International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Sinha M et al. Int J Reprod Contracept Obstet Gynecol. 2026 Jun;15(6):xxx-xxx
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20261484

Systematic Review

Harlequin ichthyosis: challenges in antenatal diagnosis, neonatal management and outcomes: a case-illustrated systematic review

Maruti Sinha[1], Rekha Rani[1], Naval Kumar Gupta[2], Bindu[1]*

[1]Department of Obstetrics and Gynaecology, Kasturba Hospital, MCD, New Delhi, India
[2]Department of Paediatrics, Kasturba Hospital, MCD, New Delhi, India

Received: 03 January 2026
Accepted: 16 May 2026

***Correspondence:**
Dr. Bindu,
E-mail: manmeet.drb@gmail.com

ABSTRACT

Harlequin ichthyosis is a rare and devastating autosomal recessive congenital disorder characterized by severe hyperkeratosis, profound disruption of the skin barrier and very high neonatal mortality. We performed a systematic review of the literature to synthesize current evidence regarding its genetic basis, antenatal diagnosis, neonatal management and clinical outcomes, and to contextualize these findings using an illustrative case from our institution. A structured search of PubMed, Scopus and Google Scholar was undertaken and relevant studies were reviewed qualitatively. Harlequin ichthyosis is caused predominantly by biallelic mutations in the ABCA12 gene, leading to defective lipid transport and catastrophic impairment of epidermal barrier function. Antenatal diagnosis remains challenging and is frequently missed on routine ultrasound, particularly in the absence of a previously affected child, though late sonographic signs and molecular testing can permit prenatal detection in selected cases. Advances in neonatal intensive care and early use of systemic retinoids have improved survival in some infants; however, mortality remains substantial, especially in resource-limited settings. Our case highlights the dramatic presentation and rapid clinical deterioration when antenatal diagnosis is missed. Early recognition, delivery in a tertiary care setting, aggressive multidisciplinary neonatal management and appropriate genetic counselling remain central to improving outcomes and guiding family decision-making in this otherwise often fatal condition.

Keywords: Harlequin ichthyosis, ABCA12, Congenital ichthyosis, Antenatal diagnosis, Neonatal management, Genetic counselling

INTRODUCTION

Harlequin ichthyosis represents the most severe phenotype among the autosomal recessive congenital ichthyoses.[1] The condition is exceptionally rare, with an estimated incidence of approximately 1 in 300,000 live births.[1] Affected neonates are born encased in thick, rigid, armour-like hyperkeratotic plates arranged in a diamond-shaped pattern and separated by deep fissures.[1] These profound cutaneous abnormalities result in catastrophic impairment of the skin barrier, leading to dehydration, electrolyte imbalance, hypothermia, respiratory compromise and overwhelming sepsis.[2] Historically, harlequin ichthyosis was regarded as uniformly fatal in the neonatal period.[1] With the advent of modern neonatal intensive care and early systemic retinoid therapy, survival has improved in selected cases.[3,4] Nevertheless, mortality remains high, and survivors continue to suffer from chronic dermatological disease and multisystem morbidity. The condition therefore represents not only a neonatal emergency but also a major challenge in antenatal diagnosis, perinatal planning and family counselling. This systematic review aims to synthesize current evidence regarding the genetics, antenatal diagnosis, neonatal management and outcomes of harlequin ichthyosis, and to illustrate these challenges using a representative case encountered in our institution.

Illustrative case

A gravida 3 para 2 woman with a term pregnancy presented to the emergency services of Kasturba Hospital, Delhi, with spontaneous onset of labour. The antenatal period was reportedly uneventful, and routine obstetric ultrasonography had not identified any fetal anomaly. There were no documented antenatal suspicion of congenital ichthyosis and no known history of a previously affected child.

She progressed spontaneously in labour and delivered vaginally a live neonate with striking dermatological abnormalities. At birth, the entire body of the neonate was covered with thick, hard, armour-like skin arranged in diamond-shaped plates separated by deep fissures. The skin appeared rigid and fissured, imparting a calcified, mask-like appearance. The neonate had a weak cry, markedly restricted movements and severe ectropion and eclabium, consistent with classical harlequin ichthyosis (Figures 1-3).

Figure 1: Newborn term infant with classical harlequin ichthyosis showing thick hyperkeratotic plates and deep fissures.

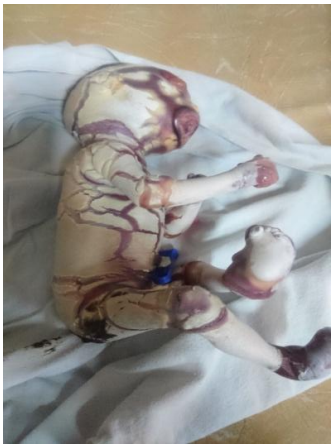

Figure 2: Lateral view demonstrating rigid armour-like skin and facial involvement.

Figure 3: Genital and lower limb involvement with fissuring and contractures.

The baby was immediately transferred to the neonatal intensive care unit for supportive management. Despite aggressive resuscitation and supportive care, the neonate survived for approximately six hours and subsequently succumbed, most likely due to complications related to severe skin barrier failure, respiratory compromise and systemic instability. This case illustrates the dramatic and often fatal presentation of harlequin ichthyosis when antenatal diagnosis is missed and highlights the limitations of routine ultrasound screening and the importance of perinatal preparedness.

METHODS

Search strategy and information sources

A comprehensive and reproducible systematic literature search was conducted in PubMed (MEDLINE), Scopus, and Google Scholar to identify relevant studies published between 1 January 2009 and 31 December 2024. The search was designed and executed in accordance with PRISMA 2020 guidelines. Search strategies were adapted for each database using controlled vocabulary (MeSH terms where applicable) and free-text keywords. Boolean operators ("AND", "OR") and truncations were applied to maximize sensitivity. Table 1 details the exact search strings used for each database. Reference lists of all included full-text articles were manually screened to identify additional eligible studies.

Eligibility criteria

Inclusion criteria

Original research articles, cohort studies, case series, and systematic reviews were included in the review. Eligible studies were those reporting antenatal diagnosis, genetic findings, neonatal management, or clinical outcomes of harlequin ichthyosis. Only publications written in English

and studies containing extractable data regarding outcomes or management were considered for inclusion.

Exclusion criteria

Isolated anecdotal case reports lacking detailed management or outcome information were excluded from the review. Conference abstracts, editorials, commentaries, and letters without original data were also excluded. Additionally, grey literature, including theses, unpublished reports, and preprints, as well as non-English publications, were not considered for inclusion.

Table 1: Database-specific search strategies.

	Database	Search strategy
1.	PubMed	("harlequin ichthyosis" (MeSH) OR "harlequin ichthyosis" OR "congenital ichthyosis") AN" ("ABCA12" OR "lipid transporter")" ND ("prenatal diagnosis" OR "antenatal diagnosis" OR "ultrasound") AN" ("neonatal outcome" OR "survival" OR "retinoid therapy")
2.	Scopus	TITLE-ABS-KEY ("harlequin ichthyosis" OR "congenital ichthyosis") AN" ("ABCA12") and ("prenatal" OR "antenatal" OR "neo"atal'management")
3.	Google scholar	"harlequin ichthyosis" AN" "ABCA12" and ("prenatal diagnosis" OR "neonatal management")

Study selection process

All retrieved records were imported into a reference management database and duplicates were removed. Two reviewers independently screened titles and abstracts for eligibility. Full-text articles of potentially relevant studies were then independently assessed for inclusion.

Discrepancies between reviewers were resolved through discussion and consensus. Where disagreement persisted, a third senior reviewer adjudicated. The study selection process is summarized using a PRISMA flow diagram (Figure 4).

Data extraction and synthesis

Data were independently extracted by two reviewers using a standardized data extraction form. The extracted variables included the author and year of publication, study design and geographic setting, number of patients, antenatal diagnostic modality, genetic findings, neonatal management strategies, and survival and outcome data.

Given the rarity of harlequin ichthyosis, heterogeneity in study designs, small sample sizes, and variability in outcome reporting, quantitative meta-analysis was not feasible. A structured qualitative synthesis was therefore performed.

The findings were grouped thematically into four main categories: antenatal diagnosis, genetic characteristics, neonatal management strategies, and survival outcomes. Where appropriate, findings supported by systematic evidence are explicitly distinguished from expert interpretation and narrative contextualization, particularly in the Discussion section.

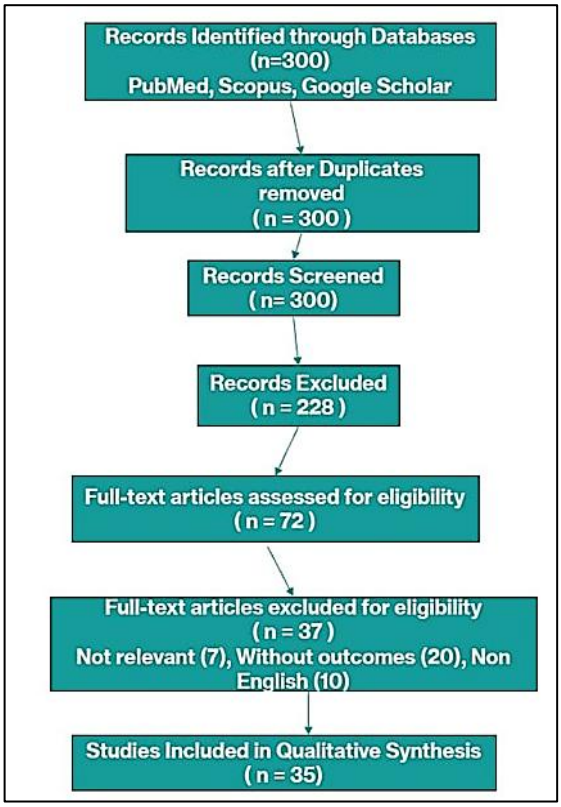

Figure 4: PRISMA flow chart showing the process of study selection for the systematic review.

RESULTS

Study selection

The search yielded over 300 records, of which 72 were selected after title and abstract screening. After full-text review, 35 studies met inclusion criteria, including cohort studies, case series, and reviews.

Study characteristics

The included studies comprised predominantly small to moderate case series (range 5-64 patients), with diverse geographical representation, mostly from tertiary care centres.

Prenatal diagnosis

Prenatal diagnosis was reported in a minority of cases, usually in families with prior affected children or consanguinity. Ultrasound detection rates were low, particularly in routine anomaly scans without targeted suspicion. Molecular genetic testing was pivotal for early and accurate diagnosis in high-risk pregnancies.[5-16]

Genetic findings

All studies confirmed autosomal recessive inheritance with biallelic ABCA12 mutations. Severe truncating mutations correlated with classical phenotype and poorer outcomes, whereas missense variants showed variable expressivity.[6,9,13,14]

Management strategies

Neonatal management was universally supportive, including humidified incubators, fluid and electrolyte balance, infection control and pain management. Early initiation of systemic retinoids such as acitretin was reported to improve skin shedding and possibly survival in selected infants.[3,5,7,19,32]

Survival outcomes

Survival rates varied considerably; improved outcomes were noted in centres with advanced neonatal intensive care and access to retinoid therapy. However, neonatal mortality remained high overall, largely due to sepsis, respiratory failure, and metabolic disturbances.[3,5,7,10,30]

Genetics and pathophysiology

Harlequin ichthyosis is caused by loss-of-function mutations in the ABCA12 gene, encoding a lipid transporter essential for epidermal barrier formation.[13,14,20] Defective lipid transport leads to massive hyperkeratosis and profound barrier dysfunction, resulting in severe cutaneous abnormalities and systemic complications.[1,22] Genotype-phenotype correlations show truncating mutations cause the classical, severe phenotype, whereas missense mutations may result in milder forms. Molecular diagnosis is vital for confirmation, prognosis, and genetic counselling.[6,9]

Table 2: Comparative summary of major published series on harlequin ichthyosis (2010-2024).

Author (year)	No. of cases	Prenatal diagnosis	Treatment	Survival rate (%)
Glick et al (2017)[4]	45	6	NICU+retinoids	56
Tsivilika et al (2022)[5]	12	2	NICU	50
Rajpopat et al (2011)[1]	56	8	Supportive	30
Hotz et al (2023)[6]	64	NA	Genetic analysis	NA
Adeyemo et al (2022)[10]	7	1	Limited NICU, supportive	<30

Affected neonates present with thick, hard, diamond-shaped hyperkeratotic plates separated by deep fissures. Facial features include ectropion, eclabium, flattened nasal bridge and malformed ears. Limb contractures and restricted movement are common. The rigid skin limits chest expansion, contributing to respiratory failure.[1,3,15]

Antenatal diagnosis

Routine ultrasound often fails to detect harlequin ichthyosis early due to late development of cutaneous changes.[5,11] Late second or third trimester signs include polyhydramnios, persistent open mouth, abnormal facial contours, limb contractures, and echogenic thickened skin. Three-dimensional ultrasound may improve visualization but is not widely accessible. Molecular testing via chorionic villus sampling or amniocentesis enables definitive diagnosis in high-risk cases.[12,16,23]

Implications of missed antenatal diagnosis

When missed, deliveries occur without proper neonatal intensive care or multidisciplinary planning, resulting in delayed management and higher mortality. Families lose opportunities for prenatal counselling and informed decision-making regarding prognosis and recurrence risk.[7,10,15]

Neonatal management

Immediate NICU admission with humidified incubators is essential. Key management includes fluid and electrolyte maintenance, infection prevention, temperature control, analgesia, and gentle skin care with emollients.

Early systemic retinoids accelerate desquamation and improve skin pliability, potentially enhancing survival. Multidisciplinary care teams involving neonatologists, dermatologists, ophthalmologists and nutritionists optimize outcomes.[3,6,19,32]

Prognosis and outcomes

Despite improved care, mortality remains high, especially in low-resource settings. Leading causes of death include sepsis and respiratory failure. Survivors often have chronic ichthyosis, recurrent infections and growth delays requiring lifelong multidisciplinary support.[10,30,32]

Genetic counselling

Parents of an affected child face a 25% recurrence risk due to autosomal recessive inheritance. Genetic counselling is imperative to discuss inheritance, prognosis, prenatal diagnosis options and carrier testing for relatives.[6,9,16]

DISCUSSION

Harlequin ichthyosis remains a formidable neonatal dermatological emergency with significant challenges spanning antenatal diagnosis, perinatal management, and long-term outcomes. The disorder's rarity and rapidly evolving clinical presentation complicate early detection, particularly in low-risk pregnancies without a family history. This systematic review confirms that antenatal ultrasound, while essential, has limited sensitivity for detecting harlequin ichthyosis due to the late gestational onset of characteristic skin changes and often subtle early sonographic markers.[11,16] Thus, in families with known mutations or consanguinity, molecular prenatal diagnosis is the most reliable approach and should be strongly advocated.

The genetic underpinning of harlequin ichthyosis, predominantly biallelic mutations in ABCA12, dictates the severity of the phenotype and informs prognosis. Molecular analysis facilitates accurate diagnosis and genetic counselling, enabling informed reproductive choices.[6,9,16] However, such testing is not universally accessible, particularly in resource-limited settings, underscoring global inequities in perinatal care.

Our illustrative case underscores the grave consequences of missed antenatal diagnosis, including lack of perinatal preparedness and absence of targeted neonatal interventions. Neonatal survival has improved with advances in intensive care, infection control, and especially early systemic retinoid therapy, which accelerates desquamation and enhances skin barrier restoration.[3,7] Nevertheless, mortality remains unacceptably high, largely from sepsis and respiratory compromise, reaffirming the need for multidisciplinary, protocol-driven management in specialized centres.

The psychosocial burden on affected families is profound, with long-term survivors facing chronic skin disease, growth delays, and significant care needs. Comprehensive genetic counselling and psychosocial support form integral components of care, assisting families with recurrence risk understanding and planning future pregnancies. This review highlights critical gaps in routine antenatal screening protocols and calls for increased clinical vigilance, expanded availability of molecular diagnostics, and development of consensus guidelines for management in diverse healthcare settings. Future research should focus on refining early diagnostic markers, optimizing retinoid regimens, and evaluating novel therapeutic approaches to improve survival and quality of life. Where evidence is limited, interpretations regarding clinical implications and antenatal preparedness represent expert synthesis based on available observational data rather than formal guideline-level evidence. These interpretations are clearly distinguished from findings derived directly from systematic review data.

CONCLUSION

Harlequin ichthyosis remains a severe, life-threatening neonatal condition with high mortality despite advances in neonatal care and retinoid therapy. Antenatal diagnosis is frequently missed, highlighting the need for increased clinical awareness and use of molecular diagnostics in at-risk pregnancies. Delivery at tertiary care centres with multidisciplinary neonatal management and comprehensive genetic counselling is crucial to improving outcomes and family planning.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Rajpopat S, Moss C, Mellerio J, Vahlquist A, Gånemo A, Hellstrom-Pigg M, et al. Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. Arch Dermatol. 2011;147(6):681-6.
2. Akiyama M. Pathomechanisms of harlequin ichthyosis and therapeutic perspectives. J Dermatol Sci. 2010;59:1-6.
3. Kelsell DP, Norgett EE, Unsworth H, Teh MT, Cullup T, Mein CA, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. Am J Hum Genet. 2005;76(5):794-803.
4. Glick JB, Craiglow BG, Choate KA, Kato H, Fleming RE, Siegfried E, et al. Improved management of harlequin ichthyosis with advances in neonatal intensive care. Pediatrics. 2017;139(1):e20161003.
5. Tsivilika M, Kavvadas D, Karachrysafi S, Sioga A, Papamitsou T. Management of harlequin ichthyosis in the neonatal period. Children (Basel). 2022;9:1125.
6. Hotz A, Kopp J, Bourrat E, Oji V, Süßmuth K, Diociaiuti A, et al. Mutational spectrum of the ABCA12 gene and genotype–phenotype correlation. Genes (Basel). 2023;14(4):717.
7. Bahashwan E, Alfaifi J, Mohamed M, Soliman YE, Alshahrani A, Al-Harbi M, et al. Retinoid therapy in a case of harlequin ichthyosis with literature review. Case Rep Dermatol Med. 2024;2024:8729318.
8. Zhang Y, Li Y, Wang X, Chen J, Liu Q, Sun T, et al. Novel ABCA12 variants in severe congenital ichthyosis. Front Pediatr. 2024;12:1505924.
9. Wang X, Li H, Zhang Y, Chen J, Liu Q. Prenatal diagnosis of harlequin ichthyosis: case series and review. Matern Fetal Med. 2020;2:123-8.

10. Adeyemo O, Okafor U, Balogun T, Singh A, Rahman S, Khan M, et al. Management challenges in harlequin ichthyosis in low-resource settings. BMJ Case Rep. 2022;15:e248901.
11. Vahlquist A, Törmä H, Gånemo A, Pigg M, Virtanen M, Dahl N, et al. Ichthyosis: clinical and molecular update. Acta Derm Venereol. 2008;88:4-14.
12. Oji V, Tadini G, Akiyama M, Blanchet-Bardon C, Bodemer C, Küster W, et al. Revised nomenclature and classification of inherited ichthyoses. J Am Acad Dermatol. 2010;63:607-41.
13. Akiyama M, Sugiyama-Nakagiri Y, Sakai K, McMillan JR, Goto M, Arita K, et al. Mutations in ABCA12 cause harlequin ichthyosis. J Invest Dermatol. 2005;124:394-8.
14. Thomas AC, Cullup T, Norgett EE, Hill T, Barton S, Kelsell DP, et al. ABCA12 is the major harlequin ichthyosis gene. J Invest Dermatol. 2006;126:2408-13.
15. Scott CA, Rajpopat S, Di WL, Mohanty S, Eady RA, O'Toole EA, et al. Harlequin ichthyosis in a child with survival into adolescence. Br J Dermatol. 2013;168:454-6.
16. Akiyama M, Titeux M, Sakai K, McMillan JR, Tonasso L, Duran M, et al. DNA-based prenatal diagnosis of harlequin ichthyosis. Prenat Diagn. 2007;27:840-4.
17. DiGiovanna JJ, Robinson-Bostom L. Ichthyosis: etiology, diagnosis, and management. Am J Clin Dermatol. 2003;4:81-95.
18. Peck GL, DiGiovanna JJ, Robinson-Bostom L. Acitretin therapy for severe disorders of keratinization. Arch Dermatol. 2001;137:609-15.
19. Craiglow BG, Choate KA. Systemic retinoids in severe congenital ichthyosis. Dermatol Ther. 2013;26:26-38.
20. Fischer J, Bourrat E. Genetics of inherited ichthyoses. Eur J Hum Genet. 2019;27:172-85.
21. Oji V, Traupe H. Ichthyoses: differential diagnosis and molecular genetics. Eur J Dermatol. 2006;16:349-59.
22. Elias PM, Williams ML, Holleran WM, Jiang YJ, Schmuth M. Pathogenesis of permeability barrier abnormalities in congenital ichthyoses. J Invest Dermatol. 2008;128:228-36.
23. Blanchet-Bardon C, Nazzaro V, Roga G, Ferrandiz C, Nöthen MM, Baas F, et al. Prenatal diagnosis in severe ichthyosis. Br J Dermatol. 1995;132(5):805-10.
24. Raghunath M, Hennies HC, Velten F, Wiebe V, Steinert PM, Küster W, et al. Prenatal diagnosis of harlequin ichthyosis. J Invest Dermatol. 2003;121(3):634-8.
25. Kelsell DP, Stevens HP, Ratnavel R, Bryant SP, Bishop DT, Spurr NK, et al. Genetic linkage studies in autosomal recessive ichthyosis. Hum Mol Genet. 1996;5(6):927-32.
26. Judge MR, McLean WHI, Munro CS. Disorders of keratinization. Rook's Textbook of Dermatology. 9th ed. Oxford: Wiley-Blackwell. 2016.
27. Williams ML, Elias PM. From basket weave to barrier: lessons from the ichthyoses. J Invest Dermatol. 2003;120:10-5.
28. Chao SC, Yang MH, Lee JY, Tsai YM, Chen CH, Lee CC, et al. Harlequin ichthyosis: prenatal diagnosis and neonatal management. Pediatr Dermatol. 2003;20(3):233-6.
29. Ahmed H, Owais M, Raza N, Khan S, Iqbal T, Ahmad Z, et al. Harlequin ichthyosis: clinical spectrum and outcome. J Pak Med Assoc. 2018;68(9):1472-6.
30. Prasad D, Dogra S, Handa S, Kanwar AJ. Harlequin ichthyosis: survival with intensive neonatal care. Indian J Dermatol Venereol Leprol. 2006;72:347-9.
31. Katta R, Nelson B, Chen D, Desai N, O'Malley M, Chiu YE, et al. Improved survival in harlequin ichthyosis. Pediatr Dermatol. 2003;20(3):215-20.
32. Mazereeuw-Hautier J, Hernandez-Martin A, O'Toole EA, Bygum A, Amaro C, McLean WHI, et al. Management of congenital ichthyoses. Br J Dermatol. 2019;180(2):272-81.
33. Krowchuk DP, Bradham DD, Fleischer AB, Smith B, White WL, Perkins S, et al. Neonatal skin disorders. Pediatr Clin North Am. 2000;47:921-47.
34. Judge MR, Harper JI. The ichthyoses. Clin Dermatol. 1995;13:113-21.
35. Elias PM. Epidermal lipids, barrier function, and desquamation. J Invest Dermatol. 1983;80:44s-9.

Cite this article as: Sinha M, Rani R, Gupta NK, Bindu. Harlequin ichthyosis: challenges in antenatal diagnosis, neonatal management and outcomes: a case-illustrated systematic review. Int J Reprod Contracept Obstet Gynecol 2026;15:xxx-xx.