ORIGINAL ARTICLE

DEVELOPMENT OF A NORMAL RANGE FOR FIRST TRIMESTER PREGNANCY INTRACRANIAL TRANSLUCENCY MEASUREMENTS

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ABSTRACT

Intracranial translucency (IT) by ultrasound in the first trimester is used in screening for open spina bifida, which is predominantly seen in the second trimester morphology ultrasound. IT has been used in many countries, including Asian and European countries. The aim of this study is to generate an IT normal range and to correlate IT measurements and neurological system abnormalities identified during second trimester ultrasound scan. A retrospective cohort study was performed using 199 foetal records taken from nuchal translucency (NT) clinic, from 1 June 2016 to 30 November 2019. Intracranial translucency (IT) measurements were assessed using existing nuchal translucency (NT) images of the foetuses aged 11 weeks to 13 weeks and 6 days of gestational age, where the foetal measurements taken for this study were between 45 and 84 mm. Eighteen samples were excluded, leaving only 181 samples that met the set criteria were used to establish the IT normal range. Inclusion criteria for this study involved all pregnant women with singleton pregnancies who had undergone NT scan with gestational ages ranging from 11 to 13 + 6 days. Based on the normal range value created, a total of 144 samples were normal foetuses, while the other 37 foetuses had various ultrasound abnormalities in the second trimester of pregnancy with no open spina bifida found. The results obtained exhibit linearly increased IT measurements with increasing crown-rump length (CRL), gestational age (GA), and nuchal translucency (NT).

***Keywords**: Antenatal, first trimester, intracranial translucency, normal range, ultrasound.*

INTRODUCTION

Intracranial translucency (IT) is a new approach used to detect foetal abnormalities as early as 11 weeks to 13 weeks and 6 days gestation, in the first trimester. A previous study[1] stated that the absence of intracranial translucency is associated with spina bifida. In foetuses with spina bifida, the ventricle is compressed due to a distorted part of the spinal cord resulting in invisibility of the intracranial translucency[1].

During ultrasonography, the midsagittal view plays an important role in determining IT position. At this level, IT would be seen to be parallel to the nuchal translucency (NT). The IT position is separated by two echogenic boundaries, where the anterior and posterior parts are the brain stem and choroid plexus, respectively. The space between these parts is the fourth ventricle of the foetal brain. The first trimester screening of intracranial structures is essential in determining normality of foetal neurological structures in second and third trimesters. Previously, IT was described as a sonographic landmark used for early detection of spina bifida[1]. Not just that, it also helps clinicians in providing information, genetic counselling, and other alternative treatment for any detected abnormalities[2]. Prenatal diagnosis of foetuses with abnormalities and aneuploids is one of the primary considerations in maternal-foetal medicine[3].

In the first trimester of pregnancy, displacement of the brain structures causes pressure in the fourth ventricle and loss of normal IT[1, 4-6]. Meanwhile, in the second trimester of pregnancy, an Arnold-Chiari malformation is observed, as well as signs of lemon and banana in the brain. At the same time, there were intracranial structure abnormalities detected with the increase and absence of IT identified in some cases in the second trimester of pregnancy[7-10]. It has reported that foetal abnormalities can be diagnosed as early as the first trimester of pregnancy[11-12].

Most countries, including Asia and Europe, have had research done on IT. Some studies demonstrate a linear increase in IT with respect to crown-rump length (CRL) and gestational age (GA) of the foetus. However, no such study has been conducted in this country. Therefore, it is important to establish our own normal reference range of the foetus' neurological system as early as the first trimester to identify any potential foetal abnormalities in neurological system and detection of spina bifida. This study aims to generate an IT normal range of first trimester

foetuses in Hospital Canselor Tuanku Muhriz (HCTM) as a single centre experience and to observe any correlation between IT measurements and neurological system abnormalities identified by ultrasound in the second trimester of pregnancy.

METHODS

This study was a retrospective cohort of pregnant women who underwent examination in the first trimester and follow-up treatment until the third trimester at the Maternal and Foetal Medicine Unit, HCTM, from 1st June 2016 to 30th November 2019. This study was approved by the Research Ethics Board of Universiti Kebangsaan Malaysia (JEP-2020-297). The image samples taken involved pregnant women who had undergone NT ultrasound examination with a foetus crown-rump length between 45 and 84 millimetres at gestation between 11 weeks and 13 weeks and 6 days. Only images with absence of foetal structural or chromosomal abnormalities in the ultrasound scan were included in this study. Twin pregnancies, genetic abnormalities, image samples with abnormal NT measurements, pregnancies assisted through procedures, induction reproduction such as IVF, and pregnancies with diabetes were excluded which will increase the chances of producing a foetus that is abnormal. Ultrasound examinations were performed using Mindray ultrasound machines (Resona 7, Resona 6, and DC 8 Expert) using 3D4D and 2D transabdominal transducers with the probe frequencies between 4 and 8 MHz.

IT measurements were performed in accordance with the method introduced by a previous study[1], and the measurements were taken in the same position as NT measurements, in the midsagittal view. The midsagittal plane of the face should be obtained with the echogenic tip of the nose, rectangular shape of the palate anteriorly, the translucent thalamus in the centre, and nuchal membrane posteriorly. In this view, the fluid-filled space will be visible in the third ventricle between the right and left of the thalamus, with the presence of a cerebral aqueduct of Sylvius between both sides of the brain tissues. The IT was defined as the space between the area between two echogenic boundaries: the posterior border of the brainstem (BS) and the anterior part of the ligament of the choroid (fourth ventricle) on the recorded image. Then, measurement was made in the central section labelled as IT, with the most thickened distance using the above 'on-to-on' technique where the callipers were placed on the anterior and posterior of the echogenic borders (Figure 1). The ultrasound examination was performed by sonographers certified by the Foetal Medicine Foundation, United Kingdom. Measurements included were CRL, foetal heart rate, NT thickness, assessment of nasal bone, ductus venosus, and some of the evident anatomical features including the structure of the brain, abdomen, and bladder. All parameters were measured in millimetre (mm) units. IT measurements were performed on NT images that had been saved to be stored as new data for this study.

Figure 1: Ultrasound image of an 11-week-old foetus. Intracranial translucency (IT) measurement: MB (Midbrain), BS (Brainstem), IT (Intracranial translucency), and CM (Cisterna Magna). The diagram shows the size of an 11-week-old foetus.

The new measurement information for IT was saved and recorded into an Excel sheet. This was analysed using the statistical software package Statistical Package for Social Sciences (SPSS) (IBM

SPSS version 26). Mean ± standard deviation, median, and percentile values of IT were calculated to determine the relationship between IT and independent variables.

Normality tests were performed on the study data, and the results of normality tests found that the IT data tested with the Kolmogorov-Smirnov test showed the data were not normally distributed, as the *p*-value was below 0.05. As a result, the median was employed as a central tendency measurement in the presentation of IT-related research results, and the Spearman correlation test was used to connect IT with independent variables. A linear regression test was adopted to establish the association between IT and CRL, GA, NT, and age.

RESULTS

A total of 199 of IT images were performed in this study to form the normal range. Eighteen samples were excluded, leaving only 181 samples that met the set criteria which were used to establish a normal reference range. Based on the normal reference value created, a total of 144 samples were normal foetuses, while the other 37 foetuses had various ultrasound abnormalities in the second trimester of pregnancy with no open spina bifida found. More than half of the respondents were Malays (157, 86.7%), followed by 17 Chinese (9.4%), 4 Indians (2.2%), and the remaining 3 (1.7%) of other races who came for screening at HCTM. The average age of the respondents is 36.13 (SD 3.86) years. Women who came to the NT clinic were aged between 21 and 44 years old, with the median age for mothers was 36 years old. Meanwhile, the gestational ages of the foetuses involved in this study were between 11 weeks and 3 days to 14 weeks and 1 day with the prompting in days at 80 days and 99 days. The mean age of the foetuses studied was 89 days, with a median value of 89 days. The median for IT was 1.9 mm (1.0 mm to 3.9 mm). Table 1 shows the demographic data and its characteristic in the first trimester.

Table 1: Demographic and IT ultrasonography characteristics in first-trimester

Demographic Data	Intracranial Translucency (IT) (mm)	Crown-Rump Length (CRL) (mm)	Age of Pregnant Mother (years)	Gestational age (GA) (days)
Mean	1.97	64.78	36.13	89.34
Median	1.90	63.80	36.00	89.00
Standard deviation	0.46	8.05	3.86	4.15
Range	2.90	36.70	23.00	19.00
Minimum	1.00	47.10	21.00	80.00
Maximum	3.90	83.80	44.00	99.00

Table 2 shows the IT value according to CRL ranges. Meanwhile, normal reference ranges for IT and CRL, GA, and NT were established and Figures 2, 3, and 4 demonstrate that all three are normally distributed. The graph of IT versus CRL revealed a linear correlation with relationship IT = 0.63 + 0.02 CRL, R^2 = 0.128, and *p*-value <0.005. Meanwhile, the relationship between IT and GA was IT = 1.69 + 0.04 GA, R^2 = 0.133 with *p*-value <0.005. Finally, IT = 1.62 + 0.22 NT, R^2 = 0.025, *p*-value = 0.003 represents the association between IT and NT. It can be shown in Figures 2, 3 and 4 that IT measurements increased linearly with increasing CRL, GA and NT.

Table 2: The IT value according to CRL ranges

CRL Ranges	Number of Foetus	Mean	Std. Deviation	Median
45.0-54.0 mm	20	1.68	0.39	1.7
55.0-64.0 mm	72	1.88	0.42	1.81
65.0-74.0 mm	67	2.05	0.47	2.0
75.0-84.0 mm	22	2.26	0.44	2.3
Total	**181**	**1.97**	**0.43**	**1.7**

Results of Spearman's correlation analysis revealed a positive and significant relationship between the foetal CRL, GA, and NT, with r values of 0.373, 0.393, and 0.221, respectively, on intracranial translucency (IT). Meanwhile, Table 3 exhibits no significant correlation between the age of pregnant mothers and IT with r value of = −0.096. On the other hand, no case of open spina bifida was discovered from the second-trimester ultrasound screening follow-up. It was observed that 144 samples were normal, while the other 37 samples showed various findings in the second-trimester ultrasound screening.

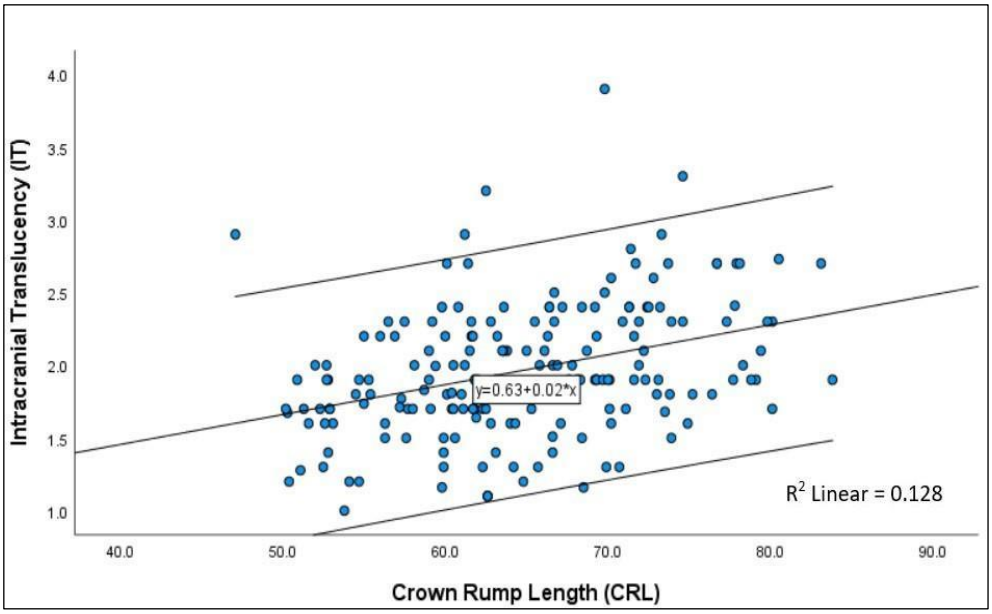

Figure 2: IT measurements according to CRL

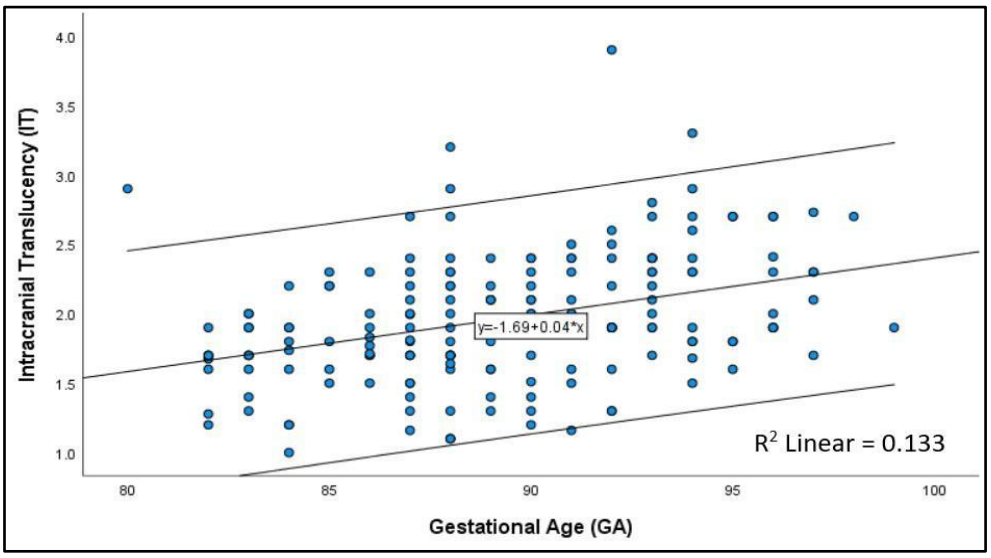

Figure 3: IT measurements according to GA in days

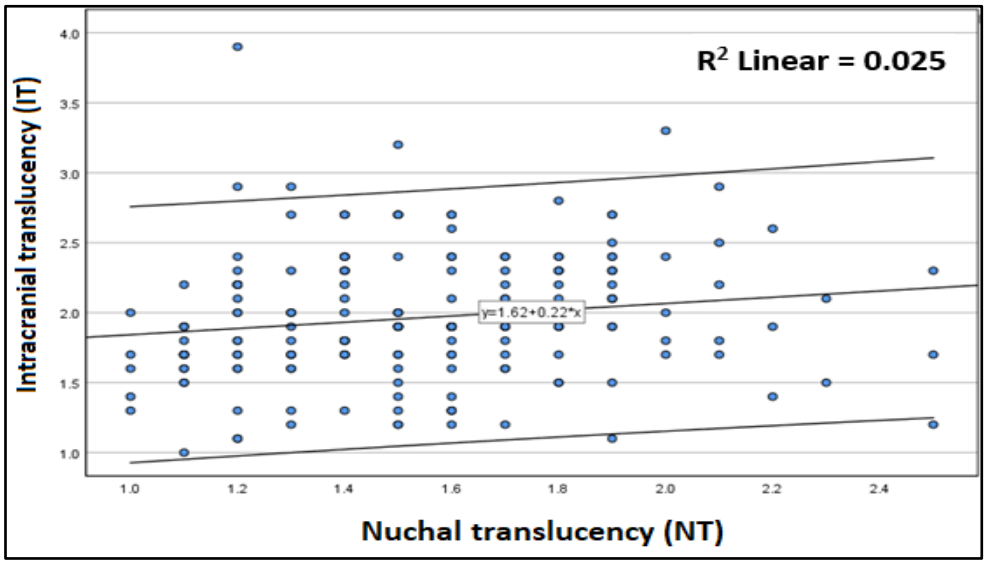

Figure 4: IT measurements according to NT

Table 3: Correlation between IT and independent variables

Independent Variables	Correlation Coefficient	*p*-value
Crown Rump Length (mm)	0.373	<0.005
Gestational Age (days)	0.393	<0.005
Nuchal Translucency (mm)	0.221	0.003
Maternal Age (year)	−0.096	0.197

DISCUSSION

This study found that the IT increases linearly with increments in CRL, GA, and NT. The results of this study are in line with previous studies conducted[13-14] for correlation between IT to NT. They found a significant correlation between IT to NT with correlation almost similar to the study conducted in this country ($r = 0.221$, $p = 0.003$)[13-14]. On the other hand, the results of the reference range for IT compared to CRL and IT compared to foetal GA showed a linear correlation similar to previous studies[1, 13, 15].

In this work, IT measurements were done with ease due to the midsagittal plane position of the samples in all the images taken. The measurements were conducted in accordance with the works from previous study[1]. The study conducted in HCTM observed that no foetus with high IT (exceeding the normal reference range) showed any chromosomal abnormalities and this is further confirmed through the karyotype testing on one out of six samples, which exceeded the IT reference range. On the contrary, this was not consistent with previous studies which had reported that IT has a significant relationship with chromosomal abnormalities[14, 16-17].

Nevertheless, this study found no case of spina bifida in the second trimester of pregnancy. Only one sample indicated a thick nuchal fold at 6.4 mm, and this sample also recorded IT within the normal reference range produced. Consequently, the baby was born normal, although the patient did not undergo the karyotype test to determine chromosomal abnormalities. The ultrasonography conducted in the second trimester of pregnancy resulted in 35 images with abnormalities other than neurological system abnormalities including samples that exceeded the normal reference range.
The normal reference range produced in this study was found to be similar to a previous study[13]. The result of this study is not statistically different from the IT mean values reported in previous studies[1, 15]. This study has a specificity value of 96.5%, which is almost similar to the value in another study with its value at 99%[18]. Meanwhile, another report mentioned that IT visualisation sensitivity and specificity values in the spina bifida diagnosis are 100%[1].

IT measurements are more easily conducted by a sonographer or operator experienced in performing ultrasonography in the first trimester of pregnancy[18-19]. Factors that could help in IT assessment and detections of foetal malformations in the first trimester of pregnancy involve large CRL size, large GA, mothers with less weight, supine position[20], experiences and advances in ultrasound technology and improvements in sonographers' skills[21-24]. Hence, higher experience and skills in performing ultrasound are recommended.

A detailed assessment of foetal anatomy can also be performed at this stage to identify foetuses with major structural abnormalities in early gestational age[25-27]. Subsequently, patients with impaired pregnancies can be detected sooner, thus providing more time to contemplate in terminating or continuing the pregnancy[26, 28-29]. Early detection in foetal IT in the first trimester pregnancy is important to ensure accuracy of foetus normal neurological structure seen in the second trimester. In this light, screening conducted in the gestational age of 11 to 13 weeks and 6 days could further help determine the NT, detection of severe malformations, and identify high-risk pregnancies.

The data on the diagnosis of structural anomalies through ultrasound in the first trimester is important for early planning[30], clinical management and decision-making in public health[31]. From a community health perspective, it can help the couple and treating doctors to prepare early for the arrival of babies with abnormal neurological systems as to provide mental and emotional support. Apart from that, early referral to maternal foetal specialist could be done without delay if the couple decide to continue the affected pregnancy from the first trimester to next trimester, for other examinations and investigations to be done further to confirm the foetal abnormalities.

On the other hand, with early diagnosis, the counselling could be challenging, in which the couple would demand termination of pregnancy before a complete diagnosis, without a thorough discussion of the prognosis yet to be accomplished[31].

Benefits and strengths

This study is very useful for future determining neurological effects on the foetus in the second trimester of pregnancy. The implication that can be derived from this study is a higher chance of

identifying a foetus with neurological system disorder as early as in the first trimester of pregnancy. These findings allow further planning for the care of a foetus with possible neurological system abnormalities or other abnormalities to be done without delay. In this regard, a test such as magnetic resonance imaging (MRI) could be offered after birth to examine the extent of the abnormality in the baby and confirmation of the diagnosis made prior. In addition, this study provides an opportunity for the couple with foetal abnormalities to detect possible pregnancy problems and prepare themselves mentally and emotionally prior to the delivery.

Moreover, early diagnosis of fatal structural defects or those linked to more severe defects provides the option time to safely end the pregnancy earlier[31]. Meanwhile, in cases with treatable anomalies, further treatments and follow-ups could be well planned before and after delivery by multi-disciplinary in the health unit[31]. Genetic analysis can be offered using methods such as the microarray analysis or series of invasive testing[32] for further confirmation.

Study limitations

There are some limitations to this study, one being that the study can only be carried up to the second trimester of pregnancy. While almost all samples studied had deliveries at HCTM, we only collected data until the second trimester as this study aimed to examine the foetal neurological system only up to the second trimester of pregnancy and compare to the IT findings in the first trimester. In addition, the study was not able to collect full data on pregnancy outcomes. As HCTM is the centre for first trimester ultrasonography screening, patients would deliver at a different hospital, according to their preferences.

Implication and practice

IT has the essence in detection of possible spina bifida and other foetal abnormalities as early as in the first trimester of pregnancy. IT would further ensure accuracy of second trimester sonography findings. Early detection foetal anomalies helps to provide timely information for couple and allows health providers to develop a comprehensive management plan. The normal reference range produced in this study provides a reference guide for other sonographers in this region when performing ultrasound examinations during the first-trimester screening for future foetal neurological system in the second trimester sonography.

CONCLUSIONS

In conclusion, the IT increases linearly with increment in CRL, GA, and NT. IT normal reference range produced is the essence of accuracy for future second trimester sonography anticipation of early foetal abnormalities.

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