First Trimester Genetic Sonogram for Screening Fetal Down Syndrome: a Population-based Study

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Research article

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Abstract

Background: To evaluate the performance of first trimester sonomarkers in the detection of fetal Down syndrome among Thai pregnant women

Methods: Pregnant women at 11-13⁺⁶ weeks' gestation underwent ultrasound examination for assessment of nuchal translucency (NT), nasal bone (NB), tricuspid regurgitation (TR), and abnormal ductus venosus (aDV) Doppler waveforms. The women were followed up for final outcomes. Fetal abnormalities other than trisomy 21 were excluded. The performances of each sonomarker and their combinations in predicting fetal Down syndrome were calculated.

Results: A total of 7,820 pregnant women meeting the inclusion criteria were available for analysis, including 20 cases with fetal Down syndrome and 7,800 unaffected cases. Of the four sonomarkers, NT, as a single sonomarker, had the highest detection rate (55.0% at a false positive rate of about 5%), whereas the remaining single sonomarkers had low detection rate (15-20%). The combination of all sonomarkers had the highest detection rate of 70% but the false positive rate was as high as 10.8%. The combination of NT and NB had a detection rate of 60% with an acceptable false positive rate of 6.9%, whereas the other combinations yielded relatively high false positive rates.

Conclusion: The first trimester genetic sonogram in screening for Down syndrome among Asian women is acceptably effective and may be offered to some selected groups of the population. NT is the best sonomarker with a detection rate of 55% at 5% false positive rate and its combination with NB can improve performance with minimal increase in false positive rate.

Introduction

Down syndrome is one of the most common genetic diseases with a prevalence of 1 in 600 - 700 live births⁽¹⁾. Because of its association with severe intellectual impairment and high frequency of structural defects, it is acceptable worldwide that Down syndrome screening should be provided to all pregnant women regardless of maternal age.⁽²⁾ Currently, several modalities are available for fetal Down syndrome screening, including cell-free fetal DNA in maternal plasma, maternal serum biomarkers in the first and second trimester, and ultrasound genetic screening. However, cell-free fetal DNA and maternal serum biomarkers, though highly effective, are not available in many parts of the world, especially developing countries. Ultrasound genetic screening, though less effective, is available worldwide and helpful in daily practice. Currently, a great number of pregnant women attend antenatal care clinic in the first trimester, permitting us to offer an option of first trimester ultrasound screening to facilitate early detection. First trimester ultrasound for Down syndrome screening is usually performed at 11-13⁺⁶ weeks of gestation, and the sonomarkers include nuchal translucency (NT)⁽³⁻⁶⁾, nasal bone (NB)⁽⁷⁻¹⁰⁾, tricuspid regurgitation (TR)^(11,12), ductus venosus waveform (DV)⁽¹³⁻¹⁵⁾ and frontomaxillary facial angle (FMA)⁽¹⁶⁻¹⁸⁾. NT is the most commonly used sonomarker for Down syndrome screening in the first trimester, giving a detection rate of 70-80% with a false positive rate of 5%⁽⁸⁾. NT has been extensively studied in Western countries.

Nevertheless, the reproducibility in other geographical areas is rarely explored. NB has also been found to be highly predictive of fetal Down syndrome with a detection rate of 73% in the first trimester⁽⁷⁾ but it has been less validated by other studies compared with NT. Although, TR and DV have been reported to be associated with Down syndrome, the number of studies focusing on them are limited⁽¹¹⁻¹⁵⁾. Importantly, most of those studies involved Western women and reported each sonomarker separately. Studies concerning the combination of NT with other sonomarkers are very limited, especially those involving Asian women. Accordingly, the aim of this study is to evaluate the performance of each first trimester sonomarker, (NT, NB, TR, and DV) and their combination in the detection of fetal Down syndrome in the first trimester among Thai pregnant women, possibly representing Southeast Asian population. To the best of our knowledge, this is the first study evaluating the performance of genetic sonogram in the first trimester among the Asian population.

Patients And Methods

This study was carried out at Maharaj Nakorn Chiang Mai hospital, a tertiary center and medical school. It is a diagnostic research performed as a second analysis using our prospective database, constructed under the project “Down syndrome screening” of National Research University of Thailand. Regarding the database development, pregnant women attending our antenatal care unit in the first trimester and those who were referred from other hospitals in the northern region of Thailand for fetal aneuploidy screening were screened with maternal serum biomarkers or nuchal translucency (NT) in the first trimester. All women participating in the project were systematically approached, and the following data were prospectively recorded: demographic data (maternal age, body weight, ethnicity, smoking habit, underlying medical disease, etc.), obstetric data (menstrual history, previous pregnancy complications, etc.), Down syndrome screening results, serum biomarker profiles and first trimester ultrasound parameters including crown-rump length (CRL), nuchal translucency (NT), nasal bone (NB), tricuspid regurgitation (TR), ductus venosus (DV) waveforms, and obstetric outcomes. A sonomarker was considered abnormal (positive test) under the following conditions: 1) NT was greater than 95th percentile of the Thai reference range⁽¹⁹⁾; 2) the absence of nasal bone; 3) the presence of tricuspid regurgitation (at least half of systole with a velocity over 60 cm./sec⁽²⁰⁾; or 4) reversed a-wave of the DV Doppler waveforms. All pregnant women were counseled and offered the first trimester combined test, and they provided written informed consent. Further, all women were followed up for pregnancy outcomes, which were assessed by the obstetricians, while neonatal outcomes were assessed by the pediatricians of the research team.

The study population was pregnant women attending our antenatal care clinic from January 2010 to November 2019, who met the following inclusion criteria: 1) singleton pregnancy, 2) gestational age of 11 to 13⁺⁶ weeks, based on crown-rump length in the first trimester, measured on the day of recruitment, and 3) known final fetal diagnosis of Down syndrome status. The diagnosis of Down syndrome was based on chromosome studies: karyotypes derived from chorionic villus sampling, amniocentesis, cordocentesis or neonatal work-up. The diagnosis of “no” Down syndrome was made by chromosome

studies or concluded by the neonatologists based on clinical findings in cases for which chromosome study was not done. Exclusion criteria were cases with fetal structural anomalies other than trisomy 21 and unavailability of final outcomes.

Ultrasound assessments of NT thickness, the presence of NB, TR and abnormal DV waveforms were performed by the maternal-fetal medicine (MFM) staff members and MFM fellows, using either Aloka machines : Prosound α -10, α -7, or α -6 (Aloka Co, Ltd, Tokyo, Japan) or Voluson E8 (GE Medical Systems, Zipf, Austria), equipped with transducers of 3.5-MHz-frequency. The measurement of NT, NB, TR and DV followed the standard techniques suggested by previous studies ^(7, 14, 20, 21).

Regarding analysis, the database was accessed to retrieve all the consecutive records meeting the inclusion criteria mentioned above. This study obtained ethical approval from the Institutional Review Boards, Faculty of Medicine, Chiang Mai University (Study code: OBG-2562-06961).

Statistical analysis: The analysis was performed using SPSS version 21.0 (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). The sensitivity (detection rate) and false positive rate with 95% CI of each parameter and their combinations in predicting fetal Down syndrome were calculated.

Results

During the study period, from January 2010 to November 2019, 8,944 Thai pregnant women underwent first trimester ultrasound genetic screening. After excluding cases with unknown final outcomes, fetal structural anomalies, and twin pregnancies, 7,820 were available for analysis, including 20 pregnancies with fetal Down syndrome and 7,800 unaffected cases, as shown in Fig. 1. The baseline characteristics of the recruited pregnancies in both groups are presented in Table 1. Note that the mean maternal age of the women with fetal Down syndrome was slightly but significantly higher than that of the unaffected women (31.7 ± 5.3 vs 29.5 ± 4.9 years; $p: 0.036$). Likewise the number of women with advanced maternal age (≥ 35 years) was significantly higher in the affected group. Other characteristics were comparable. Nearly all recruited women were of Thai ethnicity and resided in northern part of Thailand.

Table 1
Comparisons of baseline characteristics between the pregnancies with fetal Down syndrome and unaffected pregnancies

Characteristics	Unaffected	Down Syndrome	P-value
Mean (SD) maternal age (years)	29.5 (4.9)	31.7 (5.3)	0.036*
Advanced maternal age (≥ 35 years)	1012 / 7800 (13.0%)	6 / 20 (30.0%)	0.024#
Ethnicity			0.677#
• Thai	7733 (99.1%)	20 (100.0%)	
• Others	67 (0.9%)	0 (0.0%)	
Parity			0.153#
• Nulliparity	4724 (60.6%)	9 (45.0%)	
• Multiparity	3068 (39.4%)	11 (55.0%)	
Mean (SD) maternal weight at ultrasound examination (kg)	55.7 (10.7)	56.2 (13.8)	0.848*
Mean (SD) gestational age at ultrasound examination (day)	86.8 (5.9)	88.8 (4.4)	0.133*
Mean (SD) crown-rump length at ultrasound examination (mm)	61.0 (11.0)	62.4 (11.3)	0.576*
* Student's T test; # Chi-square			

The diagnostic performance of each genetic sonomarker and their combinations are presented in Table 2. Of the four sonomarkers, NT, as a single sonomarker, had the highest detection rate (55.0% at a false positive rate of about 5%), whereas the remaining single sonomarkers had low detection rates (15–20%). The combination of all sonomarkers had the highest detection rate of 70% but the false positive rate was as high as 10.8%. NT had the highest positive likelihood ratio (11.2) as a single sonomarker, followed by NB (9.3). Interestingly, the combination of NT and NB had a detection rate of 60% with an acceptable false positive rate of 6.9%, whereas the other combinations yielded relatively high false positive rates. Note that, with any combination of the sonomarkers, the test is considered positive when any of the sonomarkers is positive.

Table 2
Performance of each first trimester sonographic markers

Ultrasound markers	Detection rate% (95% CI)	False positive rate % (95% CI)	LR (95% CI)
NT	55.0 (33.2–76.8)	4.9 (4.4–5.4)	11.2 (7.4–16.8)
NB	20.0 (2.5–37.5)	2.2 (1.8–2.5)	9.3 (3.8–22.6)
TR	15.0 (0.6–30.6)	4.3 (3.8–4.8)	3.5 (1.2–9.9)
aDV	20.0 (2.5–37.5)	4.1 (3.6–4.5)	4.9 (2.0–11.9)
NT or NB	60.0 (38.5–81.5)	6.9 (6.4–7.5)	8.7 (6.0–12.5)
NT or TR	55.0 (33.2–76.8)	9.0 (8.3–9.6)	6.1 (4.1–9.2)
NT or DV	60.0 (38.5–81.5)	8.7 (8.1–9.3)	6.9 (4.8–9.9)
GSG	70.0 (49.9–90.1)	10.8 (10.1–11.4)	6.5 (4.8–8.7)
NT: nuchal translucency; NB: nasal bone; TR: tricuspid regurgitation; aDV: abnormal ductus venosus Doppler waveforms; GSG: genetic sonogram (combination of the four parameters); LR: likelihood ratio			

Discussion

The insights gained from this study are as follows: 1) NT is the best first trimester sonomarker for fetal Down syndrome screening among Thai population, possibly representing Southeast Asian women. Presumably, the effectiveness of NT is reproducible in the Asian population, though the sensitivity is not as good as reported in Western reports, 55% in this study compared with 75–80% in Western study⁽⁸⁾. 2) The combination of all four sonomarkers can increase the overall sensitivity to 70% but the false positive rate is also increased. 3) The best combination is NT and NB, which yields a detection rate of 60% with a minimal increase in false positive rate. 4) The addition of TR and DV Doppler to a combination of NT and NB causes only a minimal increase in detection rate with an obvious increase in false positive rate. Accordingly, the most attractive genetic sonogram for Down syndrome screening in the first trimester is a combination of NT and NB.

Though several studies have reported the effectiveness of the four sonomarkers in fetal Down syndrome screening as single sonomarkers, the effectiveness of their combination has been rarely studied. Moreover, most studies were performed on Caucasian pregnant women and only few studies evaluated the performance in other populations: however, racial factor has been documented to have a significant effect on the detection rate of such sonomarkers, especially NB⁽²²⁾. Notably, the diagnostic performances of the four sonomarkers were somewhat lower than those reported in Western studies. For example, DV had a sensitivity of 66.4% in screening for fetal Down syndrome in the large study at King's College Hospital reported by Maiz et al.⁽¹⁴⁾, whereas the sensitivity in this study was only 20%. Likewise, Kagan et al.⁽¹¹⁾ reported that TR had a sensitivity of 55.7% in predicting Down syndrome in the first trimester, much

better than that in this study. Additionally, Cicero et al. ⁽⁷⁾ reported a detection rate of 73% by the absence of NB at 11–14 weeks of gestation, which is much higher than that in this study. Our study indicates that the performances of NT, NB, TR and aDV in screening for fetal Down syndrome among Thai women, possibly representing Southeast Asian women, are less effective than those among Caucasian women; in the other words, their performances are not perfectly reproducible in our population. Such reduced effectiveness might be associated with racial factors. Nevertheless, our results still support the use of first trimester genetic sonogram with precaution because it can provide useful information for counseling and making decisions on further invasive diagnosis. NT as well as NT plus NB may be offered to some selected couples. NT plus NB is preferable because of the higher sensitivity with minimal increase in false positive rate. The addition of NB is not labor-intensive, because, in practice, NT and NB assessment can be accomplished on the same standard plane of the same images, mid-sagittal scan of the fetal face.

The weaknesses of this study are as follows: 1) Several sonomarkers other than the four used in this study that have been reported to be associated with fetal Down syndrome such as fronto-maxillary facial angle ^(23, 24), were not included. 2) The sample size is relatively small for the assessment of a disease with low prevalence like trisomy 21. Though this study included nearly 8,000 women, only 20 cases had fetal trisomy 21. 3) In this study, serum biomarker testing was not incorporated for analysis.

The strengths of this study are as follows: 1) The data used for analysis was based on a prospective database, recorded specifically for fetal Down syndrome screening at the time of ultrasound measurements and the final outcomes were followed by the research team. 2) The results were derived from actual practice in unselected population, probably representing the real effectiveness in daily MFM practice. 3) High reliability of ultrasound assessments because all examinations were performed by MFM specialists.

In conclusion, NT is the best sonomarker for first trimester detection of fetal Down syndrome, giving a sensitivity of 55% with a false positive rate of 5%, followed by NB, giving a sensitivity of 20%. The combination of NT and NB yields a better diagnostic performance with a sensitivity of 60% and a false positive rate of 7%. TR and DV waveform had detection rates (15–20%) that were too low to be used as single sonomarkers. The combination of all sonomarkers led to a minimal increase of approximately 10% in detection rate and an increase of more than 10% in false positive rate. Therefore, this study supports the combination of NT and NB as a sonographic screening tool in the first trimester rather than the use of NT alone but does not support the combination of all four sonomarkers because of the high false positive rate. Though the first trimester genetic sonogram of Thai women is not as effective as that reported for Caucasian women, the performance of NT as well as NT plus NB is acceptable and may be offered to some selected groups of the population.

Abbreviations

aDV

Abnormal ductus venosus Doppler waveform; CRL:Crown-rump length;DV:Ductus venosus;
FMA:frontomaxillary facial angle; MFM:Maternal fetal medicine; NT:Nuchal translucency; NB:Nasal bone;
TR:Tricuspid regurgitation

Declarations

Ethics approval and consent to participate

This study received ethnical approval from the institute review boards of Faculty of Medicine, Chiang Mai University (Ethics Committee 4; Research ID 6961; Study code: OBG-2562-06961).

Consent for publication

Not applicable

Availability of data and materials:

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

KT: contributed to the conception, design of the research and administration of the project, and drafting / revising the manuscript;

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Figures

Figure 1

Flow chart of enrollment.