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Chromosomal Aberrations in Fetuses With Isolated Persistent Right Umbilical Vein—A Nationwide Study

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ABSTRACT

Objective: To evaluate the prevalence of chromosomal aberrations in fetuses with isolated PRUV in a nationwide cohort with 1st-trimester screening for aneuploidies.

Method: A retrospective study including all pregnancies in Denmark with a due date between 2010 and 2022. We retrieved all cases from patient files, where we searched for "PRUV" in the conclusion field. All retrieved cases were manually assessed to determine if PRUV was present, associated anomalies were present, and genetic tests were performed including results. Additional data on postnatal genetics were retrieved from the Danish Cytogenetic Central Registry.

Results: A total of 262 cases with PRUV were retrieved, of which 19 (7.3%) had associated malformations. Among the isolated cases, 119 (49.0%) had a prenatal invasive genetic test that consisted of CMA, and 5 cases had an NIPT (2.1%): All tests were normal or showed low risk for aneuploidies, respectively. None of the children born with PRUV had a postnatal genetic test performed.

Conclusion: We found no chromosomal aberrations in fetuses with isolated or non-isolated PRUVs. Isolated PRUV does not seem associated with a higher incidence of chromosomal aberrations, so parents can be reassured. However, since PRUV was associated with other malformations in 7% of cases, thorough scans are needed.

1 | Introduction

Persistent right umbilical vein (PRUV) is an abnormality of the fetal vascular system, where the right umbilical vein remains open instead of regressing, which is a mirror image of the normal left portal system [1]. Postnatal circulation is unaffected. PRUV occurs in two forms: an intrahepatic and an extrahepatic form. The overall incidence of PRUV is between 0.1% and 0.5% [2–6], where the intrahepatic form accounts for 95%–98% [5, 7]. Extrahepatic PRUV is associated with congenital heart disease [3].

Scientifically, PRUV has not drawn much attention. However, as skills and equipment are improving in the clinical setting,

Summary

- What's already known about this topic?
  - Persistent right umbilical vein (PRUV) is an abnormality of the fetal vascular system, where the postnatal circulation is unaffected.
  - PRUV is associated with the presence of other malformations.
- What does this study add?
  - The incidence of chromosomal aberrations in fetuses with isolated PRUV is not higher than in a low-risk background population without malformations and parents could be reassured.

more cases of PRUV are detected during routine prenatal ultrasound screening. As a result, knowledge of PRUV's association with genetic aberrations is requested in prenatal counseling. As with other abnormalities, the risk of genetic aberrations is higher when not isolated. A review from 2016 included 16 papers that reported on a total of 240 cases [8]. Of those, 76% were isolated, and the most common associated anomaly was a single umbilical artery. Three cases had chromosomal aberrations (1.3%). More recently, two studies have published data on the association between PRUV and genetic aberrations and found between 0.7% and 1.8% including both isolated and non-isolated cases of PRUV [2, 5].

Due to few studies on the matter, we aimed to evaluate the prevalence of chromosomal aberrations in cases with isolated PRUV in a nationwide cohort who had undergone first trimester screening for aneuploidies.

2 | Method

This was a retrospective study included all pregnancies in Denmark with a due date between January 1st, 2010, and December 31st, 2022. In Denmark, all pregnant women are offered two taxpaid standardized screening exams. Screening is performed in the 1st trimester to detect gross anomalies and major aneuploidies, and in the 2nd trimester to assess fetal growth and identify malformations. More than 95% of the pregnant population attend the screening program [9].

We retrieved all cases from the fetal medicine registration system Astraia (Astraia GmBH, Munich), where we searched for occurrences of "PRUV." Maternal and pregnancy characteristics were also retrieved from Astraia and included maternal age, ethnicity, BMI, parity, and mode of conception. All retrieved cases were manually assessed to determine if (1) PRUV was present, (2) associated anomalies were present, and (3) genetic tests had been performed including the results. Cases with soft markers present including single umbilical artery (SUA) were included as isolated cases.

Any chromosomal aberrations were evaluated by a clinical geneticist. Interpretation and classification were performed according to the guidelines for the interpretation of copy number variants published by The American College of Medical Genetics and Genomics [10]. This classification allocates abnormal results into five categories according to their expected clinical relevance: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, or benign. Pathogenic and likely pathogenic were pooled and considered "abnormal genetic findings."

Additional data on postnatal genetics were retrieved from the Danish Cytogenetic Central Registry (DCCR), which contains information on all prenatal, abortion, and postnatal genetic analyses that include karyotyping, chromosomal microarray (CMA), polymerase chain reaction (PCR), multiplex ligation-dependent probe amplification (MLPA), and fluorescence in situ hybridization (FISH). All patients in Denmark are identified by a personal registration number, and the mother's identification number is linked to the child's identification number in the DCCR.

The statistical analyses were performed in Stata version 18 (StataCorp). Baseline characteristics are presented as numbers with frequencies, mean or medians with standard deviations and interquartile ranges where appropriate. Any genetic aberrations are given as total numbers with frequencies. The study was registered in the Capital Region of Denmark (p-2023–14664) and permission to assess patient files was given by the Center for Health in the Capitol Region (R-23047953).

3 | Results

We retrieved a total of 262 cases of PRUV. Between 2010 and 2022, 779,767 children were born in Denmark, resulting in an incidence of approximately 0.03%. However, the incidence of PRUV varied markedly (Figure 1). There was almost an exponential increase in the detection of PRUV from 2010 to 2022. Moreover, some hospitals detected 0 cases throughout the study period compared with other hospitals, which had an incidence of 0.4% in the last 2–3 years of the study period.

Of the 262 cases, 19 (7.3%) had associated malformations, which comprised congenital heart defects (n = 10, 52.6%), ductus venosus agenesis, diaphragmatic hernia, ventriculomegaly, short femur, talipes equinovarus, renal agenesis, and oral facial cleft. Hence, we included 243 cases with isolated PRUV, of which 10 had a soft marker present, including SUA (4.1%).

Among the 243 isolated cases of PRUV, 119 (49.0%) had a prenatal invasive genetic test performed that all consisted of CMA, and 5 cases had an NIPT performed (2.1%): All tests were normal or showed low risk for T21, T18, and T13, respectively. None of the children born with isolated PRUV had a postnatal genetic test performed.

Table 1 presents descriptive baseline characteristics for all cases with PRUV and isolated cases.

4 | Discussion

This retrospective national cohort study of 262 cases with PRUV examining the association with chromosomal aberrations is the

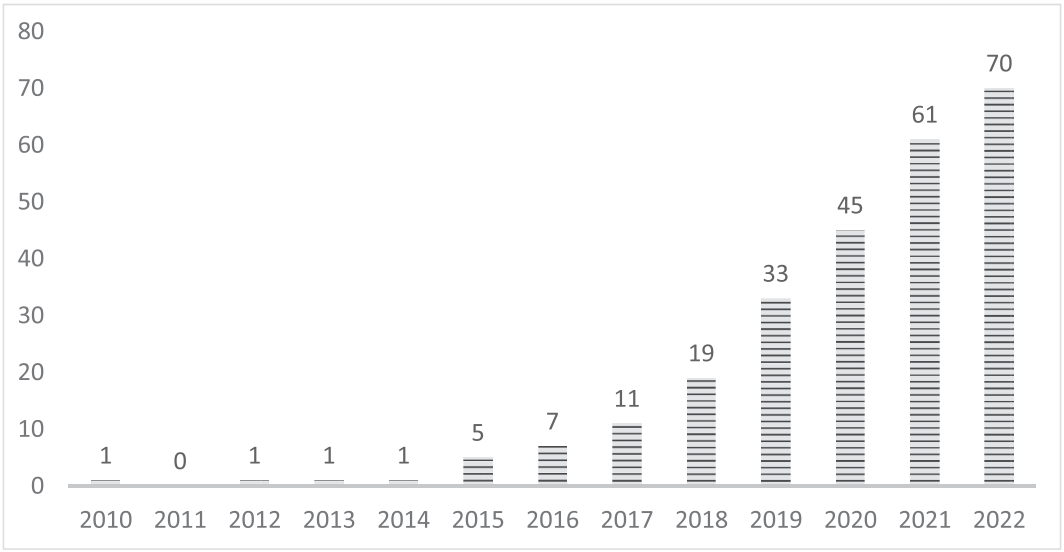

FIGURE 1 | Number of prenatally detected cases of PRUV per year between 2010 and 2022.

TABLE 1 | Maternal baseline characteristics.

	All cases with PRUV $N = 262$	Isolated cases with PRUV $N = 243$
Maternal age in years, median (IQR)	31 (28–35)	31 (28–35)
Maternal BMI, median (IQR)	23.2 (20.8–26)	23.1 (20.8–25.9)
Missing, *n* (%)	9 (3.4)	8 (3.3)
Ethnicity, Caucasian, *n* (%)	234 (94.4)	216 (88.9)
Missing, *n* (%)	14 (5.3)	13 (5.3)
Nulliparous, *n* (%)	107 (43.9)	99 (43.6)
Missing, *n* (%)	18 (6.9)	16 (6.6)
Spontaneous conception, *n* (%)	222 (84.7)	206 (84.8)
Missing, *n* (%)	11 (4.2)	10 (4.1)

first national study on PRUV performed. Our primary finding was that none of the fetuses with PRUV were found to have a chromosomal aberration—neither in the isolated cases nor in the fetuses with associated anomalies.

Previous studies on PRUV and chromosomal aberrations are limited. A systematic review from 2016 included results from 16 papers comprising 240 cases and found 1.3% to have chromosomal aberrations [8]. However, information on 1st trimester screening and associated anomalies were unavailable. More recently, two studies have found a prevalence of chromosomal aberrations of 1.8% and 0.7%, respectively. The first study did not disclose information on association with other malformations, 1st-trimester screening, or the number of pregnancies that were genetically tested. In the second study, no information on 1st-trimester screening was available, and they had genetic information available from 25% of the included cases. They did, however, differentiate between isolated and non-isolated PRUV and found only one case with isolated PRUV to have a chromosomal aberration (1/639, 0.2% of all isolated cases or 1/148, 0.7% of tested, isolated cases). Moreover, both centers were referral centers and therefore did not represent a low-risk population. In our study, we performed genetic tests on 49% of the patients and found zero fetuses with chromosomal aberrations—both in isolated and non-isolated cases of PRUV. A recent study estimated the risk of significant chromosomal aberration in a low-risk population of fetuses without structural malformations and found clinically significant copy number variants (CNVs) in 1.5% and high-penetrant CNVs in 0.4% [11]. Therefore, the prevalence of chromosomal aberrations does not appear to be higher in cases with isolated PRUV than in those without anomalies—irrespective of the studies considered.

We found an incidence of PRUV of approximately 0.03%, which is lower than previously reported. However, the incidence increased over time and varied between hospitals. Hence, the correct incidence to report is probably around 0.4%, since it was the average frequency over the last 3 years, which is in line with a more recent previous report [5].

Our results also showed that only 7.3% had associated malformations. This is lower than reported in previous studies and probably due to surveillance bias and the fact that we studied a low-risk population. High-risk pregnancies or fetuses with an anomaly are examined more thoroughly. As our population was at low risk, the prevalence of associated malformations was lower. Still, a fetus with PRUV should be scanned thoroughly, especially the heart, to rule out other malformations.

Our study has several strengths but also limitations. As the first study, we present nationwide data from a low-risk population undergone 1st-trimester screening. Almost 50% of the included pregnancies had genetic testing performed, and all patient files were evaluated to assess all prenatal findings and genetic results. Finally, we retrieved data from DCCR to link postnatal genetic findings to our cases to ensure the validity of our data. The study also had some limitations. Though half of the population had genetic testing performed, it is a limitation that it was not more. This was most likely due to different clinical practices around the country, as we did not have a national guideline regarding PRUV. We discovered that the two departments did not write in the conclusion in Astraia until halfway through the study period. However, as PRUV was generally not detected in those years, we do not believe this impacted our incidence results more than the lack of screening. Though it is a strength that we have genetic analyses on half of the fetuses, it also represents a limitation that analyses were not conducted on more cases.

In conclusion, in this national cohort of pregnant women screened in the first trimester, we found no chromosomal aberrations in fetuses with isolated or non-isolated PRUV. Compared to previous studies and studies on a population without anomalies, it does not appear that fetuses with isolated PRUV have a higher incidence of chromosomal aberrations and the parents could be reassured. Also, we found that PRUV was associated with other malformations in 7% of cases; therefore, these fetuses should be scanned thoroughly, especially to rule out congenital heart defects.

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Ethics Statement

The study was registered in the Capital Region of Denmark (p-2023–14664) and permission to assess patient files was given by the Center for Health in the Capitol Region (R-23047953).

Consent

This was not required as we were given permission to assess patient files by the Center for Health in the Capitol Region (R-23047953).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data available on request due to privacy/ethical restrictions.

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