INTRODUCTION

It has been widely recognized that maternal intake of nonsteroidal anti-inflammatory drugs (NSAIDs) leads to premature DA closure/constriction, but there are very few cases of clear association between in utero exposure to paracetamol and ductal constriction. Fetal premature DA closure causes alteration of the right heart and pulmonary circulation, resulting in right ventricle hypertrophy, right heart dilatation with severe tricuspid regurgitation until hydrops. Clinical neonatal outcomes range from mild symptomatology to lethal respiratory insufficiency due to persistent pulmonary hypertension (PPHN). Also, selective serotonin reuptake inhibitor use in pregnancy results in increased likelihood of PPHN and a recent experimental animal’s study shows that in utero sertraline exposure constricts the DA.

CASE REPORT

A 35-year-old woman in her second pregnancy underwent specific ultrasound surveillance for her monochorial (MC) twin pregnancy at our Fetal Medicine Unit and from her private obstetrician. The results of first trimester screening indicated a low risk for chromosomal abnormalities. The pregnancy was not complicated by twin-to-twin transfusion syndrome (TTTS) or discordant abnormality or selective intrauterine growth restriction (sIUGR) and up to 29 weeks’ gestational age (GA), cardiac anatomy and function appeared to be normal in both twins.

The mother was being treated with sertraline (25 mg/day), lorazepam (10 drops/day), and diazepam on request (1-2 mg/die) for panic attacks. In addition, due to severe headache, she had taken paracetamol (1-2 g occasionally in the second and third trimester).

At 33 weeks GA, the ultrasound examination revealed a normal amniotic fluid deepest vertical pocket and fetal growth for both twins but showed a severe cardiomegaly in one twin (twin A). The cardio-thoracic ratio was 0.70 with severe right heart dilatation, decreased function of the right ventricle with tricuspid annular plane systolic excursion <5th percentile (TAPSE = 3 mm), tricuspid valve regurgitation (maximum velocity > 1.80 m/seconds), and ductus venosus severe A-wave.
negativity (Figure 1). The pulmonary artery appeared normal in diameter (7.6 mm, +1.61 Z-score), while the pulmonary valve showed reduced excursion, with bidirectional flow and severe insufficiency (maximum velocity > 1.80 m/seconds; Figure 2). In the sagittal view, the ductal arch and blood flow through the ductus arteriosus (DA) could not be detected. In the co-twin (twin B), cardiac anatomy and function appeared normal. No signs of TTTS or sIUGR were present.

A discordant premature closure of DA was suspected, and after a single course of corticosteroids, cesarean section was performed at 33 weeks GA. Two female neonates were delivered: twin A, birth weight 2021 g, and twin B, birth weight 2205 g, without cardiorespiratory failure in the delivery room (Apgar score 9 at 5'). Placental color-dye injection showed two arterovenous anastomoses and one arterio-arterial anastomoses. Echocardiographic examinations performed immediately after birth confirmed twin B normal cardiac anatomy and function.

In Neonatal Intensive Care Unit, twin A showed absence of DA and persistent pulmonary hypertension (PPHN) with transient hypoxemia managed with high flow nasal cannula (HFNC), but no pharmacological therapy. Echocardiogram showed a dilated and hypertrophic right ventricle with

**FIGURE 1** Twin A, 33 weeks GA. Four-chamber view: severe right heart dilatation and paradoxical movement of the interventricular septum (right ventricular pressure overload) (LV, left ventricle; RV, right ventricle; RA, right atrium). Arrow: reversal Doppler flow in ductus venosus

**FIGURE 2** Twin A, 33 weeks GA. Short axis view: severe pulmonary regurgitation with diastolic reversal flow in the pulmonary arteries (AV, aortic valve; PA, pulmonary arteries; PV, pulmonary valve; RV, right ventricle; arrow: pulmonary insufficiency)
systolic function reduction, normal morphology of pulmonary valve with regular anterograde flow, and mild insufficiency (Figures 3 and 4). On the fifth day of life, HFNC assistance was gradually reduced and interrupted, PPHN and right ventricular dilation regressed, systolic function normalized, but severe right concentric hypertrophy persisted without outflow tract obstruction. The echocardiographic studies performed at one and five months of age showed normal right ventricular thickness and function.

3 | DISCUSSION/CONCLUSION

Premature DA constriction/closure is a very rare event with an incidence ranging from 0.17% to 1.4%. Increased transpulmonary pressure gradient can lead to heart failure with fetal hydrops and possible PPHN. It has been widely recognized that maternal intake of nonsteroidal anti-inflammatory drugs (NSAIDs) and also high doses of acetaminophen leads to premature DA closure/constriction. Paracetamol may cause DA closure by the specific inhibitory action of the enzyme peroxidase, part of the enzyme complex of prostaglandin H2 synthase (PGHS), which also includes cyclooxygenase, resulting in a reduction in concentrations of arachidonic acid. The association between paracetamol intake and DA closure is also supported by experimental studies and by increasing evidence that postnatal administration of paracetamol is an effective treatment for patent DA. There is also evidence that acetaminophen crosses the placenta and therefore
exposes the fetus to toxicity. A recent review reporting 25 different cases of possible early fetal DA closure/constriction showed in two cases normal echocardiographic parameters 7-14 days after paracetamol discontinuation. There are very few cases of clear association between in utero exposure to paracetamol and ductal constriction and this complication appears to be dose-related and temporally correlated with possible regression if NSAID intake is discontinued.2

Like all selective serotonin reuptake inhibitors (SSRIs), sertraline (5-hydroxytriptamin or 5-HT) readily crosses the placenta, as reflected by fetal cord blood levels corresponding to 30%-70% of maternal levels. A recent experimental study in mice showed that in utero sertraline exposure constricts the DA, and SSRI exposure constricts mouse DA in utero primarily via serotonin 2A (5-HT2A) and by activation of 6 receptors (5-HT6).5

In addition, prolonged exposure to SSRIs may lead to abnormal 5-HT metabolism, which may alter the expression of 5-HT receptors (the 2A receptor), leading to increased Rho kinase activity contributing to persistent anomalies of pulmonary vascular tone, reactivity, or structure. This may contribute to impaired transition of the pulmonary circulation at birth.9 Although controlled studies are inconclusive, a recent meta-analysis suggests that SSRI use in pregnancy results in an increased likelihood of PPHN (OR 1.516; CI:1.035-1.997, P < .001).10

Our case is interesting because the DA closure occurred in only one twin in an otherwise uncomplicated MC pregnancy. Two other cases of MC twin pregnancies with discordant prenatal closure of DA after indomethacin exposure have been reported. In both of these, however, the pregnancy was complicated by TTTS, and according to the author’s hypothesis,11 premature DA closure occurred in the donor due to fetal hypoxia. In the present case, we think there was a synergistic action of both the drugs involved: While no cases have been reported regarding maternal sertraline intake, several have involved paracetamol.4

The presence of only one placenta without Doppler flow anomalies or growth discrepancy suggests a homogeneous distribution of the drugs. The occurrence of DA closure in only one MC twin might also be explained by differences at the epigenetic level.12,13 Another explanation could be differences in individual sensitivity to paracetamol metabolism linked to cytochrome P450 isoforms.15 To the best of our knowledge, this is the first case of premature DA closure due to early maternal intake of SSRIs and high-dose paracetamol involving only one twin in an otherwise uncomplicated MC pregnancy.

CONFLICT OF INTEREST
No conflicts of interest and any support and financial and nonfinancial involvement to declare.

AUTHOR CONTRIBUTIONS
CGC: contributed to the conception and design of the work, drafted the work for important intellectual content. CGC, SF, MML, FC, GL, LFN, SM, and MR: contributed to final approval of the version to be published; contributed to agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SF, MML, FC, GL, LFN, SM, and MR: revised the work critically. SF: contributed to acquisition, analysis and interpretation of data for the work. MML: contributed to acquisition of data for the work. FC, GL, LFN: involved in interpretation of data for the work. SM and MR: contributed to the conception and design of the work.

ETHICAL APPROVAL
Parents have given their written informed consent to publish their case.

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**How to cite this article:** Corti CG, Faiola S, Lanna MM, et al. Monochorionic diamniotic twin pregnancy complicated by discordant premature closure of ductus arteriosus. Clin Case Rep. 2020;8:685–689. [https://doi.org/10.1002/ccr3.2717](https://doi.org/10.1002/ccr3.2717)