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Original Research

Increased nuchal translucency and fetal outcomes: a population-based study in Thailand

Kuntharee Traisrisilp[1], Supatra Sirichotiyakul[1], Fuanglada Tongprasert[1], Kasemsri Srisupundit[1], Suchaya Luewan[1], Phudit Jatavan[1], Sirinart Sirilert[1], Theera Tongsong[1,*]

[1] *Maternal Fetal Medicine Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, 50200 Chiang Mai, Thailand*

*Correspondence: theera.t@cmu.ac.th (Theera Tongsong)

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Background: To determine the association between increased nuchal translucency (INT) and fetal outcomes among Thai population. *Methods*: A prospective database of fetal Down syndrome screening project was accessed to enable retrieval of the records of any women with recorded NT measurements. The selected pregnancies were categorized into the INT group (>95th percentile) and the normal (<95th percentile) group. The effectiveness of NT for prediction of Down syndrome and hemoglobin Bart's disease was also determined. Pregnancy outcomes were compared, also using multivariate analysis to correct the major confounders. *Results*: Out of 8225 NT measurements recorded, data from 7126 fetuses were available for analysis. These included 357 in the INT group and 6769 in the normal group. INT was significantly associated with Turner syndrome, Down syndrome, Edwards' syndrome, Patau syndrome, cardiac defect and Hb Bart's disease. After exclusion of fetal abnormalities, rates of abortion, low birth weight (LBW), preterm birth and intrauterine death (IUD) were significantly higher in the INT group, with adjusted odds ratio (95% CI) of 7.82 (7.48–13.66), 0.60 (0.42–0.86) and 5.10 (1.11–23.42), respectively. INT was effective in predicting Down syndrome with a sensitivity of 61.1% with a false positive rate of 5%. *Conclusions*: In addition to effectiveness in screening aneuploidy and cardiac defect, INT significantly increased the identification of risk of some diseases specific to a certain geographical area, for example Hb Bart's disease in Thailand. Among the euploid fetuses in this study the rate of abortion, LBW, preterm birth and IUD were also significantly increased.

Keywords

Chromosome abnormality; Fetal anomaly; Fetal outcomes; Hemoglobin Bart's disease; Nuchal translucency

1. Introduction

Several studies have demonstrated that increased nuchal translucency (INT) is strongly associated with fetal cytogenetic disorders [1–5], especially trisomy 21 or 45, XO, and some specific fetal anomalies, in particular cardiac defects [3, 6, 7]. Additionally, INT in euploid fetuses or unexplained INT has been reported to be associated with various poor obstetric outcomes [8–13], including spontaneous abortion, low birth weight, preterm birth, fetal growth restriction, gestational diabetes mellitus, and preeclampsia. Nevertheless, most studies concerning effectiveness of NT measurements as a screening test of chromosome abnormalities or fetal cardiac defects are confined to the western world, the outcomes of NT screening in developing countries being reported rarely. The reproducibility of the effectiveness described in western countries has not been tested in other areas of the world. Furthermore, some fetal disorders are highly prevalent in some specific geographical areas. Such specific diseases, for example congenital heart disease, may possibly be associated with INT. A specific example fetal hemoglobin (Hb) Bart's disease (homozygous alpha-thalassemia-1) is very common in Southeast Asia [14–16], the prevalence of this trait is as high as 6.6% in Thailand [16]. In our extensive experience of ultrasound examination of fetuses with Hb Bart's disease, we have often encountered INT among such fetuses. However, the association between INT and fetal Hb Bart's disease has never been extensively explored. Although association between INT and chromosomal or structural abnormalities has been reported several times, studies from different geographical areas are needed to accumulate worldwide data. This is especially important in determining how reproducible the NT measurement as a screening test for fetal chromosome and cardiac abnormalities can be in the worldwide population and whether INT can be helpful in predicting some locally specific fetal disorders. Counseling and management of pregnant women with INT is very challenging and needs more informative specific data. Therefore, we carried out this Thai population-based research, aimed primarily at identification of the effectiveness of INT in screening for chromosomal abnormalities, congenital heart diseases and fetal Hb Bart's disease (a disease specific to our population) and secondarily to assess the association between unexplained incidence of INT and adverse obstetric outcomes. It is important to note that in Thailand the option of serum marker screening for fetal Down syndrome in the first trimester is generally not available, while the quad test in the second trimester is available and funded by the government, as a national policy. Thus, we focused on NT measurement as this would be very useful for first trimester screening in a low-resource setting as NT is more freely available than serum screening in the first trimester.

2. Materials and methods

A comparative study of pregnancy outcomes, using a prospective database of Down syndrome screening, was undertaken at Maharaj Nakorn Chiang Mai hospital, Chiang Mai University, Thailand, a tertiary center teaching hospital. The study was ethically approved by the institute review boards. On the database construction, the women who attended our prenatal care clinic in the first trimester, including those referred for fetal Down syndrome screening from peripheral hospitals in the northern part of Thailand. All were screened with serum biomarkers or nuchal translucency (NT) under the project of National University Research (Thailand). All women undergoing the screening were systematically evaluated and demographic data, obstetric characteristics, details of fetal Down syndrome screening, (biomarkers or NT), and pregnancy outcomes were prospectively recorded. The pregnant women were invited to join the project and provided written informed consent. This study included the consecutive pregnant women from January 2010 and December 2018, who met the following inclusion criteria: (1) singleton pregnancy, (2) fetal Down syndrome screening with NT between 11 and 13^{+6} weeks of gestation, relying on crown-rump length measurement in the first trimester, and (3) availability of the data on pregnancy outcomes. The pregnancies with serious maternal medical diseases, including cardiac disease, uncontrolled hypertension, and pre-gestational insulin-dependent DM were excluded from analysis.

The NT thickness was measured by the well-trained maternal-fetal medicine (MFM) team (including MFM staff members and MFM fellows), in the period 11 and 13^{+6} weeks of gestation using either Aloka scanner models: Prosound α-10, α-7, or α-6, (Aloka Co, Ltd, Tokyo, Japan) or the Voluson E8 (GE Medical Systems, Zipf, Austria), together with a transducer of 3.5-MHz-frequency. The NT measurement followed the standard techniques suggested by The Fetal Medicine Foundation Center [17]. The women undergoing NT measurement were followed-up for obstetric and fetal/neonatal outcomes, including chromosome evaluation. The obstetric outcomes were assessed by the obstetricians and neonatal outcomes were assessed by the pediatricians in the researcher group.

Demographic data included maternal age and weight, ethnicity, obstetric history such as parity, prior pregnancy complications, etc., residency, and smoking habits. Information regarding underlying medical disease was also collected. The primary outcomes are fetal adverse outcomes with a focus on the common chromosome abnormalities (trisomy 13, 18, 21 and 45, XO), congenital heart defects, Hb Bart's disease, and other major anomalies. The secondary outcomes are other adverse obstetrics outcomes including miscarriage (less than 24 weeks of gestation), preterm birth (delivery at gestational age of less than 37 complete weeks), low birth weight (less than 2500 g), fetal growth restriction (birth weight of $<$10th percentile), low Apgar score at 5 minutes (score of less than 7) and intrauterine fetal death (after 24 weeks of gestation).

The database was accessed and all consecutive records were validated to retrieve the cases meeting the inclusion criteria. The selected records were categorized into either the INT group (increased NT group; defined as the NT of more than 95th percentile of the reference ranges), or the NNT group (normal NT; defined as the NT of less than 95th percentile).

Statistical analysis was performed using SPSS version 21.0 (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Version 21.0. IBM Corp., Armonk, NY, USA). The baseline characteristics and fetal outcomes of the two groups (INT vs NNT) were compared, using Student T-test/Mann-Whitney-U for continuous data and Chi-square test as well as relative risks with 95% CI for categorical data. Logistic regression analysis was used to adjust the confounding factors of pregnancy outcomes, such as maternal age, parity and weight. P-value < 0.05 was defined as significant.

3. Results

During the study period, 8225 pregnancies underwent NT measurements. Of these, 1099 were excluded because of incomplete follow-up or no final outcome data, twin pregnancies or underlying medical diseases. Finally, data from 7126 fetuses were available for analysis, including 357 (5.0%) in the group of increased NT (INT) and 6769 (95.0%) in the group of normal NT (NNT), details are shown, as presented in Fig. 1. Baseline characteristics of the pregnancies in both groups (INT vs NNT) were comparable in terms of maternal age, weight, parity, gestational age and crown-rump length at the time of NT measurements, as presented in Table 1. Nearly all were of Thai ethnicity and lived in the northern part of Thailand.

Comparison of the fetal outcomes showed that more than a quarter of the fetuses in INT group had chromosomal or structural abnormalities, a markedly higher rate than that in the NNT group (26.9% vs 3.2%; $P < 0.001$). All major chromosomal abnormalities were significantly higher in the INT group (Turner syndrome 10.6% vs 0.2%; Down syndrome 3.1% vs 0.1%, Edward's syndrome 2.0% vs 0.15%; Patau syndrome 1.4% vs 0.1%), as shown in Table 2. The efficacy of NT as a screening test for fetal Down syndrome among an unselected pregnant Thai population, was shown to have a sensitivity of more than 60% with a false positive rate of 5%, when NT measurement was performed by MFM specialists. These results are presented in Table 3. The overall rate of structural anomalies among euploid fetuses in INT group was also higher than in the NNT group (8.4% vs 3.2%; $P < 0.001$). In a subgroup analysis of euploid fetuses with anomalies, the prevalence of congenital heart diseases (CHD) and fetal Hb Bart's disease was significantly higher in the INT group (3.6% vs 0.9%; $P < 0.001$ and 2.0% vs 0.4%; $P < 0.001$, respectively). Other fetal anomalies were not significantly different, although that in the INT group had a tendency to be increased but the difference did not reach statistical signifi-

Table 1. Baseline characteristics of pregnancies in the increased nuchal translucency (INT) and normal nuchal translucency (NNT) groups.

Outcome	INT (n: 357)	NNT (n: 6769)	*P*-value
Mean maternal age; Year ± SD	29.7 ± 7.0	29.8 ± 5.2	0.938
Maternal weight; Kg ± SD	56.4 ± 15.4	55.8 ± 11.3	0.619
Parity:			0.091
• Nulliparous women	198 (56.4%)	4124 (60.9%)	
• Parous women	153 (43.6%)	2645 (39.1%)	
Gestational age at NT measurement; Day ± SD	85.0 ± 1.2	87.6 ± 6.2	0.404
Crown-rump length at NT measurement; mm ± SD	61.5 ± 35.9	61.0 ± 16.8	0.604

Table 2. Fetal outcomes of pregnancies in the increased nuchal translucency (INT) and normal nuchal translucency (NNT) groups.

Outcome	INT (n: 357)	NNT (n: 6769)	*P*-value
Aneuploidy (with or without structural anomaly)	66 (18.5%)	50 (0.7%)	<0.001
• Turner syndrome	38 (10.6%)	15 (0.2%)	<0.001
• Down syndrome	11 (3.1%)	7 (2.0%)	<0.001
• Edward syndrome	7 (2.0%)	10 (0.15%)	<0.001
• Patau syndrome	5 (1.4%)	6 (0.1%)	<0.001
• Other chromosome abnormalities	5 (1.4%)	12 (0.2%)	<0.001
Anomalies in euploid fetuses	30 (8.4%)	218 (3.2%)	<0.001
• Congenital heart defect	13 (3.6%)	63 (0.9%)	<0.001
• Hb Bart's disease	7 (2.0%)	30 (0.4%)	<0.001
• Other anomalies	10 (2.8%)	125 (1.8%)	0.201

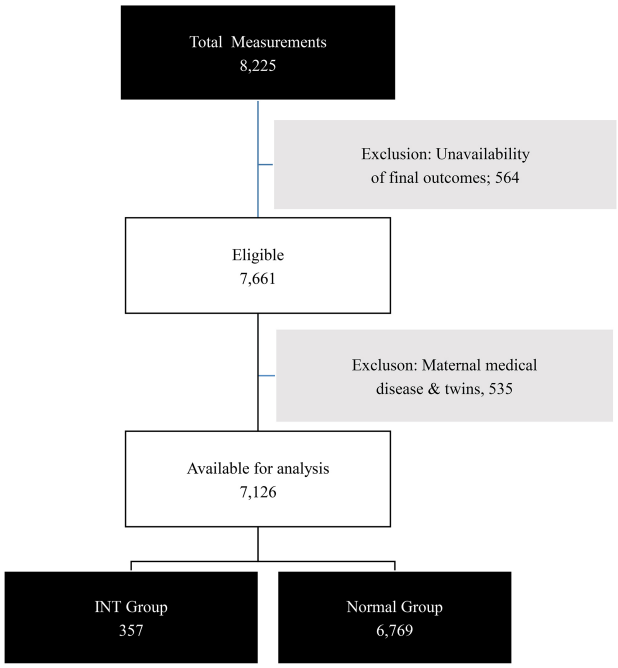

Fig. 1. Flow chart of enrollment.

cance (2.8% vs 1.8%; *P*: 0.201). Comparisons of NT thickness between normal fetuses and fetuses with major abnormalities are presented in Fig. 2. The details of structural anomalies among euploid fetuses with INT are presented in Table 4. Of note, most cases of fetal cardiac anomalies were critical to fetal hemodynamic changes. Of the cases with other anomalies, skeletal lethal dysplasia was the most common, totaling 3 cases, 1 in each of thanatophoric dysplasia, achondrogenesis and hypophosphatasia.

Finally, after excluding fetal abnormalities, based on univariate and multivariate analysis, the rates of abortion, low birth weight (LBW), preterm birth and intrauterine death (IUD) were significantly higher in the INT group, whereas the rate of fetal growth restriction was comparable, as presented in Table 5.

4. Discussion

Insights gained from this study include: (1) a significant association was found between INT (greater than 95th percentile) and fetal disorders, mainly chromosome abnormalities, congenital heart defect and Hb Bart's disease; and (2) a significant association between INT and an increased risk of adverse obstetric outcomes among pregnancies with euploid and normally formed fetuses. These included abortion, low birth weight, preterm birth and intrauterine fetal death. Although the pathogenesis of INT remains unclear, INT could be a probable sign of adverse pregnancy outcomes [18]. Accordingly, first trimester NT screening is of value and INT indicates the necessity for further prenatal follow-up or surveillance. We have noted that several incidences of anomalies could be detected at the time of NT measurement and several cases showed some abnormalities. These led to close surveillance, abnormalities showing more obviously at follow-up.

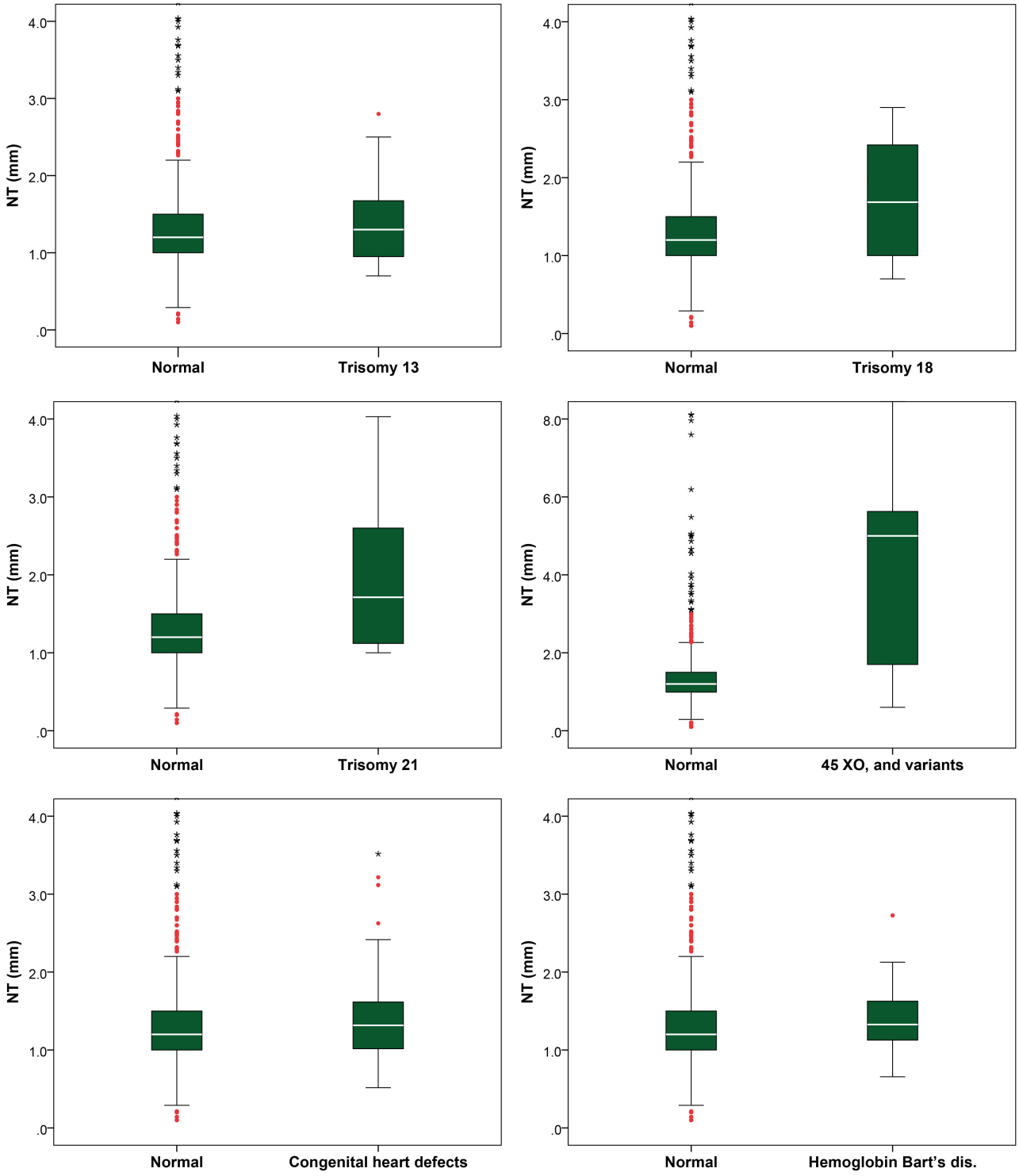

Fig. 2. Boxplots of nuchal translucency (NT) comparing normal fetuses and fetuses with major abnormalities.

For example, one case of INT showed mild ventriculomegaly at 14 weeks and Dandy-Walker malformation was diagnosed at 16 weeks of gestation. Notably, several disorders were subtle at the time of NT measurement and become more obvious on the detailed follow-up scans. Interestingly, all cardiac defects among euploid fetuses associated with INT were critical in our series, including AVSD, HLHS, HRHS, tricuspid atresia, Ebstein's anomaly, and absence of aortic valves. No single case of isolated VSD was found to have INT in this series. Though sensitivity of INT in the prediction of CHD among euploid fetuses was relatively low, 17%, in this study which was the same as in a previous study which reported a ROC 0.65 [19], a comparatively large number of critical CHD were prenatally detected in early gestation.

Table 3. The efficacy of NT in predicting fetal outcomes.

Outcomes	Sensitivity % (95% CI)	Specificity % (95% CI)
Abortion	29.8 (20.0–39.5)	95.3 (94.8–95.8)
Turner syndrome	61.5 (46.3–76.8)	95.5 (95.0–96.0)
Down syndrome	61.1 (38.6–83.6)	95.1 (94.6–95.6)
Edward's syndrome	41.2 (17.8–64.6)	95.1 (94.6–95.6)
Patau syndrome	45.5 (16.0–74.9)	95.1 (94.5–95.6)
Other chromosomal abnormalities	29.4 (7.8–51.1)	95.1 (94.5–95.6)
Heart defect	17.1 (8.6–25.6)	95.1 (94.5–95.6)
Hb Bart's disease	18.9 (6.3–31.5)	95.1 (94.6–95.6)
Other major anomaly	7.4 (3.0–11.8)	95.0 (94.5–95.5)

Table 4. The number of euploid fetuses with increased nuchal translucency.

Specific anomalies	Number of cases
Congenital heart defects	
• Ebstein's anomaly	2
• TGA	2
• TOF	2
• Absent aortic valve	1
• AVSD with small LV	1
• HLHS with interupted arch	1
• HRHS	1
• Severe pulmonary stenosis	1
• Tricuspid atresia	1
• Tricuspid dysplasia	1
Other congenital anomalies	
• Skeletal dysplasia	3
• Cystic hygroma	2
• Hydrops fetalis (lymphatic)	2
• Dandy-Walker malformation	1
• Diaphragmatic hernia	1
• Omphalocele	1

Many previous studies showed that fetal anomalies other than CHD and chromosome-associated anomalies are also significantly associated with INT [3, 9, 20, 21]. Our study found that such other anomalies tended to be increased but did not reach statistical significance. The weak relationship was possibly due to the heterogeneity of anomalies, some of which increased NT and some not. We hypothesized that INT might be associated with several specific disorders, as is CHD, but the significance could not be demonstrated because the number of cases with the diseases is too small to gain enough statistical power. We noted that only a small number of fetal anomalies showed INT but some of them occurred repeatedly, such as skeletal dysplasia, and hydrops of unknown causes. It may not be reasonable to analyze the association between INT with all non-specific anomalies but we should rather test the association with specific disorders of which INT is reported repeatedly. However, since such anomalies are relatively rare, it is impossible to perform a study even with a large sample size to assess the level of association, if it exists. However, it is worthwhile to report the case series to accumulate cases in literature for future meta-analysis to enable the correlation of some specific rare diseases and INT.

Similar to most previous studies, we found that INT is strongly associated with aneuploidy and fetal cardiac defects. Nevertheless, in contrast we also found that a significant number of fetuses with Hb Bart's disease showed INT at the end of the first trimester. Therefore, our study indicates that the significance of INT in different geographical areas might reflect different specific local problems. Hb Bart's disease is lethal, usually resulting in hydrops fetalis in the second half of the pregnancy. Several attempts have been made to perform intrauterine transfusion to term for bone marrow transplantation after birth but the outcomes are usually unsatisfactory. In cases of no early detection and pregnancy termination, the disease usually causes serious maternal complications including early-onset severe preeclampsia, dystocia and postpartum hemorrhage caused by an enlarged placenta [15]. Currently, nearly all cases of Hb Bart's disease were prenatally diagnosed, usually in the second trimester or mid-pregnancy when sonographic signs of cardiomegaly or increased MCA-PSV appear. This study supports that, in some cases, NT measurement may facilitate early detection of the affected fetuses, though NT is not sensitive enough for complete screening purpose. In high prevalence areas, Hb Bart's disease should be included in differential diagnosis in cases of unexplained INT. This is important since at the time when NT measurements are usually carried out there are no other hydropic/pre-hydropic signs. Thus, NT may be helpful in early detection of Hb Bart disease. In other words, in the areas of high prevalence of Hb Bart's disease (homozyogous alpha-thalssemia1), genetic diagnosis of the disease may be offered for pregnancies with unexplained INT. Accordingly, it is theoretically possible that INT may be more common among other non-immune types of hydrops caused by inherited inborn errors like mucopolysaccharidosis. Thus, the specific areas with high prevalence of such an inherited disease should be explored for INT.

The strengths of this study include: (1) a relatively large sample size, (2) the prospective nature of the database development, under our project of Down syndrome screening, enabling us to retrieve relative, informative data regarding newborns and obstetric outcomes, and (3) high reliabil-

Table 5. Obstetric outcomes of pregnancies in the increased nuchal translucency (INT) and normal nuchal translucency (NNT) groups (excluding pregnancies with fetal abnormalities).

	Univariate analysis*			Multivariate analysis**	
Outcome	INT (n: 261)	NNT (n: 6501)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Abortion	19 (7.3%)	59 (0.9%)	<0.001	7.82 (7.48–13.66)	<0.001
Preterm birth	31 (12.8%)	524 (8.1%)	0.010	0.60 (0.41–0.88)	0.009
Fetal growth restriction	16 (6.1%)	366 (5.9%)	0.897	1.06 (0.63–1.79)	0.831
Low birth weight	41 (16.5%)	649 (10.1%)	0.001	0.60 (0.42–0.86)	0.006
Low Apgar 5 mins	4 (1.8%)	41 (0.7%)	0.053	2.77 (0.98–7.80)	0.055
Intrauterine fetal death	2 (0.8%)	10 (0.2%)	0.021	5.10 (1.11–23.42)	0.036

* Chi-square test; ** Logistic regression analysis adjusted for maternal age, parity and weight.

ity of NT measurements since the measurements were performed by MFM fellows and MFM staff members under this prospective project, not as a part of routine work and all measurements were imaged for subsequent validation.

The weaknesses of this study are as follows: (1) a relatively large number of cases with loss to follow up, this is due to the fact that most women were referred for Down syndrome screening at our hospital but they were not the resident in our region, leading to difficulty in follow-up for the final outcomes, (2) no long term follow-up of the newborns with unexplained INT as in some studies which found that around 10% of normal children had neurological development or orthopedic problems at age 1–3 years [22], (3) although INT seems to be useful in screening for Hb Bart's disease, the sensitivity is low and the sample size of this study is relatively small, the findings do however warrant a study with a larger sample size in the future. (4) The operators, though systematically trained, following the MFM fellowship training curriculum, accredited by The Royal Thai College of Obstetricians and Gyneoclogists, not all were certified for NT measurements with the Fetal Medicine FOUNDATION (https://fetalmedicine.org/). (5) Finally, this study did not include other first trimester sonomarkers such as nasal bone, tricuspid regurgitation, or ductus venousus Doppler flow, which have additional benefits in aneuploidy screening. For example, the performance in aneuploidy screening is increased when combined NT with ductus venosus pulsatility index and maternal age [23].

5. Conclusions

The prevalence of fetuses with INT is approximately 4.7% in this unselected Thai population. This study demonstrated an association between INT with a significantly increased risk of fetal aneuploidy and critical cardiac defects, similar to other western studies. However, Hb Bart's disease, a serious common genetic disease in our population, is also associated with INT. Moreover, among fetuses with unexplained INT, the rate of abortion, LBW, preterm birth and DFU are also significantly increased.

Author contributions

KT, Conceptualization, design of the research, data validation, drafting the work/revising. SupS, data collection, final approval. FT, data collection, final approval. KS, data collection, final approval. SL, data collection, manuscript revision, final approval. PJ, data collection, final approval. SirS, data collection, final approval. TT, Conceptualization, design of the research, analysis, manuscript revision.

Ethics approval and consent to participate

Ethical approval for this study was granted by the Institute Review Boards, Faculty of Medicine, Chiang Mai University, Thailand. Study code Number: OBG-2562-06961. Informed consent was obtained from all subjects involved in the study.

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Conflict of interest

The authors declare no conflict of interest.

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