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SCIENTIFIC ARTICLE - ORIGINAL ARTICLE

PRENATAL ULTRASOUND DIAGNOSIS OF ICHTHYOSIS - IMAGE COMPILATION

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ABSTRACT

INTRODUCTION: Genodermatoses are hereditary diseases that primarily affect the skin and are often associated with increased morbidity and mortality. Ultrasound is commonly used in the prenatal diagnosis of these conditions and can reveal findings that suggest their presence. Ichthyosis, a common genodermatosis, is characterized by skin hardening, a predisposition to infections, respiratory issues, and dehydration. Obstetric ultrasound can show signs such as facial abnormalities, underdeveloped hands and feet, and skin thickening.

OBJECTIVE: This study aims to review, identify, and describe fetal imaging characteristics associated with ichthyosis.

METHODS: This narrative review focuses on compiling images from articles published over the last five years, using the MEDLINE databases via PubMed and Google Scholar. The English MeSH terms used include "Skin Diseases," "Ultrasonography," "Prenatal," and "Prenatal Diagnosis." The search strategy used in Google Scholar was: ((Genodermatosis) AND (Ultrasound)). In the PubMed platform, the search strategy used was: ((Skin Diseases) AND (Ultrasonography, Prenatal) OR (Prenatal Diagnosis)).

RESULTS AND DISCUSSION: In cases of harlequin ichthyosis, the diagnostic hypothesis may arise based on findings such as abnormal extremities, growth restriction, echogenic amniotic fluid, and facial dysmorphisms, including a flat face and a wide mouth with thick lips, observed on three-dimensional ultrasound. Prenatal ultrasound findings in restrictive dermopathy may include a fetus with asymmetric growth restriction, separation of the chorioamniotic membrane, polyhydramnios or oligohydramnios, a small and continuously open round mouth, micrognathia, fixed flexion contractures of the upper limbs, and a varix of the fetal intra-abdominal umbilical vein.

CONCLUSION: Ichthyoses are rare genetic diseases with often poor prognoses. Imaging, being non-invasive and able to detect the disease even in the absence of a family history, plays a crucial role. Therefore, imaging professionals must be familiar with the distinctive imaging characteristics of these conditions, which can be identified through ultrasound. Prenatal ultrasound, especially 3D ultrasound, plays a key role in diagnosis, although the late manifestation of the disease poses challenges for timely detection and treatment.

KEYWORDS: DERMATOSES, GENODERMATOSES, ICHTHYOSIS, PRENATAL DIAGNOSIS, MEDICAL IMAGING.

INTRODUCTION

Fetal medicine is a subspecialty of Gynecology and Obstetrics that aims to promote the health of the mother-fetus duo through diagnostic and therapeutic procedures related to pregnancy. Ultrasound is the primary method used in this field, and through it, other exams, such as guided amniocentesis, can be performed, as well as the diagnosis of diseases like genodermatoses.[1]

Genodermatoses are hereditary, heterogeneous diseases that primarily or exclusively affect the skin [2], and some of them lead to increased morbidity and mortality. The main conditions in this group include epidermolysis bullosa, ichthyotic disorders, and pigmentation disorders, such as oculocutaneous albinism.[3]

Congenital ichthyoses are diseases caused by gene mutations that lead to keratinization disorders, affecting the skin barrier function and, consequently, the ability to protect against external aggressors.[4,5] This condition represents a group of heterogeneous diseases with hereditary genetic disorders. More than 50 genetic mutations involving various essential components for maintaining the epidermal barrier have been described in the literature.

The clinical manifestations include generalized xerosis, areas of scaling, and fissuring. In more severe cases, there can be thermal dysregulation with hypothermia, protein loss that increases nutritional requirements, and frequent infections.[4] This group is divided into various subtypes based on clinical presentation, histopathology, and genetics.[6] The two major subgroups of ichthyoses are non-syndromic, which affect only the skin, and syndromic, which involve both the skin and other organs impacted by the genetic mutation.

Non-syndromic ichthyoses can also be subdivided into different groups, which include vulgar ichthyosis, X-linked

ichthyosis, autosomal recessive congenital ichthyoses, and keratinopathic ichthyoses. A severe form of autosomal recessive congenital ichthyosis is known as harlequin ichthyosis, characterized by a shiny membrane that envelops the fetus and peels off after birth. As new types of ichthyoses are discovered through advances in genetics, it becomes possible to address the specific mutation involved.[4]

Among the ichthyoses, vulgar ichthyosis is the most common form, with an incidence of 1 in 250 births, compared to X-linked ichthyosis, which has an incidence of 1 in 2,500 births and is more prevalent in males. Bullous ichthyosis of Siemens has an even lower prevalence, affecting fewer than 1 in 1,000,000 individuals.[7] Finally, in addition to being a severe and rare form, harlequin ichthyosis can be associated with serious complications and has a mortality rate of 5% in cases.[4]

Prenatal diagnosis for patients with hereditary conditions can be an important aspect of medical care, providing the opportunity to address potential problems in a timely manner. For the families of affected children, prior knowledge can facilitate better psychological and financial preparation, as well as guidance during the pregnancy.[3] Prenatal diagnosis is recommended for those fetuses at increased risk of developing genodermatoses. As this is a group of hereditary diseases, indications for prenatal diagnosis include having an affected family member or a previously affected child.[2,3]

In the past, when searching for prenatal diagnosis of genodermatoses, the only option available was fetal skin biopsy, an invasive procedure performed late in pregnancy, between 15 and 22 weeks of gestation. Subsequently, with the advent of new techniques, the fetoscope was phased out, and the procedure began to be guided solely by ultrasound. Currently, this examination is rarely used and has been replaced by fetal DNA analysis; however, in some situations, it remains an option, such as when DNA data are insufficient, like when the mutation cannot be identified or the causative gene is unknown.[2,3,8]

Over the years, with advances in medicine and the discovery of genes, DNA-based prenatal diagnosis has become a reality in clinical practice. However, invasive techniques for obtaining fetal cells remain necessary, such as amniocentesis, which is the most commonly used invasive procedure for prenatal diagnosis in the second trimester of pregnancy. Being invasive, it can lead to complications such as amniotic fluid leakage, vaginal bleeding, and the risk of fetal loss, which has drastically decreased over the years (to 0.5%).[3,8] On the other hand, chorionic villus sampling (CVS), which aspirates tissue from the placenta, is performed under ultrasound guidance using either a transcervical or transabdominal approach. This procedure has the advantage of being performed early in the pregnancy and presents a risk of fetal loss comparable to that of amniocentesis.[8]

Ultrasound is the most commonly used examination in prenatal diagnosis and has been utilized as an auxiliary method in the diagnosis of genodermatoses. In addition to the benefit of being non-invasive, it has the capacity to detect abnormalities in the absence of any family history. Some ultrasound findings during pregnancy may be suggestive of certain genodermatoses. For instance, the presence of pyloric atresia along with other features such as ureteral stenosis, arthrogryposis, and deformities of the nose or ear can raise suspicions of epidermolysis bullosa. In the case of harlequin ichthyosis, the hypothesis may arise from abnormal extremities, growth restriction, echogenic amniotic fluid, and facial dysmorphisms, including a flat face and a wide mouth with thick lips, which can also be visualized on three-dimensional ultrasound.[3,8]

OBJECTIVES

Revising, Identifying, and Describing the Imaging Characteristics of Fetal Genodermatoses.

METHODS

This is a narrative review with an emphasis on the collection of images. The databases used were MEDLINE via PubMed and Google Scholar. Studies were included (clinical trials, pictorial essays, literature reviews, case reports, among others) that address the topic, contain images from diagnostic methods, are in line with the research objective, and are available online in full text, published in the last five years, in English, Spanish, and Portuguese. The health descriptors (MeSH terms) in English are "Skin Diseases," "Ultrasonography," "Prenatal," and "Prenatal Diagnosis." The following search strategy was used in Google Scholar: ((Genodermatosis) AND (Ultrasound)). A total of 791 articles were found, which were initially selected by reading the titles, with 318 being excluded. Of the remaining 473 articles, 187 were chosen by reading the abstracts, and 33 were selected based on the presence of an ultrasonographic image, three of which specifically addressed ichthyoses and were used in this study. On the PubMed platform, the following search strategy was used: ((Skin Diseases) AND (Ultrasonography, Prenatal) OR (Prenatal Diagnosis)). A total of 4,087 articles were found, which were initially selected by reading the titles, with 3,254 being excluded. Of the remaining 833 articles, 196 were chosen by reading the abstracts, and six were selected based on the presence of an ultrasonographic image, two of which specifically addressed ichthyoses and were used in this study. The flowchart below illustrates the selection of the articles (figure 1).

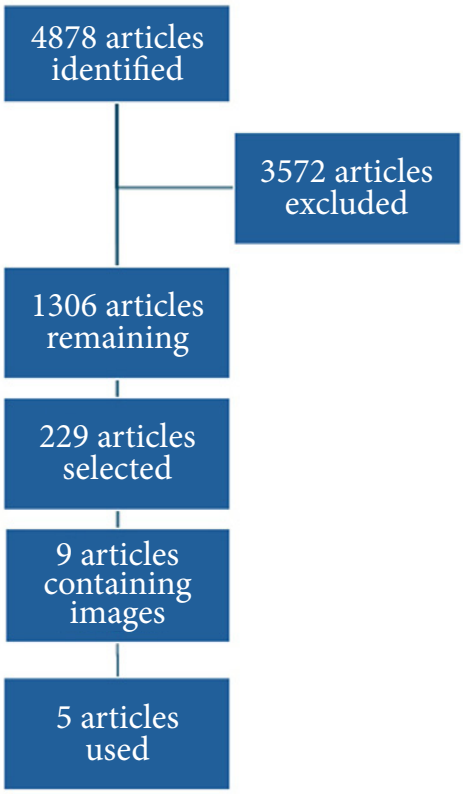

Figure 1. Flowchart illustrating the selection of articles.

RESULTS AND DISCUSSION

Table 1 illustrates the selected studies for the research, highlighting the criteria and images used.

Articles	Author	Images Used	Important Data Used
Prenatal diagnose of a fetus with Harlequin ichthyosis in a Chinese family.[9]	Jian W, Du Q, Lai Z, Li Y, Li S. (2018)	3	Ultrasonographic findings of fetal facial anomalies.
Harlequin ichthyosis – a disturbing disorder.[10]	Harish MR, Bhadbhade SP, Shashikumar BM, Deepadarshan K. (2018)	-	Various descriptions of possible alterations observed in obstetric ultrasound that contribute to diagnostic identification.
Recurrent case of a rare and devastating entity: Harlequin Ichthyosis.[11]	Alkiliç A (2019)	-	Use of 3D ultrasonography for the identification of late phenotypic expression.
Ichthyosis Prematurity Syndrome: a rare form but easily recognizable ichthyosis.[12]	Al-Khenaizan S, AlSwailem A, AlBalwi MA. (2021)	-	Identification of ichthyosis prematurity syndrome through the separation of the chorionic and amniotic membranes and polyhydramnios.
Prenatal diagnosis for restrictive dermopathy caused by novel mutations in ZMPSTE24 gene and review of clinical features and pathogenic mutations described in literatures.[13]	Wang Y, Liu C, Mai M, Ding H, Huang Y, Zhang Y, Zhao X, Du L, Xiong Y, Geng J, Yin A. (2020)	4	Ultrasonographic findings of alterations in limbs with fixed flexion and abdominal vascular alterations.

Table 1. Illustrates the main criteria used in the selected studies

Common clinical manifestations of harlequin ichthyosis include hardening of the skin's surface, which compromises the regulation of body temperature due to difficulty in water loss and increases the risk of infections. Additionally, respiratory alterations and dehydration are common.[9]

In obstetric ultrasonography, alterations such as changes in the morphology of the nasal bone or absent nose, ectropion, cleft lip, dysplastic ears, hypoplastic fingers of the hands and feet, curved toes, clenched fists, fetal growth restriction, polyhydramnios, and thick skin can be observed. Morphological ultrasonography confirms the changes found in the initial and routine obstetric ultrasound.[9,10]

In Figures 2 to 4, the following characteristics related to harlequin ichthyosis are observed: eyelid eversion, a large and open mouth, and abnormal facial features.

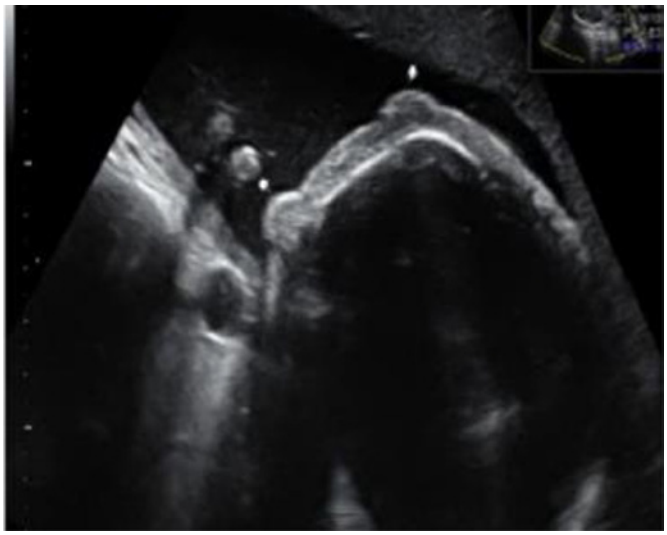

Figure 2. Two-dimensional ultrasonography – eyelid eversion of the fetus[9].

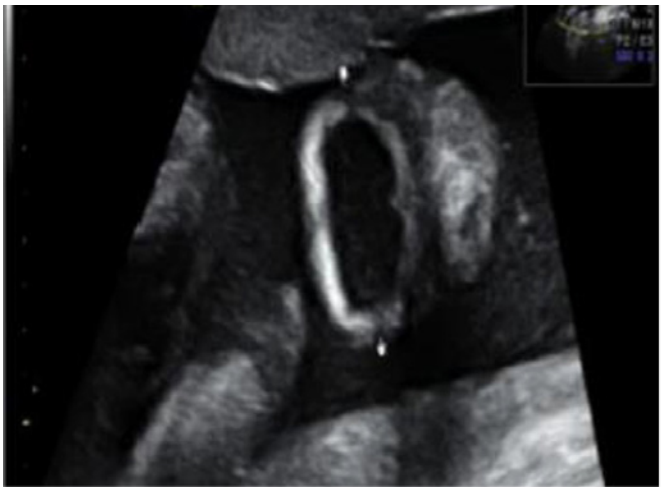

Figure 3. Two-dimensional ultrasonography – fetus with a large and open mouth[9].

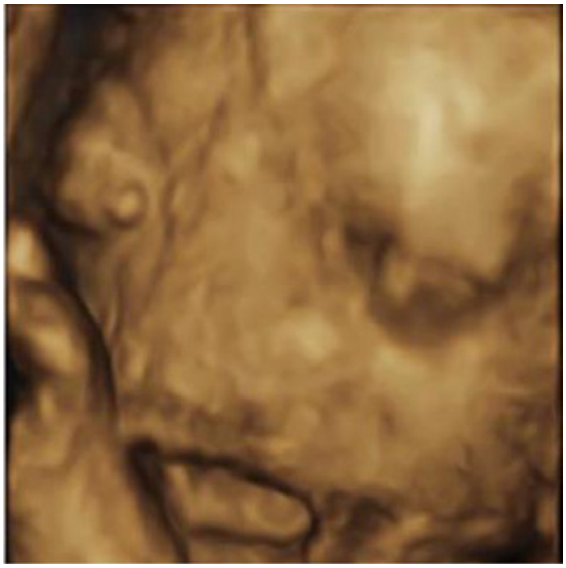

Figure 4. Three-dimensional ultrasonography – abnormal facial features [9].

Prenatal ultrasonography, especially 3D ultrasound, is a modality for prenatal diagnosis. However, despite having many distinct signs in the examination, such as short limbs, open mouth, joint contractures, edema of the hands and feet, and cloudy amniotic fluid, the late phenotypic expression of the disease poses a challenge for both timely detection and further treatment – Figure 4. [11]

In ichthyosis prematurity syndrome, another type of genodermatosis, prenatal ultrasonography may reveal separation of the chorionic and amniotic membranes and polyhydramnios with a starry sky appearance.[12]

Prenatal ultrasonography findings in restrictive dermopathy may include a fetus with asymmetric growth restriction, separation of the chorioamnionic membrane, polyhydramnios or oligohydramnios, a small continuously open round mouth, micrognathia, fixed flexion contractures of the upper limb, and varicosity of the fetal intra-abdominal umbilical vein. These findings are characterized in Figures [5-8.13]

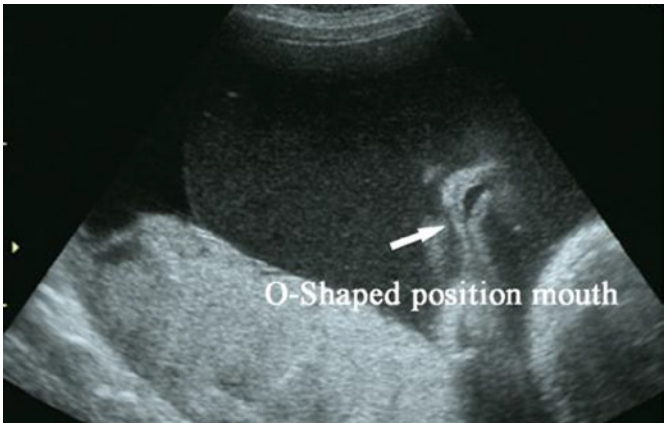

Figure 5. Ultrasound showing an open mouth in the shape of an "O". [13]

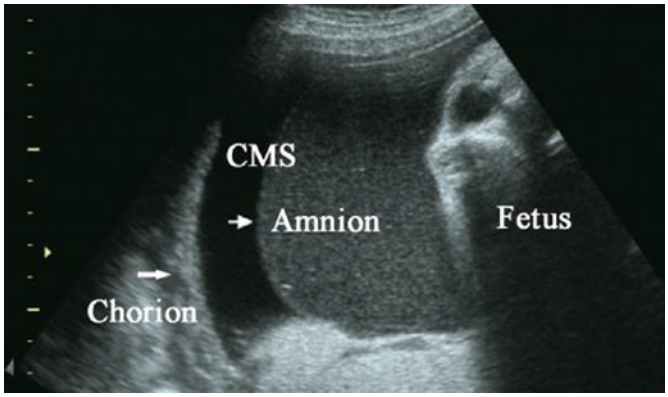

Figure 6. Ultrasound showing separation of the chorioamnionic membrane and polyhydramnios[13].

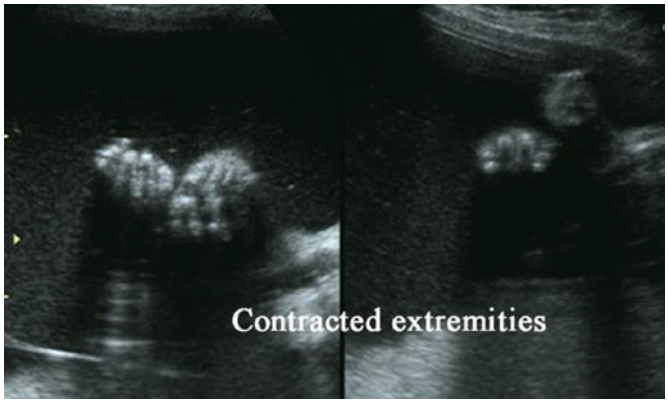

Figure 7. Ultrasound showing fixed flexion contractures of the upper limbs[13].

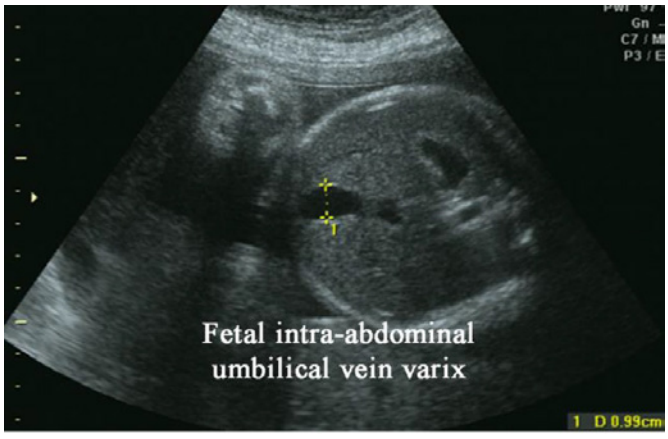

Figure 8. Ultrasound showing varicosity of the fetal intra-abdominal umbilical vein (dilation of 9.9 mm)[13].

CONCLUSION

Ichthyoses are rare genetic diseases that generally have a poor prognosis. Due to their intrauterine presentation, imaging diagnosis contributes significantly and continues to be the preferred method, offering the benefit of being non-inva-

sive and capable of detecting the disease without any family history. Therefore, it is essential for the imaging specialist to have knowledge about the pathology and, especially, about its characteristic findings identified through ultrasonography. Including the parameters of these dermatopathies in routine prenatal care is extremely important for effective screening. Consequently, due to the scarcity of studies on the subject, diagnosis often occurs late, worsening the prognosis for the fetus and increasing the family's suffering.

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