The Creation of a Cerebellar Diameter Reference Standard and its Clinical Application to the Detection of Cerebellar Hypoplasia Unique to Trisomy 18

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a short running title: Detection of Cerebellar Hypoplasia

Abstract

Aim

We created a new reference standard focusing on the hemispheric anteroposterior cerebellar diameter (APCD) in addition to the transverse cerebellar diameter (TCD) and discussed whether or not the cerebellar measurement was useful for the detection of Trisomy 18 (T18).

Material and Methods

In 150 normal fetuses between 14 and 36 weeks of gestational age (GA), the TCD and APCD were prospectively measured. In 26 cases with T18, the value was compared with the control.

Results

At <22 weeks of gestation, the TCD reference standard was calculated as follows: TCD=(1.027×GA)−0.674 (R^2=0.97, P<0.001). The reference standard of the APCD was calculated as follows: APCD=(0.682×GA)−3.925 (R^2=0.73, P<0.001). In 8 cases with T18, the TCD was below the 5th percentile value in 7/8 (88%) cases and the APCD was below the 5th percentile value in 8/8 (100%) cases. At >22 weeks of gestation, the reference standard of the TCD was calculated as follows: TCD=(1.603×GA)– 13.216 (R^2 =0.92, P<0.001). The reference standard of the APCD was calculated as follows:

APCD=(0.859×GA) – 7.30 (R^2=0.84, P<0.001). In 18 cases with T18, the TCD was below the 5th percentile value in 14/18 (78%) cases and the APCD was below the 5th percentile value in 18/18 (100%) cases.

Conclusion

APCD reference standard, divided by the gestational age of more or less than 22 weeks, might be useful to diagnose T18.

Keywords : ultrasonography, trisomy18, Cerebellar hypoplasia , prenatal diagnosis, anteroposterior cerebellar diameter

Introduction

Cerebellar hypoplasia is a fetal ultrasound finding that has been reported in the cases of several diseases, including Trisomy18 (T18).[1-4] However, as cerebellar hypoplasia standards have not been clarified based on the size, its diagnosis often depends upon subjective judgments. Although there are reports that diagnosis using the transverse cerebellar diameter or a nomogram of the cisterna magna measurement is useful,[5-11] the measured values often show within normal range. The fact makes it hard to determine if the conventional measurement methods alone are a sufficient indicator of cerebellar hypoplasia.[10] We hypothesized that it might be possible to detect cerebellar hypoplasia more objectively by determining the smaller diameter of the cerebellar hemisphere width (APCD) rather than just measuring the transverse cerebellar diameter (TCD). We created new TCD and APCD nomograms and discussed whether or not the measurement of the cerebellum is useful for the detection of T18.

Methods

The study population included 150 women and their singleton babies from October 2013 to May 2014 at the Department of Obstetrics, Okayama University Hospital. The inclusion criteria were: singleton delivery; fetal transverse and anteroposterior

cerebellar diameters were measured during a fetal ultrasound scan; and the babies were appropriate for dates and born at full term in the same hospital. Cases of fetuses with congenital abnormalities were excluded from the control, even if no cerebellar hypoplasia was observed because they were often recognized as small for gestational age due to fetal factors.

Ethical approval was obtained from Okayama University Hospital and written informed consent was obtained from the women who participated in the study.

The measurement of the cerebellum was performed on the cross-section of the cerebellum where the cerebellar hemisphere and cerebellar vermis were visualized by an ultrasonic B-mode image. The diameter of the cerebellum (lengthwise) was considered to be the TCD. APCD was determined as the vertical line to the TCD (Figure 1). The cerebellar diameter reference standards at the gestational ages (GAs) of <22 weeks and >22 weeks were determined (median, 5^{th} and 95^{th} percentile values) and the cases below the 5^{th} percentile were diagnosed with cerebellar hypoplasia. We also measured the APCD and TCD in 26 cases which T18, and compared these data with the reference standards.

The transabdominal ultrasonographies used in this research utilized the Voluson E8 (GE Healthcare Japan Corporation) and Alpha 6 (Hitachi Aloka Medical, Ltd.)

ultrasound systems with convex–type probes (3.5 MHz). The correlation between the GA and cerebellar diameters was examined by Pearson's correlation coefficient test. A P-value of <0.05 was considered to be statistically significant. The results are expressed as the mean ± standard deviation (SD).

Results

The fetal cerebellar diameters of the 150 included cases were measured at a GA of 14 - 36 weeks. Sixty-eight cases were measured at <22 weeks, while the remaining 82 cases were measured at >22 weeks. The average age of the women was 34.3±4.7 years old. The mean gestational age was 38.5±1.4 weeks. The mean birth weight was 2,983± 322g.

At < 22 weeks of gestation, the TCD increased linearly with gestation (Figure 2). The reference standard was expressed as TCD=(1.027 × GA) − 0.674 (R^2=0.97, P<0.001, SD=0.36). APCD also increased in a linear fashion (Figure 3). APCD reference standard was expressed as APCD=(0.682 × GA) − 3.925. APCD also correlated with the GA (R^2=0.73, P<0.001, SD=0.80).

In eight cases with T18 at < 22 weeks, seven cases (88%) fell below the 5th percentile value of the reference standard in TCD (Figure 4). Indeed all cases fell below the 5th

percentile value of the reference standard in APCD (Figure 5).

At > 22 weeks of gestation, the TCD increased linearly with gestation (Figure 6). The reference standard was expressed as TCD=(1.063×GA)−13.216 (R^2=0.95, P<0.001, SD=1.40). APCD also increased in a linear fashion (Figure 7). APCD reference standard was expressed as APCD=(0.859×GA)−7.30. APCD also correlated with the GA (R^2=0.84, P<0.001, SD=1.29).

In 18 cases with T18 at > 22 weeks, 14 cases (78%) fell below the 5th percentile value of the reference standard in TCD (Figure 8). Indeed all cases fell below the 5th percentile value of the reference standard in APCD (Figure 9).

Table 1 shows a TCD nomogram from 15 to 35 weeks of GA. Table 2 shows an APCD nomogram for the same GA period.

As for interobserver reliability, two examiners measured the same sample three times for each of the 10 cases. The intra-assay consistency was 0.25±1.1% for the TCD, and 0.41±1.8% for the APCD, while the inter-assay consistency values were 0.55±5.2% and 0.66±3.2% for the TCD and APCD, respectively.

Discussion

The following two facts were indicated by the present study: first, during pregnancy,

both the TCD and the APCD increase in size in a linear fashion. The range of the 5th - 95th percentile values was very narrow for both measurements. It is more useful to measure both the TCD and APCD and to compare the results with the reference standard to detect cerebellar hypoplasia. Second, the APCD fell below the 5th percentile value in all cases of T18, making it the better measurement for the purpose of detecting cerebellar hypoplasia.

We demonstrated that both the TCD and APCD increased in a linear fashion. Therefore, it was shown that the measurements of both TCD and APCD were more useful to detect cerebellar hypoplasia. To the best of our knowledge, there have been no reports on the use of the APCD as a reference standard. Several studies show that the presence of T18 sometimes enables the recognition of the enlarged cisterna magna caused by cerebellar hypoplasia [3,5,8,9]. However, the measurement of the cisterna magna alone is not capable of achieving the detection of T18 with high accuracy[12]. The enlarged cisterna magna caused by cerebellar hypoplasia was probably recognized, at the time when the thin parts on the front and back sides of the cerebellar hemispheres were observed. Therefore, the measurement of the APCD is considered to be superior for the detection of T18. In our study, we divided the population more or less than 22 weeks of gestation. According to a previous study, the TCD develops at a rate of 1 mm per week

during the gestational weeks 14 - 21. After the TCD and the GA (in weeks) reach the same value at 21 weeks, the TCD becomes longer than the GA value[6,7,10,11,13,14]. Therefore, in focusing on the slopes of the graph changed after 22 weeks of gestation, it was recognized that although both the TCD and APCD increased in proportion to the weeks of gestational age in a linear fashion and both shared a strong correlation with each other, the slopes of the graph changed. Furthermore, the range of the 5^{th} – 95^{th} percentile values of the TCD was found to be much narrower than previously reported. In the case of the TCD nomogram that has been used, at a GA of <22 weeks, the TCD has been reported to be of the 5^{th} percentile when it falls below 2mm from the median[10,13,14,15]. In this study, however, it reached the 5^{th} percentile value with a decrease of a mere 0.6mm. Therefore, it was revealed that the cerebellum diameter that had been positioned in the normal range by a different TCD nomogram was below the 5^{th} percentile value in the present study. The cases of cerebellar hypoplasia that have been overlooked with the conventional TCD nomogram could be diagnosed with cerebellar hypoplasia by using the new TCD nomogram established here.

In this research, the comparison between the measured TCD and its reference standard showed that the detection rate of cerebellar hypoplasia cases was 21/26, while the sensitivity was 80.7%. Thus it was feared that the TCD measurement alone might

overlook cases of cerebellar hypoplasia. Meanwhile, when the APCD was measured and compared with the reference standard, the detection rate of cerebellar hypoplasia cases that were recognized in the fetus was 26/26, with a sensitivity of 100%. It was suggested that APCD was superior to the TCD in diagnostic accuracy and in the ability to more objectively assess the possibility of cerebellar hypoplasia.

In contrast with other studies that measured the cerebellum by ultrasound,[6,7,10,11,13] this study developed the nomogram of TCD and APCD in Japanese fetuses on the simple view to measure cerebellum. One advantage of this method is that the APCD can be measured on the same cross-section as the TCD, which means that no complicated procedures are required.

This study had some limitations. Firstly, we only studied the cerebellum of Japanese fetuses, and it has not yet been discussed whether this method can be used in a standardized way among other races. Because the reference standard for both the TCD and APCD was separated at the 22^{nd} week of gestational age, and the 5^{th} – 95^{th} percentile value of the cerebellar diameter suddenly became large at the 22^{nd} week of gestation, there is a possibility that the actual cases of cerebellar hypoplasia were underestimated immediately beyond the 22^{nd} week. Furthermore, in the case of fetal growth restriction, the TCD may be smaller than it appears, while the APCD gives the

impression that it is within the normal range. Unfortunately, we did not have the appropriate data to investigate this issue and the cerebellum diameter on fetal growth restriction remains an issue for future investigation.

In this study, the 5^{th} - 95^{th} percentile value of TCD was reviewed, the APCD was measured and a new nomogram was created. It was shown that it is possible to accurately detect the cerebellar hypoplasia unique to T18 by measuring the TCD and APCD. Therefore, it was suggested to be clinically useful to include the measurement of APCD with the measurements of TCD using the different nomograms more or less than 22 weeks of gestation.

Disclosure

None declared.

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Figure Legend

Table1. Reference values of the transverse cerebellar diameter (TCD)

GA, gestational age.

Table2. Reference values of the anteroposterior cerebellar diameter (APCD)

GA, gestational age.

Figure1. Measuring method of cerebellar diameter: The measurement of the cerebellum was performed on the cross-section of the cerebellum where the cerebellar hemisphere and cerebellar vermis were visualized by an ultrasonic B-mode image. The diameter of the cerebellum (lengthwise) was considered to be the transverse cerebellar diameter (TCD). The diameter of the cerebellar hemisphere (widthwise) at a right angle to the TCD was considered to be the anteroposterior cerebellar diameter (APCD).

Figure2. Correlation between the TCD and a GA of <22 weeks. TCD=(1.027×GA)−0.674 (R^2=0.97). Reference ranges represent median and 5th and 95th percentile values.

Figure3. Correlation between the APCD and a GA of <22 weeks. APCD=(0.682×GA)−3.925 (R^2=0.73). Reference ranges represent median and 5th and 95th percentile values.

Figure4. Correlation between the TCD reference standard at a GA of <22 weeks with 8 cases of T18 fetuses (△) detected at a GA of <22 weeks.

Reference ranges represent median and 5th and 95th percentile values.

Figure5. Correlation between the APCD reference standard at a GA of <22 weeks with 8 cases of T18 fetuses (△) detected at a GA of <22 weeks.

Reference ranges represent median and 5th and 95th percentile values.

Figure6. Correlation between GA and the TCD in the cases where the GA was ≥22 weeks. TCD=(1.603×GA)−13.216 (R^2=0.95).

Reference ranges represent median and 5th and 95th percentile values.

Figure7. Correlation between the GA and the APCD in the cases where GA was ≥22 weeks. APCD=(0.859×GA)−7.300 (R^2=0.84).

Reference ranges represent median and 5th and 95th percentile values.

Figure8. Correlation between the TCD reference standard in the cases where GA was ≥ 22 weeks and 18 cases of T18 fetuses (△) detected at a GA of ≥22 weeks.

Reference ranges represent median and 5th and 95th percentile values.

Figure9. correlation between the APCD reference standard in the cases where GA was ≥ 22 weeks and 18 cases of T18 fetuses (△).

Reference ranges represent median and 5th and 95th percentile values.

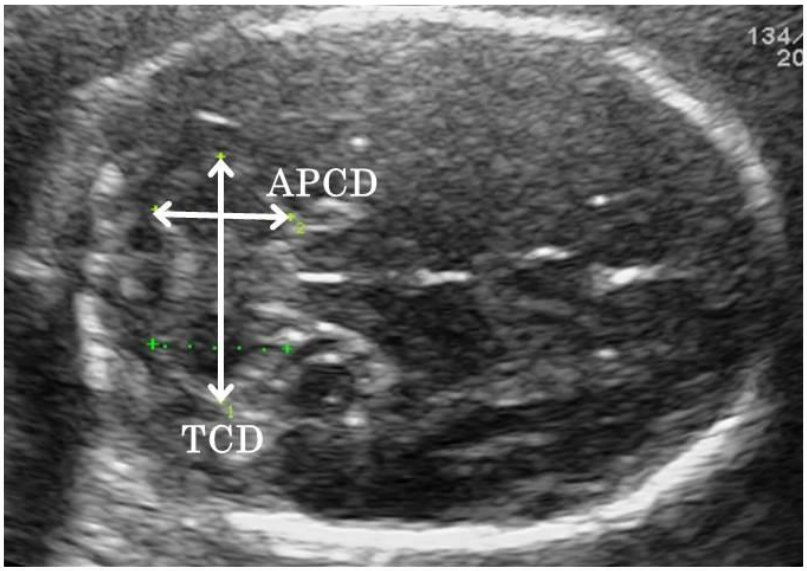
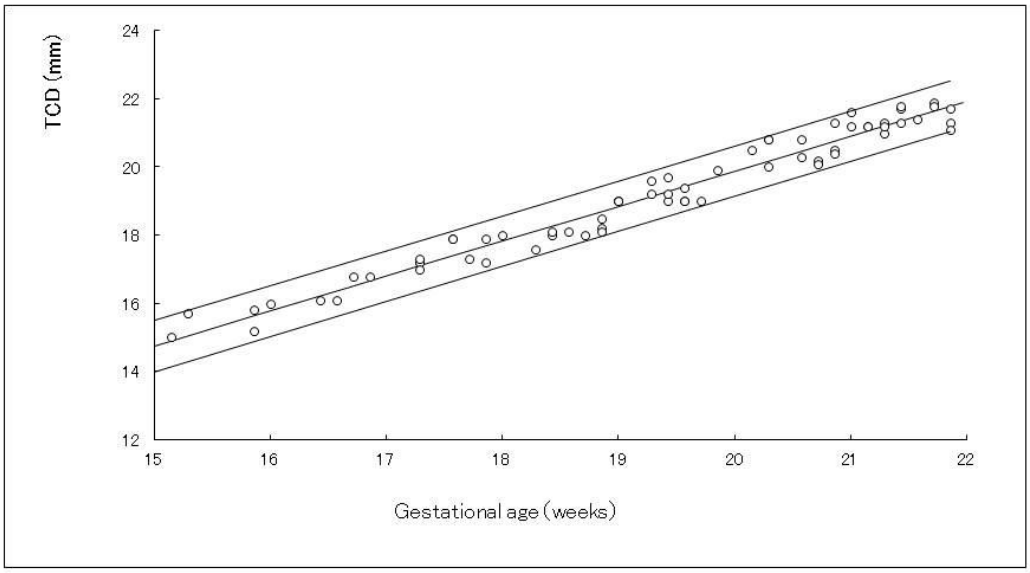


Figure 1.



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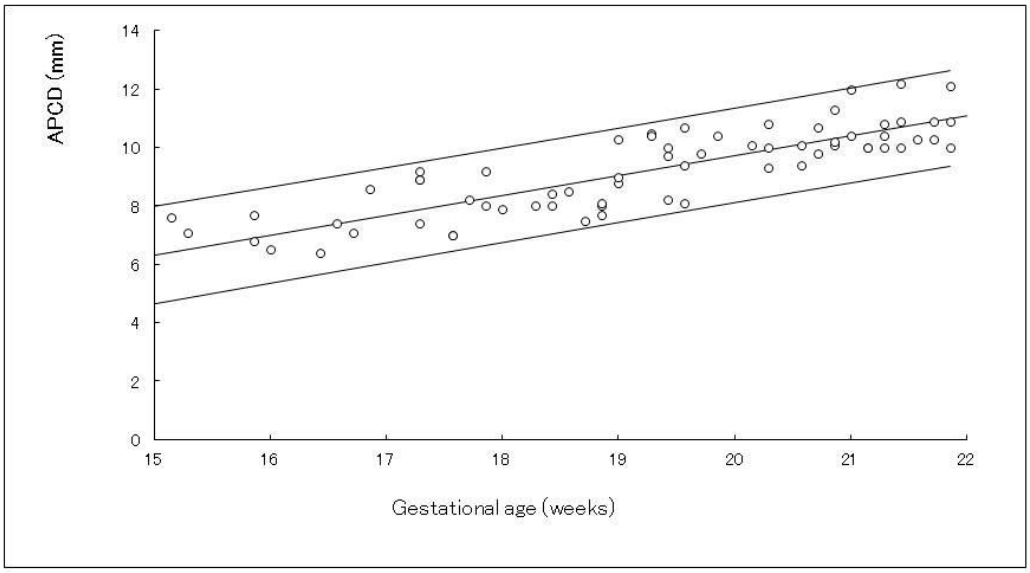

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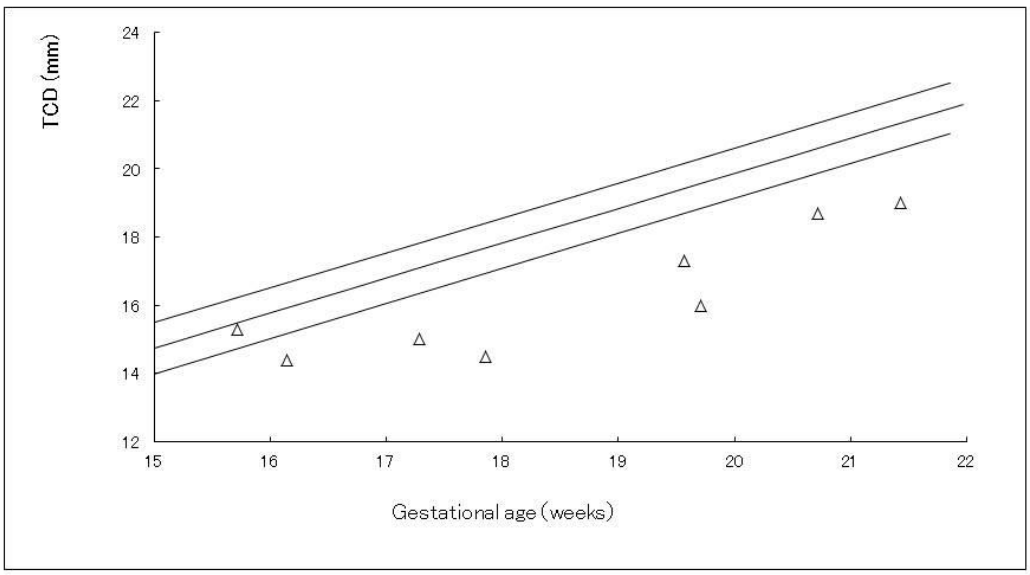

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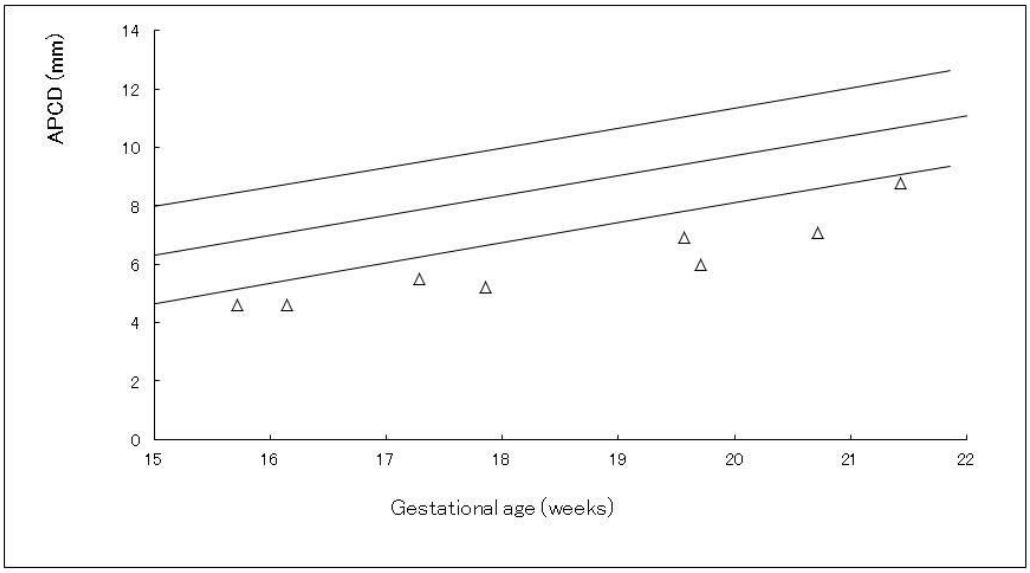

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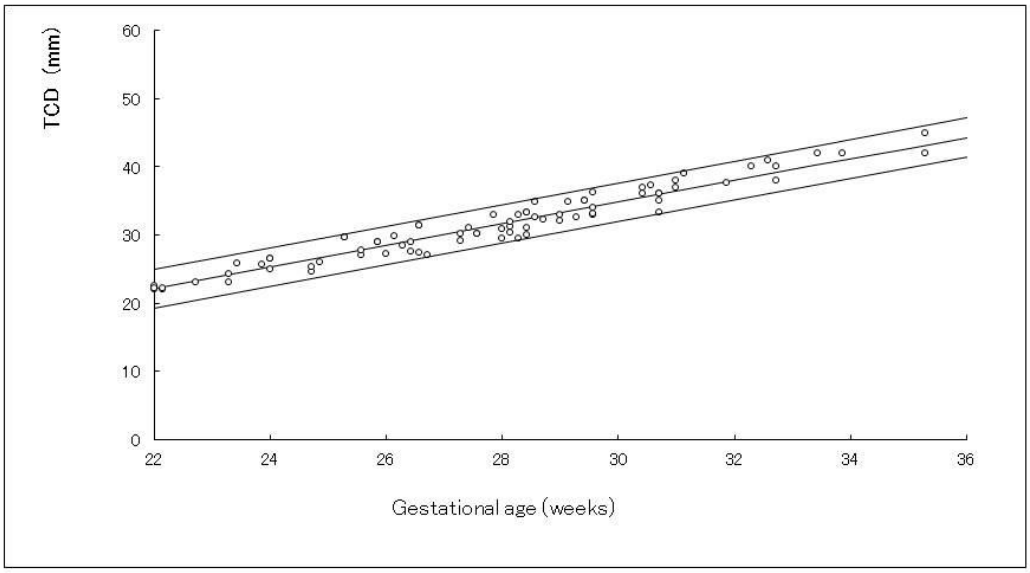
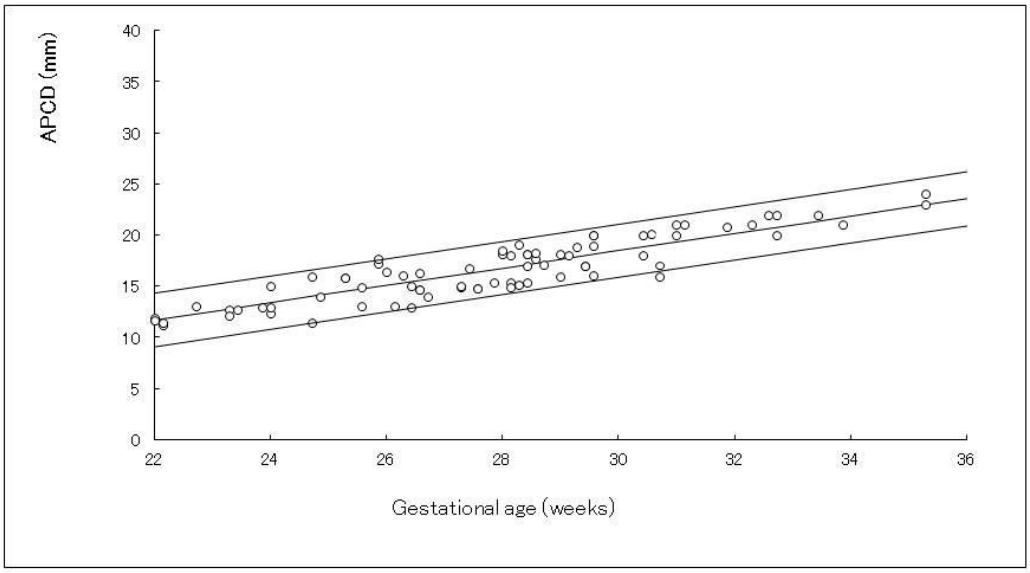


Figure 6.



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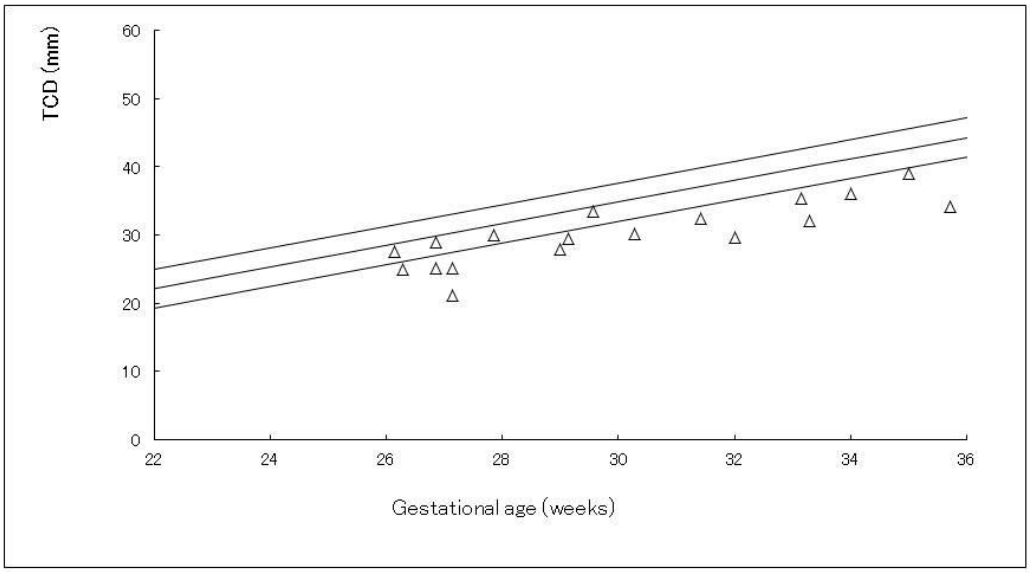

Figure 8.

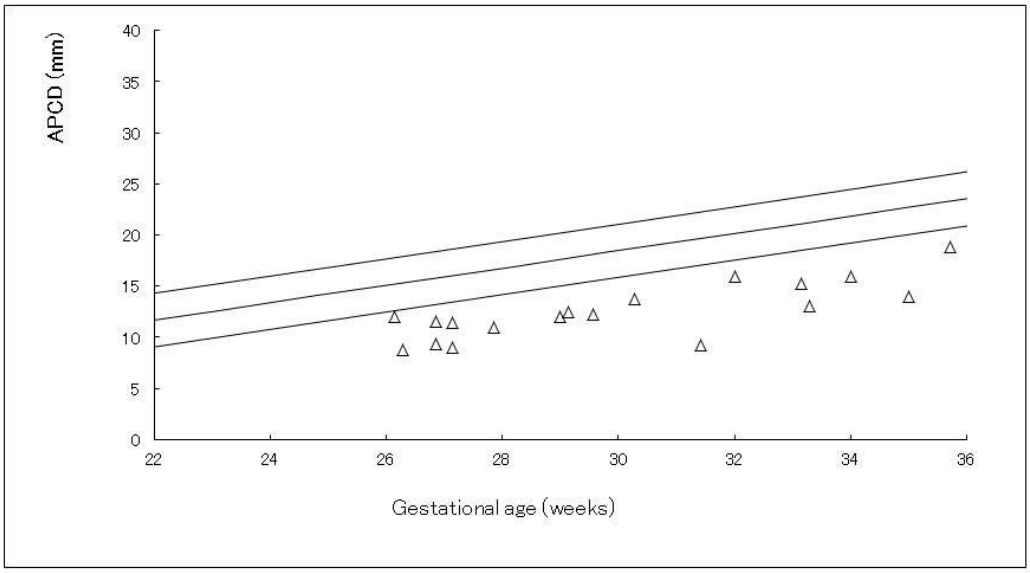
APCD (mm)
40
35
30
25
20
15
10
5
0
22
24
26
28
30
32
34
36
Gestational age (weeks)

Figure 9.

	TCD (mm)			
	Percentiles			
GA	5th	50th	95th	SD
15	14.1	14.7	15.3	0.36
16	15.2	15.8	16.4	0.36
17	16.2	16.8	17.4	0.36
18	17.2	17.8	18.4	0.36
19	18.2	18.8	19.4	0.36
20	19.3	19.9	20.5	0.36
21	20.3	20.9	21.5	0.36
22	19.8	22.1	24.4	1.40
23	21.4	23.7	26.0	1.40
24	23.0	25.3	27.6	1.40
25	24.6	26.9	29.2	1.40
26	26.2	28.5	30.8	1.40
27	27.8	30.1	32.4	1.40
28	29.4	31.7	34.0	1.40
29	31.0	33.3	35.6	1.40
30	32.6	34.9	37.2	1.40
31	34.2	36.5	38.8	1.40
32	35.8	38.1	40.4	1.40
33	37.4	39.7	42.0	1.40
34	39.0	41.3	43.6	1.40
35	40.6	42.9	45.2	1.40

Table 1.

	APCD (mm)			
	Percentiles			
GA	5th	50th	95th	SD
15	5.0	6.3	7.6	0.80
16	5.7	7.0	8.3	0.80
17	6.4	7.7	9.0	0.80
18	7.1	8.4	9.7	0.80
19	7.7	9.0	10.3	0.80
20	8.4	9.7	11.0	0.80
21	9.1	10.4	11.7	0.80
22	9.5	11.6	13.7	1.29
23	10.4	12.5	14.6	1.29
24	11.2	13.3	15.4	1.29
25	12.1	14.2	16.3	1.29
26	13.0	15.1	17.2	1.29
27	13.8	15.9	18.0	1.29
28	14.7	16.8	18.9	1.29
29	15.6	17.7	19.8	1.29
30	16.4	18.5	20.6	1.29
31	17.3	19.4	21.5	1.29
32	18.2	20.3	22.4	1.29
33	19.0	21.1	23.2	1.29
34	19.9	22.0	24.1	1.29
35	20.8	22.9	25.0	1.29

Table 2.