitment into the bilateral renal agenesis group of the trial. The DSMB acknowledged that efficacy was demonstrated by achievement of the defined primary outcome in a statistically significant proportion of neonates, but raised concern for potential harm given the disparity between short- and long-term infant survival and the burden of morbidity in longer-term survivors, especially stroke. Further investigation of this complication is ongoing. This highlights an additional complexity associated with this fetal intervention; achieving longer-term survival in a novel cohort of neonates allows description of potential comorbidities that have been previously unrecognized.

At its inception, the need to assess outcomes for infants beyond respiratory survival alone and long-term morbidity for surviving neonates lacking kidneys was recognized as a critical component of the RAFT trial. In March 2017, a multidisciplinary conference was convened to describe the complex ethical concerns associated with use of serial amnioinfusions for bilateral renal agenesis.[13] Among the ethical concerns highlighted were the need for extensive and nondirected multidisciplinary counseling for potential maternal patients, the need to assess outcomes for infants beyond respiratory survival alone, quality of life for surviving neonates lacking kidneys and requiring lifelong care for end-stage kidney disease, the impact on families, and potential moral distress among health care personnel who must balance parental hope with perceived infant discomfort and distress.[13]

Fetal intervention trials in general pose complex ethical challenges because both fetal and maternal risks and benefits must be considered. The potential hope offered to an expectant parent must be balanced with the potential lifelong burden associated with a chronic, complex medical condition. Invasive fetal interventions may be justified when the alternative to no intervention is a lethal perinatal outcome[13]; in the case of bilateral renal agenesis, expected neonatal mortality is 100% without fetal intervention. In one paradigm, a potential parent and future child's well-being may be closely aligned, especially when a single compromised organ system may be "corrected" via fetal intervention. However, the intervention in the RAFT trial can at best correct only the respiratory component of a severe pediatric chronic illness that will result in prolonged (and likely multiple) intensive care admissions, and the benefit of this to a potential child is less clear. Studies have also shown that parental quality of life is negatively affected by pediatric intensive care admissions and pediatric chronic illnesses[17]; a qualitative exploration of the extent of this impact on enrolled families is planned. It is critical for future studies that long-term developmental outcomes be assessed in neonates who survive due to prenatal amnioinfusion treatment.

This trial had several strengths. It assessed the potential of a standardized intervention to ameliorate the fatal neonatal pulmonary hypoplasia associated with anhydramnios due to bilateral renal agenesis, while also assessing maternal safety. It was conducted based on a predefined ethical framework that defined critical exploratory secondary outcomes, including long-term neonatal survival to hospital discharge and to kidney transplant and quality of life.[13] The data generated from the trial to date will inform decision-making for affected families and clinicians considering offering this intervention as part of clinical prenatal care, as well as future research priorities in long-term follow-up of neonatal survivors.

Limitations

This trial had several limitations. First, there was a notable lack of diversity among participants enrolled in RAFT. Zero participants identified as Black or African American, 11% with Hispanic ethnicity, and 94% as White. This lack of diversity in participants obviously limits the generalizability of the findings. Two potential socioeconomic barriers to enrollment include a requirement for adequate insurance coverage and the requirement to have both prenatal and postnatal care provided at 1 of the 9 RAFT centers, which in many cases requires family flexibility and resources to relocate for participation. A second limitation is small sample size. Although the initial target for recruitment was 35 maternal-fetal pairs with bilateral renal agenesis, enrollment was halted at 18. The trial was not powered to assess the secondary outcomes, including survival to hospital discharge and pediatric morbidities of end-stage kidney disease. Third, the limits of prenatal phenotyping should be acknowledged. Families considering amnioinfusions must be counseled that any additional organ system anomalies will further complicate already complex postnatal care. If additional abnormalities are identified postnatally, shared decision-

making with parents may be necessary to determine if aggressive management of end-stage kidney disease should continue. Fourth, postnatal management of neonates was purposefully not standardized across the study sites for multiple reasons, including center differences in neonatal surgical approaches to placement of dialysis access and available modes of hemodialysis when needed. Advances in neonatal hemodialysis have occurred since the start of the trial, so this impact on survival cannot be estimated. Because all centers had multidisciplinary teams with the capability to provide neonatal intensive care and kidney replacement therapy, results of this trial should not be generalized to centers without these capabilities or to patients that do not meet eligibility criteria. Fifth, collection of longitudinal quality-of-life data from infants who survive to initial hospital discharge is ongoing in both groups of the RAFT trial and will be explored in future reports, but because infants must survive to hospital discharge before these data are collected, data available to date remain limited.

Conclusions

In summary, this study demonstrates that serial amnioinfusions initiated before 26 weeks' gestation mitigated lethal pulmonary hypoplasia in the majority of neonates with bilateral renal agenesis. Survival to hospital discharge and beyond receiving peritoneal dialysis was substantially lower than survival to the short-term primary outcome and was strongly associated with gestational age at birth and birth weight, highlighting the burden of mortality independent of lung function for infants lacking kidneys. Because additional long-term data are needed to more fully characterize the outcomes in surviving neonates and assess the morbidity and mortality burden, this intervention is best offered with careful, multidisciplinary prenatal counseling in centers with collaborative multidisciplinary teams, including palliative care, with the capability to provide neonatal intensive care and kidney replacement therapy, and in the context of ongoing research.

Educational Objective: To identify the key insights or developments described in this article.

1. Without intervention, congenital bilateral renal agenesis is uniformly lethal. Why is this?

    A. Absence of kidney function leads to excessive accumulation of toxic metabolites in the fetal environment.
    B. Associated arterial shunting results in fetal high-output cardiac failure.
    C. Early-onset anhydramnios causes depressurization of the fetal airways, impairing pulmonary development.

2. The 3 neonates in the expectant management group died within 12 hours of birth. What was the survival to at least 14 days (the primary outcome) and to hospital discharge in the group receiving amnioinfusions?

    A. All neonates survived to 14 days but none had successful dialysis started or survived to hospital discharge.
    B. Most neonates survived to 14 days but only 35% survived to hospital discharge.
    C. Seventeen of 18 neonates survived to dialysis access placement at at least 14 days and then survived to hospital discharge.

3. What do the authors suggest are the implications of these results?

A. Serial amnioinfusions can now be considered the standard in cases of fetal congenital bilateral renal agenesis.
B. Serious maternal morbidity associated with serial amnioinfusions limits future application.
C. While results demonstrated efficacy, significant uncertainty remains regarding longer-term morbidity and mortality in surviving neonates.

Notes

Supplement 1.

eAppendix 1. RAFT centers and participants

eAppendix 2. Technical details of serial amnioinfusions

eTable. Postnatal respiratory and dialysis support in neonates and infants

Supplement 2.

Trial Protocol

Supplement 3.

Statistical Analysis Plan

Supplement 4.

Data Sharing Statement

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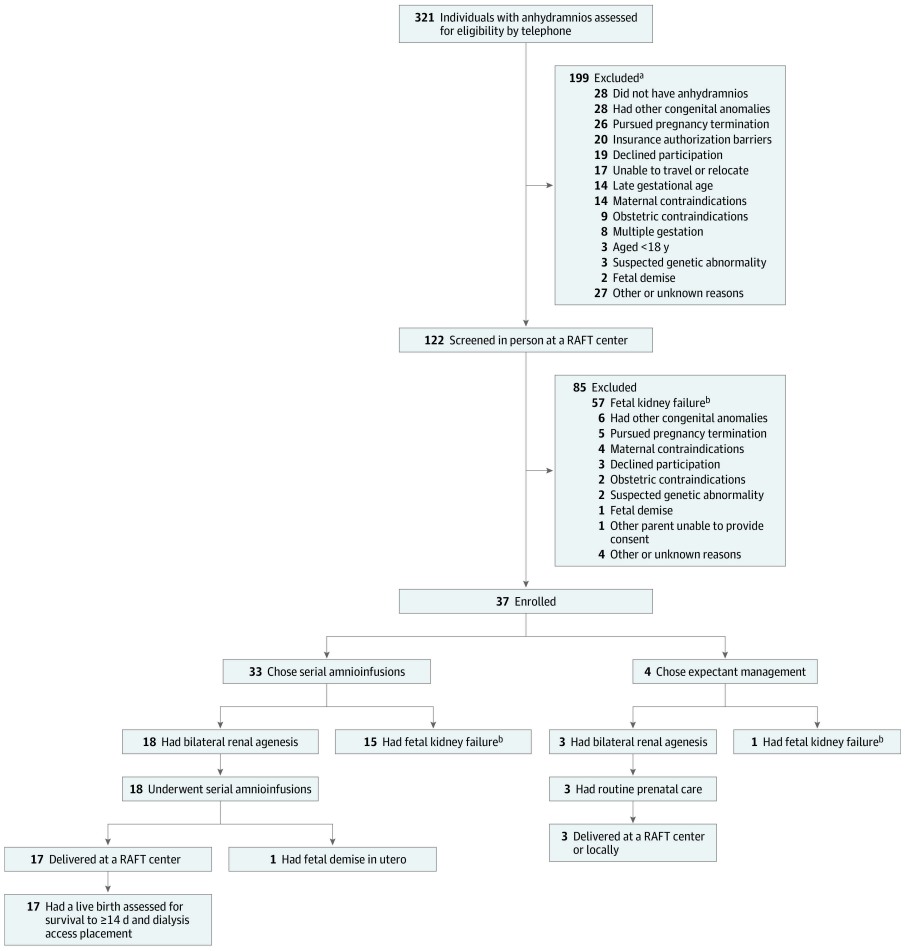
Figures and Tables

Figure.



Participant Flow Through the RAFT Trial

[a]Patients could be excluded based on more than 1 criterion.

[b]Enrolled in the non–renal agenesis (other cause of fetal kidney failure) group of the RAFT trial, in which recruitment is ongoing.

Table 1.

Demographic and Clinical Characteristics of 21 Maternal-Fetal Pairs With Bilateral Renal Agenesis (18 Undergoing Serial Amnioinfusions and 3 Expectant Management)

Characteristics	Data value
Maternal	
Age, median (IQR), y	33.0 (29-35)
Body mass index, median (IQR)	27 (25-30)
Nulliparous, No. (%)	4 (19)
Race, No. (%)	
White	20 (95)
Other[a]	1 (5)
Ethnicity, No. (%)	
Hispanic or Latino	3 (14)
Not Hispanic or Latino	18 (86)
Pregnancy and delivery	
Gestational age at first amnioinfusion, median (IQR), wk[b]	22 (21-23)
Total No. of amnioinfusions, median (IQR)	11 (9-15)
Chorioamnion separation, No. (%)	5 (24)
Time from first amnioinfusion to separation, median (IQR), d	30 (28-35)
PPROM, No. (%)	11 (52)
Time from first amnioinfusion to PPROM, median (IQR), d	55 (37-71)
Bleeding in absence of placental abruption, No. (%)	4 (19)
Gestational age at delivery, median (IQR), wk	33 (32-34)
Category, 2 groups, No. (%)	
<32	3 (17)
≥32	15 (83)
Category, 4 groups, No. (%)	
<30	2 (10)
30 to <32	1 (5)
32 to <34	10 (50)
34 to <37	7 (35)
Neonatal	
Apgar score at 1 min, median (IQR)[c]	5 (3-8)
Apgar score at 5 min, median (IQR)	8 (6-9)

Abbreviation: PPROM, preterm prelabor rupture of membranes.

[a] One participant provided “other” as their race identification.

[b] Amnioinfusions were performed during screening to allow fetal anatomic evaluation in all participants, including those in the expectant management group.

[c] The Apgar score is a health assessment score in which neonates are assigned 0 to 2 points in each of 5 categories: skin color, pulse rate, reflex irritability, muscle tone, and respiratory effort. Composite scores range from 0 to 10. Scores of 7 and above are generally considered normal; 4 to 6, fairly low, and infant may require medical assistance; and 3 and below, critically low, requiring immediate resuscitation efforts.

[d] Birth weight was missing for 1 intervention participant with fetal demise in utero and 1 expectant management participant who did not deliver at a RAFT center.

Table 2.

Obstetric and Neonatal Outcomes in Participants Who Underwent Serial Percutaneous Amnioinfusions, by Neonatal Survival to ≥14 Days and Placement of Dialysis Access

Outcomes	Survivors (n = 14)	Nonsurvivors (n = 4)	*P* value
Obstetric outcomes			
Total No. of amnioinfusions, median (IQR)	14 (11-18.2)	5 (3-8)	.01
Chorioamnion separation, No. (%)	3 (21)	2 (50)	.53
Time from first amnioinfusion to separation, median (IQR), d	28.0 (27.5-43.5)	32.5 (31.2-33.8)	.80
PPROM, No. (%)	9 (64)	2 (50)	.99
Time from first amnioinfusion to PPROM, median (IQR), d	66.0 (50.0-71.0)	13.0 (8.0-18.0)	.04
Bleeding in absence of placental abruption, No. (%)	4 (29)	0	.52
Cesarean delivery, No. (%)	7 (50)	2 (50)	.99
Neonatal outcomes			
Live birth, No. (%)	14 (100)	3 (75)	.22
Gestational age at delivery, median (IQR), wk	33.0 (32.0-34.0)	30.0 (28.0-31.2)	.006
Category, 2 groups, No. (%)			
<32	0	3 (75)	.005
≥32	14 (100)	1 (25)	
Category, 4 groups, No. (%)			
<30	0	2 (50)	.005
30 to <32	0	1 (25)	
32 to <34	8 (57)	1 (25)	
34 to <37	6 (43)	0	
Apgar score at 1 min, median (IQR)	8.0 (4.5-8.0) [n = 14]	4.0 (3.0-4.0) [n = 3]	.12
Apgar score at 5 min, median (IQR)	8.5 (8.0-9.0) [n = 14]	6.0 (6.0-6.5) [n = 3]	.07
Neonate sex (live births), No. (%)			
Female	4 (29)	1 (33)	.99
Male	10 (71)	2 (67)	
Birth weight, median (IQR), g	2010 (1840-2262.5)	1350 (1075-1470)	.03
Category, No. (%)			
<1000	0	1 (33)	.12
1000 to <1500	1 (7.1)	1 (33)	
1500 to <2500	11 (79)	1 (33)	
≥2500	2 (14)	0	

Abbreviation: PPROM, preterm prelabor rupture of membranes.

Table 3.

Complications and Causes of Death (if Applicable) in 17 Live-Born Infants With Bilateral Renal Agenesis

Gestational age, wk	Birth weight, kg	Dialysis mode[a]	Age at death	Complications and causes of death
26	<1	None	0 d	Respiratory failure
29	1.4	Aquapheresis	9 d	Necrotizing enterocolitis with intestinal perforation and sepsis
31	1.6	Peritoneal dialysis catheter placed but not used	10 d	Pulmonary hemorrhage, hypotension throughout neonatal intensive care unit course
32	2	Peritoneal dialysis and aquapheresis	7 wk	Peritonitis, sepsis, hypotension, necrotizing enterocolitis
33	1.3	Peritoneal dialysis and aquapheresis	6 mo	Chronic severe hypotension, ischemic brain injury
33	1.8	Peritoneal dialysis and aquapheresis	4 mo	Peritonitis, adenovirus-associated respiratory failure followed by multi–organ system failure, ischemic brain injury
33	2	Peritoneal dialysis	1 mo	Septic shock, peritonitis, pulmonary hemorrhage, necrotizing enterocolitis
34	2	Peritoneal dialysis	25 mo	Neonatal intensive care unit course complicated by prolonged initial intubation (6 wk), persistent hypotension, and stroke. Discharged home receiving long-term peritoneal dialysis; subsequently presented with sepsis and multi–organ system failure.
34	2.3	Peritoneal dialysis and aquapheresis	7 wk	Cardiomegaly on echocardiogram, cardiac arrest after hernia repair 12 d prior to death, subsequent apneic arrest. Autopsy with alveolar capillary dysplasia and pulmonary venous thrombus of left lower lobe.
34	2.3	Peritoneal dialysis and aquapheresis	7 wk	Methicillin-susceptible *Staphylococcus aureus* sepsis, brain hemorrhage
35	1.9	Peritoneal dialysis and hemodialysis	4 wk	Sepsis, bradycardia, pulmonary hemorrhage
35	2.1	Peritoneal dialysis	4 mo	Discharged home receiving long-term peritoneal dialysis, cardiac arrest at home
35	2.5	Peritoneal dialysis and hemodialysis	6 mo	Postnatal diagnosis of total intestinal aganglionosis, neonatal stroke, hypotension, cardiac arrest

[a] Hemodialysis indicates treatment delivered via a US Food and Drug Administration–labeled dialysis device. Aquapheresis indicates delivery of continuous hemofiltration and dialysis via a hemofiltration device not labeled for dialysis delivery in children.