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Research paper

# Fetal pericardial effusion after maternal COVID-19 vaccination: a fortuitous association?

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## Abstract

**Introduction:** Studies monitoring COVID-19 and its vaccines are warranted to expand knowledge about the virus and its effects in humans. The objective of this study was to compare the reasons for referral and the fetal echocardiographic results during (PAND: Mar/20-Aug/21) and before (PREP: Set/19-Feb/20) the COVID-19 pandemic.
**Material and methods:** Single outpatient centre, retrospective study.
**Results:** A total of 10,778 fetal echocardiograms were performed; 10,732 corresponding to initial examinations performed in 10,551 pregnancies (10,376 singletons; 171 twins; 2 triplets; 2 quadruplets). Only first-time exams were reviewed. There were 5652 during PREP and 5080 during PAND. Maternal ages ($X$) varied between 14 and 46 years ($\bar{X}_{PREP}$ = 29.1and $\bar{X}_{PAND}$ = 29.2), and gestational weeks ($Y$) varied between 16 and 39 weeks ($\bar{Y}_{PREP}$ = 26.9 and $\bar{Y}_{PAND}$ = 27.6). The exams were not performed in women with known active COVID-19 infection. In PREP, more women were referred due to maternal or fetal risk factors. During PAND, more women were referred due to a suspected heart defect on ultrasound. During PAND we identified more fetuses with congenital heart disease and arrhythmias. A higher incidence of pericardial effusion, without structural heart disease, was observed during the months of June, July, and August 2021, compared to the remaining months ($p < 0.001$).
**Conclusions:** The identification of more structural heart disease during PAND may reflect changes in referral patterns. The increase in isolated pericardial effusion coincided with the period of massive COVID-19 immunization. We hypothesize that this finding may reflect a transient inflammatory response that could signal to fetal immunization against SARS-CoV-2.

**Key words:** fetal echocardiography, pericardial effusion, COVID-19.

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## Introduction

The COVID-19 pandemic created a global health crisis of unprecedented proportions, with medical, economic, psychosocial, and behavioural challenges to populations throughout the world. Its medium- to long-term effects cannot be foreseen [1].

COVID-19 can damage the heart. Cardiovascular complications such as myocarditis, pericardial effusion, and pericarditis have been reported in adults [2, 3], children [4-6], and fetuses [7]. No reports have, thus far, suggested an increase in congenital heart malformations.

COVID-19 cardiovascular complications can be part of a complex multisystemic inflammatory syndrome or they can be isolated [8]. The latter has been described in the form of myocarditis or takotsubo cardiomyopathy [9].

Although measures such as mask-wearing and social distancing are important, immunization is the most effective tool to contain the pandemic. However, some serious adverse events have been reported after mRNA vaccine application in different age groups, and this has raised concerns about their safety and efficacy, particularly in more vulnerable groups such as the mother-fetus dyad [10-12].

Thus, short- and long-term follow-up studies after both the disease and its immunization programs remain an important aspect of the pandemic surveillance, which is necessary to determine its true impact and expand knowledge about this novel and challenging virus and its effects in humans.

This study aimed to compare results from fetal echocardiograms performed during and before the COVID-19 pandemics to see if there were differences in referral patterns or echocardiographic findings.

**Table 1.** Referral reasons for fetal echocardiogram

| Referral reason | PREP | PAND | *p*-value* |
|---|---|---|---|
| Total, *n* (%) | 5562 (100) | 4989 (100) | – |
| Fetal risk factor, *n* (%) | 313 (5.63) | 216 (4.33) | 0.0026 |
| Maternal risk factor, *n* (%) | 497 (8.94) | 375 (7.52) | 0.0091 |
| Routine, *n* (%) | 4580 (82.34) | 4118 (82.54) | 0.8103 |
| Suspected CHD, *n* (%) | 172 (3.09) | 280 (5.61) | < 0.0001 |

*PREP – pre-pandemics: September 2018 to February 2020, PAND – pandemic period: March 2020 to August 2021, CHD – congenital heart disease.*
**Z test to compare 2 proportions.*

**Table 2.** Diagnoses from fetal echocardiograms in the 2 periods

| Diagnostic groups | PREP | PAND | *p*-value* |
|---|---|---|---|
| Normal, *n* (proportion) | 5144 (0.9101) | 4790 (0.9429) | < 0.0001 |
| Congenital heart disease, *n* (proportion) | 67 (0.0119) | 107 (0.0211) | 0.0002 |
| Arrhythmia, *n* (proportion) | 16 (0.0028) | 32 (0.0063) | 0.0110 |
| Mild anomalies, *n* (proportion) | 424 (0.0750) | 152 (0.0299) | < 0.0001 |

*PREP – pre-pandemics: September 2018 to February 2020, PAND – pandemic period: March 2020 to August 2021.*
**Z test to compare 2 proportions.*

**Table 3.** Presence of pericardial effusion in fetal echocardiograms during the 2 periods

| Parameter | PREP | PAND | *p*-value* | Jun 21, Jul 21, and Aug 21 | *p*-value* |
|---|---|---|---|---|---|
| *n* | 69 | 149 | | 100 | |
| *N* | 5652 | 5080 | < 0.0001 | 1012 | < 0.0001 |
| Proportion | 0.0122 | 0.0293 | | 0.0988 | |

*PREP – pre-pandemics: September 2018 to February 2020, PAND – pandemic period: March 2020 to August 2021.*
**Z test to compare 2 proportions.*

## Material and methods

This is a single-centre, retrospective study from the Outpatient Department of Fetal Cardiology of a tertiary hospital in northeast Brazil.

We reviewed echocardiogram reports of all pregnant women referred to our unit between September 2019 and August 2021 and divided them into 2 periods: pre-pandemic (PREP: Sep/19 to Feb/20) and pandemic (PAND: Mar/20 to Aug/21). No hospitalized patients were included in the study, and all women declared that they were free of clinical symptoms suggestive of acute COVID-19 infection during the time of examination.

Five echocardiographers performed the examinations. Data collected included the reason for referral, maternal age and parity, gestational week, and final diagnosis. Only first-time examinations were reviewed.

Statistical analysis included descriptive techniques and hypothesis testing to assess statistical differences between the PREP and PAND periods. Hypothesis tests were performed by considering a level of significance of 5% ($p < 0.05$).

## Results

A total of 10,778 fetal echocardiograms were performed; 10,732 corresponding to initial examinations performed in 10,551 pregnancies (10,376 singletons; 171 twins; 2 triplets; 2 quadruplets). First-time exams numbered 5,652 during *PREP* and 5,080 during *PAND*. There were no significant differences between women's age or gestational age at the time of examination between the 2 groups. The women's ages ($X$) varied between 14 and 46 years ($\bar{X}_{PREP} = 29.1$ and $\bar{X}_{PAND} = 29.2$), and gestational ages ($Y$) varied between 16 and 39 weeks ($\bar{Y}_{PREP} = 26.9$ and $\bar{Y}_{PAND} = 27.6$).

In PREP, many women were referred for a fetal echocardiogram as part of their routine prenatal care or due to mild maternal or fetal risk factors, such as diabetes and hypertension or the presence of a golf ball or tricuspid regurgitation. During PAND, some women who were offered the exam on a routine basis declined to take it to avoid the risk of exposure to COVID-19 by entering a hospital facility. Thus, during PAND there were more fetal echocardiograms performed in women with suspected congenital heart disease on ultrasound, as shown in Table 1.

As for the echocardiographic findings, during PAND more fetuses presented with structural heart disease and arrhythmias (Table 2). Most of the arrhythmias described in the period were irregular heart rates due to supraventricular extrasystoles and without fetal cardiovascular compromise. There were 7 cases of sustained tachyarrhythmia, 2 in PREP and 5 in PAND, and 2 cases of total atrioventricular block in PAND.

Strikingly, a much higher incidence of pericardial effusion without structural heart disease was observed during the months of June, July, and August 2021, compared with the remaining months of the PAND and PREP periods ($p < 0001$), as shown in Table 3 and in Figures 1 and 2. These effusions were

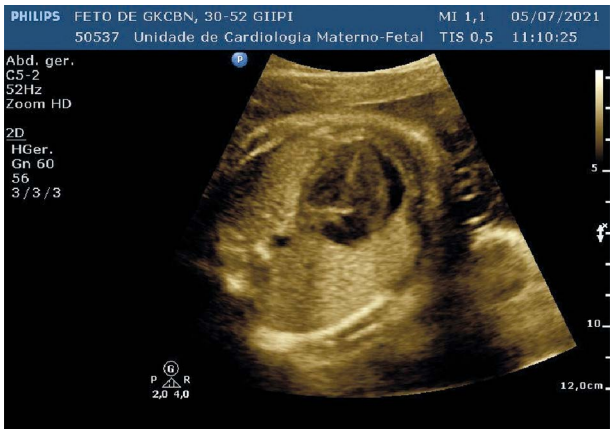


**Figure 1.** Anterior fetal pericardial effusion demonstrated on 2D echo 4-chamber view of a 30-week-old fetus

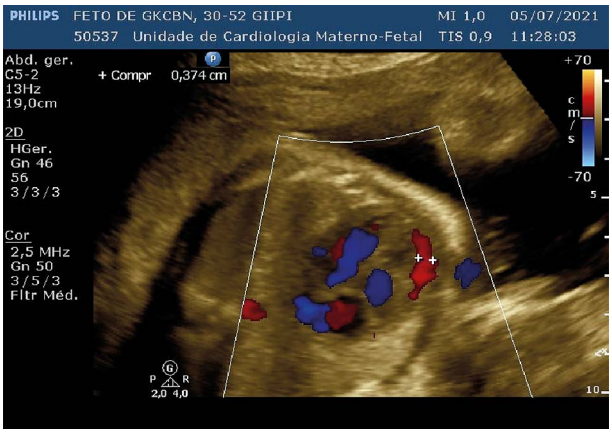


**Figure 2.** Colour flow Doppler in diastole showing flow across the atrioventricular valves and intra-pericardial flow moving in opposite direction

observed in otherwise normal fetal hearts, mostly anterior, with maximal area between 3 and 5 mm, and led to no haemodynamic compromise.

## Discussion

COVID-19 can affect the heart of adults and children, either in isolation or as part of a multisystemic inflammatory syndrome [8, 9].

Pregnant women are considered a group vulnerable to acquiring viral respiratory infections due to the physiological changes in their immune and cardiopulmonary systems. Nonetheless, as pointed out by Juan et al. [13], despite increasing numbers of published studies, there are still insufficient good-quality data to draw unbiased conclusions with regard to COVID-19 complications in pregnant women, as well as its vertical transmission and perinatal complications. This highlights the need for continuous research and complete data presentation on this challenging novel disease.

Overall, the impact of viral infections on fetuses, although documented in many situations, is still poorly understood. Racicot and Mor [14] highlight that virus-host interaction during pregnancy is complex and highly variable. Direct fetal infection, such as Cocksakie B, Cytomegalovirus, Rubella, or Zika, can have devastating effects on fetal development [15]. However, this placental barrier-crossing phenomenon is rare [16]. A consequence of the maternal inflammatory response, rather than the direct effect of the virus, is likely to be a more common mechanism behind the fetal effects of maternal viral infections [17].

Among fetal cardiovascular complications from viral infections, congenital heart malformations, pericarditis, myocarditis, and even dilated cardiomyopathy [18-20] have been reported. Thus far, only isolated cases of fetal cardiovascular complications have been reported during the COVID-19 pandemic [7, 21].

This study comes from an outpatient paediatric and fetal cardiology service. The echocardiograms were performed on women who reported being free of any clinical symptoms at the time of examination. However, no COVID-19 tests were requested prior to the exams, and thus we cannot rule out potential asymptomatic cases during the pandemic period.

More cases of fetal congenital heart disease were identified during the pandemic period, but there was also a shift in referral pattern, from more referrals due to mild maternal or fetal risk factors prior to the pandemic to more referrals due to a suspected cardiac abnormality on screening ultrasound during the pandemic. This shift in referral pattern may justify our findings; however, further studies are warranted in this area.

More strikingly, a highly significant increase in fetal pericardial effusion was observed in the months of June, July, and August of 2021 when compared with all remaining PAND and PREP periods.

In the 1980s, Jeanty et al. described the presence of 1-2 mm of pericardial fluid in otherwise normal fetuses after the 20$^{th}$ gestational week, and pointed out that with each generation of equipment one must re-evaluate what is normal and abnormal in diagnostic imaging [22].

There is no doubt that, with current imaging equipment and a good window of insonation, this normal rim of pericardial fluid can be observed and measured at the point of maximum thickness. The fluid moves toward the cardiac apex during systole and toward the atrium during diastole, and its velocity increases linearly in both systole and diastole with gestational age [23] and is not considered a pathological finding.

A true pericardial effusion, however, can be observed on routine fetal ultrasound throughout gestation. It seems to occur in approximately 2% of all pregnancies [24], but its exact incidence and significance is not clearly understood, because it can be associated with a wide spectrum of aetiologies from severe genetic and chromosomal diseases to transient, "normal" forms [25]. Isolated pericardial effusion has been associated with COVID-19 in adults [3], children [6], and fetuses [7].

In our study, we observed mostly anterior pericardial effusions with a maximal thickness of 3 to 5 mm in otherwise normal fetal hearts, with no haemodynamic compromise.

Because this observation coincided with the massive immunization program of pregnant women, which started in May

2021 in our city, we hypothesized that this finding could reflect a fetal inflammatory response to the transferred antibodies from the maternal immunization process.

The May immunization program used only the Pfizer vaccine. Most women in health professions had already received an AstraZeneca or CoronaVac shot earlier in the year, but still had their second shot, from May onwards, with the Pfizer vaccine. Some women might not have received any shots at the time of the fetal echocardiogram.

Because this report is a result of a clinical observation, no data were collected to determine the precise time interval between maternal immunization or the type of vaccine used and the development of fetal pericardial effusion. A follow-up study is being conducted to clarify these points.

Some serious adverse events have been reported after mRNA vaccine application in different age groups, and this raised concerns about their safety and efficacy, particularly in more vulnerable groups such the mother-fetus dyad [11, 12].

A recent review, however, found no increased adverse pregnancy outcomes after vaccination, and concluded that the benefits of maternal antibodies transferred through the placenta outweigh any known or potential risks [26].

Prior to this current observation, and similar to other centres, a sporadic finding of fetal pericardial effusion was occasionally documented in otherwise normal fetuses. They were generally small, with no haemodynamic compromise, and tended to disappear spontaneously. Perhaps they reflected transient, mild, inflammatory responses to maternal-fetus antibody transferal from other types of non-mRNA vaccines.

As massive immunization programs are being conducted for pregnant women in different parts of the world, our report may prompt other researchers to observe their populations, conduct similar studies, and expand knowledge for mothers and babies during and after the COVID-19 pandemic.

## Conclusions

A small increase in the number of cardiac malformations was observed since the beginning of the COVID-19 pandemic; however, it may reflect only changes in referral patterns for fetal echocardiography during the period.

More importantly, from the striking increase in fetal pericardial effusions, we raised the hypothesis of an inflammatory response to the maternal COVID-19 vaccine, which could mean that the fetuses were being effectively immunized in-utero. This would be reassuring; however, further studies are needed to determine if such a causal relationship exists and its potential mid- to long-term implications, or if our findings were simply a fortuitous association.

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## Conflict of interest

The authors declare no conflict of interest.

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