Original Article

Nomogram of Intracranial Translucency at 11 to 13^{+6} Gestational Weeks at King Chulalongkorn Memorial Hospital, Bangkok, Thailand

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Objective: To create a nomogram of intracranial translucency (IT) and to study the correlation between IT and crown-rump length (CRL), and between IT and gestational age (GA).

Materials and Methods: Thai singleton pregnant women between 11 to 13^{+6} weeks of gestation were enrolled. Fetal CRL, IT, biparietal diameter (BPD), brain stem diameter (BS), brain stem to occipital bone diameter (BSOB) and cisterna magna width (CM) were measured. Best fit equations between IT and CRL, and IT and GA were constructed. The correlation between CRL and remaining parameters were calculated.

Results: Two hundred eleven Thai pregnant women were enrolled. The mean GA was 12^{+3} weeks (SD 5 days). The IT ranged from 0.91 to 3.89 mm (SD 0.56). Curve estimation analysis demonstrated a quadratic relationship between IT and CRL [IT (mm) = 1.928701 – 0.027603*CRL + 0.000468*CRL^2 (R2=0.352, p<0.001)]. A quadratic relationship also provided the best fit between IT and GA [IT (mm) = 18.242997 – 0.425972*day + 0.002744*$days^2$ (R2=0.295, p<0.001)].

Conclusion: A nomogram of IT and other intracranial structures for open spina bifida screening at 11 to 13^{+6} weeks of gestation in Thai population has been established. The assessment of IT is feasible.

Keywords: Open spina bifida screening, Intracranial translucency, Brain stem diameter, Brain stem to occipital bone diameter, Cisterna magna width

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Neural tube defect (NTD) is the second most common malformation[1,2]. Overall incidence in the United States is around 1.90 per 10,000 live births[3]. Open spina bifida (OSB) is one of third common of NTD caused by failure of closure of the neural tube[4]. Genetic causes are major risk factors, especially in populations who have the methylene tetrahydrofolate reductase (MTHFR) gene mutation[4]. The diagnosis of OSB is usually difficult in first trimester. A study in 1997 by Sebire et al[5] reported none of the 29 fetuses with spina bifida was detected at 11 to 13 weeks in 61,972 pregnancies undergoing measurement of nuchal translucency (NT).

Chaoui et al[6] described the anechoic area of the fourth ventricle that presents as an intracranial translucency (IT) parallel to the NT. An interesting finding from the study that IT was always visible in normal fetuses but was absent in all four cases of OSB. Over the next few years, a number of reports[7-10] about additional posterior brain markers for OSB screening have been published. In cases of OSB, the diameter of brain stem (BS) and ratio between BS and brain stem diameter to occipital bone diameter (BSOB) appeared to be increased whereas the BSOB and cisterna magna width (CM) appeared to be decreased. Khalil et al[9] and Nicolaides et al[11,12] reported that

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fetuses with OSB have a smaller biparietal diameter (BPD) in the first trimester. These abnormal findings of the posterior brain in the first trimester may provide earlier diagnosis of OSB. However, no data haves been published about IT and posterior brain structure in the Thai population. The aims of the present study were to establish the reference range of IT in normal Thai fetuses at 11 to 13^{+6} weeks of gestation and to study the correlation between IT and crown-rump length (CRL) and between IT and gestational age (GA).

Materials and Methods

The study population was recruited from the Division of Maternal-Fetal Medicine, King Chulalongkorn Memorial Hospital. The present study was approved by The Ethics Committee of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB number 503/55). Thai singleton pregnant women at 11 to 13^{+6} weeks of gestation were enrolled. Pilot study was done. Mean IT and standard deviation (SD) of each group (Group 1 was 11 to 11^{+6} weeks, Group 2 was 12 to 12^{+6} weeks, and group 3 was 13 to 13^{+6} weeks) were calculated. Sample size for each group was calculated using the following formula based on Pilot study data,

$$n = Z^2_{\alpha/2}\,\sigma^2 / d^2$$

Where σ^2 was data variance and d was acceptable level of error. The required sample size for all GA was 207. The estimated dropout rate was 10 percent. The final sample was 228.

Multiple pregnancy, dead fetus, and fetal structural anomalies were excluded from the study. All participants were counseled about the study protocol and informed consents were obtained. Demographic data were recorded, included age, parity, pre-pregnancy body weight, height and previous pregnancy complications. GA and estimated due date (EDD) were calculated according to recommendations from the American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine[13]. The EDD had been changed to correlate with the ultrasound dating if the result differed by more than five days before nine weeks of gestation and seven days before 14 weeks of gestation from last menstrual period (LMP). Transabdominal ultrasound examination was performed to measure CRL, NT (according to Fetal Medicine Foundation (FMF) guideline[14]), first trimester structural screening and posterior brain parameters for OSB were screened according to measurement methods from original articles, as shown in Figure 1 and 2. The ultrasound machine used in the present study was the GE Voluson E8, GE voluson 730 Pro and GE voluson 730 Expert with a curvilinear RAB 2-5D probe (GE medical Systems, USA).

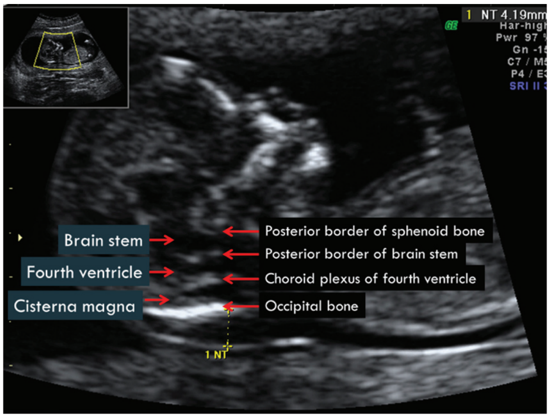

Figure 1. Ultrasound image in the mid sagittal plane of the fetal face. The fourth ventricle presents as an intracranial translucency (IT). IT is the shortest anteroposterior diameter delineated by the dorsal part of the brain stem anteriorly and the choroid plexus of the fourth ventricle posteriorly.

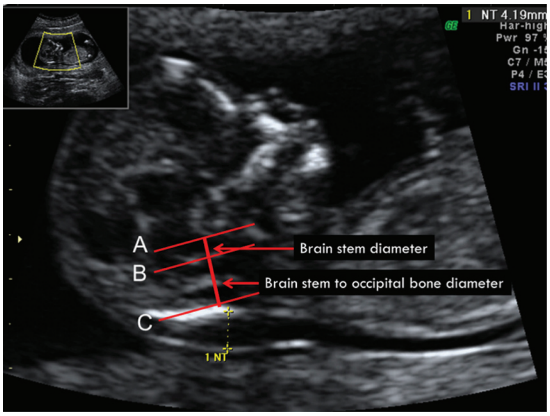

Figure 2. Ultrasound image in the mid sagittal plane of the fetal face demonstrating the measurements of brain stem diameter and brain stem to occipital bone diameter. Three lines are drawn, the first line is along the middle of the line produced by the posterior border of the brain stem and the anterior border of the fourth ventricle (line B). Other lines are paralell with line B. Line A is along the posterior border of the sphenoid bone and line C is along the anterior border of the occipital bone. The vertical distances between lines A and B and between B and C are the brain stem diameter and brain stem to occipital bone diameter, respectively.

All parameters including NT, IT, BPD, BS,

Table 1. Intracranial translucency according to week of gestation

GA (weeks)	n	Intracranial translucency (mm)			
		5^{th} percentile	50^{th} percentile	95^{th} percentile	Mean±SD
11	40	1.40	1.77	2.33	1.78±0.27
12	112	1.14	1.89	2.80	1.95±0.46
13	59	1.55	2.48	3.57	2.52±0.64

GA=gestational age; SD=standard deviation

BSOB, and CM were measured by one sonographer (MS) with certified competence in NT measurement by Fetal Medicine Foundation, London. The quality of each picture was checked. IT is delineated by the dorsal part of the brain stem anteriorly and the choroid plexus of the fourth ventricle posteriorly. BS is the distance between the posterior border of the sphenoid bone to the middle portion of the echogenic line of the posterior border of the brain stem and the anterior border of the fourth ventricle, and BSOB is the distance between the middle portion of the echogenic line of the posterior border of the brain stem and the anterior border of the fourth ventricle. CM is a translucency between the fourth ventricle and the occiput. Intra-observer variation was done to determined accuracy of measurement. The delivery results were recorded including the GA at delivery, sex of the newborn, and birth weight.

Mean and SD as well as the fifth, fiftieth, and ninety-fifth percentiles of all parameters of interest were described for each GA. Intraclass correlation coefficient (ICC) was used to determine intra-observer variation. Best fit equations were constructed using linear regression and curve estimation analysis. A p-value smaller than 0.05 was considered statistically significant.

Results

During the study period, which was between March and November 2013, two hundred eleven pregnant women between 11 to 13^{+6} weeks of gestation were recruited. The mean age of participants was 32.7 years (19 to 44). Fifty percent were primigravida. IT could be measured in all participants. The mean GA was 88 days (12 weeks 4 days), SD 5 days. The mean CRL was 62.31 millimeters (mm) (54.70 to 68.20), SD 9.97 mm. The mean GA at delivery was 38 weeks, SD 1.8 weeks. Of these, preterm birth before 37 complete weeks was 9.5%. The mean IT was 2.07 mm. The IT range from 0.91 to 3.89 mm, SD 0.56 mm. For the accuracy of the measurement, intra-observer variability was calculated. Table 1 shows the mean and SD, fifth, fiftieth, and ninety-fifth percentile of IT according to the week of gestation.

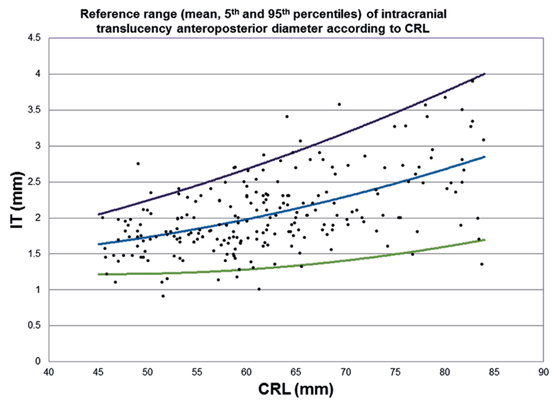

Figure 3. Relationship between IT and CRL in normal fetuses between 11 and 13^{+6} weeks of gestation. The middle line represents the regression mean while the upper and lower lines represent the 95^{th} and 5^{th} percentiles.

Curve estimation analysis showed a quadratic relationship between the IT and CRL, as shown in Equation 1 and Figure 3. Curve estimation analysis also demonstrated a quadratic relationship between the IT and GA (Equation 2 and Figure 4).

Equation 1:

$$IT\ (mm) = 1.928701 - 0.027603*CRL + 0.000468*CRL^2$$
($R2=0.352$, $p<0.001$)

Equation 2:

$$IT\ (mm) = 18.242997 - 0.425972*day + 0.002744*days^2$$
($R2=0.295$, $p<0.001$)

Intra-observer agreement of the IT was assessed. ICC was 0.865 (95% CI 0.793 to 0.913).

The result of the mean and SD, fifth, fiftieth, and ninety-fifth percentile of other parameters of interest including BPD, BS, BSOB, and CM according to week of gestation are shown in Table 2. Curve estimation analyses also showed a quadratic relationship between all parameters (BPD, BS, BSOB and CM) and CRL as shown in Equation 3-6 and Figure 5.

Table 2. BPD, BS, BSOB, and CM according to week of gestation

	GA (weeks)	5th percentile (mm)	50th percentile (mm)	95th percentile (mm)	Mean±SD (mm)
BPD	11	16.00	17.70	20.80	18.27±1.58
	12	16.62	20.60	24.64	20.57±2.29
	13	20.47	24.70	29.71	24.80±2.62
BS	11	2.14	2.69	3.30	2.69±0.35
	12	2.48	3.10	3.84	3.14±0.42
	13	2.60	3.58	4.50	3.62±0.59
BSOB	11	3.40	4.41	5.60	4.48±0.64
	12	3.93	5.28	6.94	5.34±0.90
	13	5.02	6.40	8.60	6.61±1.16
CM	11	1.10	1.54	2.11	1.57±0.28
	12	1.20	1.88	3.02	1.97±0.53
	13	1.50	2.50	4.03	2.63±0.77

GA=gestational age; SD=standard deviation; BPD=biparietal diameter; BS=brain stem diameter; BSOB=brain stem to occipital bone diameter; CM=cisterna magna width

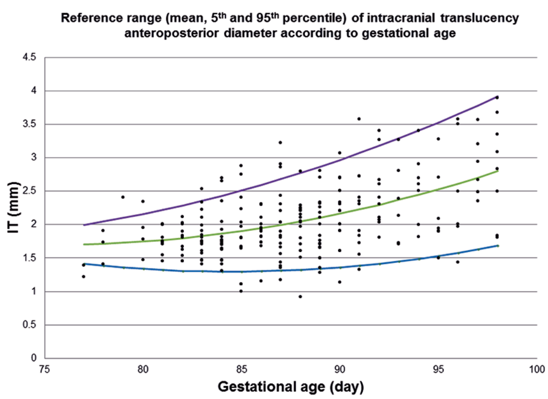

Figure 4. Relationship between IT and GA in normal fetuses between 11 and 13^{+6} weeks of gestation. The middle line represents the regression mean while the upper and lower lines represent the 95^{th} and 5^{th} percentiles.

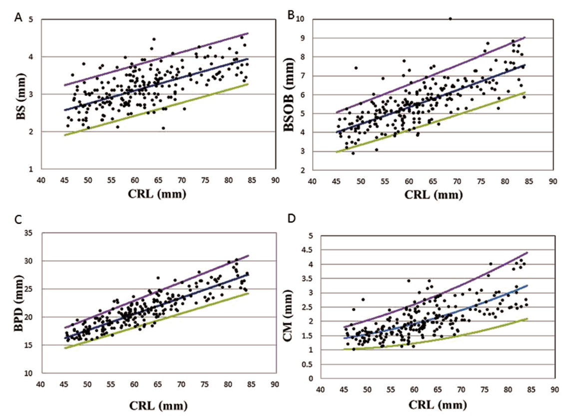

Figure 5. Relationship between BPD and CRL in normal fetuses between 11 and 13^{+6} weeks of gestation. The middle line represents the regression mean while the upper and lower lines represent the 95^{th} and 5^{th} percentiles.

Equation 3:

$$BPD\ (mm) = 4.330297 + 0.257107*CRL + 0.000243*CRL^2$$

($R2=0.787$, $p<0.001$)

Equation 4:

$$BS\ (mm) = 1.453815 + 0.020072*CRL + 0.000121*CRL^2$$

($R2 = 0.402$, $p<0.001$)

Equation 5:

$$BSOB\ (mm) = 1.038133 + 0.055250*CRL + 0.000263*CRL^2$$

($R2=0.551$, $p<0.001$)

Equation 6:

$$CM = 1.673791 - 0.033907*CRL + 0.000632*CRL^2$$

($R2 = 0.505$, $p<0.001$)

For the accuracy of the measurement, the intra-observer variability was calculated. ICC of BPD, BS, BSOB, and CM are shown in Table 3.

The ratio between BS to BSOB decreased with gestation as shown in Equation 7 and Figure 6.

Equation 7:

$$BS\ to\ BSOB\ ratio = 0.938315 - 0.008144*CRL + 0.000040*CRL^2$$

($R2=0.079$, $p<0.001$)

Discussion

The results of the present study confirm the fourth ventricle and posterior brain including brain stem and cisterna magna are easily assessed during NT measurement in mid sagittal view for routine

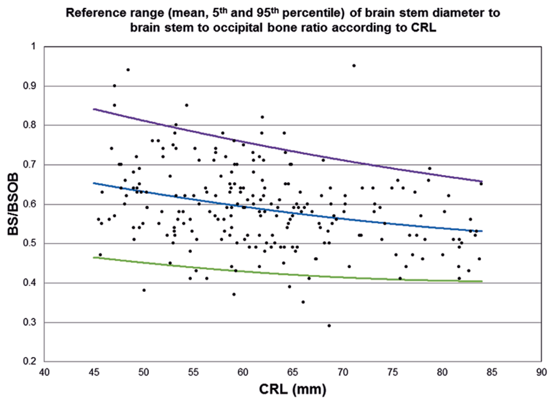

Figure 6. Relationship between brain stem and CRL in normal fetuses between 11 and 13^{+6} weeks of gestation. The middle line represents the regression mean while the upper and lower lines represent the 95^{th} and 5^{th} percentiles.

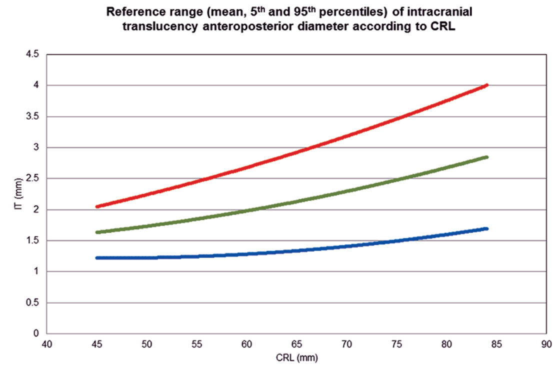

Figure 7. Relationship between BSOB diameter and CRL in normal fetuses between 11 and 13^{+6} weeks of gestation. The middle line represents the regression mean while the upper and lower lines represent the 95^{th} and 5^{th} percentiles.

aneuploidy screening in the first trimester. Many studies found obliterated IT, increased BS and decreased CM resulting from caudal replacement in fetuses with OSB.

In the present study, the IT increases with GA from a mean of 1.63 mm at a CRL 45 mm to 2.91 mm at 84 mm. The result is similar to that reported from Chaoui et al[6] and Chen et al[15], in which IT increases from 1.5 to 2.6 mm and from 1.35 to 2.6 mm at the same gestation, respectively, as shown Table 4.

From curve estimation analysis, the authors found that IT is better correlated with CRL than with GA (R2=0.352, p<0.001 and R2=0.295, p<0.001, respectively). The fact that GA has more variation than CRL may explain this finding, which supports a reference range from the equation of the IT according to CRL that could be suitably used to create a standard nomogram of the IT measurement as shown in Figure 7.

Intra-observer variability has been evaluated in the present study. ICC was 0.865 (95% CI 0.793 to 0.913). This finding is similar to the previous study by Karl et al[16] (ICC 0.940; 95% CI 0.914 to 0.959 for operator 1, and ICC 0.939; 95% CI 0.912 to 0.957 for operator 2) and Adiego et al[17] (ICC 0.79; 95% CI 0.72 to 0.84).

In addition to IT, other parameters that support OSB screening, including BPD, BS, BSOB, and CM were measured in the present study. A finding about the usefulness of BPD in OSB published in 2013 by Khalil et al[9] showed that BPD is decreased in fetuses with OSB compared with normal fetuses and 92.6% of OSB fetuses has BPD less than fifth percentile of the same gestation. A nomogram of BPD from the present study is similar to the nomogram of BPD in first trimester fetuses reported by Salomon et al[18] in 2003. When considering the posterior fossa structure

Table 3. ICC and 95% CI of BS, BSOB and CM

	ICC	95% CI
BS	0.814	0.708 to 0.883
BSOB	0.945	0.911 to 0.966
CM	0.963	0.939 to 0.978

ICC=intraclass correlation coefficient; CI=confidence interval; BS=brain stem diameter; BSOB=brain stem to occipital bone diameter; CM=cisterna magna width

Table 4. IT according to CRL

	Mean IT (mm)		Equation
	CRL 45 mm	CRL 84 mm	
The present study	1.63	2.91	IT (mm) = 1.928701 – 0.027603*CRL + 0.000468*CRL^2 (R2=0.352, p<0.001)
Chaoui et al.[6] (2009)	1.50	2.60	No data
Chen et al.[15] (2012)	1.35	2.60	IT (mm) = 1.63 + 0.004*CRL (R2=0.006)

IT=intracranial translucency; CRL=crown-rump length in normal fetuses, BS and BSOB from the present study tend to increase with gestation, the same as in a previous report in England by Lachmann et al[7]. Moreover, in normal fetuses, BS is always smaller than BSO, and the result of BS to BSOB ratio is always less than one and decreases with increasing GA. For CM, the result from the present study is not different from the study reported by Garcia-Posada et al[10] that CM width also increases with GA.

The present study set out to create a nomogram of intracranial structure associated to OSB screening in the first trimester. The usefulness of the present findings can offer an opportunity for OSB screening at the same time of the routine first trimester aneuploidy screening. In fetuses who have an abnormal measurement of any intracranial parameter, targeted second trimester ultrasound may be needed; however, the sample size in the present study was too small to demonstrate any association between abnormal measurements of each intracranial structure and OSB detection. Prospective large studies are needed. A few studies to evaluate the contribution of the examination of specific anatomical features of the fetal posterior brain on mid sagittal first trimester ultrasound to the early detection of OSB were published[19-21]. The result showed non-visualization of CM achieved the best screening performance with associated overall sensitivity of 50% to 73%, whereas, both non-visualization of the IT and posterior shift of the brainstem were associated with acceptable but lower detection rate. Overall results from the present study concluded that an abnormal posterior brain presenting at least one of these three criteria was associated with a detection rate ranging from 50% to 90%[21].

Conclusion

The nomogram of IT and other intracranial structures for OSB screening at 11 to 13^{+6} weeks of gestation in a Thai population has been established. The assessment of IT is feasible. Prospective large studies are needed to determine the performance of these intracranial structures in screening for OSB.

What is already known on this topic?

Open spina bifida could be predicted by absent IT and other posterior brain structure parameters abnormalities in first trimester.

What this study adds?

The present study creates a nomogram of intracranial structure associated OSB screening in the first trimester that can offer an opportunity for OSB screening at the same time of routine first trimester aneuploidy screening. Targeted second trimester ultrasound should be considered for the fetuses who have an abnormal measurement of any intracranial parameters.

Acknowledgement

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Conflicts of interest

The authors declare no conflict of interest.

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