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Pregnancy in Autosomal Recessive Polycystic Kidney Disease

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Abstract

Purpose—Autosomal Recessive Polycystic Kidney Disease (ARPKD) is the most common childhood-onset ciliopathy. As treatments improve, more women are reaching reproductive age, but little is known about ARPKD and pregnancy.

Methods—In our ongoing study on ARPKD and other ciliopathies, 12 females over 18 years of age were identified and systematically evaluated. Six had children; four carried pregnancies and delivered, one used Assisted Reproductive Technology and had a surrogate carry the pregnancy, and one adopted. We report the outcomes of four pregnancies with live birth deliveries and two women who chose alternate family building options.

Results—Patient one was diagnosed at six months, and at age 21 had a pregnancy complicated by transient worsening of renal function (creatinine increase from 1.15 to 1.78 mg/dL). Patient two was diagnosed with ARPKD at age seven and had an uncomplicated pregnancy at age 23. Patient three was diagnosed incidentally with ARPKD at age 23, three months after completion of an uncomplicated pregnancy. Patient four who had an uncomplicated pregnancy at age 33 was diagnosed with ARPKD at age 46. .

Conclusions—Women with ARPKD face reproductive decisions largely bereft of information about the pregnancies of other ARPKD patients. We report four cases of pregnancy and ARPKD to expand current knowledge and encourage further research.

Introduction

Autosomal Recessive Polycystic Kidney Disease (ARPKD) is the most common ciliopathy¹ of childhood, occurring in one in 20,000 live births [1]. Most patients present perinatally with kidney-predominant disease; approximately 30% of these infants die of pulmonary

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¹A ciliopathy is a disease caused by dysfunction of primary (non-motile) cilia.

complications [2,1]. A smaller subset of patients present later in childhood or, rarely, in adulthood. ARPKD is characterized in all patients by dilated renal collecting ducts resulting in renal insufficiency and congenital hepatic fibrosis (CHF), often complicated by portal hypertension. ARPKD patients have biallelic mutations in *PKHD1*, which encodes fibrocystin, a protein on the primary cilia-basal body/centriole [2,1]. The consensus clinical diagnostic criteria for ARPKD require characteristic kidney and liver involvement, family history consistent with autosomal recessive inheritance, and absence of congenital anomalies [2]. Survival into adulthood has improved with better management of early respiratory complications, hypertension and renal transplant.

Little is known about pregnancy outcomes for patients with ARPKD. Patients with other causes of chronic kidney disease are at risk of infertility, spontaneous abortion, pregnancy-related decline in renal function, preeclampsia, and impaired fetal outcomes, including higher rates of intrauterine growth retardation, pre-term delivery and fetal demise[3,4]. Particularly for patients with a pre-conception serum creatinine of 1.4 mg/dL, pregnancy may precipitate rapid and sometimes irreversible renal damage [4]. Preeclampsia is also more common and more difficult to diagnose in patients with pre-conception renal disease [4]. Since cirrhotic liver disease significantly decreases fertility, pregnancy and cirrhosis is rare [5]. Data on non-cirrhotic portal hypertension and pregnancy are sparse and conflicting [6]. Pregnancy increases blood volume and flow, resulting in worsening portal hypertension and a significantly increased risk of variceal bleeding; approximately 25% of women with varices experience bleeding during pregnancy [5,6].

In our ongoing study on ARPKD and other ciliopathies, we evaluated 78 patients who fulfilled the clinical diagnostic criteria for ARPKD, including 12 females over 18 years of age. Six had children; four carried pregnancies and delivered, one used Assisted Reproductive Technology and had a surrogate carry the pregnancy, and one adopted.

Cases

Patient one was diagnosed with ARPKD at age six months when she presented with hypertension, an abdominal mass and imaging consistent with ARPKD. Kidney and liver biopsies at age three were consistent with ARPKD. Hypertension was initially challenging to control, but stabilized in her early teens. Prior to pursuing pregnancy, she discussed the possibility with her nephrologist, who did not discourage her. She had a planned pregnancy at age 21, earlier than she would have otherwise, to take advantage of a relatively stable period of her illness. Her initial creatinine was 1.15 mg/dL with an eGFR of 63.9 mL/min/1.73m² and she was normotensive. This patient saw a maternal fetal medicine specialist early in her pregnancy, but did not follow with a high-risk obstetrician because she perceived a strong negative reaction towards her pregnancy at that initial office visit. Her pregnancy and vaginal delivery at 40 4/7 weeks were clinically uncomplicated and she did not develop preeclampsia, but her serum creatinine at delivery had increased to 1.78 mg/dL with an eGFR of 36 mL/min/1.73m². The baby's birth weight was 2835 grams (10th-25th centile). This worsening of her renal function was transient, since her eGFR returned to baseline within a year. Patient two was diagnosed with CHF at age seven after presenting with frequent nosebleeds and the finding of splenomegaly and liver cysts. Her only

endoscopy, performed at the time of diagnosis, showed mild esophageal varices. She underwent splenic embolization at age 13 with improvement in her platelet count and spleen size. MRI evaluation was consistent with CHF and portal hypertension, including splenomegaly, upper abdominal varices, and a spontaneous spleno-renal shunt. The kidneys were enlarged and diffusely cystic; renal function was normal (creatinine clearance by 24 hour urine, 130 ml/min). The patient became pregnant and delivered vaginally at age 23 following an uneventful pregnancy. She did not report upper gastrointestinal bleeding or preeclampsia during her pregnancy. Patient three is a 32 year old who was diagnosed incidentally with ARPKD and Caroli disease² at age 23 when she presented with right upper quadrant pain three months after the birth of her first child. Hepatic and renal functions were normal, with no evidence of portal hypertension and a creatinine of 0.7 mg/dL (eGFR >60 mL/min/1.73m²). The patient's pregnancy was uncomplicated. Patient four is a 61 year old who received a kidney-liver double transplantation at age 59. She was unaware of her condition until age 46 when she was diagnosed with Caroli syndrome and subsequently with ARPKD after evaluation for pancytopenia identified splenomegaly and numerous cysts in her liver. She had one spontaneous abortion (11 weeks) at age 32 and an uneventful pregnancy with no evidence of preeclampsia and full term delivery (39 4/7 weeks, birth weight 2863 grams) at age 33 via cesarean section, 13 years before the diagnosis of ARPKD was established.

In addition to the four case presentations above, two other patients chose alternate family building options due to concerns over health consequences of pregnancy. One patient was diagnosed at age 17 years with CHF and esophageal varices. She underwent a mesocaval shunt with good results. She was advised that she should not become pregnant due to her CHF and she chose to utilize Assisted Reproductive Technology and a surrogate, resulting in a healthy twin delivery. Subsequently, she decided to pursue pregnancy without success for a year, and then had an unexpected pregnancy that resulted in a spontaneous abortion at age 31. The other patient is status-post renal transplant and was told by her physician that pregnancy was not out of the question, but would be risky and necessitate changes in her immune suppression medications, so she chose instead to adopt.

Discussion

As an increasing number of patients with ARPKD survive to reproductive age, many will turn to physicians for guidance on the risks and associated maternal and fetal outcomes associated with ARPKD and pregnancy. Unfortunately, little is known about this important topic, with only two previous cases in the literature. The first case reported was a patient with ARPKD diagnosed at age six, followed by a pregnancy at age 19, which was complicated by preeclampsia in the third trimester, requiring induction at 37 weeks, and a rise in her creatinine from 1.4 mg/dL to 2.1 mg/dL in the post-partum period. By age 25, her creatinine clearance had decreased to 19mL/min [1]. A second report detailed a 19 year-old patient with ARPKD/Caroli syndrome who was first diagnosed at age 5. She was admitted to the hospital at 18 weeks' gestation for close monitoring and nutrition control. Her

²Caroli disease is characterized by macroscopic saccular or fusiform dilations of the medium and large intrahepatic bile ducts. Caroli syndrome describes the presence of Caroli disease and CHF[2].

creatinine began to increase after 34 weeks' gestation and was 3.11 mg/dL during the post-partum period. She delivered at 37 weeks' gestation and was briefly lost to follow-up. The patient had a second pregnancy, which she chose to terminate due to the risk of further renal function decline. Five years after her delivery, her creatinine was 10.33 mg/dL and she began hemodialysis [7].

The four cases and two short vignettes presented herein provide examples of normal pregnancies and deliveries of ARPKD patients. Within this small sample, there were four healthy infants delivered by mothers with ARPKD and no apparent long-term negative maternal outcomes. However, two of the four mothers were unusually late presenting, with disease manifestations only after their pregnancies. One patient only had portal hypertension related to congenital hepatic fibrosis, but no evidence of renal dysfunction despite the presence of renal cysts. The final patient had stable renal disease prior to her pregnancy, and saw a transient worsening of her renal function during the pregnancy, which resolved post-partum. Based upon knowledge of patients with renal and liver diseases of varying etiologies, it would be expected that patients with more severe pre-pregnancy manifestations of ARPKD may be at higher risk of significant disease worsening during the pregnancy. In addition, it is not known how multiple pregnancies and deliveries in this population may influence the disease course. In a study of 605 pregnancies in 235 women with Autosomal Dominant Polycystic Kidney Disease (ADPKD), women with ADPKD, hypertension, and four or more pregnancies had significantly lower creatinine clearances than women with ADPKD, hypertension, and fewer than four pregnancies [8].

Not enough information is available in the literature to guide management of female patients with ARPKD in their reproductive years. More research is necessary to accurately characterize the risks of pregnancy to both maternal and fetal health. In the meantime, it is appropriate to draw from the general body of literature of renal disease and portal hypertension in pregnancy. There is currently no evidence that outcomes for patients with ARPKD are any worse than what would be expected based upon pre-pregnancy renal function and severity of portal hypertension. Patients would potentially benefit from care with a multidisciplinary team, to include a high-risk obstetrician. Genetic counseling, preferably prior to pregnancy, would help clarify important issues surrounding the risk of ARPKD in offspring, as well as options for prenatal testing.³ Appropriate preconception counseling is critical to inform patients of pregnancy risks and alternative reproductive options.

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³As ARPKD is inherited in an autosomal recessive manner, all offspring of an affected individual will be obligate carriers. The carrier frequency in the general population is 1 in 70[9]. The risk of an affected individual having an affected child, assuming random mate selection, would then be 1 in 140.

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