Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 269-277.

OBSTETRICS

Accuracy of the Combined First Trimester Down Syndrome Screening Test and the Optimum Range of the Cut-off Point for Intermediate-risk Identification: Twelve years' experience

Thanapa Rekhawasin Pinnington, M.D.*,
Jenjira Arthan, M.Sc.IT*,
Chulaluk Komoltri, DrPH**,
Pharuhas Chanprapaph, M.D.*

** Maternal Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thaland*
*** Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thaland*

ABSTRACT

Objectives: This study aimed to determine the performance of the combined first trimester Down syndrome screening test and the appropriate cut-off points for intermediate-risk identification.

Materials and Methods: This was a retrospective study conducted from May 2019 to May 2021. All the medical charts of women with singleton pregnancy who had a first-trimester combined screening test performed between 2007 - 2018 were reviewed. A total of 3,928 women with singleton pregnancy were included in the final analysis. Data regarding neonatal outcomes were recorded, and a telephone follow-up was performed with the women who had given birth elsewhere. Statistical analysis was performed using SPSS version 18.0 software.

Results: With a high-risk cut-off point of 1:250, the test had a sensitivity of 75%, and a specificity and accuracy of 94%. When an intermediate-risk cut-off point between 1:500 and 1:1,000 was applied, the specificity and accuracy increased to 83% - 90%. When using a cut-off point between 1:251 and 1:1,000, the specificity and accuracy was 83%, while the rate of intermediate risk was 11.6%.

Conclusion: Our combined first-trimester screening test had a detection rate of 75%, and a high specificity and accuracy of 94%. The recommended cut-off point for intermediate risk was between 1:251 and 1:1,000, since this offered good specificity and accuracy with an acceptable rate of intermediate risk.

Keywords: combined first-trimester, cut-off point, Down syndrome, intermediate risk, screening.

Correspondence to: *Pharuhas Chanprapaph, M.D., Maternal Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. E-mail: pharuhasc@gmail.com*

Received: 25 August 2023, **Revised:** 17 January 2024, **Accepted:** 23 February 2024

ความถูกต้องของการตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสม ในระยะเวลา 12 ปี

ธนาภา เรขาวศิน พินนิงตัน, เจนจิรา อาจหาญ, จุฬาลักษณ์ โกมลตรี, พฤหัส จันทร์ประภาพ

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาความถูกต้องของการตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสม (combined first-trimester screening test) ในการทำนายทารกกลุ่มอาการดาวน์ในสตรีตั้งครรภ์*

วัสดุและวิธีการ*: งานวิจัยนี้เป็นการศึกษาแบบย้อนหลัง โดยทำการศึกษาข้อมูลจากเวชระเบียนของสตรีตั้งครรภ์เดี่ยวที่มารับการตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสมในช่วงปี พ.ศ.2550-2561 จำนวน 3,928 ราย และติดตามข้อมูลการเกิดกลุ่มอาการดาวน์ของทารกแรกเกิด สำหรับสตรีตั้งครรภ์ที่ไม่ได้คลอดที่โรงพยาบาลศิริราช จะทำการโทรศัพท์เพื่อสอบถามข้อมูลทารกแรกเกิด*

ผลการศึกษา*: ค่าจุดตัดที่บ่งชี้ภาวะความเสี่ยงสูงของการตรวจคัดกรองที่ 1:250 พบว่ามีความไวร้อยละ 75 ความจำเพาะและความแม่นยำ ร้อยละ 94 เมื่อพิจารณาช่วงค่าความเสี่ยงที่ใช้เพื่อบ่งชี้ภาวะความเสี่ยงปานกลาง (intermediate risk range) ระหว่าง 1:500 และ 1:1,000 พบว่ามีค่าความจำเพาะและความแม่นยำร้อยละ 83-90 สำหรับค่าจุดตัดในช่วง 1:251 ถึง 1:1,000 พบว่ามีความจำเพาะและความแม่นยำร้อยละ 83 และอัตราการตรวจพบความเสี่ยงปานกลางคิดเป็นร้อยละ 11.6*

สรุป*: การตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสมมีค่าความไวร้อยละ 75 ความจำเพาะและความแม่นยำร้อยละ 94 โดยช่วงค่าความเสี่ยงที่แนะนำเพื่อบ่งชี้ภาวะความเสี่ยงปานกลางคือ 1:251 ถึง 1:1,000 เนื่องจากค่าจุดตัดดังกล่าวมีค่าความจำเพาะและความแม่นยำที่สูง และมีอัตราการตรวจพบความเสี่ยงปานกลางที่ยอมรับได้*

คำสำคัญ*: การตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสม, ค่าจุดตัด, กลุ่มอาการดาวน์, ความเสี่ยงปานกลาง, การตรวจคัดกรอง*

Introduction

Down syndrome is the most common autosomal aneuploidy and the cause of inherited intellectual disability, with an incidence of about 1 in 800 live births[1]. In Thailand, the incidence was reported to be 1.21 per 1,000 births[2]. Affected children can present with abnormal facial features, learning disorder, seizure, congenital heart disease, bowel atresia, leukemia, and a shorter life expectancy[1]. This syndrome can be found in all pregnant women, with a higher risk with increasing maternal age.

Screening for Down syndrome has been applied in clinical practice for over a half-century now, with various methods available. The first-trimester combined test, consisting of maternal age, nuchal translucency (NT) measurement, serum free beta-hCG (human chorionic gonadotropin), and PAPP-A (pregnancy-associated plasma protein-A), is one of the methods producing a high detection rate of more than 80%1, 3-10. However, the test results cannot be compared among studies and should be interpreted individually since some factors, including various ethnicities, cut-offs, and laboratory techniques, are influential in the results. Asian women were reported to have significantly different levels of serum free beta-hCG and PAPP-A, when compared with Caucasian women[11-15]. However, the serum level inclinations were even intriguingly found to be dissimilar between northern and southern parts of Thailand[14, 15].

Accordingly, the primary objective of this study was to determine the detection rate of the first-trimester combined test for Down syndrome screening at Siriraj Hospital, while the secondary objectives were to figure out a proper cut-off point for intermediate-risk identification and to identify the factors affecting the test accuracy.

Materials and Methods

According to the study of Luo et al[16], the sensitivity and the specificity of the combined first trimester screening test was 78.79% and 98.41%, respectively. Assuming that the test accuracy was 90%, the calculated sample size should be at least 3,458 based on the 95% CI of 90% ± 1%.

This retrospective study was conducted at the Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University during May 2019 to May 2021. It was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 344/2019). All the medical charts of pregnant women who had the first-trimester combined screening test performed between 2007 - 2018 were reviewed. Women with singleton pregnancy and who had the first-trimester combined screening test were included in the study, and their neonatal outcomes were recorded. Telephone follow-up was performed to inquire about such information for the pregnant women who had given birth elsewhere. The women whose pregnancy outcomes could not be followed up were excluded.

Outcome measures

First-trimester screening was performed between 11^{+0} and 13^{+6} weeks of gestation at the Maternal Fetal Medicine Unit, where blood samples were also drawn. Gestational age was calculated based on either certain last menstrual period or the crown rump length (CRL). Nuchal translucency (NT) and CRL were measured by maternal fetal medicine (MFM) experts following the standard protocol of the Fetal Medicine Foundation (https://fetalmedicine.org/education/the-11-13-weeks-scan three times, and the widest value was used. If nuchal translucency was ≥ 3 mm, then a prenatal diagnostic test was offered. Biochemistry markers, including both serum free beta-hCG and PAPP-A, were measured using the Kryptor analyzer (Brahms AG, Berlin, Germany) and reported by the Department of Clinical Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University, whose laboratory has been accredited to a high international standard level with the receipt of ISO

15189 accreditation.

In our practice, the risk from the combined test was calculated and classified into high, intermediate and low risk. In this study, the cut-off limit of 1:250 was used to define high risk, 1:1,500 for low risk, and a value between 1:250 and 1:1,500 was classified as intermediate risk. For intermediate-risk and high-risk results, the pregnant women would receive counseling about the risks and benefits of both cell-free DNA screening and amniocentesis. They were allowed to choose either a prenatal test or postnatal evaluation.

To determine the most optimal range for the intermediate-risk group identification, we gradually lowered the cut-off point from 1:300 to 1:1,500. The test performances from each cut-off point (1:251-1:300, 1:251-1:400, 1:251-1:500, 1:251-1:600, 1:251-1:700, 1:251-1:800, 1:251-1:900, 1:251-1:1,000 and 1:251-1:1,500) were then compared and analyzed to obtain the best result.

The main outcome of interest was the number of newborns with Down syndrome who were identified by either prenatal amniocentesis or postnatal clinical diagnosis. The data of which were extracted from the electronic-based medical records. For women giving birth elsewhere than Siriraj Hospital, a telephone follow-up was made to ask about postnatal outcomes.

Statistical analysis

Descriptive statistics were used as appropriate, including N (%), mean ± standard deviation (SD), and median with interquartile range (IQR). The chi square test was used for comparison of the categorical variables. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 4,006 pregnant women were identified as having had a combined first trimester Down syndrome screening test. There were 78 cases excluded from the study due to twin pregnancy with the remaining 3,928 singleton pregnancies.

From Table 1, it can be seen that the mean age and body mass index were significantly higher in the high-risk group. Regarding the biochemical markers, PAPP-A was significantly lower, 3,981.86 ± 4,684.37 vs. 5,799.47± 4,489.09 mIU/L, and free beta-hCG was significantly higher, 97.62 ± 65.32 vs. 52.14 ± 36.37 ng/mL, in the high-risk group. Nuchal translucency was also obviously higher in the high-risk group: 1.98 ± 0.69 vs 1.43 ± 0.46 mm. Intriguingly, the mean value for the combined risk of Down syndrome in the high-risk group was about 10 times higher than that in the low-risk group (1:124.19 vs 1: 13,169.53). Around 85% (182 out of 213) of the patients in the high-risk group and 15% (99 out of 660) in the intermediate-risk group opted to undergo a prenatal diagnostic (PND) procedure, whereas only 1.04% (32 out of 3,055) did so in the low-risk group.

There were 4 affected fetuses with trisomy 21 (T21) in this study, as confirmed by amniocentesis and postnatal outcome, with 3 of these in the high-risk group, while the remaining case was in the intermediate-risk group. All 4 of the pregnant women agreed to have an abortion after knowing the result, and the procedures went off without any complications. There was one affected fetus with trisomy 13 diagnosed by amniocentesis and abortion was also accomplished without any consequence.

The flow diagram showing the overall outcomes of all screening cases were shown in Fig. 1. Applying an original threshold of ≥1:250, 3,715 pregnant women were classified into the low-risk category. Among them, 131 individuals opted for prenatal invasive testing. Within this group, 99 and 32 pregnant women fell into

the intermediate and low-risk groups using the cut-off point at 1:251–1:1,500 and <1:1,500, respectively. Despite being aware of the procedural risks, they autonomously chose to undergo the invasive test for result confirmation. According to our unpublished data, factors positively influencing maternal decision-making to obtain prenatal diagnosis (PND) included a high monthly income, and primigravida women. Nevertheless, it is noteworthy that all women who refused PND in this study eventually delivered normal babies.

Using a cut-off point of ≥1:250 for high-risk identification, the efficacy of the test was demonstrated, including a sensitivity of 75%, negative predictive value (NPV) of 99.97%, and negative likelihood ratio of 0.26 (Table 2).

Table 1. Demographic data of the low-risk and high-risk groups (cut-off point ≥1:250).

Data	Total	Low risk	High risk	p-value
	(N = 3,928)	(N = 3,715)	(N = 213)	
Maternal age[#] (years)	31.01 ± 3.94 (15–46)	30.86 ± 3.86 (15–46)	33.63 ± 4.46 (21–44)	0.00*
Body mass index[#] (kg/m^2)	21.67 ± 3.82 (12.02–52.16)	21.60 ± 3.72 (12.02–48.44)	22.96 ± 5.14 (16.23–52.16)	0.00*
GA by U/S[#] (days)	87.55 ± 5.13 (61–98)	87.50 ± 5.13 (61–98)	88.48 ± 5.14 (72–97)	0.01*
PAPP-A[$] (mIU/L)	4,774 (2,985–7,257.75)	4,887 (3,075–7,396)	3,005 (1,518–4,856)	0.00*
PAPP-A[$] (MoM)	1.07 (0.72–1.54)	1.09 (0.74–1.57)	0.68 (0.41–1.05)	0.00*
Free beta-hCG[$] (ng/mL)	44.14 (29.10-67.62)	42.75 (28.40–64.09)	79.28 (54.45–121.90)	0.00*
Free beta-hCG[$] (MoM)	1.09 (0.74–1.66)	1.06 (0.73–1.57)	2.21 (1.43–3.25)	0.00*
Nuchal translucency[$] (mm)	1.40 (1.10–1.76)	1.40 (1.10–1.70)	1.90 (1.59–2.40)	0.00*
Refusal of PND	3,615 (92.0%)	3,584 (96.5%)	31 (14.6%)	0.00**
Acceptance of PND	313 (7.97%)	131 (3.5%)	182 (85.45%)	
- Chorionic villus sampling	6	1	5	
- Amniocentesis	307	130	177	
Fetal karyotype				
- Trisomy 21	4	1	3	
- Trisomy 13	1	1	-	
- 46,XY,inv(9)(p12q13)	2	2	-	
- Other chromosomal abnormalities	6	1	5	

[#] Data were shown in mean ± standard deviation (min-max), [$] Data were shown in median (interquartile range)

* Mann-Whitney U test, **Chi square test

GA: gestational age, U/S: ultrasound, PAPP-A: pregnancy-associated plasma protein A, hCG: human chorionic gonadotropin, MoM: multiples of the median, PND: prenatal diagnosis

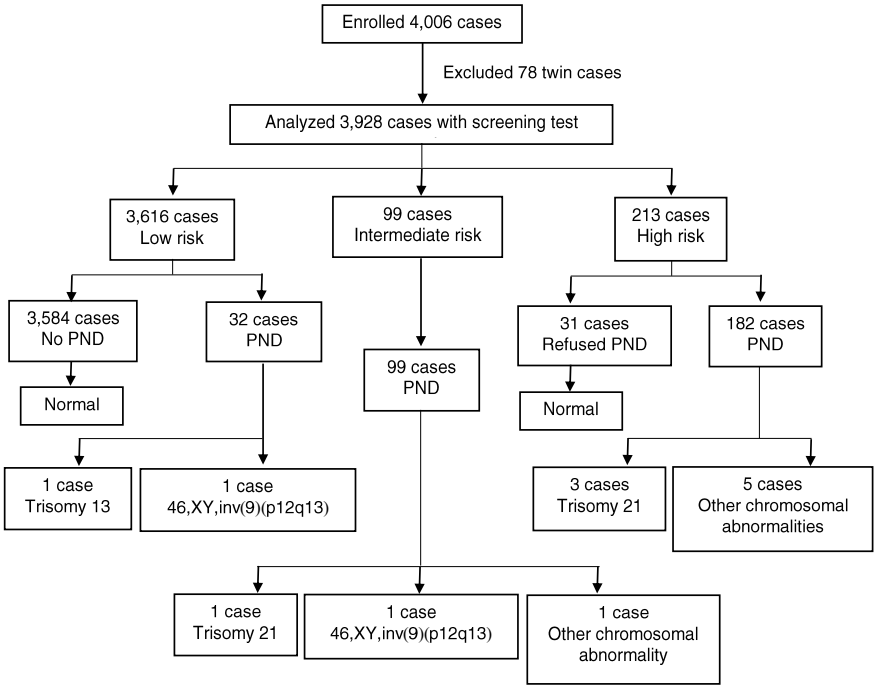

Fig. 1. Flow diagram showing the overall outcomes of all screening cases.
PND: prenatal diagnosis

Table 2. Efficacy of first trimester Down syndrome screening test in singleton pregnancy (n = 3,928) (cut-off point ≥ 1:250).

Efficacy	Percentage	95% CI (%)
Sensitivity	75.0	19.41–99.37
Specificity	94.65	93.69–95.33
Positive predictive value	1.41	0.79–2.49
Negative predictive value	99.97	99.85–100
Positive likelihood ratio	14.01	7.84–25.05
Negative likelihood ratio	0.26	0.05–1.44
Accuracy	94.63	93.88–95.31

CI: confidence interval.

The test performance results for each intermediate risk range, defined by different cut-off points, were shown in Table 3, where it can be seen that the higher the cut-off point, the better the specificity and accuracy of the test. More than 90% specificity and accuracy were reported when the cut-off point of ≥1:400 was used, 83% - 90% of which was observed between the cut-off points of 1:500 to 1:1,000. The test performance was significantly lower when the cut-off point of 1:1,500 was used. When the cut-off point was ≥ 1:250, the incidence of positive screening tests was 5.42% (213/3,928) in this study. When using a risk of 1:251 to 1:1,500 for the determination, 16.8% (660 out of 3,928) of the patients with intermediate risk could be identified.

Table 3. Range of intermediate risk and number of cases needing to be consulted.

Range of intermediate risk	Number of cases needing to be consulted	Specificity (%)	Accuracy (%)
1:251–1:300	42 (1.07%)	93.58	93.58
1:251–1:400	98 (2.49%)	92.18	92.18
1:251–1:500	163 (4.15%)	89.99	90.0
1:251–1:600	226 (5.75%)	88.91	88.93
1:251–1:700	278 (7.07%)	87.59	87.6
1:251–1:800	331 (8.42%)	86.24	86.25
1:251–1:900	390 (9.92%)	84.73	84.75
1:251–1:1,000	456 (11.6%)	83.05	83.07
1:251–1:1,500	660 (16.8%)	77.85	77.88

Discussion

This study found a prevalence of Down syndrome of 0.10%, which was similar to in other studies conducted in the northern (0.14%) and southern (0.12%) parts of Thailand. Taking a high-risk test result into consideration, we found that a combined first-trimester test was effective for Down syndrome screening, with a sensitivity of 75%, and specificity and accuracy as high as 94%. The sensitivity or detection rate was lower in this study when compared with previous studies[5, 6, 17, 18], which could be due to the lower cut-off point of 1:150 used in some studies[17, 18], and the higher maternal age in others[5, 19]. Nonetheless, various cut-off points for classifying high-risk results could merely be taken into account in this study, since there were only a few cases of fetal Down syndrome.

In this study, we also aimed to evaluate pregnant women with an intermediate-risk result, because this can give rise to a secondary screening test as a non-invasive prenatal test (NIPT) or even unnecessary amniocentesis, potentially leading to fetal loss. Based on our current intermediate risk range of 1:251 - 1:1,500, the rate of detection was 16.8%, which was just slightly higher than the 14% rate for standard contingent screening[20]. Various lower cut-off points were studied to determine the range of intermediate risk that would provide for a proper efficacy of the test.

Charoenratana et al[20] and Gil et al[21], reported higher sensitivities (88.9% and 87%); however, the performances in their studies were less than in our study as the rates of intermediate risk in both studies were even higher than in ours (38.2% and 30.4%), and their upper cut-off point was much lower than in ours (1:30 vs. 1:100), and therefore, cases of fetal Down syndrome were more likely to be included in such a wider range. Moreover, the nuchal translucency value was not included in interpreting the risk of Down syndrome screening in the former study, and thereby, the sensitivity of the test could be deemed to be lower.

When compared with the results in the study by Guanciali-Franchi et al[3], who reported a slightly better performance, as their rate of intermediate risk was 12%, and their sensitivity was higher than in our study, 93% vs. 75 %, and this could result from the much higher value of the upper cut-off point of 1:30 in this study and the higher mean maternal age, 32.4 vs. 31 years old.

Luo et al[16], using an upper cut-off point of 1:270 and a lower cut-off point of 1:1,000, reported a better performance than in our study, as their rate of intermediate risk was only 3.37%, and the efficacy of the test was also better than in our study, as follows: sensitivity 78.79%, specificity 98.41%, and positive predictive value 7.03%. Nonetheless, we could not

perform a direct comparison with this study since the median serum levels of the biomarkers have been found to be dissimilar in different ethnic groups, even among Asian populations.

We performed analysis regarding different lower cut-off points for intermediate risk to find out the proper specificity and accuracy of the test, as shown in Table 2. Despite the intermediate-risk range of 1:251 to 1,500 previously used in this study, the recommended optimal range should be 1:251 to 1:1,000, since this would provide an adequate range with great specificity and accuracy of 83%. Evidently, the latter value could reduce the rate of the intermediate-risk group from 16.8% to 11.6%, which would not exceed the standard rate in contingent screening and could avoid the need for an unnecessary invasive prenatal test.

Some studies have reported that pregnant women with an increased fetal NT of more than 3.0–3.5 mm have been convinced to undergo an invasive prenatal diagnosis, either chorionic villus sampling or amniocentesis, with a chromosomal microarray study[22, 23]. Considering fetuses with an NT of > 3.5 mm in this study, there were 7 cases observed and none of them were affected with Down syndrome, while 25 pregnant women with a fetal NT of ≥ 3 mm were found, with only one fetal trisomy 21 case detected according to the amniocentesis result following a high-risk combined test result. There was only 4% of trisomy 21 cases among the fetuses with an NT of ≥ 3 mm in our study, which was lower than the level of 8.62% (5/58) reported in a previous study[24], raising a question regarding the necessity of undergoing amniocentesis just to confirm the fetal condition of Down syndrome. Our previous study also demonstrated that using increased NT as a single marker could detect fetal trisomy 21 with a sensitivity of 50.0 % and specificity of 91.94 %, respectively[25].

There are some limitations of this study to note, such as the data were collected retrospectively, and hence some selection bias was unavoidable. Moreover, a larger sample size would be required in order to be able to analyze what the appropriate upper cut-off point should be for combined first-trimester Down syndrome screening as only a few cases were found in this retrospective study.

This study also had some strengths to note that some other studies might not, since all the serum tests were analyzed in the same certified laboratory and the NT measurements were conducted by MFM specialists in a single tertiary center hospital. Therefore, variations in the population and test results could be less when compared with performing studies among various centers.

Conclusion

Combined first-trimester screening, using a cut-off point of 1:250, provided great efficacy with a detection rate of 75 %, and specificity and accuracy of 94 %. Regarding the appropriate cut-off point for intermediate risk, we recommend a proper range of 1:251 to 1:1,000 as this elicited an acceptable rate of intermediate risk and a high specificity and accuracy of 83%.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Committee on Practice Bulletins-Obstetrics CoG, the Society for Maternal-Fetal M. Practice Bulletin No. 163: Screening for fetal aneuploidy. Obstet Gynecol 2016;127:e123-37.
2. Jaruratanasirikul S, Kor-Anantakul O, Chowvichian M, Limpitikul W, Dissaneevate P, Intharasangkanawin N, et al. A population-based study of prevalence of Down syndrome in Southern Thailand. World J Pediatr 2017;13:63-9.
3. Guanciali-Franchi P, Iezzi I, Soranno A, de Volo CP, Alfonsi M, Calabrese G, et al. Optimal cut-offs for Down syndrome contingent screening in a population of 10,156 pregnant women. Prenat Diagn 2012;32: 1147-50.
4. Crossley JA, Aitken DA, Cameron AD, McBride E, Connor JM. Combined ultrasound and biochemical screening for Down's syndrome in the first trimester: a Scottish multicentre study. BJOG 2002;109:667-76.
5. Lan RY, Chou CT, Wang PH, Chen RC, Hsiao CH. Trisomy 21 screening based on first and second trimester in a Taiwanese population. Taiwan J Obstet

Gynecol 2018;57:551-4.
6. Maxwell S, James I, Dickinson JE, O'Leary P. First trimester screening cut-offs for noninvasive prenatal testing as a contingent screen: Balancing detection and screen-positive rates for trisomy 21. Aust N Z J Obstet Gynaecol 2016;56:29-35.
7. Park SY, Jang IA, Lee MA, Kim YJ, Chun SH, Park MH. Screening for chromosomal abnormalities using combined test in the first trimester of pregnancy. Obstet Gynecol Sci 2016;59:357-66.
8. Schielen PC, Wildschut HI, Loeber JG. Down syndrome screening: determining the cutoff level of risk for invasive testing. Prenat Diagn 2009;29:190-2.
9. Soergel P, Pruggmayer M, Schwerdtfeger R, Muhlhaus K, Scharf A. Screening for trisomy 21 with maternal age, fetal nuchal translucency and maternal serum biochemistry at 11-14 weeks: a regional experience from Germany. Fetal Diagn Ther 2006;21:264-8.
10. Spencer K, Spencer CE, Power M, Dawson C, Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years prospective experience. BJOG 2003;110:281-6.
11. Manotaya S, Zitzler J, Li X, Wibowo N, Pham TM, Kang MS, et al. Effect of ethnicity on first trimester biomarkers for combined trisomy 21 screening: results from a multicenter study in six Asian countries. Prenat Diagn 2015;35:735-40.
12. Spencer K, Ong CY, Liao AW, Nicolaides KH. The influence of ethnic origin on first trimester biochemical markers of chromosomal abnormalities. Prenat Diagn 2000;20:491-4.
13. Leung TY, Spencer K, Leung TN, Fung TY, Lau TK. Higher median levels of free beta-hCG and PAPP-A in the first trimester of pregnancy in a Chinese ethnic group. Implication for first trimester combined screening for Down's syndrome in the Chinese population. Fetal Diagn Ther 2006;21:140-3.
14. Luewan S, Sirichotiyakul S, Yanase Y, Traisrisilp K, Tongsong T. Median levels of serum biomarkers of fetal Down syndrome detected during the first trimester among pregnant Thai women. Int J Gynaecol Obstet 2012;117:140-3.
15. Kor-Anantakul O, Suntharasaj T, Suwanrath C, Hanprasertpong T, Pranpanus S, Pruksanusak N, et al. Normative weight-adjusted models for the median levels of first trimester serum biomarkers for trisomy 21 screening in a specific ethnicity. PLoS One 2017;12:e0182538.
16. Luo W, He B, Han D, Yuan L, Chen X, Pang L, et al. A retrospective analysis of different contingent screening models for fetal Down syndrome In southwestern China. Sci Rep 2020;10:9457.
17. Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. N Engl J Med 2005;353:2001-11.
18. Santorum M, Wright D, Syngelaki A, Karagioti N, Nicolaides KH. Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13. Ultrasound Obstet Gynecol 2017;49:714-20.
19. Li SW, Barrett AN, Gole L, Tan WC, Biswas A, Tan HK, et al. The assessment of combined first trimester screening in women of advanced maternal age in an Asian cohort. Singapore Med J 2015;56:47-52.
20. Charoenratana C, Wanapirak C, Sirichotiyakul S, Tongprasert F, Srisupundit K, Luewan S, et al. Optimal risk cut-offs for Down syndrome contingent maternal serum screening. J Matern Fetal Neonatal Med 2018;31:3009-13.
21. Gil MM, Revello R, Poon LC, Akolekar R, Nicolaides KH. Clinical implementation of routine screening for fetal trisomies in the UK NHS: cell-free DNA test contingent on results from first-trimester combined test. Ultrasound Obstet Gynecol 2016;47:45-52.
22. Schmid M, Klaritsch P, Arzt W, Burkhardt T, Duba HC, Hausler M, et al. Cell-Free DNA testing for fetal chromosomal anomalies in clinical practice: Austrian-German-Swiss Recommendations for non-invasive prenatal tests (NIPT). Ultraschall Med 2015;36: 507-10.
23. Lund IC, Christensen R, Petersen OB, Vogel I, Vestergaard EM. Chromosomal microarray in fetuses with increased nuchal translucency. Ultrasound Obstet Gynecol 2015;45:95-100.
24. Yoshida S, Miura K, Yamasaki K, Miura S, Shimada T, Tanigawa T, et al. Does increased nuchal translucency indicate a fetal abnormality? A retrospective study to clarify the clinical significance of nuchal translucency in Japan J Hum Genet 2008;53:688-93.
25. Chanprapaph P, Dulyakasem C, Phattanchindakun B. Sensitivity of multiple first trimester sonomarkers in fetal aneuploidy detection. J Perinat Med 2015;43: 359-65.