

Preimplantation diagnosis and embryo selection in a patient with severe hereditary coproporphyrria

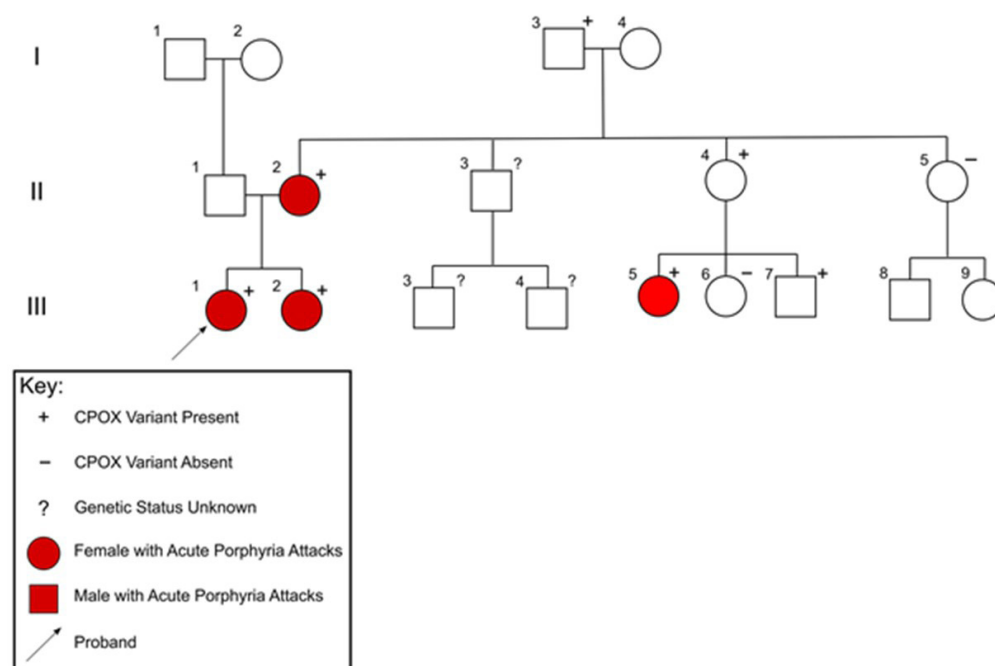
Gisela A Kristono, Leigh Searle, Cindy Towns

Hereditary coproporphyrria (HCP) is the rarest of the three autosomal dominant, acute porphyrias.¹ These metabolic disorders of haem synthesis typically have low penetrance and, even when penetrant, a limited impact on patients' health and quality of life.¹⁻³ Given the low impact of the condition, pre-implantation genetic testing for monogenetic disorder (PGT-M), a process that enables embryo selection to avoid passing on significantly debilitating genes,⁴ is not common practice in this condition. However, we have identified a family with HCP with high penetrance, recurrent attacks and significant complications (Figure 1).⁵ We present the first member of this family to undergo PGT-M to avoid passing the gene variant to subsequent generations.

Case report

A 27-year-old female first presented in 2012 with abdominal pain of unclear cause. In 2017, following the identification of HCP in her maternal cousin,⁶ she underwent genetic testing and was also revealed to carry the novel missense variant in the coproporphyrinogen oxidase (CPOX) gene, c.863T>G(p.Leu288Trp).⁵ She has had a total of 31 hospital presentations with abdominal symptoms that have since been attributed to HCP. Presentations with positive urinary porphobilinogen (PBG) tests were treated with intravenous haem arginate via central or peripherally inserted central catheter (PICC) lines. Other presentations with pain flares and negative PBG tests were treated with supportive care.

Figure 1: Pedigree with coproporphyrinogen oxidase (CPOX) variant c.863T>G(p.Leu288Trp).



The pedigree for this patient's family, adapted from Towns et al. (2022).⁵ The patient discussed in this case is III 5.

She has had a number of hospital-associated complications including three episodes of venous thromboembolism (VTE)—which occurred despite the haem arginate being administered via a central or PICC line—and a PICC-associated *Staphylococcus aureus* bacteraemia. She also developed opioid dependence secondary to pain from her HCP flares and underwent an opioid-weaning regime with buprenorphine/naloxone and input from pain specialists.⁷ Her long-term pain, recurrent hospitalisations and complications have had significant impacts on her mental health and ability to engage in education and regular employment.

She started having discussions regarding family planning with her health professionals in 2021. She wanted a child but did not want to pass on her CPOX mutation. She had a previous unplanned pregnancy (during which she had no HCP-related symptoms) that resulted in an elective termination. For this planned pregnancy, she was referred for pre-conception counselling regarding management of porphyria in pregnancy with an obstetrician and fertility specialist. She also had input from a porphyria specialist, genetic counsellor and haematologist. Collectively, the patient and her specialists agreed to *in vitro* fertilisation (IVF) with PGT-M.

In terms of specific treatment, this patient underwent a standard antagonist protocol using follitropin alpha for ovarian stimulation. She received luteal phase oestrogen pre-treatment with oestradiol valerate 2mg twice daily beginning in the mid-luteal phase. This was prior to the onset of menses when ovarian stimulation was commenced. A gonadotrophin-releasing hormone antagonist was started on day 5 of ovarian stimulation and ovulation was triggered with human chorionic gonadotrophin. Blastocysts were biopsied on day 5 and 6 post-fertilisation. She then underwent a thawed embryo transfer of an unaffected embryo using oestradiol valerate 2mg three times daily for 17 days, then following a scan to check endometrial development micronised progesterone pessaries were commenced 200mg three times daily. Both of these medications were continued until 10 weeks gestation. As this patient had a history of VTE in the past, prophylactic enoxaparin 40mg daily was given during oestrogen treatment and throughout pregnancy.

The patient completed her pregnancy without any HCP-related flares and successfully delivered her baby vaginally. The only complication she had during labour was a postpartum haemorrhage

of 3 litres due to uterine atony from retained placental fragments. This was managed with removal of the retained remnants, Bakri balloon and four units of transfused red blood cells. Her trough haemoglobin level was 80g/L and the level increased to 97g/L on discharge from hospital (3 days post-delivery). Urine PBG (analysed via a rapid qualitative screen) was negative on days 2 and 3 following delivery. The patient was discharged with a 6-week course of enoxaparin for VTE prophylaxis. The patient has remained well and has the ongoing support of primary care and psychology as needed, as well as a porphyria specialist.

Discussion

This is the first case report to document the use of PGT-M in acute porphyria. We believe this reflects genuine low use of assisted reproductive technology in this genetic disorder. There are a number of reasons for this related to both the condition and the procedure. First, with regard to the condition itself, the three acute porphyrias are characterised by low penetrance. Estimates predict that fewer than 10% of those carrying the mutation will present with symptoms, while increasingly complex whole exome sequencing suggests this could be as low as 1%.^{2,8} Second, when acute attacks occur they seldom become recurrent or severe.⁸ Third, acute attacks often have triggers—e.g., alcohol, caloric deprivation, smoking and hormonal fluctuations—that can be avoided or managed.¹ Hence, although porphyria is a genetic condition amenable to PGT-M, it would be inappropriate to consider PGT-M as clinically indicated for routine practice, especially when considering the risk and cost of PGT-M.

Although PGT-M is a relatively safe process, it is not without risks. There is an estimated <1% risk of misdiagnosis and selecting an embryo that actually carries the gene mutation.⁴ Most reports have not found increased risk of blastocyst degeneration after biopsy; however, there is a small chance of unsuccessful thawing of vitrified blastocysts of <5%.⁹ Similar to other assisted reproductive technology, there is a 1.5% chance of monozygotic twins being formed, and an increased risk of perinatal mortality if multiple embryos are transferred.⁴ IVF is also thought to be porphyrogenic and may trigger a porphyria flare.¹⁰ However, a case series by Vassiliou et al. reported no porphyria flares in nine diagnosed women who received IVF treatment, although only one out of the nine cases

Table 1: Hospitalisation costs for porphyria-related admissions in New Zealand.

Case*	Total number of porphyria-related hospitalisations	Total cost (NZD)
III 5	31	\$209,754
III 2	59	\$766,545
III 1	10	\$69,351

The total cost in New Zealand dollars (NZD) for three patients' hospitalisations associated with porphyria flares or related complications (in written correspondence from M Purves, January and June 2023).

*Case III 5 is the patient discussed in this case report, and Cases III 1 and III 2 are cousins of Case III 5, who have previously been discussed in another publication.⁵

were reported to have severe porphyria attacks.¹⁰

In New Zealand, there are strict criteria for receiving PGT-M. For familial single-gene disorders, PGT-M can only be applied if there is evidence that a family member has the disorder, that there is at least a 25% chance of the disorder being passed onto the child, and that this disorder is likely to significantly affect the child's future quality of life.¹¹ The cost of PGT-M in New Zealand (including feasibility testing, IVF, genetic testing for HCP and embryo transfer) is estimated at around NZ\$20,000 per cycle.¹²

Given the usual clinical course of acute porphyria and the risks and costs of PGT-M, the question is whether PGT-M can be clinically and ethically justified in this patient. We believe the history of this patient, alongside the experiences of the other family members with the condition, provide clear justification.⁵ Despite the involvement of a porphyria specialist and long-term attempts to avoid triggers, this patient has had numerous hospital admissions with severe pain and both medical and psychosocial complications subsequent to that. Her experience is also not isolated among her family members. Women from families with inherited mutations associated with acute porphyrias have previously been shown to have a much higher penetrance than the estimated penetrance in the general population (up to 50% compared with 1%, respectively).^{13,14} This particular family has a variant with an estimated penetrance of 71% and significant resulting morbidity.⁵ The only known curative treatment for acute hepatic porphyria, currently, is liver transplantation.¹ Although the small interfering ribonucleic acid (siRNA) molecule, Givosiran, has shown promising biochemical and clinical response,^{15,16} it does not represent a cure and may well be prohibitively expensive, particularly with the limited budget for purchasing publicly

funded medications that is given to New Zealand's Pharmaceutical Management Agency.¹⁷

From an ethical perspective, avoiding the possibility of similar clinical experiences in subsequent generations would align with the principles of beneficence and non-maleficence.¹⁸ However, demand frequently outstrips supply, particularly in a public health system. With the cost of the reproductive technology being used, consideration should be given to the just or reasonable allocation of resources. The costs of not only the hospitalisation of this patient, but also the costs attributable to the admissions of other family members, are summarised in Table 1. The patient's (Case III 5 below) hospitalisation costs over the past 11 years have been estimated at 10-fold the cost for PGT-M, at NZ\$209,754 (in an email from M Purves [Mike. Purves@ccdhb.org.nz] January and June 2023).

Financially, these figures demonstrate a significant burden to New Zealand's healthcare system to date. The cost of admission to an intensive care unit (a disproportionate amount for Case III 1)⁵ may be avoided in the future due to disease knowledge and early recognition of acute attacks. There is also some uncertainty regarding penetrance or severity of future carriers. However, the experience of this family is that acute attacks and hospitalisation cannot be avoided even with education and knowledge. The cost-benefit analysis, even from a solely financial perspective, provides justification for decreasing the frequency of this mutation in subsequent generations.

In conclusion, although we do not consider routine use of PGT-M in the acute porphyrias to be indicated, the procedure should be considered in cohorts with high penetrance, recurrent attacks and/or complications. In this patient, PGT-M is clinically and ethically justified and may also reduce the overall downstream costs to the health system.

COMPETING INTERESTS

Dr CT is a member of the Medical Advisory Board of the Australia Porphyria Association. Dr LS is a shareholder of Fertility Associates New Zealand. Dr GK is an Advisory Board Member of the *New Zealand Medical Student Journal*, which is independent from the *New Zealand Medical Journal*. The authors have no other conflict of interest to declare. No specific funding from public, commercial or not-for-profit sectors was obtained in regard to this manuscript. Written informed consent was obtained from the patient prior to publication of this case report.

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AUTHOR INFORMATION

Gisela A Kristono: Wellington Regional Hospital, Te Whatu Ora Capital and Coast, New Zealand; Department of Surgery, University of Otago Wellington, New Zealand.

Leigh Searle: Wellington Regional Hospital, Te Whatu Ora Capital and Coast, New Zealand; Department of Surgery, University of Otago Wellington, New Zealand; Fertility Associates Wellington, New Zealand; Department of Obstetrics and Gynaecology, University of Otago Wellington, New Zealand.

Cindy Towns: Wellington Regional Hospital, Te Whatu Ora Capital and Coast, New Zealand; Department of Medicine, University of Otago Wellington, New Zealand.

CORRESPONDING AUTHOR

Dr Cindy Towns: Department of General Medicine, Wellington Regional Hospital, 39 Riddiford Street, Newtown, Wellington 6021, New Zealand.
E: Cindy.Towns@ccdhb.org.nz

URL

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