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Anhydramnios in the Setting of Renal Malformations: The National Institutes of Health Workshop Summary

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Abstract

Anhydramnios in the setting of severe malformations of the fetal kidney and urinary tract is associated with a high incidence of stillbirths and life-threatening complications, including severe pulmonary hypoplasia, umbilical cord compression, and perinatal asphyxia. To prevent such adverse outcomes, some centers in the United States and elsewhere are offering amniotic fluid restoration for women diagnosed with anhydramnios in the setting of fetal renal malformations. The procedures include infusions of amniotic fluid-substitutes (normal saline), percutaneously or through an amniopore—an implanted system for serial or continuous infusion of normal saline to maintain the desired amniotic fluid volume. The procedures are intended to prevent pulmonary hypoplasia and allow the pregnancy to progress closer to term gestation, enabling postnatal renal management, including long-term dialysis and renal transplantation. However, these procedures have not been recommended as standard of care by the professional societies, since there are many knowledge gaps, including little data on short and long-term renal outcomes. The available diagnostic methods do not provide reliable prognostic information, and the current maternal and fetal interventions have not been standardized. To address these unresolved issues and to propose a research agenda, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invited a panel of experts to a workshop in August 2016. This report provides a summary of that meeting.

Introduction

The reported annual incidence of oligohydramnios in the U. S. ranges between 5% and 12%, or one in about 400,000 to 480,000 pregnant women. The variation is due to the definitions used, regional differences, and other unknown factors.^{1, 2} Anhydramnios (deepest vertical

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The summary is based on the presentations and discussions at the NIH workshop on August 8, 2016, by the invited speakers and panel members listed in Appendix 1, available online at <http://links.lww.com/xxx>.

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pocket of amniotic fluid 2 cm in the second trimester³) can lead to several devastating fetal complications. These include acute umbilical cord compression causing asphyxia or stillbirth, severe fetal skeletal structural abnormalities, and pulmonary hypoplasia that could be lethal in the neonatal period. There is also a high rate of cesarean delivery.¹ The etiology of this condition is multi-factorial, among which congenital anomalies of the kidney and urinary tract (CAKUT) are the most significant. The clinical manifestations of anhydramnios can be varied, and the management strategies, especially for CAKUT cases have not been standardized. Yet, several centers offer medical and surgical interventions to the pregnant woman and her fetus affected by CAKUT, with an intent to prevent the fetal consequences of diminished amniotic fluid volume and restricted intrauterine space,^{4, 5} and advance the pregnancy to term, with a plan for neonatal management of renal and pulmonary complications after delivery. However, the long-term outcomes from these strategies have not been uniformly assessed.

To summarize our current understanding of anhydramnios secondary to CAKUT, including diagnoses and management aspects, as well as to define knowledge gaps and propose a research agenda, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invited a panel of experts to a workshop in August 2016. This paper provides a summary of the workshop presentations and discussions to help clinicians in the management and counseling of patients affected by these complex conditions, based on existing evidence, and to invite researchers to undertake studies to address current knowledge gaps.

Physiology of Amniotic Fluid Volume Regulation

Despite our knowledge that amniotic fluid is very important for the normal development of the fetus,⁶⁻⁸ research into the biology of amniotic fluid production and absorption, as well as the pathophysiology of amniotic fluid volume abnormalities has been sparse. In normal pregnancies, the amniotic fluid volume increases as the pregnancy progresses, peaking at around 32 to 34 weeks of gestation, and decreasing thereafter. Amniotic fluid production and clearance evolve over three distinct phases: the embryonic, early fetal, and late fetal. During the embryonic period, coelomic fluid is manufactured first, which completely disappears by the early part of the fetal period, at which time the amniotic fluid that began in the embryonic period continues to accumulate. The mechanisms underlying these dynamics are not well known. Using fetal sheep models several investigators have described various pathways of amniotic fluid production and clearance channels.⁸⁻¹⁰

Four quantitatively significant inflow and outflow tracts have been shown during the late fetal period. These are: the urine flow, fetal swallowing, outflow of lung secretions, and the transport of amniotic water and solutes across the amniotic membrane into the fetal circulation, also known as intra-membranous absorption (IMA)¹¹. Fetal sheep models demonstrate that the IMA routes are the most important determinants of amniotic fluid volume—far more than the urine flow, swallowing, and secretions from the lungs. This is primarily mediated by unidirectional vesicular transport or “transcytosis” of all solutes and water, modulated by factors yet to be identified. However, membrane biologists and other

investigators consider that water diffusion via aquaporin channels is likely to be a major mechanism in the amniotic membrane.^{9, 10} Fetal urine contains a stimulator of IMA, while fetal membranes secrete an inhibitor of IMA.¹¹

Over a 24-hour period, there is a complete turnover of amniotic fluid volume through the inflow and outflow components described above. Important mediators involved in the transfer of water across the amnion include vascular endothelial growth factor (VEGF), and aquaporin 1 (AQP1). It is also worth noting that each fetus has its own unique operational set point to maintain the amniotic fluid volume throughout pregnancy.

Epidemiology and Genetics of Renal and Urogenital Developmental Abnormalities

Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading causes of chronic kidney disease in children. Since urine flow plays a significant role in amniotic fluid volume generation, there is often concern for the presence of renal anomalies in cases of anhydramnios. The incidence and outcomes of renal and urogenital malformations are listed in Table 1. While the kidneys can be visualized by week 12 of gestation, abnormalities are more commonly detected in the mid-second trimester or later. In about 30% of infants, renal malformations are associated with additional non-renal congenital anomalies.¹²

Many key molecules and pathways that govern specific components of kidney and lower urinary tract development have been described, but how these factors interact in an integrated fashion is not well understood. Most of the molecules that have been identified in animal models as having critical roles in kidney and urinary tract development have been shown to have parallel human correlates.^{13, 14} Several genes have been implicated in bilateral renal aplasia, but they are rarely the singular cause for this condition in humans. Other syndromic causes of renal anomalies such as *PAX2* and *EYA1* mutations; solitary gene ciliopathies; copy number variation with complex genetics;^{15, 16} environmental factors, such as prenatal exposure to angiotensin-converting enzyme inhibitors; and polycystic kidney disease (an aberration of terminal epithelial differentiation), can also lead to significant renal parenchymal malformations.

More than 40 dominant and recessive mutations have been identified as causes of syndromic or non-syndromic CAKUT, a heterogeneous group of conditions.¹⁷ Recessive mutations are usually associated with syndromic forms of CAKUT, while dominant mutations often result in isolated forms of CAKUT, though some may be caused by recessive mutations.¹⁸⁻²³ The presence of an unequivocal molecular genetic diagnosis enables mechanistic and physiologic studies of the disease along with genotype-phenotype correlations.

Diagnostic and Prognostic Aspects

Some components of antenatal diagnostic evaluation are listed in Box 1. Prenatal imaging of the kidneys is extremely critical to develop plans for intervention. Prenatal ultrasound is the most commonly used diagnostic imaging modality. In selected cases and in some centers,

magnetic resonance imaging (MRI) is also used to establish anatomical diagnoses of kidney anomalies in cases with anhydramnios.^{24, 25}

Ultrasound

Professional societies^{25, 26} and other experts²⁷ recommend antenatal ultrasound at 18 to 20 weeks of gestation at which time a qualitative or semi-quantitative estimate of amniotic fluid volume should be carried out, including computing the amniotic fluid index or maximum vertical pocket. Information about the kidneys should include their presence and location, as well as the existence of abnormal echogenicity, cysts or urinary tract dilation. One should also look for the presence of the urinary bladder and assess its size and shape, and the number of vessels in the umbilical cord along with its insertion point on the abdominal wall. Evaluation should include assessing whether there are other anomalies of the urogenital tract. For these reasons, antenatal ultrasound remains a good first choice even in presence of anhydramnios, to assess fetal renal and urogenital anatomy.^{25, 28}

Interpreting ultrasound findings of echogenicity and cystic changes can often be challenging because even echogenic kidneys with normal amniotic fluid volume may be associated with outcomes that range from being totally normal to seriously abnormal, or even lethal renal failure at birth. This is a particularly vexing problem for counseling. The relationship between renal size, nephron number, and renal function remains unclear.²⁹ Diagnosing the pathological significance of a dilated urinary tract can also be challenging. Due to multiple grading systems currently in use, defining urinary tract dilation and comparing findings between studies becomes more problematic. A recently-proposed urinary tract dilation classification system, yet to be validated, may become useful in the future.^{30, 31} This method incorporates parameters based on gestational and postnatal age, such as, the anterior-posterior renal pelvic diameter, calyceal dilation, parenchymal thickness, parenchymal appearance, and the appearance of the ureter and bladder.

Severe lower urinary tract obstruction can also cause oligo or anhydramnios. Causes for obstruction include posterior urethral valves, urethral atresia, and prune belly syndrome. Although isolated case reports and small-cohort studies indicate that these conditions may be associated with better lung development,^{32, 33} the pulmonary status at birth depends upon the extent of oligohydramnios–anhydramnios in relation to the timing of lung growth. Even in cases with good lung development, the renal outcomes remain poor.

The degree of renal damage is associated with the duration of the obstruction and is important in determining how much functional recovery is likely.^{34, 35} Prenatal intervention decisions are based on the ultrasound findings of lower urinary tract obstruction, the severity of oligohydramnios–anhydramnios, and fetal urinary electrolytes.³⁶ In general, antenatal ultrasound has better sensitivity than specificity for identifying lower urinary tract obstruction. For example, in a recent study, the “keyhole sign,” considered pathognomonic of posterior urethral valves (PUV), was seen only in 51% of infants confirmed to have PUV postnatally, and was seen in 37% who did not have PUV.³⁷ In spite of improved ultrasound technology, we cannot reliably predict the potential for benefit from fetal interventions based on the ultrasound imaging findings.

Magnetic Resonance Imaging (MRI)

Most of our knowledge about the value of MRI in assessing renal abnormalities comes from single case reports or small case series.³⁸⁻⁴² MRI is considered safe during pregnancy, and there are no reports of adverse fetal effects from short-term exposure to electromagnetic fields. Most safety studies have been done at 1.5 Tesla (T), and although approved by the U.S. Food and Drug Administration, the potential increase in the temperature of the amniotic fluid with 3T imaging should be considered.^{26, 38, 43, 44} Gadolinium is a class C molecule in pregnant women. It crosses the placenta and is excreted by the fetal kidney. However, gadolinium lingers in the amniotic fluid, and there is evidence in children and adults that it is deposited in the brain. Gadolinium is a heavy metal that is known to slightly retard development in rats, so it should probably be avoided for MRI in pregnancy, unless the benefits outweigh the risks, which is unlikely in the assessment of fetal renal anomalies.⁴³

The lack of amniotic fluid might limit the ability to assess some aspects of fetal renal anatomy with ultrasound. Because of the ability to obtain the images of the entire body, MRI can be more helpful in diagnosing complex anatomical pathologies compared to ultrasound studies. For example, MRI helps to visualize megacystis microcolon in association with a hugely-dilated bladder and normal amniotic fluid volume, which is difficult with ultrasound since the colon may not be easily visualized. MRI (especially T1 and T2 imaging) can also be helpful in differentiating meconium-containing colon versus dilated bladder, and in diagnosing rare abnormalities, such as cloacal or bladder exstrophy and sirenomelia.^{26, 45} However, based on the published literature, it is unclear whether the findings from MRI will alter patient care, counseling, or outcomes, as compared to an ultrasound study alone.^{44, 46-48}

Antenatal Interventions

Fetal intervention for urological obstruction can be defined as a broad group of procedures, which can be accomplished either through an “open surgical approach” that involves uterotomy, or a “closed surgical approach” which does not involve uterotomy. Currently, most surgeons prefer the closed surgical approach.^{3, 5, 24, 36, 49}

In 1982, Harrison performed the first surgical fetal intervention for congenital hydronephrosis⁵⁰ and he outlined an ethical framework for the timing of fetal interventions. He also emphasized that interventions should not be undertaken simply because of the ability of the surgeon to perform those procedures. Subsequently, several investigators have summarized that ideal candidates for successful fetal surgical intervention are those with an isolated kidney defect, who are products of singleton pregnancies with no other fetal structural anomalies. The availability of specialists including high-risk obstetrics and neonatology, advanced neonatal, pediatric, renal, and surgical units, and pediatric geneticists along with bioethicists for counseling are also required. One also needs to balance the benefit from advancing pregnancy and preventing pulmonary hypoplasia against the risk for miscarriage, premature delivery, undetected serious malformations, and amnionitis which can lead to fetal infections, fetal death or even maternal sepsis.

Choosing the appropriate timing for fetal intervention has been a major challenge. The fetus begins to form urine at 8 to 10 weeks of gestation and by 16 to 20 weeks of gestation, critical lung development begins to take place. However, the diagnosis of anhydramnios and the associated fetal anomalies are often not made until 18 to 20 weeks or later in gestation because that is when most women undergo a routine full fetal-anatomical survey with ultrasonography. By then, many critical, often irreversible, consequences of abnormal kidney development have been established.

In 1994, Cameron et al reported amniotic fluid infusions to treat a case of anhydramnios secondary to fetal renal agenesis. After ten amnio-infusions between 17 and 33 weeks' gestation, they delivered the infant due to chorioamnionitis.⁴ Despite good pulmonary growth, a normal skeletal system, and early peritoneal dialyses, the infant died on the 23rd day of age, and the autopsy revealed evidence of significant cerebral pathology. Expressing ethical concerns, the authors discouraged this approach for managing cases of anhydramnios due to renal agenesis.⁴ In one of the earliest cohorts undergoing fetal surgical interventions between 1982 and 1999, the reported mortality rate was about 43%. Preterm birth was almost universal, associated with either premature rupture of membranes or placental abruption.⁵¹ Although the risk of fetal mortality due to antenatal intervention has been reduced due to improved ultrasound evaluations and refinement of surgical techniques, such as the use of miniaturized needles and other instruments, long-term renal outcomes in this high-risk groups remains unclear.

In the well-designed European trial titled, *Percutaneous Shunting in Lower Urinary Tract Obstruction* (PLUTO), the impact of prenatal intervention on postnatal outcomes was evaluated.⁵² Patients were randomized to undergo the placement of a vesico-amniotic shunt, or no surgical intervention. Eight of 16 neonates from pregnancies with shunts survived for 28 days, compared with 4 of 15 managed conservatively. However, there were significant morbidities in both groups; only two infants in the shunted group survived to age 2 years with normal renal function. Given these results, the PLUTO investigators could not conclude that fetal vesico-amniotic shunting was beneficial in the long run. Some aspects of antenatal intervention are summarized in Box 2.

Polzin et al reported outcomes of 15 patients with severe oligohydramnios–anhydramnios due to fetal urogenital malformations.³ Six women chose comfort care, and one received percutaneous amniotomies. Nine amniotomies were performed in the remaining 8 patients with modifications of the technique described by Tachiricov et al.⁵³ The fluid restoration was successful in all. One infant died due to unrecognized laryngeal web and another died of pulmonary hypoplasia after preterm premature rupture of membranes. None of the remaining six had pulmonary hypoplasia. Three infants, all with lower urinary tract obstruction due to posterior urethral valves, survived infancy to receive renal transplantation at 19, 22, and 24 months of age, and are being followed. The remaining 3 infants with renal parenchymal malformations, died on day of life 1, 9, and 94.

Postnatal Management and Long-Term Outcomes of Infants with Abnormal Kidneys Identified Prenatally

Currently, more than 90% of women undergo antenatal ultrasound evaluation, resulting in an increasing number of fetal renal abnormalities being diagnosed in recent years. Therefore, there is an urgent need to develop evidence-based, cohesive plans for patient management and family counseling. Some suggested aspects of postnatal management are detailed in Table 2.

In a retrospective study of pregnancies diagnosed with oligohydramnios and associated kidney anomalies during 2000-2008 in the Netherlands, the pregnancy outcome, mortality and morbidity, and infants' glomerular filtration rate (GFR) during follow-up were reported. Among the 71 fetuses affected, 36 had cystic dysplasia, 15 had polycystic kidney disease and 20 hydronephrosis. Twenty-three (32%) had other associated anomalies. There were 25 live births, of whom 10 survived, 7 with a diagnosis of hydronephrosis. An isolated anomaly was associated with higher survival chances. The 1-year GFR was below 50 mL/min.1.73 m² in four of the ten survivors. The authors concluded that the overall prognosis for early onset renal oligohydramnios was poor.³⁴

In another, more recent retrospective review based on registry data from 524 infants with CAKUT,⁵⁴ the predictive factors for neonatal mortality were assessed. The overall mortality rate was 24%. Independent risk factors for early neonatal mortality included chromosomal or non-chromosomal syndromes, involvement of additional organs or systems, prematurity, low birth weight, oligohydramnios, and the degree of renal involvement. The risk of chronic kidney disease was 6% at 10 years of age and it was worse for patients with hydronephrosis associated with lower urinary tract abnormalities and dysplastic kidneys than for those with isolated hydronephrosis. Therefore, patients with CAKUT need long-term follow-up, including strict control of blood pressure and close attention to changes in renal function.

Ethical Aspects of Decision-Making Concerning Maternal-Fetal Interventions

While the goals of prenatal counseling are many, first and foremost is addressing parental concerns with openness and candor. To facilitate this, a comprehensive team of healthcare experts should be assembled.

The first step for the team is to identify whether the planned maternal-fetal intervention is an innovation—an IRB-approved experiment—on a group of fetuses and pregnant women to create generalizable knowledge, or it is part of an accepted clinical practice based on a well-established net clinical benefit to the fetus and pregnant woman. For maternal-fetal interventions classified as either innovation or research, the pregnant woman must weigh the options of *in-utero* intervention, termination of pregnancy (in accordance with applicable local and state laws), or an expectant management followed by palliation or hospice care in cases of live birth. On the other hand, maternal-fetal interventions considered “accepted clinical management” can be offered to such pregnant woman.

The first time (or very early on) a maternal-fetal intervention is planned in the absence of the results from Phase I trials should be classified as innovation. Innovation needs to have the potential for benefit based on scientific and clinical justifications, along with approvals from scientific communities, and a process for obtaining informed consent.⁵⁵ The informed consent process needs to clarify that the innovation is an experiment, in that its outcome cannot be reliably predicted. This process also needs to clarify that since the innovation is an experiment, there is no ethical obligation for the pregnant woman to authorize the intervention for her fetus.⁵⁶

Because of many unknown issues discussed in this article, maternal-fetal interventions for anhydramnios in the context of severe fetal kidney anomalies is still not considered an accepted standard clinical practice. Once many knowledge gaps have been resolved, we may get there; however, even after reaching that stage, given the complex nature of the conditions and treatments involved, the team should work with the pregnant woman and her family to develop a unified, and an up-to-date evidence-based care plan for *in-utero* treatment, timing and place for delivery, as well as postnatal management that is satisfactory to all. Moreover, the pregnant woman's autonomy in making management decisions should be respected at all times. After a detailed discussion of potential risks for her and her fetus, she would be in a better position to make an informed decision. The team needs to be aware of the anxieties of parents and be especially attentive when such anxieties seem disproportionate to the severity of the fetal anomaly, and thus may potentially interfere with the pregnant woman's exercise of her autonomy in the decision-making process. The pregnant woman and those she has involved in decision making may approach the consultation team with prior assumptions and concerns that may be different from those of the healthcare team. For instance, sometimes the family may perceive a minor renal anomaly as catastrophic, or conversely sometimes they may think even with severe anhydramnios, amnioinfusion will "cure" the lung problem and all else will be easily solved. p Therefore, the healthcare team needs to be sensitive to such perceptions, and be cohesive in its approach to counseling, while being sensitive to the wishes and concerns of the parents, and frank in explaining the possibilities and realities of good or poor outcomes.

In offering innovative or investigational maternal-fetal interventions, or when planning for an accepted maternal-fetal intervention, the team should provide an evidence-based assessment of the likelihood of fetal survival. For fetuses surviving through the birthing process, the team should provide an evidence-based assessment of whether early pulmonary support will be needed, which influences the decision for the potential of early dialysis initiation. The available data about the prognosis for an infant requiring early dialysis should also be presented^{57,58}. Other important issues to assess in the decision-making process are the availability of appropriate resources as noted above.

It is very critical to describe to the pregnant woman, the biological role of the amniotic fluid for fetal health, including its role in lung development, and how a loss of amniotic fluid can lead to a severe, often lethal pulmonary hypoplasia. The latter fact is not often appreciated by the families, yet an autonomy-based decision-making process requires that they take this important fact into account. It is also important to explain that, despite the ability to offer

dialysis to support kidney function postnatally, severe pulmonary hypoplasia alone could be the key determining variable affecting long-term management.

While all healthcare professionals know the principle of *primum non nocere* (first do no harm), a more comprehensive ethical principle is beneficence – an assessment of the situation based on the evidence-based probability of outcomes with a net balance of clinical goods over harms. Beneficence-based obligations to the fetal patient and neonatal patient, and their limits, must be considered as part of an autonomy-based decision-making process. Input from experts in the ethics of maternal-fetal interventions may facilitate the pregnant woman's autonomy.

Developing a clear management plan early in the second trimester is fraught with uncertainties. When cumulative evidence for an established treatment is conclusively beneficial, counseling could be directive with a recommendation for intervention. However, the strength of such direct recommendations for intervention for anhydramnios in the face of renal dysfunction is based on limited available medical evidence.

Some ethicists propose that since there is no currently accepted treatment for bilateral renal agenesis, serial amnioinfusion therapy during pregnancy is not to be considered the “usual care” or the “standard of care.” Because cumulative evidence on complications of pregnancy and short and long-term outcomes for fetal and neonatal patients are lacking, this maternal-fetal intervention should be considered research.

For physicians in clinical practice, there is no ethical obligation to refer a pregnant woman for innovative or investigational maternal-fetal intervention, because there is no proven benefit to the fetal patient. However, there is a beneficence-based obligation to future fetal patients to support clinical research that meets the highest scientific standards by informing pregnant women about the availability of such protocols. Providing this information supports an informed decision by the pregnant woman about the alternatives for the subsequent management of her pregnancy.

Summary and Conclusions

Severe oligohydramnios–anhydramnios can result from a complex group of conditions, and developmental renal malformations are important contributors to this condition. As more pregnant women receive routine antenatal imaging studies earlier in pregnancy, more renal and urinary malformations may be discovered, requiring caregivers to develop a comprehensive plan before birth. Some of the many knowledge gaps that exist in this field are listed in Box 3.

An evidence-based approach to the treatment and management of anhydramnios has not been established, and this field is still evolving. The fundamental understanding of amniotic fluid volume regulation in normal and oligohydramnios–anhydramnios conditions is far from complete. Treatment plans may need to be developed on a case-by-case basis including an informed and frank discussion with the family, with a collaborative team including experts in high-risk obstetrics, neonatology and pediatric care, pediatric surgery–urology, pediatric nephrology, intensive care nursing, pediatric radiology and MRI, genetics, and

most importantly, bioethicists. While innovative approaches to treating *one* pregnant woman or her fetus does not yield generalizable knowledge, they can be hypotheses-generating experiences that can be tested to produce such generalizable knowledge in subsequent IRB-approved research. Therefore, it is imperative to recognize that the more invasive the maternal-fetal intervention, the stronger the beneficence-based obligation to submit the planned innovation and research for prospective review as noted above, as well as to obtain informed consent from the pregnant woman.

If an innovative therapy leads to a testable hypothesis, the next step should be to develop a research protocol. Given that these conditions are rare, a collaborative team effort may be more conducive to developing a rigorous evidence-base for managing these complex conditions.

Similar to the National Extracorporeal Membrane Oxygenation (ECMO) Registry experience that began as an informal group in the early 1980s,^{59, 60} the scientific community involved in the management of oligohydramnios–anhydramnios and renal malformations may consider developing an ongoing voluntary registry to collect data prospectively from patients whose personal identifiers have been deleted. Two fundamental values should guide responsible innovation and research: scientific excellence and ethical excellence.

Scientific excellence requires that innovation and research provide the critical knowledge to meet an important clinical need, be well designed, rigorously conducted, analyzed, and reported. Ethical excellence requires that human study participants be protected by minimizing the number needed to test the hypothesis, minimizing the risks of participation, securing informed consent, and having the oversight of a data and safety monitoring committee.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Shrem G, Nagawkar SS, Hallak M, Walfisch A. Isolated Oligohydramnios at Term as an Indication for Labor Induction: A Systematic Review and Meta-Analysis. *Fetal diagnosis and therapy*. 2016; 40(3):161–73. [PubMed: 27160748]
2. Beloosesky, R., Ross, M. Oligohydramnios. 2017. November 18, 2017 [cited; Available from: <https://www.uptodate.com/contents/oligohydramnios>]
3. Polzin WJ, Lim FY, Habli M, Van Hook J, Minges M, Jaekle R, et al. Use of an Amniopore to Maintain Amniotic Fluid Volume in Fetuses with Oligohydramnios Secondary to Lower Urinary Tract Obstruction or Fetal Renal Anomalies. *Fetal diagnosis and therapy*. 2017; 41(1):51–7. [PubMed: 27287190]
4. Cameron D, Lupton BA, Farquharson D, Hiruki T. Amnioinfusions in renal agenesis. *Obstetrics and gynecology*. 1994 May; 83(5 Pt 2):872–6. [PubMed: 8159382]

5. Migliorelli F, Martinez JM, Gomez O, Bennasar M, Crispi F, Garcia L, et al. Successful Fetoscopic Surgery to Release a Complete Obstruction of the Urethral Meatus in a Case of Congenital Megalourethra. *Fetal diagnosis and therapy*. 2015; 38(1):77–80. [PubMed: 25613991]
6. Damiano AE. Review: Water channel proteins in the human placenta and fetal membranes. *Placenta*. 2011 Mar; 32(Suppl 2):S207–11. [PubMed: 21208655]
7. Harman CR. Amniotic fluid abnormalities. *Seminars in perinatology*. 2008 Aug; 32(4):288–94. [PubMed: 18652930]
8. Brace RA, Cheung CY. Regulation of amniotic fluid volume: evolving concepts. *Advances in experimental medicine and biology*. 2014; 814:49–68. [PubMed: 25015800]
9. Zheng Z, Liu H, Beall M, Ma T, Hao R, Ross MG. Role of aquaporin 1 in fetal fluid homeostasis. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2014 Mar; 27(5):505–10.
10. Prat C, Blanchon L, Borel V, Gallot D, Herbert A, Bouvier D, et al. Ontogeny of aquaporins in human fetal membranes. *Biology of reproduction*. 2012 Feb; 86(2):48. [PubMed: 22053096]
11. Anderson DF, Jonker SS, Louey S, Cheung CY, Brace RA. Regulation of intramembranous absorption and amniotic fluid volume by constituents in fetal sheep urine. *American journal of physiology Regulatory, integrative and comparative physiology*. 2013 Sep; 305(5):R506–11.
12. Rosenblum S, Pal A, Reidy K. Renal development in the fetus and premature infant. *Seminars in fetal & neonatal medicine*. 2017 Apr; 22(2):58–66. [PubMed: 28161315]
13. Carroll TJ, Park JS, Hayashi S, Majumdar A, McMahon AP. Wnt9b plays a central role in the regulation of mesenchymal to epithelial transitions underlying organogenesis of the mammalian urogenital system. *Developmental cell*. 2005 Aug; 9(2):283–92. [PubMed: 16054034]
14. Perantoni AO, Timofeeva O, Naillat F, Richman C, Pajni-Underwood S, Wilson C, et al. Inactivation of FGF8 in early mesoderm reveals an essential role in kidney development. *Development (Cambridge, England)*. 2005 Sep; 132(17):3859–71.
15. Sanna-Cherchi S, Kiryluk K, Burgess KE, Bodria M, Sampson MG, Hadley D, et al. Copy-number disorders are a common cause of congenital kidney malformations. *American journal of human genetics*. 2012 Dec 07; 91(6):987–97. [PubMed: 23159250]
16. Westland R, Verbitsky M, Vukojevic K, Perry BJ, Fasel DA, Zwiijnenburg PJ, et al. Copy number variation analysis identifies novel CAKUT candidate genes in children with a solitary functioning kidney. *Kidney international*. 2015 Dec; 88(6):1402–10. [PubMed: 26352300]
17. van der Ven AT, Vivante A, Hildebrandt F. Novel Insights into the Pathogenesis of Monogenic Congenital Anomalies of the Kidney and Urinary Tract. *Journal of the American Society of Nephrology : JASN*. 2017 Oct 27.
18. Hwang DY, Dworschak GC, Kohl S, Saisawat P, Vivante A, Hilger AC, et al. Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract. *Kidney international*. 2014 Jun; 85(6):1429–33. [PubMed: 24429398]
19. Skinner MA, Safford SD, Reeves JG, Jackson ME, Freemerman AJ. Renal aplasia in humans is associated with RET mutations. *American journal of human genetics*. 2008 Feb; 82(2):344–51. [PubMed: 18252215]
20. Weber S, Moriniere V, Knuppel T, Charbit M, Dusek J, Ghiggeri GM, et al. Prevalence of mutations in renal developmental genes in children with renal hypodysplasia: results of the ESCAPE study. *Journal of the American Society of Nephrology : JASN*. 2006 Oct; 17(10):2864–70. [PubMed: 16971658]
21. Barak H, Huh SH, Chen S, Jeanpierre C, Martinovic J, Parisot M, et al. FGF9 and FGF20 maintain the stemness of nephron progenitors in mice and man. *Developmental cell*. 2012 Jun 12; 22(6):1191–207. [PubMed: 22698282]
22. Kohl S, Hwang DY, Dworschak GC, Hilger AC, Saisawat P, Vivante A, et al. Mild recessive mutations in six Fraser syndrome-related genes cause isolated congenital anomalies of the kidney and urinary tract. *Journal of the American Society of Nephrology : JASN*. 2014 Sep; 25(9):1917–22. [PubMed: 24700879]

23. Weber S, Taylor JC, Winyard P, Baker KF, Sullivan-Brown J, Schild R, et al. SIX2 and BMP4 mutations associate with anomalous kidney development. *Journal of the American Society of Nephrology* : JASN. 2008 May; 19(5):891–903. [PubMed: 18305125]
24. Colodny AH. Antenatal diagnosis and management of urinary abnormalities. *Pediatric clinics of North America*. 1987 Oct; 34(5):1365–81. [PubMed: 3309853]
25. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, et al. Prenatal diagnosis of severe structural congenital malformations in Europe. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2005 Jan; 25(1): 6–11.
26. Committee Opinion No. 656 Summary. Guidelines for Diagnostic Imaging During Pregnancy and Lactation. *Obstetrics and gynecology*. 2016 Feb.127(2):418. [PubMed: 26942384]
27. Hill LM. Timing of ultrasound in pregnancy—how often? At what intervals? *Seminars in perinatology*. 2013 Oct; 37(5):327–33. [PubMed: 24176155]
28. Levine D, Goldstein RB, Callen PW, Damato N, Kilpatrick S. The effect of oligohydramnios on detection of fetal anomalies with sonography. *AJR American journal of roentgenology*. 1997 Jun; 168(6):1609–11. [PubMed: 9168737]
29. Luyckx VA, Brenner BM. The clinical importance of nephron mass. *Journal of the American Society of Nephrology* : JASN. 2010 Jun; 21(6):898–910. [PubMed: 20150537]
30. Ruano R, Dunn T, Braun MC, Angelo JR, Safdar A. Lower urinary tract obstruction: fetal intervention based on prenatal staging. *Pediatric nephrology (Berlin, Germany)*. 2017 Jul 21.
31. Ruano R, Sananes N, Wilson C, Au J, Koh CJ, Gargollo P, et al. Fetal lower urinary tract obstruction: proposal for standardized multidisciplinary prenatal management based on disease severity. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2016 Oct; 48(4):476–82.
32. Robyr R, Benachi A, Daikha-Dahmane F, Martinovich J, Dumez Y, Ville Y. Correlation between ultrasound and anatomical findings in fetuses with lower urinary tract obstruction in the first half of pregnancy. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2005 May; 25(5):478–82.
33. Stalberg K, Gonzalez R. Urethral atresia and anhydramnios at 18 weeks of gestation can result in normal development. *Journal of pediatric urology*. 2012 Jun; 8(3):e33–5. [PubMed: 22154830]
34. Grijseels EW, van-Hornstra PT, Govaerts LC, Cohen-Overbeek TE, de Krijger RR, Smit BJ, et al. Outcome of pregnancies complicated by oligohydramnios or anhydramnios of renal origin. *Prenatal diagnosis*. 2011 Nov; 31(11):1039–45. [PubMed: 21755519]
35. Sanna-Cherchi S, Ravani P, Corbani V, Parodi S, Haupt R, Piaggio G, et al. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. *Kidney international*. 2009 Sep; 76(5):528–33. [PubMed: 19536081]
36. Kilby MD, Morris RK. Fetal therapy for the treatment of congenital bladder neck obstruction. *Nature reviews Urology*. 2014 Jul; 11(7):412–9. [PubMed: 24934451]
37. Bernardes LS, Aksnes G, Saada J, Masse V, Elie C, Dumez Y, et al. Keyhole sign: how specific is it for the diagnosis of posterior urethral valves? *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2009 Oct; 34(4): 419–23.
38. Cannie M, Neiryck V, De Keyzer F, Dymarkowski S, Bogaert GA. Prenatal magnetic resonance imaging demonstrates linear growth of the human fetal kidneys during gestation. *The Journal of urology*. 2007 Oct; 178(4 Pt 2):1570–4. [PubMed: 17707049]
39. Garel C, Mizouni L, Menez F, Luton D, Guibourdenche D, Aigrain Y, et al. Prenatal diagnosis of a cystic type IV sacrococcygeal teratoma mimicking a cloacal anomaly: contribution of MR. *Prenatal diagnosis*. 2005 Mar; 25(3):216–9. [PubMed: 15791662]
40. Hawkins JS, Dashe JS, Twickler DM. Magnetic resonance imaging diagnosis of severe fetal renal anomalies. *American journal of obstetrics and gynecology*. 2008 Mar; 198(3):328.e1–5. [PubMed: 18036507]
41. Hormann M, Brugger PC, Balassy C, Witzani L, Prayer D. Fetal MRI of the urinary system. *European journal of radiology*. 2006 Feb; 57(2):303–11. [PubMed: 16386865]

42. Sozubir S, Lorenzo AJ, Twickler DM, Baker LA, Ewalt DH. Prenatal diagnosis of a prolapsed ureterocele with magnetic resonance imaging. *Urology*. 2003 Jul;62(1):144.
43. Gimpel C, Avni FE, Bergmann C, Cetiner M, Habbig S, Haffner D, et al. Perinatal Diagnosis, Management, and Follow-up of Cystic Renal Diseases: A Clinical Practice Recommendation With Systematic Literature Reviews. *JAMA pediatrics*. 2018 Jan 1; 172(1):74–86. [PubMed: 29181500]
44. Tocchio S, Kline-Fath B, Kanal E, Schmithorst VJ, Panigrahy A. MRI evaluation and safety in the developing brain. *Seminars in perinatology*. 2015 Mar; 39(2):73–104. [PubMed: 25743582]
45. Upshaw C, Roda M, Khan M. Sirenomelia: Mermaid deformity on fetal MR imaging. *Radiology case reports*. 2012; 7(1):549. [PubMed: 27326269]
46. Edwards L, Hui L. First and second trimester screening for fetal structural anomalies. *Seminars in fetal & neonatal medicine*. 2017 Dec 9.
47. Plunk MR, Chapman T. The fundamentals of fetal MR imaging: Part 1. Current problems in diagnostic radiology. 2014 Nov-Dec;43(6):331–46. [PubMed: 25060713]
48. Tee LM, Kan EY, Cheung JC, Leung WC. Magnetic resonance imaging of the fetal brain. *Hong Kong medical journal = Xianggang yi xue za zhi*. 2016 Jun; 22(3):270–8. [PubMed: 27101791]
49. Morris RK, Kilby MD. Long-term renal and neurodevelopmental outcome in infants with LUTO, with and without fetal intervention. *Early human development*. 2011 Sep; 87(9):607–10. [PubMed: 21839591]
50. Harrison MR, Golbus MS, Filly RA, Callen PW, Katz M, de Lorimier AA, et al. Fetal surgery for congenital hydronephrosis. *The New England journal of medicine*. 1982 Mar 11; 306(10):591–3. [PubMed: 7057815]
51. Holmes N, Harrison MR, Baskin LS. Fetal surgery for posterior urethral valves: long-term postnatal outcomes. *Pediatrics*. 2001 Jul;108(1):E7. [PubMed: 11433086]
52. Morris RK, Malin GL, Quinlan-Jones E, Middleton LJ, Hemming K, Burke D, et al. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. *Lancet (London, England)*. 2013 Nov 02; 382(9903):1496–506.
53. Tchirikov M, Steetskamp J, Hohmann M, Koelbl H. Long-term amnioinfusion through a subcutaneously implanted amniotic fluid replacement port system for treatment of PPROM in humans. *European journal of obstetrics, gynecology, and reproductive biology*. 2010 Sep; 152(1):30–3.
54. Melo BF, Aguiar MB, Bouzada MC, Aguiar RL, Pereira AK, Paixao GM, et al. Early risk factors for neonatal mortality in CAKUT: analysis of 524 affected newborns. *Pediatric nephrology (Berlin, Germany)*. 2012 Jun; 27(6):965–72.
55. Biffl WL, Spain DA, Reitsma AM, Minter RM, Upperman J, Wilson M, et al. Responsible development and application of surgical innovations: a position statement of the Society of University Surgeons. *Journal of the American College of Surgeons*. 2008 Jun; 206(6):1204–9. [PubMed: 18501819]
56. Chervenak, F., McCullough, L. *The Professional Responsibility Model of Perinatal Ethics*. Walter de Gruyter; 2014.
57. Carey WA, Talley LI, Sehring SA, Jaskula JM, Matthias RS. Outcomes of dialysis initiated during the neonatal period for treatment of end-stage renal disease: a North American Pediatric Renal Trials and Collaborative Studies special analysis. *Pediatrics*. 2007 Feb; 119(2):e468–73. [PubMed: 17224455]
58. Zaritsky JJ, Warady BA. Chronic kidney disease in the neonate. *Clin Perinatol*. 2014 Sep; 41(3):503–15. [PubMed: 25155723]
59. Short BL, Miller MK, Anderson KD. Extracorporeal membrane oxygenation in the management of respiratory failure in the newborn. *Clinics in perinatology*. 1987 Sep; 14(3):737–48. [PubMed: 3311547]
60. Toomasian JM, Snedecor SM, Cornell RG, Cilley RE, Bartlett RH. National experience with extracorporeal membrane oxygenation for newborn respiratory failure. Data from 715 cases. *ASAIO transactions*. 1988 Apr-Jun;34(2):140–7. [PubMed: 3370175]

Box 1**Antenatal Diagnostic Evaluation****History**

- A detailed maternal and pregnancy history
- A detailed family history of congenital malformations
- History of consanguinity

Antenatal ultrasound

- Estimate amniotic fluid volume (and/or maximal vertical pocket)
- Document presence, size, location and appearance of kidneys
- Document bladder size and shape
- Document umbilical cord insertion and vessel number
- Document sex

Magnetic resonance imaging

- Useful for complex anatomy
- Useful for rare abnormalities
- Useful for detecting some non-renal anomalies that may be missed on ultrasonography

Chromosomal testing

- Consider with family history of malformations
- Clinical features of recognizable syndromes
- When other malformations are evident

Box 2**Antenatal Interventions****Fetal cystoscopy and shunt**

For diagnostic confirmation of posterior urethral valves and shunt placement from fetal bladder to the amniotic fluid compartment

Amnioinfusion

Serial percutaneous infusions of amniotic fluid replacement fluids, such as normal saline to achieve desired volume of highest vertical pocket of amniotic fluid >2 cm during the second trimester

Amniopore

An implanted device to achieve same as above, but with a greater ability to control and manipulate amniotic fluid volume periodically without percutaneous injections.

Box 3**Knowledge Gaps****Amniotic fluid production and clearance**

- Elucidate amniotic fluid volume regulatory mechanisms by identifying the types of vesicles that mediate intra-membranous absorption and determine the vesicular transport kinetics
- Identify the stimulator(s) and inhibitor(s) in amniotic fluid and determine their metabolic pathways in regulating vesicular transport
- Identify the key genes and protein networks that regulate vesicular transport as determinants of intra-membranous absorption rate and define the associated signaling pathways.

Kidney development and function

- Understand the genetic and epigenetic causes for developmental renal anomalies
- Development of better markers for fetal kidney function and disease — biochemical or imaging
- Develop better prognostic parameters for kidney outcomes
- Develop markers of fetal and neonatal therapeutic response

Amnioinfusion or amniopore

- Timing
- Amount and frequency
- Most appropriate method.
- Tracking of short and long-term outcomes from these procedures.
- Developing methods to assess which pregnancies will benefit from antenatal amniotic fluid restoration procedures

Table 1**Congenital Abnormalities of Kidney and Urinary Tract (CAKUT): Incidence and Outcomes**

Condition	Incidence	Outcome	Comments
Any renal/urologic abnormality (CAKUT)	About 0.3-1.6/3000 births (including stillbirths, excluding hydronephrosis and urinary tract dilatation—see below)	Depends upon the anomaly Nearly 30% have non-renal anomalies	More common in males; in offspring with a family history; and in those with maternal history of renal disease or diabetes
Hydronephrosis	1/100 – 1/200 pregnancies	Depends on severity and associated anomalies and whether unilateral or bilateral	
Urinary tract dilatation	1% to 2% of pregnancies	Up to 70% are transient, or “physiologic” without negative consequences	Detecting pathological causes can be difficult.
Unilateral uretero-pelvic junction obstruction	1/1000 to 1500 livebirths.	Nearly a third have other urinary tract anomalies.	More common in males
Ureterocele	1/5000 live births		Nearly 3 times more common in female
Posterior urethral valve	1/5000 to 8000 pregnancies	Common cause chronic kidney disease in boys. May survive 2 - 15 years without chronic kidney disease.	Creatinine concentration nadirs in the 0.8 to 1 mg/dl are considered high risk; 1 cm ² increase in renal parenchyma lowers the risk for chronic kidney disease
Unilateral renal agenesis	1/450 to 1000 live births	Can result in progressive end-stage kidney disease	
Bilateral renal agenesis (formerly, Potter Syndrome)	1/3000 to 5000 livebirths	Associated with serious structural defects and severe pulmonary hypoplasia—fatal at birth	
Multicystic dysplastic kidney	1/2,000 to 4300 births.	30% have contralateral renal abnormalities: e.g., vesicoureteral reflux, or ureteropelvic junction obstruction	
Autosomal recessive polycystic kidney disease	1/20,000 live births	Oligohydramnios may or may not be present; pulmonary hypoplasia and hypertension are common	
Autosomal dominant polycystic kidney disease	1/400 to 1000 live births	CKD usually has late onset in adulthood.	
Associated rare malformations: Cloacal malformation Cloacal extrophy Bladder extrophy Sirenomelia	1/20,000-25,000 1/200,000 1/30,000 1/60,000 to 100,000	Variable depending on associated anomalies	

Table 2

Postnatal Evaluation and Management of the Infant

Steps	For whom	Procedure	What to look for
Evaluation	All cases	Physical Examination	Blood pressure; respiratory status; abdominal palpation for kidney, bladder, and abdominal musculature; Urinary output Potter sequence? Other malformations?
	All cases	Abdominal imaging—Ultrasound	Hydronephrosis Presence, size, echogenicity of kidneys; presence of cysts in the kidneys and/or the liver
	Based on ultrasound results	Isotope VCUG- or renal scan	Vesicoureteral reflux Distribution of renal function
	All cases	Renal function tests	Elevated creatinine Abnormal electrolytes
Management	Solitary kidney (Unilateral renal agenesis)	Ultrasound; traditional VCUG; and in some centers— DMSA scan	Other urinary tract abnormalities in about 30%; if contralateral pathology is seen, VCUG and a diuretic renogram to check for reflux or obstruction.
	Multicystic dysplastic kidney	Immediate and follow-up imaging scans	Look for involution of the kidney (19% to 74%) by 9 months to 10 years of age. In the remaining (contralateral) kidney, look for the presence of abnormal masses, or compensatory hypertrophy