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From Pulmonary Rescue to Kidney Transplantation: Neonatal Survival After Serial Amnioinfusion's for Anhydramnios Caused by Fetal Kidney Failure—A Contemporary Review of the RAFT Era

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ABSTRACT

Background: Early pregnancy an hydramnios caused by fetal kidney failure produces severe pulmonary hypoplasia and has historically been considered uniformly fatal.

Objective: This review contemporary evidence on the efficacy, maternal safety, neonatal morbidity, long-term survival, and ethical implications of serial amnioinfusion's initiated before 26 weeks' gestation for an hydramnios due to fetal kidney failure, with emphasis on evidence published during 2021–2026.

Methods: A critical narrative review was undertaken using recent PubMed-indexed studies, trial reports, clinical reviews, ethics analyses, and fetal therapy literature. Priority was given to multicenter prospective evidence, especially the Renal Anhydramnios Fetal Therapy (RAFT) trial.

Results: The 2023 RAFT bilateral renal agenesis cohort demonstrated survival to at least 14 days with dialysis access in 14 of 17 live-born neonates (82%), but only 6 of 17 (35%) survived to hospital discharge. The 2026 RAFT fetal kidney failure cohort, which excluded bilateral renal agenesis, reported 29 live births among 32 treated pregnancies; 19 of 29 neonates (65.5%) achieved survival to at least 14 days with dialysis access.

Conclusion: Treatment should remain concentrated in highly specialized, multidisciplinary programs with standardized protocols, transparent outcome reporting, nondirective counseling, and long-term follow-up of children and families.

Keywords: pulmonary rescue, kidney transplantation, neonatal survival

1. INTRODUCTION

Early-pregnancy renal anhydramnios is one of the clearest examples of how fetal therapy can change the natural history of a condition without correcting its underlying organ failure. In the second half of gestation, fetal urine supplies most amniotic fluid. When both kidneys are absent or severely nonfunctional, or when destructive urinary tract disease produces fetal anuria, the amniotic cavity becomes profoundly depleted. The immediate fetal problem is therefore not only kidney failure. Loss of amniotic fluid removes the fluid environment and transpulmonary pressure required for normal lung expansion, branching, vascular development, and alveolar growth. The resulting pulmonary hypoplasia and pulmonary vascular disease can make ventilation impossible after birth, even when intensive neonatal care is available [1–3]. Historically, counseling for anhydramnios caused by severe fetal kidney disease emphasized pregnancy termination where legally available, expectant management with anticipated neonatal death, or perinatal palliative care. Isolated case reports later showed that repeated instillation of isotonic fluid into the amniotic cavity could permit lung development. These reports established biological proof of principle, but they also created a difficult clinical situation: a technically simple prenatal procedure could prevent immediate respiratory death while creating a newborn with irreversible kidney failure, prolonged intensive care needs, and uncertain access to dialysis and transplantation [4–6]. The Renal Anhydramnios Fetal Therapy (RAFT) trial was developed to move this practice from scattered compassionate use into prospective, protocolized research. Its central hypothesis was deliberately narrow: maintaining amniotic fluid through serial percutaneous infusions could mitigate lethal pulmonary hypoplasia. RAFT did not propose that amnioinfusion regenerates absent kidneys or reverses established end-stage kidney disease. Consequently, interpretation of success requires several separate outcome levels: fetal survival to live birth, pulmonary survival beyond the immediate neonatal period, successful initiation of kidney replacement therapy, survival to hospital discharge, survival to transplantation, and long-term child and family outcomes [1,2,7]. The publication of the RAFT bilateral renal agenesis cohort in 2023 provided the first multicenter prospective evidence that serial amnioinfusion's can prevent otherwise lethal pulmonary hypoplasia in many treated fetuses. However, the fall from 82% achievement of the short-term primary outcome to 35% survival to discharge demonstrated that pulmonary rescue is only the first step [1]. In July 2026, the second major RAFT report extended the evidence to fetal kidney failure caused by conditions other than bilateral renal agenesis. This cohort achieved a 65.5% primary outcome and 48% survival to discharge, with several survivors reaching transplantation [2]. These findings fundamentally change the evidentiary basis for counseling, but they do not establish serial amnioinfusion as routine low-risk therapy. This review critically synthesizes evidence from the last five years, focusing on the mechanisms, candidate selection, procedural strategies, maternal risks, neonatal course, survival, transplantation, ethics, and research priorities relevant to serial amnioinfusion for renal anhydramnios. The aim is to frame the intervention not simply as a method for producing a live-born infant, but as the first stage of an integrated fetal–neonatal–nephrology treatment pathway.

2. REVIEW APPROACH AND SCOPE

This article is a critical narrative review rather than a formal systematic review or meta-analysis. Literature was identified from recent PubMed-indexed records, publisher databases, trial registries, reference lists of major reviews, and reports from fetal therapy and pediatric nephrology journals. The core search concepts combined terms related to "renal anhydramnios," "early-pregnancy renal anhydramnios," "fetal kidney failure," "bilateral renal agenesis," "serial amnioinfusion," "pulmonary hypoplasia," "neonatal dialysis," "kidney replacement therapy," and "kidney transplantation." Priority was given to studies published from January 2021 through July 2, 2026. Evidence was ranked conceptually rather than through a numerical quality score. Prospective multicenter RAFT reports were

considered the highest-level direct evidence. Single-center studies and secondary analyses were used to examine procedure optimization and complications. Contemporary reviews and observational studies of neonatal kidney replacement therapy were used to interpret postnatal feasibility. Ethics papers and parent–physician perspectives were included because clinical benefit in this setting cannot be judged solely by respiratory survival. Older sources were retained only when they represented landmark proof-of-concept cases, foundational ethics work, or essential background to the RAFT protocol. The review uses “fetal kidney failure” to describe severe bilateral renal dysfunction causing fetal anuria and anhydramnios. “Bilateral renal agenesis” is considered separately because complete absence of kidneys eliminates residual renal function and has distinct diagnostic and long-term implications. “Pulmonary rescue” refers to sufficient mitigation of pulmonary hypoplasia to permit postnatal cardiorespiratory stabilization and attempted kidney replacement therapy. It should not be interpreted as freedom from respiratory disease, pulmonary hypertension, prematurity, or later morbidity.

3. BIOLOGICAL BASIS: WHY AMNIOTIC FLUID DETERMINES PULMONARY SURVIVAL

Normal fetal lung growth depends on both biochemical maturation and mechanical forces. Fetal lungs secrete fluid into the airways, while the closed glottis and surrounding amniotic environment help maintain a positive pressure gradient across the lung. This distending pressure promotes airway branching, epithelial differentiation, vascular development, and expansion of future gas-exchanging units. Severe and prolonged anhydramnios reduces external support, alters fetal breathing mechanics, and facilitates loss of lung liquid, leading to small, structurally immature lungs and abnormal pulmonary vasculature [3,7]. The timing of fluid loss is critical. Anhydramnios beginning before approximately 22 weeks overlaps with the canalicular phase, when distal airways, capillary networks, and the future air–blood interface are developing. Prolonged fluid absence during this period is associated with the most severe pulmonary hypoplasia. Pathologic observations from untreated early renal anhydramnios support a duration-dependent relationship between anhydramnios and lung underdevelopment. This provides the mechanistic rationale for initiating treatment before 26 weeks and maintaining fluid for as long as possible [3,8]. Serial amnioinfusion does not need to reproduce the precise composition of fetal urine to exert its principal pulmonary effect. Ultrasound-guided instillation of warmed isotonic fluid restores space around the fetus and re-establishes a pressure environment that supports lung expansion. Infusions are repeated because fluid is absorbed, leaks across membranes, or is otherwise lost. The desired exposure is therefore not a single procedure but sustained restoration of an adequate amniotic fluid volume across a developmentally important interval [1,2,7]. The biological argument is supported by naturally occurring “experiments.” In rare monoamniotic twin pregnancies discordant for bilateral renal agenesis, the affected twin may avoid lethal pulmonary hypoplasia because the co-twin contributes to a shared amniotic fluid environment. Early compassionate-use cases similarly showed that a fetus without functioning kidneys could be born with adequate respiratory function after repeated fluid replacement [4,7]. These observations establish that the lethal lung phenotype is not an unavoidable direct consequence of absent kidneys; it is substantially mediated by the amniotic fluid deficit. Nevertheless, pulmonary rescue is incomplete and variable. The fetus may already have sustained irreversible impairment before treatment begins. Membrane complications can interrupt therapy. Prematurity truncates lung development, and pulmonary vascular disease may persist even when lung volume appears adequate. The neonatal phenotype can therefore range from relatively manageable respiratory distress to refractory pulmonary hypertension requiring advanced ventilation or extracorporeal support. This variability explains why infusion number and treatment duration are associated with outcomes but cannot serve as perfect individual predictors [1,2,9].

4. ETIOLOGIC SPECTRUM OF FETAL KIDNEY FAILURE

Renal anhydramnios is a final common pathway rather than a single diagnosis. Bilateral renal agenesis is the most anatomically complete form: neither kidney develops, fetal urine production is absent, and lifelong native renal function is impossible. Other causes include bilateral multicystic dysplastic kidneys, severe bilateral renal dysplasia, autosomal recessive polycystic kidney disease with profound functional failure, and lower urinary tract obstruction that has already caused irreversible renal damage. Complex syndromic or chromosomal disorders may also produce severe kidney dysfunction, although the presence of major additional anomalies changes both eligibility and prognosis [10,11]. This heterogeneity matters clinically. A fetus with bilateral agenesis and a fetus with severe obstructive nephropathy may share anhydramnios and pulmonary risk, but their postnatal renal anatomy, urinary tract reconstruction needs, infection risk, dialysis access options, and residual kidney function differ. Residual renal function, even when insufficient to sustain life, can improve fluid and electrolyte management and may reduce dialysis intensity. Conversely, residual urine output can coexist with severe dysplasia and should not be assumed to predict a benign course [10–12]. Lower urinary tract obstruction requires especially careful classification. When obstruction is diagnosed before irreversible renal destruction and the fetus still produces urine, vesico amniotic shunting or fetal cystoscopy may be considered to decompress the bladder, restore urine flow into the amniotic cavity, and potentially preserve renal function. Serial amnioinfusion occupies a different therapeutic position. It is primarily a pulmonary rescue strategy for fetuses whose renal disease is already functionally end stage and whose anhydramnios will not be corrected by relieving obstruction alone [7,11,13]. Treating these two scenarios as interchangeable risks offering amnioinfusion too early, when an etiologic intervention may still be possible, or too late, after prolonged anhydramnios has caused advanced lung injury. Modern evaluation therefore requires high-resolution ultrasonography, serial assessment of amniotic fluid, detailed renal and urinary tract anatomy, fetal echocardiography, assessment for extra-renal anomalies, and genetic testing when indicated. Fetal magnetic resonance imaging can provide complementary information, particularly for lung volume and associated anomalies, but its predictive value for individual survival remains incompletely validated. Family history and parental testing may clarify recurrence risk in genetically mediated CAKUT. The diagnostic goal is not merely to label the kidneys as abnormal; it is to establish whether the disease is isolated, whether renal failure is irreversible, whether pulmonary rescue is biologically plausible, and whether postnatal treatment is ethically and technically available [10–12]. The 2026 RAFT fetal kidney failure cohort is important precisely because it moves beyond bilateral renal agenesis. Thirty-two participants with anhydramnios before 22 weeks due to kidney failure other than bilateral agenesis underwent serial infusions before 26 weeks. The study showed that the pulmonary mechanism is sufficiently shared across etiologies for many neonates to survive the immediate postnatal period. However, etiologic heterogeneity may also explain differences in longer-term outcomes and should be explored in larger datasets rather than obscured by a single combined category [2].

5. CANDIDATE SELECTION AND MULTIDISCIPLINARY COUNSELING

Candidate selection is one of the most consequential stages of care. Because serial amnioinfusion exposes a pregnant patient to repeated invasive procedures without direct physical benefit to her, the threshold for diagnostic certainty and informed consent must be high. The fetus should have early and severe anhydramnios attributable to irreversible bilateral kidney failure, with no evidence that membrane rupture is the primary cause. A detailed anomaly assessment is required because severe neurologic, cardiac, chromosomal, or multisystem disease may make survival to meaningful discharge unlikely even if pulmonary development improves [7,10,14]. Gestational age criteria reflect developmental biology and trial evidence. RAFT focused on anhydramnios established before 22 weeks

and initiation of infusions before 26 weeks. These thresholds should not be treated as magical cutoffs, but they provide the most defensible evidence-based window. Treatment begun after prolonged anhydramnios may be unable to reverse established pulmonary hypoplasia, while very early intervention increases the number of procedures and cumulative opportunities for membrane injury. The decision should therefore integrate the estimated onset and duration of anhydramnios, not simply the gestational age on the day of referral [1,2,7]. Counseling must explain that the intervention has two linked phases. The prenatal phase attempts to support lung development and prolong pregnancy. The postnatal phase begins immediately with intensive respiratory, cardiovascular, nutritional, surgical, and nephrology care. A newborn who survives pulmonary transition but cannot receive dialysis because of size, hemodynamic instability, abdominal pathology, vascular access limitations, or institutional capacity may still die. Families should meet maternal–fetal medicine specialists, fetal surgeons, neonatologists, pediatric nephrologists, pediatric surgeons, transplant specialists, genetic counselors, palliative care clinicians, social workers, and ethics professionals before enrollment whenever possible [7,14,15]. Nondirective counseling is essential. Reasonable options may include termination of pregnancy, expectant management with comfort-focused neonatal care, or experimental/highly specialized serial amnioinfusion with planned life-sustaining postnatal treatment. The existence of a technically possible intervention does not make it obligatory. Equally, a clinician's concern about disability, dialysis burden, or resource intensity should not automatically invalidate a well-informed parental decision to pursue treatment. The counseling process should distinguish facts, probabilities, institutional limitations, and value judgments [14–16]. Families should receive outcome data in absolute numbers. For example, saying that "most infants survived the primary endpoint" is incomplete unless paired with the lower survival to discharge and the burdens of dialysis, surgery, neurologic complications, and prolonged hospitalization. Likewise, the 2026 report of seven transplants among eleven children alive at latest follow-up is encouraging, but it should not be represented as the probability that any newly treated fetus will reach transplant. The denominator changes across stages, follow-up time differs, and survivors are a selected group [2]. Institutional selection is as important as patient selection. RAFT sites were high-volume fetal therapy programs linked to neonatal intensive care, pediatric surgery, nephrology, dialysis, and transplantation. Offering serial infusions without a credible postnatal pathway creates a risk of achieving pulmonary survival while failing to provide the treatment necessary for renal survival. Regional referral networks, written delivery plans, equipment readiness, trained dialysis teams, and transparent criteria for escalation or redirection of care should be established before the first infusion [7,15,17].

6. SERIAL AMNIOINFUSION TECHNIQUE AND PROTOCOL OPTIMIZATION

In RAFT, amnioinfusion's were performed percutaneously under ultrasound guidance using isotonic fluid, beginning before 26 weeks. The volume and interval were individualized to restore an amniotic fluid volume appropriate for gestational age. Procedures were repeated as fluid decreased, often requiring numerous interventions over weeks. Ultrasound was used to identify a safe needle path, avoid the placenta and fetus, and assess fluid restoration. Because the treatment is repeated rather than definitive, procedural consistency and surveillance between infusions are central to both efficacy and safety [1,2,7]. The optimal balance between infusion volume and frequency remains under investigation. A single-center comparison of serial amnioinfusion strategies found that smaller, more frequent infusions maintained normal fluid for a longer duration and delayed preterm prelabor rupture of membranes compared with a strategy using larger, less frequent infusions. Importantly, the greater number of procedures did not appear to worsen bleeding, chorioamniotic separation, preterm labor, or other measured obstetric outcomes. Although the sample was limited and derived from early RAFT phases, the findings support the concept that avoiding large fluctuations and excessive membrane stretch may be preferable [18]. Treatment intensity should be interpreted as both a therapeutic

exposure and a marker of pregnancy stability. In both RAFT outcome cohorts, survivors received more infusions than non survivors. This does not prove that simply increasing the number of procedures causes survival. Pregnancies that remain intact longer naturally allow more infusions, greater gestational maturation, and higher birth weight. The association likely reflects a combined pathway: effective fluid maintenance supports lung growth, while delayed membrane rupture preserves the opportunity for continued treatment and prolongation of gestation [1,2]. A practical protocol should specify preprocedural assessment, sterile technique, fluid composition and temperature, ultrasound targets, maximum acceptable pressure or volume, fetal monitoring, post procedure observation, and criteria for hospitalization. Surveillance should include symptoms of membrane rupture, infection, bleeding, contractions, placental or membrane separation, fetal growth, Doppler findings when indicated, and cervical status. Because evidence remains limited, centers should record each procedure in a standardized registry, including volume infused, deepest vertical pocket or amniotic fluid index before and after infusion, technical difficulty, pain, leakage, and adverse events. Alternative delivery systems, such as indwelling amnio ports, have been considered because repeated needle access is burdensome. However, permanent devices may introduce infection, dislodgment, leakage, and device-specific complications. Current prospective evidence is strongest for repeated ultrasound-guided percutaneous infusion, and novel systems should remain within research protocols until comparative safety is established. The endpoint of prenatal therapy is not necessarily a fixed gestational age. Infusions may stop because of preterm prelabor rupture of membranes, spontaneous labor, infection, fetal compromise, technical infeasibility, or a decision that further procedures are unlikely to add benefit. Delivery planning should account for fetal presentation, obstetric indications, neonatal team availability, and proximity to dialysis and surgical services. Delivery solely to avoid another infusion should be weighed against the strong association between greater gestational age, higher birth weight, and survival [1,2].

7. DIRECT EVIDENCE OF EFFICACY

7.1. PRE-RAFT EVIDENCE

Before RAFT, evidence consisted of case reports, small series, and biologically persuasive observations. Several fetuses with bilateral renal agenesis or severe renal anhydramnios achieved neonatal respiratory survival after repeated infusions, and a small number later received dialysis and transplantation. These reports challenged the assumption that renal anhydramnios itself was uniformly incompatible with pulmonary survival. However, treatment protocols varied, genetic and anomaly evaluation was inconsistent, delivery occurred at centers with different neonatal resources, and publication bias strongly favored successful or unusual cases [4–6]. The limitations of compassionate-use literature were clinically important. Some neonates survived birth but died before dialysis could be established. Others underwent prolonged intensive care with uncertain neurologic outcomes. Maternal risks were incompletely reported. These uncertainties motivated the prospective RAFT design, which used defined eligibility, multidisciplinary review, standardized outcome collection, and an independent safety framework [7].

7.2. RAFT BILATERAL RENAL AGENESIS COHORT

The 2023 RAFT report enrolled pregnancies with isolated bilateral renal agenesis and anhydramnios. Among 18 treated maternal–fetal pairs included in the principal intervention analysis, 17 resulted in live birth at a median gestational age of 32 weeks and 4 days. Fourteen of the 17 live-born neonates (82%; 95% confidence interval 44%–99%) survived at least 14 days and underwent dialysis access placement. This result provided strong evidence that serial amnioinfusion’s can mitigate the pulmonary component of an otherwise lethal condition [1]. The same study also demonstrated why the primary

endpoint should not be equated with durable survival. Only six of 17 live-born infants (35%) survived to hospital discharge on long-term dialysis. The trial stopped enrollment in the bilateral agenesis arm early after interim review because of morbidity and mortality beyond the short-term endpoint. Complications included hypotension, dialysis difficulties, infection, seizures, stroke, gastrointestinal disease, and cardiac arrest. No infant had reached transplantation at the time of the initial publication, although later reports and follow-up have documented transplantation in some children treated for bilateral agenesis [1,19]. All treated pregnancies delivered before 37 weeks, and preterm prelabor rupture of membranes was common. Greater gestational age at birth, higher birth weight, a greater number of infusions, and a longer interval between the first infusion and membrane rupture were associated with achieving the primary outcome. These associations are clinically coherent and identify membrane preservation and pregnancy prolongation as major targets for protocol refinement [1].

7.3. RAFT FETAL KIDNEY FAILURE COHORT EXCLUDING BILATERAL RENAL AGENESIS

The 2026 RAFT report addressed the central uncertainty highlighted after the bilateral agenesis study: whether the pulmonary benefit also applies to other causes of fetal kidney failure. Thirty-two participants with anhydramnios before 22 weeks underwent serial isotonic amnioinfusion's beginning before 26 weeks at 13 US fetal therapy centers. Twenty-nine pregnancies (91%) resulted in live birth, with a median gestational age of 34 weeks and 1 day. All deliveries occurred before 37 weeks [2]. Nineteen of 29 live-born neonates achieved the primary endpoint of survival for at least 14 days with dialysis access, corresponding to 65.5% (95% confidence interval 45.7%–82.1%). Fourteen live-born infants (48%) survived to discharge at a median age of 4.7 months. At the latest reported follow-up, eleven children were alive and seven had undergone kidney transplantation between two and five years of age. These results provide the first prospective multicenter evidence that serial amnioinfusion can support not only early pulmonary survival but, in a subset, progression through chronic dialysis to transplantation in non-agenesis fetal kidney failure [2]. The difference between the 82% primary outcome in bilateral agenesis and 65.5% in the broader kidney failure cohort should not be interpreted as proof that one diagnosis responds better. Both studies were small, nonrandomized, and had wide confidence intervals. The later cohort included heterogeneous diseases and was treated over an evolving period of fetal and neonatal practice. Its median gestational age at delivery was higher, and its discharge proportion was numerically better. Meaningful comparison requires individual patient data, standardized etiologic subgroups, and adjustment for gestational age, birth weight, treatment duration, and center practices. The prognostic pattern was strikingly consistent across cohorts. In the 2026 study, survivors received a median of 14 infusions compared with 7 among nonsurvivors. The interval from first infusion to membrane rupture was approximately 63.5 days in survivors and 29 days in nonsurvivors. Gestational age above 32 weeks and higher birth weight were also associated with the primary outcome. This reproducibility strengthens the hypothesis that successful therapy depends on sustaining fluid replacement long enough to achieve both pulmonary maturation and a body size compatible with neonatal dialysis [1,2].

7.4. WHAT EFFICACY HAS—AND HAS NOT—BEEN DEMONSTRATED

The most defensible efficacy conclusion is that serial amnioinfusion's can prevent lethal pulmonary hypoplasia in a substantial proportion of carefully selected fetuses with renal anhydramnios. The intervention has therefore crossed the boundary from anecdotal plausibility to prospective clinical evidence. However, no randomized comparison has demonstrated an effect on overall survival, and randomization is ethically and practically difficult because untreated early renal anhydramnios has an extremely high risk of immediate pulmonary death and families may not accept allocation. The evidence does not establish that treatment is safe enough for routine diffusion to low-volume centers, that a particular infusion schedule is optimal, or that all etiologies have similar outcomes. It also does not

establish neurodevelopmental benefit, acceptable family quality of life, cost-effectiveness, or equitable access. Most importantly, the studies show a steep attrition curve from live birth to early dialysis, discharge, and long-term survival. Efficacy should therefore be reported as a sequence of conditional probabilities rather than a single survival percentage.

Table 01: Key contemporary studies informing serial amnioinfusion practice

Study	Design/Population	Main contribution
Atkinson et al., 2022 [7]	Multicenter trial protocol	Defined RAFT eligibility, serial percutaneous isotonic infusions, maternal safety, pulmonary survival to sustained dialysis, and long-term follow-up.
Miller et al., 2023 [1]	Prospective nonrandomized RAFT cohort; bilateral renal agenesis	17 live births; 14/17 (82%) survived ≥14 days with dialysis access; 6/17 (35%) survived to discharge; all delivered preterm.
Bendel-Stenzel et al., 2024 [9]	Survey of RAFT neonatal centers	Demonstrated substantial variation in dialysis, hemodynamic support, sedation, neuroimaging, and ECMO practices.
Lammert et al., 2024 [22]	Single-center neurologic outcome study	Highlighted stroke as an important complication and supported structured neuroimaging and developmental surveillance.
Cheng et al., 2025 [18]	Secondary comparison of infusion strategies	Smaller, more frequent infusions-maintained fluid longer and delayed PPROM without an observed increase in measured obstetric complications.
Jones et al., 2025 [19]	Contemporary review of bilateral renal agenesis	Synthesized fetal intervention, neonatal dialysis, and transplant outcomes in the post-RAFT era.
Baez et al., 2025 [24]	Systematic review of serial amnioinfusion for bilateral renal agenesis	Confirmed growing evidence of pulmonary rescue while emphasizing small samples, heterogeneity, and incomplete long-term data.

Miller et al., 2026 [2]	Prospective nonrandomized RAFT cohort; fetal kidney failure excluding bilateral agenesis	29 live births; 19/29 (65.5%) achieved primary outcome; 14/29 (48%) survived to discharge; 7 of 11 current survivors transplanted.

8. MATERNAL AND OBSTETRIC SAFETY

Serial amnioinfusion is performed on the pregnant patient for anticipated fetal benefit. Maternal safety must therefore be evaluated independently from neonatal success. Across RAFT reports, no pattern of unexpected catastrophic maternal morbidity emerged. This is reassuring, but it should not be summarized as "minimal risk." Repeated transabdominal needle procedures and sustained manipulation of the amniotic cavity predictably increase obstetric complications [1,2]. In the 2026 fetal kidney failure cohort, preterm prelabor rupture of membranes occurred in 19 participants (56%), and chorioamniotic separation occurred in 10 (29%). All participants delivered preterm. The bilateral agenesis cohort also experienced high rates of membrane rupture and universal delivery before 37 weeks. These events are not minor inconveniences. They can lead to hospitalization, infection surveillance, antenatal corticosteroids, magnesium sulfate, antibiotics, emergency delivery, separation from family and employment, and substantial psychological distress [1,2]. Causality is complex because pregnancies with severe fetal anomalies already have elevated risks and because repeated infusions are inseparable from the treatment strategy. Nevertheless, membrane injury is the dominant modifiable procedural threat. Smaller and more frequent infusions may reduce abrupt membrane stretch, but this approach needs multicenter confirmation [18]. Research should examine needle gauge, puncture location, placental relationship, infusion pressure, cumulative volume, operator experience, and biological markers of membrane integrity. Other maternal risks include pain, bleeding, uterine contractions, placental or membrane separation, infection, amniotic fluid leakage, and complications related to prolonged residence near a treatment center. The cumulative burden of travel and repeated procedures can be substantial even in the absence of a formally reportable serious adverse event. Studies should therefore include patient-reported pain, anxiety, financial burden, lost work, caregiving disruption, and satisfaction with decision-making. Future safety reports should use a maternal composite that distinguishes transient procedural events, serious obstetric morbidity, and long-term reproductive outcomes. The health of the pregnant patient should never be treated as a secondary appendix to neonatal survival. A fetal therapy program should have explicit stopping criteria when maternal risk rises, even when continued infusion might offer fetal pulmonary benefit.

9. THE NEONATAL TRANSITION: PULMONARY SURVIVAL IS ONLY THE BEGINNING

Delivery of an infant after serial amnioinfusion should be treated as a planned high-risk transition rather than a routine preterm birth. The neonatal team must anticipate variable lung volume, pulmonary hypertension, prematurity, absent or minimal urine output, electrolyte instability, fluid overload, and the need for early dialysis access. Prenatal conferences should establish resuscitation goals, availability of inhaled pulmonary vasodilators, echocardiography, high-frequency ventilation, extracorporeal membrane oxygenation criteria, surgical timing, and contingencies if dialysis cannot be initiated [9,15,17]. Respiratory status at birth is the first test of treatment efficacy. Some infants can be stabilized with conventional ventilation, whereas others require high-frequency ventilation, inhaled nitric oxide, vasoactive support, or prolonged oxygen. Pulmonary hypertension may reflect both reduced vascular bed and maladaptive transition. A small contemporary case series showed that extracorporeal membrane oxygenation can support selected neonates with congenital kidney failure and severe

pulmonary hypoplasia or pulmonary hypertension refractory to conventional therapy; four of five survived, and several later underwent transplantation. These highly selected results demonstrate possibility, not a general indication, and ECMO combined with dialysis creates major bleeding, neurologic, and vascular risks [20]. Kidney replacement therapy is obligatory for infants with bilateral agenesis and for most infants with anuric end-stage kidney failure. Peritoneal dialysis is often preferred for chronic therapy because it avoids long-term vascular access and can transition to home care. Yet very small infants have limited abdominal capacity, fragile tissues, and high risks of dialysate leak, catheter obstruction, hernia, infection, impaired ventilation, and inadequate ultrafiltration. Surgical placement may be delayed to permit growth or tissue healing, requiring a bridge therapy [15,17,21]. Continuous kidney replacement therapy and adapted ultrafiltration platforms can provide temporary support when peritoneal dialysis is not immediately feasible. Recent infant-specific devices and smaller extracorporeal circuits reduce, but do not eliminate, the problems of blood volume, anticoagulation, vascular access, hypotension, and technical expertise. The availability of devices such as CARPEDIEM-type systems or adapted aqua pheresis platforms varies widely. This variation likely contributes to center-level differences in survival and limits generalizability from RAFT sites to hospitals without dedicated neonatal KRT programs [15,17,21]. Nutrition is another central challenge. Infants with kidney failure require enough energy and protein for rapid growth while fluid intake, potassium, phosphorus, sodium, and acid–base balance are tightly constrained. Many require tube feeding or gastrostomy. Growth failure can delay transplantation because recipient size affects surgical feasibility. Recurrent operations, infection, ventilator dependence, and dialysis interruptions further compromise growth. Therefore, discharge on dialysis is a major achievement but not the end of high-risk care. The multicenter survey of RAFT neonatal management revealed substantial practice variation in dialysis modality, timing, hemodynamic support, sedation, neuroimaging, and ECMO use. This heterogeneity reflects limited evidence and differences in resources. It also means that fetal treatment outcomes cannot be separated from postnatal systems of care. Standardized neonatal pathways and collaborative learning networks are needed so that improvements in dialysis technology translate into reproducible outcomes rather than remaining center-specific expertise [9].

10. NEUROLOGIC AND OTHER MORBIDITY

Neurologic injury is one of the most concerning outcomes reported after pulmonary rescue. In the 2023 bilateral agenesis cohort, strokes and seizures occurred among survivors, contributing to the decision to stop that cohort early. A subsequent single-center analysis examined stroke patterns in infants with early renal anhydramnios treated by serial infusions and reinforced the need for systematic neuroimaging and neurologic follow-up [1,22]. Several mechanisms may converge. Prematurity increases vulnerability to germinal matrix hemorrhage and white-matter injury. Severe pulmonary hypertension, hypoxemia, hypotension, and extracorporeal support can impair cerebral perfusion. Kidney failure produces acid–base and electrolyte disturbances, uremic toxins, platelet dysfunction, and endothelial abnormalities. Dialysis initiation can cause rapid fluid and osmotic shifts. Central catheters, thrombosis, infection, and surgery add further risk. No single mechanism explains every event, and the relative contribution of prenatal disease, delivery, and postnatal treatment is unknown. A minimum surveillance framework should include serial cranial ultrasonography in preterm infants, brain magnetic resonance imaging when clinically appropriate, seizure monitoring for concerning events, standardized neurologic examinations, and long-term developmental assessment. Reporting only survival or gross motor status is inadequate. Outcomes should include cognition, language, hearing, vision, behavior, school readiness, adaptive functioning, and caregiver-reported quality of life. Other morbidity includes necrotizing enterocolitis or intestinal disease, catheter-related infection, peritonitis, sepsis, cardiac instability, arrhythmia, chronic lung disease, feeding intolerance, bone and mineral disorder, anemia, repeated anesthesia, and surgical complications. Some problems are

consequences of prematurity; others arise from congenital disease or dialysis. A useful outcome framework should attribute complications cautiously rather than labeling all morbidity as a direct harm of amnioinfusion. The possibility of substantial disability should be discussed before prenatal treatment, but uncertainty should be communicated honestly. Current samples are too small and follow-up too short to generate precise neurodevelopmental probabilities. Counseling should avoid both extremes: presenting long-term disability as inevitable or presenting respiratory survival as evidence that development will be normal.

11. SURVIVAL TO DISCHARGE, HOME DIALYSIS, AND TRANSPLANTATION

Hospital discharge is a more patient-centered outcome than survival to 14 days, but it remains an intermediate milestone. The 2023 bilateral agenesis cohort reported six of 17 live-born infants discharged on long-term dialysis. The 2026 non-agenesis cohort reported fourteen of 29 live-born infants discharged at a median age of 4.7 months. These prolonged hospitalizations reflect the need to establish stable respiratory function, reliable dialysis, adequate nutrition, caregiver training, and safe outpatient follow-up [1,2]. Home peritoneal dialysis transfers a substantial technical and emotional workload to families. Caregivers must manage sterile connections, cycler alarms, medications, feeding, fluid balance, appointments, and signs of infection, often while coordinating oxygen or other medical technology. Emergency access to pediatric nephrology and dialysis support is essential. Social determinants—housing, transportation, insurance, employment flexibility, health literacy, and family support—can influence whether discharge is feasible even when the infant is medically stable. Transplantation offers freedom from dialysis but is not a return to normal health. Infants must grow to a size compatible with donor organ placement and vascular anastomosis. They must survive infections, maintain adequate nutrition, and avoid prohibitive neurologic or multisystem complications. Donor availability and center criteria vary. After transplant, immunosuppression, rejection surveillance, infection risk, medication adherence, and future graft loss remain lifelong concerns. The transplantation data in the 2026 cohort are therefore highly significant. Seven of the eleven children alive at the latest follow-up had received a transplant between two and five years of age [2]. This demonstrates that the fetal-to-transplant pathway is achievable in a meaningful subset. Earlier reports of infants with bilateral renal agenesis bridged through chronic dialysis to transplantation provided proof of principle, and contemporary reviews now describe an emerging survivor population [5,19]. However, conditional survival must remain explicit. The probability of transplantation among children who survive years on dialysis is not the same as the probability among all fetuses offered treatment. A transparent outcome diagram should begin with all referred pregnancies, then show eligibility, treatment initiation, fetal loss, live birth, pulmonary survival, dialysis initiation, discharge, post-discharge death, transplant listing, transplantation, graft survival, and developmental follow-up. Such reporting would reduce optimism bias and allow meaningful comparison across centers. Long-term registries should also capture family outcomes. Parents of children with chronic kidney disease report elevated stress and anxiety, and the burden may be greater when treatment begins at birth. At the same time, parent narratives from RAFT survivors emphasize that families may value survival despite intensive medical needs. Quality-of-life research should therefore measure burden without presuming that disability or dependence makes life unacceptable [16,23].

12. PROGNOSTIC FACTORS AND A PROPOSED OUTCOME FRAMEWORK

Current evidence identifies several factors associated with early survival: more amnioinfusion’s, a longer interval from treatment initiation to membrane rupture, delivery beyond 32 weeks, and higher birth weight [1,2]. These variables are biologically plausible, reproducible across RAFT cohorts, and useful for program design. They are not yet validated as a bedside prediction model. The number of infusions is especially vulnerable to reverse causation. A stable pregnancy permits more procedures;

an unstable pregnancy ends treatment early. Similarly, birth weight reflects gestational age, fetal growth, disease severity, and treatment duration. Multivariable models in larger cohorts are needed to separate causal factors from markers of survival. Etiology, sex, residual renal function, lung volume, pulmonary artery measures, genetic diagnosis, membrane characteristics, and center experience may also modify outcome. Prenatal imaging is promising but not definitive. Ultrasound can document fluid restoration, thoracic size, renal anatomy, bladder findings, and fetal growth. Magnetic resonance imaging can estimate total lung volume, but thresholds derived from diaphragmatic hernia or membrane rupture may not directly apply to renal anhydramnios. Biomarkers in amniotic or fetal fluid may eventually indicate lung maturation or membrane injury. Until validated, imaging and biomarkers should inform multidisciplinary judgment rather than serve as absolute treatment or resuscitation cutoffs. A clinically meaningful endpoint hierarchy is proposed:

Level 1—Technical and maternal feasibility: successful infusion, fluid restoration, absence of severe maternal morbidity.

Level 2—Pregnancy maintenance: duration of adequate fluid, time to membrane rupture, gestational age at delivery, and birth weight.

Level 3—Pulmonary rescue: survival through initial resuscitation without death from lethal pulmonary hypoplasia.

Level 4—Renal support feasibility: successful and sustained kidney replacement therapy, including bridge modalities and peritoneal dialysis.

Level 5—Survival to discharge: home on a stable treatment plan with caregiver readiness.

Level 6—Long-term survival and transplantation: survival on dialysis, transplant listing, transplantation, graft function, and re-transplantation where applicable.

Level 7—Child and family outcomes: neurodevelopment, growth, respiratory status, quality of life, caregiver burden, financial impact, and decisional satisfaction.

This framework prevents a short-term surrogate from dominating the interpretation of an intervention whose burdens and benefits unfold over years. Future trials should prespecify outcomes at each level and provide Kaplan–Meier or competing-risk analyses from treatment initiation, not only among live-born survivors.

Table 02: Integrated fetal-to-child clinical pathway

Stage	Clinical goal	Major threats/uncertainties
Prenatal diagnosis	Confirm renal cause of anhydramnios, onset before 22 weeks, irreversibility, isolated disease where possible, and genetic context.	Misdiagnosis; unrecognized membrane rupture; syndromic disease; uncertain prognosis.
Fetal therapy	Begin serial ultrasound-guided isotonic amnioinfusion's before 26 weeks and maintain adequate fluid.	PPROM, chorioamniotic separation, infection, bleeding, contractions, treatment interruption.

Delivery	Prolong pregnancy safely and deliver at a center with neonatal KRT and surgery.	Universal/high preterm birth, low birth weight, emergent delivery, geographic access.
Pulmonary transition	Avoid death from lethal pulmonary hypoplasia and control pulmonary hypertension.	Refractory hypoxemia, pulmonary hypertension, ventilation injury, ECMO-related risk.
Kidney support	Establish bridge KRT and/or peritoneal dialysis with adequate nutrition and growth.	Access failure, leak, infection, hypotension, inadequate clearance, abdominal complications.
Discharge	Achieve stable home dialysis, caregiver competence, and multidisciplinary follow-up.	Prolonged hospitalization, caregiver burden, inequitable home resources, readmission.
Transplant and childhood	Reach transplant, preserve graft function, and optimize development and quality of life.	Death on dialysis, delayed growth, neurodevelopmental injury, rejection, lifelong chronic disease.

13. ETHICAL ANALYSIS

Serial amnioinfusion raises ethical questions because it transforms the prognosis rather than curing the disease. Without treatment, early renal anhydramnios is expected to cause neonatal respiratory death. With treatment, the fetus may become a child who requires dialysis from birth, repeated surgery, prolonged hospitalization, and transplantation. The moral question is therefore not simply whether clinicians should prevent death, but how to evaluate a pathway that substitutes one set of risks and burdens for another [14–16]. Respect for maternal autonomy is central because the pregnant patient undergoes repeated invasive procedures. Consent must be voluntary, revisited over time, and free from language that frames treatment as the only loving or courageous choice. The option to stop infusions should remain available if maternal risk, fetal findings, or family goals change. Consent for prenatal intervention should also be linked to realistic planning for neonatal care; otherwise, families may agree to pulmonary rescue without understanding the near-certainty of dialysis. The future child's interests require balanced consideration. Some ethicists caution that survival with severe medical dependence may expose the infant to suffering without a sufficiently likely long-term benefit. Others argue that clinicians should not assume that chronic disease, disability, or dialysis makes survival contrary to the child's interests, especially when transplantation is possible and families report meaningful relationships and acceptable quality of life. Current evidence does not resolve this disagreement, but it supports a shared decision model rather than categorical prohibition or obligation [14–16]. Justice is an equally important concern. RAFT care requires repeated travel to a fetal center, prolonged maternal proximity to specialized hospitals, highly resourced neonatal intensive care, infant dialysis technology, trained home caregivers, and transplant access. Families with fewer financial resources, restrictive insurance, unstable housing, limited paid leave, or geographic distance may be excluded in practice even when medically eligible. A therapy should not be labeled broadly available when only a small subset can reach and sustain the full pathway. Resource stewardship should be discussed transparently but not used selectively against rare congenital disease. Neonatal dialysis and transplantation are

expensive and labor intensive, yet so are many accepted forms of neonatal and pediatric intensive care. Fair policy requires consistent criteria based on expected benefit, burden, and patient values, not diagnosis-based stigma. Multicenter registries and cost analyses can help health systems plan equitable regional programs. Moral distress among clinicians is foreseeable. Teams may differ in their willingness to provide ECMO, repeated surgery, or prolonged dialysis when prognosis is uncertain. Institutions should establish ethics support, multidisciplinary case review, and conflict-resolution processes before offering fetal therapy. Clear criteria for potentially inappropriate treatment and compassionate redirection of care are necessary, but they should not be improvised during a crisis after birth. Finally, outcome communication itself is an ethical obligation. Publications and counseling materials should avoid describing amnioinfusion as a cure. The most accurate description is that it can rescue lung development and create an opportunity for neonatal renal replacement therapy. Hope is appropriate, but it should be "bounded hope"—hope grounded in absolute numbers, uncertainty, and preparation for both survival and death.

14. LIMITATIONS OF THE CURRENT EVIDENCE

The evidence base remains small. RAFT is the strongest available dataset, but both major outcome reports were nonrandomized and included limited numbers of treated pregnancies. Confidence intervals are wide, and uncommon maternal or neonatal harms may not yet be visible. Enrollment at expert US centers limits external validity to other health systems and countries [1,2]. Selection bias is substantial. Participants underwent detailed evaluation, had access to specialized care, and were willing and able to pursue repeated procedures and intensive neonatal treatment. Fetuses with major additional anomalies were generally excluded. Outcomes should not be generalized to syndromic disease, uncertain diagnoses, later-onset oligohydramnios, or settings without neonatal dialysis. The short-term RAFT primary endpoint was designed to test pulmonary efficacy, not comprehensive benefit. Survival to 14 days with dialysis access is clinically meaningful, but it can overstate success if presented without discharge and long-term outcomes. Follow-up duration differs among survivors, and later transplantation creates survivorship bias. Neurodevelopmental and family quality-of-life data remain limited. Etiologic heterogeneity complicates the 2026 cohort. Bilateral dysplasia, obstructive disease, cystic kidney disorders, and other causes may have different residual function and associated morbidity. Larger studies should report outcomes by diagnosis and genotype. Likewise, evolving neonatal technologies mean that outcomes from early RAFT participants may not represent current practice. Procedure protocols varied by center and were individualized. This reflects appropriate clinical judgment but limits identification of an optimal volume, interval, or target fluid level. Associations between infusion number and survival cannot establish causation. Maternal patient-reported outcomes and long-term reproductive outcomes are underdeveloped. Publication bias remains relevant outside RAFT. Successful transplant stories are compelling and may receive disproportionate attention, while deaths after prolonged intensive care are less visible. Registries should capture all referred and treated cases, including those who stop treatment, experience fetal loss, choose comfort care, or die after discharge.

15. RESEARCH PRIORITIES

The next phase of research should move from proof of pulmonary efficacy to optimization of the entire care pathway. First, infusion protocols require prospective comparison. Key variables include initiation timing, target fluid volume, smaller frequent versus larger intermittent infusions, needle gauge, infusion pressure, and strategies to preserve membranes. A randomized procedural comparison may be feasible even if randomization to treatment versus no treatment is not. Second, predictive models should combine the duration of untreated anhydramnios, gestational age at first infusion, treatment exposure, fetal lung imaging, birth weight trajectory, renal diagnosis, genotype, residual urine production, and

center-level factors. Models should predict multiple outcomes, including pulmonary survival, discharge, and transplantation, and should be externally validated. Third, neonatal management should be standardized through consensus pathways. Research priorities include optimal timing of peritoneal dialysis catheter placement, bridge KRT modality, anticoagulation, pulmonary hypertension treatment, nutritional targets, infection prevention, neuroimaging, and ECMO candidacy. Infant-specific dialysis devices should be evaluated in multicenter comparative studies [9,15,17]. Fourth, long-term follow-up must extend into childhood. Registries should capture survival, transplant timing, graft function, growth, respiratory health, hearing, vision, neurodevelopment, school performance, repeated hospitalization, and patient-reported quality of life. Family outcomes should include mental health, relationship strain, financial toxicity, caregiver employment, sibling impact, and decisional regret or satisfaction. Fifth, outcome reporting should become denominator transparent. Every publication should show the number referred, screened, eligible, treated, live-born, dialyzed, discharged, alive at each time point, transplanted, and lost to follow-up. This is especially important in rare disease, where a change of one or two patients can substantially alter percentages. Sixth, global implementation research is needed. Most current evidence comes from the United States. The therapy may be impossible to sustain where neonatal dialysis, transplantation, or maternal travel support is unavailable. International registries could identify which components are transferable and where regional centers are needed. Equity metrics should be included from the start. Seventh, ethical research should continue alongside clinical innovation. Prospective studies of counseling comprehension, parental values, clinician attitudes, and moral distress can improve consent. Parent partners should participate in protocol design and outcome selection, while avoiding the assumption that survivor families represent all families who underwent treatment. Finally, nomenclature should be standardized. “Successful amnioinfusion” should not refer merely to fluid instillation or live birth. Terms such as technical success, pulmonary rescue, dialysis survival, discharge survival, and transplant survival should be used precisely. Clear language will improve both science and counseling.

16. CLINICAL PRACTICE IMPLICATIONS

The combined RAFT evidence supports a change in counseling: selected families with isolated renal anhydramnios should no longer be told that neonatal respiratory death is absolutely inevitable. Serial amnioinfusion can permit pulmonary survival in a substantial proportion of treated pregnancies, including cases caused by fetal kidney failure other than bilateral renal agenesis [1,2]. This change should not be interpreted as endorsement of routine community-based treatment. The intervention remains highly specialized and should be offered through experienced fetal therapy programs linked to neonatal dialysis and transplantation. Referral should occur promptly after diagnosis because treatment timing and duration appear important. Clinicians should present outcome data as a staged pathway. For the 2026 non-agenesis cohort, 29 of 32 treated pregnancies resulted in live birth, 19 of 29 live-born infants achieved the primary outcome, 14 survived to discharge, and 11 were alive at latest follow-up, of whom seven had been transplanted. For the 2023 bilateral agenesis cohort, 17 live births were followed by 14 primary-outcome survivors and six discharges. These figures are more informative than a single statement that amnioinfusion “works” [1,2]. Prenatal management should prioritize membrane preservation and gestational prolongation. Postnatal planning should prioritize immediate cardiopulmonary stabilization, early KRT feasibility, nutrition, neuroprotection, and family training. Palliative care should be involved from diagnosis, not only when treatment fails, because it can support symptom management, communication, and values-based decisions alongside life-prolonging care. A center considering a program should demonstrate operator experience, maternal safety protocols, 24-hour neonatal and surgical coverage, multiple infant KRT options, transplant collaboration, ethics support, data collection, and long-term follow-up. Without these elements, the institution may be able to perform the infusion but unable to deliver the therapy as a whole.

17. CONCLUSION

Serial amnioinfusion's have changed early renal anhydramnios from a condition defined by inevitable lethal pulmonary hypoplasia into one for which survival is possible. The strongest evidence comes from the RAFT program. In bilateral renal agenesis, most live-born infants achieved short-term pulmonary survival with dialysis access, although only about one-third survived to discharge in the initial report. In fetal kidney failure excluding bilateral agenesis, nearly two-thirds of live-born neonates achieved the short-term endpoint, almost half survived to discharge, and several progressed to kidney transplantation. These results establish pulmonary efficacy but also expose the limits of a lung-centered definition of success. Maternal membrane complications and preterm birth are common. Neonatal death may occur from pulmonary hypertension, prematurity, dialysis failure, infection, neurologic injury, or multisystem complications. Survivors face years of dialysis, intensive caregiving, and transplantation. The responsible clinical position is neither to dismiss serial amnioinfusion as futile nor to present it as a cure. It is a pathway-opening fetal intervention whose value depends on careful selection, sustained pregnancy, advanced neonatal kidney support, transplant access, family goals, and long-term outcomes. Future research should standardize procedures and neonatal care, validate prognostic tools, measure neurodevelopment and family quality of life, and ensure equitable access. Until then, serial amnioinfusion should be offered within expert multidisciplinary programs using transparent, stage-specific counseling and rigorous prospective follow-up.

AUTHOR CONTRIBUTION STATEMENT

Nusrat Arif: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Drafting the work or reviewing it critically for important intellectual content; AND Final approval of the version to be published, and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplemental Material

No supplementary files, datasets, figures, or additional materials are associated with this study. Any information necessary to understand and evaluate the work is included in the main article.