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Short Communication

Can biparietal diameter-to-femur length ratio be a useful sonographic marker for screening thanatophoric dysplasia since the first trimester? A literature review of case reports and a retrospective study based on 10,293 routine fetal biometry measurements

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ABSTRACT

Objective: The aim of the study was to determine whether the biparietal diameter/femur length (BPD/FL) ratio can be used to detect thanatophoric dysplasia in the first trimester of pregnancy.
Materials and Methods: Twenty-four reported cases of thanatophoric dysplasia diagnosed based on ultrasonographic results with molecular or radiographic diagnosis were included. All sonographic measurement records were extracted and reviewed, and the BPD/FL ratio was calculated for each gestational week. In addition, 10,293 routine fetal biometry measurements from 1395 cases of patients without skeletal dysplasia were compared.
Results: The BPD/FL ratio in the control group decreased to less than 3 prior to gestational week 13, and to less than 2 prior to week 18. Of the 27 BPD/FL ratios obtained from 24 cases of thanatophoric dysplasia, none was in the control range.
Conclusion: The BPD/FL ratio may be used to detect lethal skeletal dysplasias such as thanatophoric dysplasia since the first trimester.

Introduction

Thanatophoric dysplasia (TD) is the most common neonatal lethal skeletal dysplasia [1]. Clinically, it is primarily characterized by remarkable shortening of limbs, narrow thorax, and macrocephaly. Pulmonary hypoplasia, secondary to fetal thoracic deformities, may result in severe respiratory insufficiency at birth. However, perinatal treatment remains very difficult. Consequently, early prenatal diagnosis is important because patients may choose termination if legal permission is limited by gestational weeks, or may choose not to undergo cesarean delivery of a fetus that will not survive. With advances in ultrasound technology, it is no longer difficult to observe details of fetal development in the first trimester such as sex [2], facial bones [3], and placental function [4]. However, TD is very rare, with prevalence as low as 1–6 per 100,000 [1]; only few were found in the first trimester in the reported cases. Therefore, establishing an easy early-screening method for less-experienced obstetricians remains a challenge. In general, shortened femurs on routine ultrasonography indicate skeletal dysplasia, and the prenatal sonographic detection rate for all cases is as high as 98.8% across all gestational ages [5]; however, lethal skeletal dysplasia is not distinguishable until the late second trimester or later [6,7]. Even if a short femoral bone is suspected on ultrasonography in the first or early second trimester, using a single ultrasound finding of short limbs to determine lethality might be unreliable because the accuracy of a single parameter may be affected by an incorrect estimated date of confinement. Therefore, combination with an additional fetal biometric parameter with minimal individual variation such as the biparietal diameter is considered necessary.

The aim of the present study was to determine whether the biparietal diameter/femur length ratio (BPD/FL) can be used to

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screen for lethal skeletal dysplasias such as thanatophoric dysplasia since the first trimester.

Methods

This study was approved by both, the Ethics Committees of the Center for Maternal, Fetal and Neonatal Medicine, Saitama Medical University, Saitama Medical Center (SMUSMC), and the Ethics Committees of Jichi Medical University, Saitama Medical Center (JMUSMC). The need for informed consent was waived, as only retrospective review of medical records was performed.

We included all reported cases of TD with details of fetal ultrasound biometry that were confirmed with molecular analysis or postpartum radiology. The PubMed database was searched using the terms "thanatophoric dysplasia," "first trimester," "prenatal diagnosis," and "molecular diagnosis."

For comparison, fetal biometry records of controls without skeletal dysplasia evaluated at JMUSMC during 2009–2013 were examined. All fetal biometry measurement was performed by abdominal (Voluson E8; GE Healthcare, Zipf, Austria) or vaginal (SONOVISTA FX; Siemens Healthcare, Korea) ultrasound. All fetal ultrasonography measurement records were extracted from an electronic database, and outlier data due to entry errors were excluded; the maximum, minimum, median, and standard difference of the BPD/FL ratios at each gestational week were calculated.

Results

Twenty-four cases of TD with details of prenatal sonographic and molecular diagnosis were extracted from a PubMed database search. The prenatal fetal biometry measurements and ultrasound findings of 24 cases are listed in Table 1. The median BPD/FL ratio of 27 records extracted from the 24 cases was 3.38 (range: 2.00–4.49). At JMUSMC, 10,293 routine fetal biometry measurements from 1395 cases without skeletal dysplasia were extracted, and 124 patients with recorded outliers due to entry errors were excluded. The median and range of BPD/FL ratios at weeks 12, 13, and 14 were 2.82 (1.89–4.06), 2.26 (1.68–2.87), and 2.05 (1.55–2.59), respectively; those at weeks 17, 18 and 19 were 1.70 (1.39–2.06), 1.65 (1.37–1.98) and 1.57 (1.30–1.87), respectively (Table 2). For all gestational ages, the BPD/FL ratio showed a continuous absolute decrease as a function of gestational weeks, with a rapid decrease during weeks 12–19. From weeks 20 to 36, the median of the BPD/FL ratio decreased slowly from 1.52 to 1.35, with a convergent range of 1.19–1.53 at week 36 (Table 2). Of 27 BPD/FL ratios obtained at each gestational week from 24 cases, none was in the control range (Fig. 1).

Discussion

In a normal pregnancy, the BPD/FL ratio shows a continuous absolute decrease as a function of gestational weeks, with a rapid decrease during weeks 12–18. The BPD/FL ratio decreases to less than 3 prior to gestational week 13, and to less than 2 prior to week 18. Therefore, we assume that by using the routine fetal biometry measurement, an extreme outlier such as TD can be easily detected from as early as the first trimester.

Three decades ago, the use of the BPD/FL ratio to detect trisomy 21 had been considered, but studies concluded that its usefulness was limited due to insignificant differences before 18 weeks [23,24]. The usefulness of measuring fetal nuchal

Table 1
The characteristics of fetal biometry and other clinical findings in thanatophoric dysplasia.

Case	Authors	Maternal age	Gestational week	BPD (mm)	FL (mm)	BPD/FL	Diagnosis	Molecular analyses	Radiological diagnosis
1	Sawai [8]	33	27	83.7	20.9	4.00	TD1	+	+
2	Chen [9]	28	27	82.0	19.8	4.14	TD1	+	+
3	Chen [9]	28	31	92.0	21.1	4.36	TD1	+	+
4	Chen [9]	30	18	45.4	12.9	3.52	TD1	+	+
5	Chen [9]	30	24	80.0	19.7	4.06	TD2	+	+
6	Hatzaki [10]	28	18	47.0	17.0	2.76	TD1	+	−
7	Hatzaki [10]	24	19	49.0	14.7	3.33	TD1	+	+
8	Hatzaki [10]	26	22	60.0	19.2	3.13	TD1	+	+
9	Giancotti [11]	37	12	25.3	6	4.22	TD1	+	−
10	Li [12]	34	21	54	24	2.25	TD2	+	+
11	Chen [13]	35	18	42.0	18.2	2.31	TD2	+	+
			21	51.5[a]	16	3.22			
12	Cho [14]	30	15	35.7	11.6	3.08	TD1	+	−
			18	49.4	16.8	2.94			
13	Lindy [15]	35	12	26.0	6.1	4.26	TD1	+	+
14	Ngo [16]	35	14	35[a]	10	3.50	TD1	+	+
15	Delahaye [17]	45	12	20[a]	4.6	4.34	TD1	+	−
16	Tonni [18]	38	19	46.6	19.6	2.38	TD1	+	+
17	Li [19]	26	22	54	16	3.38	TD1	+	+
18	Li [19]	34	28	75	19	3.95	TD1	+	+
19	Li [19]	38	20	47	12	3.92	TD1	+	−
20	Schild [20]	23	26	72	36	2.00	TD2	−	+
21	Schild [20]	29	20	56	21	2.67	TD1	−	+
22	Schild [20]	29	20	60	18	3.33	TD1	−	+
23	Calongos [21]	36	13	27.4	8.2	3.34	TD1	−	+
			20	53	11.8	4.49			
24	Teele [22]	NA	18	44.8[a]	18	2.48	TD1	−	+

AC, abdominal circumference; BPD, biparietal diameter; FL, femur length; NA, not available; TC, thoracic circumference; TD1, thanatophoric dysplasia type 1; TD2, thanatophoric dysplasia type 2.
[a] Estimated value.

Table 2
The BPD/FL ratios of 1271 controls without skeletal dysplasia from gestational week 12 to 36.

Distribution	Gestational age (weeks)																								
	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
100.0%	4.06	2.87	2.59	2.41	2.23	2.06	1.98	1.87	1.78	1.74	1.69	1.68	1.69	1.66	1.65	1.63	1.64	1.60	1.57	1.57	1.56	1.57	1.56	1.54	1.53
99.5%	4.06	2.87	2.59	2.41	2.23	2.06	1.98	1.86	1.78	1.74	1.69	1.68	1.69	1.65	1.64	1.63	1.61	1.60	1.56	1.55	1.56	1.55	1.54	1.52	1.53
97.5%	3.91	2.87	2.54	2.34	2.17	1.99	1.90	1.79	1.73	1.67	1.67	1.62	1.63	1.60	1.58	1.58	1.58	1.56	1.54	1.53	1.54	1.51	1.52	1.50	1.50
90.0%	3.54	2.67	2.35	2.20	2.04	1.91	1.81	1.73	1.66	1.62	1.60	1.57	1.56	1.55	1.53	1.54	1.52	1.51	1.49	1.49	1.47	1.47	1.46	1.45	1.44
75.0%	3.18	2.43	2.20	2.04	1.91	1.80	1.74	1.66	1.60	1.55	1.53	1.52	1.51	1.49	1.49	1.48	1.48	1.46	1.44	1.45	1.43	1.43	1.42	1.41	1.40
50.0%	2.82	2.26	2.05	1.89	1.78	1.70	1.65	1.57	1.52	1.49	1.48	1.45	1.45	1.44	1.42	1.43	1.42	1.41	1.40	1.40	1.39	1.38	1.37	1.36	1.35
25.0%	2.43	2.08	1.89	1.79	1.68	1.62	1.58	1.51	1.46	1.44	1.42	1.40	1.39	1.39	1.37	1.37	1.37	1.35	1.36	1.35	1.34	1.33	1.33	1.32	1.31
10.0%	2.07	1.93	1.75	1.69	1.59	1.53	1.49	1.44	1.40	1.37	1.37	1.35	1.34	1.34	1.33	1.33	1.32	1.31	1.31	1.30	1.30	1.30	1.29	1.28	1.27
2.5%	1.92	1.77	1.62	1.58	1.50	1.42	1.42	1.37	1.34	1.31	1.30	1.31	1.28	1.29	1.28	1.28	1.28	1.26	1.28	1.26	1.25	1.25	1.25	1.23	1.23
0.5%	1.89	1.68	1.55	1.46	1.39	1.39	1.37	1.30	1.28	1.26	1.25	1.30	1.24	1.26	1.26	1.22	1.26	1.21	1.25	1.22	1.23	1.22	1.20	1.20	1.20
0.0%	1.89	1.68	1.55	1.46	1.38	1.39	1.37	1.30	1.27	1.26	1.25	1.30	1.24	1.26	1.24	1.22	1.22	1.20	1.24	1.21	1.21	1.20	1.19	1.19	1.19
Mean	2.81	2.27	2.06	1.92	1.80	1.71	1.65	1.58	1.53	1.50	1.48	1.46	1.45	1.44	1.43	1.43	1.42	1.41	1.40	1.40	1.39	1.38	1.38	1.36	1.36
Std dev	0.51	0.26	0.22	0.19	0.17	0.14	0.12	0.11	0.10	0.09	0.09	0.08	0.09	0.08	0.08	0.08	0.07	0.08	0.07	0.07	0.07	0.07	0.07	0.06	0.07

translucency thickness and nasal bones at 10-weeks to detect trisomy 21 was subsequently reported [25,26], and the BPD/FL ratio in early gestational weeks is no longer being used to screen for Down syndrome. TD is subdivided into 2 types according to clinical features and mutations of the fibroblast growth factor receptor 3 (*FGFR3*) gene: type 1 (TD1) is characterized by curved femurs, with or without a cloverleaf skull, as a result of several mutations of *FGFR3*; most cases are caused by missense mutation of 742C → T [8,9]. Type 2 (TD2) is characterized by short straight femurs with a cloverleaf skull as a result of the mutation of 1948A → C [9]. These anomalies in TD possibly appear at the beginning of fetal skeletal development before 11 weeks, resulting in significant skeletal dysplasia, which can be observed at weeks 12–14 [11,16,27]. As a result, either macrocephaly or severe growth restriction of the femur will cause an increased denominator and decreased fraction of the BPD/FL ratio, with a higher ratio at an early stage of pregnancy. This can explain why the BPD/FL ratio may be useful in predicting TD since the first trimester.

Rahemtullah and Ramus et al. suggested that the fetal femur length-to-abdominal circumference ratio (FL/AC) can predict a lethal outcome, although Rahemtullah reported 2 cases of achondroplasia and Ramus reported 1 case of osteogenesis imperfecta type III with an FL/AC ratio less than 0.16, who survived after birth [28,29]. Parilla et al. also reported inaccuracy in 3 of 31 cases studied [6]. In addition, compared to Rosati's study of fetal biometry in normal pregnancy, FL/AC < 0.16 appears to be within the normal range before gestational week 16 [30] (Table 3). Therefore, the feasibility of using such a method to diagnose TD or other lethal disorders at all gestational ages remains questionable, despite Weaver et al. reporting that an FL/AC ratio of 0.124 can be a better clinical cutoff to predict lethality, based on a retrospective study of 23 cases at 21–38 weeks of gestation [31].

Ngo et al. reported that in approximately 69% of severe skeletal dysplasia cases, nuchal translucency (NT) can be seen in the first trimester [16], as well as in Down syndrome. Subsequently, several case studies reported the usefulness of this finding in skeletal disorders such as osteogenesis imperfecta type 1 [32], type 2 [33,34], and type 3 [35]. These studies highlighted the importance of closely monitoring skeletal development when increased NT is seen. However, in our experience, and based on previous reports, increased NT is not always seen in TD [11,36] or other lethal skeletal dysplasias [37]. In addition, a temporary increase in NT can be observed in some normal pregnancies [38]; therefore, the usefulness of NT to predict a rare TD is considered to be limited.

Despite our results suggesting that performing routine fetal biometry measurements since the first trimester can help detect TD, we do not recommend using this measurement alone to diagnose fetal lethality of an unknown skeletal dysplasia, without further confirmation. To avoid misdiagnosis, repeat sonographic evaluation, including that of the thorax, head, and heart, and another reliable examination such as cell-free fetal DNA in maternal plasma [7,39,40] or molecular analysis should be performed. Of note, normal BPD/FL ratio cannot deny different skeletal disorders caused by different mutations in the same *FGFR3* gene before the late second trimester, such as hypochondroplasia [41] or achondroplasia [42], as the shortened femur in these disorders is not obvious during this period [7].

TD is rare; however, according to our results, the BPD/FL ratio can probably be a useful marker to detect an extreme outlier such as TD since early pregnancy. If a higher BPD/FL ratio is obtained, fetal skeletal development should be monitored carefully.

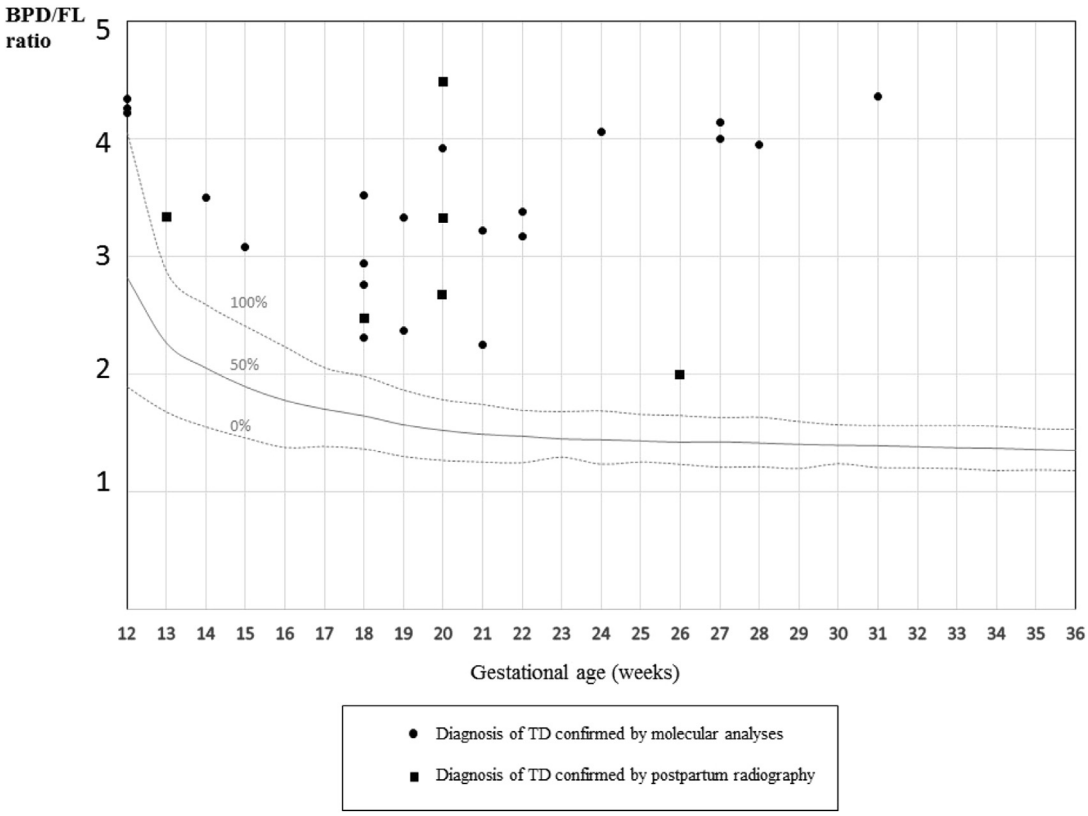

Fig 1. The distribution of the BPD/FL ratio between the thanatophoric dysplasia and control groups. Of 27 BPD/FL ratios obtained from 24 cases, none was within the control range. AC, abdominal circumference; BPD, biparietal diameter; FL, femur length, TD, thanatophoric dysplasia.

Table 3
Fetal biometry measurement at gestational weeks 12–16 (modified from Rosati's study, 1997).

Week	BPD		AC		FL		FL/AC			BPD/FL		
	5%	95%	5%	95%	5%	95%	Minimum (5%/95%)	Average (50%/50%)	Maximum (95%/5%)	Minimum (5%/95%)	Average (50%/50%)	Maximum (95%/5%)
12	18.5	22.1	51.8	65.6	6.3	8.1	0.10	0.12	0.16	2.28	2.82	3.51
13	22.5	26.0	66.2	77.4	8.4	10.8	0.11	0.13	0.16	2.08	2.53	3.10
14	26.3	30.0	77.4	91.0	11.3	14.0	0.12	0.15	0.18	1.88	2.23	2.65
15	30.8	33.8	93.7	104.0	14.4	16.7	0.14	0.16	0.18	1.84	2.08	2.35
16	34.8	38.2	104.0	125.0	18.1	21.2	0.14	0.17	0.20	1.64	1.86	2.11

AC, abdominal circumference; BPD, biparietal diameter; FL, femur length.

Conflict of interest

The authors report no conflicts of interest.

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