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PRENATAL SUSPICION OF SKELETAL DYSPLASIA WITH POSTNATAL MOLECULAR CONFIRMATION OF OSTEOGENESIS IMPERFECTA ASSOCIATED WITH A COL1A2 VARIANT: A CASE REPORT

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CASE REPORT

ABSTRACT

Skeletal dysplasias comprise a heterogeneous group of genetic disorders characterized by abnormalities in bone and cartilage development, with wide clinical variability in terms of severity and prognosis. Advances in obstetric ultrasonography have enabled the prenatal suspicion of these conditions during pregnancy. Among these disorders, osteogenesis imperfecta stands out as a hereditary connective tissue disease frequently associated with mutations in the genes responsible for type I collagen synthesis, particularly COL1A1 and COL1A2. This study reports a case of prenatal suspicion of non-lethal skeletal dysplasia with postnatal molecular confirmation of osteogenesis imperfecta associated with the COL1A2 gene. The patient was a primigravida without significant comorbidities who received regular prenatal care. Obstetric ultrasonographic examinations performed from the second trimester revealed marked shortening of the long bones in a micromelic pattern, bowing of the limbs, suspected intrauterine fractures, and reduced mineralization of the cranial vault. Bilateral clubfoot and fetal growth restriction were also observed, while thoracic proportions remained preserved, suggesting the absence of ultrasonographic criteria for lethality. Delivery was performed by cesarean section due to breech presentation. The newborn required resuscitation at birth and was subsequently admitted to the Neonatal Intensive Care Unit. Physical examination revealed limb shortening and dysmorphic facial features, maintaining the clinical suspicion of skeletal dysplasia. Diagnostic investigation was complemented by a next-generation sequencing panel for skeletal dysplasias, which identified a pathogenic heterozygous variant in the COL1A2 gene, confirming the diagnosis of osteogenesis

imperfecta. This case highlights the importance of detailed prenatal ultrasonographic evaluation for the early recognition of skeletal dysplasias and underscores the role of molecular testing in establishing the etiological diagnosis and guiding perinatal care planning.

Keywords: Skeletal dysplasias; Osteogenesis imperfecta; Prenatal diagnosis; Obstetric ultrasonography; COL1A2.

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1 INTRODUCTION

Skeletal dysplasias comprise a heterogeneous group of genetic disorders characterized by abnormalities in bone and cartilage development, with wide clinical variability in terms of severity, progression, and prognosis. These conditions are estimated to occur in approximately 1 in 5,000 live births and encompass more than 450 distinct entities described in the literature (MORTIER *et al*., 2019; BONAFE *et al*., 2015). With advances in obstetric ultrasonography techniques, it has become possible to identify suggestive signs of these abnormalities during the prenatal period, enabling the detection of impaired bone growth, limb shortening, altered bone mineralization, and other associated malformations (KRAKOW; LACHMAN, 2018).

Among skeletal dysplasias, osteogenesis imperfecta (OI) stands out as a hereditary connective tissue disorder primarily characterized by bone fragility and a predisposition to recurrent fractures. The condition is frequently associated with mutations in genes responsible for type I collagen synthesis, particularly COL1A1 and COL1A2, which are essential for the formation and stability of the bone matrix (FORLINO; MARINI, 2016; MARINI; FORLINO; BACHINGER, 2017; TREJO; RAUCH, 2019). The clinical manifestations of osteogenesis imperfecta vary widely, ranging from mild forms

compatible with near-normal life expectancy to severe presentations that may be lethal during the perinatal period (TREJO; RAUCH, 2019).

Prenatal suspicion of osteogenesis imperfecta is generally based on characteristic ultrasonographic findings, such as shortening of the long bones, limb bowing, reduced bone mineralization, and the presence of intrauterine fractures. However, distinguishing between lethal and non-lethal forms during pregnancy may represent a diagnostic challenge, particularly when fetal thoracic dimensions remain within normal limits (KRAKOW; LACHMAN, 2018). In this context, molecular genetic testing has emerged as an important tool for diagnostic confirmation and improved prognostic assessment (TREJO; RAUCH, 2019; MORTIER *et al*., 2019).

Therefore, the present study aims to report a case of prenatal suspicion of non-lethal skeletal dysplasia identified by obstetric ultrasonography, characterized by shortening and bowing of the long bones and reduced cranial mineralization, with postnatal diagnostic confirmation of osteogenesis imperfecta through the identification of a pathogenic heterozygous variant in the COL1A2 gene. This report highlights the importance of integrating ultrasonographic evaluation with molecular diagnostics in the management of these conditions (MORTIER *et al*., 2019).

2 CASE REPORT

A primigravida patient with no known previous comorbidities initiated regular prenatal care, totaling seven consultations during pregnancy. She denied tobacco and alcohol use, with the only complication being episodes of urinary tract infection during pregnancy, treated with antibiotic therapy. During prenatal follow-up, supplementation with folic acid, calcium, vitamin D, ferrous sulfate, and vitamin B12 was prescribed.

The date of the last menstrual period was reported as December 16, 2024, and was confirmed by obstetric ultrasonography performed on February 12, 2025, which estimated a gestational age of 7 weeks and 4 days, consistent with the menstrual dating. Maternal screening serologies for prenatal infections, including HIV, syphilis, and viral hepatitis, were negative throughout pregnancy.

The first findings suggestive of fetal abnormality were identified on obstetric

ultrasonography performed during the second trimester, when marked shortening of the long bones was observed, with measurements below the 1st percentile for gestational age. Subsequent examinations demonstrated progression of skeletal abnormalities, characterized by generalized shortening of the limbs in a micromelic pattern, associated with asymmetric bowing of the long bones, raising suspicion of intrauterine fractures (Figure 1).

In addition, decreased mineralization of the cranial vault was observed, associated with frontal bossing and compressibility of the skull on ultrasonographic evaluation (Figure 1). Bilateral clubfoot was also described, whereas other anatomical structures, including the spine, ribs, and hands, showed no evident abnormalities. Fetal thoracic proportions remained within normal limits, with no ultrasonographic evidence of a narrow thorax, a feature commonly associated with lethal skeletal dysplasias.

Fetal biometry demonstrated intrauterine growth restriction, with estimated fetal weight persistently below the 1st percentile for gestational age. Doppler velocimetry of the maternal–fetal circulation remained within normal limits throughout follow-up, while amniotic fluid volume became increased in later gestational assessments.

Based on these ultrasonographic findings, the diagnostic hypothesis of non-lethal fetal skeletal dysplasia was established, and the patient received counseling regarding the prognosis and diagnostic possibilities. Fetal karyotyping could not be performed during pregnancy due to financial limitations.

Delivery was performed by cesarean section due to breech presentation, without onset of labor. The newborn initially presented without crying, hypotonic and cyanotic, requiring neonatal resuscitation maneuvers, including positive pressure ventilation and endotracheal intubation. After initial clinical stabilization, the newborn was admitted to the Neonatal Intensive Care Unit for further management.

At birth, the newborn weighed 1,730 g, measured 35 cm in length, and had a head circumference of 34 cm, being classified as small for gestational age. Physical examination revealed dysmorphic facial features and limb shortening, maintaining the clinical suspicion of skeletal dysplasia.

During neonatal diagnostic investigation, a genetic panel for skeletal dysplasias using next-generation sequencing (NGS) was performed. The test identified a

pathogenic heterozygous variant in the COL1A2 gene (p.Gly370Val), confirming the diagnosis of osteogenesis imperfecta.

The main clinical, ultrasonographic, radiological, and genetic findings observed during the diagnostic investigation are summarized in Table 1. Figures 1 and 2 present representative imaging findings, demonstrating fetal long-bone shortening and bowing on ultrasonography, as well as skeletal abnormalities identified on postnatal radiography.

Table 1. Summary of the main clinical, ultrasonographic, and genetic findings

Moment of evaluation	Examination performed	Main findings	Clinical interpretation
Second trimester of pregnancy	Obstetric ultrasound	Significant shortening of the long bones (femurs) with micromelic pattern and curvature of the lower limbs	Findings suggestive of fetal skeletal dysplasia
Prenatal follow-up	Obstetric ultrasound	Reduced mineralization of the cranial vault, frontal bossing and suspected intrauterine fractures	Strengthens the diagnostic suspicion of osteogenesis imperfecta
Additional fetal assessment	Obstetric ultrasound	Thoracic, abdominal and head circumference ratios within normal limits	Suggests absence of pulmonary hypoplasia and lower probability of a lethal form
Immediate postnatal evaluation	Chest radiography	Structural skeletal abnormalities compatible with bone fragility	Findings consistent with congenital bone disease
Postnatal evaluation	Genetic sequencing (NGS)	Identification of a heterozygous pathogenic variant in the **COL1A2** gene, resulting in glycine-to-valine substitution at position 370 of the protein	Confirms the diagnosis of osteogenesis imperfecta

Table 1. Summary of the main clinical, ultrasonographic, radiological, and genetic findings identified during the diagnostic investigation of the reported case.

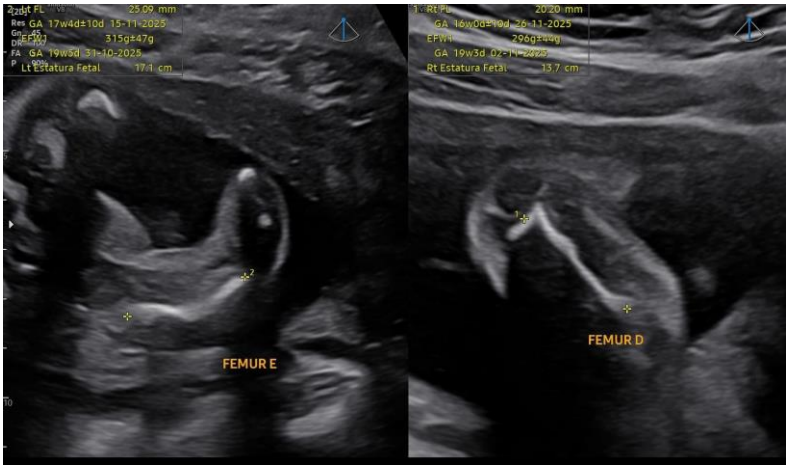

Figure 1. Obstetric ultrasonography showing shortening and bowing of the fetal long bones (femurs).

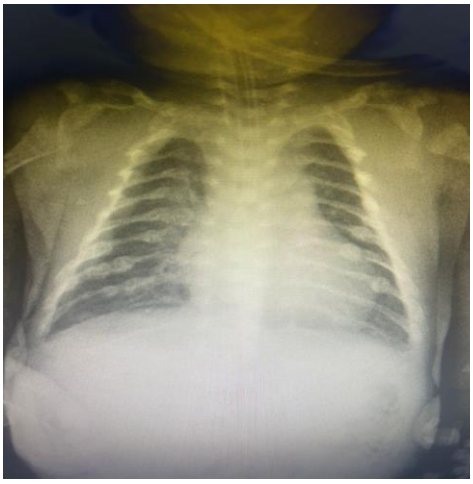

Figure 2. Postnatal radiograph showing skeletal abnormalities consistent with osteogenesis imperfecta.

These findings were crucial in supporting the diagnostic hypothesis of skeletal dysplasia during pregnancy.

3 DISCUSSION

Skeletal dysplasias comprise a broad and heterogeneous group of genetic conditions that affect bone and cartilage development, showing substantial phenotypic and prognostic variability. Although individually rare, collectively they have

an estimated incidence of approximately 1 in 5,000 live births. Prenatal diagnosis of these conditions represents an important clinical challenge, as several entities share similar ultrasonographic features, requiring careful evaluation of fetal morphological findings and, when possible, confirmation through genetic testing (MORTIER *et al*., 2019; OFFIAH *et al*., 2020).

Obstetric ultrasonography remains the primary tool for screening and raising diagnostic suspicion of skeletal dysplasias during pregnancy. The most frequently described findings include shortening of the long bones, alterations in bone mineralization, limb bowing, and the presence of intrauterine fractures (KRAKOW; LACHMAN, 2018; OFFIAH *et al*., 2020). In the present case, ultrasonographic evaluation revealed marked shortening of the long bones in a micromelic pattern, associated with asymmetric bowing of the limbs and decreased mineralization of the cranial vault, in addition to frontal bossing and suspected intrauterine fractures. These findings are considered highly suggestive of osteogenesis imperfecta, particularly when observed in combination (TREJO; RAUCH, 2019; OFFIAH *et al*., 2020).

An important aspect in the prenatal evaluation of skeletal dysplasias is distinguishing between lethal and non-lethal forms. Among the ultrasonographic criteria used for this differentiation, fetal thoracic dimensions are particularly relevant, as a narrow thorax is often associated with pulmonary hypoplasia and poor prognosis (KRAKOW; LACHMAN, 2018; MORTIER *et al*., 2019). In the present case, the relationships between thoracic, abdominal, and head circumferences remained within normal limits, suggesting the absence of significant thoracic compromise and, consequently, a lower probability of immediate lethality. This information was crucial for prenatal counseling and for planning obstetric follow-up.

Osteogenesis imperfecta is a hereditary connective tissue disorder primarily characterized by bone fragility and a predisposition to fractures. In most cases, it is associated with mutations in the COL1A1 and COL1A2 genes, which encode the chains of type I collagen, the main structural component of the bone matrix (FORLINO; MARINI, 2016; TREJO; RAUCH, 2019). Alterations in these genes can disrupt the structure of the collagen triple helix, leading to decreased bone strength and consequent skeletal fragility (MARINI; FORLINO; BACHINGER, 2017). In the present case, the diagnosis was confirmed by next-generation sequencing, which identified a

pathogenic heterozygous variant in the COL1A2 gene, resulting in the substitution of glycine by valine at position 370 of the protein, a change described as potentially disruptive to the stability of type I collagen.

Molecular confirmation of the diagnosis has become increasingly important in the management of skeletal dysplasias. In addition to enabling greater diagnostic accuracy, genetic testing contributes to family counseling, prognostic assessment, and clinical follow-up planning (MORTIER *et al*., 2019; TREJO; RAUCH, 2019). However, access to genetic testing may still be limited in many settings due to financial or structural constraints, which may hinder diagnostic investigation during pregnancy (OFFIAH *et al*., 2020). In the present case, genetic testing was only possible in the postnatal period, reflecting a situation commonly observed in several healthcare settings.

Another important aspect concerns the correlation between ultrasonographic findings and genetic results. Several studies have demonstrated that the combination of micromelic limb shortening, bone bowing, and reduced cranial mineralization constitutes a set of highly suggestive signs of osteogenesis imperfecta during prenatal evaluation (KRAKOW; LACHMAN, 2018; OFFIAH *et al*., 2020). In the present report, the simultaneous presence of these findings strengthened the diagnostic hypothesis during pregnancy, which was subsequently confirmed by molecular analysis.

Thus, this report highlights the importance of detailed ultrasonographic evaluation for the early recognition of fetal skeletal dysplasias and underscores the complementary role of molecular diagnostics in establishing the etiological diagnosis of these conditions. The integration of imaging methods and genetic investigation not only improves diagnostic accuracy but also supports prenatal counseling and appropriate perinatal management planning (MORTIER *et al*., 2019; OFFIAH *et al*., 2020).

4 CONCLUSION

This case report highlights the relevance of detailed ultrasonographic evaluation during prenatal care for the early identification of fetal skeletal dysplasias, enabling diagnostic suspicion during pregnancy and facilitating appropriate obstetric and

neonatal care planning. Findings such as micromelic shortening of the long bones, limb bowing, and decreased cranial mineralization represent important warning signs that should raise suspicion for osteogenesis imperfecta and other skeletal dysplasias.

In this context, the role of physicians working in gynecology and obstetrics is essential, from prenatal monitoring to perinatal management. These professionals are responsible not only for identifying fetal structural abnormalities but also for providing family counseling, coordinating multidisciplinary care, and planning delivery in an appropriate setting capable of providing specialized neonatal support. A careful and integrated clinical approach allows more accurate information to be offered to the pregnant woman and her family, contributing to safer clinical decision-making and improved organization of perinatal care.

Furthermore, this case underscores the importance of molecular genetic investigation as a complementary tool in the diagnostic clarification of skeletal dysplasias. The identification of a pathogenic variant in the COL1A2 gene enabled the etiological confirmation of osteogenesis imperfecta, emphasizing the value of integrating ultrasonographic findings with advanced diagnostic methods. Thus, the combination of prenatal imaging, genetic testing, and specialized clinical follow-up contributes to greater diagnostic accuracy, improved prognostic assessment, and enhanced care for pregnant women and newborns affected by fetal malformations.

REFERENCES

BONAFE, L. *et al*. Nosology and classification of genetic skeletal disorders: 2015 revision. **American Journal of Medical Genetics Part A**, Hoboken, v. 167, n. 12, p. 2869–2892, 2015. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.37365. Accessed: 10 Feb. 2026.

FORLINO, A.; MARINI, J. C. Osteogenesis imperfecta. **The Lancet**, London, v. 387, n. 10028, p. 1657–1671, 2016. Available from: https://doi.org/10.1016/S0140-6736(15)00728-X. Accessed: 10 Feb. 2026.

KRAKOW, D.; LACHMAN, R. S. Skeletal dysplasias. Genetics in Medicine, **Bethesda**, v. 20, n. 10, p. 1163–1172, 2018. Available from: https://doi.org/10.1038/gim.2018.9. Accessed: 12 Feb. 2026.

MARINI, J. C.; FORLINO, A.; BACHINGER, H. P. Osteogenesis imperfecta. **Nature Reviews Disease Primers**, London, v. 3, p. 17052, 2017. Available from: https://doi.org/10.1038/nrdp.2017.52.

Accessed: 12 Feb. 2026.

MORTIER, G. R. *et al*. Nosology and classification of genetic skeletal disorders: 2019 revision. **American Journal of Medical Genetics Part A**, Hoboken, v. 179, n. 12, p. 2393–2419, 2019. Available from: https://doi.org/10.1002/ajmg.a.61366. Accessed: 12 Feb. 2026.

OFFIAH, A. C. *et al*. Skeletal dysplasias: an overview. **Pediatric Radiology**, Berlin, v. 50, n. 12, p. 1757–1769, 2020. Available from: https://doi.org/10.1007/s00247-020-04764-7. Accessed: 14 Feb. 2026.

TREJO, P.; RAUCH, F. Osteogenesis imperfecta in children and adolescents: new developments in diagnosis and treatment. **Osteoporosis International, London**, v. 30, n. 12, p. 2313–2327, 2019. Available from: https://doi.org/10.1007/s00198-019-05178-3. Accessed: 15 Feb. 2026.