

## Case Report

## Thanatophoric Skeletal Dysplasia Type 2: Diagnostic and Management Dilemmas

### *Displasia Skeletal Tanatoforik Type 2: Dilema dalam Diagnosis dan Manajemen*

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#### Abstract

**Objective:** To report a rare case of thanatophoric skeletal dysplasia type 2 that we diagnosed during prenatal period; and to provide further review of dilemmas in diagnostic methods and management, based on appropriate literatures and guidelines available.

**Methods:** Case report

**Case:** A 33-year old primigravida women was diagnosed with pre-term pregnancy (24th weeks of gestation) and intra-uterine singleton live fetus with thanatophoric skeletal dysplasia type 2 via ultrasonography. Pregnancy termination via elected caesarean section at 26th weeks of gestation was performed per the patient request after considering the fetus's lethality. A female neonate was born weighing 980 grams with frontal bossing (Head Circumference: 26 cm), lower set of ears, hypertelorism, bilateral exophthalmos, short neck, rhizomelic short extremities, and narrow thorax (Thorax Circumference: 17 cm). The newborn was immediately transferred to NICU for post-natal management and observation. The newborn is in stable condition for the first several hours; nevertheless, significant destabilization occurred afterwards and the newborn deceased approximately 10 hours after birth due to cardiorespiratory failure. No further invasive resuscitative efforts and post-mortem examinations were performed on the parent's request.

**Conclusion:** Thanatophoric dysplasia is primarily diagnosed using ultrasonography, which has a high detection rate for both diagnosis and prognostications. Even though, There has been a dilemma in performing molecular diagnostic testing, prediction of recurrence risk in future pregnancies can be assessed with its use. Although still remains a challenge in ethical and medicolegal grounds; proper management requires holistic considerations of maternal, fetal, and perinatal aspects.

**Keywords:** Thanatophoric, Skeletal Dysplasia, FGFR3 mutation.

#### Abstrak

**Tujuan:** Melaporkan suatu kasus langka displasia skeletal tanatoforik tipe 2 yang kami diagnosa dalam periode perinatal; serta memberikan ulasan lanjut mengenai dilema dalam metode diagnostik dan manajemen, berdasarkan literatur dan pedoman ilmiah yang tersedia.

**Metode:** Laporan Kasus.

**Kasus:** Seorang perempuan primigravida berusia 33 tahun di diagnosa dengan kehamilan pre-term (24 minggu gestasi), janin tunggal hidup intrauterin dengan displasia skeletal tanatoforik tipe 2 via ultrasonografi. Terminasi kehamilan dengan Sectio Caesarea dilakukan atas permintaan pasien setelah mempertimbangkan letalitas janin. Lahir bayi perempuan berat 980 gram, dengan 'frontal bossing' (lingkar kepala: 26 cm), kedua telinga rendah, hipertelorisme, eksoftalmos bilateral, leher pendek, ekstremitas pendek rizomelik, dan rongga dada kecil (lingkar dada: 17 cm). Bayi segera dipindahkan ke NICU untuk manajemen paska-natal dan observasi. Kondisi bayi stabil selama beberapa jam pertama; namun, ketidakstabilan yang signifikan terjadi setelah itu dan bayi dinyatakan meninggal 10 jam paska kelahiran dikarenakan kegagalan kardiorespirasi. Bayi tidak dilakukan tindakan resusitasi invasif dan pemeriksaan paska kematian atas permintaan pasien.

**Kesimpulan:** Displasia tanatoforik dapat di diagnosa secara primer menggunakan pemeriksaan ultrasonografi (US) dengan tingkat deteksi diagnosis dan prognosis yang tinggi. Meskipun pemeriksaan diagnostik molekular masih menjadi dilema, pemeriksaan ini dapat memprediksi resiko rekurensi pada kehamilan selanjutnya. Walaupun masih merupakan suatu tantangan dalam segi etika dan medikolegal; manajemen ideal perlu mempertimbangkan secara holistik seluruh aspek yang mencakup: ibu, janin, dan paska kelahiran.

**Kata kunci:** Tanatoforik, Displasia Skeletal, Mutasi FGFR3.

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Received: July, 2021 Accepted: December, 2022 Published: January, 2023

## INTRODUCTION

Thanatophoric Skeletal Dysplasia (TD) is a type of lethal skeletal dysplasia disorders, which typically involves underdeveloped formation and growth of long bones; and limitation in lung growth.<sup>1</sup> The term first described by Maroteaux et al. 1967, based on the Greek term 'thanatophoric' or 'deathbringing'.<sup>2</sup> TD is considered as a rare disorder with an overall incidence of 1 in 20,000 to 1 in 60,000 births; however, it is also considered as the most common lethal skeletal dysplasia, contributing to approximately 29% of all lethal skeletal dysplasia cases.<sup>3</sup> The incidence of TD varies between congenital autosomal dominant inheritance (20% cases) and sporadic incidence (80% cases); both involve mutations in fibroblast growth factor receptor gene 3 (FGFR3). This further classifies TD into two distinct types: the more common variant of TD type 1, which is usually caused by missense, no-stop codon, or insertion variant mutations; and the less common variant of TD type 2, which is usually caused by single pathogenic variant mutation.<sup>4,5</sup> Although it is considered rare, dilemmas arise in determining proper diagnostic methods and managements. Since early prenatal recognition of the disorder will promote proper management planning; therefore we considered discussions regarding this matter necessary to raise awareness of medical personnel specifically working in the field of obstetrics and gynecology. In this paper, we reported a case of pre-term fetus with prenatal sonographic findings consistent with TD type 2 in our obstetrics and gynecology out patient department.

## CASE REPORT

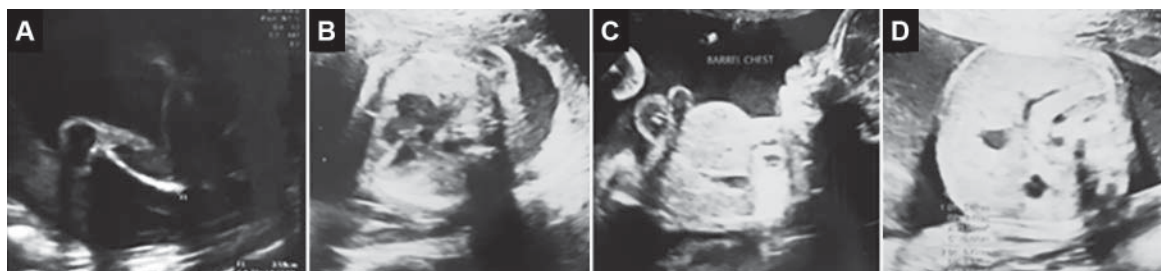
A 33-year old primigravida women (G1A0) on her 24<sup>th</sup> week of gestation visited our out patient department for a follow up prenatal check-up. The patient had five consecutive previous prenatal check-ups performed once each month in our clinic. The first and latest prenatal check-ups were performed on her 6<sup>th</sup> and 19<sup>th</sup> week of gestations respectively with no major fetal anatomic abnormalities discovered during previous visitations. Previous laboratory examinations; which include routine blood examination, urine dipstick, hepatitis B surface antigen (HbsAg), anti-syphilis (VDRL) and anti-HIV; were within normal limits. She recalled having tetanus toxoid injection once during her first prenatal check-up

visit. The patient had routinely consumed folic acid and ferrous sulfate medications; and no other medications are consumed or used. The patient has been married for a year; she was a non-smoker, non-alcoholic, and has no history of drug abuse. She has neither personal nor family history of congenital abnormalities, diabetes, hypertension, and other diseases.

General physical, vital signs, and obstetrics examinations of the patient were unremarkable. Transabdominal 2D ultrasonography with real time 4D rendering performed by a maternal-fetal specialist; revealed a singleton intrauterine pregnancy with fetal heart rate of 135 beats per minute (M-Mode) and fetal movement was unremarkable. Fetal biometry was equivalent to 24<sup>+5</sup> weeks of gestation with EFW of 766 +/- 112 grams. Neurological cranial sonography revealed megalencephaly (BPD: 79.4 mm and HC: 262.3 mm) with the appearance of cloverleaf skull, enlarged temporal lobe, hypertelorism, and slight low nasal bridge [Figure 1]. Short extremities with rhizomelic pattern were also observed (FL: 35.9 mm). Thoracic sonography revealed visible small narrow bell/barrel shaped chest cavity (TC: 164.7 mm, AC: 211.1 mm, TC/AC: 0.78, FL/AC: 0.17) with heart to chest diameter > 0.5, which further signified pulmonary hypoplasia [Figure 2]. Normal placental structure was observed along the anterior wall of the uterus with no polyhydramnios (AFI: 146 mm). In general, sonographic impressions was suggestive of thanatophoric skeletal dysplasia type 2.



**Figure 1.** (A) 2D Transabdominal Ultrasound of fetal head (Axial View) at 24<sup>+5</sup> weeks' gestation revealed megalencephaly and temporal lobe enlargement (BPD: 79.4 mm and HC: 262.3 mm, both values > 97.5th percentile of Hadlock Standard) with cloverleaf skull, (B) 4D Real Time Sonographic Rendering (from Mid-Sagittal View) revealed frontal bossing (white asterisk), hypertelorism and slight low nasal bridge (blue triangle).



**Figure 2.** (A) 2D Transabdominal Ultrasound revealed short extremities with rhizomelic pattern (FL: 35.9 mm, < 2.5<sup>th</sup> percentile of Hadlock Standard), (B) (C) Thorax at the level of four chamber view (Axial View) and (Mid-Sagittal View) respectively revealed small narrow bell/barrel chest cavity (TC: 164.7 mm, which is slightly < 50<sup>th</sup> percentile and visible heart:thorax > 0.5) which signifies pulmonary hypoplasia, (D) Abdominal Circumference (AC) measured: 211.1 mm (< 50<sup>th</sup> percentile of Hadlock Standard); hence, calculated TC:AC of 0.78 (< 0.8) and FL:AC of 0.17 (close to < 0.16) which also signifies pulmonary hypoplasia.

The case was considered lethal for the fetus; henceforth, termination of pregnancy was advised after further consultation with a maternal-fetal specialist, in which the patient agreed. The labor was then terminated via lower uterine segment caesarean section at the gestational age of 26th weeks on behalf of the patient's request. The patient's pre-operative blood examination revealed B positive blood group with blood count and infection marker results confirmed uneventful. The perinatology department was informed about the situation and parents were given proper counselling regarding the child's poor prognosis and potential post-natal management. The newborn was a 980 grams female. Head examination revealed frontal bossing (head circumference: 26 cm), lower set of ears, hypertelorism, bilateral exophthalmos, and short neck. Upper and lower extremities examination revealed visibly slight short proximal extremities (rhizomelia). Chest examination revealed slightly narrow thorax (thorax circumference: 17 cm) [Figure 3]. Placenta and umbilical cord appearances were normal. Post-operative course of the mother was uneventful.



**Figure 3.** General appearance of the newborn revealed frontal bossing, lower set of ears, hypertelorism, bilateral exophthalmos, short neck and slight short proximal extremities.

The newborn was immediately transferred to the neonatal intensive care unit (NICU) for further monitoring due to suspected lethality of the skeletal dysplasia with mild asphyxia and respiratory distress after birth (APGAR score: 7/8). At birth, the newborn was peripherally cyanotic, heart rate and respiratory rate above 100 bpm and 60 bpm respectively, cry when stimulated with flexed arms and legs; however, the condition improved after proper neonatal management was given. The newborn was given oxygen supplementation via nasal cannule with 1L/minute flow rate, and oral-gastric tube (OGT) was also installed to reduce the risk of aspiration. The newborn's condition remained stable for the first seven hours after birth; nevertheless, significant reduction in heart rate, respiratory rate and oxygen saturation occurred simultaneously afterwards. Despite the best efforts provided by the perinatology team to re-stabilize the condition, the newborn continually worsened; and unfortunately deceased approximately 10 hours after birth due to cardiorespiratory failure. No further invasive resuscitative efforts and post-mortem examinations were performed on the parent's request.

## DISCUSSION

Thanatophoric skeletal dysplasia (TD) is a part of lethal skeletal dysplasia cluster of conditions typically involving abnormal bone formation and growth in long bones of the extremities and the ribs, which consequently lead to limitation in lung growth contributing to its lethality.<sup>1</sup> The term first described by Maroteaux et al. 1967, based on the Greek term '*thanatophoric*' or 'deathbringing', which emphasizes the high mortality of such affected infants within the first few hours after birth.<sup>2</sup> The most recent nosology and classification of genetic skeletal disorders

9<sup>th</sup> ed. 2015 classified skeletal dysplasia into 436 disorders divided into 42 distinct groups with a total number of 364 genes involved.<sup>6</sup> The overall prevalence of skeletal dysplasia is approximately 3 in 10,000 births, in which approximately half is considered lethal; and contributed to approximately 9 in 1,000 cases of perinatal deaths, in which 23% are stillbirths and 32% do not survive within the first week of life. TD is considered as the most common lethal skeletal dysplasia, contributing to approximately 29% of all lethal cases (1 in 20,000 to 1 in 60,000 births).<sup>1-3</sup> There has been three cases reported in Indonesia.<sup>2,7,8</sup>

The etiopathology of TD varies between congenital autosomal dominant inheritance in minority of cases and sporadically 'de novo' new mutations in majority of cases; both involve mutations in fibroblast growth factor receptor gene 3 (FGFR3). This further classifies TD into two distinct types: (1) Type 1 (80% of cases), the more common variant of TD usually caused by missense, no-stop codon, or insertion variant mutations of R248C and Y373C in FGFR3 gene; and (2) Type 2 (20% of cases), the less common variant of TD usually caused by single pathogenic variant mutation of K650E in FGFR3 gene.<sup>4,5</sup>

### **Diagnostic Dilemma**

The diagnosis of TD can be established by initial prenatal evaluation using ultrasonography (US) and/or molecular diagnostic testing; and postnatal/termination evaluation. Prenatal diagnosis of TD with ultrasonography (US) is considered as the primary method of evaluation in order to narrow the differential diagnosis of skeletal dysplasia, hence specific confirmatory molecular testing can be performed afterwards; and to predict lethality, which affects management planning. Sonographic impressions of TD varies between short extremities seen as mild straight rhizomelic (proximal) with flared metaphyses and cloverleaf skull seen in TD type 2; and severe micromelic (proximal and distal) with bowed 'telephone receiver' shaped proximal bones of extremities with frontal bossing, midface hypoplasia and no cloverleaf head deformity seen in TD type 1.<sup>4,9</sup>

Fetal head and spine are both compulsory anatomic regions to be screened in a routine sonographic examination; therefore, craniofacial and neurological anomalies, which is commonly associated with skeletal dysplasia, can be

included or excluded. Fetal head sonographic examination of patients with TD Type 2 in axial plane view may typically revealed cloverleaf skull, which is due to premature closure of the coronal and lambdoid sutures, accompanied with megalencephaly (abnormally enlarged brain) and enlarged temporal lobes. Our case presented impressions of cloverleaf skull accompanied with megalencephaly and temporal lobe enlargement, shown by measured biparietal diameter (BPD) of 79.4 mm and head circumference (HC) of 262.3 mm, in which both values > 97.5<sup>th</sup> percentile according to Hadlock Standard. Mid-sagittal plane view with real time 4D rendering may revealed frontal bossing, hypertelorism, and slightly low nasal bridge suggestive of midface hypoplasia, just as presented in our case **[Figure 1]**.<sup>4,9</sup>

The fetal femur is one of the proximal long bones routinely examined during the second trimester sonographic evaluation; severe short femur below the 5<sup>th</sup> percentile or two standard deviation for the gestational age is typically a defining characteristic of skeletal dysplasia specifically in TD; our case presented a straight rhizomelic short extremities with average bilateral femur length (FL) of 35.9 mm, which is below 2.5<sup>th</sup> percentile for the gestational age according to Hadlock standard **[Figure 2]**. Severe short femur warrants complete examination of all the long bones of extremities, ribs and vertebrae; not only to confirm the diagnosis of TD, but also to exclude other differential diagnosis such as: homozygous achondroplasia (typically characterized by 'trident hand' formation and both parents are typically affected), and asphyxiating thoracic dysplasia ('Jeune Syndrome', typically characterized by polydactyly, slightly short extremities and normal vertebrae).<sup>4,9</sup> Mild short femur above 5<sup>th</sup> percentile for gestational age otherwise requires serial examinations in order to exclude non-skeletal dysplasia conditions such as: false measurements, constitutional short extremities, fetal growth restrictions (FGR), or aneuploidy (Trisomy 21 or Down Syndrome).<sup>10</sup>

Lethality prediction in skeletal dysplasia with ultrasonography is considered a crucial step in prenatal diagnosis, since half of skeletal dysplasia is considered lethal, which therefore affects prognosis and post-partum management in planning necessary airway and ventilation support for the newborn.<sup>3</sup> This highlights one important aspect of skeletal dysplasia, in which management requires multi-disciplinary



collaborations between obstetrician, geneticist, perinatologists, paramedics and other medical fields necessary. Skeletal dysplasia lethality is attributed to pulmonary hypoplasia with several sonographic parameters, which includes: (1) thoracic circumference/TC at the level of four chamber heart view measured < 2.5th percentile for the gestational age<sup>11</sup>, (2) thoracic to abdominal circumference ratio (TC:AC) < 0.8<sup>11</sup>, (3) heart to chest circumference ratio > 0.5<sup>11</sup>, (4) small bell/barrel shaped chest cavity<sup>4,11</sup>, and (5) femur length to abdominal circumference ratio (FL:AC) < 0.16, especially in the presence of polyhydramnios.<sup>12</sup>

Our case presented a fetus with sonographic measured thoracic circumference (TC) of 164.7 mm, this parameter may not be significant since its slightly below the 50<sup>th</sup> percentile for the gestational age according to Lian et al. 2021 chart.<sup>11,13</sup> However, our case also displayed other parameters of pulmonary hypoplasia; such as TC:AC of 0.78 (< 0.8 cut-off mentioned) and FL:AC of 0.17 without the presence of polyhydramnios (close to the 0.16 cut-off mentioned with amniotic fluid index/AFI of 146 mm, which is still within normal limits of 5 - 250 mm), while taking into account the measured AC of 211.1 mm (below 50th percentile for gestational age according to Hadlock standard).<sup>11,12</sup> Other parameters which support the lethal characteristic of our skeletal dysplasia case include visible heart to chest circumference ratio > 0.5 and small narrow bell/barrel shaped chest [Figure 2]. All sonographic impressions acquired from our case is suggestive of thanatophoric skeletal dysplasia type 2, which is considered lethal with poor prognosis.<sup>4,11</sup>

Molecular diagnostic testing and referral for genetic counseling in order to confirm specific skeletal dysplasia and predict prognostications, has been a dilemma in patients with an ongoing pregnancy affected with a 'de novo' (sporadic) skeletal dysplasia disorder, and in patients with prior pregnancy affected with a new dominant skeletal dysplasia disorder. This in part due to the fact that: (1) DNA analysis can be a lengthy process; (2) a failure or negative result to identify a specific mutation doesn't change prognostications based on sonographic findings; (3) mutations in the same gene can cause different forms of skeletal dysplasia and the opposite applied and (4) high cost for examination. Likewise, most common methods used to obtain fetal DNA for sampling are considered invasive and highly associated with miscarriage, such methods include: chorionic

villus sampling (CVS) performed transcervical (11<sup>th</sup> -14<sup>th</sup> weeks of gestation) or transabdominal (after 11<sup>th</sup> weeks of gestation), and amniocentesis performed transabdominally (after 15<sup>th</sup> weeks of gestation); however, circulating cell-free DNA (CF-DNA) in maternal blood has recently been developed as a non-invasive fetal DNA sampling method. Prenatal diagnosis of skeletal dysplasia with ultrasonography (US) has a high detection rate; nevertheless, molecular diagnostic testing in affected fetus with parental history of skeletal dysplasia is proven useful for determining prenatal or preimplantation risk of recurrence and lethality in future pregnancies rather than for prognostication in current affected pregnancy.<sup>14</sup>

Fetal DNA sample is compared with both parental leucocyte DNA samples. In TD cases, if mutated FGFR3 pathogenic variant can be detected in fetal DNA sample but not in parental leucocyte DNA samples, then the occurrence is more likely to be 'de novo' or inherited from parents with somatic and/or germline mosaicism; risk of recurrence in 'de novo' cases are presumably low, but slightly higher than in general population due to possibilities of parental mosaicism. The fetus described in our case is suspected as an example of 'de novo' thanatophoric skeletal dysplasia (TD) type 2, since both parents has recalled no history of congenital anatomic anomalies and sporadic TD accounts for majority of all cases as previously mentioned. Nonetheless, due to cost-effectivity measures with assumed high lethality within the first few hours of life and presumably low risk of recurrence in future pregnancies; after further discussion with the patients, they decided to postpone molecular diagnostic testing for the next pregnancies to come.<sup>3,4</sup>

### Management Dilemma

After lethal skeletal dysplasia specifically TD type 2 is diagnosed and prognosis is predicted, management planning is the next fundamental step. Effective doctor-patient communication must be maintained in order to communicate the difficult news, expressing empathy and give mental support. All necessary information concerning the diagnosis, prognosis, pregnancy management and postnatal management should be explained in a simple language; hence the parents can make informed decision. The recently published practice consensus of diagnosis and delivery of skeletal dysplasia published by Savarirayan et al. 2018 in American

Journal of Obstetrics and Gynecology (AJOG), summarizes management planning into three tiers: (1) Maternal: assessment for cephalopelvic disproportion and/or preterm labor risk and polyhydramnios in order to plan mode of delivery; (2) Fetal: serial assessment of malpresentation, lung volume, and/or fetal stress testing for termination consideration if necessary; and (3) Perinatal: establishment of intensive postnatal care, clinical and radiographic assessment, and post-mortem evaluation in terminated pregnancy. The consensus also recommends for referral to centers with appropriate facilities and maternal-fetal medicine specialists for diagnosis confirmation, further management and advice; if prenatal diagnosis of TD is suspected.<sup>15</sup>

One persistent challenge in management of pregnancy with lethal fetus based on both ethical and medicolegal ground is pregnancy termination consideration. Indonesian Society of Obstetrics and Gynecology (POGI)'s Good Practice Guideline, which has been cemented by Indonesian presidential decree (*Peraturan Pemerintah no. 61, tahun 2014*); settled that pregnancy termination with medical indication (therapeutic abortion) can be performed through proper counselling and informed consent of the patient. Medical indications, which includes both fetal (lethal congenital anomalies) and maternal life-threatening indications; must be re-evaluated by a medical committee of at least two experts.<sup>16,17</sup> What remains a challenging dilemma is to decide the best period for pregnancy termination, since there is not a single recommended or agreed time frame between different practitioners and the decision is mostly dependent on the patient. A few studies have proven that approximately 90% of practitioners agreed to discuss or offer late termination of pregnancy (after 21<sup>+6</sup> weeks of gestation) for the patient, in contrast to approximately 70% of practitioners who agreed to discuss delivery near term or when spontaneous labor or maternal compromise arises; patient's judgement remains a major factor in final decision making in medically legal abortion countries.<sup>18,19</sup> Patient's mindset in culture, religion, and past personal experiences affected their decision making.<sup>20</sup>

In our case, the patient had been referred to the maternal-fetal specialist and multidisciplinary discussion with the patient was conducted; pregnancy termination was considered and offered to the patient due to the fetus's lethality and presumed low survivability, the patient

agreed and requested for the termination to be conducted via caesarean section. The newborn was immediately monitored in neonatal intensive unit with stabilized condition for several hours; the condition suddenly worsened afterwards and deceased shortly afterwards due to cardiorespiratory failure.<sup>15</sup>

## CONCLUSION

Thanatophoric skeletal dysplasia (TD) is a disorder involving abnormal bone formation and growth in long bones with lung growth limitation, which is considered lethal. TD cases are considered rare with overall incidence of 1 in 20,000 to 1 in 50,000 births, however, it is considered as the most common lethal skeletal dysplasia contributing to approximately 29% of all lethal cases. Most fetus with TD do not survive in utero and in some cases do not survive the first week of life. The etiopathology of TD varies between sporadic in most cases and congenital, which further classified into two types. The prenatal diagnosis of TD is primarily established using ultrasonography (US), which has a high detection rate for both diagnosis and prognostications. Even though, There has been a dilemma in performing molecular diagnostic testing, prediction of recurrence risk in future pregnancies can be assessed with its use. Although still remains a challenge in ethical and medicolegal grounds; proper management requires holistic considerations of maternal, fetal, and perinatal aspects.

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