Updated Reference Ranges for the Ductus Venosus Pulsatility Index at 11–13 Weeks

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Key Words

Ductus venosus • Prenatal screening • Trisomy 21 • Down syndrome • Ultrasound markers

Abstract

Objective: To update the reference ranges for the ductus venosus pulsatility index (DVPI) at 11+0 to 13+6 gestational weeks. **Methods:** DVPI was calculated in 14,444 singleton fetuses at 11+0 to 13+6 weeks in two Fetal Medicine Centers, during a 4-year period. Using previously described medians, DVPI evolution was assessed both over the study period on a yearly basis and over gestation, grouping fetuses according to 5-mm crown-rump length (CRL) ranges. Weighted DVPI medians, the 5th and 95th percentiles and distribution parameters for unaffected and trisomy 21 fetuses were newly calculated. **Results:** A significant DVPI multiple of the median decrease was observed over both the study period ($p < 0.01$) and over gestation ($p < 0.01$) using previous medians, in the two centers. Newly calculated weighted medians were lower than those previously described, decreasing with CRL. Distribution parameters calculated using the new medians were different from those previously described. **Conclusion:** DVPI reference ranges were lower than those previously re-

ported and decreased with CRL. Updated medians and distribution parameters should be considered to include the DVPI as a Gaussian marker in trisomy 21 screening and for quality control purposes.

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Introduction

Ductus venosus (DV) blood velocities assessment has demonstrated to improve the effectiveness of first-trimester combined screening for trisomy 21 [1], used either as a qualitative marker (present vs. absent or reversal A-wave) [2] or as a quantitative marker [pulsatility index (PI) for veins expressed in multiples of the median (MoMs)] [3–5]. Thus, one of our centers described improved detection rates for trisomy 21, or alternatively decreased false-positive rates, when the DVPI was added to the combined test, used as a Gaussian marker in the general pregnant population [3, 4]. These results were confirmed by another European group when the DV was added in a multivariate prediction model, with a larger effect when the DV was used as a quantitative marker [5].

Fig. 1. DV Doppler recording and the corresponding automatic velocity tracing in two waveforms.

Reported DVPI reference ranges demonstrate similar medians around 1.1 MoM, but they were calculated in relatively old series, with Doppler studies performed before 2000 [3, 4, 6]. We suspected that recent technical improvements linked to ultrasound machines, such as better resolution and magnification of images together with automatic tracing, may modify the existing DVPI reference ranges. The aim of our study was to re-evaluate the DVPI reference ranges and its Gaussian distribution parameters, before being used for screening and quality control purposes.

Methods

In the two participating centers, the DVPI was calculated in consecutive singleton pregnancies undergoing first-trimester combined screening for trisomy 21, at the time of nuchal translucency (NT), at 11+0 to 13+6 weeks' gestation. The study period encompassed 4 years, 2006–2009 at Hospital Clinic Barcelona (HCB) and 2007–2010 at Dexeus University Institute (DUI). The DV blood flow was assessed using the transvaginal or the transabdominal route as described in previous studies [7]. The image of the fetus was taken in an almost sagittal view, with the fetus lying in an oblique position such that the DV was seen as vertical as possible in the screen (low insonation angle). The same magnification as for a NT measurement was used, with only the fetal trunk being included in the image. Color Doppler was applied during fetal quiescence. A 1-mm pulsed Doppler sample was placed on the isthmus portion of the vessel until homogenous waveforms were obtained (fig. 1). The ALARA principle [8] was applied and institutional review board approvals were obtained.

In both centers, DVPI MoMs were calculated using previously reported medians [3, 4, 6], and evolution over the study period (grouping fetuses on a yearly basis) and over gestation [grouping fetuses in 5-mm crown-rump length (CRL) intervals, from 45 to 84 mm] was assessed using the Kruskal-Wallis test. Differences in mean CRL at ultrasound, across each study year, were evaluated using an ANOVA test.

Our aim was to re-evaluate previously described DVPI reference ranges and construct new DVPI reference ranges in case of discordant results, including weighted medians, new DVPI 5th and 95th percentiles extrapolated from the log DVPI MoM normal distribution and Gaussian distribution parameters for non-affected fetuses. In addition, 121 trisomy 21 fetuses studied at 11+0 to 13+6 weeks' gestation in both centers during an expanded 9-year period (2002–2010) were used to estimate the DVPI MoM distribution parameters for affected fetuses.

DVPI standard deviations (SD) were estimated from normal distributions best adjusted to the corresponding log DVPI MoM values within the 10th to 90th percentiles. Correlations between DVPI, NT and first-trimester serum markers were assessed, excluding outliers above 3 SD from the mean. Truncation limits for DVPI MoMs were established after inspection of the probability plots for affected and unaffected fetuses, taking into account the reversal risk point [9].

Results

During a 4-year period, 7,493 fetuses from HCB and 6,501 fetuses from DUI were included in the study. The DVPI yearly median MoMs derived from the three previously described DVPI reference ranges were found to lie below 1.00 MoM, dropping even below 0.9 MoM during

Fig. 2. Evolution of yearly DVPI MoMs over the 4 study years in the two study centers [HCB (—) and DUI (---)], applying the three DVPI medians previously described by Borrell et al. [3] in 2005 (■), Teixeira et al. [6] in 2008 (●) and Borrell et al. [4] in 2009 (▲).

Fig. 3. Evolution of DVPI MoMs over gestation, grouping pregnancies according to 5-mm CRL ranges, in the two study centers [HCB (—) and DUI (---)], applying the three DVPI medians previously described by Borrell et al. [3] in 2005 (■), Teixeira et al. [6] in 2008 (●) and Borrell et al. [4] in 2009 (▲).

the last year of the study (fig. 2). A similar decrease was observed in median DVPI MoM over gestation, when fetuses were grouped by 5-mm CRL intervals, dropping below 0.9 MoM at 80–84 mm CRL (fig. 3). Both decreases were significant ($p < 0.01$) and were concordantly found in the two centers. In addition, a significant increase ($p < 0.01$) in mean CRL over the study years (from 63 to 65 mm in HCB, and from 59 to 65 mm in DUI) was observed in both centers.

Given that lower DVPI MoMs than expected were obtained concordantly in both centers, and that a consistent DVPI decrease was observed over gestation, we decided to calculate new DVPI reference ranges. A quadratic regression curve [median DVPI = $0.95864 + 0.0028619 \times \text{CRL (mm)} - 0.000036619 \times \text{CRL (mm)}^2$; $R^2 = 0.93$] was adjusted from the regression of the DVPI medians, obtained by grouping fetuses according to 5-mm CRL intervals, and weighted for the number of pregnancies. In figure 4, DVPI medians are plotted by CRL together with the new regression curve. Figure 5 shows raw study data by CRL, new regressed medians and the corresponding 5th and 95th percentiles.

DVPI MoM distribution parameters for unaffected and trisomy 21 pregnancies in our series and those previously published are presented in table 1, together with the

Mahalanobis distances and truncation limits. Our Mahalanobis distance between the two distributions was 1.58, slightly lower than the one previously published [3]. The DVPI MoM distribution fitted with the logarithmic Gaussian model in the 0.7–1.5 range (fig. 6). Given that reversal risk appears at 0.79 MoM, truncation limits were established at 0.8 and 1.5 MoM. When the correlation between log DVPI MoMs and other screening markers (NT, PAPP-A and free β -hCG) was assessed in 12,332 unaffected and in 111 trisomy 21 fetuses, significant correlations were obtained with NT (in both unaffected and trisomy 21 pregnancies) and with PAPP-A (only in unaffected pregnancies) (table 2).

Discussion

In this study, newly updated DVPI reference ranges have been constructed in the gestational window in which screening for trisomy 21 is commonly carried out, and new DVPI screening parameters were also calculated. The reason for new reference ranges was that observed values were lower than expected and decreased over gestation concordantly in both centers and differently from the ranges previously reported [3, 4, 6]. Updated screen-

Fig. 4. DVPI medians plotted by CRL obtained in the two participating centers [HCB (.....) and DUI (---)] together with the new regressed median (—). In addition, the three regression curves previously described by Borrell et al. [3] in 2005 (■), Teixeira et al. [6] in 2008 (●) and Borrell et al. [4] in 2009 (▲) are also plotted.

Fig. 5. Values of the DVPI measurements. Solid lines represent the calculated median and the corresponding 5th and 95th percentiles.

Fig. 6. Log DVPI MoM normality plots for unaffected and trisomy 21 fetuses. - - - = Truncation limits.

Table 1. DVPI Gaussian parameters in unaffected and in trisomy 21 pregnancies observed in our series, as compared to those previously reported

	Our series	Borrell et al. [3]	Borrell et al. [4]
Unaffected pregnancies, n	14,044	3,706	7,184
Median MoM	1	1	1
Mean log10 MoM	0	0	0
SD (log10 MoM)	0.095	0.076	0.076
Trisomy 21 pregnancies, n	121	25	66
Median MoM	1.62	1.70	1.55
Mean log10 MoM	0.21	0.23	0.19
SD (log10 MoM)	0.1685	0.1955	0.1930
Truncation limits (MoM)	0.80–1.50	0.67–1.50	0.90–1.50
Mahalanobis distance	1.58	1.71	–

ing parameters can be of use if DV is to be added to the three markers of the combined screening, and the new medians may be helpful in DV quality control.

In contrast to the expected DVPI evolution, we observed a drop over both the study period and gestation. Those changes did not appear to be center, ultrasound equipment or operator specific, because they were concordantly observed in the two participating centers. In

Table 2. Pearson's correlation coefficients between log DVPI MoM and the three markers included in the first-trimester combined screening

	Unaffected		Trisomy 21	
	coefficient	p	coefficient	p
NT	0.056	<0.001	0.397	<0.001
PAPP-A	–0.036	<0.001	0.010	0.92
β-hCG	–0.018	0.05	0.188	0.06

our opinion, this may be explained by the increasing gestational age at which the 11–13-week scan was carried out in both centers over the study years, given that a larger deviation in DVPI medians was found at larger CRLs.

Given that two of the three previous series were reported by one of our participating centers [3, 4], we speculate that the observed decrease in DVPI medians may be due to technical improvements of new ultrasound machines, allowing for larger image magnification, better DV blood flow mapping (color Doppler), better waveform acquisition (pulsed Doppler), and more standardized Doppler indexes with automatic waveform drawing. Further reports on experiences of other centers are needed to

confirm our findings. It can be speculated that the observed DVPI decrease over gestation was not apparent in previous series due to restrictions imposed by an extremely limited gestational period (3 weeks) [3, 4, 6], but it has been clearly demonstrated in wider gestational periods [10–12].

Our results came from two centers with high-level expertise in Doppler studies, although >35 sonologists were involved in DV measurements. As it has been shown by other groups [13], level of skill is an important requirement for this kind of Doppler measurements, meaning that reference ranges for DV measurements should only be applied when the corresponding skills are ensured.

A strength of our study are the concordant results observed by the two participating centers concerning a DVPI decrease over the last years of the study and at a higher gestational age. Interestingly, there is a remarkable

concordance between centers at the 60- to 65-mm CRL range (fig. 3), which is the 5-mm CRL range with a higher number of cases ($n = 3,014$), and only small differences are apparent at the extreme ranges, probably due to a decline in the number of cases (670 at the 45- to 50-mm CRL range and 694 at the 80- to 85-mm CRL range). Nevertheless, the difference between both centers in those extreme ranges is lower than the difference from the previously reported medians.

When we assessed the Gaussian parameters for both unaffected and trisomy 21 fetuses, the resulting Mahalanobis distance was similar to that previously reported [3]. Evaluation of the screening performance is out of the scope of this study, but it can be assumed that the addition of the DVPI to the first-trimester combined Down syndrome screening would maintain the described improvement in its effectiveness [3–5].

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