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# Harlequin ichthyosis in a neonate born with assisted reproductive technology: a case report

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## Abstract

Harlequin ichthyosis is a rare and the most severe form of congenital ichthyosis. Although prenatal diagnosis is difficult for this disorder, recently, this obstacle has markedly improved with the use of DNA-based prenatal diagnosis. Here in, we presented a neonate with harlequin ichthyosis born by assisted reproductive technology (ART). In this case, the diagnosis of harlequin ichthyosis was not established by conventional prenatal screening.

**Keywords:** Harlequin ichthyosis, Harlequin fetus, Assisted reproductive technology, Prenatal diagnosis, In vitro fertilization.

## Introduction

Harlequin ichthyosis (HI) is a rare genetic disorder of skin keratinization and is the most severe form of congenital ichthyosis with an incidence of about 1 in 300,000 births (1, 2). Hart reported the first case of this disorder in 1750 (3). Affected newborns have a thickened, grooved, hard ("armor like") and hyperkeratotik skin with deep fissures that are most prominent over areas of flexion and waxy, plate like scaling over the entire of the body. It is associated with specific facial appearances including ectropion, everted and gapping lips (fish mouth), and ear and nose hypoplasia. Flexion deformities of all joints due to extreme inelasticity of the skin and hypoplastic digits are other signs of HI (4, 5).

In this paper we report a case of HI who was born by assisted reproductive technology (ART). To the base of our search in scholar articles this is the first case of HI generated by ART. The aim of this report was to reinforce the importance of prenatal diagnosis, especially pre-implantation genetic diagnosis for HI in screening subsequent pregnancy.

## Case report

A 15 day-old boy was transferred to our hospital because of difficultly in feeding and dysmorphic appearance. He was the first child from first degree related healthy parents after 8 years of being infertile who born by IVF (In Vitro Fertilization) technique. He was born by cesarean section at the 35$^{th}$ week of gestation. His weight was 2,500 grams, 47 cm length and head circumference of 33 cm. Skin examination revealed thick horny shape 4-5 cm plaques with vertically and horizontally fissures. Ectropion, wide mouth and circum-oral cracking of skin were observed and ears and nose were crumpled and flattened. Heart and lung examinations were normal.

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Joints of all extremities had flexion contractures associated with limitation in motion. Digits and nails were hypoplastic. On fingers of the lower extremities, black necrotic spots were seen (Fig. 1). All of the above features were characteristic for HI.

The patient was admitted into the neonatology ward in an incubator with optimum temperature and humidity. Systemic antibiotics and fluids were started via an umbilical cut down and baby fed with feeding gavage. Topical antibiotics and emollients on the skin lesions and artificial tear drop for coverage of conjunctiva were prescribed. Pathological exam of skin biopsy revealed hyperkeratosis of epidermis layer that consisted with diagnosis of ichthyosis. On day 22 of his life while the neonate was in a good general condition and tolerated 150cc/kg/day of formula, he was transferred to another baby care center and did not return for follow up.

**Discussion**

In this article we reported a case of HI who was conceived by IVF technique. The HI is an extremely severe congenital form of ichthyosis characterized by a profound thickening of the keratin layer in fetal skin that is thought to primarily result from abnormal lipid metabolism in the epidermis (6, 7). This disorder is caused by lack of function induced by mutations of the ABCA12 (Adenosine-triphosphate-Binding Cassette A12) gene (1, 3). HI is a rare disorder with the incidence of 1:300,000 births and more than 100 cases have been reported in the literature (1, 3, 5). Most cases of HI have been recognized as having autosomal recessive inheritance although a dominant form may exist and sporadic cases occur frequently (5, 8). The current case probably has an autosomal recessive pattern given the fact that his parents showed consanguinity.

Diagnosis was essentially clinical with characteristic features supplemented by pathologic findings. Although the histological findings of the variation in subtypes were varied, their clinical features were indistinguishable (2, 5).

Affected neonates die within few days because of feeding problems, infection, and respiratory failure. Recently with the better availability of neonatal intensive care facilities and benefits from oral retinoid some of affected newborns are surviving beyond neonatal periods (8).

In 2007 Golalipour et al. reported a full term neonate with HI born in Iran (Gorgan) who died on the third day of hospitalization due to respiratory failure and sepsis.[2] Hashemzadeh et al. reported another case of HI in a female preterm newborn in Iran (Mashhad) in 2009. She also died on the third day of her life (4). Diagnosis in both cases, was based on the clinical findings, but in our case, diagnosis was supplement-

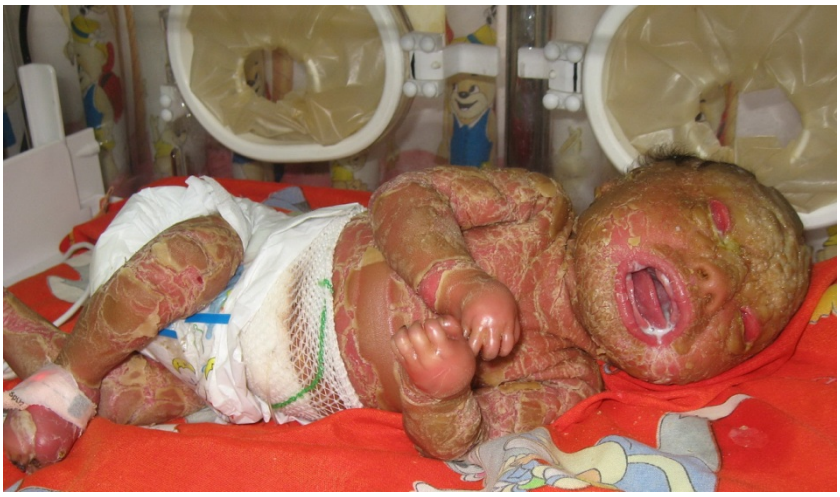

Fig. 1. Characteristic features of Harlequin ichthyosis in the baby

ed by skin biopsy. On the other hand the patient remained alive 22 days after birth during our follow up period.

Rajpopat assessed clinical outcomes of 45 cases of HI and reported an overall survival rate of 56% ranged from 10 months to 25 years, that is probably the result of early introduction of oral retinoid and improvement of neonatal care (9).

Noticeable point in our reported case is birth of affected newborn by IVF. To the best of our knowledge this is the first case of HI who is born by this technique. Although IVF and other ART techniques are generally considered safe, some studies have demonstrated an increased occurrence of major congenital malformations particularly congenital heart disease (10, 11). On the other hand recent reports have suggested association between IVF and imprinting gene disorders such as Angelman and Beckwith-Wiedmann syndrome (11).

Bowdin et al. in a survey suggested that absolute risk of imprinting disorders in children born by ART is small (< 1%) and precise risk estimates are difficult to determine because of rarity of the conditions, hence recommended further investigation (12). Indeed in spite of low incidence of abnormalities in children conceived with ARTs, continuing surveillance of them including monitoring of their birth defects is essential (13). Although it seems that HI in our presented case was due to consanguinity of the parents, it is possible that this condition may occurred randomly following ART pregnancy.

The most important point and the main aim of this report was to emphasize on the importance of prenatal genetic diagnosis of HI in next offspring. Although prenatal genetic diagnosis is too expensive for low income family but it is very neccessary in high risk pregnancies such as our case. The diagnosis was done by fetal skin biopsy at 19-23 weeks of gestation using 3D or 4D ultrasonography (14, 15). Akiyama et al reported the first DNA-based prenatal diagnosis of HI by direct sequence analysis of ABCA12 mutation from amniotic fluid cells and demonstrated the efficiency of early DNA-based prenatal diagnosis of HI. [16] This new advancement created new horizons for earlier and accurate diagnosis of genodermatosis such as HI.

## Conclusion

We present a baby born with IVF suffering from HI that is a rare genodermatosis. In similar cases with improvement in DNA-based prenatal diagnosis of HI new diagnostic procedures such as preimplantation diagnosis of HI especially for parents who had an affected child and can only be fertile by ART is very critical and important for reduction of their emotional stress. Further prenatal diagnostic procedures are needed.

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