Treatment with assisted reproduction technologies in women with acute hepatic porphyria

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Abstract

Introduction: Acute porphyrias are rare disorders of the heme biosynthetic pathway and present with acute neurovisceral symptoms that can be induced by hormonal changes and medications. Women are far more likely to present with clinical symptoms than men, particularly during parts of their lifetime with changes in the level of female sex hormones such as ovulation, menstruation, and pregnancy. Treatment of ovulatory dysfunction and controlled ovarian hyperstimulation require the administration of hormones, which are considered porphyrinogenic. Women with acute hepatic porphyria have therefore been considered unsuitable for such treatments in the past.

Material and methods: We report on nine women with acute hepatic porphyria who underwent in vitro fertilization (IVF), preceded by ovarian stimulation. Their mean age at the start of IVF was 33.2 years (range 27–38 years). Two women had been diagnosed with polycystic ovarian syndrome, two were treated for hyperprolactinemia, two had hypothyroidism, of which one also had type 1 diabetes, one had a uterus malformation, one had anovulatory cycles, and one used a sperm donor.

Results: All patients were able to undergo fertility treatment without experiencing severe porphyria attacks.

Conclusions: Women with acute hepatic porphyria considering fertility treatments should be assessed individually for potential risks, treatment should be planned in close collaboration with a porphyria specialist, and biochemical activity should be monitored regularly during ovarian stimulation. As we gather more knowledge, we hope that the porphyrinogenicity of the stimulation agents is re-assessed and that more studies will shed light on the reproductive health of women living with acute hepatic porphyria.

KEYWORDS
acute hepatic porphyria, assisted reproduction technologies, in vitro fertilization, porphyria, porphyrinogenicity
1 | INTRODUCTION

Acute hepatic porphyrias (AHP) are genetic disorders of the heme biosynthetic pathway, primarily presenting with episodic acute attacks of neurovisceral pain, peripheral neuropathy, hyponatremia, and autonomic nervous system dysfunction which, if untreated, can be life-threatening.1,2

Acute intermittent porphyria (AIP), the most common form of AHP, is associated with mutations in the gene coding for the third enzyme in the heme biosynthetic pathway, hydroxymethylbilane synthase.3 The enzyme deficiency can lead to an accumulation of heme precursors δ-aminolevulinic acid (ALA) and porphobilinogen (PBG).4 Sweden has a higher incidence of symptomatic AIP than other countries (0.51 per 10^5/year compared with 0.31 per 10^5/year) due to a founder mutation effect.5 The less common types of AHP include hereditary coproporphyria (HCP) and variegate porphyria (VP),6 associated with mutations in the genes coding for coproporphyrinogen oxidase and for protoporphyrinogen oxidase, which are the sixth and seventh enzymes in the heme biosynthetic pathway (Figure 1). The enzyme deficiencies causing VP and HCP can lead to an accumulation of porphyrins; during acute attacks, ALA and PBG are also elevated, particularly in VP.7

Hepatic heme biosynthesis is regulated by the rate-limiting enzyme δ-aminolevulinate synthase 1 (ALAS1), and the administration of certain drugs increases ALAS1 activity and causes metabolic stress with the risk of accumulation of neurotoxic metabolites, mainly ALA and PBG in individuals with AHP. As a result, these agents/drugs are regarded as porphyrinogenic, and their use increases the risk of inducing an acute attack.8 Estrogen and progesterone can induce ALAS19; of the two, progesterone and its metabolites are considered more important in precipitating attacks of AIP.10 There are several reports of cases where assisted reproduction technologies (ART) resulted in porphyria attacks.11,12 The hormonal therapies used in methods of assisted reproduction are often listed as porphyrinogenic drugs9 and there has been a consensus that in vitro fertilization (IVF) should be used with great caution in women with AHP.

We report the IVF treatment and outcomes of nine women with AHP.

FIGURE 1 Illustration of heme synthesis in the hepatocyte, highlighting the process both inside and outside the mitochondria, heme precursors, and affected enzymatic steps. Hepatic heme synthesis is regulated by its first, rate-limiting step catalyzed by ALAS1. In AIP, enzymatic deficiency in the third step of heme synthesis can cause the accumulation of heme precursors ALA and PBG in situations when heme synthesis is upregulated. Similarly, different porphyrin moieties accumulate in HCP and VP where the sixth or seventh steps are compromised, respectively. Porphyrins can inhibit the third step allosterically and so heme precursor accumulation is observed in HCP and VP. Black arrows = normal enzyme activity; gray arrows = decreased enzyme activity. AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; ALAS1, δ-aminolevulinate synthase 1; HCP, hereditary coproporphyria; PBG, porphobilinogen; VP, variegate porphyria [Color figure can be viewed at wileyonlinelibrary.com]

Key message

Women with acute hepatic porphyria considering fertility treatments should be assessed individually for potential risks. Treatment should be planned in close collaboration with a porphyria specialist and biochemical activity should be monitored regularly during ovarian stimulation.

2 | MATERIAL AND METHODS

All biochemical and genetic testing was performed at the Porphyria Center Sweden. The Porphyria Center Sweden, a part of the Center for Inherited Metabolic Diseases, is a national center of expertise with over 30 years of experience in the field of porphyrias and has a complete assortment of analyses for the investigation of porphyria diseases and porphyrin metabolic disorders.

The Porphyria Register is an authorized national register (No. 647-88) that includes all patients with a confirmed porphyria diagnosis, currently a total of approximately 1200 individuals, half of whom are women. The Porphyria Center, in close collaboration with hospitals throughout Sweden, has been offering clinical consultations to patients with porphyria and their caregivers for many decades.
Both PBG and ALA in the urine were analyzed with ion-exchange chromatography\textsuperscript{13} using the Bio-Rad PBG/ALA-Test. Normal values are below 3.9 mmol/mol creatinine for ALA and below 1.6 mmol/mol creatinine for PBG.

Total urinary porphyrin concentration was quantified by anion-exchange chromatography with the Bio-Rad Porphyrin-Test. Normal values are below 38 µmol/mol creatinine.

The women in this report consulted the Porphyria Center directly or through their fertility specialist in the process of ART. The ART treatments took place between 2005 and 2019. All women had a confirmed AHP diagnosis before ART start (Table 1).

Drug porphyrinogenicity is classified according to the current guidelines (http://www.drugs-porphyria.org/) or regional guidelines published in the Swedish Porphyria Handbook (Thunell, 2014, ISBN. 978-91-637-7375-4) (Table 2). The classification includes five categories: NP = Not Porphyrinogenic; PNP = Probably not Porphyrinogenic; PSP = Possibly Porphyrinogenic; PRP = Probably Porphyrinogenic; P = Porphyrinogenic (NC = Not yet classified).

2.1 Ethical approval

The study was approved by the Swedish Ethics Committee (Dnr 2018/372-31) on June 6, 2018 and (Dnr 2019-06004) on February 3, 2020. All women gave written consent to the retrieval of their treatment protocols and all relevant clinical and laboratory data.

3 RESULTS

The background of the women who underwent ART and were referred to the Porphyria Center Sweden is summarized in Tables 1 and 2. The detailed treatment is summarized in Table 3.

| Case | Elevated biochemical markers before treatment | Severe attacks before treatment | Menstruation-related symptoms | Mutation | Type of mutation | References |
|------|-----------------------------------------------|-------------------------------|------------------------------|----------|------------------|------------|
| 1    | Yes                                           | No                            | No                           | HMBS: c.499-1G>A; p.(?)   | Splice site | 14          |
| 2    | No                                            | No                            | No                           | HMBS: c.517C>T; p.(Arg173Trp) | Missense  | 15          |
| 3    | Yes                                           | No                            | No                           | HMBS: c.517C>T; p.(Arg173Trp) | Missense  | 15          |
| 4    | No                                            | No                            | No                           | PPOX: c.652C>T; p.(Gln218*) | Nonsense  | This study |
| 5    | Yes                                           | No                            | No                           | PPOX: c.3G>A; p.(Met17)    | Translation initiation codon | 16          |
| 6    | No                                            | No                            | No                           | HMBS: c.275T>C; p.(Leu92Pro) | Missense  | 17          |
| 7    | Yes                                           | Yes                           | No                           | HMBS 87+1G>A; p.(?)        | Splice site | 18          |
| 8    | No                                            | No                            | No (dysmenorrhea)            | CPOX: c.827G>A; p.(Trp276*) | Nonsense  | This study |
| 9    | No                                            | No                            | No (dysmenorrhea)            | HMBS: c.593G>A; p.(Trp198*) | Nonsense  | 19          |

Note: One woman had experienced acute attacks before IVF. Two described considerable pain in relation to menstruation, but neither had any signs of active disease before IVF.

Abbreviations: CPOX, coproporphyrinogen-III oxidase; HMBS, hydroxymethylbilane synthase; IVF, in vitro fertilization; PPOX, protoporphyrinogen oxidase.
A second IVF attempt at age 39 resulted in an early miscarriage (week 8). Notably, the woman was then treated with the combination mifepristone (P) and misoprostol (PNP) to induce bleeding. Despite the porphyrinogenicity of mifepristone, no porphyria attack was induced (Figure 2, Case 3). A third IVF attempt resulted in an early miscarriage (week 10).

**Case 4** (VP, Table 1) underwent an IVF treatment at the age of 27. She experienced no porphyria-related symptoms during the IVF treatment and subsequent full-term pregnancy. A slight increase in urinary PBG excretion was observed (Figure 2, Case 4).

**Case 5** (VP, Table 1) had been treated with low-dose progesterone contraceptives in the past with no porphyria-related adverse effects. Her sole VP manifestation was periodic photosensitivity. She underwent IVF starting at the age of 28. The IVF resulted in a full-term pregnancy. She experienced no porphyria-related symptoms during IVF. Biochemical testing was performed 4 months before IVF and at week 27 of pregnancy (Figure 2, Case 5).

**Case 6** (AIP, Table 1) underwent IVF treatment at the age of 37. The IVF treatment did not result in pregnancy. She experienced no porphyria-related symptoms during IVF, but her biochemical activity was, notably, never monitored during the procedure. Three months after the IVF treatment, the woman became spontaneously pregnant. On week 8 of gestation, she was admitted for severe abdominal and muscle pain, malaise, and nausea. Her clinical presentation, together with biochemical findings of significantly elevated ALA and PBG, were consistent with an acute porphyria attack (Figure 2, Case 6). She was treated with intravenous glucose and analgesics, recovered and the remainder of her pregnancy was uneventful. The high excretion of ALA and PBG persisted (Figure 2, Case 6).

**Case 7** (AIP, Table 1) had experienced sporadic acute porphyria attacks in the past, the latest one 16 years before IVF treatment. One previous spontaneous pregnancy had ended in early miscarriage. She underwent IVF treatment at the age of 37. She experienced no porphyria-related symptoms during the IVF treatment and subsequent full-term pregnancy. The woman’s baseline biochemical activity was tested before starting hormone treatment and at regular intervals during IVF (Figure 2, Case 7).

**Case 8** (HCP, Table 1) had previously been treated with clomiphene citrate (PSP, Table 2) for ovulation stimulation not resulting in pregnancy. Notably, she had been administered medroxyprogesterone (PRP, Table 2) for menorrhagia without triggering any porphyria attacks. Between the ages of 29 and 33 years, the woman underwent a total of 10 IVF treatments. The ninth IVF attempt resulted in a full-term pregnancy.

Biochemical markers (ALA, PBG, and porphyrins) were normal before start of treatment (Figure 2, Case 8, Pre-IVF). During her first stimulated cycle, 3 days after the first embryo transfer, the woman was admitted with abdominal pain, constipation, bloating, fever, urinary retention, and a culture-verified *Escherichia coli* urinary tract infection. Antibiotics, carbohydrates, and laxatives sufficed as treatment. The incident was thought to be a porphyria attack, possibly induced by the administration of vaginal progesterone, although, in retrospect, it is not possible to exclude ovarian hyperstimulation syndrome combined with urinary tract infection as a sole possible cause. Porphyria biochemical activity testing was not performed.

Additional complications for this woman included a laparotomy after the fourth IVF attempt, due to the presence of ovarian growths and dysmenorrhea. The surgery revealed bacterial salpingitis as well as endometriosis and resulted in the removal of the right salpinx. The levels of ALA, PBG, and urinary porphyrins were elevated, indicating increased porphyria activity. The values were normalized 3 months postoperatively (Figure 2, Case 8).

At the time of the eighth attempt, she was treated with medroxyprogesterone (PRP, Table 2) to stop intermittent hemorrhaging, and dehydroepiandrosterone (prasterone) (PSP, Table 4).
| Case (attempt) | Downregulation | Ovarian hyperstimulation | Ovulation induction | Egg retrieval | ET | Vaginal progesterone as luteal support | Other luteal phase support | Pregnancy |
|---------------|----------------|--------------------------|--------------------|--------------|----|--------------------------------------|--------------------------|-----------|
| 1 (1)         | Leuprolrelin (a) (P) | Follitropin α (PRP) | |                  | 2 | No | Yes (week 8 miscarriage) |
| 1 (2)         | Leuprolrelin (a) (P) | Follitropin α (PRP) | Choriogonadotropin α (PSP) | Sedation: alfentanil (NP); Anesthesia: articaine (NP) | 2 | Yes (PRP) | Full-term pregnancy |
| 2 (1)         | Buserelin (a) (P) | Follitropin β (PSP) | |                  | 1 | Yes (PRP) | No |
| 2 (2)         | Buserelin (a) (P) | Follitropin β (PSP) | Choriogonadotropin α (PSP) | Sedation: alfentanil (NP) | 1 (ICSI) | Yes (PRP) | No |
| 2 (3)         | Buserelin (a) (P) | Follitropin β (PSP) | Choriogonadotropin α (PSP) | | 1 | No | hCG (Pregnyl®) (PRP) | Yes |
| 2 (4)         | Nafarelin (a) (PSP) | Follitropin β (PSP) | Choriogonadotropin α (PSP) | Sedation: alfentanil (NP) | 1 (ICSI) | Yes (PRP) | No |
| 3 (1)         | Ganirelix (an) (PSP) | Menotropin (PSP) | Choriogonadotropin α (PSP) | | 1; ET during letrozole-stimulated cycle (PNP) | No | Yes |
| 3 (2)         | Six months after giving birth; Embryo transfer: Letrozole (PNP) day 3–7 | | | | 1 | Yes (PRP) | Yes (week 8 miscarriage) |
| 3 (3)         | New attempt, embryo transfer: Letrozole (PNP) day 3–7 | | | | 1 | Yes (PRP) | Yes (week 10 miscarriage) |
| 4 | Follitropin α (PRP) + Ganirelix (an) (PSP) | Choriogonadotropin α (PSP) | | | 1 | Yes (PRP) | Yes |
| 5 (1)         | Letrozole (PNP) day 3–7 | | | | | | |
| 5 (2)         | Follitropin α (PRP) + Ganirelix (an) (PSP) | Triptorelin (P) (attempt to downregulate) | | | | | |
| 5 (3)         | Letrozole (PNP) day 3–7 | | | | 1 | No | Yes |
| 6 (1)         | Follitropin α (PRP) + Ganirelix (an) (PSP) | Choriogonadotropin α (PSP) | | | No good-quality embryos | | |
| 6 (2)         | Nafarelin (a) (PSP) | Menotropin (PSP) | Choriogonadotropin α (PSP) | | 1 | Yes (PRP) | No |
| 7 (1)         | Follitropin α (PRP) + Ganirelix (an) (PSP) | Choriogonadotropin α (PSP) | | | 1 | Yes (PRP) | No |

(Continues)
| Case (attempt) | Downregulation | Ovarian hyperstimulation | Ovulation induction | Egg retrieval | ET | Vaginal progesterone as luteal support | Other luteal phase support | Pregnancy |
|---------------|----------------|--------------------------|--------------------|--------------|----|--------------------------------------|---------------------------|-----------|
| 7 (2)         |                | Follitropin α (PRP) + Ganirelix (an)(PSP) | Choriogonadotropin α (PSP) |              | 1  | Yes (PRP)                           |                          | No        |
| 7 (3)         |                |                          |                    |              |    |                                     |                          | Yes       |
| 8 (1)         |                | Follitropin α (PRP)      | Human chorionic gonadotropin (PRP) |              | 1  | Yes (PRP)                           |                          | No        |
| 8 (2)         |                |                          |                    |              | 1  |                                      |                          | No        |
| 8 (3)         |                | Follitropin α (PRP) + Cetorelix (an)(PNP) | Human chorionic gonadotropin (PRP) |              | 1 (AHA) | No                                | hCG (Pregnyl) (PRP) | No        |
| 8 (4)         |                | Buserelin (a) (P)        | Plan for ovulation stimulation with choriogonadotropin α (PSP); ultrasound showed bilateral ovarian cysts. The cycle was interrupted. |              |    |                                     |                          |           |
| 8 (5)         |                | Menotropin α (PSP)      | hCG (PRP)          |              | 2 (1 AHA) | No                                | hCG (Pregnyl) (PRP) | No        |
| 8 (6)         |                | Follitropin α (PRP)      | hCG (PRP)          |              | 2  | No                                  | hCG (Pregnyl) (PRP) | No        |
| 8 (7)         |                | Follitropin α (PRP)      | hCG (PRP)          |              | 1  | No                                  | hCG (Pregnyl) (PRP) | No        |
| 8 (8)         |                | Nafarelin (a) (PSP)     | Follitropin α (PRP) | Choriogonadotropin α (PSP) | No transfer; continued intermittent bleeding. Attempt to treat with medroxyprogesterone (P) |                          |           |
| 8 (9)         |                |                          |                    |              | 1  | No                                  | hCG (Pregnyl) (PRP) | Yes       |
| 8 (10)        |                | Nafarelin (a) (PSP)     | Follitropin α (PRP) | Choriogonadotropin α (PSP) |              | hCG (Pregnyl) (PRP) | No        |
| 9             |                | Follitropin α (PRP) + Ganirelix (an)(PSP) | Choriogonadotropin α (PSP) |              | 1  | Yes (PRP)                           |                          | No        |

Note: Substance porphyrinogenicity is in parentheses.
(a): GnRH agonist; (an): GnRH antagonist.
Abbreviations: AHA, assisted hatching; ET, embryo transfer; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; NC, not yet classified; NP, not porphyrinogenic; P, porphyrinogenic; PNP, probably not porphyrinogenic; PRP, probably porphyrinogenic; PSP, possibly porphyrinogenic.
was added to the treatment regime, to increase the chances of pregnancy. No clinical signs of porphyria activation were observed. She eventually developed a tubo-ovarian abscess that was treated surgically, and she went on to undergo a ninth, successful, IVF treatment.

**Case 9** (AIP, Table 1) underwent IVF treatment at the age of 30. The IVF treatment resulted in the harvest of fertilized eggs but no viable pregnancy to this date. She experienced no porphyria-related symptoms during IVF. The woman's baseline biochemical activity was tested before starting hormone treatment, and during IVF (Figure 2, Case 9).

### 4 | DISCUSSION

In clinical practice, the administration of sex steroid preparations has been reported to trigger attacks in women with AHP.\(^2^5\) Women with recurrent attacks are more susceptible during the luteal phase of the menstrual cycle; this has been attributed to changes in circulating progesterone levels.\(^2^2\),\(^2^6\)

Hormone treatment is not without controversy for women carriers of AHP pathogenic variants. This has been illustrated in conflicting reports about AIP and pregnancy.\(^2^2\),\(^2^7\)–\(^2^9\) The assumed increase in susceptibility to porphyria attacks during pregnancy has been attributed to the major hormonal changes associated with it. Although there is no evidence suggesting that AHP has any effect on fertility, women suffering from porphyria who need ART have in the past been discouraged from undergoing hormonal treatment to achieve a viable pregnancy.

A review of the current literature about AHP and IVF/ART reveals just a few single case reports. Seiden et al.\(^1^2\) report on a 36-year-old woman who presented with neurovisceral symptoms after undergoing IVF. A family history of AIP was revealed, and specific testing confirmed an AHP diagnosis. Wang et al.\(^1^1\) report on a 30-year-old woman who underwent IVF, then developed nausea, extremity weakness, and hyponatremia. She was admitted to the hospital, initially under the suspicion of ovarian hyperstimulation syndrome. However, the severity of hyponatremia (103 mmol/L) coupled with the absence of typical findings (ovarian enlargement) suggested other causes and further testing revealed markedly increased levels of urinary PBG and ALA. New et al.\(^3^0\) described a 35-year-old woman who started fertility treatment, then developed neurovisceral symptoms of increasing severity until finally she was diagnosed with AHP.

We present here the largest reported cohort of AHP and IVF: nine individuals, all genetically confirmed carriers of AHP that underwent one or several cycles of IVF. It should be noted that none of the women had severe, debilitating AHP with recurrent attacks; individuals with such a severe form of AHP would still not be considered eligible for IVF treatment. Nevertheless, four of the nine women had elevated the excretion of heme precursors before IVF. Despite the relatively large number of IVF cycles in the group in total—in only two cases was there hospitalization with signs and symptoms of an acute porphyria attack. In Case 8, the woman was admitted with abdominal/pelvic pain, nausea, and coprostasis, after stimulation and embryo transfer. She also presented with bladder retention and a urinary tract infection. There was a suspicion that the vaginal progesterone used as luteal phase support

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**FIGURE 2** Urine ALA (light gray) and PBG (dark gray), in mmol/mol creatinine, urine porphyrins (black) in μmol/mol creatinine in Cases 1–9, tested on separate occasions during disease history. Values on the x-axis are not defined by specific time units and ALA/PBG/porphyrin levels are listed consecutively over time. Straight lines indicate the upper limit of normal values; PBG <1.6 mmol/mol creatinine, ALA <3.9 mmol/mol creatinine, porphyrins <38 μmol/mol creatinine. ALA, δ-aminolaevulinic acid; IVF, in vitro fertilization; hCG, human chorionic gonadotropin; PBG, porphobilinogen
had triggered an attack; in retrospect that seems unlikely because the same individual had—both before this event and after it—taken oral medroxyprogesterone, which is theoretically far more porphyrogenic. No other individual in this group reacted to vaginal progesterone and this has also been our experience from other cases. The woman’s biochemical activity was not tested during the hospitalization and, in retrospect, it is equally likely that her symptoms were part of ovarian hyperstimulation syndrome, which is clinically hard to distinguish from a porphyria attack.

In Case 6, the woman was admitted to hospital with a biochemically verified acute porphyria attack. The attack came at the beginning of her pregnancy and soon after an IVF cycle. Unfortunately, in this case, no biochemical testing was done before the start of IVF.

In Case 3, the woman underwent stimulation that resulted in 33 follicles visible on ultrasound. On the day of extraction, she experienced abdominal pain and anxiety. Blood tests showed normal liver transaminases, inflammatory parameters, and electrolytes. No testing for porphyria biochemical activity was performed. The symptoms resolved spontaneously after 2 days; the episode was most likely due to ovarian hyperstimulation.

Our experience from monitoring women with AHP who undergo fertility treatment is that precautions (adequate nutrition), careful monitoring including the assessment of biochemical activity, and increased vigilance for emerging porphyria symptoms are beneficial to obtaining a good outcome. A well-informed patient (and partner) and close collaboration between the fertility clinic and an expert porphyria center are essential for preventing porphyria attacks. Being an AHP carrier should not in itself be an exclusion criterion for fertility treatment; still, the process has inherent risks. In general principle, the IVF treatment should be tailored to include as few substances as possible, in as low doses as possible, while still aiming for an acceptable success rate. Then new substances and higher doses can be introduced as the

### Table 4

| Substance               | Chemical description                        | Classification     | References |
|-------------------------|---------------------------------------------|--------------------|------------|
| Buserelin               | Synthetic gonadotropin-releasing hormone     | P; used in some cases without triggering attacks | 20         |
| Cetrorelix              | Gonadotropin-releasing hormone antagonist    | PNP                | 21         |
| Choriogonadotropin α    | Chorionic gonadotropin                      | PRP; increases progesterone production | 11         |
| Clomiphene citrate      | Estrogen receptor modulator                 | PSP                | 11         |
| Estradiol               | Estradiol                                   | PSP; uneventful use in postmenopausal women | 22         |
| Follitropin α           | Recombinant gonadotropic hormone            | PSP                | Swedish Porphyria Handbook, Thunell 2014 |
| Follitropin β           | Recombinant gonadotropic hormone            | PSP                | Swedish Porphyria Handbook, Thunell 2014 |
| Ganirelix               | Gonadotropin-releasing hormone antagonist    | PNP                | 21         |
| Human chorionic          | Chorionic gonadotropin                      | PRP; increases progesterone production | 11         |
| Leuprorelin             | Synthetic gonadotropin-releasing hormone     | P; used in some cases without triggering attacks | 20         |
| Medroxyprogesterone     | Progesterone                                | PRP                | 22         |
| Menotropin              | Human menopausal gonadotropin               | PSP                | Swedish Porphyria Handbook, Thunell 2014 |
| Nafarelin               | Synthetic gonadotropin-releasing hormone     | PSP                | 24         |
| Prasterone              | Dehydroepiandrosterone                      | PSP                | Swedish Porphyria Handbook, Thunell 2014 |
| Progesterone            | Progesterone                                | PRP                | 21         |
| Triptorelin             | Synthetic analogue of gonadotropin-releasing hormone | P | 12,20 |

Note: The classification is often based on in vitro predictions and/or patient case reports.

Abbreviations: NC, not yet classified; NP, not porphyrinogenic; P, porphyrinogenic; PNP, probably not porphyrinogenic; PRP, probably porphyrinogenic; PSP, possibly porphyrinogenic.
patient’s tolerability is assessed. The inherent porphyrinogenic potential of the different fertility drugs is sometimes hard to predict; our experience is that the drugs for downregulation, oocyte stimulation, and maturation that are summarized in Table 4 have an acceptable safety profile.

It is recommended to measure biochemical markers (ALA, PBG, and urinary porphyrins in HCP and VP) before treatment start, to have a baseline value for each individual case. The woman should be instructed to stop treatment and seek medical advice as soon as she experiences symptoms that could be a porphyria attack, and a plan should always be made for clinical and biochemical assessment. Nausea, abdominal pain, headache, hypertension, to name a few, are symptoms associated with both acute porphyria attacks and various conditions associated with hormone treatment and/or pregnancy.

In the search for factors that determine the porphyria phenotype other than the presence of excess heme metabolites, further studies and reporting of cases are needed to provide the best and safest care for individuals with AHP.

5 | CONCLUSION

As the methods of assisted reproduction have progressed, and the numbers of women with acute porphyria who undergo treatment increase, this knowledge must be reassessed, considering the impact of the porphyrinogenicity of the drugs used to modulate fertility on hepatic heme biosynthesis and the clinical outcome. The authors hope that this study will encourage physicians to report any observations in the very complicated matter of AHP and IVF.

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CONFLICTS OF INTEREST

DV and ES have been involved in clinical trials with Alnylam Pharmaceuticals, have received research grants from Alnylam Pharmaceuticals, and have received speaker fees from Recordati Rare Diseases. ALH reports no potential conflict of interest.

AUTHOR CONTRIBUTIONS

DV wrote the first draft of the manuscript. ES made indispensable contributions to study design and data acquisition, analysis and interpretation. ALH has provided expert knowledge in the field of reproductive health. All authors have participated in drafting and revising the manuscript gave their final agreement to the submission after inspection.

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