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Isolated fetal pericardial effusion follow-up: Should we worry?☆

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Abstract
Introduction and objectives: Fetal pericardial effusion appears in different pathologies such as hydrops fetalis, heart structural or rhythm alterations, however, it can be observed in isolation but an increase in its incidence has been observed in relation to the presence of severe pathologies.
Methods: Analysis of all cases of IFPE detected in Aragon and assessed in a cardiological consultation for prenatal diagnosis of a tertiary hospital collected over ten years, as well as the evolution of the patients to the present.
Results: A sample of 38 fetuses was obtained from 37 pregnant women diagnosed with DPFA with spontaneous resolution in 86.8%. Two abortions (voluntary interruptions after prenatal diagnosis of 22q13 deletion and primary infection by cytomegalovirus) and one spontaneous fetal death were recorded. Pathological alterations were observed in 10/38 newborns: two patients with metabolic disease, two patients with chromosomopathies, one patient with pulmonary hypoplasia and unilateral hydronephrosis, one patient with hypertrophic cardiomyopathy, and four patients studied for alterations in psychomotor development and/or congenital ophthalmological or hearing disorders. The overall morbidity rate was 34.2% and death rate 15.7%. The detection of other ultrasound alterations and the alteration in the first trimester screening were significantly associated with the presence of pathology.

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Conclusions: IFPE has been classically associated with a good prognosis, although it is sometimes related to clinical entities with high morbidity and mortality: more than a third of the patients in our sample are affected. An exhaustive pre and postnatal follow-up of these cases is recommended in order to perform an early intervention.

PALABRAS CLAVE
Derrame pericárdico fetal aislado;
Ecocardiografía;
Patología perinatal

Seguimiento del derrame pericárdico fetal aislado: ¿debemos preocuparnos?

Resumen
Introducción y objetivos: El derrame pericárdico fetal aparece en diferentes patologías como hydrops fetal, alteraciones estructurales o del ritmo cardiaco, aunque puede observarse de manera aislada. Se ha observado un incremento de su incidencia en relación a la presencia de patologías graves.
Métodos: Análisis de la totalidad de casos de derrame pericárdico fetal aislado (DPFA) detectados en Aragón y valorados en consulta cardiológica de diagnóstico prenatal de un hospital terciario recogidos durante diez años, así como la evolución de los pacientes hasta la actualidad.
Resultados: Se obtuvo una muestra de 38 fetos en 37 gestantes diagnosticados de DPFA con resolución espontánea en el 86,8%. Se registraron dos abortos (interrupciones voluntarias tras diagnóstico prenatal de deleción 22q13 y de primoinfección por citomegalovirus) y una muerte fetal espontánea. Se objetivaron alteraciones patológicas en 10/38 recién nacidos: dos pacientes con metabolopatía, dos pacientes con cromosomopatía, un paciente con hipoplasia pulmonar e hidronefrosis unilateral, un paciente con miocardiopatía hipertrófica, y cuatro pacientes estudiados por alteraciones del desarrollo psicomotor y/o alteraciones congénitas oftalmológicas o auditivas. La tasa de morbilidad fue del 34,2% y de éxitus del 15,7%. La detección de otras alteraciones ecográficas y la alteración en el cribado del primer trimestre se asociaron de forma significativa con la presencia de patología.
Conclusiones: El DPFA se ha asociado clásicamente a buen pronóstico, aunque en ocasiones se relaciona con entidades clínicas con elevada morbimortalidad: más de un tercio de los pacientes en nuestra muestra. Se recomienda un seguimiento estrecho pre y postnatal de estos casos para poder realizar una intervención precoz.

Introduction

In recent years, there have been significant advances in echocardiographic assessment during the foetal period, and echocardiography has become one of the main tools used for early diagnosis of cardiac anomalies. Knowledge of the presence of prenatal cardiac abnormalities increases the probability of providing effective treatment to the newborn immediately after birth in those cases where early intervention is necessary, helps establish the most appropriate timing and mode of delivery and in some cases allows making decisions regarding termination of pregnancy.

Many congenital cardiac structural anomalies are associated with genetic changes or other diseases that affect systems other than the cardiovascular one. It is also important to take into consider that in 50%–80% of cases, chromosome abnormalities are associated with congenital heart defects.[1] On the other hand, the prevalence of chromosome abnormalities in foetuses with cardiac anomalies ranges between 12% and 35%, so there is a clear association between these groups of disorders.[2]

In addition to congenital structural cardiac anomalies, foetal echocardiography can detect other abnormalities, such as pericardial effusion (PE). Pericardial effusion is defined as the presence of fluid surrounding the foetal heart and is considered pathological when it is more than 2 mm[3] thick. Its incidence is approximately 2%,[4] and it has been associated with a variety of diseases, such as hydrops fetalis, structural heart disease, arrhythmia or viral infection.

On the other hand, PE can appear in isolation, that is, without an evident cause explaining its presence. Historically, isolated foetal PE (IFPE) has been considered transient and as having a favourable prognosis,[5] although it has also been described in association with other abnormalities, chiefly chromosomal, most frequently Down syndrome.[6] However, few studies have been conducted on the subject to date, with the followup limited to the foetal and neonatal periods.

Notwithstanding, we wondered about the benign character of this sonographic finding, and given the dearth of the literature on the association between sonographic features and aetiology, we conducted a study in which IFPE was the

primary variable by reviewing all cases managed in a tertiary care hospital in the past 10 years with the aim of determining whether this is or not a benign sonographic finding with a favourable prognosis.

Methods

We conducted a cross-sectional descriptive study through the retrospective review of all cases of IFPE evaluated in the foetal cardiology clinic of the Hospital Universitario Miguel Servet de Zaragoza (Zaragoza, Spain) in a 10-year period (2009–2019), with a clinical followup of these patients to present.

We included every foetus in whom IFPE was detected, excluding those with any other disease that could be directly related with PE, such as hydrops fetalis, anaemia, evidence of haemorrhage, extracardiac abnormalities (including pericardial tumours, cystic adenomatoid malformation, omphalocele, congenital diaphragmatic hernia, hepatic haemangioendothelioma, portohepatic shunt, polycystic kidney or bilateral renal abnormalities), structural cardiac anomalies and conduction disorders.

We classified PE based on size as mild if they were less than 4 mm thick and moderate/severe if they were 4 mm or thicker.

The analysis included obstetric variables (maternal age, gestational age at diagnosis, history of abortion or deceased children, abnormalities in the first trimester screening, performance of amniocentesis and its results and outcome of pregnancy), neonatal variables (gestational age and birth weight, Apgar score, need of admission), sonographic evolution of PE and diagnosis of anomalies or diseases during the followup.

Echocardiographic evaluations were performed with a Siemens Acuson SC2000 ultrasound system (Siemens Medical Solution USA, Inc.; USA) fitted with an 8 MHz linear transducer, mainly using the subcostal view to detect, measure and assess changes in PE.

The statistical analysis was performed with the software SPSS version 21 for Windows (SPSS Inc., Chicago, IL, USA.) and considered *p*-values of less than 0.05 statistically significant. We performed normality tests before the descriptive analysis, after which we compared means and analysed correlations. We expressed quantitative variables as mean, standard deviation and median. We expressed categorical variables as absolute frequencies and percentages. We assessed the association between categorical variables by means of the chi square test or, in case the assumptions were not met (expected frequency ≥ 5), the Fisher exact test. We used the Pearson correlation coefficient to assess the association between quantitative variables. To analyse the association between quantitative and categorical variables, we used the Student *t* test.

Results

Applying the inclusion and exclusion criteria, we obtained a sample of 38 foetuses corresponding to 37 women that received a diagnosis of IFPE in the period under study.

Table 1 Pregnancy and perinatal history.

	Cases, n
Total pregnant women	37
History of abortion	18
History of perinatal death in child	2
Maternal preeclampsia	3
Intrauterine growth restriction	8
Maternal diabetes	2
Spontaneous resolution of effusion	33
Amniocentesis	8
High-risk in T1 screen	5
Foetal death	3
Live births	35
Small for gestational age	2
1-min Apgar > 7	29
5-min Apgar > 7	33
Caesarean delivery	2
Perinatal admission	10
Perinatal death	2

T1, first trimester.

The mean age of the pregnant woman at diagnosis was 32.89 $\pm$ 6.39 years. The mean gestational age at initial detection of PE was 22.3 $\pm$ 4.3 weeks.

We found a previous history of abortion in 48.6% of the women (a single abortion in 35.1% and 2 abortions in 13.5%). In addition, 5.4% had a history of death of a child in the perinatal period.

In the pregnancies under analysis, the risk of trisomy in the first trimester screening was low in 86.5%. Amniocentesis was performed in 21% of the foetuses, with normal results in every case but one (22q13 deletion) (Table 1).

In the sample of 38 foetuses, 35 pregnancies culminated in live births (91.4%). Two pregnancies were terminated voluntarily following prenatal genetic diagnosis of 22q13 deletion (compatible with Phelan-McDermid syndrome) and subsequent diagnosis of primary infection by cytomegalovirus. Lastly, there was one case of spontaneous intrauterine foetal death at 26 weeks of gestation. In all 3 cases, the PE was persistent, but it was not haemodynamically significant. There was sonographic evidence of IFPE resolution during pregnancy in 86.8% of the total cases.

The mean gestational age at birth was 38.4 $\pm$ 1.83 weeks. Only 5 patients were born preterm, all of them late preterm (34 to 36^{+6} weeks' gestation). The mean birth weight was 2853 $\pm$ 705 g. Only 2 patients were small for gestational age (weight below the third percentile based on the growth charts of the World Health Organization).

The Apgar score was of 7 points in 82.9% of the sample at 1 min and 94.3% of the sample at 5 min. Hospital admission during the perinatal period was required by 28.6% of the newborns (17.1% admitted to neonatal intermediate care unit and 11.4% to neonatal intensive care unit). All living newborns underwent a cardiological evaluation that evinced the complete resolution of PE at birth in all but 3, and the effusion was not haemodynamically significant in any of them.

Pericardial effusion was moderate to severe in 17.6%, and in 100% of these cases persisted throughout the follow-up echocardiographic assessments. The outcomes of these

pregnancies were spontaneous miscarriage in 1, voluntary termination of pregnancy in 2, healthy newborns in 2, and a newborn with congenital cataracts, psychomotor retardation, microcephaly and short stature in 1 case with pending genetic testing.

The mean duration of followup of the patients from the first trimester screening to date has been 61.1 months. In as many as 37.1% of cases, we found unfavourable prenatal or postnatal outcomes. When it came to neonatal outcomes, 28.6% of the newborns (10/35) presented different diseases: 2 received a diagnosis of metabolic disorder (1 of congenital mitochondrial complex V deficiency, who died at 3 months, and 1 of malonyl-CoA decarboxylase deficiency), 2 of trisomy 21, 1 of psychomotor retardation associated with cataracts microcephaly with negative genetic testing and 3 patients undergoing evaluation for abnormal psychomotor development or congenital hearing loss. Another 2 patients died in the neonatal period (1 with pulmonary hypoplasia and 1 with hypertrophic cardiomyopathy and pulmonary hypoplasia—which were not detected prenatally—without evidence in genetic testing of hypertrophic cardiomyopathy). The overall mortality was 15.7% (Table 2).

We analysed the potential association of other factors with the development of diseases diagnosed before or after birth. Among them, we found that the history of previous abortions was not significantly associated (P = .075). However, we did find a statistically significant association with the detection of any other sonographic abnormality (P < .05) and abnormal first trimester screening results (P < .05).

Discussion

Developments in the field of ultrasound and prenatal diagnosis have allowed the accurate and early detection of foetal anomalies. Pericardial effusion is easy to identify, and its detection calls for ruling out its most frequent causes (foetal anaemia, structural anomalies or arrhythmias).[7] In some cases, PE develops in isolation and there are no other sonographic abnormalities explaining its presence. Several studies support the hypothesis that this finding is not associated with other diseases and that the prognosis of these patients is excellent.[5,8] However, there are also sources that, like our study, disagree with that conclusion. Sharland and Lockhart[6] found an incidence of Down syndrome of 31% in foetuses with IFPE in the absence of other sonographic abnormalities, and even contemplated performance of amniocentesis for screening after detection of this echocardiographic abnormality. The percentage was clearly lower in our study, in which the prevalence of chromosome disorders was 7.9%, with 5.2% corresponding to trisomy 21. This is mainly due to the higher sensitivity of current ultrasound systems and the increased experience in prenatal diagnosis which, combined with the first trimester screening, allow early detection of foetuses with this abnormality, leading to a high frequency of voluntary termination of pregnancy.

In the scarce literature on the subject of IFPE, most published articles analyse prenatal PE in the context of other sonographic features that lead to suspicion of specific diseases, such as Down syndrome.[6] However, a review of the literature found with a search of the main databases (PubMed, UpToDate, TRIP database, Cochrane, etc.) did not yield any sources demonstrating an association of IFPE with other diseases, and there were only isolated reports of cases with detection of Turner syndrome, Werdnig-Hoffman disease, trisomy 16 or suspected inborn errors of metabolism.[9]

In our study, we observed that this finding, which is actually rarely found in isolation, was associated in more than one third of cases with some form of disease during intrauterine or postnatal development, mainly with neurodevelopmental disorders or errors of metabolism, which were more frequent than chromosome disorders. In all likelihood, the fact that most chromosome disorders manifest with abnormalities in several organs facilitates early diagnosis of these diseases, with a resulting increase in voluntary termination of pregnancy. We ought to highlight the substantial number of children that presented neurodevelopmental abnormalities in which genetic testing did not identify a cause.

From a cardiological standpoint, it is rare for foetal PE to be haemodynamically significant, although serial scans should be conducted to monitor its course. In addition, follow-up evaluations should search for any cardiological abnormality that could justify PE, mainly arrhythmias. In most case series, as occurred in ours, a high percentage of effusion cases are mild and resolve spontaneously even before birth.[5] On the other hand, although Kyu-Sang et al.[7] did not find an association between the size of the effusion and the presence of associated disease in the 24 cases of IFPE in their series; in our study, larger and more persistent effusions were associated with unfavourable outcomes in 66.6% of cases.

Similarly, in our sample, children with a history of IFPE considered to have an excellent prognosis turned out to have disorders that could impact their health in more than one third of cases, some of them life-threatening. This morbidity was higher compared to the proportion described by Di Salvo et al.,[5] and one possible explanation is that in our study we conducted a longitudinal followup of the patients to assess their outcomes beyond the immediate neonatal period. Therefore, we recommend close monitoring prenatally and postnatally in patients given a diagnosis of IFPE even in the absence of other diseases or abnormal echocardiographic features to allow early detection of potential signs or symptoms indicative of some form of disease.

In our study, we observed that the detection of other sonographic features combined with IFPE was associated with the development of disease in the perinatal period. Therefore, we deduce that the association of these factors carries an increased risk of having some form of disease. This is also the case with abnormalities in the first trimester screening, which means that more information could be gained from this screening in addition to the presence of chromosome disorders. With this in mind, it would be interesting to conduct a study analysing the presence of perinatal disease in relation to an abnormal first trimester screening when it is associated versus not associated with IFPE.

Given the substantial heterogeneity of the diagnosed diseases, we were unable to make a comparative analysis, so we cannot claim that there is or is not an association between the detection of IFPE and the development of those diseases. However, given our results, we recommend a more

Table 2 Characteristics of the 38 cases of isolated foetal pericardial effusion.

Patient	Maternal age	GA at diagnosis (weeks)	Previous abortions/ deceased children	Other sonographic findings	First trimester triple screen	Amniocentesis	Resolution of effusion	Final diagnosis
1	32	21	0/0	Pyelectasis	LR	NP	Yes	Down syndrome
2	33	23	0/0	No	LR	NP	Yes	Healthy
3	33	21	0/0	No	LR	NP	Yes	Healthy
4	39	35	1/0	IUGR	LR	NP	Yes	Healthy
5	39	20	1/0	Oligohydramnios. IUGR	LR	NP	Yes	Inborn error of beta oxidation (death at 3 months)
6	34	15	1/0	No	HRT21	ABN	No	22q13 deletion
7	38	32	1/0	No	LR	N	Yes	Healthy
8	34	22	1/0	No	LR	NP	Yes	Healthy
9	30	25	0/0	No	LR	NP	Yes	Healthy
10	44	20	2/0	Twin pregnancy. IUGR	LR	NP	Yes	Healthy
11	34	26	1/0	IUGR	LR	NP	Yes	Healthy
12	33	20	1/0	No	LR	NP	Yes	Healthy
13	30	20	1/0	Ventriculomegaly. Echogenic bowel	LR	ABN	No	Infection by CMV (VTP)
14	30	20	0 / 0	IUGR	LR	NP	Yes	Healthy
15	27	18	0 / 0	IUGR. Hypoplasia of corpus callosum.	HRT21	NP	Yes	Down syndrome
16	27	20	0 / 0	No	LR	NP	Yes	Healthy
17	23	23	0 / 0	No	LR	NP	No	Psychomotor retardation. Cataracts. Microcephaly. Short stature.
18	33	22	0/0	IUGR	LR	NP	Yes	Healthy
19	24	19	0/0	No	LR	NP	Yes	Healthy
20	43	26	2/0	Oligoamnios	LR	NP	Yes	Healthy
21	34	20	2/0	No	LR	NP	Yes	Healthy
22	17	29	0/0	No	LR	NP	Yes	Healthy
23	36	24	1/0	Twin pregnancy	LR	NP	No	Healthy
24	36	24	1/0	Twin pregnancy	LR	NP	No	Healthy
25	39	16	1/0	No	HRT21	N	Yes	Healthy
26	34	14	2/1	No	HRT21	N	Yes	Hypertrophic cardiomyopathy. Pulmonary hypoplasia (death at 24 hpb)
27	21	20	1/ 0	Ventriculomegaly	LR	NP	Yes	Coloboma. Laryngomalacia. Hypotonia. Hearing loss.
28	35	21	0/0	No	LR	NP	Yes	Healthy
29	34	20	1/0	No	LR	NP	Yes	Healthy
30	25	22	0/0	No	LR	NP	Yes	Healthy
31	39	24	1/0	No	LR	N	Yes	Healthy
32	44	22	2/0	Twin pregnancy. Unilateral hydronephrosis	LR	N	Yes	Pulmonary hypoplasia. Unilateral hydronephrosis (death at 28 days)

Table 2 (*Continued*)

Patient	Maternal age	GA at diagnosis (weeks)	Previous abortions/ deceased children	Other sonographic findings	First trimester triple screen	Amniocentesis	Resolution of effusion	Final diagnosis
33	32	21	1/ 0	No	LR	NP	Yes	Psychomotor retardation. Hearing loss.
34	34	29	0/0	IUGR	LR	NP	Yes	Malonyl-CoA deficiency
35	22	20	0/0	No	LR	N	No	Intrauterine foetal death (26 wGA)
36	36	22	0/0	No	LR	NP	Yes	Healthy
37	41	26	0/0	No	LR	NP	Yes	Healthy
38	34	27	0/0	IUGR	HRT21	N	Yes	Hearing loss. Genital malformation

ABN, abnormal amniocentesis; CMV, cytomegalovirus; hpb, hours post birth; HRT21, high risk of trisomy 21; IUGR, intrauterine growth restriction; LR, low risk; N, normal amniocentesis; NP, amniocentesis not performed; T21, trisomy 21; VTP, voluntary termination of pregnancy; wGA, weeks of gestational age.

thorough followup of these patients, both cardiological and obstetric, in order to contemplate performance of diagnostic tests such as amniocentesis even in the absence of other abnormal findings.

The low prevalence of IFPE in prenatal ultrasound examinations, the fact that some diseases are diagnosed after the neonatal period and the diversity of the detected diseases hinder the performance of a more exhaustive analysis. However, in light of our findings, we recommend not to underrate the importance of foetal pericardial effusion when it is detected, even if it is mild and transient, not due to the potential for haemodynamic instability, which is infrequent, but to its potential association with different severe diseases that may not manifest in the early stages of life.

Conclusion

Isolated foetal pericardial effusion is an infrequent finding. It may range from a benign abnormality with spontaneous resolution and a favourable prognosis to one of the early manifestations, possibly the first one, of a severe disease. Thus, its early detection may contribute to clinical decision-making during pregnancy and childbirth.

The detection of this feature on echocardiography calls for closer monitoring, especially if the effusion persists, extending to the first months of life. The presence of IFPE in any stage of gestation is a risk factor in itself, so the resolution during pregnancy does not exclude this risk. For this reason, we cannot assert with any certainty that foetuses with IFPE are ''healthy''.

The presence of IFPE combined with abnormalities in the first trimester screening or other sonographic abnormalities carries an increased risk of perinatal disease. It cannot be considered an additional parameter in prenatal ultrasound screens, but we believe that it is an indication for closer monitoring of patients in whom it is detected.

We did not find a pathophysiological association between IFPE and the development of the diseases detected in patients in our sample. Similarly, we were not able to establish an association between this sonographic finding and a given group of diseases.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Finch A. La importancia de la ecocardiografía fetal en la detección y el manejo de las malformaciones cardiacas congénitas. Rev Esp Cardiol. 2006;59 Suppl 3:23–8.
2. Azancot A, Diehl R, Dorgeret S, Sebag G, Baumann C, Vuillard E, et al. Isolated pericardial effusion in the human fetus: a report of three cases. Dorgeret Prenat Diagn. 2003;23:193–7.
3. Shenker L, Reed KL, Anderson CF, Kern W. Fetal pericardial effusion. Am J Obstet Gynecol. 1989;160:1505–7.
4. Dizon-Townson DS, Dildy GA, Clark SL. A prospective evaluation of fetal pericardial fluid in 506 second-trimester low-risk pregnancies. Obstet Gynecol. 1997;90:958–61.
5. Di Salvo DN, Brown DL, Doubilet PM, Benson CB, Frates MC. Clinical significance of isolated fetal pericardial effusion. J Ultrasound Med. 1994;13:291–3.
6. Sharland G, Lockhart S. Isolated pericardial effusion: an indication for fetal karyotyping? Ultrasound Obstet Gynecol. 1995;6:29–32.

7. Kyu-Sang K, Hye-Sung W, Mi-Young L, Jae-Yoon S, Pil Ryang L, Ahm K. Clinical outcomes of prenatally diagnosed cases of isolated and nonisolated pericardial effusion. Fetal Diagn Ther. 2014;36:320–5.
8. Slesnick TC, Ayres NA, Bezold LI, Eidem BW, Fraley JK, Kung GC, et al. Characteristics and outcomes of fetuses with pericardial effusions. Am J Cardiol. 2005;96:599–601.
9. Wyllie J, Hunter S. Outcome of isolated fetal pericardial effusion. Cardiol Young. 1993;3:144–6.