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## Birth prevalence of right ventricular outflow tract abnormalities in the recipient twin of monochorionic twin pregnancies complicated by twin-to-twin transfusion syndrome: amnioreduction *versus* foetoscopic laser coagulation treatment

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### ABSTRACT

**Objective.** Right Ventricular Outflow Tract Abnormalities (RVOTA) as pulmonary stenosis, atresia and insufficiency are typical cardiac anomalies of recipient twins (RTs) in untreated monochorionic diamniotic twin (MC/DA) pregnancies complicated by twin-to-twin transfusion syndrome (TTTS), affecting 8-12% of cases.

The aim of this study was to compare birth RVOTA prevalence in TTTS pregnancies treated by foetoscopic laser surgery (FLS) *versus* by serial amnioreductions (AR).

**Materials and Methods.** We conducted a retrospective analysis of neonatal medical records of TTTS referred to our centre to receive treatment. Serial ARs were the treatment up to 2004, when FLS has become the treatment. Neonatal cardiac outcomes were reviewed to assess RVOTA prevalence.

**Results.** Neonatal cardiac outcomes were available in 354 MC twins complicated by TTTS: 309 (87%) were treated by FLS and 45 (13%) by AR. All cases of RVOTA at birth involved the RT. Among 253 RTs born alive, 13 cases (5.1%) had RVOTA at birth. In FLS group, 221 (71%) RTs were born alive and 10 (4.5%) with RVOTA. In the AR group, 32 (71%) RTs were born alive and 3 (9.4%) with RVOTA. Occurrence of RVOTA was halved in FLS group (FLS = 4.5% *vs* AR = 9.4%, respectively) but this reduction did not reach statistical significance (P-value = 0.22).

**Conclusions.** In our experience, treatment for TTTS by FLS *versus* by AR was suggestive of a lower birth-rate of RVOTA in recipient twins but did not eliminate it completely. Therefore, TTTS represents an indication for careful postnatal cardiologic evaluation, including an echocardiography, regardless of the type of prenatal treatment received.

## INTRODUCTION

Right ventricular outflow tract abnormalities (RVOTA) as pulmonary stenosis, atresia and insufficiency are the typical cardiac abnormalities of the recipient twin (RT) found in 10% of monochorionic twin (MC) pregnancies complicated by twin-to-twin transfusion syndrome (TTTS) [1, 2]. It has been speculated that recipient twins' cardiomyopathy might be the consequence of both the excess of blood volume and the passage of vasoactive peptides of the renine-angiotensin system through the placental anastomoses from donor to recipient. This passage determines an increased vascular resistance and a higher pre and after-load on the right side of RT heart [3, 4].

Foetoscopic laser coagulation surgery of the placental anastomosis (FLS) has become the treatment of choice for TTTS, based on the results of Eurofoetus trial, a multicentric international randomized trial showing that FLS is a more effective treatment compared to serial amnioreduction (AR) for severe TTTS diagnosed before 26 weeks of gestation [5].

By the interruption of the passage of blood and vasoactive mediators across the placental anastomoses, FLS should lead to cardiovascular improvement in affected RT. However, the aforementioned randomized trial did not evaluate the difference of the neonatal prevalence of RVOTA between the AR and FLS group.

The aim of this study is to evaluate the prevalence at birth of RVOTA in TTTS twins treated with AR or FLS at a single institution.

## MATERIALS AND METHODS

### *Patients selection and RVOTA definition*

This was a retrospective descriptive analysis of cardiac outcome at birth of MC neonates in pregnancies complicated by TTTS, referred to the Fetal Therapy Unit of the "Vittore Buzzi" Children Hospital in Milan (Italy), between 1999 and 2018.

All data on complicated MC twin pregnancies referred to our Unit are of entered prospectively in a database, including sonographic findings, operative characteristics, neonatal outcomes and hospital where the delivery takes place. All postpartum medical records from MC pregnancies treated for TTTS, were reviewed for neonatal diagnosis of RVOTA.

All TTTS cases in which perinatal follow-up was not available were excluded from the study.

The diagnosis of RVOTA was made by postnatal echocardiography. The scan was indicated by clinical signs of RVOTA.

Newborns delivered at our hospital had a clinical cardiologic assessment by means of cardiac auscultation conducted by a neonatologist, within 24 hours from delivery. If a heart murmur was detected, then a paediatric cardiologist was involved, and an echocardiography was performed. At echocardiography, the right outflow tract was evaluated and the transpulmonary mean and maximum gradient were recorded to assess the presence and severity of the anomaly. RVOTA diagnosis was based on echocardiography and classified as pulmonary stenosis (PS), if forward flow was detected across the pulmonary valve (PV) with a peak gradient  $> 20$  mmHg; as pulmonary insufficiency (PI) if bidirectional flow was identified across the PV; and as pulmonary atresia (PA), if no flow was detectable across the PV. In cases with postnatal diagnosis of PS the grade of severity was based on the peak gradient (PG): mild if  $PG < 36$  mmHg; moderate between 36-64 mmHg; severe when  $\geq 64$  mmHg [6].

For twins delivered in the referring hospitals, local protocols for perinatal evaluation and follow-up were applied in order to assess neonatal cardiac outcome. All neonatal medical records available were reviewed for the presence of RVOTA at birth.

### *TTTS and treatment*

TTTS was defined according to the Eurofoetus criteria (*i.e.*, polyhydramnios of  $\geq 8$  cm maximum vertical pocket in the recipient or  $\geq 10$  cm from 20 weeks of gestation onwards and oligohydramnios of  $\leq 2$  cm maximum vertical pocket in the donor) and the Quintero Staging system was used to classify the severity of TTTS [7]. Treatment was performed with FLS and AR according to what previously reported [8, 9]. In our centre AR was the therapy of choice for TTTS up to 2004, when FLS became the treatment for all TTTS.

TTTS cases that did not undergo any treatment were excluded from the analysis, as the purpose of this study was to compare the perinatal cardiac outcome associated with different treatments.

The study complied with our Institution's research guidelines for clinical observational and retrospective studies.

### Statistical analysis

Continuous variables are presented as median and interquartile range (IQR), while categorical variables as numbers and percentages. The Mann-Whitney U test and Pearson  $\chi^2$  test were performed to make univariate comparisons of quantitative and qualitative variables, respectively, between groups. SPSS Statistics v. 26.0 (IBM Corp., Armonk, NY, USA) was employed for statistical analyses.

## RESULTS

354 MC twins from MC/DA pregnancies complicated by TTTS and treated either with FLS (n = 309, 87%) or AR (n = 45, 13%) were included in our study. All RVOTA cases at birth were diagnosed in the recipient twins with 13 cases of RVOTA (5.1%) among 253 RT born alive (71% of total RT). As none of the donor twins was born with RVOTA, we focused the analysis on perinatal outcome of recipient twins. **Table 1** shows the prenatal characteristics and perinatal outcomes of the recipient twins in pregnancies with TTTS treated with FLS vs treatment with AR. In the FLS group, 221 (71%) RTs were born alive and among them 10 (4.5%) showed RVOTA at the cardiologic assessment: 8 PS, 1 PA and 1 PI. All neonates born with RVOTA got through the perinatal period and 8 out of 10 (80%) (1 PA and 7 severe PS) underwent balloon valvuloplasty (BV) within 2 months of life.

In the AR group, 32 (71.1%) RT were born alive, and among them 3 (9.4%) showed RVOTA at the cardiologic assessment: 2 PS and 1 PA. The neonate born with PA died during the perinatal period while the

2 RTs born with severe PS underwent BV within 2 months of life. The RVOTA prevalence was lower in the TTTS group treated with FLS (4.5%) compared to that in the group treated with AR (9.4%). However, this difference did not reach statistical significance (p = 0.22).

As shown in **Table 1**, the median gestational age at the intervention was 19 weeks (17.5-21) in the FLS group compared to 20 weeks (18.3-24) in the AR (p = 0.002). The Quintero Stage at presentation was higher in the AR compared with the FLS group, with 51% of STAGE III or IV in the AR and 33% in the FLS group respectively (p = 0.002).

In the AR group, 17/45 cases (38%) had one AR intervention, 13/45 (30%) two AR, 7/45 (16%) three AR and 8/45 (18%) four AR or more. One case underwent nine AR procedures during pregnancy.

The prevalence of intrauterine foetal death of the RT was similar between the two groups (28.9% among TTTS treated with AR, 28.5% among TTTS treated with FLS; p = 0.54). Similarly, no significant difference was observed for the median gestational age at delivery (32.5 weeks for AR and 32 weeks for FLS respectively; p = 0.35) and birthweight (1,650 g for AR and 1,750 g for FLS respectively; p = 0.28), as shown in **Table 1**.

The prevalence of neonatal death was significantly higher in the AR group compared with FLS group (28% vs 7%; p = 0.001).

## DISCUSSION

To our knowledge this is the first study comparing the neonatal prevalence of RVOTA in two groups of MC twins treated for TTTS with serial AR or FLS at a

**Table 1.** Comparison of recipient twins' prenatal characteristics and perinatal outcome between TTTS groups treated with foetoscopic laser surgery (FLS) and with serial amnioreductions (AR).

	AR (n = 45)	FLS (n = 309)	P-value
GA (at first intervention)	20 (18.3-24.0)	19 (17.5-21.0)	<b>0.002</b>
Quintero Stage			<b>0.002</b>
I	13 (28.9%)	58 (18.8%)	
II	9(20.0%)	150 (48.5%)	
III	17(37.8%)	84 (27.2%)	
IV	6 (13.3%)	17 (5.5%)	
IUFD	13 (28.9%)	88 (28.5%)	0.54
GA at delivery, weeks, days	32.5 (29.4-36.2)	32.0 (30.0-35.0)	0.35
Weight at delivery, gr	1650 (1345-2625)	1750 (1300-2155)	0.28
NND	9/32 (28.1%)	16/221 (7.2%)	<b>0.001</b>
Postnatal RVOTA	3/32 (9.4%)	10/221 (4.5%)	0.22

Median (interquartile range); number (percentage); AR: Amnioreduction; FLS: foetoscopic laser surgery; GA: gestational age; IUFD: intrauterine foetal death; NND: Neonatal death; RVOTA: right ventricular outflow tract abnormalities.

single centre. In our cohort, the prevalence of RVOTA at birth in the FLS group is half of that found in the AR group (4.5% vs 9.4% respectively), even if the difference did not reach statistical significance.

The global birth prevalence of RVOTA has been reported to be 0.06 % in a meta-analysis on congenital heart defects [10]. Therefore, according to our data, the prevalence of RVOTA in RTs is much higher than in general population despite the prenatal treatment and, in particular, it results to be ~75 times higher in the group with FLS treatment and ~150 times higher in the group with AR treatment. Our results are in line with what reported in a systematic review on congenital heart defects in MC twins, with 16 of the 153 recipient twins treated with serial AR (10.4%), born with RVOTA [11]. This percentage is comparable to what historically reported on untreated TTTS [1, 2], as demonstration of the low power of AR as a treatment for such condition. On the other hand, in a prospective longitudinal study on TTTS treated with FLS the RVOTA prevalence at birth in the RTs was 6.7% (7/105) [12]. This figure is similar to the RVOTA prevalence in our group treated with FLS (4.5%), although slightly higher. This difference could lie on the lack of prospective echocardiographic evaluation of our cases, that might have missed mild forms of RVOTA unrecognizable to a clinical evaluation.

The percentage of NND was significantly lower after FLS than after AR (7% vs 28%), in agreement with what it is already known by the Eurofoetus. The pathophysiology of RVOTA's development in the RT is likely due to an unbalance passage of blood volume and vasoactive peptides enough to cause cardiac maladaptation. The cardiac involvement includes ventricular hypertrophy and tricuspid regurgitation. The hypertrophy leads to a stiff, non-compliant ventricle with an impaired diastolic function and a diminished forward flow across the pulmonary valve. Since intracardiac circulation is necessary for cardiac morphogenesis and vasculogenesis, the absence of sufficient forward flow due to abnormal right ventricular function may cause a failure of the pulmonary valve to grow [13]. Foetoscopic laser surgery (FLS) of placental vascular anastomoses, interrupting the passage of blood and vasoactive mediators, stops this process: however, if the functional damage on the pulmonary valve has already caused an organic change, this effect cannot be reversed. Indeed, our retrospective study has shown that FLS halves the prevalence of RVOTA at birth compared to serial

AR, even if this intervention does not eliminate completely the chance of abnormalities.

This assumption has been clearly demonstrated by studies on long-term outcomes on MC pregnancies complicated by TTTS and treated by FLS, which reported a prevalence of pulmonary stenosis in RTs of 8% [14] at a median age of 21 months and 10% [15] at a median age of 10 years.

### *Strengths and limitations*

A strength of this study is the examination of a large cohort of cases throughout years, with the same method reported in a non-TTTS population, as previously reported by our group [16]. The results of the present study further contribute to the acquisition of knowledge on the prevalence of cardiac abnormalities, in particular right ventricle outflow tract obstructions, in different MC twin pregnancies, both complicated and not complicated by TTTS, with focus on the treatment received for this condition. Follow-up was available at birth for all reported cases.

One limitation of the study is the lack of a uniform protocol to rule out postnatal RVOTA between different centres where twins were delivered, and changes in diagnoses and follow-up occurring throughout years. An underestimation of diagnoses could be due to the absence of a systematic echocardiographic examination of the newborns. However, it is reasonable to assume that critical forms of RVOTA would have been excluded by clinical evaluation alone performed by expert neonatologists before neonates' discharge.

Another limitation of this study was the small number of cases in the AR group, due to the missed information on neonates' cardiac outcome associated to the retrospective methodology of the study. A prospective randomized controlled trial comparing the two treatments would be needed to confirm the superiority of FLS over AR in decreasing RVOTA birth prevalence, but such study would be unethical as FLS has been demonstrated to be superior to AR in terms of perinatal viability and neurological outcome and has nowadays established as the gold standard treatment.

## **CONCLUSIONS**

In our experience, FLS treatment for TTTS halved, although not significantly, the birth prevalence of RVOTA in the RTs when compared to AR cases.



Nevertheless, diagnoses of RVOTA at birth were made in both groups, indicating that interventions for TTTS may not eliminate completely the chance of cardiac abnormalities, as the functional damages may have already converted into organic, not reversible changes.

Therefore, clinicians should consider TTTS as an indication for a careful postnatal cardiological evaluation, including an echocardiography, regardless of the type of prenatal treatment received.

## COMPLIANCE WITH ETHICAL STANDARDS

### *Authors contribution*

S.F.: Cases collection, writing - original draft, writing - review & editing. M.L., I.C.: Writing - original draft, writing - review & editing. D.C.: Statistical analysis. L.N.S.: Cases collection, writing - original draft. A.L., C.C., S.B.: Formal analysis.

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None.

### *Study registration*

N/A.

### *Disclosure of interests*

The authors declare that they have no conflict of interests.

### *Ethical approval*

Given the retrospective nature of the analysis, the present study complied with our Institution's research guidelines for clinical observational and retrospective studies and our ethical committee, Comitato Etico Milano Area 1, does not require an ethical approval. According with the declaration of Helsinki, this study was conducted in compliance with the "ethical standards that promote and ensure respect for all human subjects and protect their health and rights".

### *Informed consent*

All women, treated at our fetal therapy unit, provided a written informed consent for any further clinical evaluation.

## *Data sharing*

The datasets generated and analyzed during the current study are not publicly available due to the fact that not all the patients, in the written consent, approved that their data be shared with centres other than ours. On reasonable request, the corresponding author will share their clinical data after obtaining further consent to the patients.

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