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THE IMPACT OF ENDOGENOUS AND EXOGENOUS SEX HORMONES ON THE COURSE OF PORPHYRIA IN WOMEN: A NARRATIVE REVIEW

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ABSTRACT

Porphyrias are a group of metabolic diseases caused by an impairment of the heme synthesis pathway, resulting in the accumulation of heme precursors. First symptoms usually occur during puberty and can be triggered by a range of factors such as drugs, alcohol, fasting, infection, and, most importantly for this study, hormonal changes. Women in the reproductive age are known to be the main group presenting with porphyria symptoms (1.5–2.5 times more frequent in women than in men) mainly due to higher concentrations of steroid hormones, particularly progesterone. Hormonal fluctuations associated with the menstrual cycle are the most commonly identified trigger causing an AIP attack in female patients. Pregnancy and exogenous hormone administration may also precipitate attacks in susceptible individuals, although there is considerable interindividual variability, and the underlying mechanisms remain incompletely understood.

This review summarizes existing knowledge on hormonal changes induced by the menstrual cycle, pregnancy, hormonal contraception, and GnRH agonists in women diagnosed with porphyria. It compares it with the conclusions reached by the IPNET panelists in the newly published guidelines, released in May 2026.

The available evidence, derived mainly from retrospective studies, small cohorts, and case reports, indicates that endogenous and exogenous hormones can have a major impact on susceptible women with porphyria. Most data confirmed that the use of oral contraceptives appears to carry the highest risk of precipitating attacks, whereas levonorgestrel-releasing IUDs seem to be better tolerated. GnRH agonist therapy proved highly effective and significantly safer than hormonal contraception in the treatment of recurrent cycle-related porphyria, although it requires add-back therapy, posing a threat itself.

Despite recent advances and the publication of IPNET recommendations, high-quality evidence remains limited. Further prospective studies are required to establish evidence-based recommendations for hormonal management and contraception in women with acute hepatic porphyrias.

KEYWORDS

Acute Hepatic Porphyrias, Sex Hormones, Hormonal Contraception, Pregnancy, Gonadotropin-Releasing Hormone Agonists, Catamenial Porphyria

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Introduction

Porphyrias are a group of genetic or acquired conditions in which enzymes that are a part of the heme synthesis pathway do not function adequately, leading to an accumulation of heme precursors, proceeding the defective phase of production. Heme is synthesized in all human cells, but the largest production occurs in erythropoietic cells for hemoglobin synthesis and in liver parenchymal cells for the synthesis of cytochromes and hemoproteins (Kauppinen, 2005). Excessive compounds are deposited in tissues or excreted with bile and urine. Porphyrias can be divided based on their clinical presentation into two main groups: acute porphyrias, such as acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), ALA dehydratase deficiency porphyria (ADP); and non-acute (cutaneous) porphyrias: porphyria cutanea tarda (PCT), erythropoietic protoporphyria (EPP), congenital erythropoietic porphyria (CEP), and X-linked erythropoietic protoporphyria (XLEPP) (Kauppinen, 2005).

This study focuses mainly on acute porphyria since clinicians more commonly encounter it and it is significantly more susceptible to hormonal changes. Attacks of acute porphyria can manifest with a range of heterogeneous symptoms such as severe abdominal pain, peripheral neuropathy, autonomic neuropathies, and psychiatric manifestations, which can easily be confused with other diseases and require a thorough diagnostic process. Inducers of acute attacks are alcohol, infections, low caloric intake, certain drugs, and hormonal changes (Pischik & Kauppinen, 2015).

Some female patients experience recurrent cycle-related attacks, which can occur in all phases of the menstrual cycle, with the luteal phase being the most common one. The attacks can be prevented by administering givosiran – a medication causing a degradation of the first rate-limiting enzyme in the heme pathway. Nowadays, givosiran is the drug of choice in the treatment of premenstrual attacks. In cases when givosiran is not tolerated or is inaccessible, GnRH agonists may be administered.

The biochemical mechanism that causes porphyria attacks is complex and not fully understood. One of the most important metabolic changes in porphyria concerns the first rate-limiting enzyme of the heme synthesis pathway — aminolevulinic acid synthase 1 (ALAS1) — which is normally suppressed in the presence of heme via negative feedback. In porphyria, when a downstream enzymatic deficiency prevents adequate heme production, this suppression is relieved, ALAS1 remains active, and toxic heme precursors accumulate. ALAS1 can also be activated by inducers such as female steroid hormones, which might be a reason for the exacerbation of porphyria symptoms in the luteal phase (Pischik & Kauppinen, 2015).

Another hypothesis explaining the influence of hormonal changes on heme precursor production is that women with symptomatic porphyria produce more 5β-reduced steroids than their 5α counterparts due to an altered 5α-reductase-mediated steroid metabolism. According to this theory, in patients with active porphyria, progesterone metabolizes into more active ALAS1 inducers than in healthy patients. (Innala et al., 2012). This occurrence may partially explain why some AIP gene carriers are prone to developing symptoms after hormonal changes, and others are not.

Methodology

This review is based on resources published in the PubMed database between 1967 and 2026. English-language studies were searched using the following key terms: "porphyria AND oral contraception", "porphyria AND hormonal contraception", "porphyria AND GnRH agonist", “porphyria AND pregnancy”, and "porphyria". The data obtained in this way were analyzed and synthesized.

Hormonal contraception

The described impact of hormonal contraception varies between articles. Most specialists agree that attacks of AIP are a major complication of oral contraceptive drugs, and their usage should be limited as much as possible (Edel et al., 2026; Leaf et al., 2024).

In a survey-based study from 2024 (Leaf et al., 2024), researchers presented the results of a questionnaire conducted within the International Porphyria Network among specialists from 22 centers across Europe, North and South America, South Africa, Taiwan, and Australia. Of the 24 surveyed specialists, 18 stated that they would recommend non-hormonal methods of contraception, such as copper-based IUDs, to their patients with active porphyria, and five specialists said they would recommend a hormonal IUD. This survey shows that clinicians specializing in porphyria treatment are aware of the dangers associated with hormonal contraceptives and opt for non-hormonal methods of contraception. It does not explore the subject of recurring premenstrual attacks and the potential usage of oral contraceptives in this instance.

It is worth considering that in the 2026 IPNET recommendations, specialists indicated hormonal IUD — rather than copper-based — as the contraceptive method of choice (Edel et al., 2026). The apparent preference for levonorgestrel-releasing IUDs over copper IUDs may stem from a broader preference among gynecologists for these devices rather than from porphyria-specific evidence.

Oral Contraceptives

Population-based surveys from both Sweden and the United States consistently suggest that oral hormonal contraceptives are associated with worsening of symptoms in a subset of women with acute hepatic porphyria and might precipitate the first attack in AIP gene carriers (Andersson et al., 2003; Leaf et al., 2024). However, the magnitude of this effect varies between studies, likely reflecting differences in patient selection, disease severity, and contraceptive formulations used. There are also individual reports of the potential beneficial impact of oral contraceptives on recurring severe episodes (Gross et al., 1995; Andersson et al., 2003).

In a 2003 retrospective population-based study conducted in northern Sweden, researchers surveyed 166 female participants who were identified as AIP gene carriers (Andersson et al., 2003). When asked about their experiences with hormonal birth control, 94 out of 166 women reported using oral contraceptives at some point in their lives, and among them, 50 participants had experienced AIP attacks in the past or during the study. We do not have information on whether participants were encouraged by their physicians to use hormonal contraception or if they decided to take it despite being advised against it. Of the 50 women with manifest AIP who had used oral contraceptives, 12 (24%) identified them as triggering AIP attacks; in nine cases, the oral contraceptive precipitated the first attack of their lives. One participant experienced relief of AIP symptoms during her 5-year treatment period with oral contraceptives (Andersson et al., 2003).

In a similar study conducted in the US, out of 100 patients with documented AHP and at least one lifetime porphyria attack, 69 participants reported using oral contraceptives (Leaf et al., 2024). Unfortunately, the authors did not include exact numbers of women who experienced worsening of their symptoms, but the use of hormonal contraceptives was significantly associated with symptom worsening. The p-values were respectively: $p < 0.001$ for combined oral contraceptives, $p = 0.048$ for progesterone-only contraceptives, and $p = 0.003$ for depot medroxyprogesterone (Leaf et al., 2024).

Those results further confirm the hazardous effects of oral contraceptives in female patients with porphyria.

Some researchers reported the beneficial effect of oral contraception in women experiencing worsening of symptoms temporally associated with menstruation. A 1995 study conducted in Germany followed three female patients who suffered from premenstrual symptoms of AIP (Gross et al., 1995). All of them were treated with glucose after developing attacks of AIP and were administered oral contraceptives after remission. All three women experienced improvement in the course of their disease and remained symptom-free for three months, six months, and seven years, respectively.

This study has been cited for years as an argument for administering small doses of oral contraceptives as a way of treating catamenial porphyria; however, it should be noted that the study group consisted of only three women, and we do not have information on whether patients continued taking oral contraception after the study ended, and, if not, what was the reason for treatment termination.

Other forms of contraception

Data on contraceptive methods other than oral hormonal contraception in patients with porphyria remain scarce. In the above-mentioned population-based study from Sweden, 16 of the 166 women who participated in the survey reported using non-oral hormonal contraceptive methods (Andersson et al., 2003). Of these, 10 had used a levonorgestrel-releasing intrauterine device (IUD). One woman in the manifest AIP group reported symptom relief during the first part of the treatment period, and no attacks were precipitated in association with IUD use. Four women had received subcutaneous progesterone depot injections; only one of them had symptomatic AIP and reported that the injection precipitated an acute attack (Andersson et al., 2003).

In the US survey-based study, 23 out of 100 participants with active AIP reported having used a hormonal IUD, and all of them reported no change in the course of their disease (Leaf et al., 2024).

It is also worth noting that two published case reports have documented acute porphyria attacks triggered by the etonogestrel subdermal implant — one in a patient with AIP (Misek & Riitano, 2023) and one in a patient with variegate porphyria (Strome et al., 2022) — suggesting that implantable progestogens carry a similar or higher risk to oral contraceptives.

In the guidelines created by specialists from the International Porphyria Network in May 2026, the panel recommended that female patients with active porphyria avoid oral contraceptives and opt for hormonal IUDs, which, in their experience, are usually well tolerated (Edel et al., 2026).

GnRH agonist therapy

There are several ways to treat premenstrual porphyria attacks. The recommended first-line treatment consists of monthly injections of givosiran, which is a siRNA drug that causes degradation of ALAS1 and is used in the prevention of all types of AIP attacks. However, if givosiran is poorly tolerated or inaccessible, gonadotropin-releasing hormone (GnRH) agonist therapy can be administered (Edel et al., 2026). GnRH agonists are synthetic analogues of hypothalamic GnRH that, when administered continuously, progressively desensitise pituitary GnRH receptors, resulting in decreased sex-hormone production in the ovaries (Innala et al., 2010). This approach tends to be a safer way to prevent severe porphyria attacks than the administration of oral contraceptives (Pischik & Kauppinen, 2015). On the other hand, GnRH treatment induces menopause with its symptoms, which can strongly affect young women who are the primary group in need of said treatment among porphyria patients. Exogenous estradiol helps relieve unwanted symptoms, but add-back therapy usually requires administration of progesterone for endometrial protection, which can itself trigger porphyria attacks (Innala et al., 2010).

In a 2010 retrospective study in Sweden, surveys and medical records of 14 female patients were collected and analyzed (Innala et al., 2010). All women included in the study were identified as porphyria gene carriers and suffered from menstrual-cycle-related attacks (in 11 out of 14 participants, attacks occurred in the luteal phase). All participants received GnRH agonist therapy between 1984 and 2000.

Of the 14 participants, 11 reported improvement, and in four of them, attacks almost completely ceased (Innala et al., 2010). One patient who experienced both premenstrual and spontaneous attacks reported improvement only in menstrual-related episodes. One participant experienced only temporary relief from symptoms, and two reported no changes. These results, while collected from a small group of patients, imply high efficacy of GnRH treatment in women with catamenial episodes and a reduced impact of this therapy in women with recurrent spontaneous attacks (Innala et al., 2010).

After initiation of GnRH treatment, eight women reported experiencing unwanted side effects; in six of them the cause was estrogen deficiency (Innala et al., 2010). Ten patients received estradiol add-back (alone or in combination); acute attacks were precipitated in two women receiving estradiol alone. After the introduction of progesterone therapy, acute attacks of porphyria were triggered in five out of nine patients. In situations when hormonal add-back therapy was not administered, participants ended the GnRH therapy within a year, underscoring the necessity of hormonal replacement therapy for long-term tolerability (Innala et al., 2010).

GnRH agonist therapy was continued for over four years in 50% of participants. In two patients, it was ended because of a lack of results. Eight women stopped their therapy despite its beneficial effects, four of whom reported worsening symptoms afterwards. One patient who had been almost free of symptoms for two years died during a severe AIP attack after forgetting to take her medications while travelling abroad (Innala et al., 2010).

Taking into account that GnRH therapy can continue for many years and the danger of acute attacks of porphyria, adherence to treatment in the presented study was low (Innala et al., 2010). Adverse effects of GnRH agonists and add-back therapy seem to be the main reason for cessation of treatment. The authors explored various regimens of hormonal add-back therapy to limit progesterone administration. To date, there are no clear guidelines for clinicians on the safest regimens for patients.

A 2017 audit conducted in the UK gives an insight into the effects of GnRH agonist therapy in patients with porphyria attacks (Schulenburg-Brand et al., 2017). Twenty women with an AIP diagnosis who underwent GnRH treatment between 2000 and 2015 were included. Participants received a total of 23 courses of treatment, with three patients receiving a second course. Although only three of the twenty women had the menstrual cycle identified as the precipitant of their first acute attack, half of all GnRH agonist treatment courses were deemed clinically beneficial in reducing attack frequency. This indicates that GnRH agonist therapy may help reduce symptoms in patients suffering from porphyria attacks in whom the precipitant is not the menstrual cycle. In the group of participants with cycle-related attacks, one out of three had unsuccessful treatment. In 16 out of 19 courses for which this information is known, women reported unwanted menopausal symptoms. For fear of inducing porphyria attacks, only seven patients received hormone replacement therapy.

GnRH clinical case

In a paper published in 2020, researchers from New Delhi present a case of a 15-year-old female patient with premenstrual symptoms of AIP (Aggarwal & Kulshreshtha, 2020). This patient was started on GnRH therapy after a year of recurring severe episodes of AIP, which usually began a week before menses. After administration of GnRH agonist therapy, the patient reported significant improvement. In the first year after the beginning of treatment, the patient experienced just one attack, which was precipitated by an infection. After a year of successful treatment, a DEXA scan showed decreased bone density; therefore, estradiol valerate treatment at a very low dose was initiated, and after a further year, cyclical medroxyprogesterone was added for endometrial protection. At the time of writing, the patient had been symptom-free for six months and had not experienced any serious side effects from the treatment. This case confirms the efficacy of GnRH agonist therapy but also emphasizes the importance of hormonal therapy, which, in most patients, is necessary to prevent osteoporosis.

GnRH agonist therapy recommendations

According to the 2026 recommendations of the IPNET specialists, GnRH agonist therapy can be considered as a second-line treatment in patients with recurrent cycle-related AIP attacks if givosiran is not available or not tolerated (Edel et al., 2026). Some panelists stated they do not use GnRH agonists in their practice since the risk of estrogen-deficiency side effects is too high. Others found it to be an effective treatment for women with catamenial attacks of porphyria (Edel et al., 2026).

Pregnancy

Pregnancy is a time of significant changes in hormone concentrations in women. During this period, progesterone and estrogen levels grow progressively, reaching up to 100 times prenatal levels. (Jee S B, et al in 2024) In the past, pregnancy in porphyria patients often led to death. Today, there are still multiple case reports of AIP attacks triggered by pregnancy. However, with a better understanding of the disease and new ways of treatment, nowadays porphyria is not perceived as a contraindication for pregnancy, though pregnant patients require being under strict care with frequent biochemical tests being performed. (Pischik E, et al in 2015). The analysis of the influence of pregnancy on the course of porphyria can help to understand the mechanisms by which sex hormones impact women with AIP.

There are some reports of pregnancy causing a relief in symptoms of AIP in women with recurrent-cycle-related attacks. Some authors argue that hormone levels themselves may not be directly responsible for precipitating attacks, but rather that the rapid hormonal fluctuations during early pregnancy may precipitate attacks. The argument is that the most attacks occur in the first trimester, after which porphyria symptoms decrease. A case report by Pischik E, et al in 2006 presents a history of a patient suffering from menstrual-cycle-related AIP attacks. After becoming pregnant, the woman experienced four severe episodes in four months of her pregnancy, all of which were treated with heme. After that, the attacks stopped completely for the rest of the pregnancy, and the patient was symptom-free for three years at the time of writing the article. The authors suggested that pregnancy may have acted as a form of hormonal therapy in this case.

On the other hand, there are multiple cases in the literature describing women with symptoms worsening later in pregnancy. In a follow-up study from the year 2021, 33 women identified as AIP gene carriers were monitored during 44 pregnancies. Seven of them have experienced a porphyria attack in the past. All pregnancies ended with the delivery of healthy children. Four patients developed symptoms of a porphyria attack during pregnancy, and one in puerperium; one woman had experienced two episodes. Two attacks happened in the first trimester, one in the second, and two in the third. These results do not support the above-mentioned theory that most attacks occur at the beginning of pregnancy.

Discussion

Porphyrias remain a not fully understood group of diseases due to their rare occurrence and diverse range of symptoms. The available scientific literature is insufficient, and further prospective studies are needed to establish evidence-based recommendations for the treatment and prevention of attacks.

Oral contraceptives appear unsafe for female patients with AIP and, in several studies, were shown to trigger attacks and worsen symptoms (Andersson et al., 2003; Leaf et al., 2024). Though some researchers reported that hormonal contraceptives in small doses may be used as a promising therapeutic method in patients suffering from catamenial episodes (Gross et al., 1995), the described groups were fairly small, and most research contradicts that view. Intrauterine devices seem to be a much safer type of contraceptive with fewer reported incidents of triggered attacks of porphyria (Andersson et al., 2003; Leaf et al., 2024). According to the 2026 IPNET recommendations, in patients who need contraception, IUD should be the first choice; in women with latent or asymptomatic AIP, oral contraceptives can be administered if IUD is poorly tolerated (Edel et al., 2026). Although data on IUD tolerance in porphyria patients is still lacking and more surveys and clinical cases would be useful for establishing its place in managing female patients with porphyria, the above-mentioned survey results indicate that IUD is a relatively safe form of contraception (Andersson et al., 2003; Leaf et al., 2024). There are also some instances in which hormonal IUDs helped relieve symptoms of premenstrual episodes of porphyria, but they should not be treated as a first-line treatment out of concern for potentially triggering attacks. The most dangerous and discouraged by specialists form of hormonal contraceptives in patients with porphyria is injectable or implantable progestogens, which cause the greatest hepatic exposure. (Edel et al., 2026).

Population-based studies conducted in the US and Sweden, as well as a presented clinical case, indicate that GnRH therapy is relatively safe and effective (Innala et al., 2010; Schulenburg-Brand et al., 2017; Aggarwal & Kulshreshtha, 2020). However, data emphasize that this therapy is poorly tolerated in most women, making concurrent hormone replacement therapy and progesterone add-back necessary, which itself can trigger attacks (Innala et al., 2010). Specialists agree that GnRH agonist treatment should only be considered when givosiran therapy is not tolerated or accessible (Edel et al., 2026). Individual reports of the decrease in the rate of recurrent attacks unrelated to the menstrual cycle, after the administration of GnRH agonists, suggest a potential benefit of said treatment in a broader group of patients.

Information on the impact of endogenous hormonal changes taking place in a woman's body is essential for the prediction of the course of porphyria and for the understanding of the mechanisms by which medications altering hormonal balance might endanger patients or help them. Although rapid hormonal fluctuations in early pregnancy have been proposed as a potential trigger, currently available evidence is insufficient to confirm this hypothesis. Contemporary data indicate that pregnancy should not be regarded as contraindicated in women with porphyrias; however, affected patients require close multidisciplinary follow-up and regular biochemical monitoring throughout pregnancy and the puerperium.

Conclusions

Current knowledge of the biomechanics of hormonal impact on AIP is incomplete and requires further understanding to enable adequate prevention and treatment of attacks. Hormonal contraception can be administered to patients stating a need for additional prevention beyond mechanical contraception. Levonorgestrel-releasing IUD proves to be the safest option with almost no reports of attacks triggered. Oral contraception is also acceptable in patients with porphyria under increased vigilance; however, it should not be used as a treatment for recurrent attacks because of its unpredictability and the availability of safer and more effective medications. Data on progesterone-releasing implants is very scarce, but it points to a high risk of their use. The implants should be discouraged in all AIP patients. GnRH agonists prove to be an effective treatment for cycle-related attacks. Add-back therapy should always be considered for fear of complications caused by estrogen deficiency. GnRH agonists should only be administered if givosiran therapy proves unsafe for the patients or if the drug is not accessible. Pregnancy is not contraindicated in women with porphyria, although its impact on disease activity is unpredictable and requires careful monitoring.

Given the scarcity of high-quality evidence, further prospective studies are needed to clarify the mechanisms by which endogenous and exogenous sex hormones influence porphyria and to establish evidence-based recommendations, including adequate doses and treatment regimens for hormonal management in affected women.

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