

RADIOLOGIC-PATHOLOGIC CORRELATION

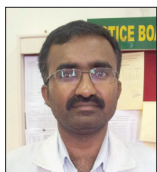
# Autosomal Recessive Polycystic Kidney Disease: Antenatal Diagnosis and Histopathological Correlation

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## ABSTRACT

Autosomal recessive polycystic kidney disease (ARPKD) is one of the most common inheritable disease manifesting in infancy and childhood with a frequency of 1:6,000 to 1:55,000 births. The patient in her second trimester presented with a history of amenorrhea. Ultrasound examination revealed bilateral, enlarged, hyperechogenic kidneys, placentomegaly, and severe oligohydramnios. The pregnancy was terminated. An autopsy was performed on the fetus. Both the kidneys were found to be enlarged and the cut surface showed numerous cysts. The liver sections showed changes due to fibrosis. The final diagnosis of autosomal recessive polycystic kidney disease was made based on these findings. In this article, we correlate the ante-natal ultrasound and histopathological findings in autosomal recessive polycystic kidney disease.

**Key words:** Antenatal, autosomal recessive polycystic kidney disease, hepatic fibrosis, placentomegaly

## INTRODUCTION

The autosomal recessive polycystic kidney disease (ARPKD) is characterized by bilateral, smooth, reniform enlargement of the kidneys secondary to diffuse dilatation of the collecting tubules. Congenital hepatic fibrosis is invariably associated with ARPKD. They

commonly present in the third trimester with severe renal damage.

A 26-year-old female during her second pregnancy presented with fever and a history of amenorrhea. Her first pregnancy was uneventful. The general physical examination on admission revealed a normal blood pressure of 120/80 mm Hg and a normal pulse rate. The per-abdominal examination revealed a uterine size of 24-26-weeks gestation. Her routine blood tests were within normal limits. The anti-phospholipid antibody levels detected by immunoassays were all within normal limits. However, the second pregnancy had to be medically terminated at a gestational age of 6-months due to fetal meningocele and spina bifida.

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## RADIOLOGIC FEATURES

The ante-natal ultrasound examination of the patient, a 26-year-old multigravida in the second trimester, revealed bilateral, symmetrical, enlarged, and hyper-echogenic fetal kidneys with loss of cortico-medullary differentiation [Figure 1]. The abdominal circumference had increased. The stomach and the bladder bubble were not visualized [Figure 2]. There was severe oligohydramnios. Placenta was thick and measured 6.1 cm [Figure 3]. The fetal biometric parameters were compatible with 26-weeks of gestational age. The maternal abdominopelvic scan was unremarkable. The final ante-natal diagnosis was autosomal recessive polycystic kidney disease with severe oligohydramnios. Under strict aseptic conditions, the pregnancy was terminated. A male fetus weighing 900 gm was delivered.

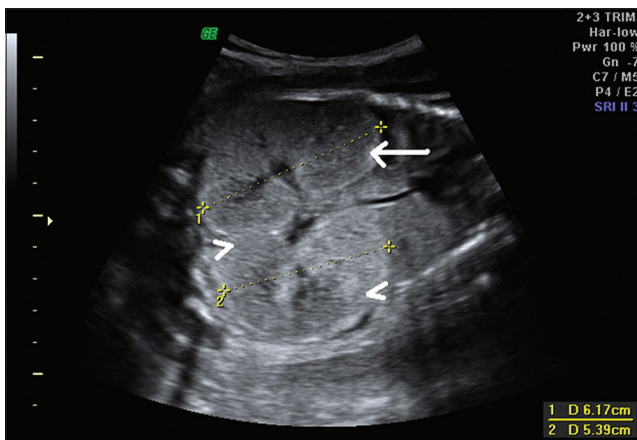
## PATHOLOGIC FEATURES

At autopsy, the fetal kidneys were symmetrically enlarged with normal reniform shape. Cut surface of both the

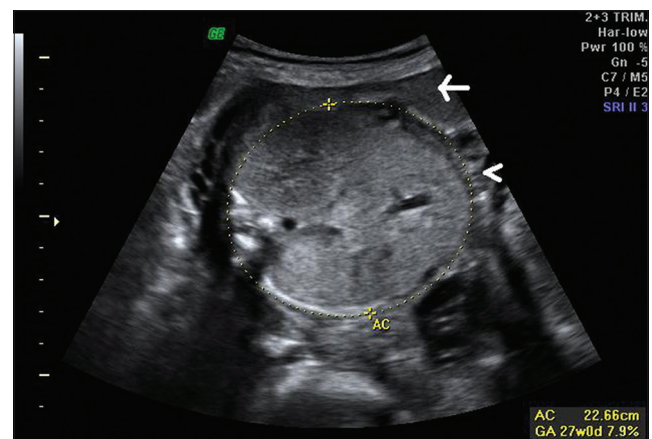
kidneys showed numerous cysts involving the inner cortex and medulla with cysts ranging from 0.5 to 0.7 cm and impaired cortico-medullary differentiation [Figure 4]. On histo-pathological examination, sections studied from both the kidneys using hematoxylin and eosin stain showed subcapsular nephrogenic zone within the glomeruli. Lower cortex and medulla showed numerous cysts of varying sizes lined by cuboidal epithelium. Interstitium showed foci of mild lymphocytic infiltrate [Figure 5]. The sections from the liver showed fatty change, intra-hepatic cholestasis and bile ductal proliferation. There was a mild to moderate lymphocytic infiltrate about the portal tract. Van-Geisons stained tissue revealed focal fibrosis [Figure 6]. The final diagnosis of ARPKD was made based on these findings.

## DISCUSSION

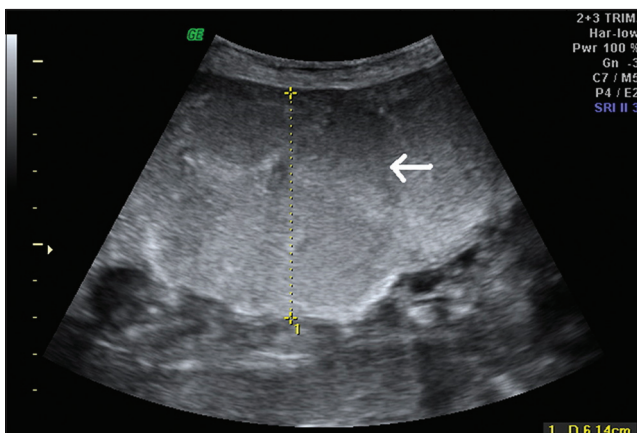
ARPKD is one of the most common inheritable diseases manifesting in infancy and childhood with a frequency of 1:6,000 to 1:55,000 births.<sup>[1,2]</sup> The gene responsible for



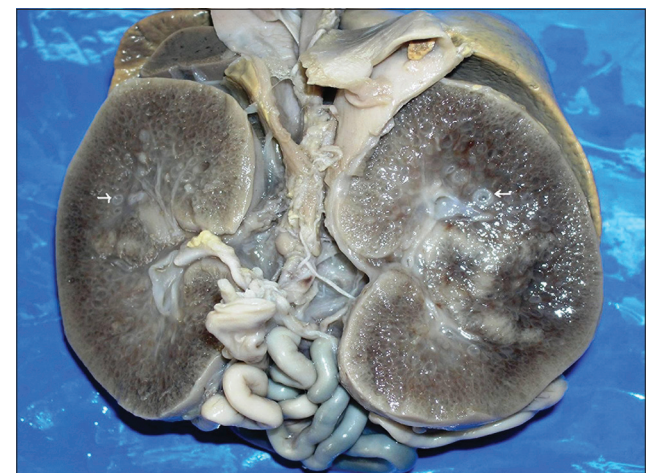
**Figure 1:** Antenatal scan in a 26-year-old female. Longitudinal scan of fetus shows bilateral enlarged and hyperechogenic kidneys (arrow) with loss of cortico-medullary differentiation (arrowhead).



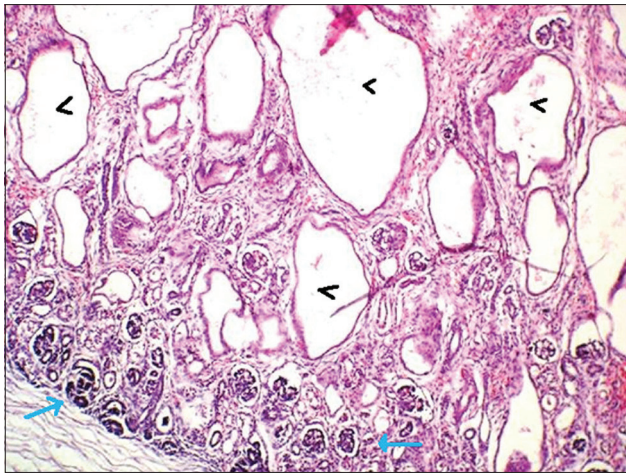
**Figure 2:** Transverse scan of the fetus at the level of liver (L) shows anteriorly located placenta (arrow). Stomach bubble could not be visualized. The amniotic fluid was grossly reduced (arrowhead).



**Figure 3:** Longitudinal scan of the fetus shows thickened placenta (arrow).

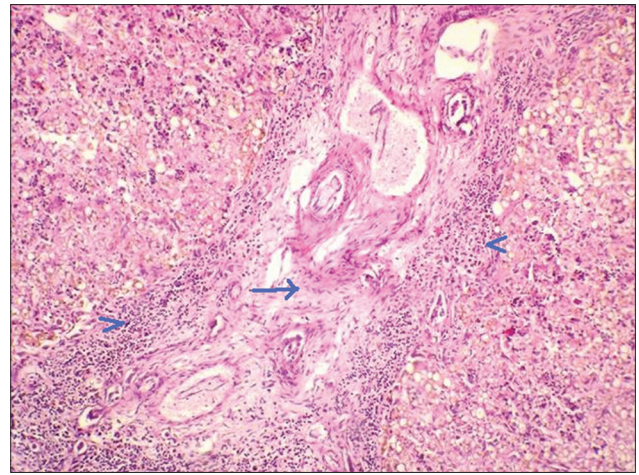


**Figure 4:** Cut surface of both the kidneys shows numerous cysts involving the inner cortex and medulla with cysts ranging from 0.5 to 0.7 cm (arrows).



**Figure 5:** Section studied from the kidneys using hematoxylin and eosin stain (H and E) shows sub-capsular nephrogenic zone with glomeruli (arrow). Lower cortex and medulla shows numerous cysts of varying sizes lined by cuboidal epithelium (arrowheads). Interstitium shows foci of mild lymphocytic infiltrate.

ARPKD (PKHD1) has been identified on chromosome 6.<sup>[3]</sup> In this case, the ante-natal scan revealed symmetrical, smooth, reniform enlargement of both the kidneys. The kidneys were diffusely hyperechogenic with loss of cortico-medullary differentiation. This is because of the numerous tiny cysts that are usually smaller than the limit of sonographic resolution that create multiple acoustic interfaces resulting in hyper-echogenicity. Sometimes, a peripheral hypoechoic rim may be seen surrounding the centrally increased echogenicity.<sup>[4]</sup> The thin hypoechoic rim of renal parenchyma at the periphery is presumed to be compressed cortex. The amniotic fluid volume was significantly decreased in this case, making evaluation of other fetal structures all the more difficult. When renal function is abnormal, there is oligohydramnios and the bladder is small or absent.<sup>[4]</sup> Kumar M et al.,<sup>[5]</sup> in a prospective study over a 3-year period from Jan 2008-Dec 2010, found 422 cases (1.8%) with gross congenital anomaly out of 24,160 deliveries studied. Out of the 422 cases, there were only 63 cases with renal anomaly (14.9%). Eight cases were lost to follow-up, and 55 cases were fully followed up. In their study, 13 cases had cystic renal disease. Autopsy was done on 6 cases and 5 of these cases had bilateral multicystic dysplastic kidneys, and only one case was of ARPKD. Zerres K et al.,<sup>[6]</sup> from December 1994 to March 1997, studied 258 prenatal analyses in 212 families. Sixty-five prenatal analyses were performed in 57 families. In the majority of the requesting families (45/57), the index children were deceased and their DNA was extracted from paraffin-embedded tissue. Eighteen fetuses were homozygous for the disease-associated haplotypes. In 12 of these fetuses, patho-anatomical examination demonstrated typical ARPKD changes consisting of dilated collecting ducts and the characteristic hepatic ductal



**Figure 6:** Section from the liver shows fatty change, intra-hepatic cholestasis, and bile ductal proliferation. There is a mild to moderate lymphocytic infiltrate (arrowhead) about the portal tract. Special stain revealed focal fibrosis (arrow). (Van-Gieson's stain,  $\times 100$ ).

plate malformation. These changes were detected in two fetuses as early as 13 weeks gestational age. These cases represent the earliest demonstration of ARPKD-associated histopathology reported to date.

Autosomal dominant polycystic kidney disease (ADPKD) in contrary to ARPKD is typically not recognized in the ante-natal scans, because the kidneys typically appear normal. But, in rare cases, there may be symmetrically enlarged hyperechogenic kidneys within which small cysts may be identified. The urinary bladder is usually present, and amniotic fluid volume is often normal. Also, unlike the ARPKD, where cortico-medullary differentiation is absent, increased cortico-medullary differentiation has been reported in ADPKD.<sup>[4]</sup> Considerable overlap in the imaging findings is well documented in ARPKD and ADPKD although they are distinct pathologic entities with different modes of inheritance. Both the ARPKD and ADPKD can present with symmetrically enlarged kidneys that are highly echogenic on fetal ultrasound. Some degree of hepatic fibrosis with ductal ectasia is always present, although initial ultrasound images may be unremarkable. However, ADPKD may be associated with normal-sized kidneys. For definitive diagnosis, histo-pathological examination of renal and hepatic tissue is frequently needed. In ARPKD, there are uniform radial cysts derived from the collecting tubules. Dilatation and proliferation of biliary ducts associated with portal fibrosis are characteristic. The cysts can be varying in size in ADPKD and may occur along any portion of nephron, and frequently involve both tubules and glomeruli.<sup>[7]</sup> However, it should also be noted that ultrasound findings of echogenic and enlarged kidneys in the fetus is not diagnostic of polycystic kidney disease. Other conditions like Meckel-Gruber syndrome and renal dysplasia too can

give similar ultrasound findings.<sup>[4]</sup> Meckel-Gruber syndrome is associated with polycystic kidney disease, polydactyly, and posterior encephalocele.<sup>[8]</sup>

Fetal kidneys are termed hyperechogenic when they appear more echogenic than adjacent liver or spleen. Renal dysplasia can be a possibility if there is ultrasound evidence of obstruction in the urinary tract, especially when the kidneys are small or normal in size and there are peripheral cortical cysts. There may be an increase in renal size in generalized overgrowth syndromes like Perlman syndrome and Beckwith-Wiedmann syndrome. There may be macroglossia and omphalocele in Beckwith-Wiedmann syndrome. In Perlman syndrome, there may be micrognathia and depressed nasal bridge. However, the most common underlying diagnosis of bilaterally enlarged hyperechogenic kidneys is ARPKD followed by ADPKD. Normal AFV favors ADPKD. Also, in ADPKD, one parent has the disease and ultrasound examination of the parents helps in establishing or excluding the diagnosis. In ARPKD, there is usually decrease in amniotic fluid volume and there may be a previously affected sibling. Other less common causes of enlarged hyperechoic kidneys are Finnish nephrosis, renal vein thrombosis, cytomegalovirus infection, nephrocalcinosis, and bilateral renal tumors.<sup>[4]</sup> The maternal alpha-fetoprotein level is raised in a case of Finnish nephrosis, and renal vein thrombosis is usually unilateral. So, these findings can help in coming to an accurate diagnosis. Dilated tubules can be potentially used to differentiate ARPKD from other conditions, although macroscopic cysts have been described in children with a variety of inheritable and non-inheritable renal cystic diseases.<sup>[9]</sup> In the gross morphological examination of the kidneys in our case, they were enlarged and had a smooth external appearance. On cut section, the renal cortex and medulla showed multiple small cysts giving the kidney a sponge-like appearance. Dilated, elongated channels were present at right angles to the cortical surface, almost totally replacing the medulla and cortex. On microscopic examination, there was cylindrical ectasia of all collecting tubules. The origin of these cysts from the collecting tubules can be inferred from the fact that they had a uniform lining of cuboidal cells. All these features are indicative of ARPKD.<sup>[9]</sup>

In almost all cases of ARPKD, the liver also usually has cysts with portal fibrosis as well as proliferation of bile ducts.<sup>[9]</sup> In ADPKD, the kidneys are usually bilaterally enlarged and may reach enormous sizes, and their external surface may appear to be composed solely of mass of cysts without any intervening parenchyma.<sup>[9]</sup>

## CONCLUSION

Although there may be many conditions showing enlarged and hyperechoic kidneys, it should be noted that ARPKD is the most likely cause when there is significant oligohydramnios, small or absent urinary bladder, a previous affected sibling, and normal renal ultrasound features in the parents. These are confirmed histopathologically by the presence of numerous tiny cysts in the smooth, enlarged kidneys and ectatic, elongated collecting tubules. ARPKD may be associated with hepatic cysts, portal fibrosis, and proliferation of bile ducts.

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## COMMENTARY

# Autosomal Recessive Polycystic Kidney Disease



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Renal cystic diseases, although well known for many centuries, were considered a simple pathological condition until some decades ago.

The improvement of ultrasonography imaging techniques has permitted accurate determination of renal cystic diseases. Renal cysts are fluid-filled cavities lined by epithelial cells and limited by extracellular matrix. Renal cysts may develop due to acquired or hereditary causes.<sup>[1]</sup> Among the inherited polycystic kidney diseases, we include autosomal recessive polycystic kidney disease (ARPKD), and autosomal dominant polycystic diseases such as von Hippel-Lindau disease, tuberous sclerosis complex (TSC1 and TSC2), and autosomal dominant polycystic kidney disease (ADPKD) that can arise from mutations in two different genes named PKD1 (located on chromosome 16p13.3) and PKD2 (located on chromosome 4q21-23).

A large number of papers relating to clinical, genetic, physiopathological, experimental, early diagnostic, and even prenatal diagnostic problems in hereditary polycystic kidney diseases has been recently published in the literature.

ARPKD is a rare inherited disease that occurs in about 1:40.000 live births, and accounts for 1.5% of children with chronic end stage renal failure (ESRF) in Europe,<sup>[2]</sup> and for 0.6% of patients with ESRF before the age of 20 years in the USA.<sup>[3]</sup> In 1971, ARPKD was identified as an entity different from other renal cystic diseases. The disease was classified into four subgroups on the basis of age at presentation, clinical symptoms, and systemic pathologic findings, The four subgroups include perinatal, neonatal, infantile, and juvenile forms.<sup>[4]</sup> Genetic studies suggest that there is a single ARPKD gene, mapped on chromosome 6p21, in spite of the different clinical phenotypes mentioned above. The PKHD1 gene is very large and consists of 86 exones; the protein encoded by the gene has been named polyductin/fibrocystin, and is composed of 4074 aminoacids.<sup>[5]</sup> Despite the identification of genes responsible for ARPKD and ADPKD, the function of these genes and their protein

products is still relatively unknown. Both these inherited cystic diseases are defined as ciliopathies because of abnormal cilia structure and function with an increased cAMP signaling that contributes to cystic cell proliferation, fluid secretion, and changes in the extracellular matrix. The primary cilium is an organelle that is present on the apical side of almost all epithelial cells as well as many endothelial cells of the body.

The pathoanatomical features of ARPKD consist of mainly bilateral and symmetric renal involvement; the kidneys appear larger in size with diffuse microcysts; the kidneys maintain a reniform aspect and show fusiform or cylindrical spaces arranged radially throughout the renal parenchyma from medulla to cortex. ARPKD is invariably associated with a generalized portal and interlobular fibrosis of the liver, accompanied by biliary duct hyperplasia, and small distal portal vein branches.

In the perinatal form of ARPKD, infants are born with large polycystic kidneys that may interfere with delivery; infants survive only a few days and pulmonary hypoplasia may be present. In the neonatal form cysts involve about 90% of renal nephrons, and renal dysfunctions are evident with progression to ESRF; mild hepatic fibrosis is present. In the infantile form, only a few nephrons appear to be cystic and patients may live for several years with progression to ESRF at adolescence. The hepatic involvement consists in portal hypertension and hypersplenism, but rarely liver symptoms are predominant. In the juvenile form, less than 10% of renal nephrons show cystic degeneration and renal insufficiency is usually absent, but liver fibrosis is generally severe with the clinical features of portal hypertension.

The diagnosis of ARPKD is established by ultrasonography, which documents enlarged, symmetrical, reniform kidneys characterized by diffuse hyperechogenicity and multiple small cysts. In addition, signs of portal hypertension, cholangiopathies, biliary dysgenesis may be evident. Severe clinical cases can be detected by antenatal ultrasonography

after 24 weeks of gestation. At this time enlarged kidneys with increased echogenicity accompanied with absence of urine bladder and oligohydramnios can be detected.<sup>[6]</sup> Antenatal ultrasonography is not useful to identify less severe clinical ARPKD forms. The children who survive the first month of life have as much as an 80% chance of living for more than 15 years, but a small number of patients may show autonomous renal function until 40-50 years of age. Hepatic involvement is always present and may represent the predominant clinical aspect with portal hypertension, gastrointestinal hemorrhage due to esophageal or gastric varices, hypersplenism, and progressive fibrotic liver disease. Usually, the children affected with ARPKD show a progressive decline of renal function, that begins with impaired concentrating ability and diluting capacity, and decreased urinary acidification capacity. Blood hypertension is very common. The management of chronic renal failure follows the general guidelines used for any child with ESRF.<sup>[7]</sup> In young adults with ARPKD it is possible to find renal cysts showing a pattern very similar to that seen in ADPKD patients. The sonographic evaluation of the hepatic abnormalities is very important in differentiating between ARPKD and ADPKD; in fact, the presence of a polycystic kidney disease in a young patient with sonographic evidence of hepatic fibrosis or Caroli disease is highly suggestive of ARPKD.<sup>[8]</sup>

In addition, in ARPKD and ADPKD, genetic diagnosis is possible either through linkage analysis or through direct mutation analysis; however, because of genetic complexity of the responsible genes, the possibility to detect gene mutations is about 65-75% in patients affected with known ARPKD and about 85% in patients with known ADPKD. Molecular testing is an expensive approach and, moreover, it does not provide clinical usable data.<sup>[7]</sup> The parents of a child with ARPKD should be made aware through

counseling that each child or new fetus will have 25% chance of developing the disease; moreover, the clinical expression of the disease may be very different in each other sibling. However, there is a fifty percent chance the child will be a carrier of the ARPKD.

Some novel pharmacological therapies, targeted at specific pathogenetic processes that promote cystic kidney disease progression have shown promising results in animal models. However, the results of large-scale clinical trials in ADPKD patients with the new drugs (Tolvaptan, Octreotide, Sirolimus, Everolimus) are not encouraging. The disease specific treatments for both ARPKD and ADPKD are not yet available and the treatment in affected patients consists in identifying and limiting the renal and extra-renal clinical complications.<sup>[8]</sup>

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