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# THANATOPHORIC DYSPLASIA: A SYSTEMATIC REVIEW WITH ILLUSTRATIVE CLINICAL CASES


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**ABSTRACT** Thanatophoric dysplasia (TD) is the most common lethal skeletal dysplasia and is invariably associated with perinatal mortality. It results from gain-of-function mutations in the fibroblast growth factor receptor 3 (FGFR3) gene, leading to severe impairment of endochondral ossification. Advances in prenatal imaging have improved antenatal detection, enabling timely counselling and informed decision-making. This systematic review summarizes current evidence on the etiology, prenatal diagnosis, clinical features, genetics, and perinatal outcomes of TD, illustrated by two clinical cases—one diagnosed postnatally and the other antenatally. The review emphasizes the importance of early diagnosis, multidisciplinary counselling, and ethical considerations in managing this uniformly lethal condition.

**KEYWORDS :** Thanatophoric dysplasia; lethal skeletal dysplasia; FGFR3 mutation; prenatal diagnosis; micromelia

## INTRODUCTION

Thanatophoric dysplasia (TD) is the most common lethal skeletal dysplasia, with an estimated incidence of approximately 1 in 20,000–50,000 live births[1,2]. The term "thanatophoric," derived from the Greek words thanatos (death) and phoros (bearing), aptly reflects the almost universally fatal outcome associated with this condition[3].

TD is characterized by profound disturbance of endochondral ossification resulting in extreme shortening of long bones, narrow thoracic cage, short ribs, relative macrocephaly, and craniofacial disproportion[4]. The condition is caused by gain-of-function mutations in the fibroblast growth factor receptor 3 (FGFR3) gene, which plays a critical role in regulating chondrocyte proliferation and differentiation during skeletal development[5,6].

Although TD follows an autosomal dominant pattern, the vast majority of cases arise due to sporadic de novo mutations, and recurrence risk in subsequent pregnancies is generally low, except in rare instances of germline mosaicism[7].

Two phenotypic subtypes are recognized. Type I TD, the more common form, is characterized by curved "telephone-receiver" shaped femurs and absence of cloverleaf skull, whereas Type II TD shows straight long bones with a characteristic cloverleaf skull deformity[8,9]. Despite these phenotypic differences, both forms are associated with uniform lethality, primarily due to severe thoracic constriction and resultant pulmonary hypoplasia[10].

With advances in antenatal imaging, prenatal diagnosis of TD has become increasingly reliable, most commonly during the second-trimester anomaly scan[11,12]. Typical sonographic features include severe micromelia, narrow thorax, relative macrocephaly, polyhydramnios, and abnormal femoral morphology[13]. Early diagnosis is crucial as it allows timely genetic counseling, informed parental decision-making, and appropriate obstetric planning[14].

Despite progress in neonatal intensive care, TD remains incompatible with long-term survival, with most affected fetuses being stillborn or dying within hours to days of birth[10,15]. Consequently, the condition presents significant clinical, ethical, and emotional challenges for both families and healthcare providers.

## MATERIAL AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

A comprehensive literature search was performed using PubMed, Scopus, and Google Scholar databases for articles published between January 2015 and December 2025. The search strategy included combinations of the keywords: thanatophoric dysplasia, lethal skeletal dysplasia, FGFR3 mutation, prenatal diagnosis, and fetal skeletal dysplasia.

Inclusion criteria were original research articles, systematic reviews, and case series, articles published in English studies focusing on prenatal diagnosis, imaging features, genetics, and perinatal outcome of thanatophoric dysplasia

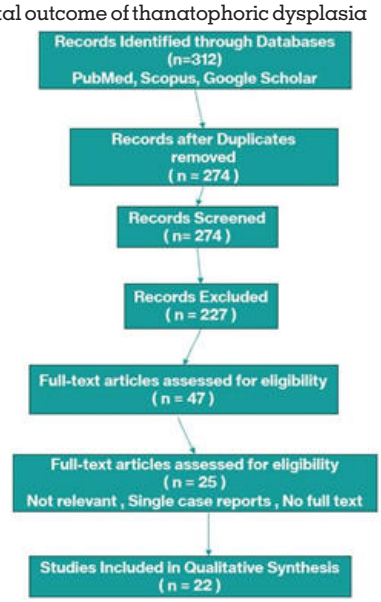


**Fig 1: The study selection process is depicted using a PRISMA 2020 flow diagram.**

Exclusion criteria were duplicate publications, isolated single case reports without review component, non-English articles and studies without accessible full text

Two reviewers independently screened titles and abstracts, followed by full-text review of eligible articles. Disagreements were resolved by consensus. The study selection process is depicted using a PRISMA 2020 flow diagram

## CASE REPORTS

### Case 1

A 23-year-old primigravida (Khushbu) presented with spontaneous preterm labor on 25/12/2023. She delivered a female neonate weighing 800 g. The neonate exhibited severe micromelia, narrow thorax, macrocephaly, and facial disproportion, consistent with a clinical diagnosis of thanatophoric dysplasia. Despite supportive neonatal care, the infant succumbed after approximately two days due to respiratory failure.

**Fig 2. Case 1: Pre term delivery of female neonate weighing 800 g.**

### Case 2

A second gravida (Nida) underwent a detailed anomaly scan at 22 weeks' gestation, which revealed severe shortening of all long bones, narrow thoracic cage, and relative macrocephaly, suggestive of TD. After counseling regarding the uniformly lethal prognosis, medical termination of pregnancy was performed. A 700 g stillborn fetus with classical features of TD was delivered on 14/11/2025.

**Fig 3. A 700 g stillborn fetus delivered by medical termination of pregnancy**

## RESULTS

The initial database search identified 312 records. After removal of duplicates and screening of titles and abstracts, 47 full-text articles were assessed for eligibility. Finally, 22 articles fulfilling the inclusion criteria were included in the qualitative synthesis.

The reviewed literature consistently confirms that thanatophoric dysplasia is a uniformly lethal skeletal dysplasia with near-100% perinatal mortality. Prenatal ultrasonography remains the primary diagnostic modality, with molecular confirmation by FGFR3 mutation analysis in selected cases. Most studies emphasize that diagnosis is usually possible in the second trimester, and in some cases as early as the late first trimester.

Across studies, the most consistent prenatal features were severe micromelia, narrow thoracic cage, relative macrocephaly, shortened ribs, and abnormal femoral morphology. Early antenatal diagnosis was shown to significantly influence parental counseling, decision-making regarding continuation of pregnancy, and obstetric management.

## DISCUSSION

Thanatophoric dysplasia represents one of the most devastating fetal skeletal disorders because of its uniformly fatal prognosis and absence of any curative therapy. The two cases presented in this review illustrate the contrasting clinical scenarios encountered in practice — one diagnosed postnatally and the other identified antenatally.

In the first case, diagnosis was established only after preterm delivery, resulting in a brief period of neonatal survival under supportive care. This highlights the consequences of missed or delayed antenatal diagnosis, which may occur due to late antenatal booking, inadequate anomaly scanning, or limited access to advanced imaging facilities[1]. Such situations deprive parents of anticipatory counseling and often result in unexpected neonatal loss with profound psychological impact.

In contrast, the second case demonstrates the benefits of timely antenatal diagnosis, allowing informed parental decision-making and planned medical termination of pregnancy. Several studies emphasize that early recognition of lethal skeletal dysplasias helps families avoid the emotional trauma associated with carrying a non-viable fetus to term and witnessing inevitable neonatal demise[1],[1].

Diagnosis of TD relies primarily on characteristic ultrasonographic features, particularly severe micromelia and markedly narrow thoracic cage[11,13]. Adjunctive modalities such as three-dimensional ultrasonography, fetal CT, or fetal MRI may aid in equivocal cases or in differentiating TD from other lethal skeletal dysplasias[12],[1]. Molecular confirmation through FGFR3 mutation analysis provides diagnostic certainty and allows accurate counseling regarding recurrence risk[],[1].

The lethality of TD is mainly attributable to pulmonary hypoplasia secondary to thoracic constriction, sometimes compounded by brainstem compression in cases with severe cranial abnormalities[1],[1]. Although rare long-term survivors have been reported with aggressive ventilatory support, these cases are exceptional and associated with severe morbidity[],[2].

From an obstetric perspective, early diagnosis permits individualized care planning, including counseling regarding prognosis, mode of delivery, and neonatal resuscitation preferences. Cesarean delivery is generally not indicated for fetal benefit, as it does not improve neonatal outcome and only increases maternal morbidity[1],[21].

## CONCLUSION

Thanatophoric dysplasia is a rare but uniformly lethal skeletal dysplasia. Early antenatal diagnosis through meticulous ultrasonography, supported by genetic testing where feasible, is essential for appropriate counseling and management. The presented cases emphasize the importance of timely

diagnosis and multidisciplinary care in addressing the complex clinical and ethical challenges associated with this condition.

### Ethical approval

Ethical approval was obtained from the Institutional Ethics Committee. The study was conducted in accordance with the ethical standards of the responsible committee and with the principles of the Declaration of Helsinki.

### Consent

Written informed consent was obtained from the patients for publication of anonymized clinical information and images. Patient identity has been adequately anonymized, and no identifying details are disclosed in this manuscript.

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### Conflict of interest

The authors declare no conflict of interest.

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