Employ ductus venous blood flow in the early detection of trisomy 21, trisomy 18, and trisomy 13
A meta-analysis

Yibing Ge, MD^a, Lili Xia, MD^b, Yun Wu, MD^c,, Hongbao Cao, PhD^d^e^,*

Abstract

Background and objective: Ductus venous (DV) Doppler has been suggested as a biomarker for the early screening of trisomy diseases. However, results from different studies have been largely inconsistent. This study aimed to investigate the relationship between DV and top 3 fetal aneuploidies by a systematical meta-analysis: trisomy 21 (T21), trisomy 18 (T18), and trisomy 13 (T13).

Methods: We performed a literature search covering articles from Medline, PubMed, RePORTER, and Elsevier publications. DV-T21/T18/T13 relation data were extracted from 9, 7, and 6 previous studies, respectively, including 31,053, 28,092 and 26,721 pregnant women worldwide. Both random-effects and fixed-effect model were used to study the log odds ratio (LOR) of T21, T18, and T13 in case of DV. Four potential influential factors were studied using a multiple linear regression (MLR) model, including maternal age, data age, sample size, and population region.

Results: DV was significantly related to T21, T18, and T13 (LOR=3.44, 3.89 and 3.46; P value<2.1E-13). Significant between-study variance was observed for T21 (P value<1.71E-14), but not for T18 (P value>.05) and T13 (P value>.87). MLR results suggested that significant influential factors could include population region (P value<.0021), but not sample size, data age, and maternal age (P value>.078).

Conclusions: Integrating DV could help in the detection of trisomy. However, accuracy and validity may vary depending on the population regions, which need further study.

Abbreviations: CI = confidence interval, DV = ductus venous, LOR = log odds ratio, MLR = multiple linear regression, T13 = trisomy 13, T18 = trisomy 18, T21 = trisomy 21.

Keywords: ductus venous, multiple linear regression, random model, trisomy 13, trisomy 18, trisomy 21.

1. Introduction

Down syndrome (DS), Edwards syndrome (ES), and Patau syndrome (PS) are genetic disorders caused by abnormalities of chromosome 21, chromosome 18, and chromosome 13, respectively.[1] Thus, DS, ES, and PS are also known as trisomy 21 (T21), trisomy 18 (T18), and trisomy 13 (T13). In most cases, aneuploidy results in miscarriage. Among these fetus that survival an aneuploidy, T21, T18, and T13 is the most commonly diagnosed cases.[2] Using prenatal screening and diagnostic tests, T21, T18, and T13 can be identified during pregnancy, and the most popular option is the first trimester screening.[3] It has been suggested that increased risks of fetal aneuploidy were associated with abnormal DV flow.[4] In recent years, Doppler imaging of ductus venous (DV) has been increasingly used to screen for chromosome abnormalities related diseases during pregnancy, such as aneuploidy, cardiac dysfunction.[13-15] With a color Doppler scan, the DV blood flow waveforms can be easily captured in the first trimester of the pregnancy.[5]

However, in case of T21/T18/T13, the co-occurrence rate of abnormal DV could vary significantly.[6-14] Therefore, a systematic analysis is necessary to study the relationship between abnormal DV and the 3 trisomies to generate a comprehensive conclusion. Here, we address this issue by a systematical review and meta-analysis of the results from previous related studies of the past 20 years, with the purpose to provide a comprehensive evaluation of the validity of using DV blood flow as a biomarker in the clinical diagnosis of T21, T18, and T13.

2. Methods and materials

All results and analyses were based on previous ethically approved studies, thus no further ethical approval and patient consent are required.
2.1. Data collection

Articles were collected using Science Direct, PubMed, RePORT-ER, and Medline. The keyword “ductus venosus” was used in the search, which identified in total 1951 articles. Then the following criteria were applied for data filtering:

1) The study includes relationship data between DV and T21/T18/T13;
2) The screen time is the first trimester;
3) The required statistics were included: samples number; the number of samples with T21/T18/T13; the number of samples with abnormal DV; and number of samples with T21/T18/T13 also presenting abnormal DV.

There were 10 studies satisfied the above criteria and were included in this study. The detailed data information was presented in Tables 1 to 3. The screened flow chart was shown in Figure 1.

2.2. T21-DV data

For the 31,053 cases collected from 9 studies, there were 344 T21 cases, 1467 abnormal DV cases, and 217 overlapped cases between them (Table 1). These studies were from 1998 to

### Table 1

| Study Name               | Data age | #Total cases | #Total T21 | #Total DV | #T21 with DV | Population regions | Maternal age median |
|--------------------------|----------|--------------|------------|-----------|--------------|--------------------|---------------------|
| Matias et al, 1998       | 19       | 486          | 38         | 70        | 35           | UK and Portugal    | 36                  |
| Antolín et al, 2001      | 16       | 1371         | 9          | 78        | 5            | Spain              | 35                  |
| Murta et al, 2002        | 15       | 372          | 18         | 34        | 18           | Brazil             | 35                  |
| Zoppo et al, 2002        | 15       | 325          | 20         | 61        | 14           | Italy              | 35                  |
| Bomell et al, 2003       | 14       | 3382         | 48         | 222       | 36           | Spain              | 36                  |
| Toyama et al, 2004       | 13       | 1097         | 7          | 84        | 5            | Brazil             | 37.4                |
| Prefumo et al, 2005      | 12       | 572          | 47         | 101       | 18           | UK                 | 37                  |
| Maiz et al, 2009         | 8        | 19600        | 122        | 752       | 81           | Mixed              | 34.5                |
| Stressig et al, 2011     | 6        | 3648         | 35         | 65        | 5            | Germany            | 38.1                |

DV = ductus venosus, T21 = trisomy 21.
2011. The range of median maternal age was between 34.5–38.1.

2.3. T18-DV data

As shown in Table 2, the number of total pregnancy samples was 28,092 from 7 studies, with 106 T18 cases, 1,235 abnormal DV cases, and 78 cases with both T18 and abnormal DV. These studies were from 1998 to 2016. The range of median maternal age was between 32.1–38.5.

2.4. T13-DV data

As shown in Table 3, the total number of pregnancy samples was 26,721 from 6 studies, including 44 T13 cases, 1,157 abnormal DV cases, and 28 with both. These studies were from 1998 to 2016. The range of median maternal age was between 32.1–35.0.

2.5. Model selection for meta-analysis

The log odds ratio (LOR) of T21/T18/T13 in case of DV was used as effect size in this meta-analysis. The between- and within-study variances were analyzed to study the heterogeneity of the effect size and select the meta-analysis model. Both random-effects model and fixed-effect model were tested.

2.6. Analysis of potentially influential factors

Four potential influential factors were analyzed using a multiple linear regression (MLR) model, including population region, maternal age, sample size, and data (study) age.

3. Results

3.1. Heterogeneity analysis and model selection

Heterogeneity analysis was conducted for each study to decide a proper model for the corresponding meta-analysis. Table 4 presents the total variance related statistics for the relation measurement in terms of LOR: DV-T21, DV-T18, and DV-T13.

As shown in Table 4, the ISq of DV-T21 and DV-T18 was about 90.28% and 50.46%, means that over half of the total variance (Q) was coming from between-study variance (P value = 1.71E-14 and .06). Therefore, we selected random-effects model for the meta-analysis of DV-T21 and DV-T18, with between-variance (TauSq) estimated as 1.70 and 0.45, respectively. For DV-T13, Q was smaller than the expected variance (df) under the non-between-study-variance assumption, with the P value (.87) as .87. This suggested that the total variance of the DV-T13 LOR was highly likely coming from within-study variances alone. Therefore, a fixed-effect model was more suitable for the meta-analysis of DV-T13 relation. The following analysis and corresponding discussion were using the selected models accordingly.

3.2. Meta-analysis results

Table 5 present the meta-analysis estimated LOR for the 3 relations: DV-T21, DV-T18, and DV-T13. All of the 3 LORs were significant (P value < 2.1E-13). Although the estimated LOR from all 3 meta-analyses were similar (3.44, 3.89, and 3.46), the LOR of DV-T18 and DV-T13 presented narrower 95% confidence interval (CI): 1.50 and 1.16 vs 1.86, which led to
higher z-values and much lower P values (P value <1E-324), as shown in Table 5.

Figure 2 displays the mean, 95% CI and weights from the meta-analysis results for the LOR of 3 relations. To note, for DV-T21 and DV-T18 analysis, a random-effects model was used, and a fix-effect model was used for DV-T13. From Figure 1 (a) it can be seen that there was a significant between-study variance (mean LOR were ranged from 1.20 to 6.63), which resulted in a larger 95% CI (1.86).

### 3.3. MLR-analysis results

The potential influence of 4 factors on the DV-T21/T18/T13 relations was presented from an MLR-analysis: maternal age, data age, sample size, and population regions, as shown in Table 6. The P values of the regression coefficients for each variable were calculated, representing the significance of these variables.

As shown in Table 6, data age, sample size, and maternal age presented no significant relation with the DV-T21/T18/T13

---

**Table 5**

| Study name | Effect size, LOR | Lower limit of CI | Upper limit of CI | Z-value | P value |
|------------|------------------|-------------------|-------------------|---------|---------|
| DV-T21     | 3.44             | 2.51              | 4.37              | 7.25    | <2.10E-13 |
| DV-T18     | 3.89             | 3.14              | 4.64              | 10.14   | <1.00E-324 |
| DV-T13     | 3.46             | 2.88              | 4.04              | 11.68   | <1.00E-324 |

CI=confidence interval, DV=ductus venosus, LOR=log odds ratio, T13=trisomy 13, T18=trisomy 18, T21=trisomy 21.
For population regions, $P$ values are significant for all 3 cases ($P < .001$). Interestingly, the population regions coefficient $P$ values of using population regions alone were slightly bigger in all 3 cases than that of using the 4 predictors together in the MLR analysis (see last 2 columns of Table 6). This indicates that multiple factors fit the MLR model better than using population regions alone.

In Figure 3, the linear regression relationships (LRR) between the population region and the LORs of DV-T21/T18/T13 were presented. Interestingly, we see that the LORs of Italy is relatively low in all 3 cases while other country regions showed mixed results for different trisomies (Fig. 3A–C). For an instant, for the population in Germany, the LORs for DV-T21 was low (≈2.3), but LORs were relatively high for DV-T18 and DV-T13 relation (≈4.9 and 3.9, respectively).

### 4. Discussion

T21, T18, and T13 have been the most common types of autosomal trisomy.\(^{(5)}\) Although the associations between abnormal DV and aneuploidy has been reported in multiple studies in the past years, many different studies have been conducted

| $P$ value | Data age | Sample size | Maternal age (median) | Population regions | Population regions (alone) |
|-----------|----------|-------------|-----------------------|-------------------|-------------------------|
| DV-T21    | 0.88     | 0.901       | 0.97                  | 0.0010            | 0.0021                  |
| DV-T18    | 0.91     | 0.80        | 0.536                 | 0.000034          | 0.000065                |
| DV-T13    | 0.078    | 0.11        | 0.66                  | 0.00071           | 0.0021                  |

DV = ductus venosus, MLR = multiple linear regression, T13 = trisomy 13, T18 = trisomy 18, T21 = trisomy 21. “Population regions (alone)” represents the case of using population regions alone in the MLR analysis.
revealing associations between aneuploidy and DV, the results were largely inconsistent, providing noise information for employing DV in screening aneuploidies. Here, we performed a systematic review and a meta-analysis, presenting a comprehensive result for the relations between DV and T21/T18/T13.

There were 9 studies selected for T21 analysis, including 31,053 samples with 344 (1.11%) diagnosed as T21 (Table 1). Among these cases, 4.72% also demonstrated abnormal DV. As shown in Table 5, abnormal DV and T21 presented significant association (LOR: 3.44±0.47, P value < 2.10E-13). Nevertheless, we observed significant between-study variance (I-Squared=90.28; P value <1.7e-14), which suggested that influential factors exist for the DV-T21 relations. MLR results suggested population region could be a significant influential factor (p-value < 0.001), while maternal age, sample size, and data age were not (P value >0.88, Table 6).

For T18, there were 106 (0.38%) T18 cases out of the total 28,092 samples (from 7 studies), and around 4.40% (1235/28,092) presented abnormal DV. Among these cases, 4.72% also demonstrated abnormal DV. As shown in Table 5, abnormal DV and T18 presented significant association (LOR: 3.44±0.47, P value < 2.10E-13). MLR results suggested population region could be a significant influential factor (p-value < 0.001), while maternal age, sample size, and data age were not (P value >0.88, Table 6). For DV-T18, clinical data of 26,721 samples were collected from 6 studies, including 44 T13 cases, 1157 abnormal DV cases, and 28 cases with both (Table 3). As shown in Table 5, there were extremely significant associations between abnormal DV and both T18 and T13 (P value <1E-324). Moreover, LOR for the DV-T18 relationship demonstrated mild between-study variance (I-Squared=50.46%; P value >0.6), and no significant between-study variance was observed for DV-T13 (P value >0.87), as shown in Table 6. Same as the DV-T21 relation, population region was also a significant influential factor for DV-T18/T13 relations (P value <0.0021), but the maternal age, data age, and sample size were not (P value >0.78) (Table 6).

The results from this study were summarized as follows. First, abnormal DV in the first trimester presented significant associations with T21/T18/T13, especially T18 and T13; Second, there was no significant statistical change during the past 20 years for the DV-T21/T18/T13 association at a given population region; Third, the DV-T21/T18/T13 association should not vary significantly with maternal age. However, the between-study variance suggests that there may exist influential factors in the LOR measurement, and population region could be one of them.

Although the meta-analysis results suggested significant odds of trisomy in case of DV, we noted that patients with no trisomy may also present abnormal DV, while trisomy patient may not necessarily present DV abnormality. In this study, out of 1476 DV cases, only 217 presented T21, and there were 127 T21 patients that showed normal DV. Therefore, using DV alone may not have sufficient power for the prediction of T21. As a matter of fact, several previous studies suggested the integration of DV and other clinical markers (e.g., NT) in the screening of T21. A similar option should be taken for the screening of T18 and T13.

5. Conclusion
Our results demonstrated that abnormal DV in the first-trimester was significantly associated with T21/T18/T13. Therefore, integrating DV as a biomarker in the screening of these trisomies may increase the prediction power. However, samples of different population region may expect different validity, which is worthy of further study.

Author contributions
Data curation: Yun Wu.
Investigation: Yun Wu.
Methodology: Yibing Ge, Lili Xia, Yun Wu.
Project administration: Hongbao Cao.
Resources: Yun Wu, Hongbao Cao.
Software: Hongbao Cao.
Supervision: Yun Wu.
Writing – original draft: Yibing Ge, Lili Xia, Yun Wu.
Writing – review & editing: Yibing Ge, Yun Wu, Hongbao Cao.

References
[1] Mulvey S, Wallace EM. Women’s knowledge of and attitudes to first and second trimester screening for Down’s syndrome. BJOG 2000;107:102–5.
[2] Florjanci J, Fuchs T, Zimmer M, et al. The role of ductus venosus Doppler flow in the diagnosis of chromosomal abnormalities during the first trimester of pregnancy. Adv Clin Exp Med 2013;22:393–401.
[3] Ob C, Harman C, Baschat AA. Abnormal first-trimester ductus venosus blood flow: a risk factor for adverse outcome in fetuses with normal nuchal translucency. Ultrasound Obstet Gynecol 2007;30:192–6.
[4] Maiz N, Valencia C, Emmanuel EE, et al. Screening for adverse pregnancy outcome by ductus venosus Doppler at 11-13 + 6 weeks of gestation. Obstet Gynecol 2008;112:198–603.
[5] Maiz N, Staboulidou I, Leal AM, et al. Ductus venosus Doppler at 11 to 13 weeks of gestation in the prediction of outcome in twin pregnancies. Obstet Gynecol 2009;113:860–5.
[6] Matias A, Gomes C, Flack N, et al. Screening for chromosomal abnormalities at 10-14 weeks: the role of ductus venosus blood flow. Ultrasound Obstet Gynecol 1998;12:380–4.
[7] Antolini E, Comas C, Torrents M, et al. The role of ductus venosus bloodflow assessment in screening for chromosomal abnormalities at 10-16 weeks of gestation. Ultrasound Obstet Gynecol 2001;17:295–300.
[8] Murtu CG, Moron AF, Avila MA, et al. Application of ductus venosus Doppler velocimetry in the detection of fetal aneuploidy in the first trimester of pregnancy. Fetal Diagn Ther 2002;17:305–14.
[9] Zoppiti MA, Putzuoli M, Ibba RM, et al. First-trimester ductus venosus velocimetry in relation to nuchal translucency thickness and fetal karyotype. Fetal Diag Ther 2002;17:32–7.
[10] Borrell A, Martinez JM, Seres A, et al. Ductus venosus assessment at the time of nuchal translucency measurement in the detection of fetal aneuploidy. Prenat Diagn 2003;23:921–6.
[11] Toyama JM, Brizot ML, Liao AW, et al. Ductus venosus blood flow assessment at 11 to 14 weeks of gestation and fetal outcome. Ultrasound Obstet Gynecol 2004;23:341–5.
[12] Prefumo F, Serthna F, Saizam S, et al. First-trimester ductus venosus, nasal bones, and Down syndrome in a high-risk population. Obstet Gynecol 2005;105:1348–54.
[13] Streiss R, Kozolowski P, Froehlich S, et al. Assessment of the ductus venous, tricuspid blood flow and the nasal bone in second-trimester screening for trisomy 21. Ultrasound Obstet Gynecol 2011;37:444–9.
[14] Wagner P, Sonnek J, Hoopmann M, et al. First-trimester screening for trisomies 18 and 13, triploidy and Turner syndrome by detailed early anomaly scan. Ultrasound Obstet Gynecol 2016;48:446–51.
[15] Mavrides E, Moscoso G, Carvalho JS, et al. Screening for aneuploidy in the first trimester by assessment of blood flow in the ductus venosus. BJOG 2002;109:1015–9.
[16] Geipel A, Gembruch U. Screening performance of first trimester nuchal translucency, ductus venosus blood flow and tricuspid regurgitation for cardiac defects. Z Geburtshilfe Neonatol 2012;216:137–61.