Review

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Review

Unveiling the Enigma: Exploring the Influences of Sexual Hormones in ADPKD Women and the Urgency for Novel Insight

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Abstract: This in-depth review navigates the intricate relationship between gender, hormonal influences, and the progression of autosomal dominant polycystic kidney disease (ADPKD), highlighting the limited literature on this crucial topic. The study explores the impact of female sex hormones on liver and renal manifestations, uncovering gender-specific differences in disease progression. Actually hormonal therapy in women with ADPKD remains a challenging issue and is a source of concern regarding its potential impact on disease outcomes, particularly at the hepatic level. Notably, women with ADPKD exhibit a slower renal disease progression compared to men, attributed to hormonal dynamics. The review sheds light on the role of estrogen in regulating pathways of the renin-angiotensin-aldosterone system, revealing its complex interplay and implications for cardiovascular and renal health. Therapeutic considerations for fertile women with ADPKD, including contraception options, are discussed, emphasizing the necessity for personalized approaches. In the postmenopausal phase, the review evaluates the role of hormonal replacement therapy, considering its potential benefits and risks in the context of ADPKD. The review concludes by underscoring the imperative need for tailored treatment approaches for ADPKD patients, considering individual risks and benefits. The scarcity of literature underlines the call for further research to enhance our understanding of optimal hormonal therapies in the context of ADPKD, ultimately paving the way for innovative and personalized therapeutic interventions.

1. Preface

Gender exerts a significant influence on the occurrence and progression of many renal diseases, including ADPKD. ADPKD, impacting roughly 12 million individuals globally, affects both men and women equally. Mutations in PKD1 and PKD2 genes contribute to ADPKD, with gender playing a crucial role in disease manifestation and progression (1).Women with ADPKD generally exhibit a slower progression to end-stage renal disease (ESRD) compared to men. The Predicting Renal Outcome in Polycystic Renal Disease (PROPKD) Scoring system identifies gender as a significant factor in disease progression (2).

While renal cyst growth and kidney enlargement are central to ADPKD, gender differences emerge in renal complications. Men are more prone to hypertension and extensive hematuria, while women often experience earlier and more severe polycystic liver disease, likely influenced by estrogen activity. Pregnancy, oral contraceptives, and menopausal hormone therapy can impact disease course.

This study aims to comprehensively review the role of female sex hormones in ADPKD progression, emphasizing the need for tailored therapeutic approaches for affected women. In clinical practice, navigating challenges related to contraception and menopausal therapy in women with ADPKD is a common aspect Hormonal therapy in women affected by ADPKD remains a complex and often debilitating aspect, the genuine risks of which have yet to be fully elucidated, requiring a nuanced understanding of the disease's complexities.

2. Background

- *ADPKD:*

Autosomal Dominant Polycystic Kidney Disease (ADPKD) stands as the most prevalent genetic cystic kidney disorder, with 85% of cases attributed to mutations in the PKD1 gene on chromosome 16 and 10% to mutations in the PKD2 gene on chromosome 4. ADPKD diagnosis relies on familial history and ultrasound assessments, with approximately 25% of cases lacking a familial link, suggesting latent forms or novel genetic mutations (3). Renal manifestations include bilateral cysts leading to increased renal volume and progressive renal failure, affecting around 50% of individuals by age 60. Notably, a meta-analysis indicated a less aggressive progression of ADPKD in women compared to men (4).

Beyond renal complications, ADPKD can present with high blood pressure, hematuria, mitral valve prolapse, pericardial effusion, diverticulosis, pancreatic cysts, and cerebral aneurysms. The prevalence of cerebral aneurysms is notably elevated, especially in those with a family history of aneurysms or subarachnoid hemorrhages (5,6).

The primary extrarenal manifestation involves multiple liver cysts, affecting 10% of ADPKD patients with severe polycystic liver disease (PLD). Autosomal Dominant Polycystic Liver Disease (ADPLD) and rare renal parenchymal cysts are associated with different mutations. Although hepatic involvement occurs equally in males and females, it manifests earlier and more severely in females (7). Approximately 80% of women develop numerous liver cysts by age 60, particularly those with a history of pregnancies and/or estrogen-progestin therapy for contraception. A prospective study in postmenopausal women with ADPKD revealed the crucial role of estrogen in hepatic cystogenesis and increased liver volume, establishing it as a primary contributing factor (8).

Regarding pregnancy recent studies suggest that it does not necessarily cause new cyst formation, but may affect pre-existing cyst growth. Hormonal changes during pregnancy, specifically increased levels of estrogen and progesterone, may contribute to liver cyst enlargement and kidney cyst growth to a lesser extent. Additionally, increased renal blood flow during pregnancy could exacerbate cyst growth.

It is worth noting that the effect of pregnancy on ADPKD can differ among individuals. Certain women may observe a marked increase in cyst size, whereas others may exhibit no notable alteration. This interindividual variability is consistent with all clinical presentations of the disease. A crucial aspect is the involvement of a multidisciplinary team, including a nephrologist, gynecologist, and geneticist. Their aim is to offer tailored advice based on the patient's clinical characteristics to effectively address this pathway.

- ADPKD, Female Sexual Hormones and RAAS:

1. Female sex hormones

In recent decades, there has been a notable shift in medical research towards prioritizing women's well-being. Previously underestimated conditions, often labeled as "hidden diseases," have received increased attention and scrutiny. Simultaneously, there has been a heightened focus on understanding and addressing aspects of female sexual health and the physiological but impactful stages of a woman's life, including menopause.

It is crucial to acknowledge that women of fertile age are increasingly seeking hormonal therapies, not solely for contraceptive purposes but also for managing various conditions such as abnormal uterine bleeding, endometriosis, adenomyosis, chronic pelvic pain, dysmenorrhea, polycystic ovary syndrome (PCOS), and premenstrual syndrome. Gynecologists often recommend hormonal-based treatments, although non-hormonal alternatives are also available.

The use of hormonal contraception in women with Autosomal Dominant Polycystic Kidney Disease (ADPKD) has been a subject of significant debate. During the post-menopausal period, gynecological care is directed towards addressing climacteric symptoms like hot flushes and genito-urinary syndrome, along with osteoporosis prevention.

The established role of estrogen in modulating various pathways of the renin-angiotensin-aldosterone system, influencing blood pressure, and above all the proliferative impact of estrogen on hepatic cysts has been well-documented. Consequently, ADPKD has conventionally been considered a contraindication for hormonal treatments.

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Steroid Hormones and Reproductive Regulation:

Steroid hormones, including estrogen and progesterone, play a pivotal role in regulating mammalian reproduction, especially in uterine development and function. Operating primarily through gene transcription control within the uterus, these hormones exert their effects via specific receptors, acting as nuclear transcription factors. Their regulatory activity is triggered by binding steroid molecules, initiating a cascade of events that influence gene transcription. Estradiol, estrone, and estrone sulfate, varying in proportions based on menopausal status, are the primary estrogens in women's bloodstream, with crucial roles in cellular processes, including the regulation of cell proliferation.

Metabolism of Endogenous Progesterone:

Endogenous progesterone undergoes metabolic transformation into three biologically active metabolites. Approximately 50% is converted to 5α-dihydroprogesterone in the corpus luteum, 35% undergoes hepatic metabolism to 3β-dihydroprogesterone, and 10% transforms into 20α-dihydroprogesterone.

Estrogen Receptors in Hepatocytes and Proliferation:

Estrogen receptors (ERs), specifically ER-alpha and ER-beta in hepatocytes, have direct and indirect effects on cell proliferation. Binding of estrogen to these receptors can directly influence gene transcription related to cell proliferation, promoting cell progression through the G1 phase. Indirectly, estrogen stimulates the transcription and release of hepatocyte growth factor (HGF) and insulin-like growth factor (IGF), enhancing cell growth. Estrogen also interacts with other cell proliferation signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway, potentially amplifying proliferative effects.

On the contrary, there are no data in the literature demonstrating the primary role of progesterone in the growth of liver cysts.

2. Estrogen and Renin-Angiotensin-Aldosterone System (RAAS): Unraveling the Complex Interplay

The Renin-Angiotensin-Aldosterone System (RAAS) intricately regulates cardiovascular and renal functions, exerting a profound impact on arterial blood pressure (BP) regulation. Elevated RAAS activity is implicated in various cardiovascular and renal diseases, including hypertension. Estrogen emerges as a key modulator of RAAS, and its absence, as seen in menopause, may contribute to heightened RAAS activity.

Menstrual Cycle Influence on RAAS:

RAAS modulation exhibits variations across the menstrual cycle. In the luteal phase, characterized by high estrogen and progesterone, RAAS components increase. However, during simulated orthostatic stress, estrogen-induced decreases in tissue responsiveness to RAAS or opposing vasodilatory effects may prevent the maintenance of mean arterial blood pressure.

Estrogen's Impact on RAAS in Menopausal Women:

Postmenopausal women (PMW) show RAAS activation during orthostatic stress, and estrogen therapy restores RAAS responsiveness. Interestingly, despite RAAS activation, systolic blood pressure remains lower with estrogen therapy. Estrogen's complex effects include upregulating angiotensinogen gene expression, altering renin concentrations, and increasing vasodilators like cardiac atrial natriuretic peptide (ANP).

Hormonal Influence on RAAS Components:

Estrogen generally elevates angiotensinogen levels while decreasing renin, ACE activity, AT(1) receptor density, and aldosterone production. It also activates RAAS counterparts like natriuretic peptides, AT(2) receptor density, and angiotensinogen. Progesterone competes with aldosterone for mineralocorticoid receptors, while testosterone, less understood, appears to increase renin levels and ACE activity.

Implications for Gender Differences:

These hormonal effects on RAAS contribute to gender differences in cardiovascular and kidney diseases. Understanding this complex interplay sheds light on conditions influenced by RAAS dysregulation.

-*The Role of Estrogens on Renal Function:*

Estrogen's Unanticipated Renoprotective Role in ADPKD Progression

Contrary to expectations, estrogen emerges as a safeguard against renal failure progression in females with autosomal dominant polycystic kidney disease (ADPKD). Although this insight originates from a mouse model, it unveils critical mechanisms. In ADPKD, males face an elevated risk of progressing to end-stage renal disease compared to their female counterparts.

Hormonal Dynamics in RAAS and ET1 Axis:

In a groundbreaking finding, male sex hormones are implicated in stimulating Renin-Angiotensin-Aldosterone System (RAAS) activation and endothelin-1 (ET1) release. In contrast, estrogen intervenes by suppressing this axis and instigating the upregulation of vascular endothelial growth factor (VEGF), thereby preserving renal function (9).

Chloride Channels and Androgen-Responsive Elements:

Recent evidence underscores the pivotal roles of chloride channels, specifically protein kinase A and transmembrane calcium channel 16A (TMEM16A), in ADPKD pathology. The TMEM16A promoter region houses androgen-responsive elements crucial for testosterone-dependent regulation. This mechanism holds promise for mitigating renal cyst growth in women (10).

CFTR Expression and Estrogen Influence:

While TMEM16A expression displays variations, cystic fibrosis transmembrane conductance regulator (CFTR) expression appears diminished in ADPKD women. This decrease in CFTR expression is attributed to estrogen-dependent regulation. Understanding these subtleties is essential, given the implications for cyst development (11).

Gender-Specific Phenotypic Variations:

Recent studies point to the possibility that TMEM16A expression and hormonal regulation contribute to a more severe phenotype in men with ADPKD. The observed heightened cell proliferation, driven by increased intracellular calcium levels, likely underlies a more severe cyst-related phenotype, emphasizing gender-specific differences in renal calcium homeostasis (10).

Early Menopause as a Risk Indicator:

Compelling evidence indicates that women experiencing early menopause (before age 45) face an elevated risk of developing renal failure. This underscores the intricate interplay between hormonal regulation and ADPKD severity.

On the flip side, the impact of estrogens on liver cyst involvement and growth, as mentioned, seems to be detrimental.

Considering what has been discussed so far and in light of the scientific evidence and literature, we can attempt to outline a therapeutic approach aimed at maximizing benefits while minimizing potential risks.

3. Possible Therapeutic Strategies in Adpkd Patients

-Childbearing Age:

Copper Intra-Uterin Device

When ADPKD patients' needs are limited to contraception, we consider the copper intra-uterin device (IUD) the best choice. The copper IUD is the only long-acting non-hormonal contraceptive option currently available. approved by the FDA in 1988. It consists of a polyethylene T-shaped device wrapped in copper wire (12). The precise mechanisms of action of non-medicated IUDs are

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still sometimes not completely known. However, their presence creates a sort of hostile environment for pregnancy onset. First of all, the release of copper ions changes the intrauterine fluid, inhibiting sperm mobility. Secondarily, the presence of a foreign intrauterine device causes an inflammatory response, which has a spermicidal effect. It is important to underline how ovulation is not inhibited by the presence of copper IUDs (12–15). Therefore, this treatment is not effective for some important pathologies in women, such as endometriosis, dysmenorrhea, menorrhagia, or PCOs. Indeed, these are very common reasons for women to use hormonal-based treatments (16).

The use of the copper-IUD is well tolerated by patients; however, the side effects can be troubling for both users and clinicians. Some of them improve over time, while others do not. They mainly include: spotting, dyspareunia, dysmenorrhea, cramping, backache, vaginitis, prolonged periods, and, rarely, spontaneous expulsion. However, side effects caused by the device are sometimes so important as to lead to early removal in some cases (14).

Another aspect to be taken into consideration is the possible pain of IUD insertion in nulliparous women and young patients.

Copper IUDs still represent a really good alternative in cases of contraindicated hormonal treatment, such as hypertension, obesity, breast cancer, and deep venous thrombosis. Most importantly for this review, copper IUDs can be used in patients with hypertension and both benign and malignant liver tumors, such as focal nodular hyperplasia, hepatocellular adenoma, and hepatoma (17).

For this reason, the use of copper IUD as a contraceptive method for ADPKD is safe, easily reversible, inexpensive, highly effective, and long-acting.

Levonorgestrel-IUDs

Levonorgestrel-IUDs can be an adequate treatment option for endometriosis, adenomyosis, chronic pain, an irregular period, or abnormal uterine bleeding in ADPKD patients.

There are three different types of progestin-impregnated intrauterine systems currently available. The 52-mg Levonorgestrel-IUD (LNG-IUD) contains 52 mg of levonorgestrel and releases 20 mcg of LNG per day. The two types available in the US are Mirena and Liletta, and they have been approved by the FDA for up to 8 years. Another type of LNG-IUD contains 19.5 mg of LNG (Kyleena) and releases 13 mcg per day. It can be used for up to 8 years. The third type is the 13.5 mg LNG-IUD (Skyla), also called “low-dose LNG-IUD," which releases 8 mcg of LNG per day and can be used for only 3 consecutive years. These devices act mostly by thickening the cervical mucus and changing the pattern of the endometrium (12,15). Sometimes they can also suppress ovulation, but most women continue to ovulate with LNG-IUD, especially the low-dose one (15).

Patients often become amenorrheic while the LNG-IUD is in place. LNG-IUDs are highly effective at preventing pregnancy, but they are also employed for the management of other medical conditions. For example, the 52 mg of LNG-IUD represents the current standard non-surgical treatment of endometrial intraepithelial neoplasia (EIN) and grade 1 endometrioid endometrial cancer (18). Because of its endometrial suppressing action, LNG-IUD is also used to treat menstrual-related disorders such as menorrhagia and dysmenorrhea. LNG-IUDs are proven to be more effective than oral contraceptives in reducing heavy menstrual bleeding (HMB) (19). LNG-IUDs also play an important role in decreasing uterine volume in patients affected by adenomyosis and uterine fibroids (20). LNG-IUD has shown benefits in treating endometriosis-related pain (17,21,22). The most common side effects of LNG-IUD are caused by the progestin and include headaches, nausea, breast tenderness, and decreased libido. Women who use LNG-IUD can also experience vulvovaginitis because of the modification of the vulvovaginal microbiota (23,24). IUD insertion is contraindicated whenever a woman has anatomical anomalies affecting the uterus (e.g., bicornuate uterus, fibroids altering the endometrial cavity, etc.). Additionally, there may be risks of infection, uterine perforation, partial or complete expulsion, mispositioning, and pain and/or bleeding post-insertion.

Combined Estrogen-Progestin Oral Contraceptives (COCs)

COCs suppress ovulation by inhibiting the gonadotropin-releasing hormone (GnRH) from the hypothalamus, inhibiting luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and disrupting the LH surge in the middle of the cycle. They also cause endometrial atrophy, thickening

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of the cervical mucus, and impairment of tubal mobility. All these mechanisms of action together contribute to the contraceptive effect.

There is an enormous variety of COCs on the market nowadays, differing in the type and dosage of progesterone and estrogen contained. COCs are recognized to have numerous non-contraceptive benefits, such as: treatment of pelvic pain in patients affected by endometriosis; treatment of PCO-related symptoms such as hirsutism and acne; reduction of dysmenorrhea, menorrhagia, and consequently iron deficiency anemia; reduction of the risk of ovarian, colorectal, and endometrial cancer; reduction of the risk benign breast disease; and reduction of ovary cysts (25–30).

However, hepatic diseases are a contraindication for the use of COCs, and, therefore, they cannot be administered in patients affected by ADPKD with hepatic involvement (17).

In an interesting recent study focused on the role of estrogen-containing oral contraceptives in the severity of liver disease in women with polycystic liver disease, premenopausal women demonstrated increased volume associated with COC use. More specifically, a 15.5% higher total liver volume for every 10 years of use. In conclusion, patients with PLD should avoid exogenous estrogens (31).

Vaginal Contraceptive Ring

If hormonal treatment inducing ovulation inhibition is strictly necessary, extremely well-pondered and informed options can be considered.

The vaginal contraceptive ring is a combined hormonal option. The mechanism of action is the same as that of the estroprogestinic pill: mainly, the suppression of ovulation. Vaginal rings are plastic polymer rings releasing ethinyl estradiol and the third-generation progestinic (etonogestrel). Hormones are absorbed directly through the vaginal epithelium into the systemic circulation. Vaginal rings are kept in place for three weeks and then removed for one week; during the discontinuation week, endometrial bleeding occurs. They present the same side effects of combined oral contraceptives (COCs): headache, breast tenderness, nausea, mood changes, and vaginal discharge, mainly (17,19,20,32).

They also present the same contraindications: high BMI, migraine, history of DVT, hypertension, smoking after 35 years of age, breast cancer, and history of liver health issues (17).

Interestingly, for this review, vaginal rings present a key characteristic: their local absorption. This implies a diminished probability of systemic estrogen-related adverse effects without compromising cycle control. Their local absorption allows them to bypass the gastrointestinal and liver passages, and, moreover, they have been observed to maintain a stable estrogen level during the day. In contrast, indeed, classic combined oral contraceptives (COCs) present hormonal concentration oscillations in the blood during the day based on their time of assumption (23–25). This extremely important characteristic of the vaginal ring makes this treatment the only hormonal treatment that may eventually be considered for ADPKD women. Their low hormonal dosage delivered at stable levels, bypassing the hepatic metabolism, may represent a chance for personalized, tailored treatment in extremely selected cases with strict follow-up.

Progestogen-Only Contraceptives (POPs)

Progestogen-only contraceptives are considered a safer alternative to traditional methods involving external estrogens, specifically ethinylestradiol. POPs are widely utilized due to their noninvasive and easily reversible nature as a contraceptive method. POPs function by inhibiting ovulation and modifying cervical mucus.

Desogestrel 75 mg, administered continuously over a 28-day regimen, achieved an ovulation inhibition rate of 99%. POPs are considered the primary choice for hormonal contraception in specific groups of women, including older women, those who are breastfeeding newborns, and individuals for whom estrogen-based COC pills are not suitable (33,34). Unlike COCs, POPs can be used safely by women with conditions such as thrombophilia, venous thromboembolism (VTE), myocardial infarction, or stroke. However, there are contraindications for the use of POPs, which include patients with venous thromboembolic disease, undiagnosed vaginal bleeding, current or past severe liver disease, and individuals with known or suspected sex steroid-sensitive malignancies. Studies have shown that the rates of ovulation inhibition are similar between women taking COC pills and those using desogestrel-containing POPs [WHO].

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Some authors consider progesterone-only pills a better first-line treatment for endometriosis than combined estrogen-progesterone contraceptive pills (35). In PCOs, while COCs represent the first-line treatment, particularly for women desiring contraception with hyperandrogenism-related symptoms, POPs are recommended for those with contraindications to COCs (36).

Considering the safety profile of POPs with regard to thrombotic risk and the limited action of progesterone on the renin-angiotensin-aldosterone system, ADPKD patients without hepatic involvement may be suitable for their use. It is evident that a risk-benefit balance, together with an informed consensus and strict follow-up, is mandatory.

- Menopausal Transition:

With the general population living longer, menopause is becoming a focus of research. More and more women seek treatment for all the discomforts brought by this condition. More and more women seek treatment for all of the discomforts brought on by this condition. Most women complain of extremely bothersome, sometimes invalidating, climacteric symptoms. HRT is the gold standard therapy for symptomatic women in menopause, particularly for symptomatic women <60 years of age or within 10 years of menopause. HRT has optimal results in managing all symptoms and also reducing the risk of osteoporosis. The North American Menopause Society considers HRT to be the first line of treatment for osteoporosis in climacteric symptomatic women within the window of opportunity (before the age of 60 and within 10 years of menopause) (37).

Furthermore, growing evidence is revealing how vasomotor symptoms may be biomarkers of cardiovascular disease risk, inducing physicians to pay more attention to this group of patients regarding whether to prescribe HRT (38,39).

The safety profiles of all different HRT therapies have improved. However, all treatments include the use of estrogen in different methods and dosages. The indications and contraindications of HRT are now well defined by the major menopause society (40–43).

One of the main contraindications to HRT is hypertension, which is common in women affected by ADPKD as well as hepatic chronic disease.

Currently, all symptoms of menopause can be addressed by treatments tailored to each symptom.

Vasomotory symptoms can be partially controlled by natural preparations, although because of their low efficacy, patient compliance is consequently limited (44,45).

Vulvo-vaginal atrophy can be treated by hyaluronic acid-based ointments and lubricants. Vitamin D supplementation is vitally important for osteoporosis prevention, and, in the case of the development of the disease, it can still also be addressed specifically (46).

Vasomotory symptoms remain the most bothersome conditions impacting menopausal women's quality of life; however, a new, specific treatment is imminent. In 2023, the FDA approved the use of a new drug called Fezolinet specifically for vasomotor symptoms. Fezolinet is a neurokinin-3 receptor (NK3R) antagonist. NK3R plays a key role in modulating the thermoregulatory center, triggering the so-called vasomotor response. This new drug stops the development of this response. This is a totally non-hormonal alternative. Given the presence of this new drug on the market, in the author's opinion, clinicians should consider avoiding HRT in ADPKD women due to the unfavourable risk-benefit ratio. With new treatments available, ADPKD post-menopausal patients should aim for personalized, efficacious therapies tailored to each symptom (47).

Given the complexity of ADPKD and the potential risks associated with hormone therapy, non-hormonal interventions play a key role in the management of postmenopausal symptoms.

Lifestyle changes, such as dietary changes and regular exercise, can contribute to overall well-being. In addition, cognitive-behavioral therapies may help women manage mood disorders.

Postmenopausal women are at increased risk for osteoporosis, and this risk is exacerbated in women with ADPKD due to renal insufficiency associated with changes in calcium and phosphorus metabolism. Adequate calcium and vitamin D supplementation, along with regular bone density monitoring, are essential components of a comprehensive management plan for these women.

4. Conclusions

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Although it is challenging to draw definitive conclusions in such a difficult situation, we will try to highlight the main strategies and focuses of hormone therapy and contraception in ADPKD patients. The treatment approach must always be tailored to each patient.

Therefore in fertile ages the first analysis to carry out is the patients' request. If contraception is the only desire of the patient, copper IUDs are the best choice. These devices have no hormonal risk and are to be considered safe in ADPKD patients.

On the other side, if symptoms such as dysmenorrhoea, endometriosis or PCOS are also present, hormone replacement therapy may be considered in these women, after assessing the effect of estrogens on the liver and renin-angiotensin system.

According to the ESHRE Endometriosis Guideline (February 2022) (48), prescribing progestin-only contraceptives and levonorgestrel intrauterine release systems is highly recommended for reducing endometriosis-related pain.

The LNG IUD device which has a local release of low progestin in absence of estrogens, making it a safe option for ADPKD patients.

POPs, which induce amenorrhea, may also be useful in managing abnormal uterine bleeding with few side effects. Evidence regarding their effect on ADPKD is expected to be limited, as it is not available in the literature. As previously mentioned, there are no data about the effect of progesteron on liver cyst's growth.

PCOS is recognized as a syndrome that combines reproductive and metabolic abnormalities, with lifelong health implications. Combined oral contraceptives (COCs) are typically favored as the first-line treatment, although progestin-only pills are recommended in cases where COCs are contraindicated.

In certain patients where an estrogen-progestin combination is deemed necessary, the vaginal ring may be a viable option. The released level of estrogens is low and remains constant throughout the day, on the contrary of estrogen-progestin pill. It is important to underline that the transvaginal absorption skips the hepatic first pass effect. Both these aspects appear to be the key of a possible safer strategy in ADPKD patients at least for a limited period of time. Current literature indicates strong support for this option.

Menopause is another pivotal event in a woman's life. Hormonal replacement therapy has revolutionized menopausal transition characterized by climacteric syndrome. The risk-benefit ratio of administering HRT to ADPKD patients is nonsensical, given recent scientific medical research. The hot flushes is for sure the most impacting symptom of menopausal transition. The approval of Fezolinetant by the AIFA represents the future, but the presence of a non-hormonal effective alternative is imminent. In the interim, natural alternatives are recommended also for these patients.

Conclusively, every individual patient ought to receive an accurate and personalized assessment, resulting in a customized treatment plan aimed at delivering maximum benefits with the least possible risks.

Further research is required to gain a more comprehensive understanding of the optimal systemic hormonal therapy for ADPKD patients.

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Fig.1 ESTROGEN AND RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

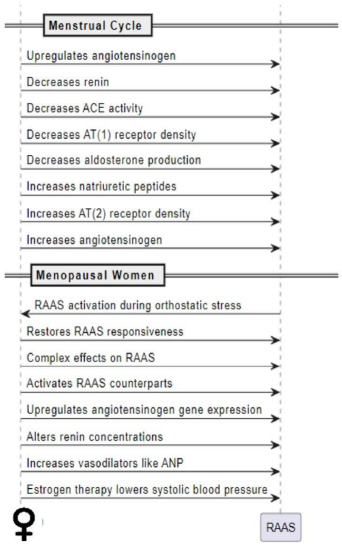
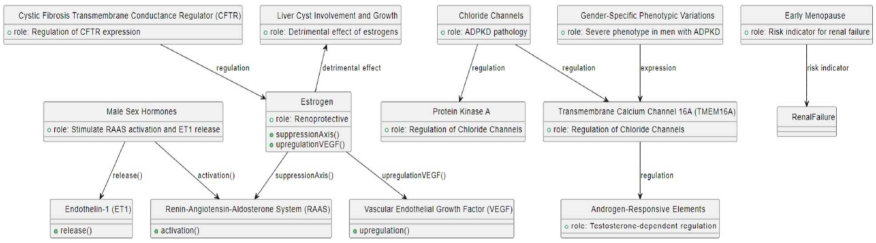


Fig. 2 THE ROLE OF ESTROGENS ON RENAL FUNCTION



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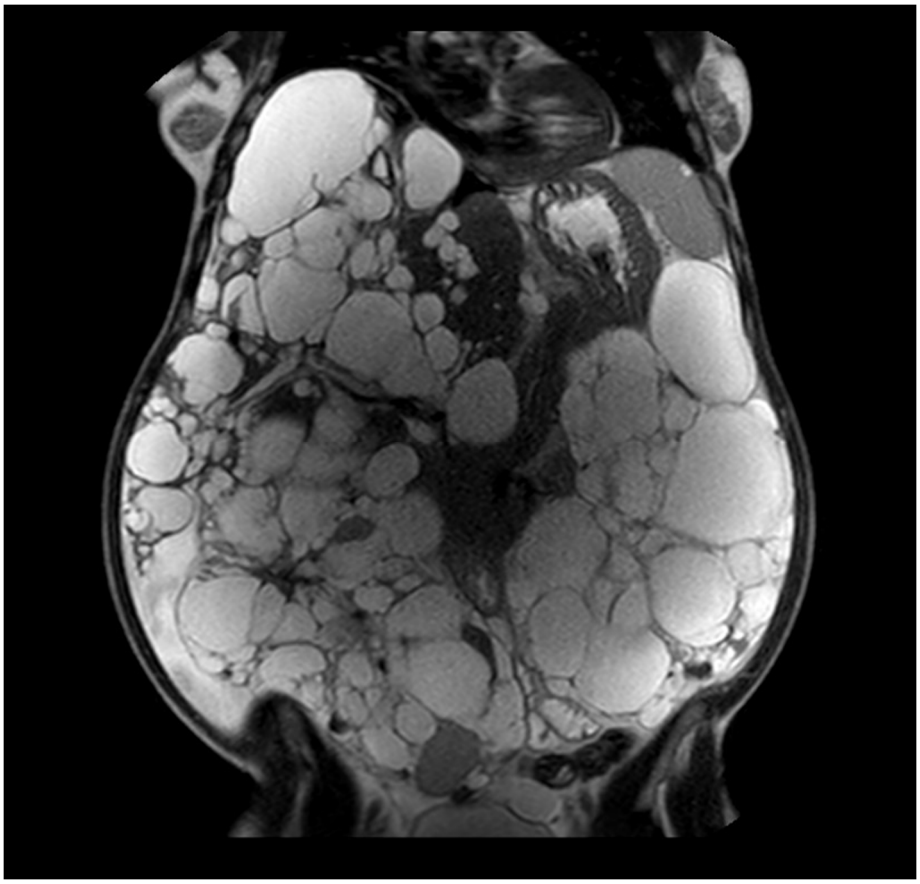

Figure 3. ADPKD woman with enlargement of liver and kidneys.

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