Attitudes in Patients with Autosomal Dominant Polycystic Kidney Disease towards Prenatal Diagnosis and Preimplantation Genetic Diagnosis

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Running title: Attitudes in ADPKD patients to PND and PGD

Abstract

Aims: No recommendations currently exist regarding implementation of both prenatal diagnosis and preimplantation genetic diagnosis (PGD) for Autosomal Dominant Polycystic Kidney Disease (ADPKD). This study evaluated attitudes in ADPKD patients with either chronic kidney disease (CKD) stages I-IV or end stage renal failure (ESRF) towards prenatal diagnosis and PGD.

Methods: 96 ADPKD patients were recruited from an outpatient clinic, wards and dialysis units. 38 patients had end stage renal failure (ESRF) and 58 had chronic kidney disease (CKD) stages I-IV. Participants were given an information sheet on prenatal diagnosis and PGD and subsequently completed a questionnaire.

Results: The median age of participants was 51.5 years. 17% ADPKD patients with CKD and 18% ADPKD patients with ESRF would consider prenatal diagnosis and termination of pregnancy for ADPKD. 50% with CKD would have opted for PGD (or might consider it in the future) were it available and funded by the UK National Health Service, compared to 63% in the ESRF group ($p = 0.33$). 69% in the CKD group and 68% in the ESRF group believed that PGD should be offered to other patients.

Discussion: There was a spectrum of attitudes amongst this cohort. A proportion of patients believe that PGD should be made available to prospective parents with this disease. The discrepancy between the low proportion (17%

CKD, 18% ESRF) who would consider prenatal diagnosis and termination of pregnancy and the higher number who hypothetically express an intention or wish to access PGD (50% CKD and 63% ESRF) indicate far greater acceptability for diagnostic methods that occur before embryo implantation. It is not known how the development of methods to identify patients whose renal function is likely to decline rapidly and treatments altering the natural history of ADPKD will affect these attitudes.

Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most prevalent potentially lethal monogenic disorder (Torres *et al.*, 2007). Recent estimates have put the overall prevalence of ADPKD at 32.7 per 100000 with a maximum prevalence of 57.3 per 100000 in the 6th decade of life (Neumann *et al.*, 2013). 7 to 10% of patients receiving haemodialysis have ADPKD. Extrarenal manifestations of the disease include liver cysts, cardiac valve abnormalities and aortic and intracranial aneurysms (Wilson, 2004).

Average age at diagnosis for ADPKD has been previously quoted at 31.4 years (Bajwa *et al.*, 2004). ADPKD is a genetically heterogeneous disorder; median age at death or onset of end stage renal failure (ESRF) is 53.0 years in individuals with a *PKD1* mutation (responsible for approximately 85% of cases) and 69.1 years in those with *PKD2* (responsible for approximately 15% of cases)(Hateboer *et al.*, 1999). However, there is variation in age of onset of end stage renal failure; previous estimates suggest that 2% of subjects affected by ADPKD develop ESRF by the age of 40; 23% by the age of 50, and 48% by the age of 73 (Churchill *et al.*, 1984). As patients with ADPKD are often diagnosed in their third or fourth decade of life, this may impact on their family planning attitudes.

Offspring of an affected parent have a 50% risk of inheriting ADPKD. Prenatal diagnosis usually involves taking a sample of placenta or amniotic fluid (typically in the late first trimester or early second trimester), for DNA analysis. Parents can

then be offered the option of terminating an affected pregnancy. In practice, prenatal diagnosis is rarely performed in ADPKD, and a previous survey of patients with ADPKD suggested that only 4-8% would terminate a pregnancy for ADPKD (Hodgkinson *et al.*, 1990). Since then, preimplantation genetic diagnosis (PGD) has become available as an alternative to prenatal diagnosis (Sermon *et al.*, 2004; ESHERE PGD Consortium Steering Committee, 2002). However, although attitudes to prenatal diagnosis have been studied in the ADPKD population (Sujansky *et al.,* 1990) we are not aware of any literature regarding patient attitudes to PGD in this setting. In PGD one or two cells from an embryo, made by in vitro fertilization, can be tested for a genetic abnormality and only embryos that do not carry the genetic abnormality are then implanted into the uterus. This enables parents with a genetic disease to have an unaffected child without needing to consider whether they would terminate an affected pregnancy. Although PGD is licensed in the UK by the Human Fertilisation and Embryology Authority for ADPKD (Human Ferilisation and Embryology Authority, 2015) and has been utilized for ADPKD previously (De Rycke *et al.*, 2005), it is not available widely on the UK National Health Service, and the cost for treatment is approximately £6000 to £9000 per treatment cycle (Genetic Alliance UK, 2015). Importantly, it is unclear whether this approach is widely considered acceptable to patients.

The scope of this study was to investigate attitudes of patients affected by ADPKD to determine whether there might be demand for PGD to be offered more widely to this population. This study aimed to compare interest for prenatal diagnosis and PGD in ADPKD patients with CKD (not requiring renal replacement therapy

(RRT)) and with ESRF . It has been demonstrated previously that disease severity in patients with hereditary cancer syndromes affected perceptions of the acceptability of PGD (Rich *et al.*, 2014). ADPKD patients with ESRF receiving RRT have greater disease severity, are likely to have a poorer quality of life, and will probably have experienced a greater number of medical interventions. We hypothesized that this would translate into a greater acceptability towards PGD in the ESRF group.

This study also evaluated attitudes towards termination of pregnancy in the ADPKD population and the influence of ADPKD on current and future family planning. .

Materials and methods

Study design and setting

Ethical approval for data collection was obtained and authorised by South Yorkshire Research Ethics Committee (REC reference 14/YH/006, IRAS project ID 145961).

This was a prospective study with patients recruited from two separate nephrology units in the UK: Royal Free London NHS Foundation Trust and East and North Hertfordshire NHS Trust. The study recruited two distinct groups of patients diagnosed with ADPKD:

1) 58 consecutive patients with ADPKD and CKD stages 1-4 (i.e. eGFR >15ml/min and not receiving RRT were recruited from a renal genetics clinic at the Royal Free Hospital looking after patients not receiving RRT

2) 38 consecutive patients with end-stage renal failure (ESRF) treated with either dialysis or transplantation, who were recruited from dialysis units and the inpatient ward setting at East and North Hertfordshire NHS Trust. No patients with CKD stage 5 (eGFR <15ml/min) not receiving renal-replacement therapy were included.

Inclusion and exclusion criteria

Although the two study groups were recruited at different sites, inclusion and exclusion criteria were otherwise identical. All patients ≥18 years with a diagnosis of ADPKD were considered eligible. Additionally, patients included were required to have CKD stage 1-4 (Royal Free Hospital (RFH) cohort) or end-stage renal failure treated with either dialysis or transplantation (East and North Hertfordshire NHS Trust (ENHT) Cohort). There were no exclusion criteria other than the language requirements sufficient to understand the information and consent sheets provided. All patients who were approached participated in the study.

Study procedure

A doctor approached patients for inclusion in the study face-to-face either in clinics, on an inpatient hospital ward or in their dialysis unit. After consenting to participate, an information sheet on PGD was provided whose content had been

agreed between a local clinical genetics department and the specialist ADPKD clinic. This was developed from a patient information sheet in clinical use; the University College London Centre for Reproductive and Genetic Health's Patient Information Leaflet. The Research Ethics Committee also reviewed the information sheet content.

The items in the questionnaire were based on a previous study (Menon *et al.*, 2007) that explored the views of BRCA carriers to PGD. Items relating to views on having children, prenatal diagnosis, termination of pregnancy and PGD were adapted to reflect the disease of interest, ADPKD. Additional items were included in the questionnaire relating to the patients' experience of ADPKD e.g. age at diagnosis, circumstances leading to diagnosis, family history, genetic testing; these were developed from clinical experience. Members of the research team with expertise in both genetics and ADPKD reviewed the questionnaire. Please refer to the supplementary material for a copy of the questionnaire and patient information sheet.

Data analysis

Basic demographic and questionnaire data in the two study groups were reported descriptively and compared using Student's T and chi-squared tests as appropriate. To determine potential factors influencing response to questions we compared age, gender, marital status, family history of ADPKD-related events and group (CKD or ESRF) between questionnaire response groups (yes, no or

unsure) using ANOVA, Chi-squared or T-tests as appropriate. In these analyses, family history of ADPKD-related events was considered a binary variable, which was 1 if any family member had required dialysis, transplant or suffered subarachnoid haemorrhage. Statistical analysis was performed using IBM SPSS version 22.

Results

Population demographics

Overall, 96 patients with diagnosed ADPKD were included, comprising 58 with CKD stages 1-4 (RFH cohort) and 38 with ESRF (ENHT cohort). All patients who were approached consented to participation in the study.

Of the ESRF group, 33 were receiving haemodialysis, 1 peritoneal dialysis and 4 had a functioning renal transplant. Demographic data relating to gender differences, presence of ESRF and marital status by age group are detailed in Table 1. Median age of diagnosis of ADPKD was 30 years in the CKD group and 42 years in the ESRF group.

Diagnosis of ADPKD, family history and exposure of patients to ADPKD-related complications

ADPKD-related events (defined as ESRF requiring RRT or subarachnoid haemorrhage) in family members are detailed in Table 2. Table 3 illustrates

proportions of participants with a family history of ADPKD and how the diagnosis of ADPKD was established in this cohort.

Access to genetic counseling

A genetic counselor had seen 13% patients (17% in the CKD group compared to 5% in the ESRF group (n=2)) and 9% (n=9) had undergone genetic testing to confirm the diagnosis of ADPKD (see table 3).

Attitudes to family planning and termination of pregnancy

Family planning attitudes are detailed in Figure 1. Participants were able to answer yes to more than one question relating to family planning attitudes, hence percentages in this figure add up to more than 100%.

In the CKD group 55% had children, compared to 74% in the ESRF group. In the CKD group, 17% had plans for children in the future, compared to 0% in the ESRF group, likely explained by the greater age of individuals in the ESRF group.

Examination of attitudes amongst the subgroup of patients (all with CKD) who have plans for children in the future (median age 27 years, range 20-38) showed that 80% of this cohort are worried about their children having ADPKD.

Regarding attitudes to termination of pregnancy, 45% in the CKD group and 26% in the ESRF group considered it acceptable to terminate an apparently normal pregnancy if the woman decided she did not want to be pregnant ($p = 0.09$). In

the CKD group 57% participants and in the ESRF group 50% participants thought it acceptable to terminate a pregnancy if the child has a serious genetic abnormality, such as Trisomy 21 or cystic fibrosis. The majority of patients in both the CKD group (59%) and ESRF (65%) would not consider termination of pregnancy or prenatal diagnosis for ADPKD; 17% ADPKD patients with CKD and 18% ADPKD patients with ESRF would consider prenatal diagnosis or termination of pregnancy for ADPKD (See figure 2). There were no significant differences in age (p= 0.68), gender (p=0.38), marital status (p=0.35), previous family experience of ADPKD-complications (p=0.12) or group (CKD or ESRF) (p= 0.67) between patient response categories of acceptability of prenatal diagnosis and termination of pregnancy.

Regarding attitudes of patients who still have plans for children in the future, 70% thought it acceptable to terminate a pregnancy if the couple or woman decides she does not want to be pregnant in an apparently normal pregnancy, or if the child has a serious genetic abnormality, such as Trisomy 21 or cystic fibrosis. Termination of pregnancy or prenatal diagnosis for ADPKD would not be considered by 60% of participants.

Attitudes of patients to PGD and its funding source

In the CKD group, 50% of participants reported that they would either opt for or consider PGD compared to 63% of the ESRF group. There were no significant differences in age (p= 0.54), gender (p=0.33), marital status (p=0.76), previous

family experience of ADPKD-complications (p=0.21) or group (CKD or ESRF) (p= 0.33) between patient response categories of acceptability of PGD. In the subgroup of patients who had plans for children in the future, 40% (n =4) stated they would opt for PGD if the UK National Health Service funded it.

Additionally, 69% of the CKD group and 68% of the ESRF group thought that PGD should be offered to other people with ADPKD, even if they would not consider it for themselves (See figure 3). In comparison, 19% of the CKD group (mean age 50) and 2.6% (n=1) of the ESRF group (mean age 60) believed that PGD should not be offered (p=0.049). The cost of undertaking PGD if self-funded was cited as the most common factor (27% all patients) that made participants decide against PGD. The inconvenience of having to go through in-vitro fertilization (IVF) being mentioned next most frequently (8%).

Comments made by patients on topic of PGD

There was an opportunity for patients to leave comments at the end of the questionnaire. Comments reflected the varying attitudes and experiences to ADPKD, prenatal diagnosis and PGD including: 'Having kidney disease that is inherited makes it really stressful to decide about having children…PGD should be available as a free option'; 'I wouldn't want my children to go through what I have gone through'; 'I would certainly take up PGD as any child I might have…has a high chance of having ADPKD too. Definitely should be offered'; 'I have had a full and complete life and to a certain extent continue to do so…my middle child has polycystic kidneys... She is now 34, with a child of 4…Would I have done

anything different - including terminating her when I found out she had polycystic kidneys - absolutely not!'

Discussion

Attitudes towards prenatal diagnosis and PGD in CKD and ESRF groups

There were no statistically significant differences between the CKD and ESRF groups in attitudes towards prenatal diagnosis and termination of pregnancy, with 61% of all patients not regarding ADPKD as justifying termination and less than 20% reporting that they would consider this themselves. In contrast, the majority of patients thought that termination of pregnancy was acceptable for Trisomy 21 or cystic fibrosis.

In contrast, PGD appeared to have greater acceptability amongst both the CKD and ESRF groups than prenatal diagnosis or termination of pregnancy. There was no significant difference in attitudes between CKD and ESRF groups, which went against the hypothesis that there would be a greater acceptability within the ESRF group because of greater disease severity, poor quality of life and increased exposure to medical interventions. Age, gender, marital status, previous family experience of ADPKD-complications and group (CKD and ESRF) were not significant factors in the response of patients to PGD acceptability. Interestingly, a greater proportion of patients with CKD compared to those with ESRF believed that PGD should *not* be offered to patients with ADPKD. Mean age and relationship status within this subgroup was similar to the overall cohort thus these factors are unlikely to explain the differences found. Whether this divergence in views reflects differences in general life experience between the

groups, or results from direct experience of undergoing RRT in the ESRF group is unknown. Experience of significant ADPKD related events in family members were similar in both the CKD and ESRF groups. It may be that certain participants, irrespective of age and stage of family planning, do not feel that their disease is serious enough to warrant invasive testing such as PGD and that PGD would create a delay in having a child. The fact that ADPKD is an adult onset condition may also play a role. Previous studies that investigated attitudes towards family planning and theoretical intentions towards prenatal diagnosis and PGD amongst patients known to carry the *BRCA1/2* mutation have identified that PGD would be pursued by just under a third of patients, with half stating that they would opt for prenatal diagnosis (Julian-Reynier *et al*., 2012).

It should also be noted that exposure to genetic services and investigations, in the form of either genetic counselling or genetic diagnosis of ADPKD, was low in our cohort. Discussions between clinicians and patients at diagnosis regarding genetic counselling and genetic testing options should be encouraged in order to help inform family planning decision-making and potentially increase access to these services.

The impact of severe ADPKD complications in family members did not significantly influence attitudes towards PGD. Equally, the impact of still having plans for children in the future did not significantly alter attitudes towards PGD. Thus it may be that additional personal factors, such as religious and moral views, play a role in deciding whether to pursue PGD prior to having a family.

Recent advances in management of ADPKD

Recent advances in genetic testing with cheaper, automated high-throughput tests (Rossetti *et al.*, 2012) may mean that genetic testing becomes more available, thus patients with the worst outlook as a result of a truncating mutation in *PKD1* (Hateboer *et al.*, 1999; Cornec-Le Gall *et al.*, 2013) would be more aware of their prognosis and more likely to be referred for genetic counseling or consider PGD.

In addition to the recent developments regarding prognostication, there have been encouraging advances in the treatment of ADPKD using the vasopressin ($V_{2)}$ receptor antagonist tolvaptan. Tolvaptan has been shown to reduce the rate of increase of total kidney volume and slow decline in estimated glomerular filtration rate (Torres *et al.*, 2012). The impact of such disease modifying agents may reduce demand for PGD as patients may die naturally of other causes before they develop ESRF. Conversely, these new therapeutic agents may mean that more young patients with a family history of ADPKD undergo genetic testing in order to secure a diagnosis that may not be radiologically obvious prior to commencing treatment. As a result, an increasing number of ADPKD patients may have a confirmed genetic diagnosis when planning their family and may be more aware of the reproductive options available to them.

Potential obstacles to performing PGD in ADPKD

However, it is also important to also consider some of the complications and difficulties that occur in performing PGD in ADPKD. There is no certainty of IVF being successful and there is an increased risk of multiple pregnancy and ovarian hyperstimulation syndrome (Khalid *et al.*, 2015). PGD is also technically difficult

and there is a risk of sample contamination and allele drop-out (where one of the two alleles fails to amplify, giving rise to a false negative result in autosomal dominant diseases).

In addition, prospective parents would require a genetic diagnosis to identify their own mutation prior to commencing PGD. In ADPKD 5% of mutations arise spontaneously (Grantham, 2008) and as a result these patients cannot undergo linkage analysis. Furthermore, 333 truncating *PKD1* (including missense mutations and silent polymorphisms) and 95 truncating *PKD2* mutations have been described in ADPKD (Torres and Harris, 2009). Screening individuals with ADPKD detects mutations in up to 91% of cases. However only approximately 65% of patients have definite mutations with approximately 26% having variants of uncertain significance that require further evaluation (Harris and Rossetti, 2010).

Study limitations and overall conclusion

The limitations of this study include the fact that the results are patients' speculative intentions. Not all patients were given time to ask questions regarding the information about prenatal diagnosis and PGD. Participants completed the questionnaire unsupervised and may have benefited from a researcher presence to clarify certain points. However, we felt the presence of a researcher may unduly bias responses to questions. Consequently, participants may not have correctly understood some of the information about prenatal diagnosis and PGD. In particular, the potential complications of prenatal diagnosis and PGD were not explained in detail. Information about patient's

theoretical plans is interesting however, as it gives an idea as to how attitudes in ADPKD patients to prenatal diagnosis and PGD may change with the evolution of disease modifying agents.

In addition, the CKD group and ESRF group were obtained from two separate populations. This could have introduced factors that were not evaluated that may have influenced attitudes towards prenatal diagnosis and PGD (and hence affected the results) including religion, personal values, social status and income.

If PGD for ADPKD were to become more widely funded by the UK National Health Service, there could be uptake as high as 69% among patients with ADPKD based on our survey results . It is not known how advances in methods to stratify prognosis or the availability of treatments that alter the natural history of this disease, such as tolvaptan, will affect these attitudes.

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Transparency declaration and conflict of interest statement:

DPG is supported by the UK Medical Research Council and has received payment for consultancy from Otsuka, who manufacture tolvaptan. There are no other

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Table 1 Demographics of CKD and ESRF groups

		Group		Comparison
		CKD	ESRF	p
Total (n)		58	38	
Sex (% of group)	*Male*	44.8	48.6	0.83
	Female	55.2	51.4	
Age-whole group (mean±SD, years)		44.6±12.7	64.2±12.4	<0.001
Age subgroups (% of group)	*<30*	15.5	0	<0.001
	31-40	22.4	2.6	
	41-50	31	10.5	
	51-60	19	31.6	
	61-70	12.1	15.8	
	71-80	0	36.8	
	81+	0	2.6	
Marital status (% of group)	*Married*	39.7	60.5	<0.001
	Single	34.5	7.9	
	Divorced	12.1	5.3	
	Living with partner	13.8	10.5	
	Widowed	0	15.8	

Table 2 Prevalence of ADPKD related events in family members

	Nil n (%)	Dialysis n (%)	Transplantation n (%)	Subarachnoid haemorrhage n (%)
CKD patients (n= 58)	25 (43)	21 (36)	22 (38)	5 (9)
ESRF patients (n= 38)	14 (37)	19 (50)	16 (42)	8 (21)

Table 3 Prevalence of family history of ADPKD amongst participants and method of diagnosis

	Diagnosed by ultrasound for investigation of renal disease n (%)	Diagnosed by ultrasound for investigation of other health problems	Diagnosed by genetic testing	Uncertain about diagnosis
Family history of ADPKD (n=65)	45 (69)	13 (20)	5 (8)	2 (3)
No family history of ADPKD (n =31)	8 (26)	23 (74)	0 (0)	0 (0)

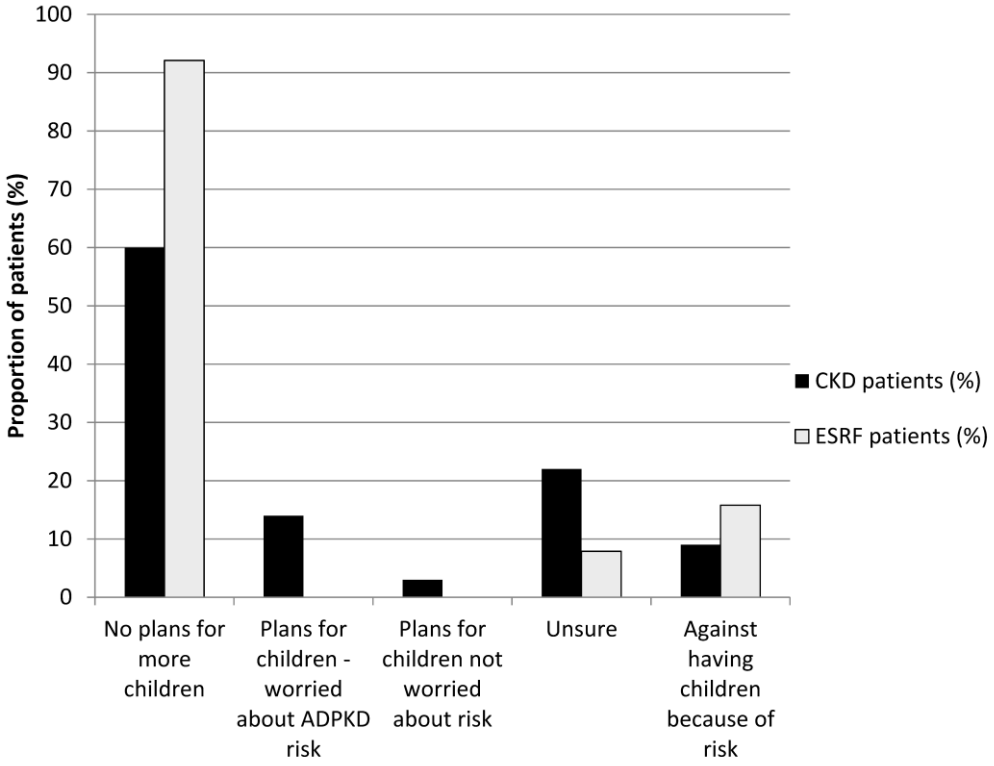

Figure 1. Family planning attitudes among ADPKD patients. ADPKD, autosomal dominant polycystic kidney disease.

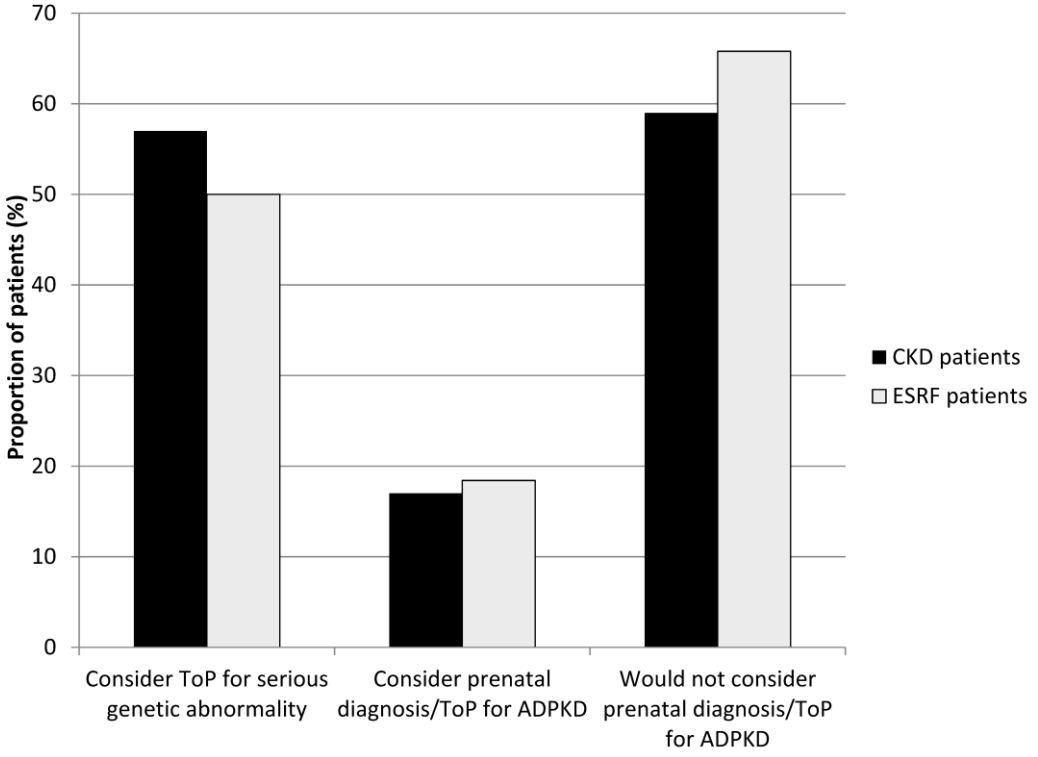

Figure 2. Attitudes to prenatal diagnosis and termination of pregnancy in ADPKD patients.

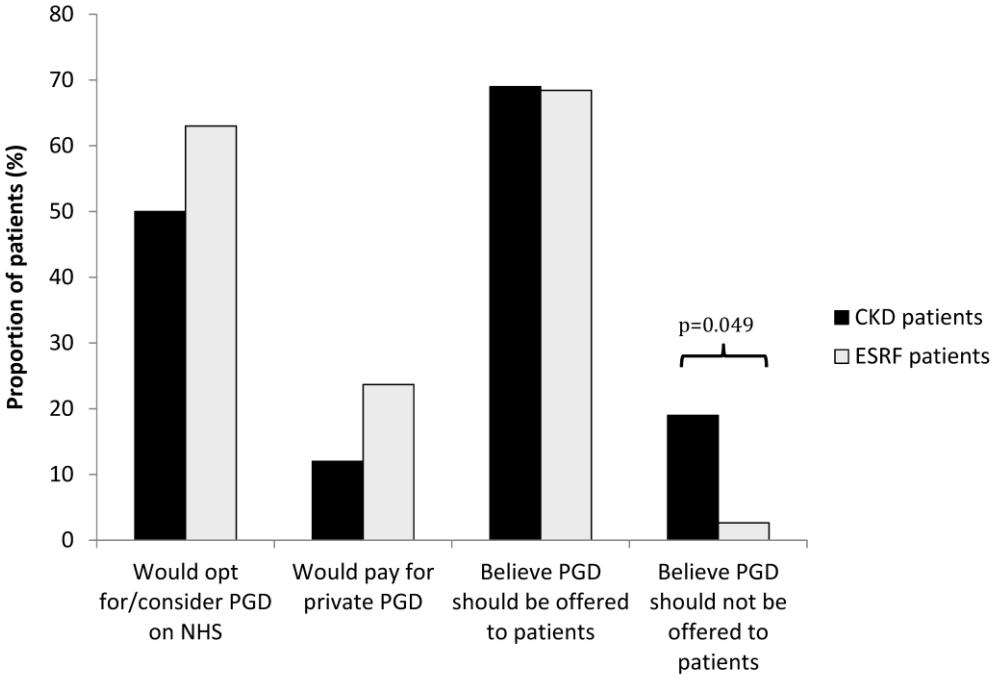

Figure 3. Attitudes to PGD in ADPKD patients. PGD, preimplantation genetic diagnosis.