Brief Report

Design and Protocol of the Renal Anhydramnios Fetal Therapy (RAFT) Trial

Meredith A. Atkinson, MD, MHS[1]; Eric B. Jelin, MD[2]; Ahmet Baschat, MD[3]; Yair J. Blumenfeld, MD[4]; Ramen H. Chmait, MD[5]; Elizabeth O'Hare[2]; Julie S. Moldenhauer, MD[6]; Michael V. Zaretsky, MD[7]; Russell S. Miller, MD[8]; Rodrigo Ruano, MD, PhD[9]; Juan M. Gonzalez, MD, MS, PhD[10]; Anthony Johnson, DO[11]; W. Andrew Mould, MPH[12]; Jonathan M. Davis, MD[13]; Daniel F. Hanley, MD[12]; Amaris M. Keiser, MD[14]; Mara Rosner, MD, MPH[3]; and Jena L. Miller, MD[3]

[1]Department of Pediatrics, Division of Nephrology, Johns Hopkins University, Baltimore, Maryland; [2]Department of Surgery, Division of Pediatric Surgery, Johns Hopkins University, Baltimore, Maryland; [3]Center for Fetal Therapy, Department of Gynecology and Obstetrics, Johns Hopkins University, Baltimore, Maryland; [4]Department of Obstetrics and Gynecology, Stanford University, Palo Alto, California; [5]Department of Fetal Surgery, Children's Hospital Los Angeles–USC Fetal-Maternal Center, Los Angeles, California; [6]Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [7]Fetal Care Center, Children's Hospital Colorado, Aurora, Colorado; [8]Department of Obstetrics and Gynecology, Columbia University, New York, New York; [9]Department of Obstetrics, Gynecology & Reproductive Sciences, University of Miami Medical School, Miami, Florida; [10]Department of Obstetrics and Gynecology, University of California, San Francisco, San Francisco, California; [11]Department of Obstetrics and Gynecology, University of Texas Health Center, Houston, Texas; [12]Department of Neurology, Division of Brain Injury Outcomes, Johns Hopkins University, Baltimore, Maryland; [13]Department of Pediatrics, Tufts Children's Hospital, Boston, Massachusetts; and [14]Department of Pediatrics, Division of Neonatology, Johns Hopkins University, Baltimore, Maryland

ABSTRACT

Purpose: Anhydramnios secondary to anuria before 22 weeks of gestational age and congenital bilateral renal agenesis before 26 weeks of gestational age are collectively referred to as early-pregnancy renal anhydramnios. Early-pregnancy renal anhydramnios occurs in at least 1 in 2000 pregnancies and is considered universally fatal when left untreated because of severe pulmonary hypoplasia precluding ex utero survival The Renal Anhydramnios Fetal Therapy (RAFT) trial is a nonrandomized, nonblinded, multicenter clinical trial designed to assess the efficacy, safety, and feasibility of amnioinfusions for patients with pregnancies complicated by early-pregnancy renal anhydramnios. The primary objective of this study is to determine the proportion of neonates surviving to successful dialysis, defined as use of a dialysis catheter for ≥14 days.

Methods: A consortium of 9 North American Fetal Therapy Network (NAFTNet) centers was formed, and the RAFT protocol was refined in collaboration with the NAFTNet Scientific Committee. Enrollment in the trial began in April 2020. Participants may elect to receive amnioinfusions or to join the nonintervention observational expectant management group. Eligible pregnant women must be at least 18 years of age

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with a fetal diagnosis of isolated early-pregnancy renal anhydramnios.

Findings: In addition to the primary study objective stated above, secondary objectives include (1) to assess maternal safety and feasibility of the serial amnioinfusion intervention (2) to perform an exploratory study of the natural history of untreated early pregnancy renal anhydramnios (3) to examine correlations between prenatal imaging and lung specific factors in amniotic fluid as predictive of the efficacy of serial percutaneous amnioinfusions and (4) to determine short- and long-term outcomes and quality of life in surviving neonates and families enrolled in RAFT

Implications: The RAFT trial is the first clinical trial to investigate the efficacy, safety, and feasibility of amnioinfusions to treat the survival-limiting pulmonary hypoplasia associated with anhydramnios. Although the intervention offers an opportunity to treat a condition known to be almost universally fatal in affected neonates, the potential burdens associated with end-stage kidney disease from birth must be acknowledged. ClinicalTrials.gov identifier: NCT03101891. (*Clin Ther.* 2022;44:1161–1171.) © 2022 Elsevier Inc.

Keywords: amnioinfusion, anhydramnios, fetal renal failure, Potter syndrome, pulmonary hypoplasia, renal agenesis.

INTRODUCTION

Severe fetal renal malformations, including congenital bilateral renal agenesis and other disorders resulting in fetal renal failure, such as severe lower urinary tract obstruction and bilateral multicystic dysplastic kidney, render the fetus anuric.[1] Because urine produced by the fetal kidneys constitutes nearly all the amniotic fluid volume by 16 to 20 weeks of gestational age, nonfunctional fetal kidneys lead to anhydramnios (no observable amniotic fluid).[2] Anhydramnios secondary to anuria before 22 weeks of gestational age and congenital bilateral renal agenesis before 26 weeks of gestational age are collectively referred to as early-pregnancy renal anhydramnios.[3] Historically termed Potter sequence, early-pregnancy renal anhydramnios occurs in at least 1 in 2000 pregnancies and is considered universally fatal when left untreated because of severe pulmonary hypoplasia precluding ex utero survival.[4,5] Amniotic fluid is necessary for lung development because it maintains transpulmonary pressure in the tracheobronchial tree. This pressure gradient is essential, leading to alveolar distension, mechanotransduction, and physiologic lung growth.[6–8]

Established fetal interventions for lower urinary tract obstruction are currently limited to vesicoamniotic shunting and fetal cystoscopy in fetuses who have renal function and produce urine. These procedures aim to bypass the obstruction via shunt or resolve the obstruction through ablation. The goals of therapy are to restore normal amniotic fluid volume, promote pulmonary development, and potentially limit further kidney damage in infants with lower urinary tract obstruction.[9,10] However, these treatments do not benefit the fetus with early-pregnancy renal anhydramnios with anuric renal failure. In recent years, there have been anecdotal reports of early-pregnancy renal anhydramnios fetuses that received serial amnioinfusions of isotonic fluid and had lung function consistent with survival at birth.[11–13] These early attempts at therapy were motivated in part by reported survival of monoamniotic twins discordant for congenital bilateral renal agenesis in which the congenital bilateral renal agenesis twin did not develop pulmonary hypoplasia because of shared amniotic fluid, indicating the possibility of lung maturation for early pregnancy renal anhydramnios fetuses with fluid replacement.[14–17]

The first case report of successful serial amnioinfusions to treat early pregnancy renal anhydramnios received wide attention in the lay press and on social media before the prospective tolerability, feasibility, and efficacy of the intervention were investigated.[11,18] However, this early enthusiasm led to additional retrospective reports of amnioinfusions with variable inclusion and exclusion criteria and techniques used to treat pulmonary hypoplasia in early-pregnancy renal anhydramnios–like fetuses with varying outcomes. In one study, 9 fetuses with severe oligoanhydramnios at variable time points in pregnancy and with unclear pathophysiology received serial amnioinfusions in a heterogenous fashion. Six had sufficient pulmonary function at birth for survival. Three of these surviving infants survived to dialysis and renal transplant.[3,19] In another single-center retrospective study, serial amnioinfusions were administered to 8 singleton fetuses with isolated fetal congenital bilateral renal agenesis; 3 patients survived past the first 48 hours of life. None survived to hospital discharge.[20] This study

included heterogenous amnioinfusion techniques, incomplete genetic evaluations, and multiple nontertiary delivery hospitals.[21] The maternal tolerability of repeated amnioinfusions for early pregnancy renal anhydramnios, the feasibility of performing multiple infusions, and the immediate and long-term outcomes for neonates with early-pregnancy renal anhydramnios remain unknown, and an evidence-based approach to the treatment and management of anhydramnios has not been established. Thus, systematic investigation in the setting of a standardized prospective and ethically designed trial was warranted.[3]

In 2012, a neonate with congenital bilateral renal agenesis whose mother received experimental amnioinfusions throughout pregnancy did not have survival-limiting pulmonary hypoplasia at birth.[11] This success increased attention in the lay press about using amnioinfusions as a potential fetal therapy for congenital bilateral renal agenesis.[18] Following this and other case reports of successful prenatal intervention for early-pregnancy renal anhydramnios, both a workshop sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) of the National Institutes of Health (NIH), and a national ethics symposium, were convened to discuss the ethical and practical implications of administering amnioinfusions in the setting of early pregnancy renal anhydramnios.[3,22] These conferences included fetal interventionalists, ethicists, pediatric nephrologists, neonatologists, pediatric surgeons, and previously treated patients, and proposed the framework for an ethically sound, regulated prospective trial which became the RAFT trial.

The primary objective of the RAFT trial is to determine the proportion of affected neonates surviving to successful dialysis (defined as ≥14 days of use of a dialysis catheter) after serial amnioinfusions. Secondary objectives include (1) to determine the maternal safety and feasibility of serial amnioinfusions for early-pregnancy renal anhydramnios; (2) to perform an exploratory study of the in utero natural history of untreated early-pregnancy renal anhydramnios; (3) to examine correlations among prenatal ultrasonography, echocardiography, magnetic resonance imaging (MRI), and lung-specific factors in amniotic fluid as predictive biomarkers of the success of serial percutaneous amnioinfusions in terms of neonatal survival; and (4) to determine short- and long-term outcomes and quality of life (QOL) in neonates and families enrolled in RAFT.

PARTICIPANTS AND METHODS

Trial Design

The initial RAFT protocol was approved by the John Hopkins University Institutional Review Board as a pilot single-center feasibility study. National interest in trial participation culminated in the creation of a consortium of 9 North American Fetal Therapy Network (NAFTNet) centers that, together with the NAFTNet Scientific Committee, further refined the protocol in anticipation of use across multiple sites. An R01 grant application to support the multicenter trial was submitted to and successfully funded by the NICHD. The multicenter study uses a single institutional review board and includes an executive committee, a data safety monitoring board (DSMB), a clinical coordinating center, and a data coordinating center to support and coordinate research efforts. Enrollment into the multicenter study using the refined protocol began in December 2018, and in the NICHD-funded trial in April 2020

RAFT is a nonrandomized, nonblinded, prospective, multicenter, institutional review board–approved clinical trial with 2 parallel intervention groups (congenital bilateral renal agenesis and fetal renal failure) within a population of patients with isolated early-pregnancy renal anhydramnios. The trial also has an observational expectant management group. Randomization was not planned because of ethical concerns regarding the near certainty of fetal or neonatal death without the intervention (Figure 1). The public has been represented in this trial from its inception. Previously treated patients and family members were present at the national ethics symposium in 2017, which laid the framework for the RAFT trial.[22] All sample size calculations were based on the intervention group only. Potential participants are referred by a physician or self-referred for enrollment at 1 of 9 participating centers, which include the University of Texas Houston, the Mayo Clinic, Columbia University, Johns Hopkins University, Stanford University, University of California San Francisco, University of Colorado, University of Southern California, and The Children's Hospital of Philadelphia. Table I lists RAFT center site qualification criteria.

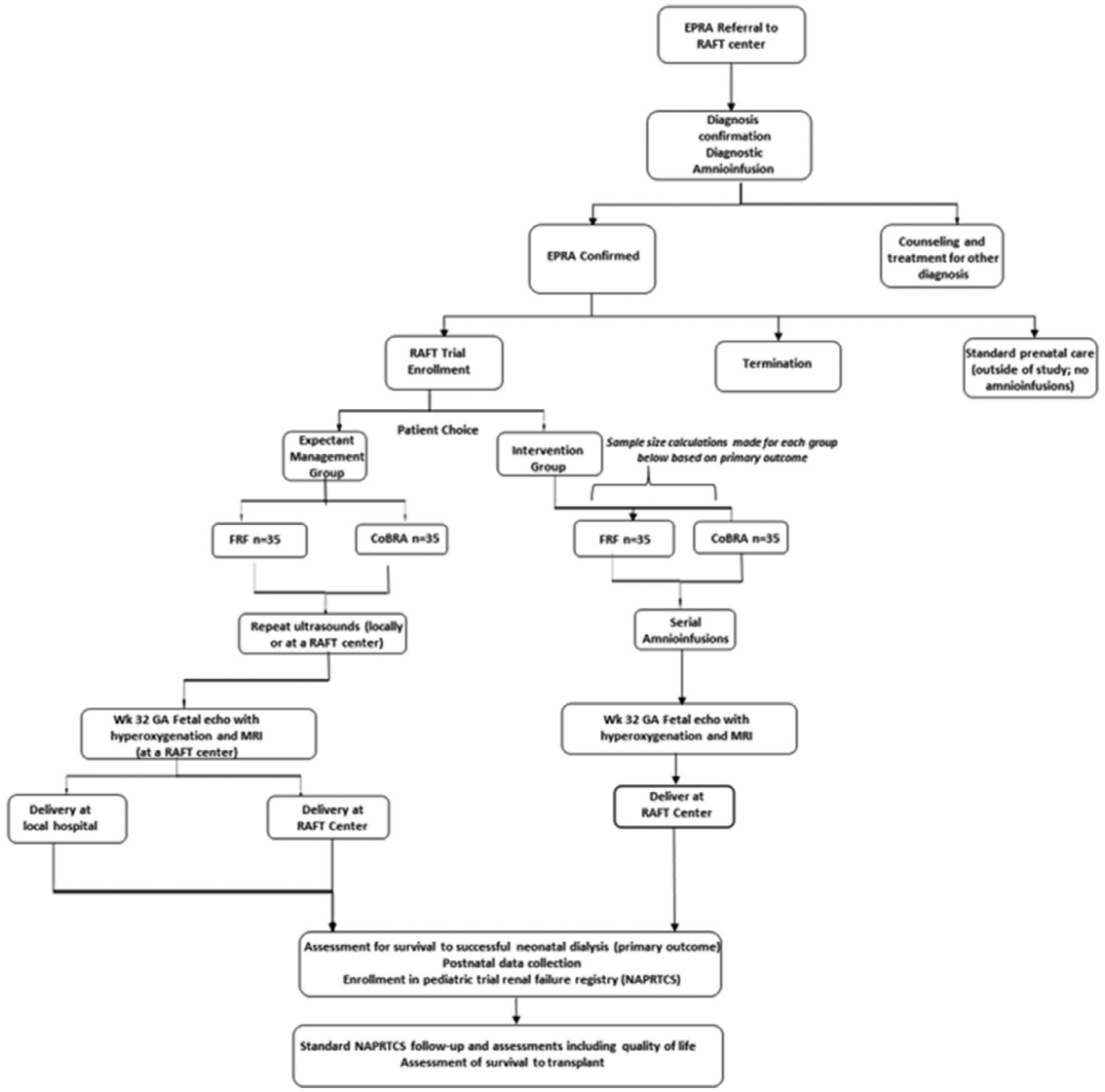

Figure 1. Renal Anhydramnios Fetal Therapy (RAFT) design. Patients referred to the RAFT trial center for suspicion of early-pregnancy renal anhydramnios (EPRA) undergo counseling and a diagnostic aminoinfusion. If the diagnosis is confirmed (anhydramnios in the absence of ruptured membranes and absent bladder filling), inclusion and exclusion criteria are applied (Table II). If the parents do not wish to be a part of the study, standard prenatal care will be offered. Once enrolled in the study, participants have the choice of expectant management or serial aminotransfusions. Those in the intervention group are allowed to switch to expectant management if they do not wish to continue amnioinfusions. All participants are delivered at a RAFT center and enrolled in the North American Renal Trials and Collaborative Studies (NAPRTCS) registry for long-term follow-up in the RAFT trial. CoBRA = congenital bilateral renal agenesis; FRF = fetal renal failure; GA = gestational age.

Table I. Renal Anhydramnios Fetal Therapy trial site qualification criteria.

1. Board-certified maternal-fetal medicine specialist who has performed >15 amnioinfusion procedures for anhydramnios
2. Neonatologists with willingness to provide active management for infants with prenatally diagnosed congenital bilateral renal agenesis and the experience to care for neonates as small as 1.8 kg requiring dialysis
3. Pediatric nephrologists with experience and willingness to perform dialysis in neonates ≥1.8 kg
4. Pediatric surgeons with experience and willingness to place dialysis catheters in neonates ≥1.8 kg
5. Multidisciplinary meeting before study initiation to include local principal investigator, study coordinator, maternal-fetal specialist, pediatric surgeon, neonatology and nephrology champions, and hospital administration to ensure that study objectives and procedures are communicated to the entire team
6. Availability of all required subspecialties and counselors for subject consent

RECRUITMENT GOALS AND TIMELINE

The target enrollment is 140 maternal-fetal pairs, with 70 in the intervention group (35 congenital bilateral renal agenesis and 35 fetal renal failure) and approximately 70 in the nonintervention expectant management group. A total of 15 to 20 participants are estimated to be enrolled in the trial each year. Given that amnioinfusion is currently the only potential fetal therapy for early-pregnancy renal anhydramnios, all eligible individuals who do not opt for termination will be offered the option of interventional or expectant management. Specific inclusion and exclusion criteria are outlined in Table II. Feasibility data collected using the electronic health record using *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, Tenth Revision* (ICD-10) codes for renal agenesis bilateral, renal agenesis unspecified, or Potter syndrome during the past 4 years and in the calendar year of 2018 at multiple RAFT centers suggest that the target enrollment of 140 participants is conservative, suggesting that the recruitment goal of 140 maternal-fetal pairs is achievable. Because of heterogeneous diagnoses within these search codes, approximately 50% of patients are estimated to be eligible for the study, with an estimated 50% of these consenting to participate. The trial has been publicized through NAFTNet, the Society for Maternal Fetal Medicine, ClinicalTrials.gov, the Trial Innovation Network, the trial website (www.raft-trial.org), and printed educational materials at participating centers.

Enrollment under the multicenter protocol began with consent of the first participant in December 2018, with NIH funding beginning in April 2020. Figure 2 shows the results of modeling with optimistic, at-plan, and conservative recruitment rates. Amnioinfusions will be administered and neonatal survivors will be followed up for up to 4 years (Figure 3). Intrapartum assessments include fetal MRI, lung evaluation, brain evaluation, fetal echocardiography, and other standard (obstetric) evaluations.

Study End Points

The primary outcome measure is the proportion of neonates surviving to successful dialysis, defined as continuous use of a dialysis catheter for ≥14 days. For the secondary objective to determine maternal tolerability and feasibility of the intervention, outcome measures include the number of amnioinfusions performed before rupture of membranes, the interval after initiation of amnioinfusions to rupture of membranes, and mean gestational age at delivery among those in the intervention arm. For the exploratory study of the in utero natural history of untreated early-pregnancy renal anhydramnios in the nonintervention arm, secondary outcome measures include rate of fetal demise in utero and gestational age at delivery. Correlations among prenatal ultrasonography, echocardiography, MRI, and lung-specific factors in amniotic fluid as predictive biomarkers of the success of serial percutaneous amnioinfusions will be examined in terms of neonatal survival. Finally, secondary neonatal outcome measures include survival to hospital discharge or transition to outpatient care, survival to successful renal transplantation, and long-term QOL.

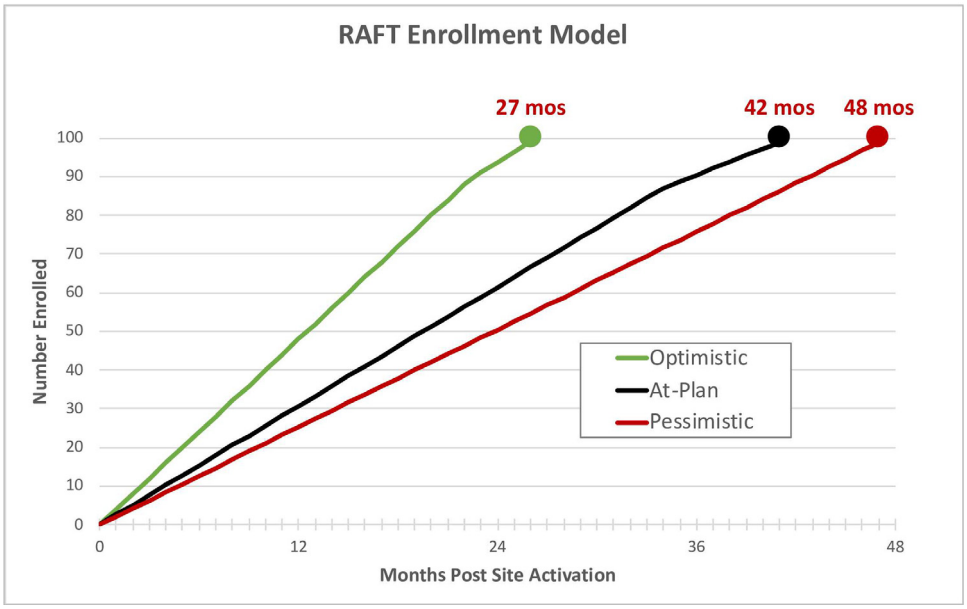

Figure 2. Renal Anhydramnios Fetal Therapy (RAFT) enrollment model. Explore optimistic (5.5 per site per year) and pessimistic (3 per site per year) estimates of combined enrollment rates for at least 30 participants in the expectant management group and 70 participants in the treatment group. At-plan enrollment will end in 42 months, leaving 18 months of follow-up for the last patient enrolled.

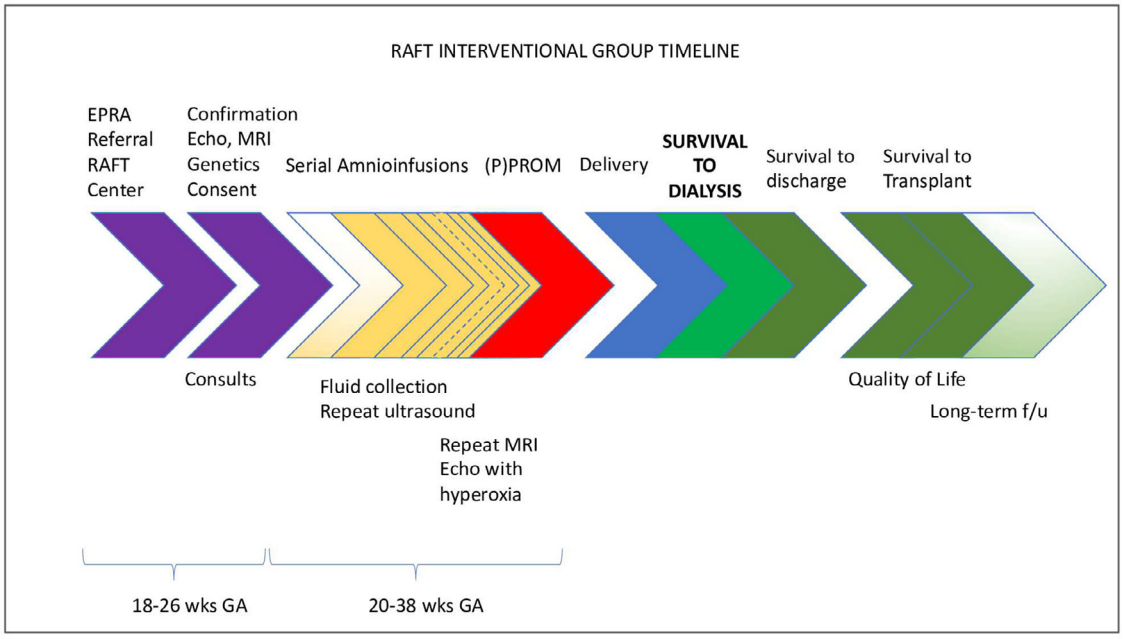

Figure 3. Timeline of Renal Anhydramnios Fetal Therapy (RAFT) study procedures for the intervention group. All study visits, including delivery, occurred at a RAFT center.

Table II. Renal Anhydramnios Fetal Therapy (RAFT) inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
1) Confirmed anhydramnios before 22 weeks of gestational age • Anhydramnios without membrane rupture • Absent significant bladder filling (diagnosis may require vesicocentesis for lower urinary tract obstruction) 2) Eligible for first amnioinfusion before 26 weeks of gestational age 3) Confirmation that participant does not wish to terminate pregnancy 4) Participant age ≥18 years 5) Willingness to receive prenatal care and deliver at RAFT center 6) Willingness for postnatal care for infant at RAFT center until discharge 7) Prenatal consultations: pediatric nephrology, neonatology, transplant surgery, pediatric surgery, maternal-fetal medicine, licensed clinical social worker, and a genetic counselor	1) Cervix <2.5 cm in length by transabdominal or transvaginal ultrasonography 2) Abnormal karyotype or microarray 3) Other clinically relevant congenital anomalies (eg, cardiac, gastroenterological, neurologic) 4) Evidence of chorioamnionitis or placental abruption 5) Evidence of rupture of membranes or chorioamniotic separation 6) Evidence of preterm labor 7) Multiple gestation 8) Severe maternal medical condition in pregnancy 9) Maternal depression as assessed by a Beck Depression Inventory score ≥17 that is refractory to treatment 10) Technical limitations precluding amnioinfusion

DSMB and Trial Stopping Rules

The DSMB will examine the data after the first 5 participants reach the primary outcome variable and then every 10 participants or every 6 months thereafter, whichever is more frequent. If there are no survivors to successful dialysis in the first 5 participants or any survivors in the expectant management group, then the study will be considered for early termination. In addition, if the primary outcome (neonatal survival to ≥14 days use of a dialysis catheter) is successfully reached in <10% or >90% of participants after 18 participants were enrolled, the DSMB will be convened and continuation of the trial will be considered. In the event of any instance of a serious adverse event (AE) (Table III), continuation of the study willb e considered. Finally, additional DSMB meetings will be called at any time in response to AEs or other study participant experience at the request of the principal investigators, the DSMB chair, or the executive committee chair.

Participant Screening

Thorough counseling about the multidimensional risks of trial participation, including possible financial burdens, family stress, opportunity costs, the likely high morbidity of neonatal survivors, and the near certainty of the requirement for lifelong renal replacement therapy, is the standard and is conducted before enrollment through multidisciplinary consults. A licensed clinical social worker works with the participant to ensure the appropriate arrangements can be made so that the participant can participate for the entirety of the study.

Intervention

Participants in the intervention group receive serial amnioinfusions between 18 and 34 weeks of gestational age after referral to a RAFT center by a physician or self-referral and inclusion into the trial. Participants return to the RAFT center every 2 to 12 days to receive amnioinfusion of isotonic fluid with antibiotics. Either oxacillin (1 g) or nafcillin (1 g) diluted in 500 mL of normal saline is used for antibiotic prophylaxis based on each center's standard operating procedure for amnioinfusions and hospital formulary. Clindamycin 600 mg diluted in 500 mL of normal saline is used as an alternative for participants with a penicillin allergy. Amnioinfusions of normal

Table III. Definition of serious adverse events in the Renal Anhydramnios Fetal Therapy trial.

1) Maternal death
2) In utero fetal demise
3) A life-threatening maternal event
4) A persistent or significant maternal incapacity or substantial disruption of the ability to conduct normal life functions

saline or lactated Ringer solution are administered using a US Food and Drug Administration–approved 20- or 22-gauge needle with local anesthesia for maternal comfort. The volume of fluid infused at each amnioinfusion ranges from 300 to 800 mL of warmed isotonic fluid, following general guidelines of 10 to 20 mL of isotonic fluid for each week of pregnancy. The aim is a maximum vertical pocket of 4 to 5 cm measured by transabdominal ultrasonography and low-normal amniotic fluid index for gestational age. If preterm premature rupture of membranes (PPROM) occurs, amnioinfusions will cease. This approach iss standard across centers. Delivery and neonatal care are performed at the RAFT center. Figure 3 illustrates the study timeline for intervention participants.

Participants are not compensated for their participation and have the option to switch from the intervention group to expectant management group or to withdraw from the trial at any time. At enrollment, participants must be at least 18 years of age and amenable to postnatal dialysis. Participants enrolled in the intervention group return to the RAFT center for all treatment from enrollment up to and including birth.

Expectant Management

Participants in the expectant management group will not receive serial amnioinfusions throughout pregnancy. Like the intervention group, these participants undergo 2 fetal ultrasonograms, 2 fetal MRIs, and 2 fetal echocardiograms. These fetal imaging studies are obtained during the study screening period and again at a 32-week assessment visit. This close monitoring allows the first ever detailed, standardized view of the in utero natural history of untreated early-pregnancy renal anhydramnios and will allow for a *descriptive* comparison of these radiologic prenatal markers of lung maturity between the 2 trial groups as well as a descriptive comparison of maternal and fetal risks. This comparison aimed to identify noninvasive imaging signatures in the intervention group indicative of adequate lung development to predict which fetuses were likely to survive postnatally, providing valuable prognostic information to families. Participants in both study arms have a consultation with a clinical social worker as part of the study screening and have access to social work support at the fetal center throughout their participation in the study.

Imaging Studies

Participants in both the intervention and expectant management group undergo 2 fetal MRI examinations. The first MRI examination occurrs during the study screening period. The second MRI examination in participants enrolled in the intervention arm occurs after a minimum of 4 therapeutic amnioinfusions between 30 and 32 weeks of gestational age. For those in the expectant management groups, the second fetal MRI occurs at the 32-week assessment visit. The fetal lung (volume and apparent diffusion coefficient) and brain (apparent diffusion coefficient and ventricular size) examinations are assessed throughout enrollment.

Follow-up

Participants will be followed up through all their study visits during pregnancy and up to delivery. Follow-up will continue up to 4 years of age for surviving neonates. Neonates who survived to discharge from the hospital will be enrolled in the multicenter North American Renal Trials and Collaborative Studies (NAPRTCS) registry (https://naprtcs.org/) to facilitate long-term data collection of end-stage kidney disease outcomes.

Data Collection and Management

Trial data are collected at each trial site and entered into the secure, Health Insurance Portability and Accountability Act–compliant REDCap platform.

Prenatal data are collected by each RAFT site study team using standardized intake forms, a screening log, and standardized case report forms for each participant visit. The RAFT trial has a quality, risk management, and monitoring plan that uses risk-based monitoring as recommended by the US Food and Drug Administration. Error and consistency checks were built into the data entry application. The coordinating center conducts regular audits of the data during the trial every 7 to 10 days via remote monitoring. Postnatal hospital data are recorded on the case report forms by the study team at birth (day of life 0); day of life 15, 30, 60, and 90; and time of discharge or death. AEs are reported on standardized AE forms at each center. Data are entered in near real time from these sites and exports generated at least monthly to be included in the data warehouse at the Johns Hopkins Data Coordinating Center. Data related to patient safety and outcomes are source-document verified, and other data are monitored for completeness and plausibility. Together, the clinical coordinating and data coordinating centers review parameters, including but not limited to enrollment, patient disposition (completed, discontinued, and loss to follow-up), and any complications (AEs, serious AEs, and protocol deviations). Long-term follow-up data for neonatal survivors are collected via the NAPRTCS registry platform and transferred to the data coordinating center every 6 months.

RESULTS

Neonatal lung development and short-term survival to dialysis are critical steps for long-term survival of an infant with early-pregnancy renal anhydramnios. \The primary outcome of interest will be neonatal respiratory survival and use of a dialysis catheter for > 14 continuous days. Data analysis will reveal if pulmonary survival after serial amnioinfusions can be predicted based on amniotic fluid contents and prenatal imaging. Lung fluid produced by pneumocytes to distend the tracheobronchial tree are released into the amniotic cavity during fetal breathing movements, therefore allowing analysis of lung secretions by amniotic fluid analysis. Insight into the mechanism of amnioinfusion action may be gained by observing the relationships among protein, lipid, and molecular markers during treatment. Previous investigators have indicated that amniotic fluid protein and lipid ratios and concentrations are predictive of neonatal respiratory distress.[23–25] When there is sufficient residual fluid remaining from the previous amnioinfusion, a clinically safe fluid sample from the amniotic cavity can be aspirated before each amnioinfusion and processed following a standardized protocol. Other perinatal variables, such as gestational age at delivery, delivery mode, Apgar scores, and umbilical cord blood gases, are recorded, along with neonatal pulmonary and renal interventions and success rates. Important morbidities, including cardiopulmonary, gastrointestinal, and neurologic outcomes, are also be recorded.

The RAFT trial will also allow prospective determination of the maternal and fetal tolerability of serial amnioinfusions, the number of amnioinfusions without PPROM that can be feasibly performed, the rate of chorioamnion separation, the range gestational age at delivery after serial amnioinfusions, and, in patients who experience PPROM, the latency period until delivery. This first objective of this study is to determine the rates of the following potential maternal complications of amnioinfusion: bleeding, chorioamnionitis, placental abruption, uterine rupture, amniotic fluid embolism, and death. Rates of the following potential fetal complications will also be calculated: fetal demise (risk of spontaneous fetal demise with isolated early-pregnancy renal anhydramnios is reported to be as high as 1 in 3), fetal injury, and amniotic band syndrome.[26] We hypothesize that the rates of potential maternal and fetal complications would be the same as published rates in normal pregnancies of women who underwent a diagnostic amniocentesis.[27] We hypothesize that 75% of patients eligible for RAFT who choose intervention would be able to undergo at least 4 amnioinfusions before PPROM or preterm labor or delivery occurred.

Long-term survival will be evaluated by (1) infant survival to hospital discharge while receiving long-term dialysis, (2) survival to renal transplantation, and (3) family-reported health-related QOL with end-stage kidney disease. Although short-term neonatal dialysis is technically possible in infants with early-pregnancy renal anhydramnios who receive amnioinfusions prenatally, indicators of long-term efficacy must include hospital discharge and transition to home, survival with dialysis to renal transplantation, and QOL that is, ideally, comparable to children undergoing dialysis and with kidney transplants due of other underlying causes of end-stage kidney disease (as

measured using Pediatric Measurement Models for the Pediatric Quality of Life Inventory scores). QOL will assessed in infants who survive to hospital discharge and their families every 6 months during the study period. Parents and caregivers will be asked to submit 2 forms for each surviving infant at each 6-month check-in: 1 PedsQL Family Impact Module and 1 additional form specific to the age of the infant or child (PedsQL Infant Scales up to and including 24 months of age), followed by the age-specific end-stage kidney disease modules for those ≥2 years of age.

DISCUSSION

The RAFT trial is the first clinical trial investigating the efficacy, safety, and feasibility of serial amnioinfusions to treat the survival-limiting pulmonary hypoplasia associated with anhydramnios secondary to fetal renal failure. Although the intervention of amnioinfusion offers an opportunity for the treatment of a condition that is known to be almost universally fatal in affected neonates, the potential burdens associated with the care of neonates with end-stage kidney disease from birth must be acknowledged, and participation requires thorough multidisciplinary counseling as part of the study screening process. The RAFT consortium is committed to the open and timely dissemination of research outcomes and recognizes that promising new methods, technologies, and immunologic insights may arise during research. The data generated by this trial will be presented and disseminated in a timely fashion.

The RAFT trial will produce generalizable knowledge about the extent to which life-sustaining pulmonary function can be achieved by artificial correction of the amniotic fluid volume in pregnancies complicated by anhydramnios secondary to fetal renal failure. Although survival may be possible, the range of morbidities that may affect infants with severe prenatally acquired renal impairment or even absence of renal tissue altogether cannot yet be estimated. Noting the potential range of health outcomes in neonates with renal agenesis, it will be critical to follow up outcomes in surviving neonates over time. Despite these significant issues, a robust scientific approach to assessing the benefits and risks of serial amnioinfusions to promote lung development is required to generate generalizable knowledge from a systematically recruited, representative cohort of pregnancies complicated by early-pregnancy renal anhydramnios, rather than drawing conclusions from individual or single-center case reports.

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Address correspondence to: Meredith A. Atkinson, MD, MHS, Division of Pediatric Nephrology, Johns Hopkins University School of Medicine, 200 N Wolfe St, Room 3064, Baltimore, MD 21287. E-mail: matkins3@jhmi.edu.