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Review Article

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ADPKD, pregnancy and preimplantation selection: clinical and bioethical considerations

Diana Zarantonello[1,*], Giorgina Barbara Piccoli[2], Daniela Zuccarello[3], Mauro Tescaro[4], Ilaria Mariani[5], Arne Luehwink[6], and Giuliano Brunori[1,7]

[1]Department of Nephrology, Santa Chiara Hospital, ASUIT, Trento, Italy
[2]Nephrology, Department of Internal Medicine, Centre Hospitalier du Mans, Le Mans, France
[3]Unit of Medical Genetics and Genomics, San Bortolo Hospital, AULSS8 Berica, Vicenza, Italy
[4]Department of Law, University of Verona, Verona, Italy
[5]Department of Medical and Surgical Sciences, Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[6]Provincial Health Authority - Autonomous Province of Trento, Assisted Reproductive Unit, Arco, ASUIT, Italy
[7]CISMed, University of Trento, Trento, Italy
*Corresponding author: Diana Zarantonello, Department of Nephrology, Santa Chiara Hospital, ASUIT, 38122, Trento, Italy (diana.zarantonello@asuit.tn.it).

Abstract

Preimplantation genetic diagnosis for monogenic disorders makes it possible to identify and select embryos free of specific genetic mutations prior to uterine transfer, using embryos produced via medically assisted reproductive technologies. Since 2015, the Italian legal system has allowed parents who are carriers of, or affected by, monogenic hereditary conditions, including autosomal dominant polycystic kidney disease (ADPKD), to access preimplantation genetic diagnosis.

However, the experience remains limited, and its application in particular to a late onset disease like ADPKD raises clinical and ethical concerns. These include the potential health risks associated with assisted reproductive technologies for the woman, the risk of assisted reproductive technology failure, moral permissibility of embryo selection, psychosocial implications for the couple and child, and issues related to equitable access to these treatments.

An effective preconception counseling strategy should be grounded in a shared decision-making framework involving the prospective parents and a multidisciplinary medical team, including specialists in nephrology, obstetrics, and human genetics.

This review aims to discuss the principal bioethical considerations surrounding preimplantation genetic diagnosis for ADPKD, in order to support clinicians involved in genetic counseling and reproductive decision-making.

Keywords ADPKD, preimplantation genetic diagnosis, ART (assisted reproductive technology), ethical concerns

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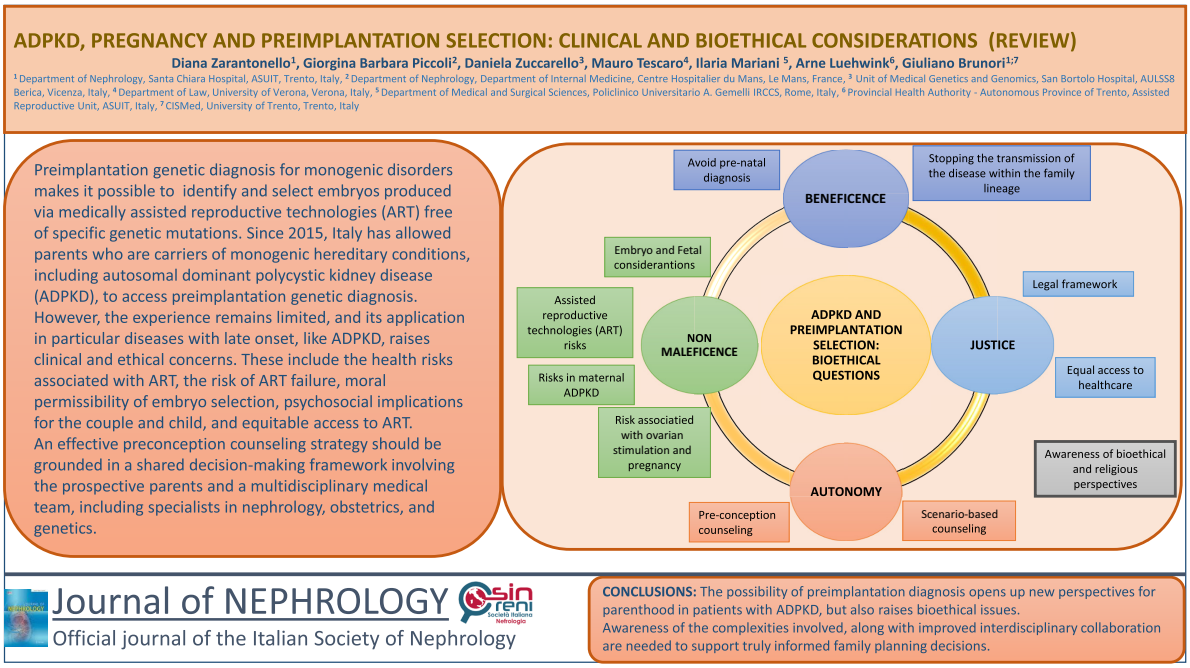
Graphical abstract



Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, with an estimated incidence of 1 in 400 to 1 in 1000 live births. It affects approximately 12 million individuals globally and represents the fourth leading cause of kidney failure, accounting for approximately 6%–10% of the patients living with kidney replacement therapy (KRT).[1,2]

Although ADPKD exhibits complete penetrance, its phenotypic expression is variable and influenced by genetic factors such as gene locus involved, specific mutation (allelic heterogeneity), individual genetic background, epigenetic modifications, and environmental factors.[3]

Even in the absence of associated extrarenal manifestations,[4] the overall life expectancy in individuals with ADPKD remains reduced compared with the general population.[5,6] Although difficult to quantify, the physical and psychological burden of the disease can be considerable, when assessed with disease-specific instruments—such as the ADPKD-Pain and Discomfort Scale (ADPKD-PDS) and the ADPKD Impact Scale (ADPKD-IS).[7,8]

As in other chronic kidney diseases (CKD), quality of life is closely related to the disease stage, with a significant decline when CKD progresses, and in individuals with markedly enlarged kidneys.[9,10]

Currently, there is no cure nor treatment capable of halting disease progression. Although emerging therapeutic options show promise, they are currently not devoid of adverse effects.[11]

Context

Genetic alterations responsible for the disease

In approximately 90%–95% of cases, ADPKD is inherited from an affected parent, while in the remaining cases the mutation arises *de novo*. Diagnosis is classically based on a combination of family history and imaging studies; however, genetic testing has become an essential component, also for prognostic evaluation.[2]

The most common genetic alterations occur in the *PKD1* gene, located on chromosome 16 and encoding polycystin-1. Mutations are generally associated with a more severe disease course compared with alterations in the *PKD2* gene, located on chromosome 4, which encodes polycystin-2.[12,13]

Rarely, pathogenic variants in other genes may be responsible for ADPKD, including *GANAB* (<0.5%), *DNAJB11* (<0.5%), *IFT140* (1%–2%), *ALG5* (<0.5%), and *ALG9* (<0.5%). In approximately 1%–5% of cases, no causative genetic alteration is identified.[14]

The marked heterogeneity of mutations—more than 1500 have been described in the polycystin genes—along with the broader genetic background, the presence of comorbid conditions, environmental and epigenetic factors, contribute to the phenotypic variability observed between families and among members of the same family.[2] Many variants in the *PKD1/PKD2* genes are unique, and are considered to be nearly "private mutations" specific to an individual family, and this underlines the need for in-depth family studies to better highlight the prognosis and inform counseling.

As a result, individuals carrying the same mutation may exhibit different outcomes, a relevant consideration in clinical and ethical discussions regarding reproductive choices.[15]

The main technical challenges related to the genetic diagnosis of *PKD1* and *PKD2* mutations are summarized in Table 1[16–19]; results may be inconclusive in approximately 10% of cases.[20] Combined with potential delays in accessing assisted reproductive techniques and the lack of guaranteed success, the time factor may become critical, particularly for older couples. Furthermore, as we will discuss later, the risk of pregnancy-related complications in women affected by ADPKD must be considered.[21]

Preimplantation genetic diagnosis in ADPKD

If the components of a couple wish to avoid transmitting the disease to their offspring, they can consider four alternatives: adoption (in this case the child is not genetically related), prenatal genetic testing (typically via chorionic villus sampling), preimplantation genetic testing, and heterologous assisted reproductive technology (egg or sperm donation)[21] (Figure 1). While adoption is an invaluable choice that may be beneficial for the child and the family, due to its lack of clinical implications, we will not discuss it in this review.

About two-thirds of couples with identified mutations achieve disease-free childbirth with preimplantation genetic diagnosis.[20]

The likelihood of success is influenced by the couple's fertility status. Maternal age is the principal predictor of reproductive potential, with fertility beginning to decline after 30–35 years of age.[22]

During counseling for assisted reproductive technology with preimplantation diagnosis, a comprehensive fertility assessment is performed with evaluation of ovarian reserve through measurement of anti-Müllerian hormone levels and antral follicle count via transvaginal ultrasound in women and semen analysis (spermiogram) in men. A markedly diminished ovarian reserve and/or advanced maternal age (>40 years) may lead to discouraging this option, even if these indications may vary across centers and countries.[23]

Preimplantation genetic testing for monogenic disorders has been an available option for over 3 decades.[24] It is performed as part of the assisted reproductive technology cycle (Figure 2)[25,26],

Table 1 Technical difficulties related to the diagnosis of genetic alterations in autosomal dominant polycystic kidney disease (ADPKD).

Technical difficulties in diagnosis of ADPKD genetic mutations	***PKD1* may present diagnostic difficulties related to:** large size of the gene with the presence of regions with high homology and other genomic sequences, including pseudogenes, which complicate amplification;[16] mutations located in exons 1–30, which are highly susceptible to sequencing difficulties due to repetitive elements and structural variations in the region, making traditional sequencing, such as Sanger sequencing, particularly prone to error.[17] ***PKD2* may present diagnostic difficulties related to:** large deletions and duplications; point mutations in regulatory regions or splice sites that may escape standard sequencing methods.[18] **Presence of somatic mutations or mosaicism:** These mutations may not be present in every tissue sample or may be present at low frequencies that escape detection by conventional techniques.[19]

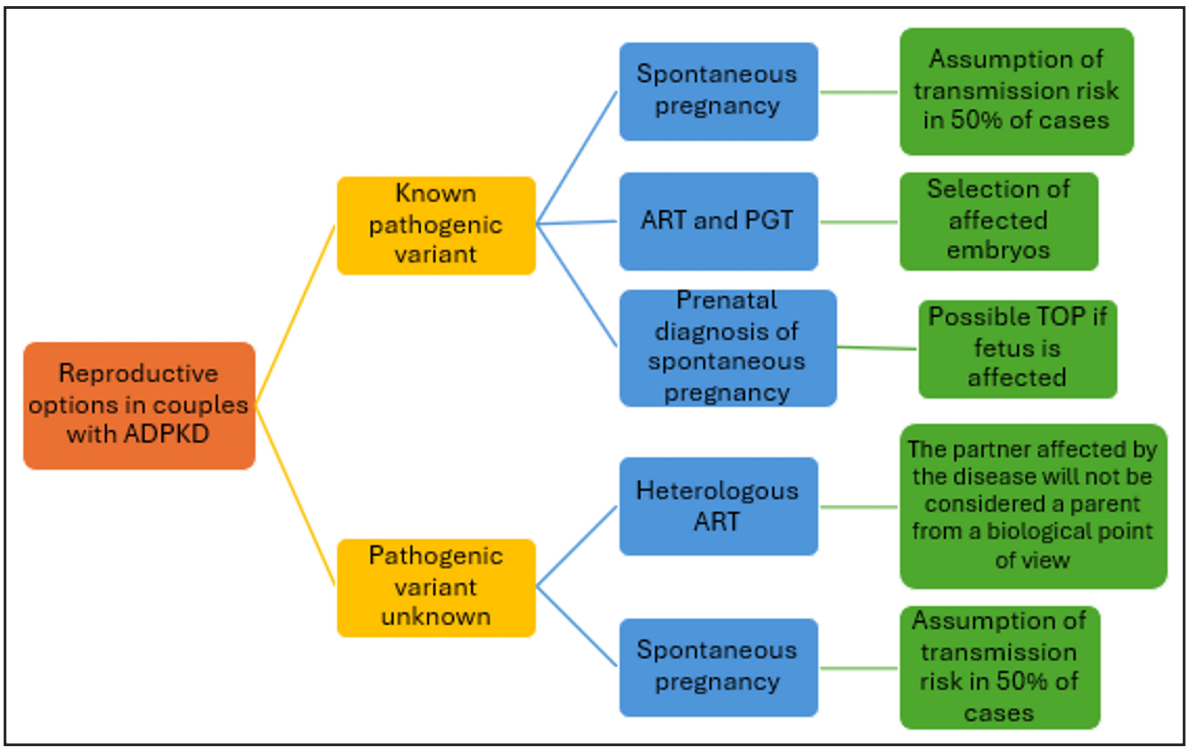


Figure 1 Reproductive possibilities in the couple with autosomal dominant polycystic kidney disease (ADPKD) and, in the green boxes, what they entail from a bioethical point of view. ART, assisted reproductive technology; PGT, preimplantation genetic testing; TOP, termination of pregnancy. Modified from reference [21].

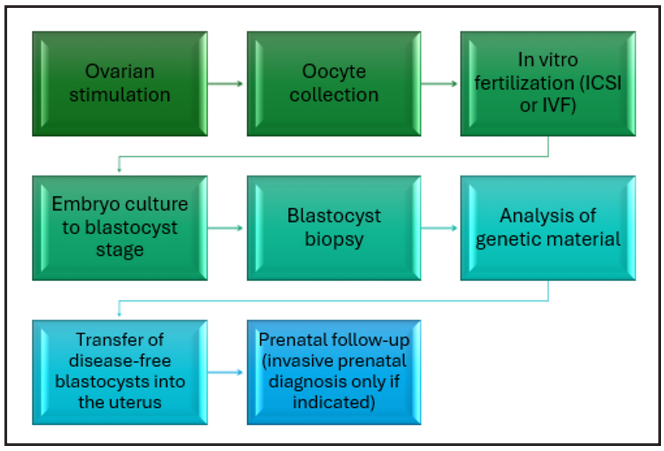


Figure 2 Preimplantation genetic diagnosis is performed on the embryo obtained through assisted reproductive technology (ART) and allows a selection to be made before transfer to the uterus. In all pregnancies, spontaneous or with ART, a prenatal genetic diagnosis can be performed through amniocentesis or chorionic villus sampling. ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization. Modified from references [25] and [26].

which involves controlled ovarian stimulation, oocyte retrieval, and *in vitro* fertilization, most commonly via intracytoplasmic sperm injection.

Embryo biopsy can be performed at either the cleavage stage (day 3), involving the removal of 1–2 blastomeres, or at the blastocyst stage (days 5–7), during which up to 10 trophectoderm cells may be sampled.[27] The 2020 European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend day 5 biopsy for its higher diagnostic accuracy.[28,29]

The most widely used genetic technique is massively parallel sequencing. Alternative methods include karyomapping, single nucleotide polymorphism array, and mini-sequencing.[30] The disease-specific genetic test is now routinely combined with preimplantation genetic testing for aneuploidy, which screens for common chromosomal abnormalities such as trisomies 13, 18, and 21. These abnormalities increase with maternal age and represent a major cause of early pregnancy loss.[31,32]

In women of advanced age, multiple cycles—entailing repeated ovarian stimulation—may be required to obtain embryos suitable for transfer. As for confirmatory prenatal diagnosis, since preimplantation genetic testing reduces the risk of disease transmission to ≤1%, only a small proportion of couples proceed with further invasive prenatal testing.[33]

Available evidence from the literature

The most frequent current indications for preimplantation gentic testing for monogenic disorders are cystic fibrosis and hereditary hemoglobinopathies in autosomal recessive disorders, and myotonic dystrophy type 1, neurofibromatosis, Huntington's disease, and hereditary cancer syndromes for autosomal dominant disorders.[34] To date, only a limited number of studies have evaluated the impact of preimplantation genetic testing in patients with ADPKD and the maternal complications related to this procedure remain poorly investigated.

A retrospective analysis conducted in the United States between 2010 and 2020 reported that approximately 12% of assisted reproductive technology cycles with preimplantation genetic analysis were performed for renal-related genetic disorders, with ADPKD representing the most common indication.[27]

Conversely, a Chinese case series involving 64 couples with hereditary nephropathies reported that the most frequent indication was autosomal recessive polycystic kidney disease (ARPKD) (55% of cases), followed by ADPKD (29%). Of the 339 embryos created, only 63 (18%) were deemed suitable for transfer. The cumulative live-birth rate was 55%, significantly lower than the approximately 75% reported in the general assisted reproductive technology population.[35]

In a further Chinese study involving 17 couples with ADPKD, 14 achieved either the birth of a live child or produced embryos suitable for transfer. Although the fertilization rate was lower when the male partner was affected, this did not significantly impact the live-birth rate.[36]

A Belgian cohort study of 43 couples with ADPKD reported that, of the 545 embryos produced, only 215 (37%) were genetically suitable for transfer. These transfers resulted in the birth of 31 singleton infants and 4 twins. The cumulative live-birth rate per couple was 58% after up to 5 treatment cycles. Interestingly, while the live-birth rate appeared lower in couples with affected males, the multivariate analysis identified maternal age as the only significant predictor of live birth.[37]

Finally, a Dutch study involving 98 couples with monogenic kidney diseases found that 53% opted for assisted reproductive technologies and genetic testing, with ADPKD accounting for 38% of cases. Among the couples in whom at least one embryo was transferred, 65% achieved the birth of a child unaffected by the disease.[22]

The proportion of unaffected embryos expected to be available in each cycle depends on the inheritance pattern, and is obviously 50% in autosomal dominant diseases. However, the actual proportion of healthy embryos can be limited by other factors. If preimplantation genetic testing for aneuploidies is performed together with preimplantation genetic testing for monogenic disorders, embryos unaffected by the tested disease can be excluded due to aneuploidy.[38] Couples with exhausted reproductive capacity may therefore find themselves in a situation where the only euploid embryos available are positive for monogenic disease and are the only opportunity for a genetically related child.[38]

Positions of health professionals and patients on prenatal diagnosis in ADPKD

A recent European survey involving pediatricians, nephrologists, and clinical geneticists revealed a substantial divergence in opinions regarding the ethical acceptability of genetic testing for ADPKD. The majority of respondents did not consider prenatal diagnosis via amniocentesis or chorionic villus sampling to be ethically justified in the case of ADPKD. However, geneticists were generally more permissive than both pediatric and adult nephrologists.[39]

Similarly, most respondents deemed termination of pregnancy for a fetus affected by ADPKD to be unjustifiable, although geneticists more broadly supported the ethical legitimacy of preimplantation genetic testing.

Patients' perspectives were likewise heterogeneous: in a recent study, fewer than 20% considered termination of pregnancy in the case of ADPKD diagnosis, while lower (4%) prevalence was previously reported.[40,41]

In contrast, more than half of the patients expressed interest in assisted reproductive technologies with preimplantation genetic testing, and nearly 70% believed the procedure should be systematically offered.[40] Another study indicated that approximately 80% of the individuals at risk of transmitting a monogenic disorder would prefer preimplantation genetic testing to adoption, gamete donation, or prenatal diagnosis.[42,43]

These data highlight the different perception of ADPKD among health-care professionals, who consider this disease likely to have a lower impact on survival compared with other genetic conditions, unlike those patients who, having experienced the disease themselves or in a family member, are determined to avoid transmitting it to their children.

Bioethical discussion

The clinical complexity of ADPKD is mirrored by a corresponding bioethical complexity. While the application of the 4 classical principles—beneficence, nonmaleficence, justice, and autonomy—has well-recognized limitations when addressing individual patient scenarios, within the framework of personalized medicine, their analysis nonetheless offers a useful structure for bioethical reflection. A narrative, patient-centered approach may be combined with a principlist framework, which remains a valuable foundation for an ethical dialog with potential parents living with ADPKD.[44]

Beneficence

The clinical and psychological benefits of having a child unaffected by the familial genetic condition are readily apparent. Likewise, the advantages for the offspring—being "*disease-free*"—are evident, as is the intergenerational benefit of halting disease transmission. The selection and transfer of unaffected embryos avoids the need for prenatal diagnosis and therapeutic abortion. Furthermore, this may reduce anxiety in parents, since they do not have to subject their children to specific tests to detect the disease.

From a societal perspective, the avoidance of a chronic, resource-intensive disease has potential public health implications, in light of the costs associated with long-term kidney care. While cost-benefit analyses of preimplantation genetic testing have been performed for cystic fibrosis, no such studies are currently available for ADPKD.[45] Additionally, the coverage of assisted reproductive technology and genetic testing costs varies significantly across countries and often remains inconsistent within the same country.

A delicate issue concerns the timing of disease onset and the potential evolution of therapeutic options. Although a precise prediction is impossible, it is conceivable that gene editing technologies or DNA repair therapies will emerge as effective treatments, especially for monogenic disorders.[46] Given that ADPKD symptoms typically manifest in adulthood and that kidney failure often occurs later in life,[9] potential parents should consider the ethical implications of avoiding a disease that may eventually become treatable before it leads to significant health deterioration.

Non-maleficence

Embryo and fetal considerations

The use of embryo selection inevitably entails the discarding of embryos carrying the pathogenic mutation, which may raise ethical and religious concerns regarding the moral status of embryos. These are addressed in a later section. Furthermore, embryos not affected by the targeted genetic condition may be harmed by the biopsy procedure—involving the removal of cells in the early stages of development—or by cryopreservation, particularly when biopsy is performed at the blastocyst stage. Emerging noninvasive diagnostic methods, such as the analysis of cell-free DNA in the embryo culture medium, may mitigate such risks by eliminating the need for biopsy.[34]

Despite rigorous protocols, a low but non-negligible risk of diagnostic error persists. False positives and false negatives may result from technical limitations such as failed DNA amplification, incorrect use of probes or primers, parental DNA contamination, or mosaicism.[38,47] When preimplantation testing is combined with confirmatory prenatal genetic testing (eg, amniocentesis or chorionic villus sampling), a risk—estimated between 0.1% and 1%—of iatrogenic pregnancy loss should be considered, although recent meta-analyses have reported a lower incidence.[48]

Importantly, the concept that a child free from ADPKD is not necessarily "healthy" must be explicitly discussed. Moreover, intracytoplasmic sperm injection—the fertilization method most commonly employed in these cases—has been associated with a modestly increased risk of congenital anomalies (notably of the genitourinary tract), ventricular septal defects, and neurological impairment, often related to prematurity.[49] Although these risks remain low in absolute terms, they underscore the inherently non-physiological nature of assisted reproductive technologies.

Risks associated with medically assisted reproductive technology (paternal disease)

Pregnancies conceived through assisted reproductive technologies are associated with a higher incidence of preterm birth, intrauterine growth restriction, and low birth weight—outcomes that are in turn associated with an increased risk of metabolic, cardiovascular, and kidney diseases in adulthood.[50–53] However, the risks have mainly been assessed in the context of infertility, which itself constitutes an independent risk factor for adverse pregnancy outcomes.[50] Therefore, in otherwise healthy and fertile women who undergo assisted reproductive technologies solely to prevent transmission of a paternal disease, the risks may be significantly lower.[54]

Risks in cases of maternal ADPKD

Pregnancy in women with ADPKD is considered high risk, even during the preclinical phase, that is, in the presence of normal kidney function and the absence of proteinuria or hypertension (Table 2). The degree of risk is modulated by the presence of preexisting hypertension (especially if not optimally controlled), proteinuria (especially if >1 g/d) or any reduction in baseline kidney function.[55–57] In women with markedly enlarged kidneys, preconception counseling may benefit from the involvement of a urologist.[41]

Currently, limited data are available regarding pregnancy outcomes in women with ADPKD undergoing assisted reproductive technologies.[26] As a result, it remains unclear to what extent assisted reproductive technology confers an additional risk in this specific patient population.

Table 2 Main indications in the autosomal dominant polycystic kidney disease (ADPKD) patient who becomes pregnant.[a]

When	Indications
Before pregnancy	Discontinue tolvaptan and other potentially teratogenic drugs
	Folic acid intake
	Correction of overweight, anemia, iron and vitamin D deficiency
	Optimization of blood pressure and other potential comorbidities
	RASi can be discontinued with a positive pregnancy test.
During pregnancy	Women are advised to take a low dose of aspirin from conception (or ultrasound confirmation of pregnancy) until 34–36 weeks or at delivery (according to the obstetrician's choice)
	Check blood pressure (target <130/80 mmHg) and possibly start therapy (labetalol, hydralazine, nifedipine, clonidine, methyldopa)
	Monitor of kidney function and proteinuria
	Monitor urine culture (and treat if positive).
After the 20th gestational week	If available, plasma monitoring every 4–6 weeks of the sFlt-1/PlGF (fms-like tyrosine kinase 1/placental growth factor) ratio may help identify placental problems
	Natural delivery is compatible with maternal ADPKD.
After delivery	Nephrological visit after delivery to reassess the situation and resume therapies during or after breastfeeding
	Closer follow-up in the presence of adverse events during pregnancy.

[a]Taken from references [21] and [55].

Risks associated with ovarian stimulation

Ovarian stimulation is a fundamental component of assisted reproductive procedures. The risk of developing ovarian hyperstimulation syndrome is influenced by the patient's age, ovarian reserve, and the presence of polycystic ovaries. While pharmacological strategies—such as the administration of gonadotropin-releasing hormone antagonists during stimulation and ovulation induction with gonadotropin-releasing hormone agonists—significantly reduce the risk of severe ovarian hyperstimulation syndrome, this adverse effect should be discussed at counseling.[58] Given that about 50% of the embryos are expected to be non-implantable, multiple stimulation cycles are often required, resulting in an increased treatment burden and cumulative risk of complications for the woman.

Assisted reproductive technologies have been associated with increased cardiovascular risk in women. The elevated estrogen levels during ovarian stimulation promote a prothrombotic state, and the assisted reproductive technology itself—particularly in the case of frozen embryo transfer—has been linked to an increased incidence of hypertensive disorders of pregnancy, irrespective of kidney disease.[59]

When the female partner is unaffected by ADPKD, the ethical implications of medicalizing a physiological process should be carefully discussed. Conversely, if the female partner is affected by ADPKD, assisted reproductive technology-related risks are added to the baseline risks associated with CKD (Figure 2). Specifically, exposure to elevated estrogen levels may promote hepatic cyst growth, and assisted reprodictive technology is generally contraindicated in severe polycystic liver disease.[55,60] Although the risk of peripartum cyst rupture is considered low, it should be weighed against the increased risk of infection associated with cesarean section; indeed, current evidence does not support choosing cesarean delivery based solely on cyst volumes.[21]

Pregnant women with ADPKD are at increased risk of upper urinary tract infections, which may be difficult to treat due to limited antibiotic penetration into the cysts. In contrast, there is no consistent evidence of increased nephrolithiasis incidence during pregnancy in this population.[25]

The need for multiple assisted reproductive technology cycles prolongs the period of contraindication for certain medications such as tolvaptan and similar agents that must be discontinued before conception, while angiotensin-converting enzyme (ACE) inhibitors may be discontinued upon confirmation of pregnancy.[56]

Finally, preeclampsia is not only a risk factor for the development and progression of CKD in the mother, but also a contributor to low birth weight and prematurity, both of which are associated with reduced nephron endowment and long-term kidney vulnerability in the offspring.[61]

Psychological repercussions on children and family

There are potential psychological implications of disclosing to the children, once they have grown up sufficiently to understand what this means, that they were "selected because they were healthy," with the accompanying burden of expectations that such knowledge might entail. Given that ADPKD is a familial disease, it is likely that children will become aware of its presence within the family and, in turn, question their own health status. While the relief of knowing they are not at risk of developing the disease may be significant, it may be counterbalanced by the psychological weight of having been conceived through a deliberate process of genetic selection.

Legal framework, ethical justice, and Italian law

Various interpretations of justice are possible: the legal framework, equity of access to care, the moral and religious legitimacy of the procedures, and the societal burden they may imply.

In the United Kingdom, the Human Fertilisation and Embryology Authority (HFEA) has established a list of monogenic disorders for

which access to preimplantation genetic testing is permitted, and this includes ADPKD.[62] In contrast, no such official list exists in Italy, where reproductive technologies are governed by Law 40/2004, titled "*Rules on Medically Assisted Procreation*." This law has undergone several revisions following Constitutional Court ruling no. 96/2015. The 2004 implementation guidelines explicitly prohibited preimplantation genetic diagnosis, later overturned by the Lazio Regional Administrative Court (TAR Lazio ruling no. 398/2008), leading to updated guidelines in 2008 that lifted this ban.[63] This position was subsequently backed by the Italian Constitutional Court, which affirmed the right of fertile couples who are carriers or affected by serious heritable genetic diseases to access preimplantation diagnosis, provided the condition would justify voluntary termination of pregnancy under current law and is verified by an authorized public institution.[64]

Further, Constitutional Court ruling no. 229/2015 declared the criminalization of any form of embryo selection for so-called "eugenic purposes" as unconstitutional However, embryos identified as affected by disease and not selected for implantation cannot be discarded. The Court stated that: "… the need arises to protect the dignity of the embryo, for which no other response can currently be given other than cryopreservation. The embryo, regardless of the broad and debated recognition of its subjectivity in the origin of life, certainly cannot be reduced to mere biological material."[65]

In addition, Constitutional Court ruling no. 84/2016 reaffirmed the ban on using surplus embryos for research purposes, declaring that: "The dignity of the embryo, as an entity that contains the principle of life within itself (even if at a stage of development not specifically defined by the legislator and still not unanimously recognized by science), constitutes a constitutionally protected value under Article 2 of the Constitution." It also stated that "The protection afforded to the embryo cannot be diminished solely on the grounds that it is affected by genetic abnormalities…."[65,66]

The current legal situation in Italy, in which, albeit with the restrictions mentioned above, the original ban on preimplantation genetic diagnosis has been lifted, can be considered in line with the trend that seems to be spreading increasingly at the international level, as over the past decade changes in many national regulations have demonstrated an increasing acceptance of preimplantation genetic testing, albeit with various differences between countries.[67]

Equity of distribution and access

The high costs associated with assisted reproductive technologies and genetic testing raise concerns regarding the equitable allocation of health-care resources. Globally, there is considerable variability in the reimbursement of these procedures, and costs vary between centers, depending in part on the specific techniques employed. In settings where the procedure is not publicly funded, financial barriers significantly limit access. This issue exists both within countries and between high-income and medium-low-income countries. In the latter, also access to KRT may be limited.

In Italy, several public centers offer preimplantation diagnosis, but access remains unequal, also because of lack of adequate information, leading to disparities in access based on location, educational level, and awareness and engagement of the reference clinicians.

For example, at the Medically Assisted Procreation Centre of Arco Hospital in the Autonomous Province of Trento, which has offered preimplantation genetic diagnosis since 2018,[68] 17 couples affected by ADPKD have undertaken medically assisted procreation with preimplantation genetic testing. Only 2 of these couples were residents of Trentino Alto Adige, while the majority came from other regions.

Autonomy: pre-conception counseling

In a secular context, pre-conception counseling aims to inform couples about the likelihood of disease transmission to offspring. This includes consideration of phenotypic expression based on family history and the specific genetic mutation, as well as outlining reproductive options to prevent transmission. While pre-conception genetic counseling can provoke anxiety, it is fundamental for supporting patients' self-determination and shared decision-making.[69]

The decision to pursue preimplantation genetic testing is often motivated by the desire to ensure a better future for their children, after experiencing the physical, psychological, and social burden of a disease. From a bioethical perspective, however, this aspiration raises concerns about a potential drift toward eugenics. When taken to an extreme, the pursuit of genetic "perfection" reduces the child to a product of parental design. As Sandel notes in his reflections on the ethics of genetic engineering: "*Being called upon to take care of our children without being able to choose them according to our tastes teaches us to be open to the unsought … It invites us to accept the unexpected, to live with dissonances, to keep the impulse to control at bay.*"[70]

It is therefore essential to communicate that preimplantation testing does not eliminate the possibility of other genetic disorders, nor can it prevent complications related to prematurity, which may lead to long-term disability. The availability of such technologies may also generate subtle or overt pressure on prospective parents, who may feel morally responsible for avoiding disease transmission. This pressure may be reinforced by family members or by clinicians managing the patient's condition.[69]

Using a scenario-based approach in counseling

Given the challenges in providing precise risk estimates for pregnancy in women with CKD, a counseling approach based on "possible scenarios" may offer a practical and comprehensible framework to narratively outline risks and outcomes[71] (Figure 3). A scenario-based approach may be further adapted to the single cases, to personalize discussion, allowing potential parents to emotionally explore various outcomes. In cases involving advanced maternal age, comorbidities, or high-risk profiles, acknowledging and integrating the possibility of an adverse outcome can support a strong therapeutic alliance and foster realistic expectations.

Bioethical perspectives on preimplantation genetic diagnosis in ADPKD patients

Liberal-libertarian bioethical theory

The liberal-libertarian approach holds that human life is a good over which individuals may exercise autonomy. Personhood is dependent on cognitive development and the capacity to

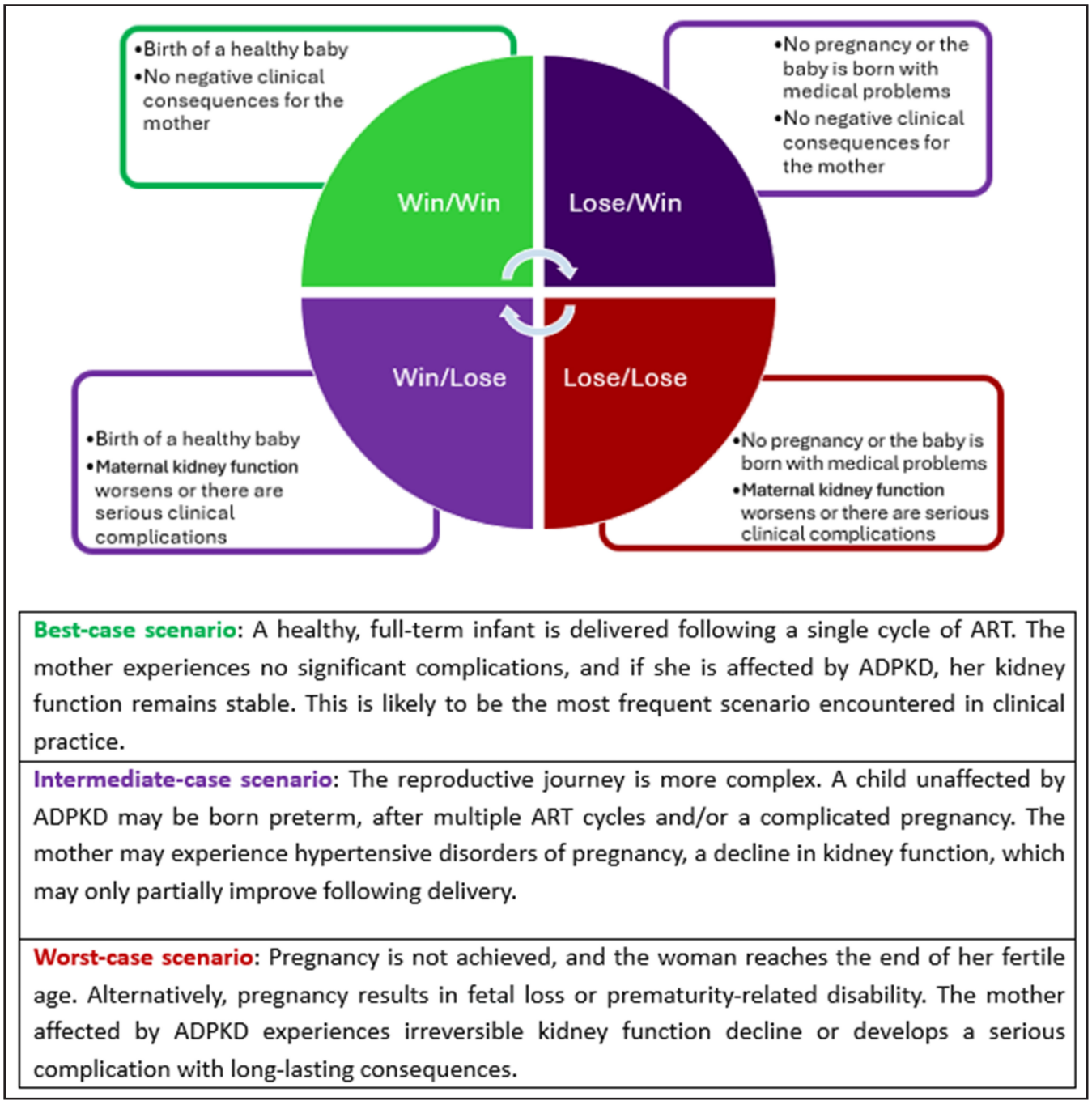


Figure 3 Schematic representation of possible outcomes from assisted reproductive technologies (ART) in couples at risk of transmitting autosomal dominant polycystic kidney disease (ADPKD).

participate in moral life. As a result, embryos and fetuses do not warrant the same moral protection as autonomous adults. This theory supports reproductive self-determination, considering decisions—including the use of genetic selection—a private choice. Within this paradigm, the right of parents to select embryos based on genetic health is affirmed, and the destruction of affected embryos or their use for research purposes is deemed acceptable. Furthermore, this perspective posits a moral responsibility to prevent the transmission of diseases, with the suggestion that future offspring could otherwise regard their birth as a "wrongful life."[72]

Utilitarian bioethical theory

Utilitarian theory prioritizes actions that maximize well-being and minimize suffering for the greatest number of individuals possible. Since embryos are not capable of experiencing pain, their moral status does not require protection. This theory supports preimplantation diagnosis as a strategy to reduce the burden of disease and suffering for individuals and systems. By enabling the birth of children free from severe hereditary conditions, utilitarianism promotes outcomes aligned with greater societal and familial benefit, including reducing the need for intensive treatments such as

Table 3 Religious perspectives on assisted reproductive technologies (ART), preimplantation genetic testing (PGT), and abortion.

	FIVET/ICSI	PGT	Abortion/fetal reduction
Christianity	No	No	No
Catholicism	No	No	No
Protestantism	Not unanimous	No	No
Orthodoxy	Yes	No	No
Judaism	Yes	Yes	Yes
Islam	Yes	Yes	Yes
Hinduism	Yes	Yes	Yes
Buddhism	Yes	Yes	Yes

Abbreviations: FIVET, Fertilization in vitro and embryo transfer; ICSI, Intracytoplasmic sperm injection; PGT, Preimplantation genetic testing.

dialysis. Like the liberal-libertarian model, utilitarianism favors reproductive autonomy and endorses genetic selection as a legitimate expression of "procreative beneficence."

Personalist bioethical theory

Personalist bioethics asserts the inviolability of human life from conception and considers that embryos possess inherent dignity and personhood. Consequently, this view recognizes the embryo's right to life and protection irrespective of developmental stage or health status. Under this framework, preimplantation genetic diagnosis is deemed morally permissible only when used for therapeutic purposes—specifically, to treat or correct a genetic defect in the embryo. In the case of ADPKD, where no treatment currently exists, embryo selection is not deemed ethically justified and it is also held that embryos diagnosed with a pathogenic variant should be cryopreserved indefinitely, rather than destroyed.[73]

Religious perspectives

The position of major world religions on medically assisted procreation and preimplantation genetic testing varies and is often aligned with their underlying bioethical frameworks (Table 3).

Catholicism

Consistent with personalist bioethics, the Catholic Church emphasizes the sanctity of human life from conception. It opposes preimplantation genetic diagnosis on the grounds that it leads to embryo selection and involves a discriminatory evaluation of life based on health status. Official documents such as *Donum Vitae* and *Dignitas Personae* emphasize the moral inadmissibility of procedures that undermine the dignity of human life. Furthermore, assisted procreation may be viewed as ethically unacceptable because it replaces the conjugal act and separates procreation from marital union.[74]

Protestant christianity

The Protestant tradition does not have a unified ethical stance on this issue. Some denominations permit its use but generally prohibit the creation of supernumerary embryos or embryo selection. Ethical acceptance depends on individual interpretation and denominational doctrine.[75]

Orthodox christianity

The Orthodox Church permits medically assisted fertilization in the context of infertility but draws a firm ethical boundary against the production and destruction of excess embryos. Consequently, it does not support preimplantation genetic testing.[76]

Judaism

Judaism strongly supports procreation, grounded in the Torah's commandment to "be fruitful and multiply." Within this context, medically assisted fertilization and preimplantation testing are generally permitted, including embryo selection, as the soul is believed to enter the body only 40 days after conception. This understanding also permits the use of embryos for research and their cryopreservation for future use.[77]

Islam

Sunni Islam, followed by the majority of Muslims worldwide, generally allows assisted fertilization provided the gametes are those of the married couple. Cryopreservation and research on embryos are permissible up to 120 days post-fertilization, considered the time of ensoulment. However, some recent recommendations have proposed reducing this period to 14 days. Preimplantation genetic testing is permitted and preferred over prenatal diagnosis and abortion for preventing heritable disease.[78]

Hinduism and Buddhism

Both the Hindu and Buddhist religions generally take a liberal stance on reproductive technologies. The use of donor gametes is accepted, as is the use of assisted reproductive techniques, including genetic testing and embryo selection.[79]

Final reflections and conclusions

For too long, nephrologists have discouraged pregnancy in patients affected by ADPKD, due to concerns about adverse maternal and fetal outcomes, as well as the risk of transmitting the disease to offspring. Enhanced awareness of the complexities involved, with improved interdisciplinary collaboration among nephrologists, geneticists, and gynecologists to support truly informed family planning decisions, are needed to support reproductive freedom for potential parents living with ADPKD. Early exploration of reproductive options, including adoption, is important to make an informed decision. Variables related to family history, genetic characteristics, the woman's reproductive potential (many issues may coexist), and the couple's preferences should be considered. Each decision in this area should be personalized and carefully evaluated with the couple, especially if it is the woman who is to be affected, assessing the risk of pregnancy-related complications for the mother and fetus, and the progression of the kidney disease, as well as the timing, likelihood of success, and risks of assisted reproductive technologies. In the specific case of ADPKD, genetic selection through assisted

reproductive technologies presents a nuanced challenge given the risks inherent in the procedure, ongoing medical advances, and the multifaceted, and individually perceived clinical and psychological burden imposed by the disease. Counseling on these options may enable prospective parents to make a truly informed decision.

Author contributions

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