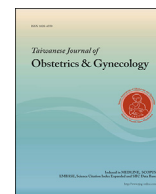Contents lists available at ScienceDirect

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Original Article

# Are congenital malformations more frequent in fetuses with intrahepatic persistent right umbilical vein? A comparative study

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A B S T R A C T

Objective: Persistent right umbilical vein (PRUV) is a vascular anomaly where the right umbilical vein remains as the only conduit that returns oxygenated blood to the fetus. It has classically been described as associated with numerous defects. We distinguish the intrahepatic variant (better prognosis) and the extrahepatic variant (associated with worse prognosis). The objective of this study was to compare rates of congenital malformations in fetuses with intrahepatic PRUV (I-PRUV) versus singleton pregnancies without risk factors.
Materials and Methods: A multicenter, crossover design, comparative study was performed between 2003 and 2013 on fetuses diagnosed with I-PRUV ($n = 56$), and singleton pregnancies without congenital malformation risk factors ($n = 4050$).
Results: Fifty-six cases of I-PRUV were diagnosed (incidence 1:770). A statistically significant association between I-PRUV and the presence of congenital malformations (odds ratio 4.321; 95% confidence interval 2.15–8.69) was found. This positive association was only observed with genitourinary malformations (odds ratio 3.038; 95% confidence interval 1.08–8.56).
Conclusion: Our rate of malformations associated with I-PRUV (17.9%) is similar to previously published rates. I-PRUV has shown a significant increase in the rate of associated malformations, although this association has only been found to be statistically significant in the genitourinary system. Noteworthy is the fact that this comparative study has not pointed to a significant increase in the congenital heart malformation rate. Diagnosis of isolated I-PRUV does not carry a worse prognosis.

## Introduction

Persistent right umbilical vein (PRUV) is a vascular anomaly that involves the obliteration of the left umbilical vein, leaving the right umbilical vein as the only conduit that returns oxygenated blood from the placenta. Two variants are described: intrahepatic (I-PRUV), with proper development of ductus venosus; and extrahepatic, in which the umbilical vein drains directly into the inferior vena cava or right atrium [1].

The first set of cases, published by Jeanty [2] in 1990, presented a rate of associated malformations of 50%, most of them being congenital heart diseases. Therefore, this entity has traditionally been considered a rare anomaly associated with poor prognosis. Recent studies report a better prognosis [3–5], but rates of associated malformations in the latest series show extremely dissimilar results, between 8% and 40.9% [3,6].

I-PRUV is one of the most common fetal venous anomalies, with an estimated incidence varying from 1:250 to 1:1000 pregnancies [2–11]. This study was designed to compare malformations' rate of

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fetuses with I-PRUV with other fetuses from pregnancies without risk factors for associated congenital anomalies.

## Material and methods

Data were collected from the pregnant patients with fetal ultrasound diagnosis of I-PRUV from two tertiary centers: Hospital Universitario Puerta de Hierro, Madrid, Spain (since 2003) and Hospital Universitario Miguel Servet, Zaragoza, Spain (from 2007 to May 2013).

First-trimester combined tests for early screening of chromosomal abnormalities was carried out in all patients. Inclusion criteria for cases were: fetus with ultrasound diagnosis of I-PRUV; singleton pregnancy, obstetric referral hospital control, and execution of at least three ultrasound scans (1st, 2nd, and 3rd trimesters). Cases whose data collection could not be completed were excluded. We used the criteria described by Jeanty [4] to diagnose this entity. A case of prenatal diagnosis of I-PRUV is shown in Figure 1.

Patients with singleton pregnancies, whose pregnancies were controlled at Hospital Universitario Miguel Servet in Zaragoza between January 1, 2011 and December 31, 2013, were recruited consecutively for the control group. Those who met the following criteria were excluded: smoking mother; incomplete prenatal screening; maternal congenital malformation; gestational diabetes; maternal conditions that may be associated with congenital malformations such as diabetes, obesity, bariatric surgery, autoimmune disease, hematologic disease, neoplasia, neurological, or psychiatric illness on drug therapy; and documented use of other drugs with teratogenic potential (U.S. Food and Drug Administration category X). After applying these inclusion and exclusion criteria, a database was obtained for the control group of 4050 pregnancies, without risk factor for congenital anomalies.

For the statistical analysis, firstly all the variables analyzed were described, and then a bivariate analysis was conducted, comparing both groups. The variables were described using percentages. In the bivariate analysis, an analysis of contingency tables with odds ratio (OR) calculation was performed, using SPSS Statistics for Mac OsX. 1999. V19.0. Chicago: IBM. The confidence interval (CI) used was 95%.

## Results

During the study period, 43,149 pregnancies were examined, of which 56 fetuses with I-PRUV were identified, corresponding to an incidence rate of 1:770.

The proportion of cases founded was almost identical in both hospitals, 51.8% and 48.2% respectively.

The profile of mothers corresponded in 55.4% of cases to nulliparous women with a mean age of $31.83 \pm 4.29$ years. The majority of fetuses were male (62.5%), with a male to female ratio of 1.66:1. I-PRUV fetuses were diagnosed between Weeks $19^{+0}$ and $35^{+2}$ of gestation (mean gestational age, $20^{+1}$ weeks).

Of fetuses with I-PRUV, 82.1% showed no associated malformation. In the 10 cases with associated malformations (17.9%) the most frequent were genitourinary (7.1%) and vascular abnormalities of the umbilical cord (3.6%).

Furthermore, 17.9% of I-PRUV fetuses underwent karyotyping, showing no abnormality. The antenatal survey was also completed by echocardiography in 19.6% of cases, diagnosing a ventricular septal defect (as displayed in mid trimester ultrasound) and an aberrant right subclavian artery (Table 1).

The malformation rate presented by I-PRUV cases was compared with the group of 4050 risk factor-free pregnancies. When we classified these malformations into systems, we noted that the proportion of genitourinary system's malformations was 4.67 points higher in fetuses with I-PRUV regarding to those without I-PRUV, followed by umbilical cord (2.34 points), skeletal system (1.49 points) and heart (1.3 points) malformations.

A positive association between the presence of I-PRUV and the presence of any congenital malformations (OR, 4.321; 95%CI, 2.15–8.69)] was found. Malformations of the genitourinary system were the only ones that showed this positive association (OR 3.038; 95%CI 1.08–8.56). We did not observe significant association when congenital heart defects, skeletal, and umbilical cord malformations were compared. No malformation of the central nervous
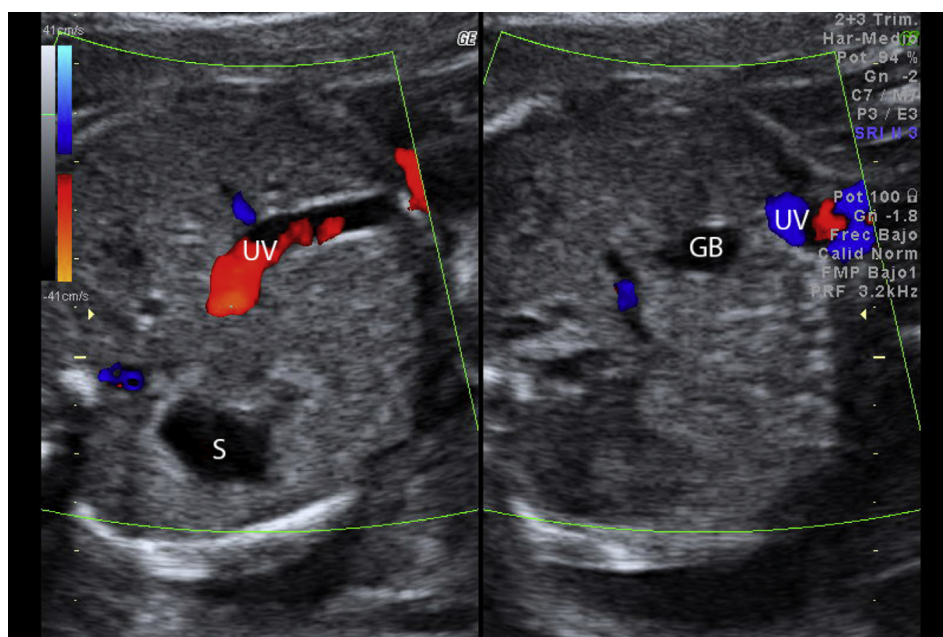


**Figure 1.** Ultrasound prenatal diagnosis of persistent right umbilical vein. GB = gallbladder; S = stomach; UV = umbilical vein.

**Table 1**
Malformations associated with persistent right umbilical vein.

| | | | |
|---|---|---|---|
| Associated malformation | Yes | | 10 (17.9 %) |
| | No | | 46 (82.1 %) |
| Malformations | Umbilical cord | SUA (2) | 2 (3.6 %) |
| | Heart | VSD (1) | 1 (1.8 %) |
| | Genitourinary | Duplicated collecting system<br>Hydronephrosis (2)<br>Bilateral cryptorchidism (1) | 4 (7.1 %) |
| | Genetic syndromes | Microretrognathia, camptodactyly (1) | 1 (1.8 %) |
| | Others | Congenital stenosis of lachrymal duct (1) Aberrant right subclavian artery (1) | 2 (3.6 %) |
| Karyotype | Not performed | | 46 (82.1 %) |
| | Performed (Normal) | | 10 (17.9 %) |
| Echocardiography | Not performed | | 45 (80.3 %) |
| | Performed: no findings | | 9 (16.1 %) |
| | Performed: findings of CHD | | 2 (3.6 %) |

CHD = congenital heart disease; SUA = single umbilical artery; VSD = ventricular septal defect.

system was diagnosed in our cases of I-PRUV, so the OR could not be calculated (Table 2).

## Discussion

Although there are many publications on I-PRUV, solely descriptive studies are carried out in all of them, and preferably of associated congenital malformations. Our work, by contrast, is the first analytical study, that we are aware of, where rates of congenital anomalies, both overall and by systems, are compared between fetuses with I-PRUV and singleton pregnancies free from congenital anomaly risk factors.

In the 56 cases of I-PRUV included in our study, we observed 10 cases of associated congenital malformations, equal to a percentage of 17.9%, which is close to the midpoint of data published by other authors (8–40.9%) [2,3,6,11]. Remarkable is the fact that the rate of associated congenital malformations in the control population (4.79%) is similar to those reported previously [12], asserting that both major and minor congenital anomalies are included therein.

The discrepancy in the published rates, mostly during the 1990s and early 2000s, could be explained, firstly, by the improved quality of ultrasound machines and, secondly, by the establishment of aneuploidy screening in the first trimester, over the last few years. This allowed the earlier detection of cases of more common chromosomal abnormalities and major malformations that could associate an I-PRUV, from which a high percentage end up in abortion.

After performing a comparative study between the group of cases and controls, I-PRUV has statistically proven to be a risk factor for the presence of other associated congenital malformations, in particular, in the genitourinary system. Note that the umbilical cord malformations, if isolated and associated with normal intrauterine growth, will have no impact on postnatal life. No significant differences were found in birth defects relating to congenital heart defects, umbilical cord, skeletal, or nervous systems.

The rate of cardiac malformations showed no statistical differences between I-PRUV and control cases. In addition, the proportion of associated cardiac anomalies (1.8%) is substantially lower than previously published (11.5%). Many congenital cardiac malformations, when associated with chromosomal abnormalities and diagnosed in the first trimester, could have led mothers to opt for a legal abortion, so this rate, which would potentially be detectable in morphological ultrasound, would be reduced. However, we are not a national reference center for this type of pathology. Many of the studies on PRUV [2,6] were conducted in reference centers for the study of heart diseases, and the relative frequency of these malformations is increased in their target population. Although we are aware that sensitivity in the diagnosis of cardiac abnormalities is not 100%, our rate of cardiac malformations (0.5%) in the control group is consistent with that reported by other tertiary centers with a similar target population to ours [13,14]. Furthermore, there are entities that are classically considered as cardiac anomalies, such as echogenic intracardiac foci, which, over the years, are no longer considered as such, and are treated today as benign entities.

No additional tests (echocardiography or fetal karyotype) were systematically performed, backed up by the good prognosis described by the new published data [15], as well as by the centralized execution of all the scans of our health areas by experienced sonographers who performed in all the scans the Yagel [16] cuts. This is the reason why not all the fetuses diagnosed at our

**Table 2**
Relationship between malformations (by systems) among fetuses with intrahepatic persistent right umbilical vein and controls.

| | | Cases<br>n (%) | Controls<br>n (%) | OR | CI (95%) |
|---|---|---|---|---|---|
| Malformations | Yes | 10 (17.86) | 194 (4.79) | 4.321 | 2.15–8.69 |
| | No | 46 (82.14) | 3856 (95.21) | | |
| Umbilical cord | Yes | 2 (3.57) | 50 (1.23) | 2.963 | 0.70–12.49 |
| | No | 54 (96.43) | 4000 (98.77) | | |
| Heart | Yes | 1 (1.79) | 20 (0.49) | 3.664 | 0.48–27.78 |
| | No | 55 (98.21) | 4030 (99.51) | | |
| Genitourinary | Yes | 4 (7.14) | 100 (2.47) | 3.038 | 1.08–8.56 |
| | No | 52 (92.86) | 3950 (97.53) | | |
| Skeletal | Yes | 1 (1.79) | 12 (0.30) | 6.118 | 0.78–47.87 |
| | No | 55 (98.21) | 4038 (99.70) | | |
| Central nervous system | Yes | 0 (0.0) | 14 (0.34) | — | — |
| | No | 56 (100) | 4036 (99.66) | | |

CI = confidence interval; OR = odds ratio.

center with PRUV underwent an echocardiography and fetal karyotype, and so we have only performed 21 additional tests: 11 echocardiographic studies and 10 fetal karyotypes.

Alterations were found in two of the 11 echocardiographic studies performed.

One case of ventricular septal defect was diagnosed, as described in the midtrimester scan, and in another case aberrant right subclavian artery was diagnosed; this entity did not present any postnatal complication.

In view of our results, which have shown a significantly higher rate of associated malformations, we recommend conducting a comprehensive morphological study on fetuses that present I-PRUV to rule out other associated malformations, paying particular interest to umbilical cord vascularization and genitourinary morphology. By contrast, we cannot recommend the presence of I-PRUV as an ultrasound marker for congenital heart disease. This contrasts with other authors [2,4] who proposed that the PRUV should be an ultrasound marker of heart disease, recommending the performance of fetal echocardiography when this is suspected.

Another argument for reserving fetal echocardiography for selected cases is that in our clinical setting, the five cuts described by Yagel [16] to detect heart diseases are routinely performed in all morphologic ultrasound scans.

Karyotype was performed by amniocentesis on 10 fetuses with isolated I-PRUV. No chromosomal abnormalities were observed in any of these cases. No evidence was found either, in the postnatal control that pointed to the need for this type of test. Because of these results, we consider that when diagnosing isolated I-PRUV, we must be cautious when indicating the execution of an amniocentesis to study fetal karyotype, as this is an invasive test with miscarriage rates of around 0.6% [17]. Diagnosis of isolated PRUV does not seem to carry a worse prognosis. When another malformation is associated, the outcome is given by the characteristics of malformation associated in each case.

## Conclusion

I-PRUV has shown a significant increase in the rate of associated malformations (mainly genitourinary system); therefore, we recommend conducting a more detailed morphological study when this entity is diagnosed.

By contrast, a significant increase in association with congenital heart disease has not been proven. Diagnosis of isolated I-PRUV does not carry a worse prognosis.

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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