Effect of In Utero Non-Steroidal Anti-Inflammatory Drug Therapy for Severe Ebstein Anomaly or Tricuspid Valve Dysplasia (NSAID Therapy for Fetal Ebstein anomaly)

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Ebstein anomaly (EA) and tricuspid valve dysplasia (TVD) are rare congenital malformations associated with nearly 50% mortality when diagnosed in utero. The diseases often produce severe tricuspid regurgitation (TR) in the fetus and in some cases, pulmonary regurgitation (PR) and circular shunting ensue. Since the ductus arteriosus (DA) plays a critical role in the circular shunt and may be constricted by transplacental nonsteroidal anti-inflammatory drugs (NSAIDs), we sought to assess the effect of NSAIDs on fetuses with EA/TVD. We reviewed mothers of singleton fetuses with EA/TVD and PR, indicative of circular shunting, who were offered NSAIDs at multiple centers from 2010 to 2018. Initial dosing consisted of indomethacin, followed by ibuprofen in most cases. Twenty-one patients at 10 centers were offered therapy at a median gestational age (GA) of 30.0 weeks (range: 20.9 to 34.9). Most (15/21 = 71%) mothers received NSAIDs, and 12 of 15 (80%) achieved DA constriction after a median of 2.0 days (1.0 to 6.0). All fetuses with DA constriction had improved PR; 92% had improved Doppler patterns. Median GA at pregnancy outcome (live-birth or fetal demise) was 36.1 weeks (30.7 to 39.0) in fetuses with DA constriction versus 33 weeks (23.3 to 37.3) in fetuses who did not receive NSAIDs or achieve DA constriction (p = 0.040). Eleven of 12 patients (92%) with DA constriction survived to live-birth, whereas 4 of 9 patients (44%) who did not receive NSAIDs or achieve DA constriction survived (p = 0.046). In conclusion, our findings demonstrate the proof of concept that NSAIDs mitigate circular shunt physiology by DA constriction and improve PR among fetuses with severe EA/TVD. Although the early results are encouraging, further investigation is necessary to determine safety and efficacy. **(Am J Cardiol 2021;141:106−112)**

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Ebstein anomaly (EA) and tricuspid valve dysplasia (TVD) are associated with nearly 50% perinatal mortality when diagnosed in utero.[1] These defects often produce severe tricuspid regurgitation (TR) in the fetus with resultant diminished antegrade pulmonary blood flow and reversed, left to right shunting at the ductus arteriosus (DA). When there is pulmonary regurgitation (PR), a circular shunt ensues with ineffective systemic blood flow that may lead to fetal demise or neonatal death.[1,2] The pathophysiology may progress throughout gestation,[3−7] resulting in premature birth, which is a significant risk factor for mortality among live-born infants with EA/TVD.[1,2,8,9] Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits prostaglandin synthetase and may cause constriction of the fetal DA by placental transfer.[10,11] Constriction of the DA in fetuses with EA/TVD and PR may improve hemodynamics by interrupting the circular shunt (Figure 1). Although single-center cases have been reported,[12,13] the proof of concept of this approach in a larger series of fetuses across institutions has not been demonstrated. We sought to assess the effect of transplacental NSAID therapy on fetuses with EA/TVD and circular shunting at multiple institutions.

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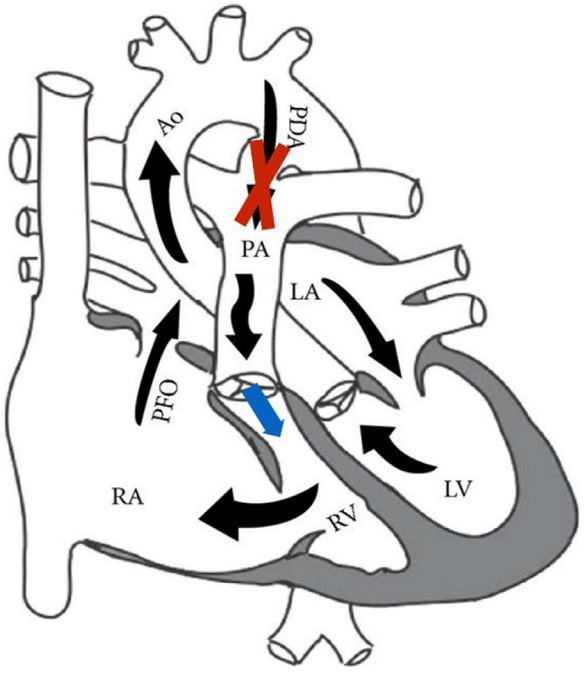

Figure 1. Diagram illustrating the role of constriction of the ductus arteriosus (PDA; red) in the context of severe EA/TVD with circular shunting and pulmonary regurgitation (blue arrow). Ao = aorta; PFO = patent foramen ovale; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle.

Methods

In this retrospective case series, we included mothers of second- and third-trimester fetuses with severe EA/TVD and circular shunting who were offered NSAID therapy at multiple international centers from 2010 to 2018. Severe EA/TVD was defined as having severe TR, and circular shunting was defined by at least moderate PR. Both TR and PR were assessed qualitatively by the width of the vena contracta jet. Fetuses with and without hydrops (defined as ≥2 of the following: pericardial effusion, pleural effusion, ascites, scalp edema, polyhydramnios, or placentomegaly) were included. Twin or higher order multiple gestations were excluded, as were mothers with a contraindication to NSAID therapy, that is, history of gastric ulcers. Approval was obtained for retrospective case review per institutional protocol.

A general clinical practice guideline was employed across centers with modifications decided on a case-by-case basis by the treating physicians. Among mothers who agreed to receive NSAIDs, high-dose indomethacin (100 mg 2 to 4 times daily) was typically administered as initial therapy to achieve DA constriction. Fetal echocardiograms were performed approximately every 24 to 48 hours to assess whether DA constriction was achieved. If DA constriction was achieved, then therapy was commonly transitioned to maintenance ibuprofen (200 to 600 mg 3 to 4 times daily), since prolonged exposure to indomethacin may decrease fetal urine output and cause oligohydramnios irrespective of maternal serum level.[14–16] Ibuprofen is less effective at DA constriction in neonates, but it leads to less renal dysfunction[17] and was therefore felt to be safer for the fetus throughout the remainder of gestation.

Serial fetal echocardiography and obstetric ultrasounds for oligohydramnios were performed. DA constriction was defined as visible narrowing and flow acceleration with a peak systolic velocity >2 m/s and/or increase in diastolic flow with pulsatility index <1.9. The outcomes of all mothers who were offered therapy, including those who declined, were documented. Pregnancy outcome was defined as live-birth or fetal demise. There were no elective terminations of pregnancy in this series.

Data are displayed as frequency (%) or median (range) where appropriate. Nonparametric testing was performed due to the small sample size with Fisher's exact test for categorical variables and Wilcoxon rank sum test for quantitative variables. A two-sided p-value <0.05 was considered statistically significant.

Results

Twenty-one maternal-fetal dyads at 10 centers in 4 countries were offered NSAID therapy at a median GA of 30.0 weeks (20.9 to 34.9). All fetuses had severe EA/TVD with severe TR and circular shunting with at least moderate PR. As demonstrated in Table 1, there were not significant

Table 1.
Fetal echocardiographic findings at presentation by receipt of non-steroidal anti-inflammatory (NSAID) therapy

	NSAID therapy	
	Yes (n = 15)	No (n = 6)
Gestational age	30.3 (22.3 to 32.3)	29.0 (20.9 to 34.9)
Severe tricuspid regurgitation	15 (100%)	6 (100%)
≥Moderate pulmonary regurgitation	15 (100%)	6 (100%)
Antegrade pulmonary blood flow	0 (0%)	0 (0%)
Cardiothoracic ratio	0.55 (0.39 to 0.80)	0.55 (0.54 to 0.60)
Tricuspid regurgitation peak gradient	16 (12 to 25)	15 (12 to 18)
Tricuspid valve z-score	+5.09 (+2.77 to +9.4)	+8.44 (+7.07 to +11.62)
Pulmonary valve z-score	-0.40 (-1.76 to +1.88)	-1.57 (-2.76 to -0.39)
Main pulmonary artery z-score	+1.00 (-2.04 to +1.43)	-0.65 (-1.23 to +0.88)
Right ventricular dysfunction	11 (73%)	5 (83%)
Left ventricular dysfunction	7 (47%)	3 (50%)
Pericardial effusion	11 (73%)	3 (50%)
Hydrops	5 (33%)	2 (33%)
Abnormal extracardiac Doppler pattern	12 (80%)	4 (67%)

Data are presented as n (%) or median (range).

differences between those who received and did not receive NSAIDs at presentation. The median TR jet for the entire cohort was 16 mm Hg (12 to 30), and most had accompanying cardiomegaly, ventricular dysfunction, and pericardial effusion. One-third of the fetuses had hydrops. In addition, the majority had abnormal extracardiac Doppler findings; namely, reversed or absent end-diastolic flow in the umbilical artery and/or middle cerebral artery suggestive of an inadequate fetal circulation with systemic steal.

Fifteen of the mothers (71%) agreed to receive NSAIDs at a median GA of 30.3 weeks (22.0 to 33.1). Table 2 summarizes the NSAID therapy provided. Following initial therapy with indomethacin (or ibuprofen in Case 3), 12 fetuses (80%) achieved DA constriction after a median of 2.0 days (1.0 to 6.0). The 3 patients who did not achieve DA constriction were treated at 33.1, 31.0, and 28.0 weeks. Only the fetus who was furthest along in gestation, delivered at 34.1 weeks, survived.

Among the 12 fetuses who achieved DA constriction, 10 (83%) were transitioned to maintenance therapy of ibuprofen 200 to 400 mg 2 to 3 times daily. Seven patients experienced loss of constriction on ibuprofen: 2 were placed back on indomethacin for 1 to 2 days before resuming ibuprofen, 4 were transitioned to low-dose indomethacin (50 to 100 mg 3 times daily), and 1 received alternating doses of ibuprofen and low-dose indomethacin for the remainder of pregnancy. Two of the 12 with DA constriction never transitioned to maintenance ibuprofen. One remained on indomethacin due to lack of ductal constriction with initial therapy (Case 15); the dose was reduced to 50 to 75 mg 4 times daily. In the other patient (Case 5), there was complete constriction of the DA after initial therapy of indomethacin (100 mg twice daily for 6 days) at 31.1 weeks. The DA remained constricted throughout the rest of pregnancy without therapy. The median duration of NSAID therapy for the entire cohort was 31 days (6 to 103), typically until the time of delivery.

All 12 fetuses with DA constriction had improved PR, with 1 having complete resolution, and half achieved antegrade pulmonary blood flow as demonstrated in Figure 2. All fetuses demonstrated improvement or normalization of the extracardiac Doppler patterns. Of the patients presenting with a pericardial effusion or hydrops, 44% experienced resolution.

The clinical outcomes are summarized in Figure 3. In the entire cohort, 15 of 21 patients (71%) survived to live-birth at a median GA of 35.9 weeks (30.7 to 39.0). The 6 fetal demises occurred at a median GA of 31.9 weeks (23.3 - 37.3). There was no significant difference in GA at pregnancy outcome or survival to live-birth between mothers who received or declined NSAID therapy (35.9 vs 34.5 weeks, $p = 0.38$ and 12/15 [80%] vs 3/6 [50%], $p = 0.29$, respectively).

Among the 15 mothers who received transplacental therapy, 12 fetuses achieved ductal constriction. No constriction occurred in fetuses whose mothers declined therapy. Fetuses who achieved DA constriction ($n = 12$) had a greater median GA at pregnancy outcome as compared with fetuses who did not achieve DA constriction or did not receive NSAIDs ($n = 9$): 36.1 (30.7 to 39.0) versus 33.0 weeks (23.3 to 37.3), $p = 0.040$. Eleven of 12 patients (92%) with DA constriction survived to live-birth, whereas 4 of 9 patients (44%) who did not achieve DA constriction or did not receive NSAIDs survived ($p = 0.046$). Among only those mothers who received treatment ($n = 15$), those who achieved DA constriction ($n = 12$) had a greater median GA at pregnancy outcome that approached statistical significance (36.1 vs 31.3 weeks, $p = 0.060$) as compared with those who did not achieve DA constriction ($n = 3$). Similarly, in this smaller intervention cohort, achievement of DA constriction resulted in a trend toward survival to live-birth (11/12 [92%] versus 1/3 [33%], $p = 0.081$).

Between fetuses with hydrops ($n = 7$) and without hydrops ($n = 14$) at presentation, there was no significant difference in GA at outcome or survival to live-birth. Of the fetuses who presented with hydrops, 5 mothers received NSAIDs and 3 achieved DA constriction. All 3 of these fetuses survived to live-birth at 34.0, 36.0, and 38.0 weeks.

With regard to safety, 1 fetus (Case 5) developed complete DA constriction after 6 days of indomethacin therapy as mentioned previously. The fetus had resolution of hydrops and normalization of the extracardiac Dopplers and was delivered at 38.0 weeks. Ten patients (67%) developed oligohydramnios, ranging from 3 to 42 days after initiation of indomethacin and/or ibuprofen therapy. In 5 cases, therapy was transitioned from indomethacin to ibuprofen or briefly stopped with resumption of normal amniotic fluid volume. In 2 cases that developed oligohydramnios at 33.6 and 35.7 weeks, the decision was made to proceed with delivery at 34.1 and 35.9 weeks, respectively. The remainder was monitored without intervention until delivery.

Postnatally, 2 neonates had renal failure requiring peritoneal dialysis. In 1 patient (Case 6) who had loss of DA constriction on ibuprofen and received low-dose indomethacin throughout the remainder of pregnancy, delivery occurred at 36.0 weeks. The patient was diagnosed with trisomy 21 postnatally; the renal failure resolved after 19 days of dialysis. The second neonate (Case 15) was the patient who was never transitioned to ibuprofen due to inability to achieve ductal constriction. The fetus also developed supraventricular tachycardia, which was treated with digoxin and sotalol, and due to concerns regarding impaired renal clearance and antiarrhythmic toxicity, delivery was performed at 34.0 weeks. A postnatal diagnosis of chromosome 22q11.2 duplication syndrome was made, and the neonate died at 9 days of life.

One mother complained of heartburn on maintenance ibuprofen, which responded to lowering of her dose. No additional maternal issues were noted.

Discussion

In this case series of fetuses with severe EA/TVD and PR across multiple institutions, our findings demonstrate the proof of concept that transplacental NSAIDs mitigate circular shunt physiology by causing DA constriction. Constriction was achieved in the majority of fetuses and led to less PR with improvement or normalization of abnormal extracardiac Doppler patterns in all fetuses and the resolution of hydrops in nearly half. Coincident with these hemodynamic changes, fetuses who achieved DA constriction

Table 2.
Summary of nonsteroidal anti-inflammatory drug therapy for each case

Case No.	GA at therapy (weeks)	Duration of initial therapy* (days)	Ductal constriction	Duration of maintenance therapy (days)**	Total duration of NSAIDs (days)	Oligo-hydramnios at any time	Outcome (LB or FD)	GA at outcome (weeks)
1	28.7	6	+	45	51	+	LB	36.1
2	29.4	4	+	27	31	+	LB	33.9
3	28.0	2	+	63	65	+	LB	38.0
4	32.0	3	+	39	42	+	LB	38.0
5	30.3	6	+	—	6	+	LB	38.0
6	32.0	4	+	20	24	+	LB	36.0
7	27.3	1	+	22	23	+	LB	30.7
8	22.7	2	+	103	105	-	LB	37.7
9	22.0	3	+	74	77	+	FD	33.0
10	32.3	2	+	22	24	+	LB	35.9
11	30.9	3	+	53	56	-	LB	39.0
12	33.1	5	-	—	5	+	LB	34.1
13	31.0	2	-	—	2	-	FD	31.3
14	28.0	3	-	—	3	-	FD	29.1
15	30.9	1	+	21	22	-	LB	34.0

* Initial therapy consisted of indomethacin in all cases, except Case 3 where ibuprofen was used.

** Maintenance therapy started with ibuprofen in all cases, except for Case 5 who experienced complete ductal constriction after 6 days of indomethacin and Case 15 where maintenance therapy consisted of a lower dose indomethacin. After subsequent loss of ductal constriction, Cases 3, 4, 6, and 11 were transitioned to low-dose indomethacin therapy and Case 2 alternated between ibuprofen and low-dose indomethacin for the remainder of pregnancy.

FD = fetal demise; GA = gestational age; LB = live-born.

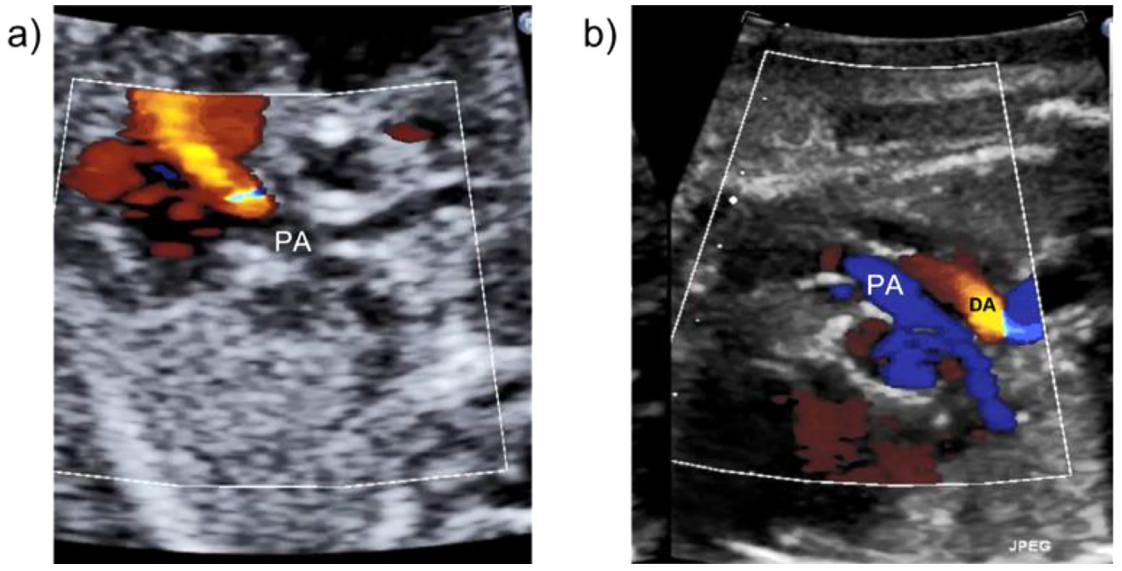

Figure 2. Echocardiographic images of a fetus with severe EA/TVD prior to and on NSAID therapy. Image (a) demonstrates severe pulmonary regurgitation in the context of a large ductus arteriosus with reversed flow prior to NSAID therapy and b) demonstrates antegrade pulmonary blood flow with no pulmonary regurgitation with a constricted DA on NSAID therapy. PA = pulmonary artery.

had a greater GA at pregnancy outcome and improved survival to live-birth as compared with fetuses who either did not achieve DA constriction or whose mothers declined NSAID therapy.

A recent fetal cardiac MRI study corroborated these hemodynamic changes in a patient with severe EA on NSAID therapy. The authors demonstrated that following DA constriction, there was a reduction in circular shunt flow or systemic steal from 42% to 10%. In our series, beyond substantiating the underlying mechanism of NSAID therapy, we were able to demonstrate that fetuses with successful DA constriction had prolonged gestation, which is clinically important. By permitting delivery closer to term, subsequent neonatal morbidity and mortality may be improved,[18,19] beyond survival to live-birth alone.

Although these early results are encouraging, it is important to acknowledge that, despite similar fetal characteristics between mothers who received and declined NSAID therapy, significant changes were noted only when patients who did not receive NSAID therapy and did not achieve DA constriction on therapy were combined. While this supports the concept that DA constriction may prolong gestation and contribute to survival to live-birth, the small sample size limited comparisons. Due to the heterogeneity of postnatal care that exists for this population,[20] postnatal outcomes were not evaluated. As such, even though efficacy has been partly demonstrated in this series, equipoise remains, and a prospective study involving a greater number of patients with a standardized protocol is essential.

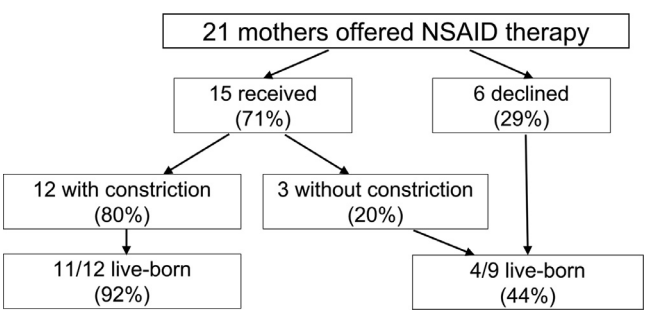

Figure 3. Flow chart depicting outcomes among all mothers offered NSAID therapy.

Beyond more rigorous methods to establish the efficacy of NSAID therapy for fetuses with EA/TVD and circular shunting, there are safety concerns that warrant further evaluation. Although transplacental indomethacin has not been systemically associated with adverse outcomes in neonates with a normal circulation[21] and DA constriction is typically reversible regardless of underlying cardiac anatomy,[22,23] there was 1 patient who experienced complete DA constriction after 6 days of therapy. In addition, 10 of 15 patients developed oligohydramnios at some point during the pregnancy, suggestive of impaired fetal renal function. In 2 cases, this finding prompted delivery. Two neonates had renal failure requiring peritoneal dialysis; however, aside from the impact of the aberrant cardiac pathophysiology itself on renal function, both were postnatally diagnosed with significant underlying genetic conditions (trisomy 21 and 22q11.2 duplication syndrome) and 1 was known to be receiving additional nephrotoxic therapy. It will be important to understand how NSAID therapy impacts the development of oligohydramnios and/or postnatal renal dysfunction. Fortunately, no significant maternal safety issues have arisen thus far, but careful monitoring will need to be employed on this front as well.

Although we herein describe 21 patients with a rare disease treated with novel transplacental therapy, the findings are derived from a case series. Despite general guidelines for treatment, individual providers modified the NSAID therapy on a case-by-case basis and ultimately made their own judgments regarding management and delivery. Moreover, there were occasional missing data and incomplete follow-up. These limitations would

be overcome by a prospective study with an extended follow-up interval.

From an ethical standpoint, Chervenak et al outlined that fetal therapy may be offered when it is potentially life-saving and of "low or manageable risk" to the fetus and mother.[24] Severe EA/TVD is one of the most lethal forms of congenital heart disease in utero with unacceptably high mortality in the current era[1] and with no proven therapy beyond expectant management. NSAID therapy is likely to be low risk to both the mother and fetus, particularly with close monitoring of fetal renal function and amniotic fluid volume, and is substantially more benign than fetal surgery, for example, which has also been suggested for this disease and poses considerable risk to the mother.[25] Thus, proceeding with prospective investigation is ethically justified from our perspective.

In summary, this large, multicenter case series builds upon the prior single-center case reports[12,13] and demonstrates considerable promise for the application of NSAID therapy to fetuses with severe EA/TVD. Not only did NSAID therapy promote DA constriction and mitigate aberrant circular shunting pathophysiology in utero, but it also increased the duration of pregnancy, which may improve neonatal morbidity and mortality, and enhanced survival to live-birth. Nevertheless, there are unanswered questions about the merits of therapy, particularly when DA constriction does not occur, and safety. In light of this equipoise and guided by the ethical principles above, we plan to proceed with a multicenter, prospective investigation to address the pressing need for treatment of this highly lethal disease.

Disclosures

This manuscript addresses novel, off-label use of NSAID therapy. There are no relevant financial, personal or professional relationships to disclose.

Author Statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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