Specificity of Fetal Tricuspid Regurgitation in Prediction of Down Syndrome in Thai Fetuses at 17-23 Weeks of Gestation

Sanitra Anuwutnavin MD*,
Prapat Wanitpongpan MD*, Pharuhas Chanprapaph MD*

** Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Objective: *To assess the specificity of tricuspid regurgitation (TR) in prediction of Down syndrome in Thai fetuses at 17-23 weeks' gestation and to determine the prevalence of TR among normal chromosome fetuses in a high-risk population.*

Material and Method: *A prospective study was performed in 395 high-risk pregnant women who underwent amniocentesis or cordocentesis for fetal karyotyping at 17-23 weeks. The presence or absence of TR was determined by pulsed wave Doppler at the time of prenatal diagnosis. TR was diagnosed when the regurgitation flow was observed for at least half of systole or ≥ 70 milliseconds with maximum velocity of ≥ 100 cm/sec. The diagnostic values of TR for detection of Down syndrome were calculated.*

Results: *The prevalence of TR was 3.8% (14/370) in normal chromosome fetuses and 40% (2/5) in Down syndrome fetuses. Fetuses with TR had a higher chance to be Down syndrome (11.1%) than those without TR (0.8%) (95% CI of the difference, 0.09-32.9, p = 0.036). Specificity, sensitivity, NPV and PPV of TR in prediction of Down syndrome were 95.9%, 40%, 99.2% and 11.1%, respectively. Among normal chromosome fetuses with TR, 14.3% (2/14) had congenital cardiac abnormalities.*

Conclusion: *TR is not only a high specificity secondary ultrasound marker at 17-23 weeks to identify fetuses with Down syndrome in high-risk pregnant women but also associates with the risk of cardiac defects in normal chromosome fetuses.*

Keywords: *Second trimester, Tricuspid regurgitation, Pulsed wave Doppler, Ultrasound markers, Down syndrome*

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Down syndrome is the most common aneuploidy among live-born infants and the prevalence increases with maternal age[1]. Traditionally, women aged 35 years or older at the time of delivery have been classified as a high-risk group of having a child with Down syndrome and genetic counseling and prenatal diagnosis for fetal karyotyping were usually offered[2]. When using maternal age as a screening method for invasive testing, the detection rate of Down syndrome is only 30% and some of these women refused amniocentesis due to the chance of fetal loss from the procedure[3]. In the 1990s, the combination of maternal age and second-trimester biochemical serum screening improved the detection rate of Down syndrome to approximately 70% by triple test and 80% by quadruple test at a 5% false-positive rate[2,3]. Nowadays, there are many screening protocols that select the most suitable candidates for invasive prenatal testing to decrease procedure-related losses of normal fetuses while remaining a high detection rate.

The genetic sonogram is the second-trimester ultrasound examination that provides an alternative approach for screening fetal Down syndrome. Major malformations have been sonographically detected

Correspondence to: Anuwutnavin S, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. E-mail: asanitra@hotmail.com

in about 25% of affected fetuses[4,5]. Nonstructural abnormalities or soft markers are more common than major abnormalities but these markers are non-specific, can also be present in normal fetuses, and are often transient. Several soft markers have been reported to be associated with aneuploid fetuses and risk of fetal Down syndrome is directly related to the number of the markers identified. Using the combination of these sonographic findings can improve the sensitivity and specificity of the screening[1,4,5].

Currently, many studies have reported that fetal tricuspid regurgitation (TR) which was detected by pulsed wave Doppler have been associated with an increased risk of fetal Down syndrome, especially in the first trimester (11-13^{+6} weeks)[6-11]. While during the second trimester, there is only one study by DeVore GR[12] who firstly used color Doppler and confirmed with pulsed wave Doppler ultrasound to diagnose TR and found that 28.8% of Down syndrome fetuses had TR, compared to only 1.7% of normal chromosome fetuses. However, there is very limited data of TR diagnosed by pulsed wave Doppler to predict fetal Down syndrome in the second trimester, therefore the purposes of the present study were to assess the specificity of TR which determined by pulsed wave Doppler in prediction of Down syndrome in Thai fetuses at 17-23 weeks' gestation and to determine the prevalence of TR among normal chromosome fetuses in high-risk population.

Material and Method

Between March and October 2008, this prospective study was performed in high-risk pregnant women who underwent prenatal diagnosis for fetal karyotyping in the Division of Maternal Fetal Medicine (MFM), Department of Obstetrics and Gynecology, Siriraj Hospital, Mahidol University, Bangkok, Thailand. The present study was approved by the institutional review board of Siriraj Ethics Committee. The inclusion criteria consisted of singleton pregnancy, gestational age at 17 + 0 to 23 + 0 weeks which based on a history of certain last menstrual period and/or confirmed by ultrasound examination in the first or second trimester, indicated for fetal karyotyping either by amniocentesis or cordocentesis. Informed consent was obtained from all participants. The cases whose results of tricuspid flow profile or fetal karyotype were not acquired were excluded from the present study. The indications of prenatal diagnosis for fetal karyotyping were advanced maternal age ($\geq$ 35 years at the time of delivery), family history of abnormal chromosome, increased risk of chromosomal defects from abnormal serum screening or other sonographic markers and present of fetal anomaly.

Ultrasonography was accomplished using an abdominal 3.3-4.1 MHz curvilinear transducer of Voluson E8 (GE medical Systems, Austria).

All abnormal chromosome fetuses were diagnosed by karyotype study. Normal variants, common inversion and balanced translocations were defined as normal chromosome result in this study.

The fetal TR was determined by pulsed wave Doppler at the time of prenatal diagnosis demonstrating an abnormal reverse flow from right ventricle back into right atrium during ventricular systole similar to the protocol for assessment of fetal tricuspid flow in the first trimester[10]. The sample volume (3-4 mm.) was placed across the tricuspid valve, including right atrium and right ventricle, in the apical four-chamber view and the angle of the ultrasound beam and blood flow direction was less than 30 degrees (Fig. 1). TR was diagnosed when a regurgitation flow was observed for at least half of systole or duration $\geq$ 70 milliseconds with maximum velocity of $\geq$ 100 cm/sec[13], in order to avoid misinterpretation from normal flow of right outflow tract which never exceeded 100 cm/sec during this gestation[14]. A single, short reverse spike produced by tricuspid valve closure or valve click in an early systole was not diagnosed as TR

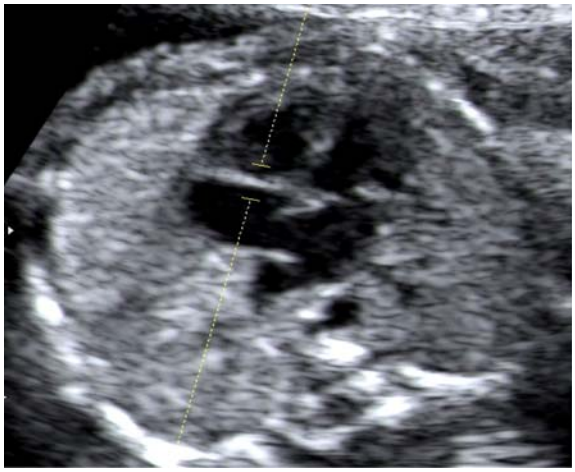


Fig. 1 Cross-sectional of fetal thorax showing an apical four-chamber view of the fetal heart. The sample volume (3-4 mm) was placed across the tricuspid valve and the angle of blood flow direction should parallel to the direction of the ultrasound beam

(Fig. 2). The severity of TR was defined as two grades[13]; trivial (non-holosystolic jet or maximum velocity < 200 cm/sec.) and significant (holosyslolic jet and maximum velocity ≥ 200 cm/sec.) (Fig. 3). The examiner spent less than 20 minutes for each patient.

Demographic data, ultrasound findings, evaluation of TR, and results of fetal chromosome were recoded in a computer database. If TR was present, the maximum velocity and duration of reversed flow during ventricular systole were also noted. The normal chromosome fetuses with TR were appointed for detailed echocardiography and followed-up. And autopsy of aneuploidy fetuses were reported if available.

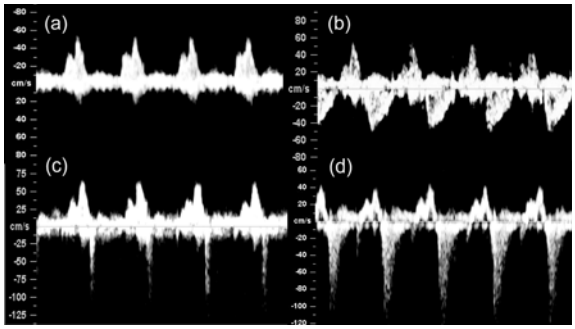


Fig. 2 The pulsed wave Doppler assessment of fetal tricuspid flow (a) no regurgitation was observed during ventricular systole, (b) a jet from aortic or main pulmonary artery which peak systolic velocity were not more than 100 cm/sec during the second trimester, (c) A single, short reverse spike produced by tricuspid valve closure in an early systole (duration 30-40 milliseconds), and (d) tricuspid regurgitation was seen at least half of systole (duration ≥70 milliseconds) and maximum velocity ≥ 100 cm/sec

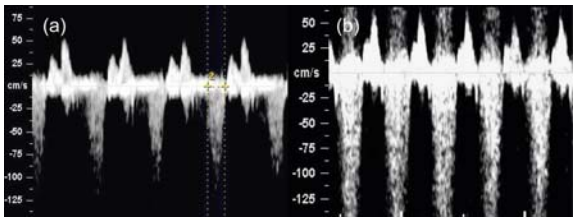


Fig. 3 The grading of TR (a) trivial TR has nonholosystolic jet or maximum velocity < 200 cm/sec and (b) significant TR was described by holosyslolic jet and maximum velocity ≥ 200 cm/sec (in this case had velocity 200 cm/sec)

Intra-observer reliability between two repeated examinations in 15 minutes apart was evaluated in 50 cases. The validity was accessed in another 30 cases by the examiner versus the other two experienced perinatologists (Wanitpongpan P and Chanprapaph P).

Statistical analysis

The demographic data, ultrasound findings and chromosome results were presented as percent or mean ± SD or median with range where appropriate. To compare quantitative variables with and without normal distribution between fetuses with and without TR, unpaired t-test and Mann-Whitney U-test was performed. Fisher's exact test was used to test the association between TR and qualitative characteristics *e.g.*, parity, underlying maternal diseases. The kappa coefficient was used to assess the intra-observer reliability. The validity of the examination between the observer and experienced perinatologists was analyzed. The difference in the proportions of chromosome abnormalities between fetuses with and without TR was tested using Fisher's exact test. The diagnostic values of TR for detection of Down syndrome were presented as sensitivity, specificity, NPV and PPV.

The p-value of less than 0.05 was considered statistically significant. All statistical data analyses were performed by using SPSS 15.0 (SPSS Inc, Chicago, IL, USA).

Results

During the study period, 395 high-risk pregnant women were enrolled into the present study. The maternal demographic characteristics between fetuses with and without TR are listed in Table 1. There were no significant differences between the 2 groups in maternal age, gestational age, height, weight, body mass index (BMI), parity and underlying maternal diseases. The mean ± SD of maternal age and gestational age were 37.2 ± 3.4 years and 18.8 ± 1.2 weeks, respectively. The indications for prenatal diagnosis in theses fetuses were as follows: advanced maternal age in 366 cases, family history of abnormal chromosome in 7 cases, increased risk of chromosomal defects from abnormal serum screening or other sonographic markers in 5 cases, present of fetal anomaly in 8 cases and 9 patients had more than one indication. Fetal karyotyping was obtained from amniocentesis in 375 cases and cordocentesis in 20 cases. There were 25 abnormal chromosome fetuses detected including

Table 1. The maternal demographic characteristics between fetuses with and without tricuspid regurgitation

Maternal demographics	Fetal tricuspid regurgitation		p-value
	Absent (n = 377)	Present (n = 18)	
Maternal age (y)	37.3 ± 3.3	35.9 ± 5.0	0.092*
Gestational age (wk)	18.8 ± 1.2	19.3 ± 1.7	0.239*
Height (cm)	156.5 ± 5.7	156.0 ± 7.4	0.710*
Weight (kg)	59.0 ± 10.8	59.1 ± 8.9	0.977*
BMI	24.1 ± 3.9	24.4 ± 3.9	0.731*
Parity			0.319+
Nulliparous	138 (36.6)	9 (50)	
Multiparous	239 (63.4)	9 (50)	
Maternal diseases	51 (13.5)	3 (16.7)	0.723+
DM	17 (4.5)	1 (5.6)	0.576+
Heart diseases	4 (1.1)	0 (0)	1.000+
Chronic hypertension	7 (1.9)	0 (0)	1.000+
Thyroid diseases	9 (2.4)	2 (11.1)	0.085+
Others	17 (4.5)	0 (0)	1.000+

BMI, body mass index; DM, diabetes mellitus and gestational diabetes mellitus; others, central nervous system, respiratory, thalassemia, skin and breast diseases
Data are mean ± SD or n (%)
* Unpaired t-test
+ Fisher's exact test

trisomy 21, trisomy 18, trisomy 13, Turner syndrome and others (5,8,2,5 and 5 cases respectively).

Intra-observer reliability showed an excellent agreement (k = 0.78; 95% CI, 0.49-1.00; p < 0.001). Validity of TR by observer compared to experienced perinatologists revealed sensitivity, specificity and accuracy of 83.3% (95% CI, 51.6-97.9), 94.4% (95% CI, 72.7-99.9) and 90% (95% CI, 73.5-97.9), respectively.

TR was identified in 4.6% (18/395) of the total population. The prevalence of TR was 3.8% (14/370) in normal chromosome fetuses and 40% (2/5) in Down syndrome fetuses (Table 2). In 22.2% (4/18) of fetuses with TR had abnormal chromosomes whereas those without TR had chromosomal defects in 5.6% (21/377) (95% CI of the difference, 0.4-40.3, p = 0.042). Fetuses with the presence of TR had a higher chance to be affected by Down syndrome (11.1%, 2/18) than those without TR (0.8%, 3/377) (95% CI of the difference, 0.09-32.9, p = 0.036) (Fig. 4).

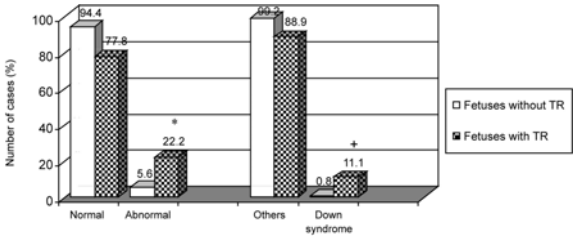
The specificity, sensitivity, NPV and PPV of TR in prediction of Down syndrome were 95.9% (95% CI, 93.4-97.6), 40% (95% CI, 5.3-85.3), 99.2% (95% CI, 97.7-99.8) and 11.1% (95% CI, 1.4-34.7), respectively (Table 3).

The severity of TR based on the maximum velocity and the duration of reversed flow during ventricular systole. In the normal chromosome fetuses, trivial TR and significant TR were presented in 9 and 5 cases, respectively. The median maximum velocity was 160 (range, 110-225) cm/sec and the median duration of reversed flow was 170 (range, 80-270) milliseconds in the normal chromosome group. Whereas the abnormal chromosome fetuses were found to

Table 2. The prevalence of tricuspid regurgitation in normal and abnormal chromosome fetuses

Fetal karyotype	Number of cases	Tricuspid regurgitation	
		Absent (n (%))	Present (n (%))
Normal	370	356 (96.2)	14 (3.8)
Down syndrome	5	3 (60)	2 (40)
Trisomy 18	8	8 (100)	0 (0)
Trisomy 13	2	2 (100)	0 (0)
Turner syndrome	5	4 (75)	1 (25)
Others*	5	4 (75)	1 (25)
Total	395	377 (95.4)	18 (4.6)

* Sex chromosome abnormalities (47,XXX in 2 cases, 47,XYY, 47,XYY/45,X) and trisomy 9



* 22.2% (4/18) of fetuses with TR had abnormal chromosome compared to 5.6% (21/377) of fetuses without TR (95% CI of the difference, 0.4-40.3, p = 0.042)

+ 11.1% (2/18) of fetuses with TR were found to have Down syndrome, compared to 0.8% (3/377) of fetuses without TR (95% CI of the difference, 0.09-32.9, p = 0.036)

Fig. 4 The proportions of normal and abnormal chromosome between fetuses with and without tricuspid regurgitation (TR)

Table 3. The diagnostic values of tricuspid regurgitation in prediction of Down syndrome

TR	Abnormal chromosome (n)		Normal chromosome (n)	Total
	Down syndrome	Others		
Present	2	2	14	18
Absent	3	18	356	377
Total	5	20	370	395

Remarks: sensitivity = 40% (2/5), specificity = 95.9% (374/390), NPV = 99.2% (374/377), PPV = 11.1% (2/18)

have only mild TR in 4 cases with the median maximum velocity of 120 (range, 105-150) cm/sec and the median duration of reversed flow was 150 (range, 80-200) milliseconds. There were no statistical significant differences in the severity of TR between the normal and the abnormal chromosome fetuses (type of grading; p = 0.278, the maximum velocity; p = 0.072 and the duration of reversed flow; p = 0.741).

Among 14.3% (2/14) of euploidy fetuses which presented with significant TR had congenital cardiac abnormalities including Ebstein anomaly with pulmonary stenosis and atrioventricular septal defect. While the others (12/14) had normal fetal echocardiography and TR disappeared thereafter within 3-12 weeks, all of them had normal pregnancy outcome.

Discussion

All of our cases were at high risk of chromosomal anomalies with 6.3% (25/395) of the fetuses proved to have chromosomal defects by karyotyping. The TR prevalence in normal chromosome and Down syndrome fetuses were 3.8% (14/370) and 40% (2/5), respectively. Regarding the risk of Down syndrome, fetuses with the presence of TR had a significant higher chance to be affected (11.1%) than those without TR (0.8%) (p = 0.036).

The use of TR in prediction of Down syndrome had a sensitivity of 40%, specificity of 95.9%, likelihood ratio for positive test of 9.8, and false-positive rate of 4.1%. This data was comparable to DeVore's study[12] which reported the sensitivity, specificity, likelihood ratio, and false-positive rate of 28.8%, 98.3%, 23.3 and 1.7, respectively. The authors' results of sensitivity and likelihood ratio differ from the previous report; these could be the effect of smaller sample size in the present study.

The findings of the present study can confirm that the second-trimester TR which determined by pulsed wave Doppler is a highly specific marker for fetal Down syndrome. The fetus with absent TR is less likely to have Down syndrome while the presence of TR increases the risk of fetal Down syndrome. This useful information can help to select the most suitable candidates for invasive testing to decrease procedure-related losses of normal fetuses, especially in high-risk pregnant women who refuse invasive testing in order to avoid the potential fetal loss.

TR has been described in association with several pathologic conditions including congenital heart defects, congestive heart failure, ductal constriction or abnormality, non-immune hydrops, fetal cardiac arrhythmias and twin-to-twin transfusion syndrome[13,15-17]. The etiology of TR may be explained by an increased preload, after load or cardiac dysfunction[13,15-17]. TR found in normal fetuses without cardiac defects may be a physiologic process[13,15-18], explained by the high placental resistance in early gestation. The physiologic regurgitation flow usually disappeared when placental resistance falls around 12-16 weeks[6]. This is consistent with the present study that TR in all normal fetuses without cardiac diseases had disappeared when the authors re-examined in later gestation whereas persistent or severe TR in normal chromosome fetuses may indicate the cardiac malformations and should warrant detailed fetal echocardiography[8,10]. The present study also

Table 4. Association of Down syndrome fetuses with tricuspid regurgitation and cardiac defects

Down syndrome cases ref.	Tricuspid regurgitation	Cardiac defects (postnatal autopsy)
1	Present	TOF with ASD secundum
2	Absent	-
3	Absent	ASD secundum
4	Absent	-
5	Present	-

TOF, Tetralogy of Fallot; ASD, atrial septal defect

demonstrated that 14.3% (2/14) of euploidy fetuses which presented with significant TR were diagnosed for congenital cardiac defects including Ebstein anomaly with pulmonary stenosis and atrioventricular septal defect.

In Down syndrome fetuses, TR was associated with both presence and absence of congenital heart diseases (CHD) (Table 4). Faiola S, et al[8] found that the prevalence of TR in trisomy 21 with CHD was 97.5% and 50% in those without CHD. The high prevalence of CHD in Down syndrome fetuses may result in higher rate of TR in Down syndrome. However, prevalence of TR in Down syndrome fetuses without CHD (50%) is still higher than the normal population that has no CHD (5.6%)[8]. So there might be some unknown mechanisms or intrinsic factors that cause higher prevalence of TR in Down syndrome fetuses without CHD. These intrinsic factors could be related to compromised myocardial compliance or placental and pulmonary resistance in Down syndrome fetuses[6,18]. More detailed study may shed light on this issue.

Compared to the first trimester, assessment of TR in the second trimester is simpler due to larges size of fetal heart. TR may be physiologic phenomenon in the early gestation. So the determination of TR in the second trimester may have lower false-positive rate which resulted in higher specificity when compared to examination in the first trimester, although the sensitivity may be decreased (from 55.7-74%[6,8-11] to 28.8-40%[12] and our study).

TR was commonly found in abnormal chromosome fetuses which most likely to be associated with Down syndrome, however trisomy 18, trisomy 13 and Turner syndrome were also seen in the association[6,8,10,11]. Our study demonstrated that TR was present in 16% (4/25) of the chromosome abnormalities including Down syndrome in 2 cases, Turner syndrome in 1 case and 47,XYY/45,X in 1 case. None of all fetuses with trisomies 18 and 13 presented TR. This is probably due to a small number of aneuploidy fetuses in the present study.

The determination of TR in this study primarily based on pulsed wave Doppler, which is more consistent setting modality between ultrasound machines than color Doppler and can clarify specific criteria to diagnosis of TR[6,8]. Occasionally, it was unable to detect TR on color Doppler, whereas pulsed wave Doppler could readily identify[6]. Nevertheless, the possible usefulness of color flow mapping is to help the examiner to place the sample volume of pulsed wave Doppler onto the regurgitation flow properly.

Because the accurate diagnosis of TR requires appropriately trained examiners, therefore it is difficult to add this marker in routine screening ultrasound scan or to use as a primary marker. As a result, TR was reserved as a secondary marker for the subgroup with intermediate risk in a contingent policy[7]. As shown in Kagan's study[11], a two-stage first-trimester screening which tricuspid blood flow was assessed only in intermediate risk group had similar detection rates of trisomy 21 compared to routine tricuspid flow assessment in the combined test which include maternal age, fetal nuchal translucency, fetal heart rate and maternal biochemical serum screening.

The present study was limited by the small numbers of Down syndrome fetuses and the study was conducted only in a high-risk population. Caution is advised in extrapolating the results of the present study to a low risk population. Further researches should enroll a higher number of aneuploidy fetuses and give rise into the general population for an additional implement in routine screening.

In conclusion, TR is not only a high specificity secondary ultrasound marker at 17-23 weeks to identify fetuses with Down syndrome in high-risk pregnant women but also associates with the risk of cardiac defects in normal chromosome fetuses.

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ความจำเพาะของภาวะลิ้นหัวใจไทรคัสพิดรั่วในการทำนายโอกาสเกิดทารกกลุ่มอาการดาวน์ที่อายุครรภ์ 17-23 สัปดาห์

ศนิตรา อนุวุฒินาวิน, ประภัทร วานิชพงษ์พันธุ์, พฤหัส จันทร์ประภาพ

วัตถุประสงค์*: เพื่อศึกษาถึงความจำเพาะของการนำภาวะลิ้นหัวใจไทรคัสพิดรั่วของทารกที่อายุครรภ์ 17-23 สัปดาห์มาใช้ทำนายโอกาสเกิดทารกกลุ่มอาการดาวน์และศึกษาอุบัติการณ์ของลิ้นหัวใจไทรคัสพิดรั่วในกลุ่มทารกที่มีโครโมโซมปกติ*

วัสดุและวิธีการ*: ศึกษาหญิงตั้งครรภ์ที่มีความเสี่ยงสูงต่อการเกิดทารกกลุ่มอาการดาวน์จำนวน 395 ราย โดยใช้เครื่องดอปเลอร์อัลตราซาวด์ตรวจหาภาวะลิ้นหัวใจไทรคัสพิดรั่วของทารกก่อนการเจาะน้ำคร่ำ หรือ เจาะเลือดสายสะดือ เพื่อตรวจโครโมโซมทารก ภาวะลิ้นหัวใจไทรคัสพิดรั่ววินิจฉัยโดยตรวจพบระยะเวลาที่เลือดไหลย้อนกลับต้องเกินครึ่งหนึ่งของช่วงหัวใจบีบตัวหรือ ≥ 70 มิลลิวินาทีและความเร็วสูงสุดของเลือดที่ไหลย้อนกลับต้อง ≥ 100 เซนติเมตรต่อวินาที ใช้สถิติวิเคราะห์หาค่าคุณสมบัติของการทดสอบของภาวะลิ้นหัวใจไทรคัสพิดรั่วในการทำนายโอกาสเกิดทารกกลุ่มอาการดาวน์*

ผลการศึกษา*: อุบัติการณ์ของลิ้นหัวใจไทรคัสพิดรั่วในทารกที่มีโครโมโซมปกติเท่ากับ 3.8% (14/370) และทารกกลุ่มอาการดาวน์เท่ากับ 40% (2/5) ทารกที่ตรวจพบภาวะลิ้นหัวใจไทรคัสพิดรั่ว (11.1%) มีโอกาสเสี่ยงต่อการเกิดกลุ่มอาการดาวน์มากกว่าทารกที่ตรวจไม่พบ (0.8%) (95% CI of the difference, 0.09-32.9, P = 0.036) ค่าความไวความจำเพาะ การทำนายโรคเมื่อตรวจพบและไม่พบภาวะลิ้นหัวใจไทรคัสพิดรั่วกับโอกาสเกิดทารกกลุ่มอาการดาวน์คือ 40%, 95.9%, 11.1%, 99.2% ตามลำดับ ในทารกที่โครโมโซมปกติและมีลิ้นหัวใจไทรคัสพิดรั่ว พบโครงสร้างหัวใจผิดปกติร่วมด้วย 14.3% (2/14)*

สรุป*: ภาวะลิ้นหัวใจไทรคัสพิดรั่วของทารกที่อายุครรภ์ 17-23 สัปดาห์มีความจำเพาะสูงในการทำนายโอกาสเกิดทารกกลุ่มอาการดาวน์ในสตรีตั้งครรภ์ที่มีความเสี่ยง และนอกจากนี้ยังสัมพันธ์กับความผิดปกติของหัวใจในทารกที่มีโครโมโซมปกติ*