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REVIEW

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Transplacental non-steroidal anti-inflammatory drugs versus expectant management in fetal Ebstein anomaly with circular shunt: Systematic review and meta-analysis

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Abstract

Ebstein anomaly (EA) is a rare congenital cardiac malformation associated with high perinatal mortality. In this systematic review and meta-analysis, we aimed to investigate the outcomes of pregnancies affected by EA or tricuspid valve dysplasia (TVD) with circular shunt, focusing on two prenatal management approaches: (1) expectant management (EM) and (2) transplacental non-steroidal anti-inflammatory drugs (NSAID) therapy. We searched PubMed, Scopus, and Web of Science systematically from its inception until June 2023. The random-effect model was used to pool the data. Heterogeneity was assessed using the I^2 value. Twenty-one studies with a total of 610 fetuses with EA/TVD with circular shunt were included in the synthesis, of which 17 studies (583 fetuses) were on EM and 4 studies (27 fetuses) used transplacental NSAID therapy. The NSAID group had higher rates of moderate to severe tricuspid regurgitation, hydrops, and pericardial effusion on prenatal ultrasound compared with the EM group. However, ductal constriction was achieved in 81% of NSAID cases, mitigating the disease pathophysiology, although 65% of them experienced oligohydramnios. Notably, the NSAID group showed significantly higher rates of live birth (86%) and survival to hospital discharge (89%) compared with the EM group (67% and 43%, respectively). Despite these promising results, it's important to acknowledge that the number of cases treated with NSAIDs was small, with limited safety data. Therefore, caution is advised in interpreting these findings, and patients considering NSAID therapy should be informed about these limitations. Future multicenter studies are necessary to further explore the safety and effectiveness of NSAID therapy in this particular population.

Key points

What's already known about this topic?

- Ebstein anomaly (EA) and tricuspid valve dysplasia (TVD) are associated with severe tricuspid regurgitation (TR) and pulmonary regurgitation (PR).

- When PR is present, a circular shunt ensues with ineffective systemic blood flow leading to perinatal mortality.
- Transplacental administration of non-steroidal anti-inflammatory drugs (NSAIDs) may result in a narrowing of the fetal ductus arteriosus (DA) and PR improvement in fetuses with severe EA/TVD.

What does this review add?

- This is the first systematic review and meta-analysis that comprehensively compares expectant management (EM) versus treatment with NSAIDs in fetal EA/TVD with a circular shunt.
- Among fetuses with EA/TVD with circular shunt with EM, only 43% survived to hospital discharge versus 89% of those treated with NSAIDs.

1 | INTRODUCTION

Ebstein anomaly (EA) and tricuspid valve dysplasia (TVD) are congenital cardiac disorders of the tricuspid valve affecting 1 in 20,000 live births and represent 0.5% of congenital heart defects.[1] Despite its rarity, its perinatal mortality is reported in up to 50% of the cases when diagnosed in-utero.[2] EA is caused by failure of delamination of tricuspid valve leaflets, resulting in the displacement of basal insertions of its posterior and septal leaflets and ensuing atrialization of the inlet portion of the right ventricle.[3,4] Although this is common in all EA cases, each can present with unique cardiovascular pathologic and hemodynamic features.[5–7]

In the setting of severe fetal EA/TVD with significant TR and PR, circular shunt results in a portion of the left ventricular output bypassing the systemic circulation via an unrestricted DA[2,8] and a patent foramen ovale returning blood to the left ventricle without having traverse the systemic capillary bed.[9,10] The pathophysiology may progress throughout gestation,[11,12] resulting in preterm birth (PTB), which is a significant risk factor for mortality among newborns with EA/TVD.[8,13–15]

Scoring systems exist to assess EA severity and possible outcomes and may aid in counseling families. The Great Ormond Street Score (GOSE or Celermajer index) is defined as the ratio of the area of the right atrium and atrialized right ventricle to the combined area of the functional right ventricle, left atrium, and left ventricle; the greater the ratio, the worse the prognosis.[16,17] The prognostic Simpson-Andrews-Sharland (SAS) score, assesses the severity of EA by combining the Celermajer index and echocardiographic findings such as cardiothoracic ratio, pulmonary valve and ductal flow, and right-left ventricular ratio.[7]

Individuals with EA/TVD and PR may benefit from improved hemodynamics following DA constriction as it limits the circular shunt.[10,18,19] This desired narrowing of the fetal DA is potentially achieved through the maternal administration of ibuprofen, or indomethacin, which are classified as NSAIDs and are known inhibitors of prostaglandin synthetase.[18]

Owing to the rarity of the condition, assessing prenatal therapeutic management for EA/TVD by large and reliable cohort studies is difficult. In this systematic review and meta-analysis, we aimed to investigate outcomes of pregnancies with EA/TVD with circular shunt that were managed expectantly versus those treated with prenatal NSAIDs.

2 | MATERIALS AND METHODS

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines.[20] The study protocol for this systematic review was registered in the PROSPERO international prospective register of systematic reviews (Registration number CRD42022333994).

PubMed, Web of Science, and Scopus were searched from inception to June 2023. Initially, selected studies were reviewed for eligibility by two independent authors (ZAB and IM) and conflicts were resolved by consulting the third investigator (HJM). Search was conducted using combinations of the relevant medical subject heading terms, keywords, and word variants were used to search ("Ebstein") AND ("prenatal"). The complete search strategy is presented in Table S1.

2.1 | Eligibility criteria

We used the Patient/Population, Intervention, Comparison, and Outcomes (PICO) framework[21,22] to establish the following inclusion criteria for all relevant original articles. The population consisted of singleton pregnancies with a prenatal diagnosis of EA. The intervention was NSAID therapy. The comparator was EM. The outcomes included gestational age (GA) at diagnosis, echocardiographic findings including TR, cardiothoracic ratio (CTR), Pericardial Effusion (PE), and presence of oligohydramnios, hydrops, and chromosomal abnormalities. PTB, GA at delivery, and survival at birth and survival to

hospital discharge. Exclusion criteria included review articles, systematic reviews and meta-analyses, guidelines, conference papers, articles published in non-English language, and animal studies.

2.2 | Data extraction and outcome measures

Two independent authors (ZAB and IM) extracted data using a standardized Excel spreadsheet and resolved disagreements following a discussion with a third author (FA). The following data were abstracted: (1) Study characteristics including author, study type, period, setting, (2) Prenatal characteristics including GA at diagnosis, echocardiographic findings including TR, CTR, PE, presence of oligohydramnios, hydrops, chromosomal abnormalities, and PTB and GA at delivery, and (3) Survival outcomes included fetal demise, LB, and survival to hospital discharge. Only variables reported in two or more studies were included in the final analysis. In case of overlap or duplications in patients between studies, the study with a larger sample size was included for review. The overlap of the population was assessed according to the authors and institution where the study was performed and the year of publication. If overlapped studies reported on different variables, then they were not excluded.

2.3 | Quality assessment

We employed the Newcastle-Ottawa Scale (NOS) to assess the quality and risk of bias of the cohort studies included in the analysis. The NOS assesses the selection, comparability, and outcome of cohorts. A study with a score of 7 or higher is regarded to be of good quality on this scale.[23] In addition, we used the Joanna Briggs Institute (JBI) Critical Appraisal tool checklist for case reports[24] to evaluate the quality of case reports. This checklist consisted of questions to assess the quality of the case presentation and learning points. Two independent reviewers (ZAB and IM) assessed the risk of bias and quality of the research.

2.4 | Data synthesis and statistical analysis

Statistical analysis was performed using *R*[25] (version 4.2.1) in RStudio (version 2022.07.0).[26] If data were reported as median (range or interquartile range), we converted them to mean and standard deviation using the Wan formula[27] to convert data to mean and standard deviation. To estimate the pooled proportion of categorical binary variables, a meta-analysis of proportions (metaprop function) was applied. A meta-analysis of means (metamean function) was used to pool the data of continuous variables including GA at diagnosis.[28]

I square tests (I^2) were used to examine heterogeneity across the included studies; $I^2 \geq 50\%$ and $p < 0.05$ indicates the presence of heterogeneity, while $I^2 > 75\%$ suggests substantial heterogeneity. Given the projected heterogeneity of the included studies, a random-effects model was employed.[29]

3 | RESULTS

3.1 | Search strategy and study characteristics

As shown in the PRISMA flow chart (Figure 1), a total of 719 articles were retrieved from three databases. Of those articles, 250 were excluded from the duplication. The remaining 469 studies were screened for eligibility. Title and abstract screening resulted in 68 potentially eligible studies.

After a full-text assessment was performed, 21 studies reporting on 610 fetuses with EA/TVD with a circular shunt met the criteria for inclusion in the meta-analysis. Seventeen studies (583 fetuses) included EM and were published between 1991 and 2019, while 4 studies (27 fetuses) used transplacental NSAID therapy and were published between 2019 and 2021.[7,17,30,31] All studies reporting on NSAID therapy achieved DA constriction with high dose indomethacin and subsequently switched to maintenance ibuprofen. Nine studies were retrospective cohorts and 8 were in the form of case reports or case series. Further study characteristics can be seen in Table 1.

3.2 | Pooled proportions of prenatal variables and survival outcomes in the EM and the NSAID groups

GA at diagnosis was comparable between groups (Mean: 27.06, 95% CI 24.93; 29.19 in EM vs. Mean: 27.94, 95% CI 25.35; 30.54 in NSAID), similarly was cardiothoracic ratio (Mean: 0.56, 95% CI 0.46; 0.65 in EM vs. Mean: 0.56, 95% CI 0.47; 0.64 in NSAID). Moderate to severe TR, PE, and hydrops were higher in the NSAID group [moderate to severe TR PP: 100%, (95% CI 0–100)], [PE PP: 75%, (95% CI 11, 85)] and [Hydrops PP: 45%, (95% CI 11, 85)] versus that in the EM group [Moderate to severe TR PP: 78%, (95% CI 65, 88)], [PE PP: 25%, (95% CI 8, 56)], and [Hydrops PP: 13%, (95% CI 8, 20)]. PTB <37 weeks in survivors was higher in the NSAID group (PP: 65%, 95% CI 17, 94) versus the EM group (PP: 25%, 95% CI 19, 34) (Table 2 and Figures S1–S6).

The risk of fetal demise was comparable between groups [PP: 15%, (95% CI 11, 19) in EM versus PP: 14%, (95% CI 2, 55) in NSAID]. Both chances for LB and survival to hospital discharge were higher in the NSAID group [PP: 86% (95% CI 45, 98) and PP: 89% (95% CI 42, 99), respectively] versus the EM group [PP: 67% (95% CI 51, 80) and PP: 43% (95% CI 23, 65), respectively] (Table 2 and Figures S7–S9). In the NSAID group, Ductal constriction was achieved in 81% (95% CI 42, 96) of cases and oligohydramnios was seen in 65% (95% CI 20, 93) of cases (Table 2 and Figures S10 and S11).

3.3 | Publication bias and risk of bias assessment

There was no evidence of small study effects for any outcome. The risk of bias using NOS for cohort and case control studies showed a minimum score of 6 and JBI risk of bias for case reports and a series

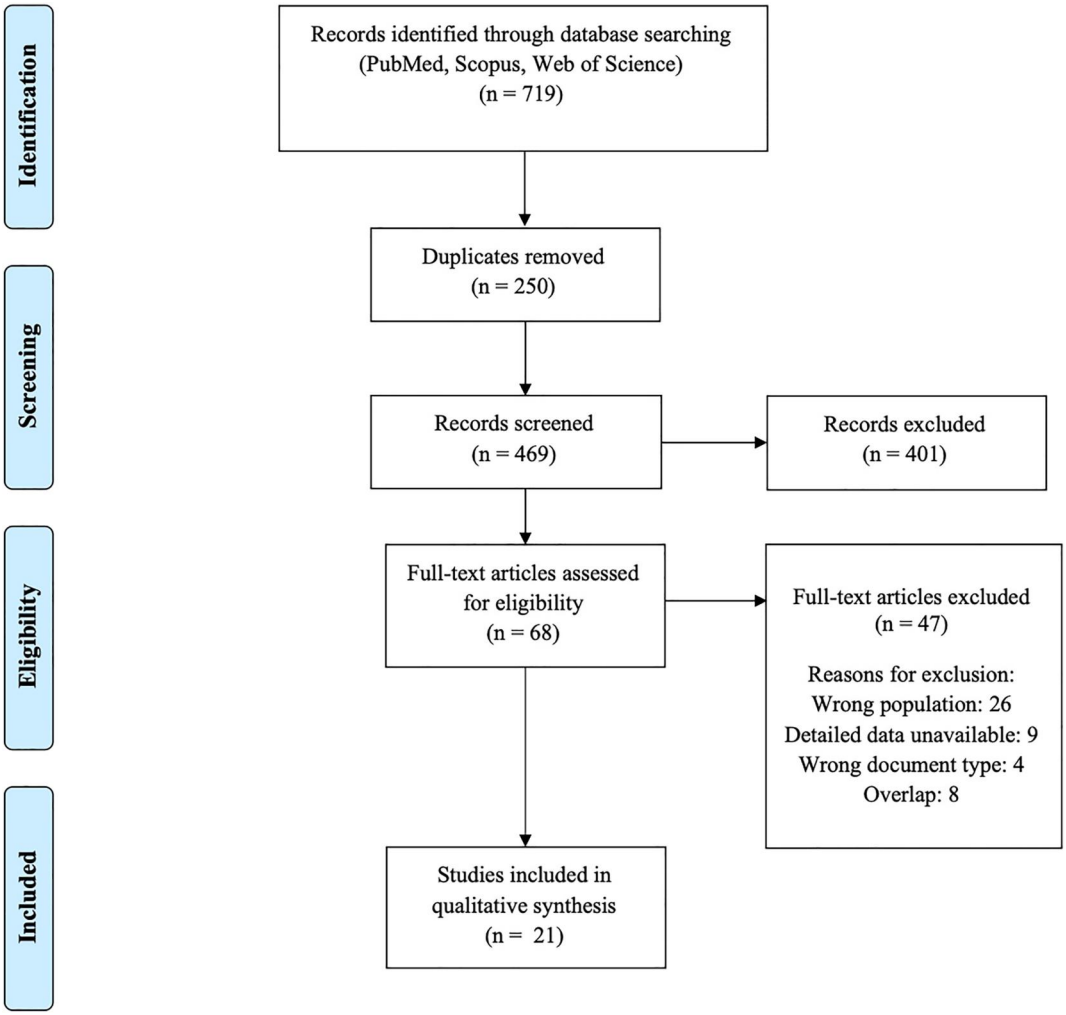

FIGURE 1 PRISMA flow diagram of the selection process.

of minimum scores of 6 (total score in Table 1, details of scoring in Table S2).

4 | DISCUSSION

4.1 | Principle findings

Among the 21 included studies, we report on 610 fetuses with EA or TVD (EA/TVD) and circular shunt of which 583 fetuses were managed expectantly and 27 fetuses were treated with NSAIDs in the form of high dose indomethacin followed by maintenance ibuprofen. Groups were comparable in terms of GA at diagnosis and cardiothoracic (CT) ratio. NSAID group had a more severe presentation in terms of the presence of moderate to severe TR, hydrops, and PE. The EM group had a LB rate of 67%, with survival to hospital discharge in 43%, while the LB rate was 86% with 89% survival to hospital discharge in the NSAID therapy group. Ductal constriction mitigating the circular shunt was achieved in 81% of fetuses receiving treatment. Oligohydramnios, as a potential side effect, occurred in 65% of patients in the NSAID therapy group.

4.2 | Interpretation of the literature

Circular shunting may be defined as a condition in which shunted blood returns to the same cardiac chamber without traversing a capillary bed. Various structural congenital cardiac anomalies, as well as significant ventricular dysfunction, may be associated with a circular shunt. A typical circular shunt involves semilunar valve and atrioventricular valve regurgitation in addition to the presence of a patent foramen ovale and a DA.[7] Although a circular shunt in EA and TVD is not common, the Toronto experience reported only 3 of 28 cases having this physiology; these lesions have a higher incidence of significant TR and PR, which is a setup for this unique hemodynamic situation.[31]

TABLE 1 Study characteristics of the included studies.

Author	Study period	Country	Hospital and data setting	Study design	Study population no.	Prenatal management	Studied outcomes	Risk of bias assessment result
Barre et al. (2012)[32]	1984–2010	France	University hospital	Retrospective cohort	26	EM	GA at EA diagnosis, TR, hydrops, IUFD, LB, survival to hospital discharge	7[c]
Freud et al. (2015)[2]	2005–2011	USA, Canada	University hospital (23 medical centers)	Retrospective cohort	243	EM	GA at EA diagnosis, TR, PE, hydrops, IUFD, LB, PTB survival, survival to hospital discharge	8[c]
Freud et al. (2021)[18]	2010–2018	USA, Canada, Spain, Brazil	University hospital (10 medical centers)	Case series	21	NSAID, EM	GA at EA diagnosis, post-therapy ductal constriction, TR, CTR, PE, post-therapy oligohydramnios, hydrops, LB, PTB survival, survival to hospital discharge, IUFD	8[a]
Gill et al. (2021)[19]	-	Canada	University hospital	Case report	1	NSAID	GA at EA diagnosis, post-therapy ductal constriction, TR, LB, survival to hospital discharge	7[b]
Gottschalk et al. (2017)[33]	1999–2013	Germany	University hospital	Retrospective cohort	76	EM	GA at EA diagnosis, PE, hydrops, IUFD, LB	7[c]
Hakim et al. (2013)[34]	-	Tunisia	Public hospital	Case report	1	EM	GA at EA diagnosis, TR, LB	8[b]
Inamura et al. (2020)[35]	-	Japan	University hospital	Case report	1	EM	GA at EA diagnosis, TR, LB	6[b]
Lasa et al. (2012)[36]	2000–2008	USA	University hospital	Retrospective cohort	17	EM	GA at EA diagnosis, CTR, IUFD, LB, survival to hospital discharge	7[c]
Lopes et al. (2021)[30]	-	Brazil	University hospital	Case report	1	NSAID	GA at EA diagnosis, post-therapy ductal constriction, TR CTR, PE, post-therapy oligohydramnios, hydrops, LB, PTB survival, survival to hospital discharge	7[b]
Masoller et al. (2020)[37]	2002–2018	Spain	University hospital	Retrospective cohort	31	EM	GA at EA diagnosis, TR, IUFD, LB, survival to hospital discharge	7[c]
Rato et al. (2019)[38]	-	Portugal	University hospital	Case report	1	EM	GA at EA diagnosis, TR, LB, survival to hospital discharge	7[b]
Sasikumar et al. (2015)[9]	-	India	University hospital	Case report	1	EM	GA at EA diagnosis, TR, hydrops	5[b]
Satomi et al. (1994)[39]	-	Japan	University hospital	Case series	5	EM	GA at EA diagnosis, TR, CTR, IUFD, LB, PTB survival, survival to hospital discharge	7[a]
Selamet Tierney et al. (2017)[12]	-	USA	University hospital (23 medical centers)	Retrospective cohort	51	EM	GA at EA diagnosis, TR, CTR, PE, hydrops, IUFD, LB	7[c]

(Continues)

TABLE 1 (Continued)

Author	Study period	Country	Hospital and data setting	Study design	Study population no.	Prenatal management	Studied outcomes	Risk of bias assessment result
Sharland et al. (1991)[40]	1980–1991	England	University hospital	Retrospective cohort	38	EM	GA at EA diagnosis, hydrops, IUFD, LB, survival to hospital discharge	7[c]
Suneja et al. (1996)[41]	1993	India	University hospital	Case report	1	EM	GA at EA diagnosis, PE, hydrops, IUFD, PTB survival	6[b]
Tongsong et al. (2005)[42]	-	Thailand	University hospital	Case report	2	EM	GA at EA diagnosis, TR, PE, hydrops, IUFD, PTB survival	7[b]
Torigoe et al. (2019)[10]	-	Canada	Hospital for sick children	Case series	4	NSAID	GA at EA diagnosis, post-therapy ductal constriction, TR, CTR, post-therapy oligohydramnios, hydrops, LB, PTB survival, survival to hospital discharge	9[b]
Torigoe et al. (2020)[43]	2000–2015	Japan	University hospital	Retrospective cohort	36	EM	GA at EA diagnosis, TR, PE, hydrops, IUFD, LB, alive at hospital discharge	7[c]
Tsukimori et al. (2012)[44]	-	Japan	University hospital	Case report	1	EM	GA at EA diagnosis, ≥ moderate TR, overall PR, CTR, live birth, PTB survival, survival to hospital discharge	6[b]
Wertaschnigg et al. (2016)[8]	2000–2014	Canada	University hospital	Retrospective cohort	52	EM	GA at EA Diagnosis, TR, hydrops, IUFD, LB, PTB survival	8[c]

Abbreviations: CTR, Cardiothoracic Ratio; EA, Ebstein Anomaly; EM, Expectant management; GA, Gestational Age; IUFD, Intrauterine fetal death; LB, Live birth; NSAID, Nonsteroidal anti-inflammatory drugs; PE, Pericardial Effusion; PTB, Preterm Birth; TR, Tricuspid Regurgitation.

[a]Case series Risk of bias assessed using JBI checklist for case series.

[b]Case reports Risk of bias assessed using JBI checklist for case reports.

[c]Cohort studies Risk of bias assessed using NOS for cohort studies.

TABLE 2 Pooled proportions of variables of interest in pregnancies with fetal Ebstein anomaly with circular shunt managed expectantly or with transplacental NSAIDs.

Variable	Studies (*n*)	Events (*n*/*N*) or *N*	Proportion or mean (95% CI)	I^2
Expectant management				
GA at diagnosis (weeks)	18[2,8,9,12,18,32–40,42–44]	598	27.06 [24.93; 29.19]	98.1%
≥Moderate TR	14[2,8,9,12,18,32,34,35,37–39,42–44]	343/435	0.78 [0.65; 0.88]	68.6%
CTR	5[12,18,36,39,44]	84	0.56 [0.46; 0.65]	81.9%
Pericardial effusion	7[2,12,18,33,41–43]	90/412	0.25 [0.08; 0.56]	69.6%
Oligohydramnios	2[41,43]	2/37	0.28 [0.00; 1.00]	0.0%
Hydrops	13[2,8,9,12,18,32,33,40–43]	62/567	0.13 [0.08; 0.20]	51.3%
IUFD	13[2,8,12,18,32,33,36,37,39–43]	89/593	0.15 [0.11; 0.19]	20.7%
PTB <37 weeks	6[2,8,39,41,42,44]	55/217	0.25 [0.19; 0.34]	0.0%
Live birth	15[2,8,12,18,32–40,43,44]	388/595	0.67 [0.51; 0.80]	79.2%
Survival to hospital discharge	9[2,32,36–40,43,44]	177/402	0.43 [0.23; 0.65]	72.9%
Transplacental NSAID therapy				
GA at diagnosis (weeks)	4[10,18,19,30]	21	27.94 [25.35; 30.54]	0.0%
Ductal constriction	4[10,18,19,30]	17/21	0.81 [0.42; 0.96]	0.0%
≥Moderate TR	4[10,18,19,30]	21/21	1.00 [0.00; 1.00]	0.0%
CTR	3[10,18,30]	20	0.56 [0.47; 0.64]	0.0%
Pericardial effusion	2[18,30]	12/16	0.75 [0.00; 1.00]	0.0%
Oligohydramnios	3[10,18,30]	13/20	0.65 [0.20; 0.93]	0.0%
Hydrops	3[10,18,30]	9/20	0.45 [0.11; 0.85]	0.0%
IUFD	4[10,18,19,30]	3/21	0.14 [0.02; 0.55]	0.0%
PTB <37 weeks	3[10,18,30]	11/17	0.65 [0.17; 0.94]	0.0%
Live birth	4[10,18,19,30]	18/21	0.86 [0.45; 0.98]	0.0%
Survival to hospital discharge	4[10,18,19,30]	16/18	0.89 [0.42; 0.99]	0.0%

Abbreviations: CTR, Cardiothoracic Ratio; EA, Ebstein Anomaly; GA, Gestational Age; IUFD, Intrauterine fetal death; PR, Pulmonary Regurgitation; PTB, Preterm Birth; TR, Tricuspid Regurgitation.

Management of EA before the use of prenatal NSAIDs was restricted to the EM or preterm delivery to prevent in-utero demise and to offer medical or surgical therapy. These strategies are associated with poor a prognosis.[8] If left untreated, fetal EA/TVD with a circular shunt can cause left ventricular volume overload, leading to heart failure and reduced cardiac output in newborns, particularly if combined with decreased pulmonary vascular resistance.[17] These severe cardiovascular complications may cause the need for urgent cardiac reconstructive surgery in infancy.[45]

Early administration of low dose prenatal transplacental NSAID therapy after diagnosis, may constrict DA and mitigate circular shunt in fetuses with severe EA/TVD, resulting in a reversal of complications such as hydrops and decreasing perinatal mortality.[10,18,46] Maternal use of NSAIDs during pregnancy poses some risks to the fetus, especially during the second and third trimesters of gestation. NSAIDs cause reduced renal perfusion and dysfunction, and as fetal urine is the main source of amniotic fluid in the second trimester and beyond, oligohydramnios.[47] Even though oligohydramnios is commonly seen after days to weeks of NSAID use, it has also been occurred as soon as 48 h after initiation.[48] Knowing that the majority of NSAID–induced oligohydramnios cases in the literature were transient and reversible upon cessation,[49–51] we may justify its use for long-term benefits of DA constriction and circular shunt mitigation in these patients. However, the data come mainly from small studies and long-term data are lacking,[49] so it is necessary to examine each severe EA/TVD with circular shunt case individually and before considering prenatal treatment with NSAIDs. In our study, DA constriction was achieved in 81% and 65% of cases had oligohydramnios.

It is worth mentioning that some studies reported on using maternal hyperoxygenation as another form of prenatal treatment

for EA/TVD with circular shunt; two studies in 2017 and 2018 reported that the use of chronic antepartum maternal oxygen therapy for constriction of the fetal DA led to modification in pulmonary vascular resistance and improved outcomes.[52,53]

4.3 | Strengths and limitations

The strengths of this review are the thorough search and assessment in three large databases that resulted in the largest case numbers of EA/TVD with circular shunt with EM providing valuable clinical and echocardiographic data along with rates of fetal demise and postnatal survival rates. Even though the NSAID group case number was small, it is the first study to systematically evaluate the data of this innovative approach that is attempting to improve outcomes in a population with very high perinatal mortality.

We acknowledge our limitations. The small number of cases, particularly in the NSAID therapy arm, retrospective non-randomized design of the included studies, heterogeneity in prenatal management and different periods of follow-up represent the major limitations of this systematic review. We initially intended to evaluate more vast prenatal variables and postnatal outcomes, but due to limited data in the included studies, that was not possible. The heterogeneity of postnatal care of this population related to different neonatal intensive care and cardiac care unit levels could result in different postnatal outcomes. The findings are also subject to potential publication bias because the nature of some outcomes and the small number of studies limit the reliability of formal tests.

5 | CONCLUSION

In summary, our data show the high perinatal mortality in EA/TVD with circular shunt and implies that NSAIDs may be an effective prenatal intervention given the high success rate in achieving ductal constriction; the significant incidence of oligohydramnios suggests fetuses may be at risk of renal complications. Knowing that the NSAID therapy data comes from a small sample size pooled from case reports and small series that lack safety data, the results should be interpreted with caution and patients counseled regarding these limitations if NSAID therapy is being considered. Future multicenter studies at fetal and neonatal care centers that are somehow homogenous in follow-up and management are needed to address a number of unanswered questions regarding the pharmacodynamics and proper dosage of NSAIDs, as well as exploring important short- and long-term safety data.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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