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Overview of ADPKD in Pregnancy

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Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disorder that often affects patients in their third to fifth decades of life and is characterized by kidney cysts, chronic kidney disease (CKD), hypertension, and hepatic cysts. The development of clinical symptoms often coincides with childbearing years. Consequently, there are several considerations regarding pregnant patients with ADPKD. In this review, we detail the effects and management of ADPKD in the peripartum period and discuss family planning options, including assisted reproductive techniques (ART) and preimplantation genetic testing.

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ADPKD is the most common genetic kidney disease.[1] The genetic mutations associated with ADPKD include those in *PKD1* (approximately 78% of cases) and *PKD2* (approximately 15% of cases). [2] Other genes have been identified (such as *IFT140*) but are less common, and 5% to 10% of patients with ADPKD do not have an identifiable mutation.[3-5] Because the disease is autosomal dominant, a patient's offspring has a 50% chance of developing ADPKD.

ADPKD is equally distributed between males and females, and its clinical manifestations tend to present in the third and fourth decade. Clinically, ADPKD is characterized by enlarged kidneys, numerous parenchymal cysts (which can become painful and/or infected), and progressive decline in kidney function.[3] Patients can also develop urinary tract infections, cyst infections, and kidney stones. Extrarenal manifestations include hepatic cysts, valvular heart disease, and cerebral aneurysms.[6]

Because the disease becomes clinically active during the childbearing years, patients with ADPKD face unique reproductive challenges. In this review, we discuss prepregnancy considerations, (such as ART and preimplantation genetic testing for monogenic disorders [PGT-M]). We then review the management of ADPKD during pregnancy and postpartum considerations such as birth control and future family planning.

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PREPREGNANCY

Prepregnancy Assessment and Counseling

Before conception, patients with ADPKD should be evaluated and counseled by a multidisciplinary team, including an obstetrician/gynecologist, a maternal-fetal medicine specialist, and a nephrologist.[7]

The patient should be adequately counseled on risks and timing of pregnancy, because both CKD and ADPKD increase the risk of maternal and fetal complications during pregnancy.[8-10] Patients should be counseled that pregnancy can worsen kidney function. This is in contrast to normal pregnancy physiology, which is typically associated with glomerular hyperfiltration and an increase in glomerular filtration rate by 40% to 50% (despite upregulation of the renin-angiotensin-aldosterone system).[11] Nonpregnant patients with ADPKD typically have increased renal artery vasoconstriction and decreased renal blood flow, and it is unknown if pregnant patients with ADPKD experience the same degree of hyperfiltration seen in healthy pregnancy.[11,12] In patients with a baseline creatinine < 1.4 mg/dl, there may be good maternal and fetal outcomes. However, if the creatinine is > 2.0 mg/dl, the patient is at risk of further decline in kidney function during pregnancy.[13]

Regarding fetal risk, patients should be counseled that, in general, CKD stage is a risk factor for preterm delivery, small-for-gestational-age birthweight, and higher admission rate to the neonatal intensive care unit.[10] Nevertheless, patients with ADPKD appear to have similar rates of fetal complications compared with the general population, although the risk is higher if they are aged > 30 years and have preeclampsia.[14] Another study indicated that patients

with ADPKD tended to have more preterm delivery, intrauterine growth restriction, and small-for-gestational-age birthweight; however, these findings were not statistically significant.[15]

Patients with ADPKD who have undergone transplantation should ideally delay conception until 1 to 2 years posttransplantation.[16] This delay ensures that viral prophylaxis has been completed and immunosuppression is at a minimum, while also reducing the risk of infertility that can occur because of CKD development in older allografts.[16]

Medication changes that need to occur before and/or at the time of conception should be reviewed by the patients (Table 1). If tolvaptan is being used, this can be continued until pregnancy is confirmed. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are typically stopped before conception.[7] However, newer guidelines suggest that if there is a strong indication for continuing the angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, such as proteinuric CKD, it can be continued until pregnancy is confirmed.[7] In patients with ADPKD who are post-transplant, sirolimus/everolimus and mycophenolate mofetil should be discontinued 6 and 12 weeks before conception, respectively. This timing allows for washout before pregnancy while ensuring stable graft function on a different immunosuppression regimen.[7,16]

In addition, as part of the early discussions regarding pregnancy planning, patients with ADPKD should be educated on fertility and options regarding family planning, such as ART and genetic testing, as well as considerations of surrogacy.

Table 1. Approach to a pregnant patient with ADPKD

Stage	Management	Medications safe to continue	Medications to discontinue or avoid
Prepregnancy	Evaluate and counsel on individual risks and benefits of pregnancy. Counsel on PGT-M options Discuss ART - IVF and/or ISCI - PGT-M – FET with natural or artificial cycle (natural cycle may be preferred in patients with PLD) - Gestational Surrogacy	Tolvaptan Antihypertensives - ACEi/ARB – if strong indication (proteinuric CKD) - Labetalol - Nifedipine - Hydralazine - Loop diuretics (if compelling indication) Immunosuppression - CNIs - Azathioprine - Prednisone	Antihypertensives - ACEi/ARB - Thiazides - Spironolactone Immunosuppression - MMF – stop 12 wks before conception - Sirolimus/ Everolimus – stop 6 wks before conception
Pregnancy	Regular appointments with multidisciplinary team (OB/GYN, MFM, nephrology) Routine testing: Renal function panel, urinalysis, quantified proteinuria. Hypertension Goal blood pressure < 135/85 mmHg and > 110/70 mmHg Preeclampsia/eclampsia - Prophylaxis:ASA 81–162 mg/d before 16 wks until delivery - Consider use of sFlt1:P1GF assay (if available) Personal or family history of cerebral aneurysms - Standard screening - Consider cesarian delivery	Antihypertensives - Labetalol - Nifedipine - Hydralazine - Alpha-methyldopa - Loop diuretics (if compelling indication, otherwise not recommended.) Immunosuppression - CNIs - Azathioprine - Prednisone	Tolvaptan Antihypertensives - ACEi/ARB - Thiazides - Spironolactone Immunosuppression - MMF - Sirolimus/everolimus - Belatacept (limited data)
Postpartum/breastfeeding	Follow-up within 4–6 wks - If HDP, within 1–3 wks Future family planning discussions should be individualized.	Antihypertensives - Enalapril/Captopril - Labetalol - Nifedipine - Hydralazine - Alpha-methyldopa - Thiazides, loop diuretics (low dose) - Spironolactone Immunosuppression CNIs Azathioprine Prednisone Estrogen-containing contraceptives Mild to moderate PLD: risks and benefits discussion	Tolvaptan Antihypertensives - Other ACEi/ARB - Other beta blockers: Atenolol/nadolol/sotalol - Thiazides, loop diuretics (higher doses can suppress breastmilk) Immunosuppression - MMF - Sirolimus/everolimus - Belatacept (limited data) Estrogen containing contraceptives Severe PLD: Avoid use

ACEi, angiotensin-converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin receptor blocker; ART, assisted reproductive technologies; ASA, aspirin; CKD, chronic kidney disease; CNI, calcineurin inhibitor; FET, frozen embryo transfer; HDP, hypertensive disorders of pregnancy; ICSI, intracytoplasmic sperm insertion; IVF, *in vitro* fertilization; MFM, maternal-fetal medicine specialist; MMF, mycophenolate mofetil; OB/GYN, obstetrician/gynecologist; PGT-M, preimplantation genetic testing for monogenic disorders: PLD, polycystic liver disease; PlGF, placental growth factor; sFlt1, soluble fms-like tyrosine kinase 1.

Fertility

Historically, ADPKD was not associated with infertility. Some studies have suggested that ADPKD may be associated with male infertility; this relationship is unclear because most studies are small and/or case reports. Previous studies have shown anatomical changes in males, such as seminal vesicles and/or ejaculatory duct cysts.[12,17,18] In addition, men with ADPKD may have abnormal sperm parameters, such as impaired sperm motility because of structural flagellar defects.[4,12,19] Two small prospective studies of men with ADPKD showed that the majority had abnormal semen parameters (most commonly, impaired sperm motility).[20,21] However the small study size makes it challenging to apply these findings to the general ADPKD population.

ADPKD has not been shown to reduce fertility in women. Some studies indicate an increased risk of ectopic pregnancy in ADPKD, possibly related to abnormal ciliary function of the fallopian tubes.[12,14] However, a small study comparing patients with ADPKD with controls showed no difference in conception, spontaneous abortion, or live birth.[22,23] In contrast, the decreased kidney function that occurs in ADPKD is associated with infertility and is thought to be because of reduced pulsatile release of gonadotropin-releasing hormone and impaired ovulation.[24]

In patients who experience infertility, ART is available and includes methods like *in vitro* fertilization (IVF).[24]

IVF

IVF involves using exogenous gonadotropins to cause varying degrees of controlled ovarian hyperstimulation to develop multiple follicles.[25] Once multiple follicles are $\geq$ 18 mm, ovulation is induced and the patient undergoes egg retrieval.[25] Owing to the supraphysiologic hormone levels, patients are at risk of ovarian hyperstimulation syndrome (OHSS). OHSS develops when vascular endothelial growth factor (released from hyperstimulated follicles) causes widespread vascular permeability, "third spacing" of fluid, and reduced intravascular volume.[26] Symptoms from this range include mild nausea or bloating of pulmonary edema, ascites, and acute kidney injury.[26,27]

After retrieval, embryos are created by either traditional IVF (where multiple sperms are introduced into the egg) or intracytoplasmic sperm insertion (needle-guided direct insemination of the egg). Intracytoplasmic sperm insertion may be an option for males with ADPKD with abnormal sperm parameters. In a prospective study involving 22 infertile males with ADPKD who underwent intracytoplasmic sperm insertion, the average fertilization rate was 82%.[21]

The embryo is then implanted in the intrauterine space. Implantation can either be within 5 days after retrieval (also known as fresh embryo transfer) or later, as frozen embryo transfer (FET).[28] FET can be performed with either the patient's natural ovulatory cycle or using exogenous hormones to create an artificial cycle. Importantly, genetic testing is generally not done during fresh embryo transfer.[28]

Although considered safe, IVF has associated risks, including OHSS, hypertension, and preterm delivery.[28] These risks are higher in patients who undergo fresh embryo transfer than those who undergo FET.[28] However, the risk of preeclampsia or eclampsia is higher in artificial FET than in natural-cycle FET or fresh embryo transfer.[29]

A recent systematic review evaluated the outcomes of 68 patients with CKD who underwent IVF.[27] Fifty-six (76%) were posttransplant, and only 5 patients had ADPKD. Among those who did not undergo transplantation, patients had CKD stages 1 and 2 or end-stage kidney disease on dialysis, and none had stage 3 or 4 CKD. Hypertensive disorders of pregnancy (including preeclampsia) developed in 38.3% (26/68) of the patients. OHSS occurred in of 4 of 54 patients (4.7%), 3 of whom developed severe OHSS with associated acute kidney injury.[27] Compared with the general population, severe OHSS is reported to occur in 0.3% to 1% of patients and 1% to 5% of IVF cycles.[30,31] Despite this, patients with CKD who undergo ART have a live birth rate of approximately 86.7%.[27]

Although it has not been studied directly, the high amounts of estrogen required for IVF likely increases progression of polycystic liver disease (PLD), because previous studies have shown that supplemental estrogen in postmenopausal women correlated with an increase of total liver volume by 7% and symptoms of abdominal pain and dyspnea.[32,33] The new Kidney Disease Improving Global Outcomes guidelines discourages IVF in patients with ADPKD and severe PLD.[34,35] However, as noted above, IVF utilizing FET with a natural cycle eliminates exogenous estrogen exposure, and may offer an alternative option for patients with PLD.[29]

Preimplantation Genetic Testing

PGT-M is an important tool for patients with ADPKD. PGT-M can identify embryos with the pathologic gene for ADPKD and reduce the risk of transmission of ADPKD to the fetus to 1% to 2%.[4] Importantly, PGT-M requires previous identification of the variant gene in the affected parent.[34] A survey of patients with ADPKD indicated that approximately 100% are in favor of genetic testing themselves; however, only 19% would support fetal genetic testing.[36] Notably, this

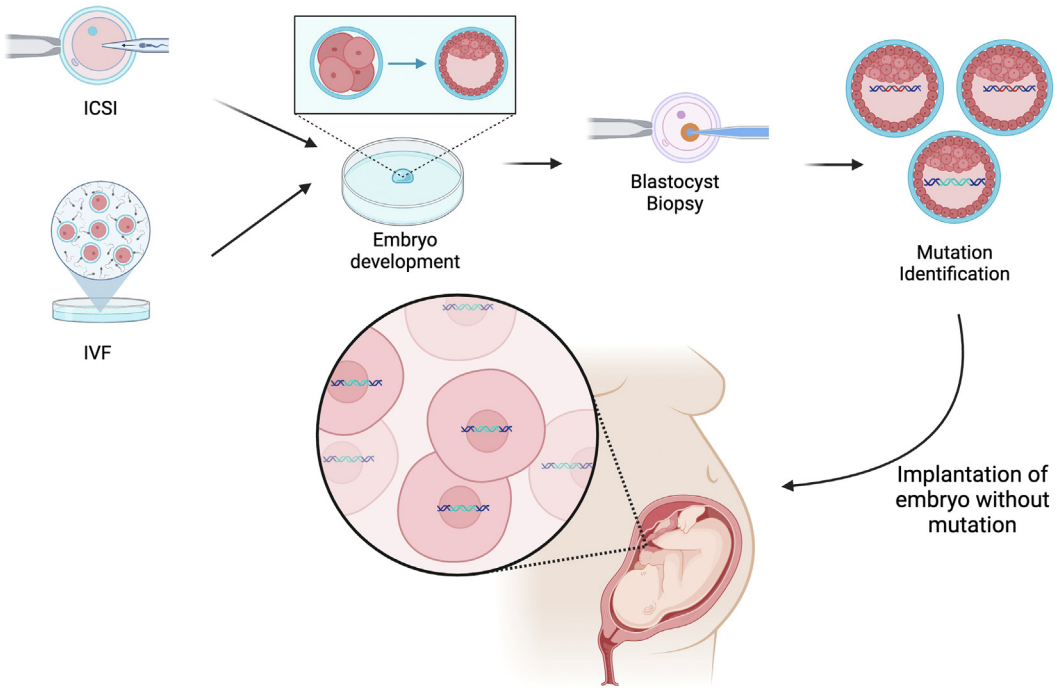

Figure 1. Preimplantation genetic testing. Embryos are created through either IVF or ICSI. The blastocyst is then biopsied, and the mutation of interest is identified. An embryo without the mutation is implanted into the mother. Created in BioRender. Campbell, R. (2024) https://BioRender.com/m16w704.IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm insertion.

survey was conducted in the 1990s, when IVF and PGT-M were not routinely used and may not reflect current attitudes.

PGT-M is a stepwise process that requires the creation of an embryo via IVF or intracytoplasmic sperm insertion (Figure 1). Then, DNA from the embryo is extracted by blastomere biopsy and analyzed for genetic mutation (via either direct mutation testing or linkage analysis).[4,34] The embryo without the identified mutation is then selectively implanted.[4] Confirmation that the fetus does not carry the mutated gene is done by invasive testing with either a chorionic villus sampling or amniocentesis.[4] The entire process can be prolonged, because it may take some time to develop an embryo without the mutation.[4]

Gestational Surrogacy

In patients with ADPKD who are at high risk for pregnancy, gestational surrogacy (GS) is another option. In GS, the intended parents create embryos using either their own (or donor) oocytes or sperm via IVF (and PGT-M, if desired). The embryo is implanted into a surrogate uterus for gestation.[37] A recent case report described a woman with rapidly progressive ADPKD who utilized PGT-M and GS to deliver a healthy child.[38] Although GS is a valuable option, there are a number of legal and ethical issues surrounding surrogacy. Surrogates may be compensated; however, compensated surrogacy prompts ethical concerns regarding the exploitation of vulnerable populations. In the US, the legality of GS varies between states.[37] Internationally, uncompensated GS is legal in the UK, Canada, and South Africa, whereas compensated GS is legal in Russia.[37] In addition, there are significant financial considerations; the average US cost is over $100,000 and is variably covered by insurance.[37]

Summary

In summary, when counseling patients with ADPKD during pregnancy, it is important to discuss the ideal timing as well as the maternal and fetal risks of pregnancy. Patients should be counseled regarding ART options, PGT-M, and GS. Importantly, IVF and PGT-M can be a prolonged process, which can delay pregnancy, increasing the chance of CKD progression and further complicate pregnancy.[4] Finally, patients need to consider financial implications, which vary worldwide. In the US, 1 cycle of IVF (including medications) costs up to $25,000 and insurance coverage varies between states.[39] In the UK, the National Health Service only covers 1 to 3 cycles of IVF; and in Japan, IVF is not covered by insurance.[39,40] PGT-M is rarely covered in the US and average PGT-M costs are an additional of approximately $4268 per IVF cycle.[41]

PREGNANCY

Maternal Risk and Clinical Management

Once pregnant, patients with ADPKD should undergo routine visits with their nephrologist, as well as

obstetrician/gynecologist and maternal-fetal medicine specialist.[7] Baseline testing includes serum creatinine levels and formal quantification of proteinuria by urine albumin-to-creatinine and urine protein-to-creatinine ratios.[7]

Medication reconciliation should be repeated. If angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are still in use, they should be discontinued when a pregnancy is confirmed. Antihypertensives that are safe during pregnancy include labetalol and nifedipine.[7,42,43] Second-line medications, such as hydralazine and alpha-methyldopa, can be used, although alpha-methyldopa does not currently appear to be on the formulary in the US. Tolvaptan should be discontinued when the patient becomes pregnant. In patients who have undergone transplantation, calcineurin inhibitors (tacrolimus and cyclosporine), azathioprine, and prednisone are considered safe to continue during pregnancy.[16]

Hypertension

Previous studies have shown that pregnant patients with ADPKD have a higher risk of developing chronic or gestational hypertension, preeclampsia, and eclampsia.[14,15] The optimal blood pressure goal for pregnant patients with ADPKD is unclear. The HALT-PKD study indicated that nonpregnant patients with ADPKD benefit from intensive blood pressure control of $< 110/70$ mmHg.[44] However, historically, chronic hypertension during pregnancy was not treated unless $\geq 160/110$ mmHg, because of concerns for decreased fetal blood flow and risk of small-for-gestational-agebirthweight. Recently, the Chronic Hypertension and Pregnancy trial showed that targeting a goal blood pressure $< 140/90$ mmHg had no increased risk of small-for-gestational-age weight and improved pregnancy outcomes.[45] Guidelines for pregnant patients with CKD recommend targeting a blood pressure $< 135/85$ mmHg but $> 110/70$ mmHg.[7] Although these studies do not distinguish between ADPKD and other CKD, previous reviews recommend $< 135/85$ mmHg for ADPKD.[12]

Preeclampsia and Eclampsia

As discussed above, patients with ADPKD are at an increased risk of developing preeclampsia and eclampsia. Therefore, prophylactic low-dose aspirin (81–162 mg/d) is recommended before 16 weeks of gestation and continued daily until delivery.[23,46,47] The most recent American College of Obstetricians and Gynecology update indicates that low-dose aspirin is not a contraindication for neuraxial anesthesia, such as epidural anesthesia; however, at our institution, aspirin is typically stopped at 37 weeks.[48]

To monitor for preeclampsia developing in high risk patients, biomarkers such as soluble fms-like tyrosine kinase 1 and placental growth factor are starting to be utilized.[49] A recent study showed that in patients with chronic or gestational hypertension, soluble fms-like tyrosine kinase 1–to–placental growth factor ratio ≥ 40 predicts the risk for developing preeclampsia with severe features and risk for delivery within 2 weeks.[50] This trial included patients with CKD, though it did not specify if patients had ADPKD. Consequently, in 2023 the US Food and Drug Administration (FDA) approved the soluble fms-like tyrosine kinase 1 placental growth factor assay for assessing the risk of developing preeclampsia with severe features within 2 weeks.[51]

Kidney Function and Total Kidney Volume

Patients with CKD and ADPKD are at increased risk of worsening kidney function during pregnancy. A recent case-control study by Wu *et al*. evaluated pregnancy outcomes in patients with ADPKD compared with those without ADPKD. In this study, there was only 1 patient with ADPKD who had a serum creatinine ≥ 1.2 mg/dl prepregnancy; however, the creatinine worsened to ≥ 1.2 mg/dl in 12% of patients with ADPKD postpartum.[15] In addition, proteinuria was newly detected in 6 patients with ADPKD during pregnancy, compared with 1 in the control group.[15]

Physiological changes during pregnancy may increase the height-adjusted total kidney volume (TKV) in patients with ADPKD. In normal pregnancy, there is an increase in kidney volume by 30%.[12] In addition, renin-angiotensin-aldosterone system upregulation and increased circulating vasopressin (because of reset osmostat of pregnancy) have the potential to contribute to cyst growth and height-adjusted TKV.[11,12,52] Chapman *et al*. showed that mean TKV in pregnancy is not affected by parity or age, though hypertension in pregnancy correlated with larger TKV.[14] However, a more recent case-control study indicated that nulliparous pregnant patients with PKD demonstrate a faster increase in height-adjusted TKV compared with nonpregnant patients with PKD.[53]

Liver Cyst and Volume Changes

As discussed previously, PLD is affected by estrogen exposure.[12,54] However, the effect of pregnancy on liver volume is unclear. Whereas some studies suggest an effect of pregnancy on height-adjusted total liver volume, in others, the effect was lost after adjusting for confounders such as age and fertility treatments.[32,55,56] Regardless, PLD can increase abdominal pressure during pregnancy and contribute to gastroesophageal

reflux (which occurs in 30%–50% of all pregnancies because of both esophageal sphincter relaxation and the enlarging uterus.)[54,57]

Nephrolithiasis and Infections

During pregnancy, the uterus can compress the ureters, leading to a physiologic hydronephrosis and increased urinary stasis.[12] In the patient with ADPKD, this physiologic effect can increase the risk for both urinary tract infections and kidney stones.[12] Wu *et al.* showed that 14.1% of pregnant patients with ADPKD developed urinary tract infection, compared with 0.7% of those without PKD. Interestingly, the rate of nephrolithiasis was the same between the groups.[15]

Cerebral Aneurysms

The effect of pregnancy on intracerebral aneurysms is controversial, although hemodynamic and hormonal changes may increase the risk of aneurysmal growth and rupture, and rupture risk appears highest in the third trimester.[58,59] There are no additional guidelines for intracerebral aneurysm screening during pregnancy outside of the standard recommendations.[60] Cesarian deliveries are often recommended for patients with unruptured intracerebral aneurysms, although the data do not clearly support this.[58]

Summary

In summary, ADPKD increases pregnancy risk, with studies demonstrating higher rates of hypertensive disorders of pregnancy and urinary tract infection.[14,15] Antihypertensives should be adjusted to target a blood pressure $<$ 135/85 mmHg, and patients should be started on prophylactic aspirin before 16 weeks to reduce the risk of preeclampsia. In addition, pregnancy itself can worsen kidney function, increase TKV, and requires close monitoring.[15]

POSTPARTUM

Postpartum Monitoring

Given the risk of worsening kidney function, follow-up with the patient's nephrologist should be performed within 1 month postpartum. In patients with hypertensive disorders of pregnancy, monitoring of blood pressure is critical in the postpartum period. Hypertensive disorders can worsen or even occur *denovo* (in a subset termed "postpartum preeclampsia") in the first 2 to 5 days to 6 weeks postpartum.[61] The American College of Obstetricians and Gynecology guidelines recommend an outpatient blood pressure check within 3 to 10 days of delivery.[62] Additional follow-up should be within 1 to 3 weeks, instead of the standard 6-week follow-up.[62]

Breastfeeding

In breastfeeding women, certain angiotensin-converting enzyme inhibitors such as enalapril or captopril are safe during lactation. Tolvaptan should be avoided in breastfed patients. Diuretics, such as thiazides, are safe but can reduce breast milk production. In transplant patients, breastfeeding is safe while on calcineurin inhibitors, azathioprine, and prednisone; whereas breastfeeding should be avoided in patients taking mycophenolate, sirolimus, everolimus, and belatacept.[16]

Contraception and Future Pregnancy

Future pregnancy planning should be discussed and individualized foreach patient. Birth control is an important consideration for postpartum patients. As discussed above, estrogen-containing birth control directly correlates with worsening height-adjusted total liver volume in premenopausal patients. A meta-analysis showed that exposure to estrogen-containing oral contraceptives in premenopausal patients led to a 1.45% per year increase in height-adjusted total liver volume.[56] The new Kidney Disease Improving Global Outcomes guidelines recommend a discussion of risks and benefits with patients with mild to moderate PLD, but avoid estrogen-containing contraceptives in those with severe PLD.[35]

CONCLUSION

In summary, ADPKD is a complex systemic disorder that affects all aspects of pregnancy from family planning to the postpartum period. Advances in ART, such as IVF and PGT-M, have improved patients' options and ability to pursue pregnancy. However, like other forms of CKD, patients with ADPKD are at risk of complications during pregnancy as well as worsening kidney function following pregnancy. Patients require individualized counseling and close management during pregnancy by a multidisciplinary team of specialists.

DISCLOSURE

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